GREEN SYNTHESIS OF HETEROCYCLES

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GREEN SYNTHESIS OF HETEROCYCLES

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EDITORIAL
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Editorial: Green Synthesis of Heterocycles

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Keywords: green chemistry, heterocycles, cyclic compound, sustainable, green principles

Editorial on the Research Topic

Green Synthesis of Heterocycles

INTRODUCTION

Over the last two centuries, new approaches to the synthesis of heterocycles have had an enormous impact on both organic and inorganic chemistry. Natural products, renewable resources, agrochemicals, pharmaceuticals, and macromolecules (polymers and macrocycles) often feature heterocyclic substructures. Approaches to the synthesis of these compounds have been evolving constantly from classical condensation procedures to click reactions and new multicomponent domino procedures. Furthermore, the development of new approaches to heterocycle synthesis has been a major research interest for green and sustainable chemists.

In this perspective, the Research Topic "Green Synthesis of Heterocycles" encompasses a collection of research and review articles focusing on heterocyclic compounds synthetized according to Green Chemistry principles. The focal point was to build on efficient catalytic methodologies aiming at high process performances by means of non-toxic/green and biodegradable chemicals. Industrial applications, process developments, and future perspectives of the so-synthetized heterocyclic compounds have also been addressed.

This collection of articles features two reviews and six original research papers.

The first review focuses on the synthesis of heterocycles via 1,3-dipolar cycloaddition employing Green approaches (Martina et al.). The authors report on the preparation of numerous cyclic structures, including pyrrolizidines pyrrolo[2,3-a]pyrrolizidino derivatives, isoxazolidines, pyrazoles, pyrrolidines and ispirooxindolopyrrolidines, diazaheptacyclic rings, etc. The use of green solvents, i.e., ionic liquids, fluorinated solvents, and water is discussed. Improvements over commonly used organic solvents are highlighted and, in specific cases, the enhancement in regio- and stereo-selectivity addressed. Besides, catalyst-free reactions and alternative reaction conditions—such as microwave irradiation and activation by light exposure—are also reported for several substrates.

The second review is centered on the use of dialkyl carbonates (DACs) as green reagent and solvent molecules for the synthesis of several heterocycles (Tundo et al.). The preparation of tetrahydrofuran systems, pyrrolidines, indolines, isoindoline, and 1,4-dioxanes was generally conducted in the presence of a base and dimethyl carbonate (DMC). Interestingly, a new class of compounds, namely, mustard carbonates was explored for the synthesis of piperidines. In the case of bio-based platform chemical 5-hydroxymethylfurfural (HMF), DMC was employed as an efficient extracting solvent. In all the reported cyclizations, DACs acted as reaction media and as a sacrificial molecule, mimicking the typical reactivity of chlorine compounds but without the intrinsic toxicity of halogen-based molecules.

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Some of the major issues in heterocycle synthesis are the recycling of solvent/catalyst systems and avoiding purification and, consequently, waste production. In this view, one of the original research papers in this collection reports on isoxazole and 1,2,3-triazole preparation by developing efficient protocols that feature recycling of both solvent and catalyst. Within this scope, Polarclean, an alternative to a classical polar solvent, is shown to be an efficient medium in dipolar cycloaddition reactions and intramolecular C–H activation to synthetize isoxazoles and hetero-fused triazoles, respectively (Ferlin et al.). Both cyclization reactions were conducted in one step, in an atom economical fashion, minimizing waste generation. Isolation of the product was achieved via re-crystallization without the need for further purification. Most importantly, the solvent/catalyst system could be effectively reused.

The preparation of 1,2,3-triazoles, and specifically 1,4-disubstituted-1,2,3-triazoles, is also addressed in the research article by Aflak et al.. In this work, triazoles were prepared selectively via click chemistry by copper on carbon-catalyzed [3+2] cycloaddition reactions of azides and alkynes in water. Catalytic systems employed for the reaction were based on copper(I) catalysts heterogenized onto commercially activated carbon materials (Cu-CC) and on carbon material produced from vegetable biomass using Argan nut shells (Cu-CANS). In the reaction conditions found to be most optimal, a series of azides and alkynes were reacted in water in the presence of the new catalytic system (0.5 mol %) at room temperature. The reported heterogeneous copper on carbon catalysts were recovered and reused for up to 10 catalytic runs with minor activity loss.

A topic that is attracting growing attention is the preparation of bio-based platform chemicals via biomass valorization. One of the published research papers focuses on the catalytic conversion of levulinic acid into N-heterocycles (Rodríguez-Padrón et al.). The catalytic system employed was achieved from graphitic carbon nitride (g-C_3N_4) functionalized with a low platinum loading (g-C_3N_4/Pt). The catalytic performance of the so-prepared material was investigated in the continuous-flow transformation of levulinic acid to N-heterocycles. The reaction conditions (temperature, pressure, and concentration of starting compound) were optimized. The catalytic system displayed high selectivity for the preparation of 1-ethyl-5-methylpyrrolidin-2-one and very good stability after 3 h of reaction.

Oxazinanones (six-membered cyclic urethanes) are interesting heterocycles that are key structural units in bioactive natural products and pharmaceuticals. The research study reported by Gallo et al. focuses on the synthesis of 1,3-oxazinane-2,5-diones via acid catalyzed intramolecular cyclization of N-Cbz-protected diazoketones derived from α-amino acids. The reaction was carried out in metal-free conditions, being promoted by a silica-supported catalyst and with methanol as the solvent. In a typical reaction, diazo carbonyl reagent was mixed with the catalyst at room temperature, and a good yield of the products was achieved (90%); no further purifications were required.

Flash vacuum pyrolysis (FVP) has recently been reported as a viable technique for the synthesis of several heterocycles. In this view, one of the research articles focuses on a gas-phase reaction of 1,3-dithiolane-2-thione over molybdenum trioxide supported on pumice stone that resulted in its conversion into 1,3-dithiolan-2-one (Aitken et al.). The reaction was carried out by physical mixing of MoO_3 and pumice or by solution impregnation, resulting, under the reaction conditions found to be most optimal, in an isolated yield of up to 67%. At the end of the reaction, besides the wanted 1,3-dithiolan-2-one, partially sulfurized MoO_3 is recovered; the latter is regenerated to the active catalyst on exposure to air.

The development of sustainable synthetic methods for the construction of complicated cyclic target molecules with minimum environmental impacts is a challenging aim for academia and industry. In this view, the article by Jang and co-workers focuses on cyclobuta[a]naphthalen-4-ols construction employing a bicyclization reaction of yne-allenones with indoles (Li et al.). This reaction was performed using commercially available $FeCl_3$ as the catalyst and EtOH as a benign solvent. The reaction proceeded via a [2+2] cycloaddition/1,6-conjugate addition cascade, which led to a good yield of the desired product (up to 90%). This protocol has the advantages of a broad scope of substrates, good tolerance of functional group, and high atom utilization together with mild reaction conditions.

The present article collection illustrates some of the recent advances in heterocycle preparation that employ more sustainable synthetic procedures. This topic is particularly important for drug development since the pharmaceuticals industry is environmentally very problematic. As a result, investigations on greener approaches to heterocyclic compounds are gaining ever-growing attention in the scientific community. The most relevant future directions to achieve this goal are evidently depicted in the above-summarized articles, i.e., employing multicomponent reactions, using green/renewable-based solvents, and heterogeneous catalysis, better if in combination with alternative reaction conditions. Besides, waste consumption should be reduced, and any purification avoided.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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ORIGINAL RESEARCH
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Fe(III)-Catalyzed Bicyclization of Yne-Allenones With Indoles for the Atom-Economic Synthesis of 3-Indolyl Cyclobutarenes

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A new Fe(III)-catalyzed bicyclization reaction of yne-allenones with indoles has been established, enabling the direct construction of cyclobuta[*a*]naphthalen-4-ols with an all-carbon quaternary center in good to excellent yields. This reaction was performed by using low-cost $FeCl_3$ as the catalyst and EtOH as the environmentally benign solvent, providing a green protocol for constructing the cyclobutarene framework with a high degree of atom economy and functional group compatibility. The reaction mechanism was proposed to proceed through a [2 + 2] cycloaddition/1,6-conjugate addition cascade.

Keywords: Fe(III)-catalysis, bicyclization, 1,6-addition, yne-allenones, cyclobutarenes

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INTRODUCTION

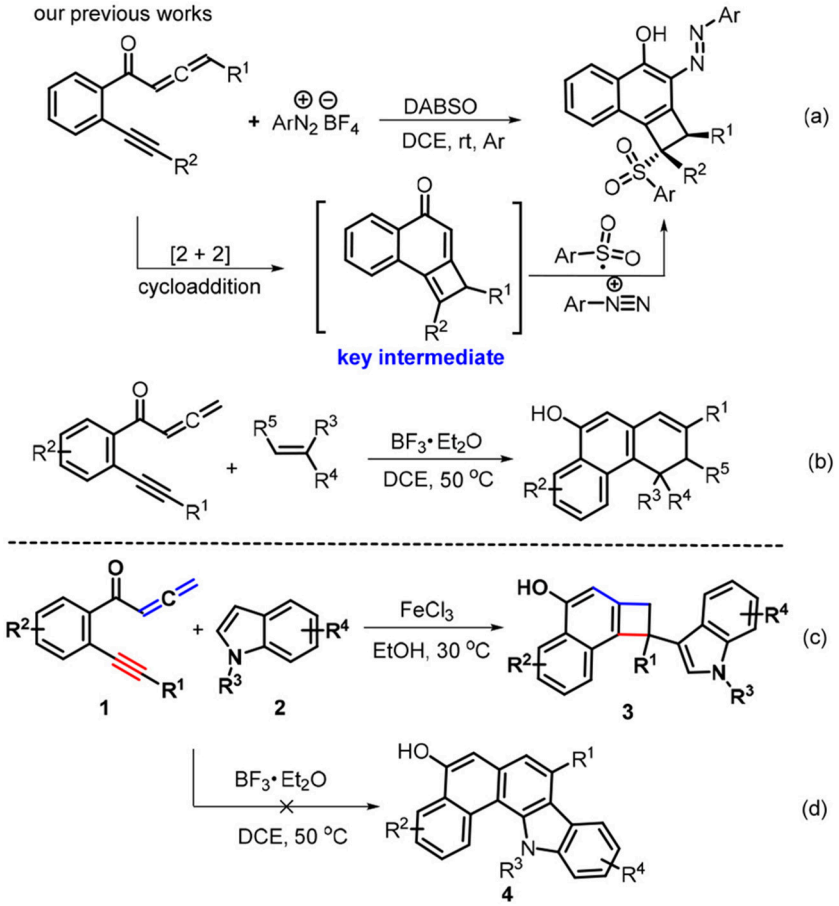
Development of practical and sustainable synthetic methods for the rapid construction of valuable cyclic target molecules, along with minimum environmental impacts, represents an endeavor of utmost importance in both academia, and industry (Anastas and Warner, 1998; Bruckmann et al., 2008; Martins et al., 2009; Jiang et al., 2010; Huang et al., 2018a). In this context, chemical transformations following the principles of atom-economy are generally believed to be green since such reactions enable different molecular fragments into integrated cyclic frameworks by recombining chemical bonds with maximum atom utilization and minimum generation of the chemical waste (Trost, 1995, 2002; Trost et al., 2003; Banert and Plefka, 2011; Kotha et al., 2013). The key to realize this goal is to implement reaction cascades, which allow the direct formation of multiple chemical bonds in a one-pot operation and can lead to a remarkable increase in resource efficiency for the overall process (Barluenga et al., 2009; Fuerstner, 2009; Tietze et al., 2009; Jones et al., 2010; Wang et al., 2015; Sugimoto and Matsuya, 2017; Zhang et al., 2017). Specifically, bicyclization cascades have emerged as an important platform for the synthesis of bioactive small-molecule libraries for their SAR studies (Dömling et al., 2012; Brauch et al., 2013; Vlaar et al., 2013; Koopmanschap et al., 2014; Rotstein et al., 2014; Huang et al., 2018b). Due to their annulation efficiency, economic and environmental aspects, and ease of operation as well as diminished waste disposals (Jia et al., 2014; Su et al., 2014; Tian et al., 2015; Chen et al., 2017; Huang et al., 2017; Liu et al., 2017b,c; Wang L. et al., 2017). In view of the environmental awareness of the chemical community, the combination of the presented bicyclization strategy and the use of environmentally benign solvents will furnish the transformations under avoidance of potential

pollutants (Bihani et al., 2013; Wang J.-Y. et al., 2017; Sha et al., 2018a). Nevertheless, the design and development of environmentally compatible bicyclization cascades without generation of toxic waste and by-products holds considerable challenges.

Cyclobutarenes are a class of structurally unique bicarbocyclic molecules which show a wide spectrum of biological activity (Christophe et al., 1998; Sadana et al., 2003). Due to the thermodynamic stability associated with the aromatic system and the kinetic reactivity of the strained cyclobutene ring (Cava and Napier, 1956; Mehta and Kotha, 2001), these molecules behave as reliable and synthetically useful feedstocks (Christophe et al., 1998) and have been extensively applied in natural product syntheses (Funk and Vollhardt, 1977, 1979; Grieco et al., 1980; Taber et al., 1987; Nemoto et al., 1995; Michellys et al., 2001). With these contributions in mind, great efforts to establish synthetic protocols for cyclobutarene synthesis have been developed which include 1,4-elimination-cycloaddition of functionalized arenes (Gray et al., 1978; Schirch et al., 1979; Sekine et al., 1979; Lenihan and Shechter, 1994, 1998; Chou et al., 1995), Parham cyclization (Bradsher and Hunt, 1981; Buchwald et al., 1987a,b; Beak and Selling, 1989; Aidhen and Ahuja, 1992), photo-induced cycloadditions (Parham et al., 1976; Kaneko and Naito, 1979; Neckers and Wagenaar, 1981; Kaneko et al., 1982; Kanao et al., 1983; Sato et al., 1987; Hoffmann and Pete, 1996), thermal extrusion reactions (Toda et al., 1988; D'Andrea et al., 1990; Hickman et al., 1991; Shimada et al., 1993; Andersen et al., 1996; Craig et al., 1998), intramolecular addition of carbanions to benzynes (Bunnett and Skorcz, 1962; Krohn et al., 1978; Gowland and Durst, 1979), [2 + 2 + 2] cycloadditions of 1,5-hexadiyne (Peter and Vollhardt, 1977, 1984; Funk and Vollhardt, 1980; McNichols and Stang, 1992), ring expansion of cycloproparenes (Birch et al., 1964; Iskander and Stansfield, 1965; Buckland et al., 1987; Kagabu and Saito, 1988; Müller et al., 1989), and [2 + 2] cycloadditions of allene precursors (Inanaga et al., 1992; Ezcurra and Moore, 1993; Toda et al., 1994) and other methods (Markgraf et al., 1969; Garratt and Nicolaides, 1972, 1974; Bilyard et al., 1979; Warrener et al., 1993). However, these methods encounter some drawbacks such as high temperatures (400°C-800°C), strong bases (*n*-BuLi and $NaNH_2$), multiple steps, or a narrow substrate range. Moreover, indole derivatives stand for another important class of heterocyclic compounds present in a myriad of bioactive substances and natural products. Therefore, the development of general and sustainable entries toward cyclobutarene-indole pairs in atom- and pot-economic manner is of potential significance. Recently, we reported the combination of [2 + 2] cycloaddition with 1,4-radical addition reaction by treating yne-allenones with aryldiazonium salts and DABCO-bis(sulfur dioxide) (DABSO), affording functional cyclobuta[*a*]naphthalen-4-ols (**Scheme 1a**, Liu et al., 2017a). Subsequently, we developed a BF_3•Et_2O-catalyzed double [2 + 2] cycloaddition relay between yne-allenones and unactivated alkenes, enabling C-C triple bond cleavage to access phenanthren-9-ols (**Scheme 1b**, Li et al., 2018a). To continue our efforts in this project (Liu et al., 2017a; Wang J.-Y. et al., 2017; Li et al., 2018a,b; Sha et al., 2018b; Wang et al., 2018), we attempted to employ indoles **2** to be subjected with the reaction of yne-allenones **3** under our previous conditions (Li et al., 2018a) to assemble naphtho[1,2-*a*]carbazol-5-ols **4** (**Scheme 1d**), owing to indoles with C2 and C3 reactive sites could acted as C_2 synthons for the synthesis of fused indoles (Haibach et al., 2011; Li et al., 2015; Liu et al., 2016; Ozaki et al., 2017). Unexpectedly, a double [2 + 2] cycloaddition relay did not occur. Instead, the reaction involved another [2 + 2] cycloaddition /1,6-addtition cascade to furnish 3-indolyl substituted cyclobuta[*a*]naphthalen-4-ols **3** by suitably adjusting the catalysts and solvents (**Scheme 1c**). Notably, the current green protocol represents an atom-economic and eco-friendly entry to structurally unique cyclobutarene-indole pairs through the combination of [2 + 2] cycloaddition with 1,6-conjugate addition by $FeCl_3$ as a low-cost catalyst and EtOH as an environmentally benign solvent. Herein, we elaborate this attractive and benign transformation.

RESULTS AND DISCUSSION

At the beginning of our studies, yne-allenone **1a** and *N*-methylindole (**2a**) were chosen as the model substrates to explore the feasibility of double [2 + 2] cycloaddition relay reaction with our previous conditions (**Table 1**, entry 1). Instead of the expected naphtho[1,2-*a*]carbazol-5-ol **4a**, 3-indolyl substituted cyclobuta[*a*]naphthalen-4-ol **3a** was obtained in 60% yield. The following screening of solvents, such as *N*,*N*-dimethylformamide (DMF), 1,4-dioxane, tetrahydrofuran (THF), MeOH, and EtOH, showed that use of DMF and 1,4-dioxane as reaction media completely suppressed the reaction process (entries 2–3) whereas the latter three all made the transformations work more efficiently (entries 4–6). Among these, EtOH proved to be the best choice, providing the product **3a** with the highest yield of 76% (entry 6). Increasing the component ratio to 1:2 is not beneficial for this transformation as a lower conversion was observed (63%, entry 7). In contrast, fine-tuning the component ratio to 1:1.2 could improve the reaction efficiency, resulting in a higher yield of **3a** (81%, entry 8). As the next optimization step, we conducted the screening of a variety of Lewis acid catalysts, such as $ZnCl_2$, $Y(OTf)_3$ and $FeCl_3$ that are often employed in the catalytic transformations, for this cyclization-addition cascade by using EtOH as the reaction media. The former two led to remarkably lower conversions (entries 9–10). Delightingly, the latter one showed the best catalytic performance in this transformation, delivering higher yield of **3a** as compared with BF_3•Et_2O (85%, entry 11 vs. 8). It is found that the reaction efficiency was proven to display an important dependence on the loading of the Fe-catalyst. An increase in the $FeCl_3$ loading had a detrimental impact on the reaction yield (entry 12) whereas reducing the catalytic amount of $FeCl_3$ to 10 mol% could accelerate the conversion into **3a** in an increased the yield to 88%. When the reaction temperature was elevated to 70°C, the reaction process was inhibited in some extent (entry 14). On the contrary, decreasing the reaction temperature to 30°C facilitated



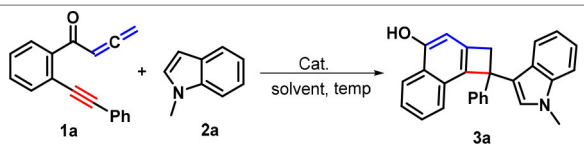
SCHEME 1 | Profiles for [2 + 2] cycloaddition of yne-allenones.

the current transformation and gave a higher yield of 90% (entry 15).

With these optimal conditions in hand (**Table 1**, entry 15), we set out to examine the scope of this Fe-catalyzed [2 + 2] cycloaddition /1,6-addition cascade by using a variety of yne-allenones and indoles. As depicted in **Scheme 2**, *N*-methylindole (**2a**) was first selected to evaluate the influence of substituents (R^1) in the arylalkynyl moiety of yne-allenone **1**. Both electron-poor and electron-rich groups at different positions of the arylalkynyl moiety (R^1) can all tolerate this catalytic system, efficiently accessing the corresponding products **3b-3j** in 75–98% yields. Diverse substituents, such as fluoro (**1b**), chloro (**1c** and **1d**), bromo (**1e**), methyl (**1f** and **1g**), methoxy (PMP = *p*-methoxyphenyl, **1h**), ethyl(**1i**), *t*-butyl (**1j**) were suitable for this transformation. The presence of soft electron-withdrawing substituents (chloro, **1c** and bromo, **1e**) at the *para*-positions seemed to result in higher reactivity than that of electron-donating counterparts (**3c** and **3e** vs. **3f** and **3h-3j**). Moreover, a sterically encumbered 1-naphthyl (1-Np) analog **1k** was an effective candidate, which proceeded through a similar cyclization-addition process to give the corresponding product **3k** in 77% yield. Besides, 2-thienyl counterpart **1l** still showed high reactivity, delivering 2-thienyl product **3l** in 91% yield. Next, we placed different functional groups (R^2) including methoxy, methyl, and fluoro into the C4 or C5 position of the internal arene ring of substrates **1** and explored the synthetic utility of these substrates. Satisfyingly, all those substituents (**1m−1u**) would be compatible in the present reaction protocol, and the corresponding functionalized cyclobuta[a]naphthalen-4-ols **3m-3u** in 72–92% yields were produced. Interestingly, the pyridine-tethered yne-allenone **1v** could be successfully converted into cyclobutarene product **3v** in 68% yield.

Next, the scope with respect to indoles components was evaluated. As anticipated, the different substituents including methoxy (**2b**), chloro (**1c** and **1d**), bromo (**1e**), methyl (**1f** and **1g**), located at different positions of the indole ring would be accommodated, confirming the reaction efficiency, as the cyclobuta[a]naphthalen-4-ol products **3w-3bb** were offered in 76–92% yields. Finally, the free indole turned out to be a suitable reaction partner, leading to the formation of products **3cc** and **3dd** in 78 and 81% yields, respectively. Products **3** were fully characterized by their NMR and HR-MS spectral analysis. In the case of product **3a**, its structure was further confirmed by X-ray crystallography (**Figure 1**).

TABLE 1 | Optimization of Reaction Conditions[a].



Entry	Ratio (1a:2a)	Cat. (mol%)	Solvent	Temp (°C)	Yield (%)[b]
1	1:1.5	$BF_3•Et_2O$ (15)	DCE	50	60
2	1:1.5	$BF_3•Et_2O$ (15)	DMF	50	N.D.
3	1:1.5	$BF_3•Et_2O$ (15)	1,4-dioxane	50	N.D.
4	1:1.5	$BF_3•Et_2O$ (15)	THF	50	66
5	1:1.5	$BF_3•Et_2O$ (15)	MeOH	50	62
6	1:1.5	$BF_3•Et_2O$ (15)	EtOH	50	76
7	1:2	$BF_3•Et_2O$ (15)	EtOH	50	63
8	1:1.2	$BF_3•Et_2O$ (15)	EtOH	50	81
9	1:1.2	$ZnCl_2$ (15)	EtOH	50	60
10	1:1.2	$Y(OTf)_3$ (15)	EtOH	50	25
11	1:1.2	$FeCl_3$ (15)	EtOH	50	85
12	1:1.2	$FeCl_3$ (20)	EtOH	50	74
13	1:1.2	$FeCl_3$ (10)	EtOH	50	88
14	1:1.2	$FeCl_3$ (10)	EtOH	70	72
15	1:1.2	$FeCl_3$ (10)	EtOH	30	90

[a] *Reaction conditions: Benzene-tethered yne-allenone (**1a**, 0.1 mmol, 1.0 equiv), N-methylindole (**2a**, x mmol), catalyst (y mol%), solvent (5.0 mL), air, 8 h*
[b] *Isolated yield based on **1a**.*

MECHANISM

Based on the above experimental observations and literature reports (Haibach et al., 2011; Li et al., 2015, 2018a; Liu et al., 2016, 2017a; Ozaki et al., 2017; Sha et al., 2018b), a feasible mechanism for forming products **3** was proposed in **Scheme 3**. Initially, the intramolecular [2 + 2] cycloaddition of yne-allenones **1** rapidly occurs to yield cyclobutene intermediate **A**. In the presence of Fe-catalyst, 1,6-addition of indoles into intermediate **B** gives intermediate **C**, which converts into the final products **3** through proton transfer (PT), together with the regeneration of Fe-catalyst.

CONCLUSION

In summary, starting from readily available yne-allenones and indoles, we have established a new Fe-catalyzed [2 + 2] cycloaddition/1,6-conjugate addition cascade for the high-efficient and benign synthesis of a variety of 3-indolyl cyclobuta[*a*]naphthalen-4-ols with good to excellent yields. The current green protocol has the advantages of broad scope of substrates, good tolerance of functional group and high atom utilization as well as mild reaction conditions. Further application of the resulting cyclobutarenes is underway in our laboratory.

MATERIALS AND METHODS

General

All melting points are uncorrected. The NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a 400 MHz instrument with TMS as internal standard. Chemical shifts (δ) were reported in ppm with respect to TMS. Data are represented as follows: chemical shift, mutiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constant (J, Hz) and integration. HRMS analyses were carried out using a TOF-MS instrument with an ESI source. X-Ray crystallographic analysis was performed with a SMART CCD and a P4 diffractometer (the copies of NMR see **Supplementary Material**). All yne-allenones **1** are known compounds and their preparation followed the previously reported procedures (Wei et al., 2009; Liu et al., 2017a; Li et al., 2018b).

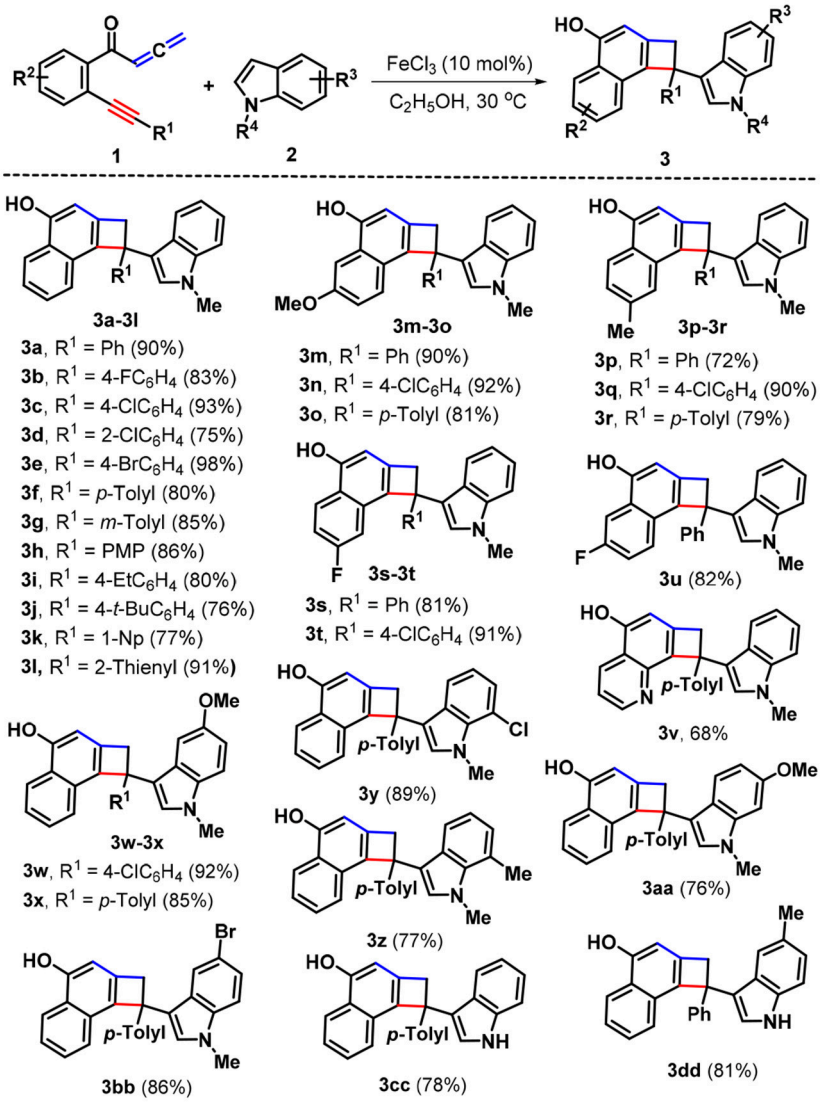
General Procedure for the Synthesis of 3

Example for the Synthesis of 3a

1-(2-(Phenylethynyl)phenyl)buta-2,3-dien-1-one (**1a**, 0.3 mmol, 73.2 mg) was added to a 10-mL reaction tubing under the air conditions. Then, *N*-methylindole (**2a**, 0.36 mmol, 47.2 mg) and EtOH (5 mL) were continuously added into the above reaction mixture. Subsequently, $FeCl_3$ (10 mol%, 4.8 mg) was added to the reaction system. Then the mixture was stirred at 30°C for 8 h until complete consumption of **1a** as monitored by TLC analysis. After the reaction was finished, the reaction mixture was concentrated in vacuum, and the resulting residue was purified by column chromatography on silica gel (eluent, petroleum ether/ethyl acetate =20:1) to afford the desired product **3a** as a white solid.

1-(1-methyl-1H-indol-3-yl)-1-phenyl-1,2-dihydrocyclobuta[a]naphthalen-4-ol (3a)

White solid, 102 mg, 90% yield; mp 179-181°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.23 (s, 1H), 8.24 (d, J = 8.0 Hz, 1H),



SCHEME 2 | Substrate scope for products 3.

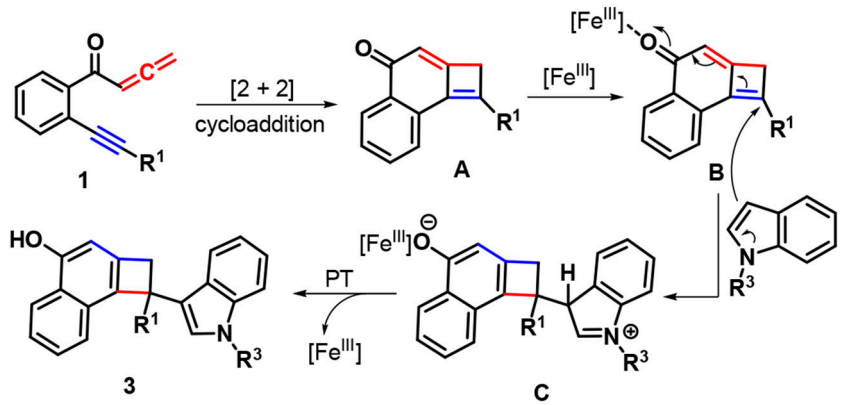
7.51 (d, $J = 7.6$ Hz, 1H), 7.38 (m, 5H), 7.29 (m, 2H), 7.21 (m, 1H), 7.07 (m, 1H), 6.91-6.78 (m, 4H), 3.88 (m, 2H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 154.8, 146.1, 140.3, 137.7, 137.0, 130.1, 128.5, 128.1, 127.5, 127.4, 126.8, 126.5, 125.2, 124.4, 123.9, 122.4, 121.5, 120.1, 119.0, 118.8, 110.3, 104.9, 54.4, 47.7, 32.7; IR (KBr, ν, cm^{-1}) 3341, 3044, 1579, 1474, 1228, 1181, 1024, 905, 806, 738; HRMS (APCI-TOF) m/z calcd for $C_{27}H_{20}NO$ $[M\text{-}H]^-$ 374.1545; found 374.1546.

1-(4-fluorophenyl)-1-(1-methyl-1H-indol-3-yl)-1,2-dihydrocyclobuta[a]naphthalen-4-ol (3b)

White solid, 97 mg, 83% yield; mp 160-162°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.24 (s, 1H), 8.25 (d, $J = 8.0$ Hz, 1H), 7.49 (d, $J = 8.0$ Hz, 1H), 7.43-7.34 (m, 5H), 7.11 (m, 3H), 6.87 (m, 4H), 3.88 (m, 2H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 162.2 ($^1J_{CF} = 240.5$ Hz), 159.8, 154.9, 142.3 ($^4J_{CF} = 2.9$ Hz), 142.2, 140.3, 137.7, 136.8, 129.9, 129.4 ($^3J_{CF} = 7.9$ Hz), 129.3, 128.1, 127.5, 126.7, 125.2, 124.4, 123.9, 122.2, 121.6, 120.0, 119.1, 118.6, 115.3 ($^2J_{CF} = 21.0$ Hz), 115.1, 110.4, 105.0, 53.7, 47.9, 32.7; IR (KBr, ν, cm^{-1}) 3399, 3051, 1573, 1464, 1226, 1188, 1014, 904, 808, 748; HRMS (APCI-TOF) m/z calcd for $C_{27}H_{19}FNO$ $[M\text{-}H]^-$ 392.1451; found 392.1453.

1-(4-chlorophenyl)-1-(1-methyl-1H-indol-3-yl)-1,2-dihydrocyclobuta[a]naphthalen-4-ol (3c)

White solid, 114 mg, 93% yield; mp 170-172°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.27 (s, 1H), 8.24 (d, $J = 8.0$ Hz, 1H), 7.47 (d, $J = 7.6$ Hz, 1H), 7.44-7.31 (m, 7H), 7.12-7.06 (m, 1H),



SCHEME 3 | Plausible reaction pathway.

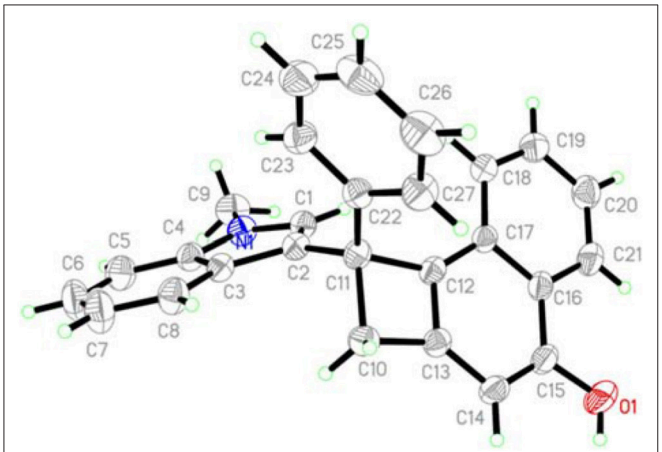


FIGURE 1 | X-Ray structure of product **3a**.

6.93 (s, 1H), 6.87 (m, 3H), 3.82 (m, 2H), 3.69 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 154.9, 145.1, 140.3, 137.7, 136.5, 131.0, 129.9, 129.3, 128.5, 128.2, 127.6, 126.7, 125.2, 124.4, 124.0, 122.1, 121.6, 120.0, 119.1, 118.2, 110.4, 104.9, 53.7, 47.8, 32.7; IR (KBr, ν, cm^{-1}) 3407, 3031, 1563, 1441, 1223, 1103, 1012, 909, 838, 741; HRMS (APCI-TOF) m/z calcd for $C_{27}H_{19}ClNO$ [M-H]$^-$ 408.1156; found 408.1143.

1-(2-chlorophenyl)-1-(1-methyl-1H-indol-3-yl)-1,2-dihydrocyclobuta[a]naphthalen-4-ol (3d)

White solid, 92 mg, 75% yield; mp 177-179°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.31 (s, 1H), 8.30-8.19 (m, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.44-7.28 (m, 6H), 6.99 (m, 1H), 6.93 (s, 1H), 6.79 (s, 1H), 6.69 (m, 1H), 6.60 (d, J = 8.0 Hz, 1H), 4.32 (d, J = 14.4 Hz, 1H), 3.71 (s, 1H), 3.66 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 155.2, 143.4, 140.3, 137.7, 135.9, 134.0, 131.0, 130.5, 130.1, 128.9, 127.9, 127.6, 127.4, 126.2, 125.2, 124.4, 123.9, 122.2, 121.1, 119.3, 118.9, 116.1, 110.2, 104.7, 55.3, 47.5, 32.7; IR (KBr, ν, cm^{-1}) 3442, 3022, 1533, 1421, 1203, 1123, 1010, 903, 834, 721; HRMS (APCI-TOF) m/z calcd for $C_{27}H_{19}ClNO$ [M-H]$^-$ 408.1156; found 408.1162.

1-(4-bromophenyl)-1-(1-methyl-1H-indol-3-yl)-1,2-dihydrocyclobuta[a]naphthalen-4-ol (3e)

White solid, 133 mg, 98% yield; mp 166-168°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.26 (s, 1H), 8.24 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 8.4 Hz, 3H), 7.43-7.34 (m, 3H), 7.30 (d, J = 8.4 Hz, 2H), 7.09 (m, 1H), 6.93 (s, 1H), 6.92-6.83 (m, 3H), 3.81 (m, 2H), 3.69 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 154.9, 145.5, 140.3, 137.7, 136.5, 131.5, 129.9, 129.7, 128.2, 127.6, 126.7, 125.3, 124.4, 124.0, 122.1, 121.6, 120.0, 119.6, 119.1, 118.1, 110.4, 104.9, 53.8, 47.8, 32.7. IR (KBr, ν, cm^{-1}) 3412, 3021, 1538, 1391, 1202, 1129, 1017, 906, 818, 733; HRMS (APCI-TOF) m/z calcd for $C_{27}H_{19}BrNO$ [M-H]$^-$ 452.0651; found 452.0634.

1-(1-methyl-1H-indol-3-yl)-1-(p-tolyl)-1,2-dihydrocyclobuta[a]naphthalen-4-ol (3f)

White solid, 94 mg, 80% yield; mp 155-157°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.20 (s, 1H), 8.23 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.42-7.34 (m, 3H), 7.26 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.0 Hz, 3H), 6.92-6.79 (m, 4H), 3.80 (m, 2H), 3.68 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 154.7, 143.0, 140.3, 137.7, 137.2, 135.3, 130.0, 129.1, 128.0, 127.4, 127.3, 126.8, 125.2, 124.3, 123.8, 122.4, 121.5, 120.2, 119.0, 118.9, 110.3, 105.0, 54.0, 47.8, 32.7, 21.1; IR (KBr, ν, cm^{-1}) 3418, 3009, 1541, 1401, 1192, 1121, 1012, 916, 813, 730; HRMS (APCI-TOF) m/z calcd for $C_{28}H_{22}NO$ [M-H]$^-$ 388.1702; found 388.1723.

1-(1-methyl-1H-indol-3-yl)-1-(m-tolyl)-1,2-dihydrocyclobuta[a]naphthalen-4-ol (3g)

White solid, 99 mg, 85% yield; mp 149-151°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.20 (s, 1H), 8.23 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.38 (m, 3H), 7.23 (s, 1H), 7.18 (d, J = 5.6 Hz, 2H), 7.09-7.01 (m, 2H), 6.85 (m, 4H), 3.82 (m, 2H),

3.68 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 154.7, 146.0, 140.3, 137.7, 137.4, 137.1, 128.4, 128.0, 127.4, 127.2, 126.8, 125.2, 124.8, 124.3, 123.8, 120.1, 118.9, 110.3, 105.0, 54.3, 47.7, 32.7, 21.8; IR (KBr, ν, cm^{-1}) 3411, 2966, 1511, 1406, 1162, 1091, 1015, 911, 833, 727; HRMS (APCI-TOF) m/z calcd for $C_{28}H_{22}NO$ [M-H]$^-$ 388.1702; found 388.1720.

1-(4-methoxyphenyl)-1-(1-methyl-1H-indol-3-yl)-1,2-dihydrocyclobuta[a]naphthalen-4-ol (3h)

White solid, 105 mg, 86% yield; mp 167-169°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.19 (s, 1H), 8.25 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.42-7.33 (m, 3H), 7.29 (d, J = 8.8 Hz, 2H), 7.07 (m, 1H), 6.91-6.81 (m, 6H), 3.79 (m, 2H), 3.70 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 157.9, 154.7, 140.3, 138.1, 137.7, 137.3, 130.0, 128.5, 128.0, 127.3, 126.8, 125.2, 124.4, 123.8, 122.4, 121.5, 120.2, 119.2, 118.9, 113.8, 110.3, 105.0, 55.4, 53.7, 47.9, 32.7; IR (KBr, ν, cm^{-1}) 3417, 2996, 1517, 1403, 1177, 1096, 1013, 914, 845, 720; HRMS (APCI-TOF) m/z calcd for $C_{28}H_{22}NO_2$ [M-H]$^-$ 404.1651; found 404.1638.

1-(4-ethylphenyl)-1-(1-methyl-1H-indol-3-yl)-1,2-dihydrocyclobuta[a]naphthalen-4-ol (3i)

White solid, 97 mg, 80% yield; mp 165-167°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.19 (s, 1H), 8.24 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.42-7.33 (m, 3H), 7.29 (d, J = 8.0 Hz, 2H), 7.13-7.04 (m, 3H), 6.90-6.77 (m, 4H), 3.80 (m, 2H), 3.68 (s, 3H), 2.56 (m, 2H), 1.15 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 154.7, 143.3, 141.7, 140.3, 137.7, 137.2, 130.0, 128.0, 127.9, 127.4, 127.4, 126.8, 125.2, 124.3, 123.8, 122.4, 121.5, 120.2, 119.0, 118.9, 110.3, 105.0, 54.0, 47.8, 32.7, 28.2, 16.0; IR (KBr, ν, cm^{-1}) 3387, 3013, 1510, 1406, 1167, 1091, 1012, 918, 832, 722; HRMS (APCI-TOF) m/z calcd for $C_{29}H_{24}NO$ [M-H]$^-$ 402.1858; found 402.1874.

1-(4-(tert-butyl)phenyl)-1-(1-methyl-1H-indol-3-yl)-1,2-dihydrocyclobuta[a]naphthalen-4-ol (3j)

White solid, 104 mg, 80% yield; mp 178-180°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.19 (s, 1H), 8.24 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.35 (m, 7H), 7.07 (m, 1H), 6.93-6.78 (m, 4H), 3.81 (m, 2H), 3.68 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 154.7, 148.5, 143.0, 140.3, 137.7, 137.1, 130.1, 128.0, 127.4, 127.2, 126.8, 125.3, 125.2, 124.3, 123.8, 122.5, 121.5, 120.2, 119.0, 118.9, 110.3, 104.9, 54.0, 47.7, 34.5, 32.7, 31.6; IR (KBr, ν, cm^{-1}) 3402, 3010, 1512, 1423, 1177, 1093, 1018, 933, 814, 711; HRMS (APCI-TOF) m/z calcd for $C_{31}H_{28}NO$ [M-H]$^-$ 430.2171; found 430.2187.

1-(1-methyl-1H-indol-3-yl)-1-(naphthalen-1-yl)-1,2-dihydrocyclobuta[a]naphthalen-4-ol (3k)

White solid, 98 mg, 77% yield; mp 162-164°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.25 (s, 1H), 8.27 (d, J = 8.0 Hz, 1H), 7.89-7.81 (m, 3H), 7.71 (d, J = 7.2 Hz, 1H), 7.57 (m, 2H), 7.47-7.34 (m, 5H), 7.08 (m, 1H), 6.95 (s, 1H), 6.91 (d, J = 6.0 Hz, 2H), 6.81 (m, 1H), 3.93 (s, 2H), 3.69 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 154.9, 143.7, 140.4, 137.8, 137.1, 133.3, 132.1, 130.1, 128.2, 128.1, 127.8, 127.5, 126.9, 126.6, 126.5, 126.0, 125.3, 125.2, 124.4, 123.9, 122.3, 121.5, 120.1, 119.0, 118.6, 110.4, 105.1, 54.5, 47.5, 32.7; IR (KBr, ν, cm^{-1}) 3422, 3014, 1510, 1413, 1171, 1088, 1015, 937, 825, 727; HRMS (APCI-TOF) m/z calcd for $C_{31}H_{22}NO$ [M-H]$^-$ 424.1702; found 424.1713.

1-(1-methyl-1H-indol-3-yl)-1-(thiophen-2-yl)-1,2-dihydrocyclobuta[a]naphthalen-4-ol (3l)

White solid, 104 mg, 91% yield; mp 158-160°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.26 (s, 1H), 8.26 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.48 (m, 1H), 7.43-7.36 (m, 2H), 7.31 (d, J = 4.8 Hz, 1H), 7.12 (m, 2H), 6.99 (d, J = 5.6 Hz, 2H), 6.92 (m, 2H), 6.85 (s, 1H), 3.98 (d, J = 13.6 Hz, 1H), 3.77 (d, J = 13.6 Hz, 1H), 3.69 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 155.0, 151.2, 140.1, 137.6, 136.8, 129.5, 127.5, 126.9, 126.6, 125.3, 124.6, 124.5, 124.4, 124.0, 122.4, 121.6, 120.2, 119.1, 119.0, 110.4, 105.0, 50.9, 48.9, 32.7; IR (KBr, ν, cm^{-1}) 3427, 3050, 1517, 1421, 1178, 1068, 1020, 936, 821, 734; HRMS (APCI-TOF) m/z calcd for $C_{25}H_{18}NOS$ [M-H]$^-$ 380.1110; found 380.1108.

6-methoxy-1-(1-methyl-1H-indol-3-yl)-1-phenyl-1,2-dihydrocyclobuta[a]naphthalen-4-ol (3m)

White solid, 110 mg, 90% yield; mp 172-174°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.11 (s, 1H), 7.58 (d, J = 2.4 Hz, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.37 (m, 3H), 7.29 (m, 2H), 7.20 (m, 1H), 7.11-7.05 (m, 2H), 6.88-6.79 (m, 4H), 3.87 (d, J = 13.2 Hz, 1H), 3.84 (s, 3H), 3.76 (d, J = 13.6 Hz, 1H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 156.1, 153.7, 146.1, 137.7, 137.3, 137.2, 128.5, 128.1, 127.5, 126.8, 126.4, 126.2, 125.5, 124.0, 121.5, 120.1, 119.6, 118.9, 110.3, 105.4, 103.2, 55.5, 54.3, 47.7, 32.7; IR (KBr, ν, cm^{-1}) 3387, 3045, 1507, 1422, 1172, 1058, 1011, 932, 827, 739; HRMS (APCI-TOF) m/z calcd for $C_{28}H_{22}NO_2$ [M-H]$^-$ 404.1651; found 404.1630.

1-(4-chlorophenyl)-6-methoxy-1-(1-methyl-1H-indol-3-yl)-1,2-dihydrocyclobuta[a]naphthalen-4-ol (3n)

White solid, 121 mg, 92% yield; mp 175-177°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.15 (s, 1H), 7.59 (d, J = 2.4 Hz, 1H), 7.44-7.31 (m, 6H), 7.13-7.05 (m, 2H), 6.94-6.81 (m, 4H), 3.85 (s, 3H), 3.83-3.72 (m, 2H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 156.2, 153.9, 145.1, 137.7, 137.2, 136.7, 131.0, 129.3, 128.5, 128.1, 126.7, 126.3, 125.3, 123.8, 121.6, 120.0, 119.7, 119.1, 118.3, 110.4, 105.4, 103.2, 55.5, 53.7, 47.7, 32.7. IR (KBr, ν, cm^{-1}) 3382, 3025, 1523, 1421, 1192, 1074, 1008, 934, 828, 736. HRMS (APCI-TOF) m/z calcd for $C_{28}H_{21}NClO_2$ [M-H]$^-$ 438.1261; found 438.1277.

6-methoxy-1-(1-methyl-1H-indol-3-yl)-1-(p-tolyl)-1,2-dihydrocyclobuta[a]naphthalen-4-ol (3o)

White solid, 102 mg, 81% yield; mp 170-172°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.09 (s, 1H), 7.59 (d, J = 2.4 Hz, 1H),

7.43 (d, J = 9.2 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 8.0 Hz, 2H), 7.07 (m, 4H), 6.89-6.80 (m, 4H), 3.84 (s, 3H), 3.83-3.72 (m, 2H), 3.67 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 156.1, 153.6, 143.1, 137.7, 137.4, 137.3, 135.3, 129.1, 128.0, 127.4, 126.8, 126.2, 125.5, 124.0, 121.5, 120.2, 119.5, 119.1, 118.9, 110.2, 105.4, 103.1, 55.5, 54.0, 47.7, 32.6, 21.1; IR (KBr, ν, cm^{-1}) 3387, 3022, 1521, 1425, 1202, 1094, 1016, 942, 835, 721; HRMS (APCI-TOF) m/z calcd for $C_{29}H_{24}NO_2$ [M-H]$^-$ 418.1808; found 418.1822.

7-methyl-1-(1-methyl-1H-indol-3-yl)-1-phenyl-1,2-dihydrocyclobuta[a]naphthalen-4-ol (3p)

White solid, 84 mg, 72% yield; mp 147-149°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.12 (s, 1H), 8.14 (d, J = 8.8 Hz, 1H), 7.38 (m, 3H), 7.32-7.26 (m, 3H), 7.20 (m, 2H), 7.08 (m, 1H), 6.88 (d, J = 4.4 Hz, 2H), 6.86-6.77 (m, 2H), 3.86 (d, J = 13.6 Hz, 1H), 3.73 (d, J = 13.6 Hz, 1H), 3.69 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 154.8, 146.2, 140.5, 137.7, 136.6, 136.3, 130.4, 128.5, 128.1, 127.5, 126.8, 126.4, 126.0, 124.3, 123.5, 121.5, 121.3, 120.2, 118.9, 118.9, 110.3, 104.2, 54.4, 47.9, 32.7, 22.0; IR (KBr, ν, cm^{-1}) 3507, 3052, 1522, 1420, 1201, 1098, 1015, 944, 841, 727; HRMS (APCI-TOF) m/z calcd for $C_{28}H_{22}NO$ [M-H]$^-$ 388.1702; found 388.1727.

1-(4-chlorophenyl)-7-methyl-1-(1-methyl-1H-indol-3-yl)-1,2-dihydrocyclobuta[a]naphthalen-4-ol (3q)

White solid, 114 mg, 90% yield; mp 152-154°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.16 (s, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.40-7.33 (m, 5H), 7.25 (s, 1H), 7.19 (d, J = 8.8 Hz, 1H), 7.09 (m, 1H), 6.94-6.83 (m, 3H), 6.79 (s, 1H), 3.85 (d, J = 13.6 Hz, 1H), 3.73 (s, 1H), 3.70 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 154.9, 145.2, 140.4, 137.7, 136.7, 135.9, 131.0, 130.2, 129.4, 128.5, 128.2, 126.7, 126.1, 124.4, 123.5, 121.6, 121.1, 120.1, 119.1, 118.3, 110.4, 104.2, 53.7, 47.9, 32.7, 22.0; IR (KBr, ν, cm^{-1}) 3495, 3042, 1520, 1402, 1221, 1084, 1016, 947, 831, 709; HRMS (APCI-TOF) m/z calcd for $C_{28}H_{21}ClNO$ [M-H]$^-$ 422.1312; found 422.1314.

7-methyl-1-(1-methyl-1H-indol-3-yl)-1-(p-tolyl)-1,2-dihydrocyclobuta[a]naphthalen-4-ol (3r)

White solid, 96 mg, 79% yield; mp 153-155°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.10 (s, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.26 (d, J = 8.0 Hz, 3H), 7.18 (d, J = 8.8 Hz, 1H), 7.08 (m, 3H), 6.90 (d, J = 8.8 Hz, 2H), 6.83 (m, 1H), 6.79 (s, 1H), 3.88-3.69 (m, 2H), 3.68 (s, 3H), 2.32 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 154.7, 143.1, 140.4, 137.7, 136.5, 136.5, 135.3, 130.3, 129.1, 128.0, 127.4, 126.9, 126.0, 124.3, 123.4, 121.5, 121.3, 120.3, 119.0, 118.9, 110.3, 104.2, 54.0, 47.9, 32.7, 22.0, 21.1; IR (KBr, ν, cm^{-1}) 3490, 3031, 1500, 1422, 1213, 1090, 1012, 948, 843, 719; HRMS (APCI-TOF) m/z calcd for $C_{29}H_{24}NO$ [M-H]$^-$ 402.1858; found 402.1844.

7-fluoro-1-(1-methyl-1H-indol-3-yl)-1-phenyl-1,2-dihydrocyclobuta[a]naphthalen-4-ol (3s)

White solid, 96 mg, 81% yield; mp 144-146°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.36 (s, 1H), 7.87 (m, 1H), 7.55 (m, 1H), 7.33 (m, 6H), 7.21 (m, 1H), 7.08 (m, 1H), 6.93 (s, 1H), 6.91-6.77 (m, 3H), 3.84 (m, 2H), 3.68 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 160.3 ($^1J_{CF}$ = 239.4 Hz), 157.9, 154.2, 154.1, 145.8, 139.7 ($^6J_{CF}$ = 2.4 Hz), 139.6, 137.7, 137.3, 128.6, 128.1, 127.5, 127.2, 126.8, 126.7 ($^3J_{CF}$ = 19.7 Hz), 125.9 ($^5J_{CF}$ = 8.1 Hz), 125.8, 125.1 ($^4J_{CF}$ = 8.4 Hz), 125.0, 121.5, 120.0, 119.0, 118.6, 117.5, 117.3, 110.3, 108.0 ($^2J_{CF}$ = 21.7 Hz), 107.8, 106.0, 54.4, 47.8, 32.7; IR (KBr, ν, cm^{-1}) 3501, 3021, 1502, 1421, 1215, 1099, 1014, 962, 883, 712; HRMS (APCI-TOF) m/z calcd for $C_{27}H_{19}FNO$ [M-H]$^-$ 392.1451; found 392.1459.

1-(4-chlorophenyl)-7-fluoro-1-(1-methyl-1H-indol-3-yl)-1,2-dihydrocyclobuta[a]naphthalen-4-ol (3t)

White solid, 117 mg, 91% yield; mp 149-151°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.44 (s, 1H), 8.30 (m, 1H), 7.41-7.32 (m, 5H), 7.24 (m, 1H), 7.12-7.04 (m, 2H), 6.98 (s, 1H), 6.86 (d, J = 13.2 Hz, 3H), 3.82 (m, 2H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 160.0 ($^1J_{CF}$ = 231.6 Hz), 157.1, 155.3, 144.8, 142.4, 137.8, 136.2 ($^6J_{CF}$ = 3.4 Hz), 136.1, 131.1, 130.5 ($^5J_{CF}$ = 9.6 Hz), 130.4, 129.3, 128.6, 128.2, 127.8 ($^4J_{CF}$ = 9.9 Hz), 126.6, 122.4, 121.6, 119.9, 119.2, 117.8, 113.9 ($^2J_{CF}$ = 24.1 Hz), 113.6, 110.5, 105.5 ($^3J_{CF}$ = 20.3 Hz), 105.3, 104.5, 53.7, 47.7, 32.7; IR (KBr, ν, cm^{-1}) 3512, 3020, 1505, 1411, 1210, 1095, 1010, 966, 861, 740; HRMS (APCI-TOF) m/z calcd for $C_{27}H_{18}ClFNO$ [M-H]$^-$ 426.1061; found 426.1066.

6-fluoro-1-(1-methyl-1H-indol-3-yl)-1-phenyl-1,2-dihydrocyclobuta[a]naphthalen-4-ol (3u)

White solid, 97 mg, 82% yield; mp 148-150°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.41 (s, 1H), 8.30 (m, 1H), 7.38 (d, J = 8.8 Hz, 3H), 7.30 (m, 2H), 7.24 (m, 2H), 7.08 (m, 2H), 6.94 (s, 1H), 6.90-6.79 (m, 3H), 3.84 (m, 2H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 162.3 ($^1J_{CF}$ = 243.8 Hz), 160.0, 155.1, 145.8, 142.4, 137.8, 136.7 ($^6J_{CF}$ = 5.1 Hz), 130.7 ($^5J_{CF}$ = 9.3 Hz), 130.6, 128.6, 128.1, 127.8, 127.7 ($^4J_{CF}$ = 9.6 Hz), 127.4, 126.7, 126.6, 122.4, 121.5, 120.0, 119.0, 118.4, 113.8 ($^2J_{CF}$ = 24.8 Hz), 113.5, 110.4, 105.7 ($^3J_{CF}$ = 20.1 Hz), 105.5, 104.6, 54.3, 47.7, 32.7; IR (KBr, ν, cm^{-1}) 3502, 3047, 1502, 1422, 1235, 1099, 1015, 946, 851, 733; HRMS (APCI-TOF) m/z calcd for $C_{27}H_{19}FNO$ [M-H]$^-$ 392.1451; found 392.1450.

8-(1-methyl-1H-indol-3-yl)-8-(p-tolyl)-7,8-dihydrocyclobuta[h]quinolin-5-ol (3v)

White solid, 80 mg, 68% yield; mp 162-164°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.56 (s, 1H), 8.88 (m, 1H), 8.60 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.0 Hz, 2H), 7.41 (dd, J = 8.4, 4.2 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.07 (d, J = 8.0 Hz, 3H), 7.01 (s, 1H), 6.90 (s, 1H), 6.85 (m, 1H), 3.91 (m, 2H), 3.64 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ,

ppm) 155.0, 151.2, 145.1, 143.9, 137.5, 137.1, 135.0, 132.7, 128.8, 128.3, 128.1, 126.5, 121.3, 120.4, 120.3, 120.1, 119.3, 118.8, 110.1, 105.3, 55.2, 46.1, 32.6, 21.1; IR (KBr, ν, cm^{-1}) 3545, 3067, 1552, 1421, 1230, 1129, 1012, 949, 840, 730; HRMS (APCI-TOF) m/z calcd for $C_{27}H_{21}N_2O$ $[M-H]^-$ 389.1654; found 389.1657.

1-(4-chlorophenyl)-1-(5-methoxy-1-methyl-1H-indol-3-yl)-1,2-dihydrocyclobuta[a]naphthalen-4-ol (3w)

White solid, 121 mg, 92% yield; mp 166-168°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.27 (s, 1H), 8.27 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.44-7.33 (m, 6H), 7.27 (d, J = 8.8 Hz, 1H), 6.88 (d, J = 10.8 Hz, 2H), 6.74 (m, 1H), 6.24 (d, J = 2.0 Hz, 1H), 3.81 (m, 2H), 3.64 (s, 3H), 3.49 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 155.0, 153.3, 145.0, 140.5, 136.5, 133.1, 131.1, 130.0, 129.4, 128.7, 128.5, 127.6, 127.0, 125.3, 124.4, 124.0, 122.2, 117.6, 111.0, 110.9, 104.8, 102.4, 55.5, 53.8, 47.7, 32.8; IR (KBr, ν, cm^{-1}) 3504, 2997, 1534, 1401, 1233, 1149, 1010, 942, 847, 736; HRMS (APCI-TOF) m/z calcd for $C_{28}H_{21}NClO_2$ $[M-H]^-$ 438.1261; found 438.1267.

1-(5-methoxy-1-methyl-1H-indol-3-yl)-1-(p-tolyl)-1,2-dihydrocyclobuta[a]naphthalen-4-ol (3x)

White solid, 107 mg, 85% yield; mp 170-172°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.21 (s, 1H), 8.25 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.43-7.33 (m, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.8 Hz, 1H), 7.11 (d, J = 7.6 Hz, 2H), 6.88 (s, 1H), 6.82 (s, 1H), 6.72 (m, 1H), 6.22 (d, J = 2.0 Hz, 1H), 3.79 (m, 2H), 3.63 (s, 3H), 3.47 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 154.8, 153.1, 143.0, 140.5, 137.1, 135.3, 133.1, 130.2, 129.1, 128.6, 127.5, 127.4, 127.1, 125.2, 124.4, 123.8, 122.4, 118.4, 110.8, 110.7, 104.9, 102.6, 55.5, 54.1, 47.7, 32.8, 21.1; IR (KBr, ν, cm^{-1}) 3487, 3022, 1520, 1422, 1200, 1097, 1012, 944, 833, 725; HRMS (APCI-TOF) m/z calcd for $C_{29}H_{24}NO_2$ $[M-H]^-$ 418.1808; found 418.1838.

1-(7-chloro-1-methyl-1H-indol-3-yl)-1-(p-tolyl)-1,2-dihydrocyclobuta[a]naphthalen-4-ol (3y)

White solid, 113 mg, 89% yield; mp 163-165°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.24 (s, 1H), 8.24 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.38 (m, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H), 6.93 (s, 1H), 6.88-6.76 (m, 4H), 3.99 (s, 3H), 3.78 (s, 2H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 154.8, 142.5, 140.2, 136.9, 135.5, 132.6, 131.2, 130.2, 129.9, 129.2, 127.4, 127.3, 125.2, 124.4, 123.9, 123.0, 122.2, 120.1, 119.6, 119.3, 116.5, 104.9, 53.6, 47.6, 36.5, 21.0; IR (KBr, ν, cm^{-1}) 3505, 3022, 1524, 1400, 1209, 1082, 1012, 945, 833, 719; HRMS (APCI-TOF) m/z calcd for $C_{28}H_{21}ClNO$ $[M-H]^-$ 422.1312; found 422.1304.

1-(1,7-dimethyl-1H-indol-3-yl)-1-(p-tolyl)-1,2-dihydrocyclobuta[a]naphthalen-4-ol (3z)

White solid, 93 mg, 77% yield; mp 165-167°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.17 (s, 1H), 8.23 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.37 (m, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 6.85 (s, 1H), 6.79-6.64 (m, 4H), 3.93 (s, 3H), 3.77 (s, 2H), 2.68 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 154.6, 143.0, 140.3, 137.4, 136.3, 135.3, 129.9, 129.6, 129.1, 128.0, 127.3, 125.2, 124.3, 124.0, 123.8, 122.4, 121.8, 119.1, 118.5, 118.4(5), 118.3(9), 105.0, 53.8, 47.6, 36.6, 21.1, 19.7; IR (KBr, ν, cm^{-1}) 3468, 3056, 1480, 1424, 1203, 1095, 1010, 958, 844, 722; HRMS (APCI-TOF) m/z calcd for $C_{29}H_{24}NO$ $[M-H]^-$ 402.1858; found 402.1844.

1-(6-methoxy-1-methyl-1H-indol-3-yl)-1-(p-tolyl)-1,2-dihydrocyclobuta[a]naphthalen-4-ol (3aa)

White solid, 96 mg, 76% yield; mp 171-173°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.18 (s, 1H), 8.23 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.41-7.32 (m, 2H), 7.26 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 2.0 Hz, 1H), 6.85 (s, 1H), 6.70 (d, J = 10.4 Hz, 2H), 6.48 (m, 1H), 3.81 (m, 2H), 3.75 (s, 3H), 3.63 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 156.0, 154.6, 143.1, 140.3, 138.5, 137.3, 135.3, 130.0, 129.1, 127.4, 127.3, 126.8, 125.2, 124.3, 123.8, 122.4, 121.1, 120.7, 119.1, 109.0, 105.0, 93.6, 55.7, 54.0, 47.8, 32.7, 21.1; IR (KBr, ν, cm^{-1}) 3487, 3020, 1521, 1420, 1212, 1091, 1011, 944, 836, 729; HRMS (APCI-TOF) m/z calcd for $C_{29}H_{24}NO_2$ $[M-H]^-$ 418.1808; found 418.1822.

1-(5-bromo-1-methyl-1H-indol-3-yl)-1-(p-tolyl)-1,2-dihydrocyclobuta[a]naphthalen-4-ol (3bb)

White solid, 121 mg, 76% yield; mp 175-177°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.22 (s, 1H), 8.25 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.40 (m, 3H), 7.25 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 8.0 Hz, 2H), 6.95 (s, 1H), 6.93 (s, 1H), 6.86 (s, 1H), 3.84-3.74 (m, 2H), 3.69 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 154.8, 142.5, 140.3, 136.8, 136.5, 135.5, 129.9, 129.6, 129.2, 128.4, 127.5, 127.3, 125.2, 124.4, 124.0, 122.2, 118.8, 112.6, 111.6, 104.9, 53.7, 47.8, 32.9, 21.1; IR (KBr, ν, cm^{-1}) 3531, 3050, 1522, 1404, 1242, 1121, 1017, 945, 836, 720; HRMS (APCI-TOF) m/z calcd for $C_{28}H_{21}BrNO$ $[M-H]^-$ 466.0807; found 466.0815.

1-(1H-indol-3-yl)-1-(p-tolyl)-1,2-dihydrocyclobuta[a]naphthalen-4-ol (3cc)

White solid, 88 mg, 78% yield; mp 156-158°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.86 (s, 1H), 10.20 (s, 1H), 8.26 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.38 (m, 3H), 7.27 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 7.02 (m, 1H), 6.96-6.88 (m, 3H), 6.81 (m, 1H), 3.82 (m, 2H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 154.6, 143.2, 140.3, 137.4, 137.4, 135.3, 130.0, 129.1, 127.4, 127.3, 126.6, 125.2, 124.4, 123.8, 123.7, 122.4, 122.0, 121.3, 120.0, 119.7, 118.8, 112.1, 105.0, 54.1, 47.6, 21.1; IR (KBr, ν, cm^{-1}) 3501, 3408, 3051, 1520, 1402, 1240, 1118, 1010, 943, 816, 723; HRMS (APCI-TOF) m/z calcd for $C_{27}H_{20}NO$ $[M-H]^-$ 374.1545; found 374.1529.

1-(6-methyl-1H-indol-3-yl)-1-phenyl-1,2-dihydrocyclobuta[a]naphthalen-4-ol (3dd)

White solid, 91 mg, 81% yield; mp 172-174°C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 10.72 (s, 1H), 10.18 (s, 1H), 8.25 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.44-7.34 (m, 4H), 7.26 (m, 3H), 7.18 (m, 1H), 6.86 (d, J = 6.8 Hz, 3H), 6.79 (s, 1H), 3.83 (s, 2H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 154.6, 146.2, 140.4, 137.5, 135.7, 129.9, 128.5, 127.3, 127.1, 126.9, 126.3, 125.2, 124.4, 123.8, 123.0, 122.4, 119.6, 119.0, 111.9, 105.0, 54.2, 47.5, 21.9; IR (KBr, ν, cm^{-1}) 3518, 3401, 3050, 1570, 1392, 1242, 1110, 1023, 941, 826, 721; HRMS (APCI-TOF) m/z calcd for $C_{27}H_{20}NO$ [M-H]$^-$ 374.1545; found 374.1553.

X-Ray Structure of Product 3a (CCDC 1867087)

The crystal of compound **3a** belongs to Triclinic, space group *P-1* with a = 8.5599(7) Å, b = 12.1512(11) Å, c = 12.5112(12) Å, α = 100.943(2)°, β = 94.2510(10)°, γ = 106.823(3)°, V = 1211.40(19) Å^3, Mr = 433.53, Z = 2, Dc = 1.743 g/cm^3, μ(Mo$K\alpha$) = 0.074 mm^{-1}, F(000) = 460, the final R = 0.0495 and wR = 0.1118.

AUTHOR CONTRIBUTIONS

HL, BJ, and GL designed the project. HL performed the experiments. HL, W-JH, and S-JT analyzed the data. HL, BJ, and GL wrote the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2018.00599/full#supplementary-material

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Polarclean as a Sustainable Reaction Medium for the Waste Minimized Synthesis of Heterocyclic Compounds

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Herein we report the use of Rhodiasolv© Polarclean as a novel polar aprotic solvent for the synthesis of decorated heterocycles via dipolar cycloaddition (isooxazoles) or intramolecular C–H functionalization processes (benzo-fused chromenes). The use of Polarclean allowed to isolate the final products in good yields by simple solid filtration or liquid-liquid phase separation, avoiding the need for chromatographic purification. Moreover, since in the synthesis of benzo-fused chromenes, the metal catalyst is retained in Polarclean, the catalyst/reaction medium can be easily reused for consecutive reaction runs, without any apparent loss in efficiency. This methodology is associated with a limited waste production. These results extend the applicability of Polarclean as a promising reaction medium for the replacement of toxic petrol-based solvent.

Keywords: heterocycles, green-synthesis, isoxazoles, triazoles, C–H activation

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INTRODUCTION

Heterocyclic compounds are ubiquitous and find multiple applications in different fields of applied chemistry such as in medicinal chemistry, as key motifs in pharmaceutically active ingredients (Gomtsyan, 2012), and in material science (Yin and Shreeve, 2017). Thus, chemists have always been looking for novel synthetic methodologies that would allow to access heterocyclic cores in more efficient, economical and selective ways and, as a result, many efficient examples are available in the literature. The most effective and straightforward way to access heterocyclic cores is probably still represented by cycloaddition reactions (Heravi et al., 2015; Padwa and Bur, 2016). These reactions typically occur with perfect atom economy and, since they allow the simultaneous formations of two bonds, they are generally also very efficient in terms of step economy. One of the possible limitations of cycloadditions reactions is that often they have rather strict structural requirements on the substrates for the cycloaddition to occur, which results in the potential need for subsequent transformations to decorate the heterocyclic core and access the target molecule.

In recent years, great advancements in transition metals catalyzed reactions provided synthetic organic chemists with many more tools to efficiently obtain heterocyclic molecules (Gulevich et al., 2013). In particular, the last decade saw enormous improvements in the available methodologies to activate and directly functionalize C–H bonds, and many of these methodologies indeed are specifically directed toward the synthesis of heterocycles (Thansandote and Lautens, 2009; Mei et al., 2012; Inamoto, 2013). However, these reactions typically require hazardous conditions

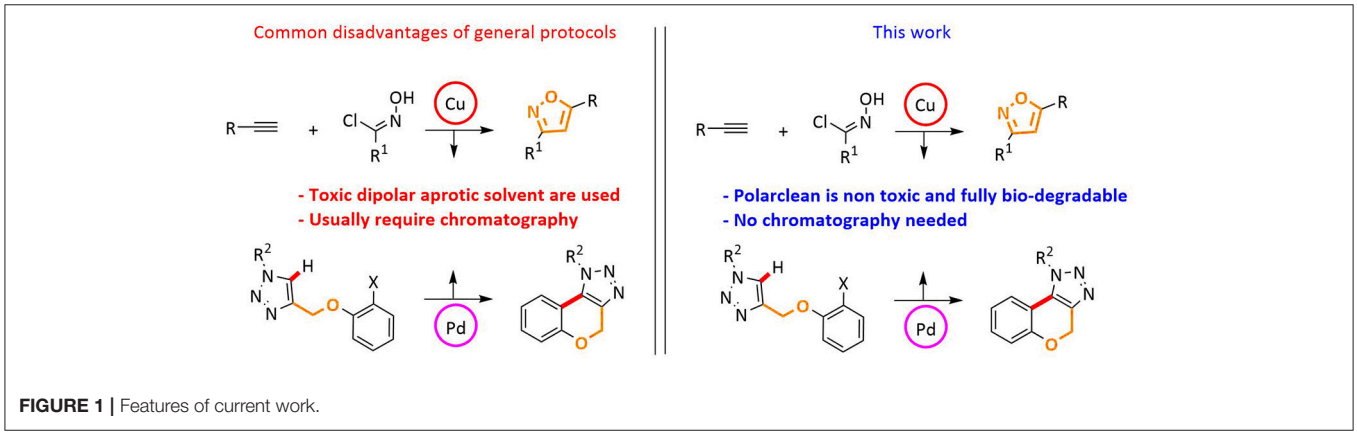
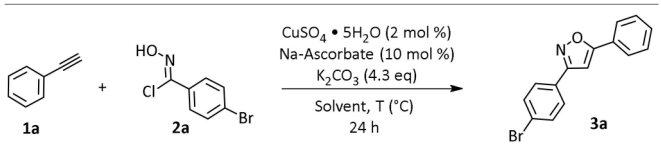


FIGURE 1 | Features of current work.

TABLE 1 | Optimization of reaction conditions for the synthesis of **3a**[a].



Entry	Solvent	T (°C)	Yield (%)[b]
1	Polarclean 1 M	70	40
2	Polarclean/H_2O (9:1) 1 M	70	50
3	Polarclean/H_2O (4:1) 1 M	70	60
4	Polarclean/H_2O (4:1) 0.5 M	70	33
5	Polarclean/H_2O (4:1) 1 M	50	70

[a]*Reaction conditions:* ***1a*** *(1 mmol),* ***2a*** *(1 mmol),* $CuSO_4$ *pentahydrate (2 mol%), Na-Ascorbate (10 mol %),* K_2CO_3 *(4.3 equivalent).*
[b]*Isolated yield of* ***3a****.*

and the use of common toxic organic solvents and suffer from procedural limitations such as the need of strictly anhydrous conditions. The need to develop more sustainable procedures for chemical production has recently brought some results also in the realm of C–H functionalization methodologies, particularly in the use of recoverable and reusable catalysts (Santoro et al., 2016) and of benign bio-based reaction media (Santoro et al., 2017, 2018). In fact, waste disposal represents one of the major issues related to chemical productions due to economic and environmental reasons. Increasingly stringent regulations impose strict limitations on the use of toxic organic solvents and more in general to the large use of potentially harmful substances and volatile organic compounds. Solvents constitute the largest portion of the waste associated to a chemical process and the prime responsible for the related CO_2 emissions (Bruntland's report the World Commission on Environmental Development, 1987; Pollution Prevention Act, 1990; Anastas and Warner, 1998; Jiménez-González et al., 2004; Jimenez-Gonzalez et al., 2011).

As a part of our research program devoted to the search for novel environmentally benign reaction media, we are interested in the use of sustainable green solvents in the synthesis and functionalization of heterocycle systems (Rasina et al., 2016; Tian et al., 2016; Ferlin et al., 2017, 2018a; Bechtoldt et al., 2018; Vaccaro et al., 2018). In this context, we have recently reported the use of Rhodiasolv© Polarclean as an efficient system for the waste-minimized synthesis of fully decorated 1,2,3-triazoles (Luciani et al., 2018). Rhodiasolv© Polarclean, is composed by methyl-5-(dimethylamino)-2-methyl-5-oxopentanoate and its diamide derivative in a 20:1 ratio. It is commercially available and finds application as a solvent, co-solvent, or crystal growth inhibitor in agrochemical formulations (Vidal, 2012). It is miscible with water and has a boiling point of 278–282°C and a melting point of −60°C. Polarclean is industrially produced from methyleneglutarodinitrile (MDN), a by-product of Nylon-66 manufacturing, otherwise needed to be burnt to be disposed (Vidal, 2012). To the best of our knowledge Polarclean has been rarely used as a reaction medium and it has been tested among other solvents in metathesis polymerization (Lebarbé et al., 2014), olefin epoxidation (Mouret et al., 2014), and fiber membranes fabrication (Hassankiadeh et al., 2015).

In this contribution, we report our results on the use of Polarclean for the synthesis of widely interesting heterocyclic such as isoxazoles and polycyclic fused 1,2,3-triazoles. These heterocyclic systems are rather common and, for instance, triazole moiety is present in active pharmaceutical ingredients (Wu et al., 2018) as well as in optoelectronics and material sciences (Marrocchi et al., 2016). Isoxazoles are recognized as privilege structures for the synthesis of beta-lactamase resistant antibiotics (Decuyper et al., 2018), and recently they found application in the field of lithium ion batteries (Yang et al., 2017).

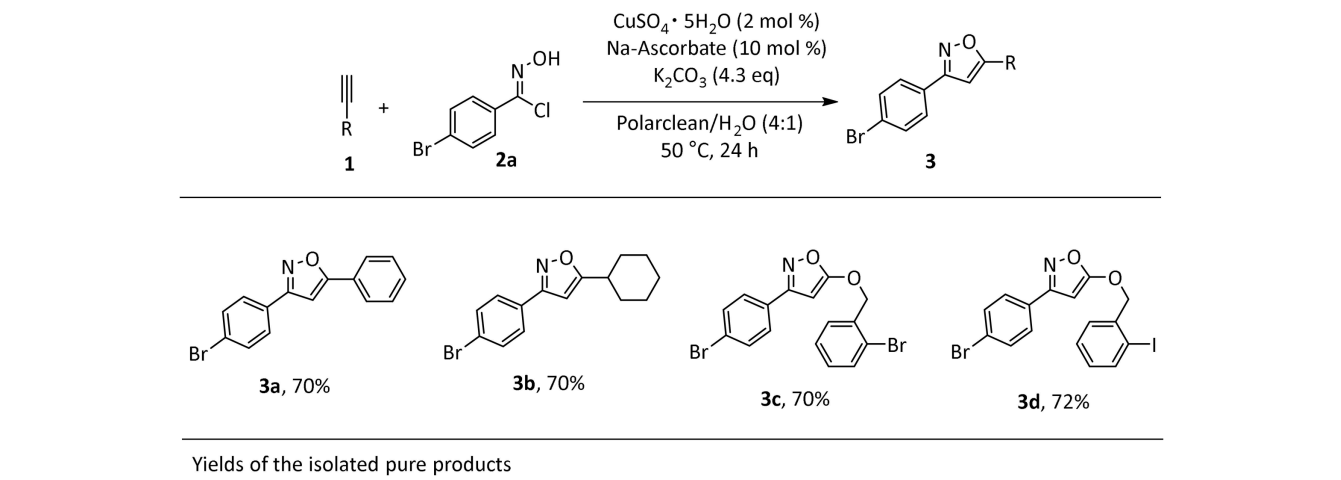
Our investigations were directed toward the definition of protocols featuring recycle and reuse of solvent/catalyst systems, avoidance of wasteful chromatographic purification, and therefore minimization of waste production (**Figure 1**).

RESULTS AND DISCUSSION

We started our investigation by testing the use of Polarclean in the representative reaction of phenylacetylene (**1a**) with 4-bromo-*N*-hydroxybenzimidoyl chloride (**2a**), using 2 mol% of $CuSO_4 \cdot 5H_2O$ as copper source together with 10 mol% of sodium ascorbate as a reductant (Himo et al., 2005) (**Table 1**). The

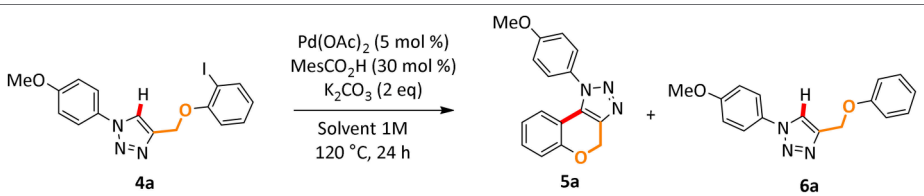
reaction was tested at 70°C for 24 h in Polarclean 1 M as medium and the corresponding isoxazole **3a** was obtained in 40% yield (**Table 1**, entry 1). In this case, due to high solubility of **3a** in pure Polarclean, the pure product could only be isolated after a classic purification procedure (aqueous work-up followed by column chromatography). Slightly better results were achieved when a 9:1 mixture of Polarclean/water was used as medium at 70°C (**Table 1**, entry 2). In these conditions, the reaction mixture was partially heterogeneous and product **3a** precipitated while forming and could be isolated in 50% yield by simple filtration. Increasing the amount of water by using a 4:1 Polarclean/H_2O mixture lead to a further improvement in reaction yield, which reached 60% (**Table 1**, entry 3). An attempt to further increase the amount of water relative to the substrates and product while keeping the 4:1 Polarclean/H_2O ratio, thus performing the reaction at 0.5 M concentration, resulted in drastically lower yield (33%, **Table 1**, entry 4). Finally, optimal results were obtained when Polarclean and water were used in 4:1 ratio at 1 M concentration and at 50°C (**Table 1**, entry 5). In these conditions in fact pure product **3a** could be obtained in 70% yield by simple filtration as it precipitates in the reaction mixture. The beneficial effect of lowering the temperature can possibly be attributed to a reduced degradation of imidoyl chloride **2a**.

The identified optimal reaction conditions were then applied to investigate the substrate scope. The protocol worked smoothly using combinations of aryl- or alkyl-substituted alkynes in combination with imidoyl chloride **2a**, affording the products in good yields (**Scheme 1**). Importantly, the presence of halogen substituents on the aromatic rings was well-tolerated, potentially allowing for late stage transformations of these functionalities. Very importantly, the final work-up for the synthesized products was consistent with our initial intent. In fact, the products were insoluble in the reaction media and in all cases precipitated at the end of the reaction, thus allowing a very easy isolation



SCHEME 1 | Scope of isoxazole **3a-d**[a]. [a]Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), $CuSO_4$ pentahydrate (2 mol%), Na-Ascorbate (10 mol %), K_2CO_3 (4.3 equivalent), Polarclean/H_2O (4:1) 1 M, 1mL.

TABLE 2 | Optimization of reaction conditions for the cyclization of **4a** to **5a**[a].



Entry	Solvent	Selectivity[b] 5a:6a	Yield of 5a (%)[c]
1	Polarclean/H_2O (4:1) 1 M	2:88	–
2	Polarclean/H_2O (9:1) 1 M	5:85	–
3	Polarclean 1 M	99:1	87%

[a]*Reaction conditions:* ***4a*** *(1 mmol),* $MesCO_2H$ *(30 mol %, 0.3 mmol),* K_2CO_3 *(2 equivalent, 2 mmol),* $Pd(OAc)_2$ *(5 mol %, 0.05 mmol).*
[b]*Measured by GC analyses using samples of pure compounds as reference.*
[c]*Isolated yield.*

by filtration and washing with water to remove solvent impurities.

Next, we began our investigation on the use of Polarclean as reaction medium in the cyclization reaction by C–H functionalization of 1,2,3-triazole **4a** (**Table 2**). Starting from our experience in this transformation (Ferlin et al., 2018b), which suggested the use of simple $Pd(OAc)_2$ as catalyst with a substoichiometric amount of 2,4,6-trimethylbenzoic acid as additive and potassium carbonate as base, we performed the reaction using Polarclean, pure or in combination with different amount of water, as reaction medium (**Table 2**).

In this process, the best selectivity was found when pure Polarclean was used as reaction medium (**Table 2**, entry 3). In fact, the presence of water influenced dramatically the final composition of the reaction mixture, favoring the formation of the de-halogenated side-product **6a** (**Table 2**, entries 1 and 2). With the optimized reaction conditions, we further explored the scope of this process (**Scheme 2**). A wide range of substrates could be employed in the intramolecular C–H arylation of 1,2-3-triazole-based substrates **4**, giving access to either triazolo-fused chromenes or triazolo-fused isoindoles, depending on the substitution pattern on the triazole substrate. The reaction is compatible with the presence of an oxygen atom in the side-chain, giving rapid access to benzo-fused chromene **5a** in 87% yield. Aryl- or alkyl-substituted [1,2,3]-triazolo[5,1-a]isoindoles **5b**, **5c,** and **5e** could also be obtained in good yields (78–84%). To our delight, the optimized reaction conditions proved effective on more complex substrates, giving access both to triazolo-fused benzazepine **5d** and to the steroid-substituted [1,2,3]-triazolo[5,1-a]isoindoles **5f** in 68 and 52% yields, respectively. In some cases (**5b**, **5d,** and **5f**) the formation of traces amount of dehalogenation products (<2%) was observed.

Also in this case the isolation of the product was conducted *via* re-crystallization without the need for further purification, except in the case of the steroid product **5f** in which filtration over a silica pad and precipitation in water were necessary to achieve the pure compound. Finally, we also investigated the recycle and reuse of the solvent/catalyst system (**Table 3**).

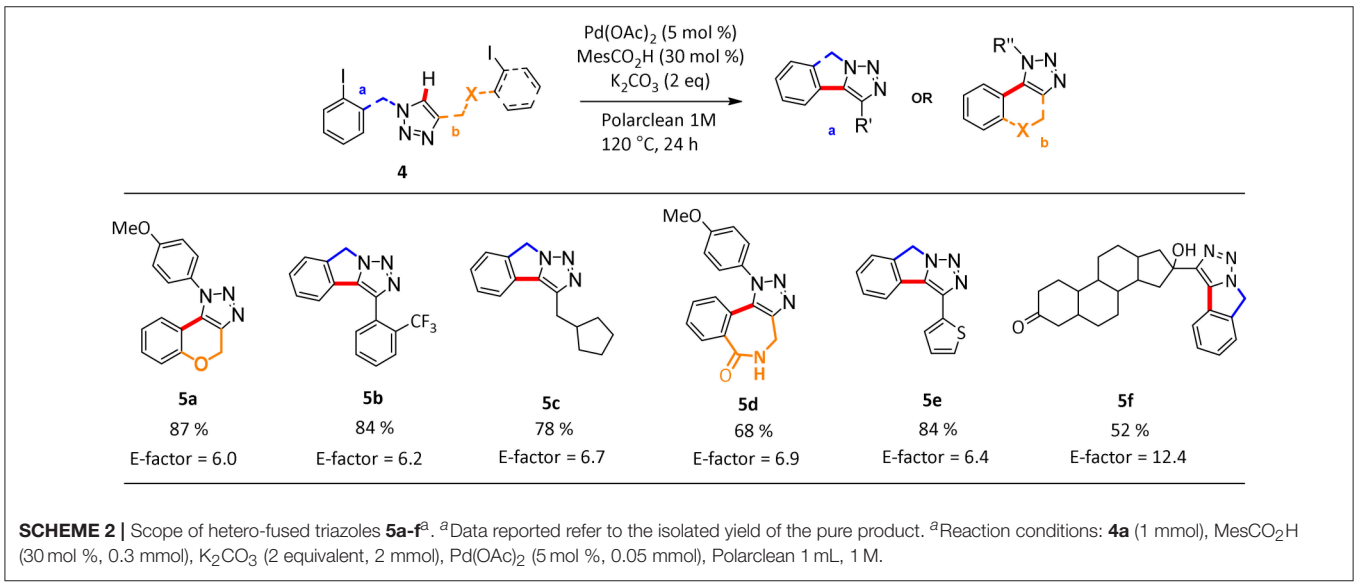
We found that for almost all of the substrates it was possible to filtrate the reaction mixture on a Büchner funnel, collecting the product, and reuse the solvent system, which also retains the palladium catalyst, without any treatment for at least three consecutive cycles and with a limited loss in efficiency and selectivity (**Table 3**). The latter is likely caused by an increase in water content of the solvent/catalyst system over consecutive reaction runs, which was already demonstrated to be detrimental for the selectivity of the process.

We also calculated the green metrics associated with the C–H functionalization protocol to compare the results of the reactions conducted in Polarclean with those obtained using other media. We were pleased to find that, compared to other common synthetic protocols present in literature (see **Supplementary Information**), the use of our recyclable system for the intramolecular C–H activation allows us to achieve very low E-factor values around 6 for the synthesis of polycyclic heterocycles (**Scheme 2**). The only exception is represented by the cyclization of the steroid substituted substrate to give product **5f**, for which recycling of the solvent/catalyst system was hampered by the necessity to add water to isolate the pure product.

TABLE 3 | Recycle of solvent/catalyst system for the synthesis of representative compound **5a**[a].

	1st run	2nd run	3rd run
Selectivity **5a:6a**[b]	99:1	95:5	92:8
Yield of **5a** (%)[c]	87%	82%	78%

[a] *Reaction conditions:* ***4a*** *(1 mmol), $MesCO_2H$ (30 mol %, 0.3 mmol), K_2CO_3 (2 equivalent, 2 mmol), $Pd(OAc)_2$ (5 mol %, 0.05 mmol).*
[b] *Measured by GC analyses using samples of pure compounds as reference.*
[c] *Isolated yield of the pure* ***5a****.*



SCHEME 2 | Scope of hetero-fused triazoles **5a-f**[a]. [a]Data reported refer to the isolated yield of the pure product. [a]Reaction conditions: **4a** (1 mmol), $MesCO_2H$ (30 mol %, 0.3 mmol), K_2CO_3 (2 equivalent, 2 mmol), $Pd(OAc)_2$ (5 mol %, 0.05 mmol), Polarclean 1 mL, 1 M.

CONCLUSION

In conclusion, we have reported that Polarclean, a novel solvent deriving from the waste valorization of Nylon 66 manufacturing, can be an effective alternative to common petrol-based solvents in the reactions object of the current investigation. Dipolar cycloadditions benefit from the use of Polarclean in terms of isolation of final products and therefore in achieving a waste minimized protocol for the synthesis of isoxazole **3**. Intramolecular C–H activation also proved to be feasible using Polarclean allowing the synthesis of polycyclic heterocycles **5** in a step and atom economical fashion and with the reuse of the medium/catalyst system, thus effectively minimizing the waste generation.

AUTHOR CONTRIBUTIONS

FF, LL, OV, FB, OP, and SS performed the experiments. FF and LV contributed to conception and design of the study. SS and LV wrote the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2018.00659/full#supplementary-material

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ORIGINAL RESEARCH
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Synthesis of Oxazinanones: Intramolecular Cyclization of Amino Acid-Derived Diazoketones via Silica-Supported $HClO_4$ Catalysis

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A Brønsted acid catalyzed intramolecular cyclization of *N*-Cbz-protected diazoketones, derived from α-amino acids, is described. The reaction proceeds under metal-free conditions and is promoted by ecofriendly silica-supported $HClO_4$ as the catalyst and methanol as the solvent. This transformation enables the short synthesis of various 1,3-oxazinane-2,5-diones under mild reaction conditions and in good yields (up to 90%). The set-up is very simple; by just mixing all reagents together with no work-up necessary before purification, this protocol takes a greener approach.

Keywords: heterocycles, oxazinanones, intramolecular cyclization, Brønsted acid, diazo carbonyls

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INTRODUCTION

Oxazinanones (six-membered cyclic urethanes) are an important class of heterocycles, which have been found to be key structural units in bioactive natural products and pharmaceutically important molecules. Some important examples are the anti-HIV drug Efavirenz (Staszewski et al., 1999) and the potent anticancer agent Maytansine (Rao et al., 1979) and its synthetic derivatives Maytansinoid (Blanc et al., 2011) and Ansamitocin P3 (Taft et al., 2012). Other significant biological activities described for this class of compounds are: antibacterial (Zanatta et al., 2006; Wang, 2008), anti-influenza (Kuznetsov et al., 2017), anti-inflammatory (Ullrich et al., 2004), antidiabetes [11β HSD1 inhibitor (BI 135585)] (Zhuang et al., 2017), antithrombotic (Jin and Confalone, 2000), antialzheimer (Fuchs et al., 2007), and enzyme inhibiting [(Latli et al., 2017); **Figure 1**]. Furthermore, they are extensively used as valuable synthetic intermediates in fine chemicals (Woodward et al., 1981; Wang et al., 1982; Hilborn et al., 2001; Takahata et al., 2002; Wang and Tunge, 2006), cosmetics (Zofchak, 2003), and pesticides (Hino et al., 2008). They have also showed wide applications as ligands, auxiliaries and as phase transfer catalysts in organic synthesis (Davies et al., 2006; Lait et al., 2007).

Thus, it is therefore not surprising that various synthetic methods for the construction of 1,3-oxazinan-2-one rings have been reported in literature. Among many current methodologies, reactions of CO_2 (Kubota et al., 1993) or Urea (Bhanage et al., 2004) with amino alcohols, cycloaddition of isocyanates to oxetanes (Fujiwara et al., 1989), coupling of the adducts from the reaction between $(Bu_3Sn)_2O$ and haloalkyl isocyanate with alkyl halides (Shibata et al., 1989), iodine-mediated (Fujita et al., 1997; Quinodoz et al., 2017), gold-catalyzed (Robles-Machín et al., 2006; Alcaide et al., 2013), Pd/sulfoxide-catalyzed C-H amination (Rice and White, 2009), intramolecular Michael addition reactions (Hirama et al., 1985) of appropriately functionalized

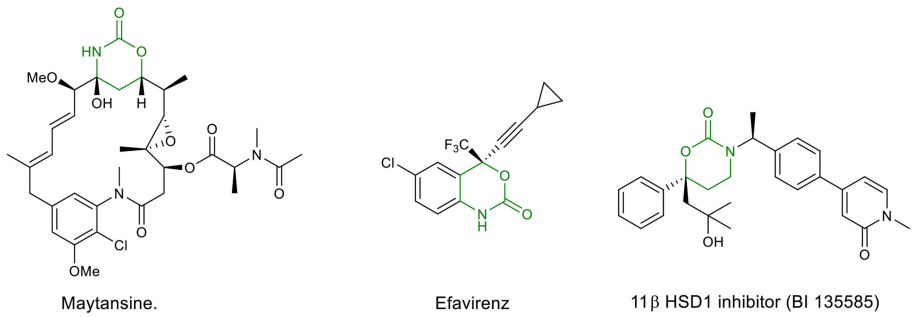


FIGURE 1 | Bioactive molecules bearing an oxazinanone moiety.

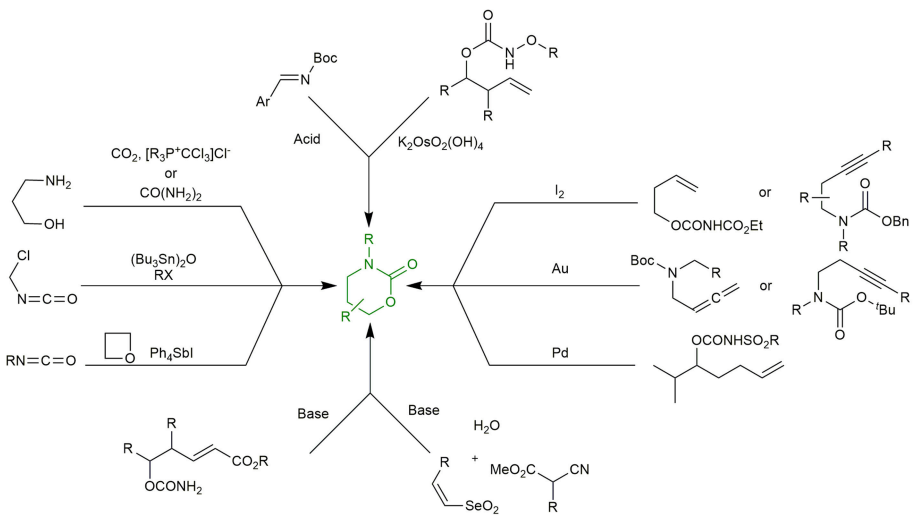


FIGURE 2 | Synthetic methodologies for the preparation of oxazinanone moiety.

allylic/homoallylic/homopropargyl/allenic carbamates, tethered aminohydroxylation (Donohoe et al., 2007), Brønsted base catalyzed Michael addition of α-isocyanoacetates to phenyl vinyl selenones (followed by domino oxidative cyclization) (Buyck et al., 2014) and Brønsted acid catalyzed elimination-cycloaddition reaction of Boc-imines (Uddin et al., 2011) are the most interesting ones (**Figure 2**).

All the methodologies described above are dedicated to 1,3-oxazinan-2-one skeletons, whereas only a few are reported for the preparation of 1,3-oxazinane-2,5-dione rings. Hanessian and Fu (2001) described the synthesis of this class of compound as a by-product, during a rhodium catalyzed N-H insertion reaction of a diazoketone (synthesis of 3-azetidinones) (**Figure 3A**). Pansare et al. (1999) treated a diazoketone derived from *N*-Cbz-phenylalanine with scandium triflate ($Sc(OTf)_3$) as the catalyst in methanol, to obtain the oxazinanedione moiety (**Figure 3B**). Similarly, Jung and Avery (2006) successfully demonstrated the synthesis of cyclic urethanes from Boc-protected diazocarbonyl substrates through an indium triflate [$In(OTf)_3$] catalyzed intramolecular cyclization reaction (**Figure 3C**).

Despite the fact that numerous modern, scalable and greener methods to obtain diazo carbonyl compounds were described over the past few years (Maas, 2009; Burtoloso et al., 2018), the development of greener, metal free, cheap and easily available catalysts for the efficient synthesis of cyclic urethanes is still highly desirable. With these demands in mind, efforts have been made to use Brønsted acid catalyst as a potential substitute to perform the desired transformation. It is also important to mention here that our group has developed an O-H insertion reaction into diazo carbonyl compounds employing Bronsted acid catalyst (Gallo and Burtoloso, 2018). Herein, we report the operationally simple and greener synthesis of 1,3-oxazinane-2,5-diones via silica-supported $HClO_4$ catalyzed cyclization of *N*-Cbz-protected diazoketones, offering an interesting alternative to the existing synthetic methods (**Figure 3D**). Although a single example for a *N*-Boc-protected diazoketone was described by Jung and Avery with $HClO_4$, the conditions employed (solution in CH_2Cl_2) and the use of Boc protecting group makes this method less interesting when compared to the present protocol.

RESULTS AND DISCUSSION

We initiated our screening by selecting phenylalanine-derived *N*-Cbz-protected diazoketone **1** as the model substrate and

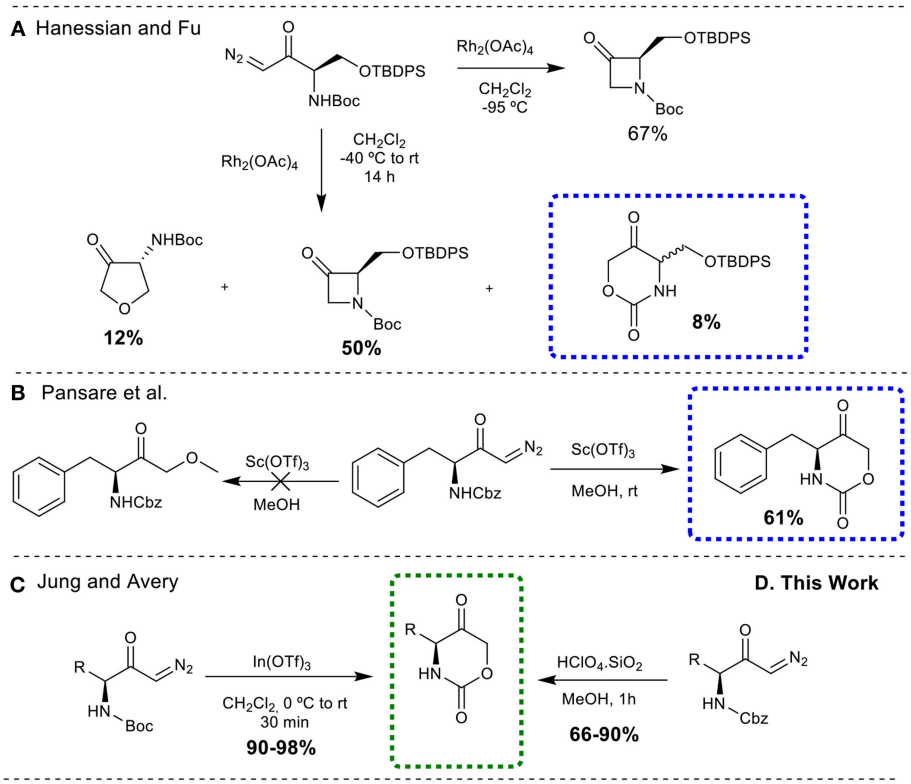
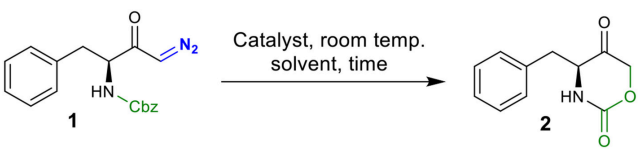


FIGURE 3 | Synthesis of 1,3-oxazinane-2,5-diones from diazo carbonyl moieties. **(A)** Through rhodium catalyzed N-H insertion reaction; **(B)** through scandium triflate ($Sc(OTf)_3$) catalyzed insertion reaction; **(C)** through an indium triflate [$In(OTf)_3$] catalyzed intramolecular cyclization reaction; **(D)** through silica-supported $HClO_4$ catalyzed intramolecular cyclization reaction.

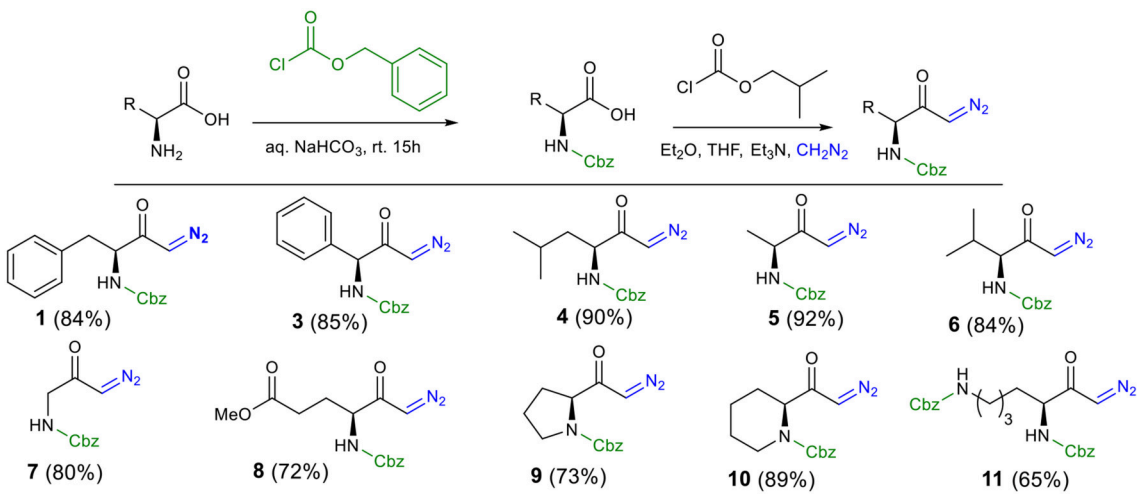
TABLE 1 | Optimization conditions of Bronsted acid cyclization of diazo carbonyl **1**.



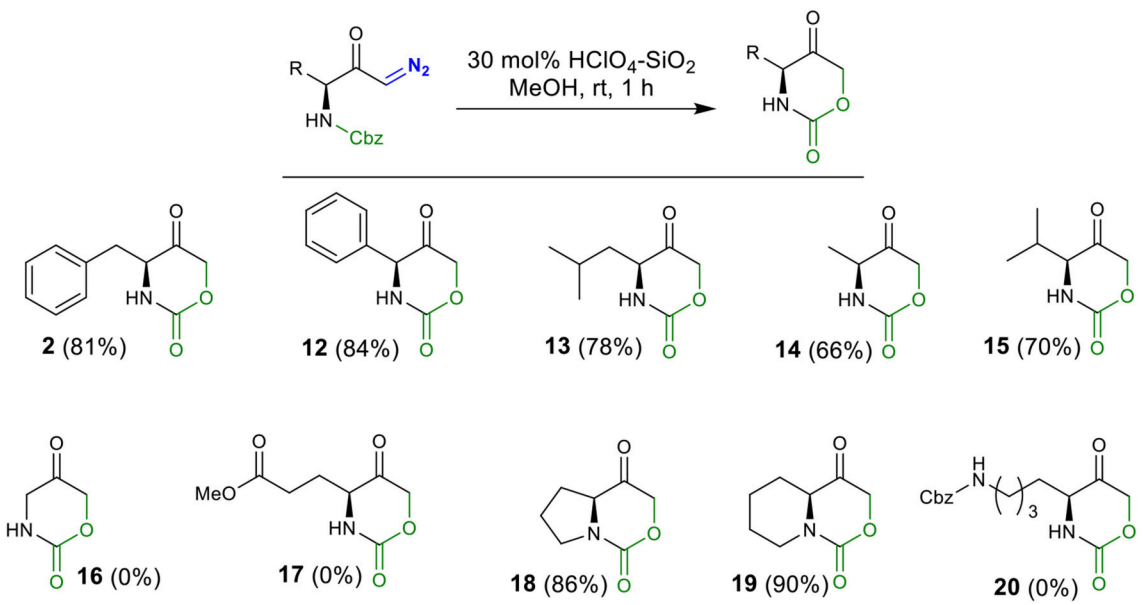
Entry	Catalyst	(mol%)	Solvent	Time (h)	Yield (%)[a]
1	H_2SO_4	10	BnOH	24	12
2	$HClO_4$	10	BnOH	24	27
3	H_2SO_4-SiO_2	10	BnOH	24	35
4	$HClO_4$-SiO_2	10	BnOH	24	44
5	$HClO_4$-SiO_2	10	EtOH	24	62
6	$HClO_4$-SiO_2	10	MeOH	12	71
7	$HClO_4$-SiO_2	10	DCE	12	13
8	$HClO_4$-SiO_2	10	THF	12	0
9	$HClO_4$-SiO_2	10	Toluene	12	0
10	$HClO_4$-SiO_2	20	MeOH	12	75
11	$HClO_4$-SiO_2	30	MeOH	12	83
12	$HClO_4$-SiO_2	40	MeOH	12	82
13	$HClO_4$-SiO_2	30	MeOH	1	81

[a]*Isolated yield.*

investigated its behavior under different reaction conditions (**Table 1**). Based on our previous work (Gallo and Burtoloso, 2018), compound **1** was simply mixed with 10 mol% of H_2SO_4 (pKa = −3.0) as the BrØnsted acid in benzyl alcohol (BnOH) as the solvent for 24 h at room temperature. To our delight, we isolated the intramolecular cyclization product, oxazinanone **2**, in 12% yield instead of getting O-H insertion product (entry 1). A slight improvement in the yield was observed while using stronger acid $HClO_4$ (pKa = −10) as the catalyst under similar reaction conditions (entry 2). In order to minimize side product formation, as well as ease in acid handling, H_2SO_4 was immobilized on silica gel (230–400 mesh) (Chakraborti and Gulhane, 2003; Chakraborti and Chankeshwara, 2006; Rudrawar et al., 2006). This manipulation proved to be useful, providing target molecule **2** with 35% yield (entry 3). Encouraged by this outcome, we used silica-supported $HClO_4$ which led to a further increase in the yield of the reaction (entry 4). Significant increase in the yield (up to 62%) was noticed when EtOH was employed as a reaction medium (entry 5). Using MeOH as the solvent improved the reaction efficiency and the desired product **2** was isolated in 71% yield in shorter reaction times (12 h) (entry 6). Poor yield or no product formation was observed in the presence of non-nucleophilic solvents such as DCE, THF, and toluene (entries 7–9). Increasing catalyst loading to 20 and 30 mol % provided product **2** in 75 and 83% yield, respectively (entries 10 and 11). Further increasing the catalyst loading (40 mol %) did not affect the reaction yield (entry 12). Under similar conditions of entry 11, comparable yield (81%) of compound **2** was obtained when the reaction was carried-out during 1 h. Thus, conditions



SCHEME 1 | Preparation of *N*-Cbz-protected diazo carbonyls compounds **1** and **3**–**11**.



SCHEME 2 | Synthesis of oxazinanones from diazo carbonyls via silica-supported $HClO_4$ catalysis.

in entry 13 were chosen as the optimal to explore the scope of the reaction.

To explore the scope and generality of the reaction, we prepared several *N*-Cbz-protected diazoketones (**1** and **3–11**) with different substituents (**Scheme 1**, for detail procedure see **Supplementary Material** for the synthesis of diazoketones). In our approach, diazoketones **1** and **3–11** were accessed in excellent yields by protection of the respective amino acids with benzyl chloroformate in aqueous $NaHCO_3$, followed by reaction with isobutyl chloroformate (to activate the carboxylic acid as a mixed anhydride) and freshly prepared diazomethane.

Employing the conditions from entry 13 (**Table 1**), the substrate scope was investigated (**Scheme 2**). The $HClO_4$-SiO_2 catalyst smoothly converted 2-phenylglycine derived diazo carbonyl **3** into cyclic urethane **12** in 84% yield. Similarly, for leucine-, alanine-, and valine-derived substrates **3–6**, the corresponding oxazinanones **13–15** were obtained in good yields. Surprisingly, no product formation was observed with glycine-derived diazo compound **7** under the standard reaction conditions (complex mixture) and this result is under investigation for a better understanding. Diazoketone **8**, possessing terminal ester functionality, also render no product. In the case of bicyclic oxazinanones **18** and **19**, derived from **9** and **10**, high yields were obtained. Finally, diazoketone **11**, with terminal Cbz-protected amine chain, did not provide the desired product.

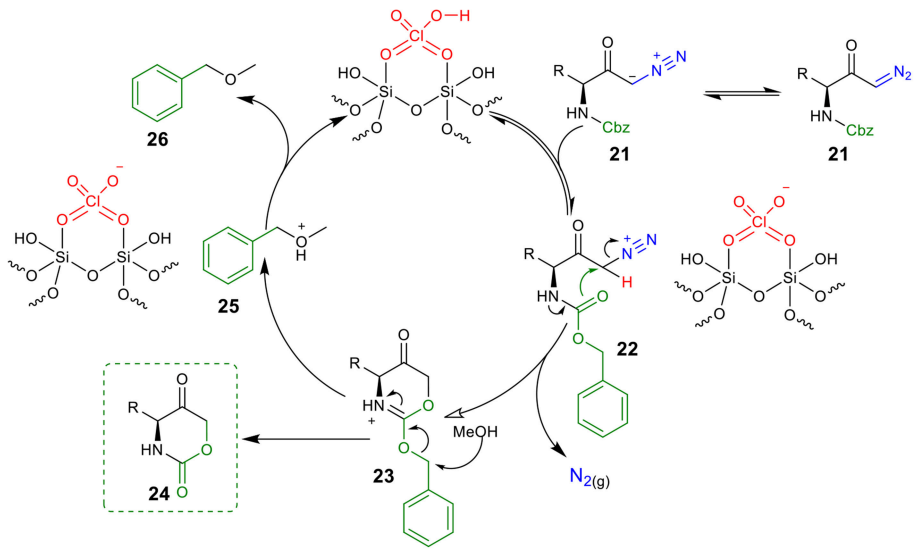


FIGURE 4 | A proposed mechanism for the synthesis of oxazinanones from diazo carbonyls through silica-supported $HClO_4$ catalysis.

Although merely speculative (studies are being carried-out), the two cbz groups in compound **11** can compete against each other for attack in the protonated diazo carbon (in an inter- or intramolecular fashion). In diazoketone **8**, the ester functionality can also compete with the cbz group during the insertion in the protonated diazo carbon. Moreover, the formation of the enol ether from **8** in acidic medium can furnish by-products through competing reactions.

Based on the above experimental results, a proposed mechanism to rationalize the formation of the 1,3-oxazinano-2,5-diones skeleton is shown in **Figure 4**. Protonation of diazo compound **21** by the Brønsted acid generates diazonium intermediate **22**. Next, the intramolecular nucleophilic attack from the Cbz carboxyl group at C1 releases molecular nitrogen and furnishes ammonium intermediated **23**. Finally, intermediate **23** is converted into the desired oxazinanone **24** after the nucleophilic attack of MeOH to the benzyl group. Hydrogen abstraction from **25** by the conjugate base of the catalyst regenerates the catalyst and provides (methoxymethyl)benzene **26** (detected by ^{1}H NMR) as a byproduct.

In conclusion, we have disclosed a direct cyclization of amino acid-derived diazoketones via a silica-supported $HClO_4$ catalysis, offering a practical and efficient route for the construction of several 1,3-oxazinane-2,5-diones in 66–90% yield. This protocol features a metal free, inexpensive, stable, and easy to handle catalyst, simple reaction set-up, short reaction time, non-chlorinated solvent and broad substrate scope.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2019.00062/full#supplementary-material

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Sustainable Construction of Heterocyclic 1,2,3-Triazoles by Strict Click [3+2] Cycloaddition Reactions Between Azides and Alkynes on Copper/Carbon in Water

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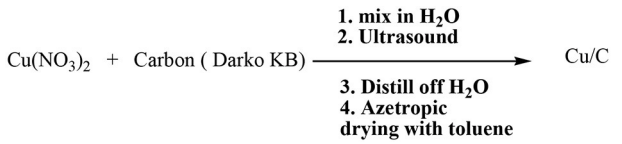
1,4-Disubstituted-1,2,3-triazoles, considered as an important and useful class of heterocycles with potential applications in material science and biology, have been prepared in an efficient and selective manner by copper on carbon-catalyzed [3+2] cycloaddition reactions of azides and alkynes (CuAAC) in water under strict click chemistry conditions. Copper(I) catalysts heterogenized onto commercially activated carbon materials (Cu-CC) and on another carbon material produced from vegetable biomass *using Argan nut shells* (Cu-CANS) were found to be versatile catalytic sources for sustainable CuAAC. These copper on carbon supports were prepared and fully characterized by using two types of activated carbons that exhibit different porosity and specific surface. The delineation of the nature of the catalytic copper species and the role of the carbon support in the CuAAC were addressed. These heterogeneous copper on carbon catalysts were recovered and reused until ten catalytic runs without any noticeable loss of activity.

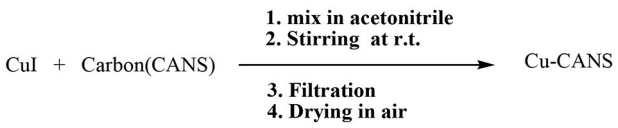
Keywords: copper, activated carbon, 1, 2, 3-triazole, click chemistry, heterogeneous catalyst, recovery/recycling, water

INTRODUCTION

1,2,3-Triazoles are important and useful non-classical bioisostere linkage heterocycles. They have several applications as agrochemical agents, dyes, corrosion inhibitors, photostabilizers, and photographic materials. Several 1,2,3-triazole derivatives show interesting biological activities under the so-called peptidomimetic substances (Chung et al., 2002; Mark, 2006; Run et al., 2007; Ostapenko et al., 2008; Zheng et al., 2008). The most popular method for the construction of 1,2,3-triazole moiety is the Huisgen reaction of [3+2] dipolar cycloaddition of azides with alkynes (Yan et al., 2005; Zhang et al., 2006). Copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) (Tornøe et al., 2002; Pachón et al., 2005; Bock et al., 2006) has emerged as one of the most reliable reactions under the click chemistry regime (Kolb and Sharpless, 2003; Yadav et al., 2007) that enables the practical and efficient preparation of 1,4-disubstituted-1,2,3-triazoles, from a wide range of substrates with excellent selectivity, which cannot be achieved by traditional Huisgen non-catalyzed thermal approaches (Huisgen, 1963).



SCHEME 1 | Lipshutz's protocol for the preparation of "copper-in-charcoal."



SCHEME 2 | Preparation scheme of copper on carbon support made from *Argan nut shells* Cu-CANS.

The synthesis of 1,2,3-triazoles under CuAAC proceeds in the presence of copper salts as homogeneous catalysts, which make the separation and recovery of such copper catalysts very difficult (Gaetke and Chow, 2003; Hong et al., 2010; Yang et al., 2014). In addition, it is most likely that under homogeneous catalytic fashion, the final 1,2,3-triazoles can be contaminated by copper particles. So far, many challenges remain and much work still needs to be done in terms of the copper catalyst recovery and the obtention of copper-free 1,2,3-triazolic compounds. Therefore, an efficient and simple way to synthesize 1,2,3-triazoles is still necessary by working under strict click chemistry conditions and taking into account the sustainable chemistry criteria. In order to overcome these problems, recent works have focused on heterogeneous catalytic systems, which have several advantages such as good dispersion of the catalytically active sites, easier and safer handling, easy separation of the products from the reaction mixture and reusability of the catalyst. Thus, a good number of heterogeneous catalytic systems has been developed. For instance, immobilizing copper salts on silica and their use as heterogeneous catalysts in CuAAC (Miao and Wang, 2008; Coelho et al., 2010; Diz et al., 2015; Jumde et al., 2015), as magnetic nanoparticles (Xiong and Cai, 2013; Moghaddam and Ayati, 2015; Pourjavadi et al., 2015, 2016; Tajbakhsh et al., 2015; Bahrami and Arabi, 2016; Jahanshahi and Akhlaghinia, 2016), polymers (Bonami et al., 2009; Wallyn et al., 2011; Xiong et al., 2016), zeolites (Chassaing et al., 2007, 2008), hydroxyapatite (Masuyama et al., 2011), and carbon support such as charcoal (Lipshutz and Taft, 2006) have been subject of previous works.

The Lipshutz group has in fact described the preparation of copper-in-charcoal by impregnating of copper(II) nitrate in activated carbon (Darco-KB) using water as solvent under ultrasound radiation followed by distillation of water by azeotropic drying with toluene. The prepared copper-in-charcoal namely Cu/C was employed to assist the click of 1,2,3-triazoles using high temperature microwave conditions (**Scheme 1**).

Although the Lipshutz's copper-in-charcoal was efficient in assisting CuAAC, the studied triazole click reactions made use of a high catalyst loading of 10 mol%, an additional base (Et_3N) and were peformed at high temperature (60 °C) in a hazardous solvent such as dioxane. The catalyst could be reused for only just three catalytic cycles without any loss of its activity (Lipshutz and Taft, 2006; Buckley et al., 2015).

In recent years, green synthesis and nature-friendly as well as sustainable resources and processes involving supported catalysts from agricultural wastes biomass have been found to be of increasing interest in the synthesis of heterocycles. In the context of our efforts to develop green, highly eco-efficient, and practical chemical methods utilizing bio-heterogeneous catalysts in [3+2] cycloaddition reactions of azides with alkynes (Bahsis et al., 2018), we herein report an easy sustainable protocol for the synthesis of 1,2,3-triazoles. For that, we use a new supported copper(I) on activated carbon materials easily made from agricultural wastes biomass such as *Argan Nut Shells*, namely Cu/CANS (**Scheme 2**). The choice of starting from CuX (X = I, Br, Cl) precursor and its impregnation into the pores of the carbon material in acetonitrile arises from the fact that such precursor of Cu(I), considered as the catalytically active specie in CuAAC, is nicely soluble in acetonitrile and the solutions are air stable and may be stored at room temperature.

Such a copper-supported on carbon Cu/CANS was found to be highly eco-efficient to assist CuAAC in water at room temperature as well as a recyclable heterogeneous catalyst. The commercially available activated carbon material (Cu/C) was also used for comparative purposes.

EXPERIMENTAL SECTION

General Methods

All chemicals were used as purchased without further purification. The reactions were performed under ambient conditions. NMR analyses were carried out on a spectrometer Bruker AC-400 MHz (400 MHz for proton, 100 MHz for carbon) by using deuterated chloroform as solvent. The chemical shifts (δ) are expressed in ppm. The high resolution mass spectra (HRMS) were recorded in the EI (70 eV) or FAB mode at the mass spectrometry service of the University of Valencia. Melting points were determined using a Stuart melting point apparatus SMP3, employing the capillary tubes. FT-IR spectra (4000–450 cm^{-1} range) were recorded with a Nicolet 5700 FT-IR spectrometer on samples prepared as KBr pellets. The polycrystalline sample of each support was lightly ground in an agate mortar, pestle and filled into 0.5 mm borosilicate capillary prior to being mounted and aligned on an Empyrean PANalytical powder diffractometer using Cu-Kα radiation (λ = 1.54056 Å). Three repeated measurements were collected at room temperature in the $10^\circ < 2\Theta < 60^\circ$ range with a step size of 0.01°. Scanning Electronic Microscopy (SEM) images were obtained with a HITACHI-S4100 equipment operated at 20 kV. The specific surface areas were determined from the dinitrogen adsorption/desorption isotherms (at 77 K) on a Quantachrome Autosorb-1 nautomatic analyzer using the BET (Brunauer-Emmett Teller) method. The pore size distribution was calculated from the N_2 adsorption isotherms with the classic theory model of Barrett, Joyner and Halenda (BJH).

The Scanning Electron Microscopy was carried out by using a VEGA3 TESCAN microscope and a high resolution JEOL Field Emission Gun-Scanning Electron Microscope (FEG-SEM).

Procedure for the Synthesis of the Benzyl Azide Derivative

Benzyl bromide derivative (10.0 g, 58.5 mmol) and NaN_3 (11.4 g, 175 mmol) were dissolved in 200 mL of dimethylformamide. The reaction mixture protected from light is stirred for 20 h at room temperature. After filtration, water was added to the filtrate and the product was extracted with dichloromethane three times. The organic phases were combined, dried over anhydrous $MgSO_4$, then filtered-off and the solvents evaporated under reduced pressure, yielding a liquid product.

Synthesis of 1-(Azidomethyl)Benzene

Colorless liquid. Yield: 90%. $R_f = 0.8$ in hexane/ethyl acetate (4:1 v/v). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 4.39 (s, 2H, CH_2); 7.41–7.5 (m, 5H, CH_{ar}). FT-IR (film on NaCl, cm^{-1}): 2,096 cm^{-1} (N_3).

Synthesis of (Azidomethyl)-4-Methoxybenzene

Brown liquid. Yield: 87%. $R_f = 0.64$ in hexane/ethyl acetate (4:1 v/v). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.68 (s, 3H, OMe); 4.13 (s, 2H, CH_2); 6.78–6.81 (d, $J = 12.00$ Hz, 2H, CH_{ar}); 7.11–7.14 (d, $J = 12.00$ Hz, 2H, CH_{ar}). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 54.3 (CH_2); 55.2 (CH_3); 114.2 ($2CH_{ar}$); 127.4 (C_{ar}); 129.7 ($2CH_{ar}$); 159.64 (C_{ar}).

Procedure for the Synthesis of 1-Azidobenzene

Aniline (13 mmol) was suspended in 80 mL of hydrochloric acid (17%) at room temperature, then ethanol was added until a clear solution was obtained. The solution was cooled to 0°C and $NaNO_2$ (19.5 mmol) was added in small portions. After stirring at 0°C for 15–30 min, NaN_3 (19.5 mmol) was slowly added (*caution!! when handling NaN_3*) and the mixture was stirred for additional 2 h at room temperature. The reaction mixture was extracted with diethyl ether (3 × 80 mL) and the combined organic fractions were washed with saturated $NaHCO_3$ solution (3 × 50 mL) and with brine (50 mL). After drying over $MgSO_4$ the ether was removed under reduced pressure and the desired azidobenzene was obtained without further purification as a brown liquid. Yield: 90%. $R_f = 0.86$ in hexane. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.08–7.44 (m, 5H, CH_{ar}). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 119.46 (CH_{ar}); 125.31 ($2CH_{ar}$); 130.19 ($2CH_{ar}$); 140.6 (C_{ar}). FT-IR (film on NaCl, cm^{-1}): 2,119 cm^{-1} (N_3).

Procedure for the Preparation of Activated Carbon-*Argan Nut Shells* (CANS)

The argan oil shells were collected, washed with distilled water, dried at room temperature and crushed by a plunger ball mill until a fine powder was obtained. The unmodified *Argan nut shells* material is abbreviated as ANS. The prepared raw material was treated by phosphoric acid with a mass proportion of H_3PO_4/ANS 1:1. The mixture was stirred using the plaster mill with a speed of 400 rpm/mn for 10 min. Subsequently, the mixture was kept at 120°C during 4 h. The carbonization of the obtained dried material was carried out in a muffle furnace at 500°C for 1 h at air atmosphere, whereas the activation with phosphate group would produce a well-developed porosity of the as-prepared activated carbon. After cooling, the recovered solid was crushed, washed several times with 0.15 M HCl solution, then with distilled water until the pH of the solution becomes neutral (pH ∼ 7). The resulting material was dried completely and then crushed again by the plunger ball mill at a speed of 400 rpm for 15 min. Finally the obtained phosphate-containing carbon material was kept in a hermetic glass bottle.

Synthetic Procedure of Copper on Carbon Catalyst

The commercially available carbon (CC) or carbon prepared from *Argan nut shells* (CANS) (1 g) was added to a solution of copper(I) iodide (250 mg) in acetonitrile (50 mL). The suspension was stirred overnight at room temperature and the resulting solid compounds were filtered-off, washed with acetonitrile (2 × 15 mL), diethyl ether (2 × 15 mL) and dried overnight. The catalyst was characterized by X-ray diffraction (XRD), scanning electronic microscopy (SEM), and infrared spectroscopy (FT-IR). Atomic Absorption Spectroscopy (AAS) (Aurora AI800) was used to determine the copper contents in both carbon materials.

General Procedure of Copper on Carbon-Catalyzed Click of 1,2,3-Triazole From Azides and Alkynes

Azide (0.751 mmol, 1.2 equivalent), alkyne derivative (0.622 mmol, 1 equivalent), and CuI (0.005 equivalent) on carbon catalyst were placed in a reaction tube and 5 mL of water was added. The mixture was stirred for 6 h at room temperature. After completion of the reaction as evidenced by TLC, the 1,2,3-triazol product was extracted using diethyl ether and the Cu on carbon catalyst separated by filtration. The combined diethyl ether washings were evaporated under reduced pressure to afford the corresponding final pure 1,2,3-triazole. The recovered catalyst was dried and reused at least 10 times without any noticeable loss of its activity.

Synthesis of 1-Benzyl-4-Phenyl-1*H*-1,2,3-Triazole (3a)

White solid. Yield: 94%. R_f= 0.3 in hexane/ethyl acetate (3:1 v/v). Mp = 130–132 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 5.60 (s, 2H, CH_2); 7.28–7.44 (m, 8H, CH_{ar}); 7.68 (s, 1H, $CH_{triazole}$); 7.81–7.83 (d, J = 8.00 Hz, 2H, CH_{ar}). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 54.4 (CH_2); 119.5 (CH_{ar}); 125.9 ($3CH_{ar}$); 127.8 ($2CH_{ar}$); 128.2 ($2CH_{ar}$); 129.2 ($CH_{triazole}$); 131,5 (C_{ar}); 135.0 (C_{ar}); 148.3 ($C_{triazole}$). HRMS (FAB^+) *m/z*: Calcd for $C_{15}H_{14}N_3$: 236.1188; Found: 236.1177.

Synthesis of Methyl 4-(1-Benzyl-1*H*-1,2,3-Triazol-4-yl)Benzoate (3b)

White solid. Yield: 88%. R_f= 0.42 in hexane/ethyl acetate (2:1 v/v). Mp = 176–178 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.91 (s, 3H, OCH_3); 5.58 (s, 2H, CH_2); 7.33–7.38 (m, 5H, CH_{ar}); 7.74 (s, 1H, $CH_{triazole}$); 7.86–7.89 (d, J = 12.00 Hz, 2H, CH_{ar}); 8.05–8.08 (d, J = 12.00 Hz, 2H, CH_{ar}). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 52.3 (CH_3); 54.5 (CH_2); 120.4 (CH_{ar}); 125.6 ($2CH_{Ar}$); 128.3 ($2CH_{ar}$); 129.1 ($2CH_{ar}$); 129.4 ($2C_{ar}$); 129.7 ($CH_{triazolic}$); 130.3 (C_{ar}); 134.5 ($C_{triazolic}$); 134.9 (C_{ar}); 147.3 (C_{ar}); 166.9 (CO). HRMS (FAB^+) *m/z*: Calcd for $C_{17}H_{16}N_3O_2$: 294.1243; Found: 294.1245.

Synthesis of 4-(1-Benzyl-1*H*-1,2,3-Triazol-4-yl)-N,N-Dimethylbenzenamine (3c)

Yellow solid. Yield: 89%. R_f= 0.26 in hexane/ethyl acetate (2:1 v/v). Mp = 202–204 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.97 (s, 3H, CH_3); 5.54 (s, 2H, CH_2); 6.72–6.75 (d, J = 12.0 Hz, 2H, CH_{ar}); 7.26–7.38 (m, 5H, CH_{ar}); 7.53 (s, 1H, $CH_{triazole}$); 7.65–7.68 (d, J = 12.00 Hz, 2H, CH_{ar}). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 40.6 (CH_2); 54.2 (CH_3); 112.5 ($2CH_{ar}$); 118.1 (C_{ar}); 126.8 (CH_{ar}); 128.1 ($2CH_{ar}$); 128.8 ($2CH_{ar}$); 129.2 ($2CH_{ar}$); 135.1 (C_{ar}+ $CH_{triazolic}$); 150.5 ($C_{triazolic}$). HRMS (FAB^+) *m/z*: Calcd for $C_{17}H_{19}N_4$: 279.1609; Found: 279.1599.

Synthesis of 4-(1-Benzyl-1*H*-1,2,3-Triazol-4-yl)Benzenamine (3d)

White solid. Yield: 92%. R_f = 0.48 in hexane/ethyl acetate (1:2 v/v). Mp = 184°C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 4.85 (s, 2H, NH_2); 5.56 (s, 2H, CH_2); 6.72–6.75 (d, J = 12.00 Hz, 2H, CH_{ar}); 7.31–7.35 (m, 5H, CH_{ar}); 7.49–7.52 (d, J = 12.00 Hz, 2H, CH_{ar}); 8.05 (s, 1H, $CH_{triazole}$). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 55.36 (CH_2); 116.83 ($2CH_{ar}$); 121.07 (C_{ar}); 121.44 (CH_{ar}); 128.17 ($2CH_{ar}$); 129.43 ($2CH_{ar}$); 129.96 ($2CH_{ar}$); 130.44 ($CH_{triazolic}$); 137.32 (C_{ar}); 149.90 ($C_{triazolic}$); 150.36 (C_{ar}). HRMS (FAB^+) *m/z*: Calcd for $C_{15}H_{15}N_4$: 251.1297; Found: 251.1299.

Synthesis of Ethyl 1-Benzyl-1*H*-1,2,3-Triazole-4-Carboxylate (3e)

White solid. Yield: 95%. R_f = 0.29 in hexane/ethyl acetate (2:1 v/v). M_p = 83–85°C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.35–1.40 (t, J = 10.00 Hz, 3H, CH_3); 4.35–4.42 (q, J = 9.33 Hz, 4H, OCH_2); 5.57 (s, 2H, CH_2); 7.26–7.29 (m, 3H, CH_{ar}); 7.37–7.4 (m, 3H, CH_{ar}); 7.96 (s, 1H, $CH_{triazole}$). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 14.4 (CH_3); 54.6 (CH_2); 61.4 (CH_2); 127.4 (CH_{ar}); 128.4 ($2CH_{ar}$); 129.3 (CH_{ar}); 129.4 (CH_{ar}); 133.8 ($CH_{triazolic}$); 140.7 ($C_{triazolic}$); 160.8 (CO). HRMS (FAB^+) *m/z*: Calcd for $C_{12}H_{14}N_3O_2$: 232.1086; Found: 232.1087.

Synthesis of 1,4-Diphenyl-1*H*-1,2,3-Triazole (3f)

White solid. Yield: 89%. R_f = 0.48 in hexane/ethyl acetate (3:1 v/v). Mp = 183–184°C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.33–7.4 (m, 2H, CH_{ar}); 7.44–7.49 (t, J = 7.47 Hz, 2H, CH_{ar}); 7.53–7.58 (t, J = 7.56 Hz, 2H, CH_{ar}); 7.79–7.81 (d, J = 7.80 Hz, 2H, CH_{ar}); 7.92–7.94 (d, J = 7.93 Hz, 2H, CH_{ar}); 8.22 (s, 1H, $CH_{triazole}$). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 118.07 ($2CH_{ar}$); 120.98 (C_{ar}); 126.34 (2 CH_{ar}); 128,98 (CH_{ar}); 129,31 (CH_{ar}); 129,37 ($2CH_{ar}$); 130,23 ($2CH_{ar}$); 130.34 ($CH_{triazolic}$); 130.73 (C_{ar}); 137.47 ($C_{triazolic}$). HRMS (FAB^+) *m/z*: Calcd for $C_{14}H_{12}N_3$: 222.1031; Found: 222.1029.

Synthesis of N,N-Dimethyl-4-(1-Phenyl-1*H*-1,2,3-Triazol-4-yl)Benzenamine (3g)

Yellow solid. Yield: 87%. R_f= 0.5 in hexane/ethyl acetate (2:1 v/v). M_p = 169–171 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.19 (s, 1H, CH_3); 6.81–6.84 (d, J = 12.00 Hz, 2H, CH_{ar}); 7.43–7.58 (m, 5H, CH_{ar}); 7.80–7.82 (d, J = 8.00 Hz, 2H, CH_{ar}); 8.08 (s, 1H, $CH_{triazole}$). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 40.6 ($2CH_3$); 112.6 ($2CH_{ar}$); 116.1 ($2CH_{ar}$); 120.6 ($5CH_{ar}$); 126.9 (C_{ar}+$CH_{triazolic}$); 130.1 ($C_{triazolic}$); 141 (C_{ar}). HRMS (FAB^+) *m/z*: Calcd for $C_{16}H_{17}N_4$: 265.1453; Found: 265.1444.

Synthesis of Ethyl 1-Phenyl-1*H*-1,2,3-Triazole-4-Carboxylate (3h)

White solid. Yield: 73%. R_f = 0.56 in hexane/ethyl acetate (2:1 v/v). M_p = 75–77°C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.41–1.45 (t, J = 8.00 Hz, 3H, CH_3); 4.43–4.5 (q, J = 9.33 Hz, 4H, CH_2); 7.46–7.58 (m, 3H, CH_{ar}); 7.74–7.76 (m, 3H, CH_{ar}); 8.51 (s, 1H, $CH_{triazole}$). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 31.1 (CH_3); 61.6 (CH_2); 120.9 (C_{ar}); 125.6 ($2CH_{ar}$); 129.6 ($2CH_{ar}$); 130.1 ($CH_{triazolic}$); 136.5 ($C_{triazolic}$); 141 (CO). HRMS (FAB^+) *m/z*: Calcd for $C_{11}H_{12}N_3O_2$: 218.0929; Found: 218.0924.

Synthesis of 1-(4-Methoxybenzyl)-4-Phenyl-1*H*-1,2,3-Triazole (3i)

White solid. Yield: 96%. R_f = 0.28 in hexane/ethyl acetate (3:1 v/v). M_p = 132–135°C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.73 (s, 3H, OCH_3); 5.43 (s, 2H, CH_2); 6.82–6.85 (d, J = 12.00 Hz, 2H, CH_{ar}); 7.18–7.82 (m, 5H, CH_{ar}); 7.54 (s, 1H, $CH_{triazole}$); 7.69–7.72 (d, J = 12.00 Hz, 2H, CH_{ar}). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 53.9 (CH_2); 55.4 (CH_3); 114.6 ($2CH_{ar}$); 119.3 ($2CH_{ar}$); 125.8 ($2CH_{ar}$); 128.2 (CH_{ar}); 128.9 ($2CH_{ar}$); 129.8 (C_{ar}); 128.8 ($2CH_{ar}$); 130.7 (C_{ar}+$CH_{triazolic}$); 148.2 ($C_{triazolic}$); 160.1 (CH_{ar}). HRMS (FAB^+) *m/z*: Calcd for $C_{16}H_{16}N_3O$: 266.1293; Found: 266.1286.

Synthesis of Methyl 4-(1-(4-Methoxybenzyl)-1*H*-1,2,3-Triazol-4-yl)Benzoate (3j)

White solid. Yield: 80%. R_f = 0.66 in hexane/ethyl acetate (1:1 v/v). M_p = 183–185°C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.74 (s, 3H, OCH_3); 3.84 (s, 3H, OCH_3); 5.44 (s, 2H, CH_2); 6.83–6.86 (d, J = 12.00 Hz, 2H, CH_{ar}); 7.19–7.22 (d, J = 12.00 Hz, 2H, CH_{ar}); 7.63 (s, 1H, $CH_{triazole}$); 7.77–7.80 (d, J = 12.00 Hz, 2H, CH_{ar}); 7.97–8.00 (d, J = 12.00 Hz, 2H, CH_{ar}). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 52.1 (CH_3); 53.9 (CH_2); 55.3 (CH_3); 114.5 ($2CH_{ar}$); 125.4 ($2CH_{ar}$); 129.5 ($2CH_{ar}$); 129.7 ($2C_{ar}$); 130.1 ($CH_{triazolic}$); 134.9 ($C_{triazolic}$); 147.1 (C_{ar}); 160.0 (C_{ar}); 166.7 (CO). HRMS (FAB^+) *m/z*: Calcd for $C_{18}H_{18}N_3O_3$: 324.1348; Found: 324.1338.

TABLE 1 | The specific surface area, average pore diameter, and V_{total} of pores of CANS and CC.

Activated carbon	S_{BET} (m^2/g)	Average pore diameter (nm)	V_{Total} of pores (cm^3/g)
CANS	1151.75	2.204	0.635
CC	702.76	1.168	0.193

CANS, carbon from Argan Nut Shells biomass; CC, commercially carbon.

Synthesis of 4-(1-(4-Methoxybenzyl)-1*H*-1,2,3-Triazol-4-yl)Benzenamine (3k)

Yellow solid. Yield: 78%. R_f = 0.34 in hexane/ethyl acetate (1:1 v/v). M_p = 121–123°C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.09 (s, 1H, NH_2); 3.73 (s, 3H, OCH_3); 5.40 (s, 2H, CH_2); 6.61–6.64 (d, J = 12.00 Hz, 2H, CH_{ar}); 6.81–6.84 (d, J = 12.00 Hz, 2H, CH_{ar}); 7.17–7.19 (d, J = 8.00 Hz, 2H, CH_{ar}); 7.41 (s, 1H, $CH_{triazole}$); 7.49–7.52 (d, J = 12.00 Hz, 2H, CH_{ar}). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 53.6 (CH_3); 55.3 (CH_2); 114.4 ($2CH_{ar}$); 115.1 ($2CH_{ar}$); 117.9 ($2CH_{ar}$); 126.8 ($2CH_{ar}$); 126.9 ($2C_{ar}$); 129.6 (C_{ar} + $CH_{triazolic}$); 146.4 ($C_{triazolic}$); 159.8 (C_{ar}). HRMS (FAB^+) *m/z*: Calcd for $C_{16}H_{17}N_4O$: 381.1402; Found: 281.1398.

RESULTS AND DISCUSSION

Synthesis and Characterization of Copper on Carbon Catalyst

The synthesis of activated carbon from the local biomass such as *Argan nut shells* by the chemical activation method was adopted in this study. The advantage of this activation is to opt for low pyrolysis temperatures and a smaller activation cost. The high quality of activated carbon with a very large porous texture and high surface area was prepared from *Argan nut shells* biomass by using orthophosphoric acid as activating agent. This activation process aims to develop and modulate the porous structure of carbon, leading to a very sharp increase in its specific surface area. Indeed, the specific surface area of activated carbon is one of the most important physical structure parameters, the accuracy of its measured value being essential for realistic reference significance. In this work, the dinitrogen adsorption method was adopted to measure the specific surface area of activated carbon and the results obtained are summarized in **Table 1**. In this work, the Brunauer–Emmett–Teller (BET) method was adopted to measure the specific surface area of activated carbon and the corresponding results are also summarized in **Table 1**. It can be deduced from such results that commercially available carbon material CC, used for comparative purposes, presents a specific surface area equal to S_{BET} = 702.76 m^2/g with microspores rounding a size <2 nm, while the prepared carbon material CANS exhibits a highly porous structure as shown by the high found value of the specific surface area found to be S_{BET} = 1151.75 m^2/g) and the mesoporous character evaluated at 2.2 nm. This behavior allows easy access and contact between the reagents employed in a given heterogeneous catalytic protocol.

The Cu-carbon catalysts were prepared by impregnation of carbon supports with CuI in acetonitrile overnight at room temperature. The reaction mixture filtered, and the solid successively washed with acetonitrile, diethyl ether and dried under vacuum. The catalysts were characterized by several techniques such as Scanning electron microscopy (SEM), Energy-dispersive X-ray (EDX), X-ray diffraction (XRD) analysis, and FT-IR spectroscopy.

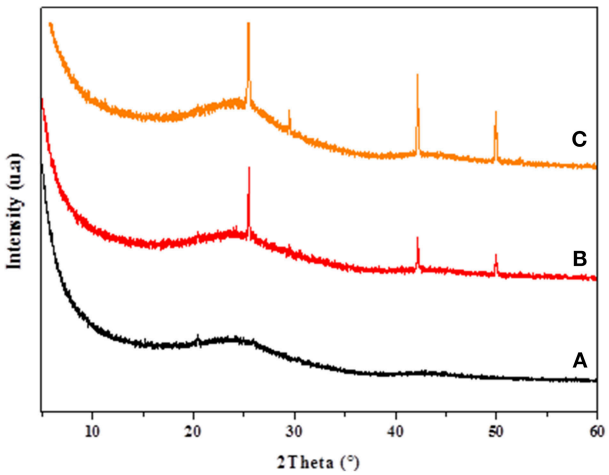


FIGURE 1 | XRD results of CANS support **(A)**, Cu-CANS material **(B)**, and phenylacetylene in Cu-CANS **(C)**.

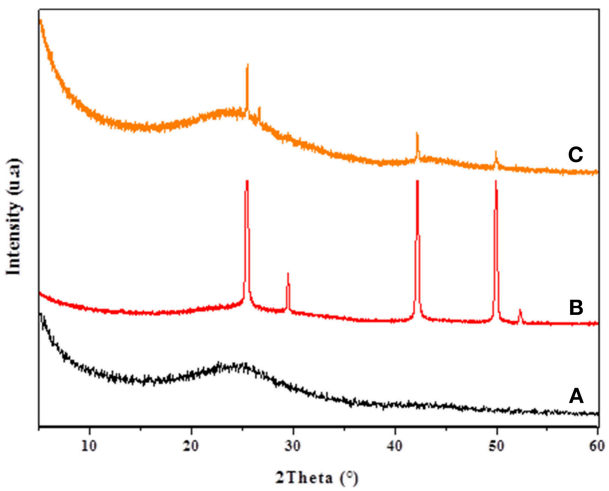


FIGURE 2 | XRD results of CC support **(A)**, Cu-CC material **(B)**, and phenylacetylene in Cu-CC **(C)**.

The XRD patterns of CC, CANS, Cu-CC, and Cu-CANS are presented in **Figures 1**, **2**. The obtained XRD patterns displayed the following diffraction peaks (2θ [°]): 25.5, 29.46, 42.19, and 49.91° for Cu-CANS, (**Figure 1**) which can be correlated to the (111), (200), (220), and (311) *hkl* indices, respectively, of CuI (JCPDS no. 06-0246). As shown in **Figure 2**, five peaks at 2θ = 25.47, 29.46, 42.34, 49.96, and 52.30° corresponding to the (111), (200), (220), (311), and (222) planes of CuI (JCPDS no. 06-0246) were observed in the pattern of the Cu-CC composite,

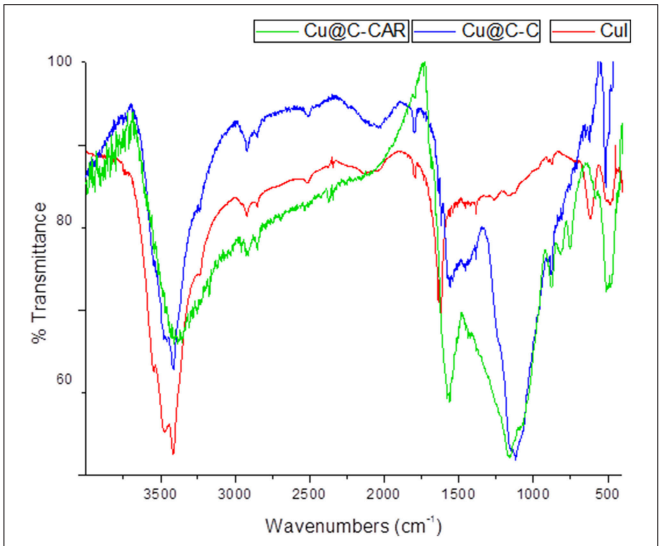


FIGURE 3 | Comparative FT-IR spectra of CuI precursor (red), Cu-CC (blue), and Cu-CANS material (green).

indicating that CuI has been successfully loaded on the carbons. The average crystallite size D of the nanoparticles is calculated from the Scherrer equation: $D = K\lambda/(\beta\cos\theta)$, where K is the Debye-Scherrer constant (0.9), λ is the X-ray wavelength, β FWHM (full-width at half-maximum or half width) is in radians, and θ is the Bragg diffraction angle. Here, the (111) peak of the highest intensity was picked out to evaluate the particle diameter of CuI. The values of the D constants were calculated to be about 18.81 and 26.15 nm for nm for Cu-CC and Cu-CANS, respectively.

Infrared spectroscopy is one of the most widely used techniques in heterogeneous catalysis to characterize and identify the purity of solids by the presence of characteristic bands of extraneous compounds. Comparison between FT-IR spectrum of copper particles on activated carbon with that of copper iodide and with the carbon support reveals the appearance of weak absorption bands at 496 cm^{-1} (**Figure 3**). This is related to the supported copper particles on activated carbon. Furthermore, the change observed in the absorption peaks of the carbonyl group from 1654.7 to 1650.4 and 1561.4 to 1557 cm^{-1} is related to the coordination of oxygen atoms (acetate and phosphate) to copper metal ions (Samim et al., 2007; Ghouma et al., 2017). The presence of oxygen atoms (phosphate-containing groups) may afford the assembly of polynuclear copper ions in the carbon support because of the known bridging ability of the phosphate groups (Ikotun et al., 2010).

We used the scanning electron microscopy (SEM) to study and visualize the morphology of the surface before and after the immobilization of copper on activated carbons. The SEM images of activated carbons and catalysts clearly reveal the presence of different size pores on the raw activated carbons and showed that both catalysts have the same shape and contain a mosaic of copper particles of different sizes and morphologies (**Figure 4**). The energy dispersive X-ray

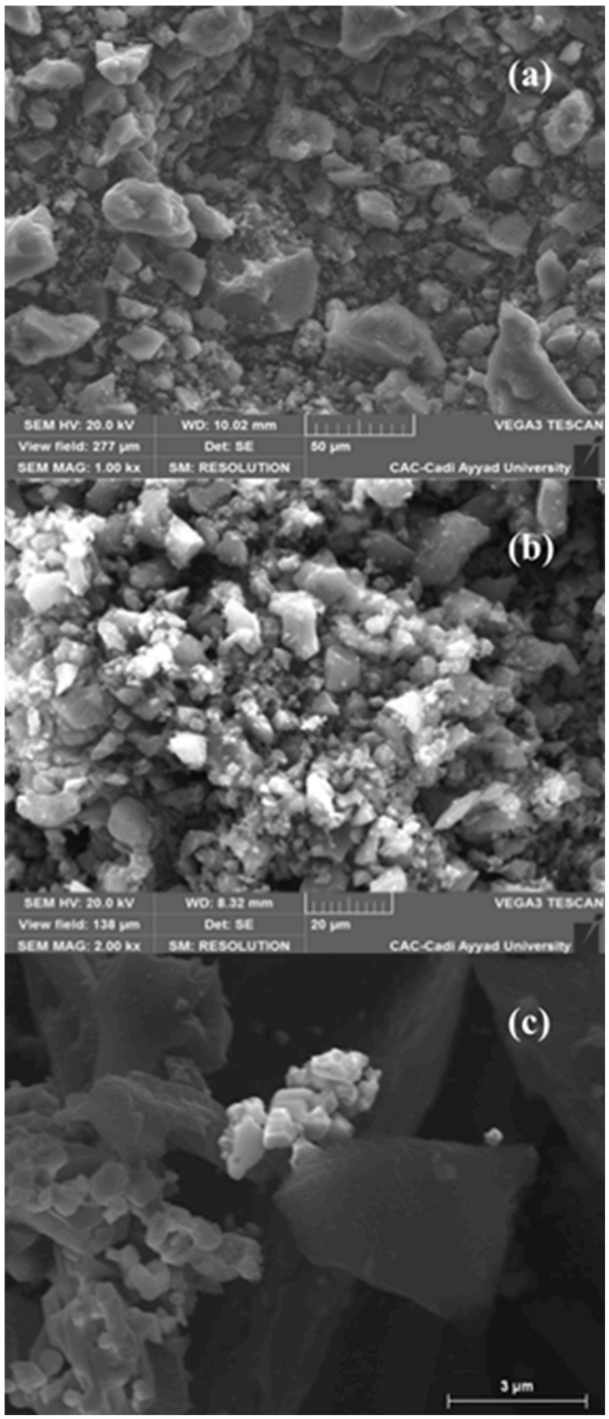


FIGURE 4 | SEM images of CANS support **(a)**, Cu-CANS **(b)**, and Cu-CC material **(c)**.

(EDX) results obtained from the SEM analysis for the CANS, and Cu-CANS showed the presence of C, O, Al and P atoms for the former and C, Cu, and P atoms for the latter (**Figure 5**).

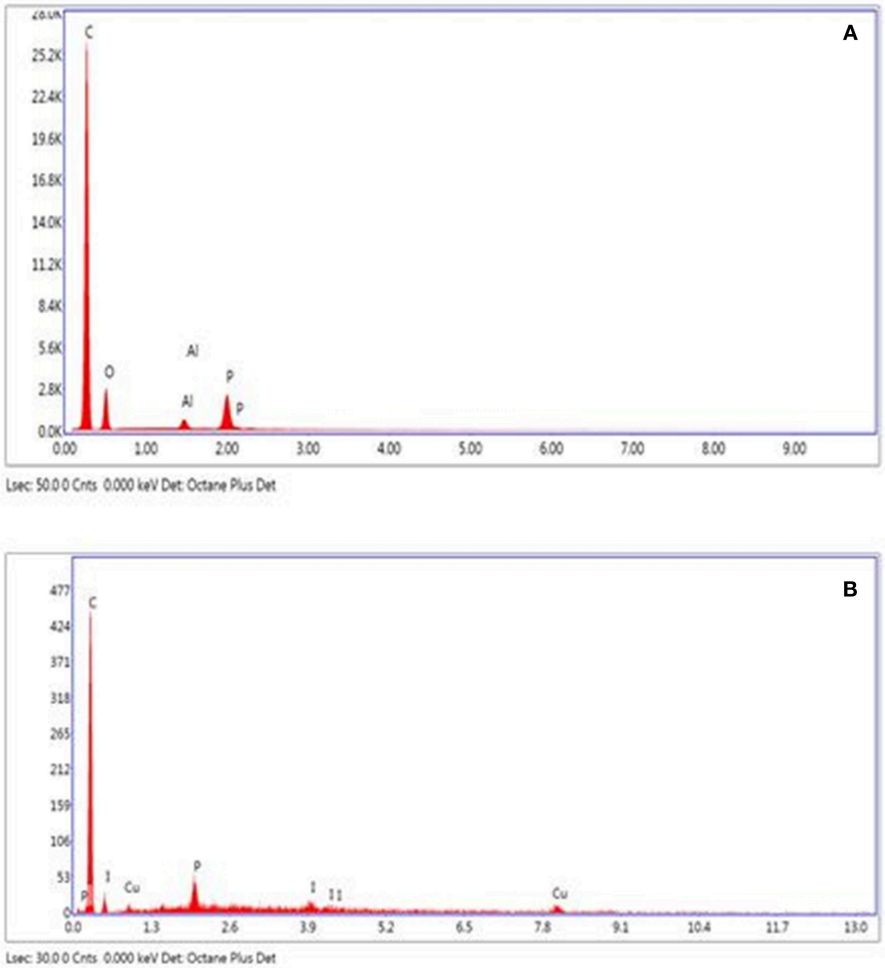


FIGURE 5 | EDX spectrum of **(A)** CANS and **(B)** Cu-CANS catalyst.

The copper contents in the carbon materials were determined by AAS analysis and found to be 1.38 wt% of Cu for Cu-CANS and 3.82 wt% of Cu for Cu-CC. Thus, 100 mg of carbon composite contains 2.18 mol% of copper for Cu-CANS and 6.01 mol% of copper for Cu-CC. The low copper loadings in Cu-CANS compared with Cu-CC can be explained by their respective preparation method and the functionalizing groups that may coordinate to the copper ions in the carbon material.

Adsorption Isotherms

The equilibrium adsorption isotherms are very important for understanding the mechanism of the CuI adsorption on both activated carbons investigated. The adsorption data were analyzed with the help of the following linear forms of Freundlich and Langmuir isotherms.

The Langmuir isotherm is valid for monolayer adsorption on surface containing a finite number of identical sites (Langmuir, 1916). The linear form of the Langmuir isotherm can be represented by the following equation:

$$\frac{C_e}{q_e} = \frac{1}{\overline{q}_m K_L} + \frac{1}{q_m} C_e$$

where C_e (mg/L) represents the equilibrium concentration of the adsorbate, q_e is the amount adsorbed at equilibrium (mg/g), and K_L (L/mg) and q_m (mg/g) stand for the Langmuir constant and the maximum amount of adsorbate, respectively.

The Freundlich isotherm model is an empirical equation based on sorption on a heterogeneous surface or surface supporting sites of varied affinities (Freundlich, 1906). The linearized Freundlich model is represented by the following equation:

$$\log\left(q_e\right) = \log\left(K_f\right) + \frac{1}{n}\log\left(C_e\right)$$

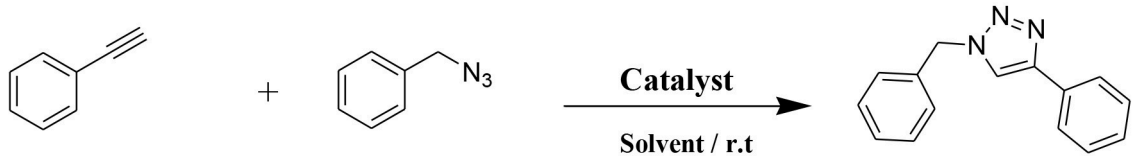
where K_f (mg/g) is the Freundlich constants related to the sorption capacity and n is the heterogeneity factor.

As shown in **Table 2**, the comparison of the Freundlich and Langmuir models, reveals that the values of the correlation

TABLE 2 | Isotherm constants for adsorption of CuI on CANS and CC activated carbons.

Isotherm model	Langmuir			Freundlich		
	q_{max}	K_L	R^2	K_F	n	R^2
CANS	1,250	0.003	0.86	7.58	1.29	0.98
CC	0.63	0.037	0.90	1.05	1.09	0.95

TABLE 3 | Catalyst and conditions screening for the cycloaddition of benzyl azide and phenylacetylene[a].



alkyne (**1a**) azide (**2a**) 1,4-isomer

Entry	Catalyst	Cat. loading (mol %)	Solvent	Time (h)	Yield (%)[b]
1	–	–	Water	24	0
2	CC	–	Water	24	0
3	CuCl-CC	5	Water	6	66
4	CuBr-CC	5	Water	6	74
5	CuI-CC	3	Water	6	99
6	CuI-CC	2	Water	6	98
7	CuI-CC	0.5	Water	6	77
8	CuI-CC	0.1	Water	6	74
9	CuI-CC	5	Ethanol	6	85
10	CuI-CC	5	Methanol	6	74
11	CuI-CC	5	Toluene	6	80
12	CuI-CC	5	Acetonitrile	6	98
13	CuI-CC	5	Hexane	6	35

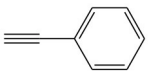
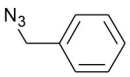
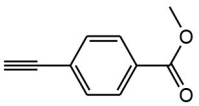
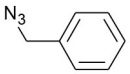
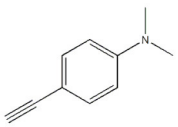
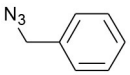
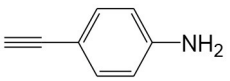
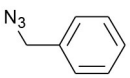
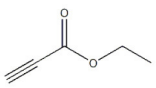
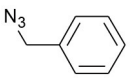
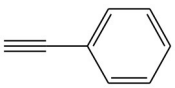
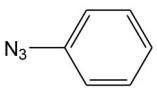
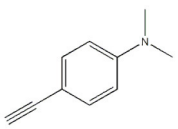
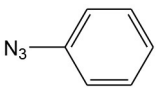
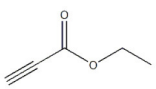
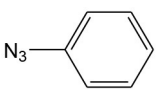
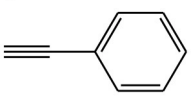
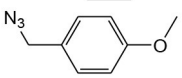
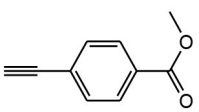
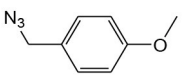
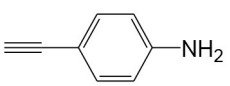
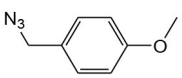
[a] *Reaction conditions: benzylazide (0.75 mmol); phenylacetylene (0.62 mmol); solvent (5 mL); and catalyst were mixed and stirred at room temperature.*
[b] *Isolated yields.*

coefficient of the Freundlish isotherm ($R^2 = 0.98$ and 0.95) are high for both activated carbons. This result suggests that the CuI was heterogeneously adsorbed on a multilayer surface and the values found for n were >1, a feature which proves that the adsorption on both adsorbents is favorable.

Catalytic Activity of the Cu-Carbon Catalytic System in the Synthesis of 1,2,3–Triazole Derivatives

In order to explore the catalytic activity of the synthesized catalysts and to optimize the reaction conditions for the [3+2] cycloaddition, the reaction between benzyl azide and phenylacetylene was chosen as a model [3+2] cycloaddition reaction. As starting point, different reaction conditions such as copper sources, solvent, and amount of catalyst were investigated (see **Table 3**). The control experiments show that the [3+2] cycloaddition reaction azide-alkyne does not take place in the absence of the catalyst (entries 1–3, **Table 3**). Moreover, the effect of copper(I) sources supported within the pores of both CC and CANS was examined (entries 4–6, **Table 3**). In fact, the results shown in **Table 3** confirm the recently established catalytic activity trend found in CuAAC assisted by several N-heterocylic carbene copper(I) complexes, namely [(NHC)CuX] [NHC = *N*-Heterocycle carbene; X = I, Cl, Br]: [CuI(NHC)] > [CuBr(NHC)] > [CuCl(NHC)] (Díez-Gonzalez et al., 2010). Our results show that among the studied Cu(I)-carbon catalysts, CuI-CC and CuI-CANS are the most efficient ones for the 1,2,3-triazole click reactions performed under strict click chemistry conditions, specifically by using water as solvent and working at room (entries 4–6, **Table 3**). Having identified the CuI-CC and CuI-CANS as efficient catalytic systems for the reactions; we then explored the effect of the catalyst amount on the conversion yields and the catalyst loading being enhanced from 0.1 to 3 mol%. As a result, the conversion yields were increased from 70 to 99 % by the increasing of catalyst amount (entries 6–8, **Table 3**). However, no elevated conversion yields were observed once the catalyst amount becomes greater than 3 mol%. Consequently, in both Cu(I)-CC and Cu(I)-CANS catalysts, a catalyst loading of 0.5 mol% appears to be optimal with respect to excellent yields

TABLE 4 | Cycloaddition of azides and alkynes catalyzed by copper-carbon catalysts[a].

Entry	Alkyne	Azide	Product	Catalyst	Yield[b] (%)	TON[c]	TOF[d]
1			**3a**	Cu-CC	77	154	25.66
				Cu-CANS	95	190	31.66
2			**3b**	Cu-CC	60	132	22.00
				Cu-CANS	88	176	29.33
3			**3c**	Cu-CC	91	182	30.33
				Cu-CANS	89	178	29.66
4			**3d**	Cu-CC	71	142	23.00
				Cu-CANS	92	184	30.66
5			**3e**	Cu-CC	76	152	25.33
				Cu-CANS	95	190	31.66
6			**3f**	Cu-CC	75	150	25.00
				Cu-CANS	94	188	31.33
7			**3g**	Cu-CC	76	152	25.33
				Cu-CANS	87	122	20.33
8			**3h**	Cu-CC	61	182	30.33
				Cu-CANS	73	146	24.33
9			**3i**	Cu-CC	76	152	25.33
				Cu-CANS	96	192	32.00
10			**3j**	Cu-CC	74	148	24.66
				Cu-CANS	80	160	26.66
11			**3k**	Cu-CC	76	152	25.33
				Cu-CANS	78	156	26.00

[a] *Reaction conditions: azide (0.75 mmol); alkyne (0.62 mmol); water (5 mL); catalyst (0.005 equivalent) mixed at room temperature.*
[b] *Isolated yields.*
[c] *TON, Turnovers number (moles substrate/moles of catalyst).*
[d] *TOF, Turnover frequency (TON/time of reaction).*

and short reaction times. Furthermore, the catalytic reaction was performed in different organic solvents, as shown in **Table 3**. We found that the catalytic conversion yields in water and acetonitrile were higher than those in other organic solvents, such as ethanol, methanol, toluene and hexane (entries 8–12, **Table 3**). As a matter of consequence, water known as a benign and inexpensive solvent, was then used as the solvent of choice.

After optimizing the reaction conditions, in order to explore the scope and generality of this protocol, several alkynes such as para-substituted aryl alkyne derivatives and activated alkyne with azides such as para-substituted benzyl and phenyl azides were used as substrates for the synthesis of 1,4-disubstituted-1,2,3-triazoles. The results are given in **Table 4**. They show that the reactions are equally facile with both electron-donating and electron-withdrawing substituents present on the aryl alkynes and benzyl azides, as most of the reactions were completed within 6 h, resulting one regioisomer in good to high yields of the corresponding 1,4-disubstituted-1,2,3-triazole (see **Table 4**). These 1,2,3-triazoles were obtained in good turnover numbers ranging from 122 to 196. All the synthesized triazole

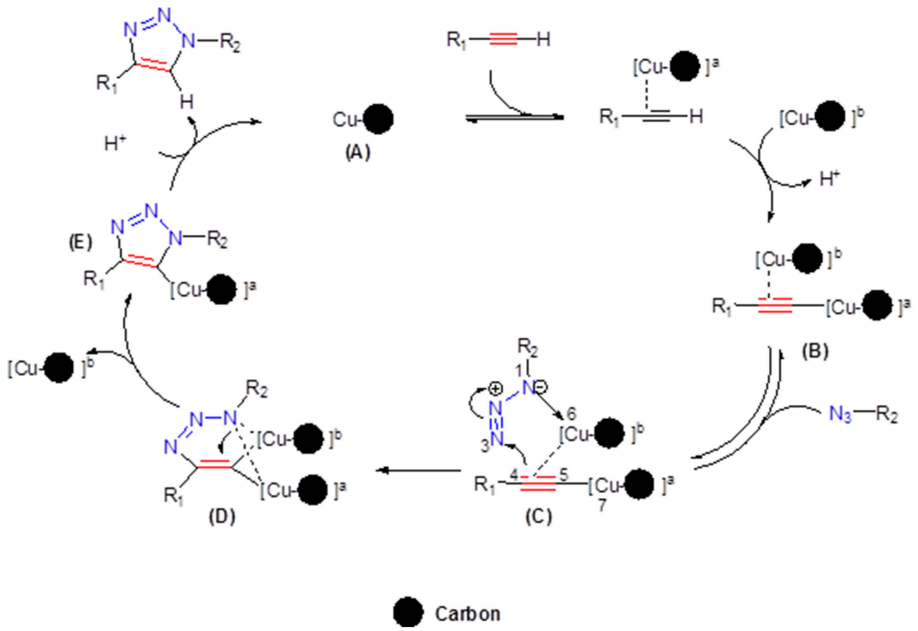


FIGURE 6 | The proposed mechanism for the formation of 1-4-disubstituted-1,2,3-triazoles catalyzed by Cu/carbon.

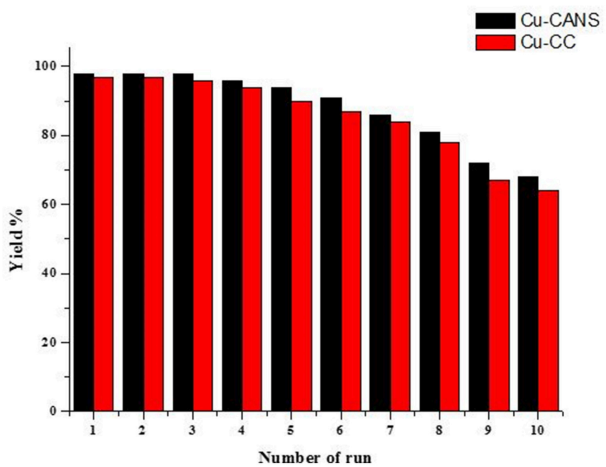


FIGURE 7 | Recycling results of the Cu-CC and Cu-CANS catalytic systems in the copper-catalyzed cycloaddition reaction of phenylacetylene and benzyl azide.

TABLE 5 | Loadings of copper in each 100 mg of copper-carbon catalyst.

Catalyst	Copper loading (wt%)		
	Before reaction	After the first cycle	After the eighth cycle
Cu-CC	3.82	3.65	0.82
Cu-CANS	1.38	1.09	0.58

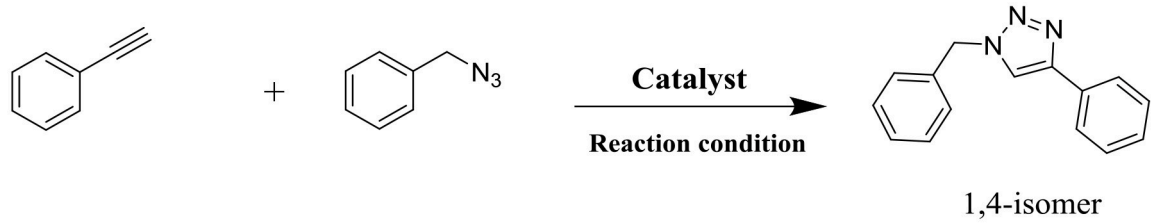
derivatives were characterized by NMR spectroscopy and HRMS analysis (see **Supplementary Material**).

On the basis of our previous reports (Ben El Ayouchia et al., 2018), a stepwise mechanism of CuAAC is outlined in **Figure 6**. The electron density of the alkyne in the proposed mechanism is reduced by the copper(I) ion stabilized in pore of the carbon support (**A**) forming the dinuclear copper-acetylide (**B**), enabling a facile nucleophilic attack by the organoazide, and then resulting in the corresponding complex (**C**). The next step consists of a nucleophilic attack at N3 of the organoazide by the acetylide carbon C4 forming the first covalent C—N bond and then producing the intermediate (**D**). The ring contraction of D leads to the formation of the triazolyl-copper (**E**). The last step corresponds to a fast protonation of the copper triazolide, releasing the final 1,2,3-triazole product as 1,4-regioisomer.

Stability and Recycling of the Copper-Carbon Catalyst

Generally copper(I) catalysts are unstable and can readily oxidize to copper(II). However, it is legitimate to question also the stability of Cu-carbon entities as reagents in organic reactions. The conservation of the copper(I)-carbon catalysts under non-inert conditions (under air), did not cause any change in their external aspects and it has been observed, unexpectedly, that after 1 year nothing has been lost of their activities. This heterogeneous catalytic system offers easy manipulation and separation by simple filtration, thus facilitating the recycling of the copper-carbon catalysts. The recyclability of copper-carbon was tested in the model cycloaddition reaction of phenylacetylene and benzyl azide (**Figure 7**). After completion of the cycloaddition reaction

TABLE 6 | Comparison of the catalytic activity of cooper-carbon catalysts with others heterogeneous copper-based catalytic systems.



1,4-isomer

Entry	Catalyst	Time (h)	Cat. loading (mol %)	Temperature/solvent	Number of cycle	Yield (%)	Reference
1	Cu-CC	6	1	r.t./water	10	98	This work
2	Cu-CANS	6	1	r.t./water	10	98	
3	Cu/C	48	10	23°C/dioxane	–	65	Lipshutz and Taft, 2006
4	Cu_2O/C	2	5	r.t./i-PrOH:H_2O	3	82	López-Ruiz et al., 2012
5	TRGO/Cu	48	2	40°C/THF	4	99	Shaygan Nia et al., 2014
6	Cu-Alginate	18	21	r.t./water	3	98	Rajender Reddy et al., 2007
7	Cu-Chitosan	6	10	r.t./water	5	90	Anil Kumar et al., 2015
8	Cu-Hydroxyappatite	16	5	50°C/water	8	95	Masuyama et al., 2011
9	Cu-zeolite	15	10	r.t./toluene	5	83	Chassaing et al., 2007

in water at room temperature, the catalyst was recovered by simple filtration and reused after washing with diethyl ether and drying in the air. The catalyst was reused directly for the next run under the same conditions. This process was performed until 10 times without any significant loss of efficiency and selectivity of the Cu-carbon as shown by the catalytic histogram in **Figure 7**.

The percentages of the copper contents of the fresh and recycled Cu-CC and Cu-CANS after the first and the eight consecutive trial were determined by AAS analysis. The AAS results shown in **Table 5** indicate that the weight percentage of the copper contents of the recycled catalysts after the first cycles is around 3.65 wt% for Cu-CC and 1.01 wt% for Cu-CANS, values which are lower than those of the fresh catalyst, 3.82 and 1.38 wt%, respectively. After the eight catalytic trial, the percentages of the copper content were found to be around 0.82 wt% for Cu-CC and 0.58 wt% for Cu-CANS. The decrease of the 1,2,3-triazole products yields is caused by the loss of the catalytically active species copper(I) during the work-up processes.

Comparison of the Copper-Carbon Catalysts With Other Heterogeneous Catalysts Containing Copper Particles

In principle, any efficient prepared catalytic system is expected be superior to the commercially available catalysts used for the same purpose. Taking into account this principle, it seemed important to compare also the catalytic activity of the copper(I)-carbon with that of other copper-containing heterogeneous catalysts among the most active known for this type of cycloaddition reaction such as Cu-charcoal, Cu_2O-C, copper-graphene, copper-alginate, copper-chitine, copper-hydroxyappatite, copper-argile, and copper-resin (**Table 6**). The series of catalysts used proved to be effective since the product was obtained with excellent yields in all the cases. However, the total conversion of the substrates was possible only after 15–18 h of reaction, proving the lower reactivity of these catalysts in this type of reaction. Remarkably, the Cu-CANS and Cu-CC catalysts have a higher activity, allowing the formation of the desired product using only 0.5 mol% during 6 h of reaction. In addition, this catalytic system has many advantages: it is robust, inexpensive, readily available, non-toxic, and has no sensitivity to humidity or air.

CONCLUSIONS

In summary, we have successfully developed a highly efficient and recyclable inexpensive copper on carbon heterogeneous catalyst for the regioselective construction of 1,4-disubstituted 1,2,3-triazoles by the [3+2] cycloaddition reactions of azides with alkynes under very strict click chemistry conditions with a sustainable fashion. The copper on carbon Cu-CANS was readily prepared by the copper(I) impregnation of carbon material that has been made from a naturally raw vegetable biomass. A wide range of azides and alkynes can be combined to form the important biologically active 1,2,3-triazoles by using Cu-CANS in water as solvent at room temperature. Cu-CANS was recycled and reused for several catalytic trials without noticeable loss of its catalytic activity. The use of benign water as solvent at room temperature makes the entire catalytic protocol an environmental friendly one.

AUTHOR CONTRIBUTIONS

S-ES and HB designed the project and supervised the synthetic and characterization chemistry works. NA and LB undertook all the synthetic experimental works and characterizations of the copper on carbon material catalysts. EE and SR carried out the synthesis of the natural carbon material originated from vegetable biomass using *Argan nut shells* (CANS). SR performed the characterization of the carbon precursor material CANS. S-ES, HB, MJ, SR, and HA contributed to the writing of the manuscript and interpretation of the results. MJ supplied the funding for the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2019.00081/full#supplementary-material

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ORIGINAL RESEARCH
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Continuous Flow Synthesis of High Valuable N-Heterocycles via Catalytic Conversion of Levulinic Acid

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Graphitic carbon nitride (g-C_3N_4) was successfully functionalized with a low platinum loading to give rise to an effective and stable catalytic material. The synthesized g-C_3N_4/Pt was fully characterized by XRD, N_2 physisorption, XPS, SEM-Mapping, and TEM techniques. Remarkably, XPS analysis revealed that Pt was in a dominant metallic state. In addition, XPS together with XRD and N_2 physisorption measurements indicated that the g-C_3N_4 preserves its native structure after the platinum deposition process. g-C_3N_4/Pt was applied to the catalytic conversion of levulinic acid to N-heterocycles under continuous flow conditions. Reaction parameters (temperature, pressure, and concentration of levulinic acid) were studied using 3 levels for each parameter, and the best conditions were employed for the analysis of the catalyst's stability. The catalytic system displayed high selectivity to 1-ethyl-5-methylpyrrolidin-2-one and outstanding stability after 3 h of reaction.

Keywords: N-heterocycles, heterogeneous catalysis, graphitic carbon nitride, continuous flow, platinum, Levulinic acid

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INTRODUCTION

Biomass has emerged as a competitive alternative for the generation of highly sustainable fuels, chemicals, and drugs (Tuck et al., 2012; Sankaranarayanapillai et al., 2015; Ruppert et al., 2016; Hu et al., 2017; Tang et al., 2017; Filiciotto et al., 2018; Kucherov et al., 2018; Xu W. et al., 2018). A useful strategy for converting biomass feedstocks into fuels and chemicals is based on the transformation of platform molecules, which exhibit high functionality, to form added-value compounds (Serrano-Ruiz et al., 2011; Verma et al., 2017). In this direction, levulinic acid (LA) is a well-known platform molecule that has been widely used toward the fabrication of several valuable compounds such as γ-valerolactone (GVL), which represent a promising fuel source, levulinate esters, which are viable additives for gasoline and diesel transportation fuels, and pyrrolidones, which are involved in industry as surfactants, intermediates for pharmaceuticals, dispersants in fuel additive compositions, solvents and agrochemicals (Huang et al., 2011; Bermudez et al., 2013; Colmenares and Luque, 2014; Touchy et al., 2014; Chatzidimitriou and Bond, 2015; Yan et al., 2015; Ruppert et al., 2016; Gao et al., 2017; Sun et al., 2017; Xu C. et al., 2018).

In the last years, the use of heterogeneous catalysts for the valorization of LA into useful compounds, especially pyrrolidones, has been widely applied (Du et al., 2011; Ogiwara et al., 2016). For instance, the reductive amination of LA with amines in liquid phase has been described using precious metals such as Au, Pd, Pt, Ru, In, and Ir, supported on carbon or metal oxides owing

to their large portfolio of versatile applications (Du et al., 2011; Chatzidimitriou and Bond, 2015; Ogiwara et al., 2016; Zhang et al., 2017). Additionally, a number of endeavors have been made to synthesize novel materials with desirable catalytic properties in order to improve the efficiency of the LA catalytic upgrading toward the production of pyrrolidones (Gao et al., 2017; Sun et al., 2017; Wu et al., 2017). Ultimately, innovative advancements on the design of active and stable heterogeneous catalysts composed of carbon-based materials have been proposed. Zheming Sun et al. have reported a new class of solid molecular N-heterocyclic carbon (NHC) catalysts for the solvent-free reductive amination of biomass-derived levulinic acid to obtain a large variety of interesting structural configurations of *N*-substituted pyrrolidones (Sun et al., 2017). In this regard, NHC-Ru polymer showed high catalytic performance and remarkable reusability, allowing the development of one-pot tandem reductive reactions of LA with aldehydes or ketones.

Graphitic carbon nitride, generally known as g-C_3N_4, is recognized as the most stable allotrope among various carbon nitrides under ambient conditions. The surface chemistry of its polymeric structure can be easily controlled via molecular-level modification and surface engineering. Additionally, the polymeric nature of g-C_3N_4 guarantees sufficient flexibility of the structure, which can serve as a compatible matrix for the anchorage of various inorganic nanoparticles and consequently can be successfully applied in a myriad of photocatalytic applications (Muñoz-Batista et al., 2015b, 2016, 2018; Xue et al., 2015; Fontelles-Carceller et al., 2016; Sastre et al., 2016; Zeng et al., 2017; Hak et al., 2018; Majeed et al., 2018). Despite the mentioned applications, graphitic carbon nitride-based materials have not been broadly employed toward the catalytic valorization of biomass-derived chemicals. A representative example in which an organic sulfonated graphitic carbon nitride was used for conversion of carbohydrates into furanics and related value-added products can be highlighted (Verma et al., 2017).

We report herein the reductive amination of levulinic acid into highly valuable pyrrolidones driven by g-C_3N_4/Pt composites as a competitive catalyst. The catalytic processes were performed under flow conditions which ensure high control over reaction conditions, fast and effective reagent mixing and shorter times of reactions (Bermudez et al., 2013; Chen et al., 2015; Gemoets et al., 2016; Muñoz-Batista et al., 2018).

EXPERIMENTAL

Materials

All chemicals were obtained from Sigma–Aldrich with pure analytical degree.

Synthesis of g-C_3N_4/Pt Composites

The graphitic carbon nitride was obtained by calcination of melamine in a semi-closed system at 580°C for 4 h using a heating rate of 5°C min^{-1}. In order to improve its superficial area, the obtained bulk g-C_3N_4 was treated by ultrasonication for 5 h in deionized water using 1 mg mL^{-1}. The platinum component was deposited using a simple chemical reduction method. The g-C_3N_4 support was suspended by stirring in deionized water solution for 30 min. Then, the proper quantity of H_2PtCl_6 was added to the solution to get 1 wt.% of Pt on metal basis and kept under stirring for 15 min. Finally, a hydrazine aqueous solution was quickly added, where the molar ratio between Pt and hydrazine was fixed to 1:5. The resulting mixture was stirred for 30 min and separated by filtration. The separated solid was rinsed with distilled water and dried at 80°C for 16 h. The Pt loading in the sample was 1 wt.%, confirmed by ICP-MS analysis in an Elan DRC-e (PerkinElmer SCIEX) spectrometer.

Catalyst Characterization

XRD experiments were performed in the Bruker D8 Advance Diffractometer with the LynxEye detector. The XRD patterns were recorded in a 2θ scan range from 10 to 80°. Phase identification was carried out using Bruker Diffrac-plus Eva software, supported by the Power Diffraction File Database. N_2 physisorption experiments were accomplished with the Micromeritics ASAP 2000 instrument. The sample was previously degassed for 24 h under vacuum ($p < 10^{-2}$ Pa). Moreover, TEM images were recorded in the JEOL JEM 1400 instrument and assembled with a charge-coupling camera device. Samples were previously suspended in ethanol and deposited on a copper grid. SEM-EDX micrographs were acquired in the JEOL-SEM JSM-7800 LV scanning microscope. XPS measurements were accomplished with an ultrahigh vacuum multipurpose surface analysis instrument, SpecsTM. Prior to the analysis, the sample was evacuated overnight under vacuum (10^{-6} Torr). XPS spectra were acquired at room temperature using a conventional X-ray source with a Phoibos 150-MCD energy detector. XPS CASA software was employed to analyze the obtained results.

Catalytic Experiments

Catalytic performance of the obtained catalytic materials was evaluated in the H-Cube Mini Plus™ flow hydrogenation

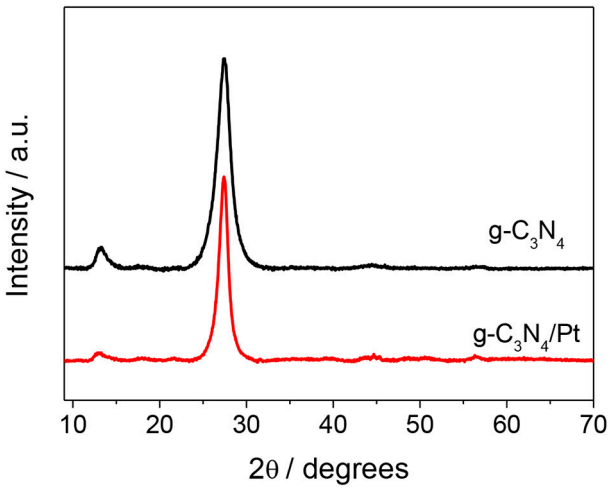


FIGURE 1 | XRD patterns of g-C_3N_4/Pt sample and g-C_3N_4 reference.

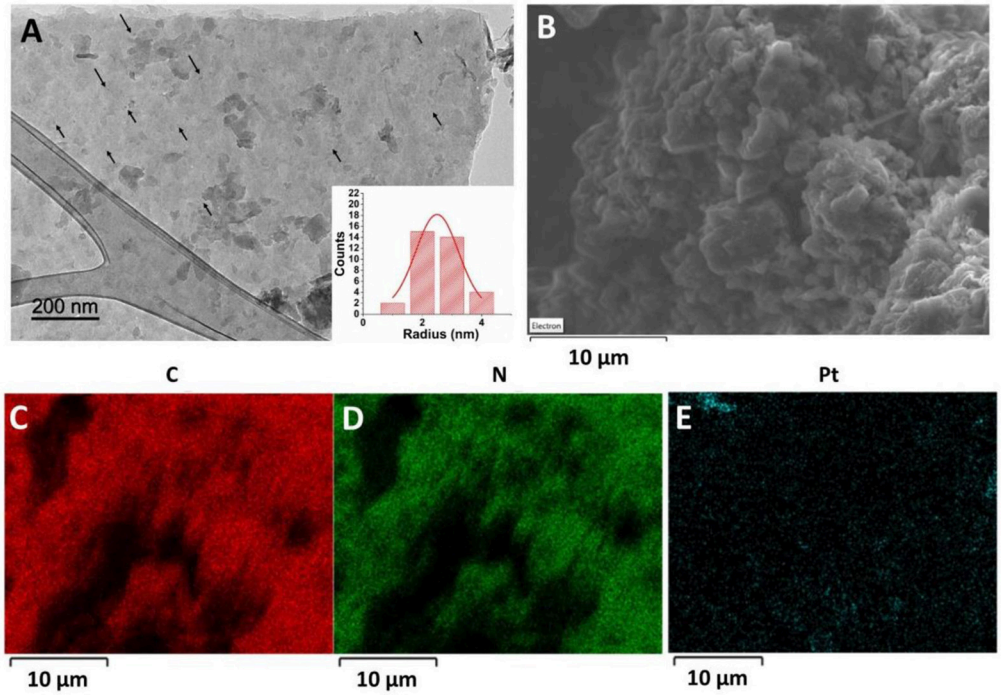


FIGURE 2 | (A) TEM image of g-C_3N_4/Pt (Inset: size distribution of Pt nanoparticles), **(B)** SEM image of g-C_3N_4/Pt, SEM-mapping micrograph of g-C_3N_4/Pt for **(C)** carbon, **(D)** nitrogen, and **(E)** platinum.

TABLE 1 | Morphological properties of g-C_3N_4/Pt sample and g-C_3N_4 reference.

Sample	BET surface area (m^2 g^{-1})	Pore volume (cm^3 g^{-1})	Pore size (nm)	Pt particle size (nm)
g-C_3N_4	58	0.2	15.7	–
g-C_3N_4/Pt	54	0.2	15.8	2.5

reactor. The catalysts were packed (ca. 0.1 g of catalyst per cartridge) in 30 mm-long ThalesNano CatCarts. The system was firstly washed with (1) methanol and (2) acetonitrile (0.3 mL/min, 20 min for each solvent). A solution of levulinic acid in acetonitrile was subsequently pumped through and the reaction conditions were set. The required hydrogen was generated *in situ* during the reaction by water electrolysis in the H-Cube equipment. The reactions were followed for 120 min, where a stationary situation was reached, and the collected samples were analyzed by GC-MS.

The conversion, selectivity and stability achieved for the catalyst in the reaction were investigated by gas chromatography (GC) in an Agilent 6890N gas chromatograph (60 mL min^{-1} N_2 carrier flow, 20 psi column top head pressure) using a flame ionization detector (FID). The capillary column HP-5 (30 m × 0.32 mm × 0.25 mm) was employed. In addition, the collected liquid fractions were analyzed by GC-MS—using the Agilent 7820A GC/5977B High Efficiency Source (HES) MSD—in order to identify the obtained products.

RESULTS AND DISCUSSION

X-ray diffraction analysis was employed to identify the structure and arrangement of the synthesized graphitic carbon nitride as well as the platinum-modified sample. As shown in **Figure 1**, both samples presented the typical interlayer-stacking (002) reflection of disordered carbon in a graphitic g-C_3N_4 layered structure and a peak around 13.1°, associated to the (100) reflection (Muñoz-Batista et al., 2016). The position of the (002) plane also showed the typical shift (∼0.3), in comparison with the bulk counterpart, which can be related to the decrease of the interlayer distance, which takes place during the ultra-sonication process (Muñoz-Batista et al., 2017). As has been analyzed in previous reports, the limitation of the number of sheets stacked produces the weakening of interlayer forces with effect in the corrugation of the layers and the subsequent decrease of the corresponding distance between layers (Niu et al., 2012; Muñoz-Batista et al., 2017). The XRD pattern of g-C_3N_4/Pt has not displayed considerable changes in comparison with the unmodified material and therefore did not offer information about the Pt phases, most likely due to the relatively limited amount of the noble metal in the final material.

Morphology of the synthetized g-C_3N_4/Pt was studied by microscopy (TEM and SEM) analyses (**Figure 2**). g-C_3N_4/Pt exhibited a laminar structure, as can be observed in **Figure 2A**. TEM analyses also allowed the identification of small platinum nanoparticles with a mean diameter of 2.5 nm on the g-C_3N_4/Pt surface (**Table 1**). Importantly,

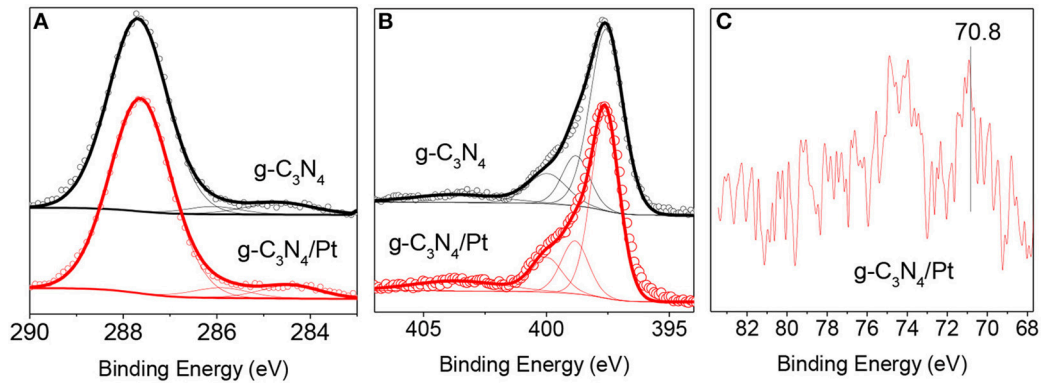


FIGURE 3 | High-resolution XPS spectra of **(A)** C1s, **(B)** N1s, and **(C)** Pt4f in g-C_3N_4/Pt sample and g-C_3N_4 reference.

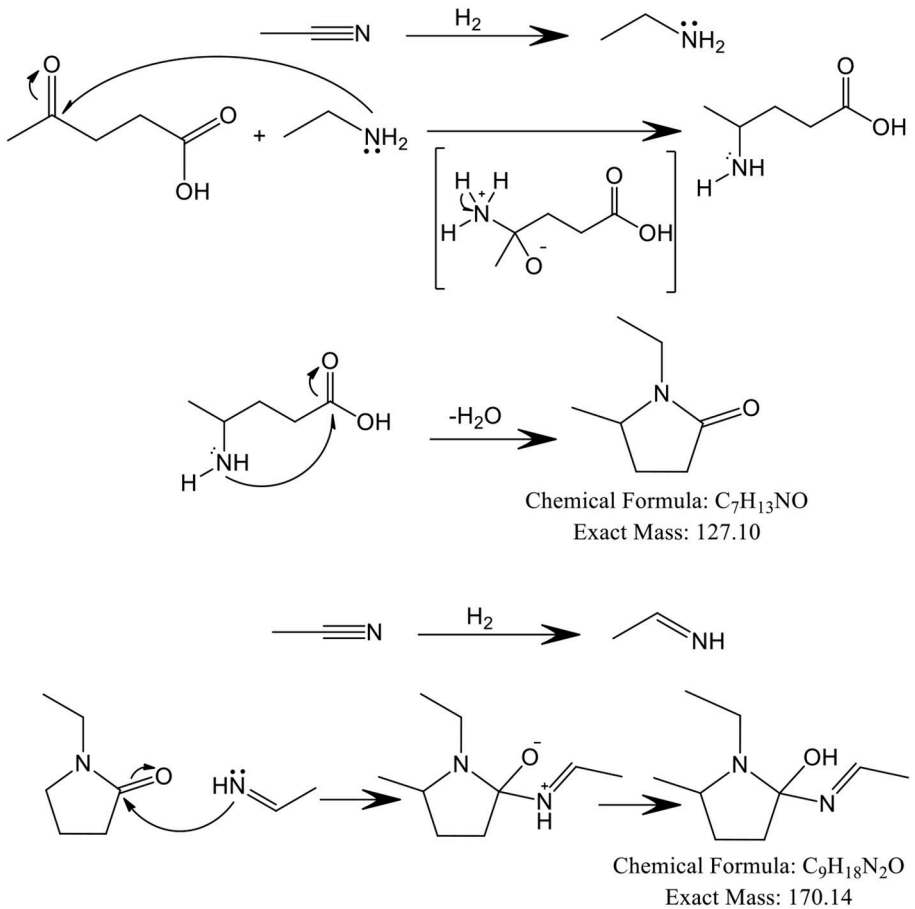
TABLE 2 | C1s and N1s XPS region fitting results of g-C_3N_4 and g-C_3N_4/Pt.

N1s								
Sample	**C-N-C**	**%**	**(C)3-N**	**%**	**N-H**	**%**	**Pi-exc.**	**%**
g-C_3N_4	397.5	58.5	399.2	24	400.5	12	403.4	5.5
g-C_3N_4/Pt	397.2	58	399.0	24	400.4	12.5	403.6	5.5
C1s								
Sample	**C-C**	**%**	**(C)3-N**	**%**	**C-N-C**	**%**		
g-C_3N_4	284.6	8	286.2	5	287.6	87		
g-C_3N_4/Pt	284.6	9	286.2	5.5	287.5	85.5		

EDX-mapping micrographs of g-C_3N_4/Pt also confirmed the successful functionalization of graphitic carbon nitride with platinum, which depicts a relative homogeneous distribution. As is summarized in **Table 1**, the Pt-modified material showed rather similar values to the pure g-C_3N_4 reference in all the parameters determined by N_2 physisorption (BET Surface area, pore volume, pore size). BET surface area above 50 m^2 g^{-1} and a dominant mesoporous structure could be originated from the void volume created by the agglomeration of the g-C_3N_4 sheets, allowing an efficient deposition of the metallic entities (**Table 1**).

The structural analysis of g-C_3N_4/Pt and g-C_3N_4 was completed with the help of X-ray photoelectron spectroscopy. XPS measurements were carried out in order to provide information related to the carbon, nitrogen, and platinum components. **Figure 3** shows the XPS spectra for the two catalytic systems, including C1s (**Figure 3A**), N1s (**Figure 3B**), and Pt4f (**Figure 3C**) regions. The summary of the N- and C-containing species contributing to the C1s and N1s peaks of the sample and g-C_3N_4 reference is presented in **Table 2**. The C1s XPS region showed contributions from C_3-N (∼286.2 eV), N-C-N (∼287.6 eV) and C-C (∼284.6 eV) (Muñoz-Batista et al., 2015a). C_3-N and N-C-N can be exclusively ascribable to g-C_3N_4 while C-C contribution, which was also used as reference, energy can be associated with surface residues or defects in the nanopolymer structure (Wanger et al., 1979). For the N1s XPS region, besides C_3-N (∼399.1 eV) and N-C-N (∼397.5 eV), two more contributions were used during the deconvolution procedure; N-H (∼400.4 eV) and the typical broad pi-exc (∼403.5 eV) (Muñoz-Batista et al., 2015a). In conclusion, **Figures 3A,B** as well as the data of **Table 2** provide evidence of the strong similitude detected between the pure g-C_3N_4 and Pt/g-C_3N_4 samples. XPS also allowed the detection of minority components in the structure, namely Pt nanoparticles. Although the signal-to-noise ratio of the Pt XPS region (**Figure 3C**) is relatively low, the shape of the Pt4f is indicative of a dominant metallic state (∼71 eV) (Fontelles-Carceller et al., 2017).

The catalytic performance of the prepared materials was evaluated in the conversion of levulinic acid to nitrogen-heterocycles under continuous flow conditions. N-heterocycles were obtained via condensation of levulinic acid, an 1,4-dicarbonyl compound, with an excess of ethylamine (**Scheme 1**) (Li, 2014). In this case, acetonitrile acts both as solvent and reactant, giving rise to ethylamine by *in situ* hydrogenation. The cyclization step involves a nucleophilic addition on a carbonyl group by the nitrogen of an intermediate. Levulinic acid acts as an electrophile both in the initial step of the reaction with the amine and in the cyclization step. After formation of the cyclic compound, the reaction proceeded via alcohol dehydration to produce the corresponding alkene. The hydroxyl (OH) group donates two electrons to H^+, generating an alkylloxonium ion, which can act as a good leaving group. The formed alkene is effectively hydrogenated under hydrogen pressure to give rise to 1-ethyl-5-methylpyrrolidin-2-one, $C_7H_{13}NO$ (127.10 g/mol).



SCHEME 1 | Proposed mechanism for the conversion of levulinic acid to N-heterocycles.

In addition, the formation of 1-ethyl-2-(ethylideneamino)-5-methylpyrrolidin-2-ol, $C_9H_{18}N_2O$ (170.14 g/mol) can be understood if we take into account that hydrogenation of acetonitrile did not just give rise to ethylamine but also to ethanimine, which can further attack the carbonyl group of 1-ethyl-5-methylpyrrolidin-2-one with the consequential formation of 1-ethyl-2-(ethylideneamino)-5-methylpyrrolidin-2-ol.

Firstly, a complete parametric analysis was accomplished in order to optimize the reaction conditions. In this regard, three levels of temperature, pressure and concentration were explored in the reaction of levulinic acid to N-heterocycles for 120 min (**Figure 4**). Carbon balance was achieved above 97% in all catalytic tests. Influence of the concentration in conversion and selectivity values was unraveled, as shown in **Figure 4A**. 0.3 mol/L was selected as the optimum concentration for the employed catalytic system. Although a lower concentration (0.1 mol/L) resulted in higher selectivity to 1 ethyl-5-methylpyrrolidin-2-one and the 0.5 mol/L concentration showed similar selectivity values, 0.3 mol/L gave rise to the best balance between conversion and selectivity.

The effect of temperature in the catalytic performance has been investigated by performing the reaction at 80, 90, and 100°C (**Figure 4B**). Additionally, influence of the system pressure was evaluated by accomplishing the reaction at 40, 50, and 60 bars (**Figure 4C**). In both cases an increment of the conversion and a decrease of the selectivity (1-ethyl-5-methylpyrrolidin-2-one) was observed for higher pressure and temperature values. Although 60 bars and 100° C conditions showed similar catalytic performance, 50 bars and 90° C were selected as the optimum pressure and temperature due to the good balance in conversion and selectivity, avoiding higher energy consumption reaction parameters. In addition, blank measurements were performed without a catalyst or employing g-C_3N_4, revealing that the reaction does not proceed in absence of an effective catalytic system.

Once the reaction parameters were optimized, the stability of the prepared catalytic system was investigated by performing the reaction for 3 h. After obtaining a stationary state (typically obtained after 120 min of reaction), a conversion of 36.8% employing g-C_3N_4/Pt was achieved. **Figure 5** shows details of the flow catalytic process in terms of conversion and selectivity. The

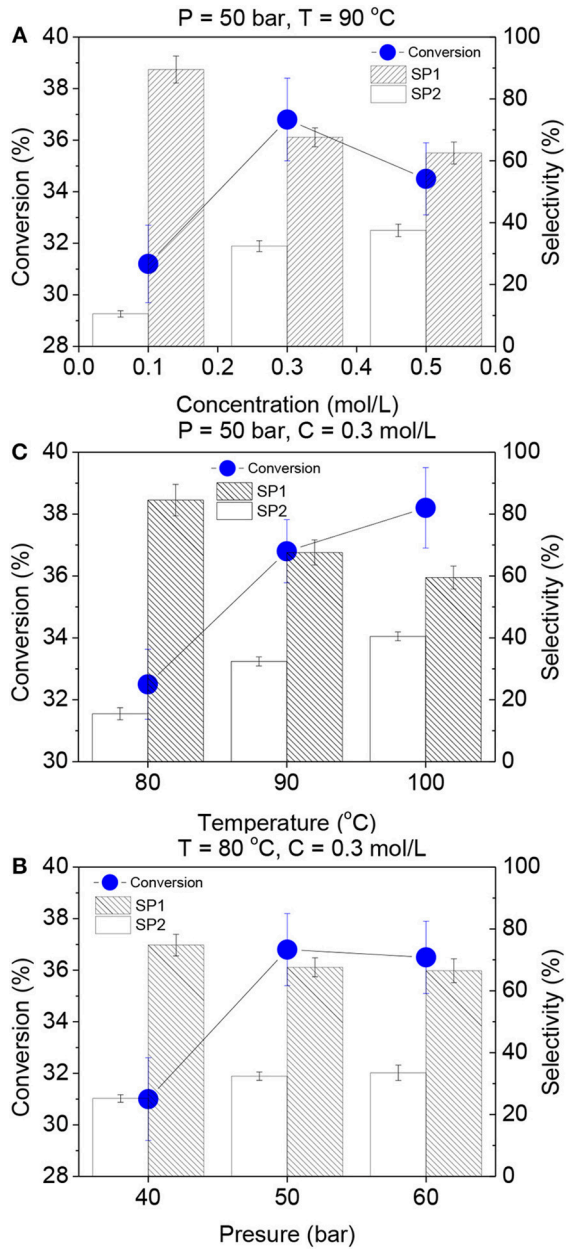


FIGURE 4 | (A) Catalytic performance of g-C_3N_4/Pt at different concentrations of levulinic acid, **(B)** catalytic performance of g-C_3N_4/Pt at different temperatures, **(C)** catalytic performance of g-C_3N_4/Pt at different pressures. SP1: selectivity to 1-ethyl-5-methylpyrrolidin-2-one, SP2: selectivity to 1-ethyl-2-(ethylideneamino)-5-methylpyrrolidin-2-ol.

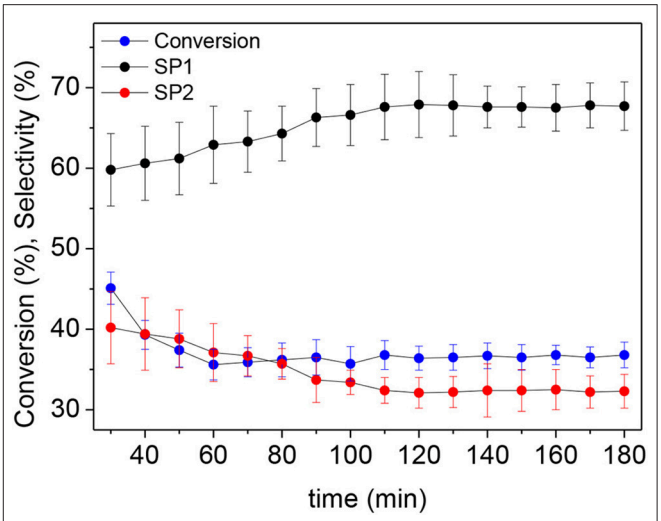


FIGURE 5 | Catalytic performance of g-C_3N_4/Pt nanocatalyst during 180 min of reaction. Reaction conditions: 0.3 M levulinic acid solution in acetonitrile, 0.1 g of catalyst, T = 90 °C, P = 50 bar, Flow = 0.3 mL/min. SP1: selectivity to 1-ethyl-5-methylpyrrolidin-2-one, SP2: selectivity to 1-ethyl-2-(ethylideneamino)-5-methylpyrrolidin-2-ol.

performed reaction gave rise to 1-ethyl-2-(ethylideneamino)-5-methylpyrrolidin-2-ol, $C_9H_{18}N_2O$ (170.14 g/mol), and 1-ethyl-5-methylpyrrolidin-2-one, $C_7H_{13}NO$ (127.10 g/mol), with the last being the major product (67.6% of selectivity). Remarkably, the catalytic system displayed outstanding stability without considerable loss of activity for up to 3 h of reaction.

The structure of both products was proposed considering the fragmentation pattern in the MS spectra (**Figure S1**). The aforementioned compounds have a common fragmentation pattern and therefore a common skeleton. The molecular ions of $C_7H_{13}NO$ and $C_9H_{18}N_2O$ were found at m/z 127.1 and 169.1, respectively.

CONCLUSIONS

In summary, this contribution has aimed to explore a strategy for biomass valorization through the catalytic conversion of levulinic acid, a platform molecule, to N-heterocycles. A simple procedure has been applied for the synthesis of an active, effective and stable catalytic system with a low noble-metal concentration (g-C_3N_4/Pt). The catalytic performance of the aforementioned material was investigated in the continuous flow transformation of levulinic acid to valuable N-heterocycles. A complete parametric analysis was performed by changing the reaction conditions, namely temperature, pressure and concentration of levulinic acid. The optimum balance between conversion and selectivity was found by using 3 M levulinic acid solution in acetonitrile at T = 90°C and P = 50 bars. Remarkably, the catalyst was highly selective (67.5%) to the formation of 1-ethyl-5-methylpyrrolidin-2-one and exceptionally stable during 3 h of reaction.

AUTHOR CONTRIBUTIONS

DR-P performed all experiments and wrote the first draft of the manuscript. AP-S supported the experimental work and revised the manuscript draft. AB finalized the draft with RL, conceived the experimental work and provided lab and financial support. MM-B conceived and planned the experiments with RL and finished the manuscript for submission. RL provided the lab for

all experiments, planned the experimental work, and finalized and submitted the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2019.00103/full#supplementary-material

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The reviewer CL declared a past co-authorship with one of the authors RL to the handling editor.

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Green Protocols in Heterocycle Syntheses via 1,3-Dipolar Cycloadditions

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The aim of this review is to provide an overview of green protocols for the organic synthesis of heterocycles via 1,3-dipolar cycloaddition. Particular attention has been devoted to the use of green solvents; reactions performed in ionic liquids, fluorinated solvents and water have been included. Also explored are several protocols that make use of catalyst-free reaction conditions, the use of microwave irradiation and activation by light exposure. Improvements over commonly used organic solvents will be underlined in order to highlight environmental protection aspects and enhancements in regio- and stereo-selectivity.

Keywords: green chemistry, dipolar cycloadditions, heterocycles, aqueous medium, Ionic liquids

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INTRODUCTION

The design of efficient and sustainable synthetic protocols is of primary importance to green pharmaceutical chemistry. The selection of suitable starting materials, methodologies with good atomic balance, a minimum number of steps and green solvents will allow this beneficial goal to be achieved. Heterocyclic chemistry plays a key role in drug production and the application of efficient green synthetic processes has a significant impact on pharmaceutical industries. There are a number of successful examples of benign synthetic protocol, including the use of non-conventional technologies such as microwave of ultrasound irradiations (Garella et al., 2013) and the use of water or green organic solvents (Moulay and Touati, 2010; Butler and Coyne, 2016). In the last decade, in this area, green chemistry and click chemistry have respected a pathway of rigorous principles, by means of which more efficient and greener processes can be defined (Anastas and Eghbali, 2010). Since the capital discovery by the teams of Meldal (Tornøe et al., 2002) and Sharpless (Rostovtsev et al., 2002), copper-catalyzed azide-alkyne cycloaddition (CuAAC) provides regioselectivity under mild conditions substituted triazole. Based on its large applicability, several research areas have taken advantage of its peculiar benefits and this reaction can be considered the click reaction *par antonomasia*. More in general, 1,3-dipolar cycloadditions are six π-electrons, concerted reactions that have a wide range of applications in organic synthesis and, specifically, in the preparation of five membered heterocyclic rings. Their good atomic balance and their synthetic potential resulted maximized when 5 terms heterocycles are obtained in sustainable solvents with high stereo or enantioselectivity.

Many authors still use the terms "[2+3] or [3+2] cycloaddition," which count the number of involved atoms, but do not follow IUPAC recommendations. In this paper, we follow the

IUPAC requirements, meaning that all reactions are referred to in accordance with the following rules:

- *A (i + j +...) cycloaddition is a reaction in which two or more molecules (or parts of the same molecule), provide units of i, j, in which i and j stand for linearly connected atoms. In the final product, these units become joined by new σ -bonds so as to form a cycle containing (i + j +...) atoms.*
- *The terminology [i + j +...] for a cycloaddition identifies the numbers, i and j, of π electrons in the interacting units that participate in the transformation of reactants to products* (see http://goldbook.iupac.org/html/C/C01496.html).

The aim of this review is to provide an overview of green protocols for the organic synthesis of heterocycles via 1,3-dipolar cycloaddition. The azides-alkynes cycloadditions, well-known as Huisgen reactions, will not be taken into detailed account because of their large presence in literature, both in original publication and in review. In the present review particular attention has been devoted to the use of green solvents; reactions performed in ionic liquids, fluorinated solvents and water have been included. Also explored are several protocols that make use of catalyst-free reaction conditions, the use of microwave irradiation and activation by light exposure. Improvements over commonly used organic solvents will be underlined in order to highlight environmental protection aspects and enhancements in regio- and stereoselectivity.

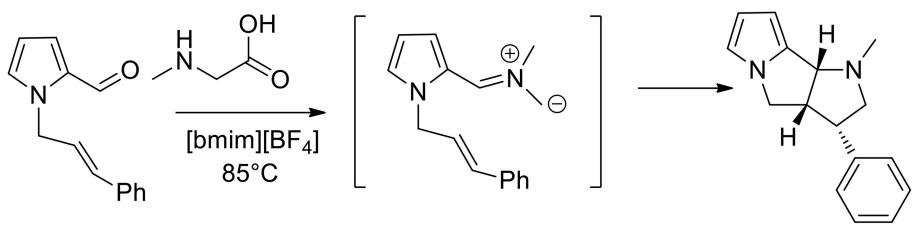
1,3-DIPOLAR CYCLOADDITION IN IONIC LIQUIDS

The elimination of the use of volatile organic solvents and their replacement by non-inflammable, non-volatile, non-toxic, and inexpensive green solvents is an important aspect of green chemistry. Their unique properties, including high chemical and thermal stability, solvating ability, ability to behave as both acidic and basic catalysts and recyclability, have led to ionic liquids gaining widespread recognition as green solvents that are advantageous to use in organic synthesis. Their manifold use in this context has therefore emerged as a formidable ally for green chemistry. Besides the catalyzing ability of ionic liquids, their solubility, viscosity, density, acidic, or basic character and refractive index, can be tuned by judiciously modifying the anion/cation combinations. This means that for multicomponent reactions and 1,3-dipolar cycloadditions, they might be the reaction media of choice.

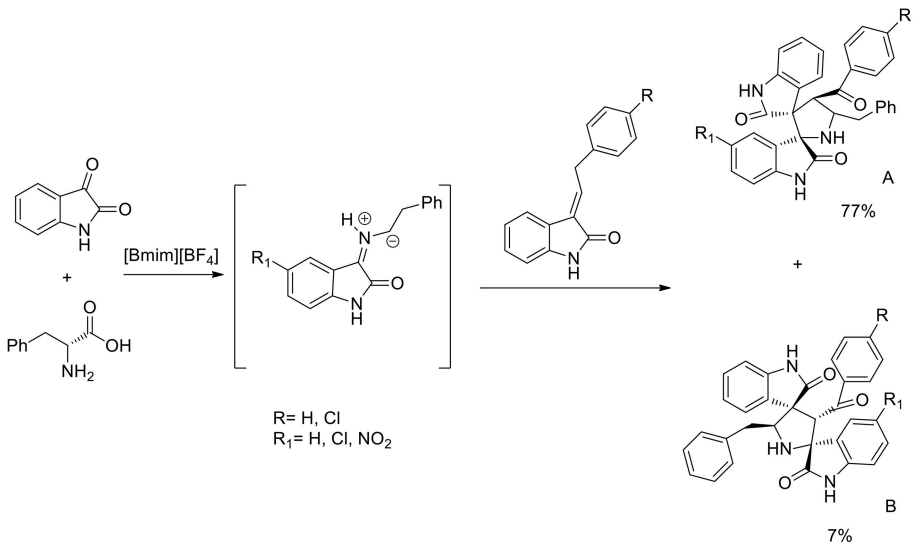
In 2007, 1,3-dipolar azomethine ylide cycloaddition has been studied in ionic liquid and the authors observed that pyrrolizidines can be obtained in high yield at 50°C in ionic liquid 1-butyl-3-methylimidazolium [bmim][BF_4] in 10–40 min, while under conventional conditions in boiling acetonitrile it requested 90–300 min (Jadidi et al., 2007). Kathiravan and Raghunathan (2013) studied an intramolecular 1,3-dipolar in [bmim][BF_4] as the medium and pyrrolo[2,3-a]pyrrolizidino derivatives were obtained, as described in **Scheme 1**. Starting from pyrrole-2-carbaldehyde and allyl bromide, the authors obtained N-alkenyl pyrrole-2-carbaldehyde that converted in presence of sarcosine in pyrrolo[2,3-a]pyrrolidines, pyrrolizidines, indolizidines, and isoquinolines. The reaction was performed at 85°C and in 3 h, and pyrrolopyridines were obtained in good yields (80–92%) from the 1,3-dipolar cycloaddition reactions. To provide an optimization of the method the authors also carried out the reaction in different organic solvents, including methanol, toluene, and acetonitrile. The reaction was slower and afforded lower yields of the desired products when performed in the organic solvents compared to ionic liquid.

A three component 1,3-dipolar cycloaddition, one pot reaction has been described (Almansour et al., 2015) to obtain dispirooxindolopyrrolidines. *In situ* generated azomethine ylides from L-phenylalanine and substituted isatins were used in equimolar ratio with a series of (E)-2-oxoindolino-3-ylidene acetophenone in [bmim][BF_4] to furnish the cycloadducts in 70–77% yield and high regioselectivity (**Scheme 2**). When compared with organic solvent such as methanol, ethanol, dioxane, and a dioxane/methanol (1:1) mixture under heating in an oil-bath, they gave the desired product in lower yield (28–38%) with low selectivity. The same reaction was investigated in ionic liquids using catalyst in 10 mol%, [bmim][BF_4]/CuI, [bmim][BF_4]/$Zn(OTf)_2$. These reactions furnished both regioisomers A and B, but good yield and high selectivity were observed toward the product A. The ionic liquids [bmim]BF_4 and [bmim]Br were found to be the most suitable reaction media and as described by the authors in the proposed mechanism (**Scheme 3**), ionic liquids play the dual role of solvent and catalyst and an increase in reaction rate is observed when compared to other organic solvents.

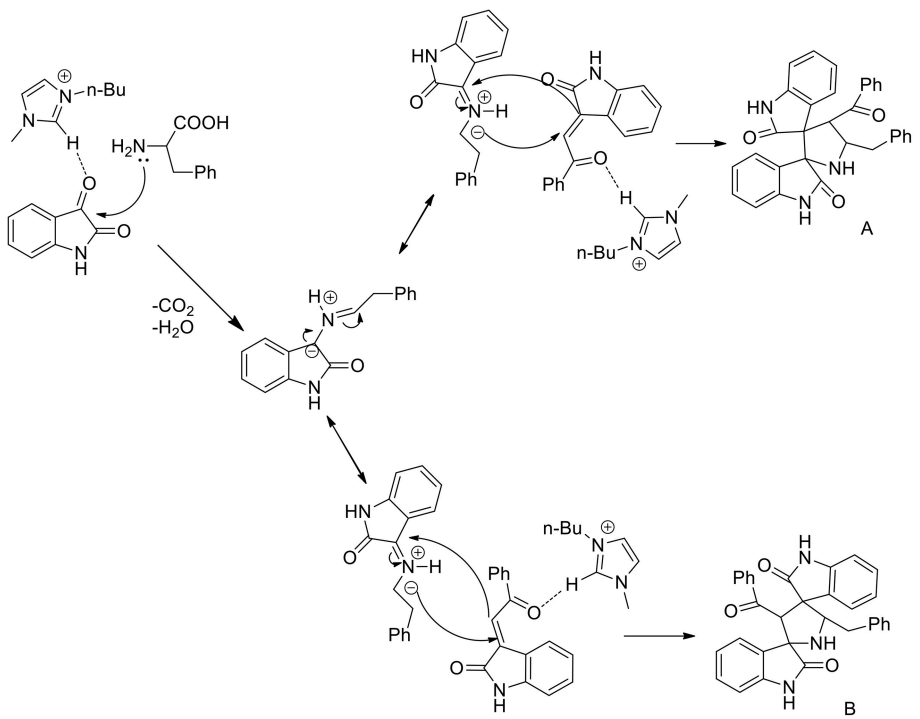
Another example of one pot three components reactions was published in 2015 by the same authors (Arumugam et al., 2015)



SCHEME 1 | Synthesis of *N*-methylpyrrol[2,3-a]pyrrolizidine.

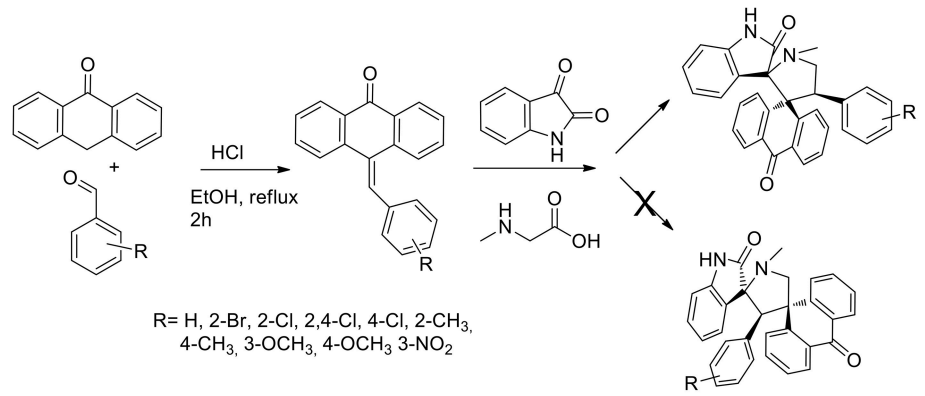


SCHEME 2 | Synthesis of dispirooxindolopyrrolidines.



SCHEME 3 | Possible mechanism of the synthesis of dispirooxindolopyrrolidine regioisomers.

that described a general and efficient path for the regio- and stereo-selective synthesis of dispirooxindole-fused anthrones. The reaction was a reaction pathway (**Scheme 4**) started from acid-catalyzed condensation of anthracen-9(10*H*)-one in presence of benzaldehydes to obtain 10-benzylideneanthracen-9(10*H*)-ones that was submitted to 1,3-dipolar cycloaddition with non-stabilized azomethine ylide from sarcosine and isatin (*in situ* generated). When performed in ethanol, methanol, dioxane, and a dioxane/methanol (1:1 v/v) at reflux, the 1,3-dipolar cycloaddition failed. The desired product was obtained in 65% yield in 3 h in DMF at reflux. Working in the presence of [bmim]Br at 100°C, the product was obtained in high yield (89%) and the reaction rate increased compared to DMF. Moreover, the ionic liquid was recovered and reused. The



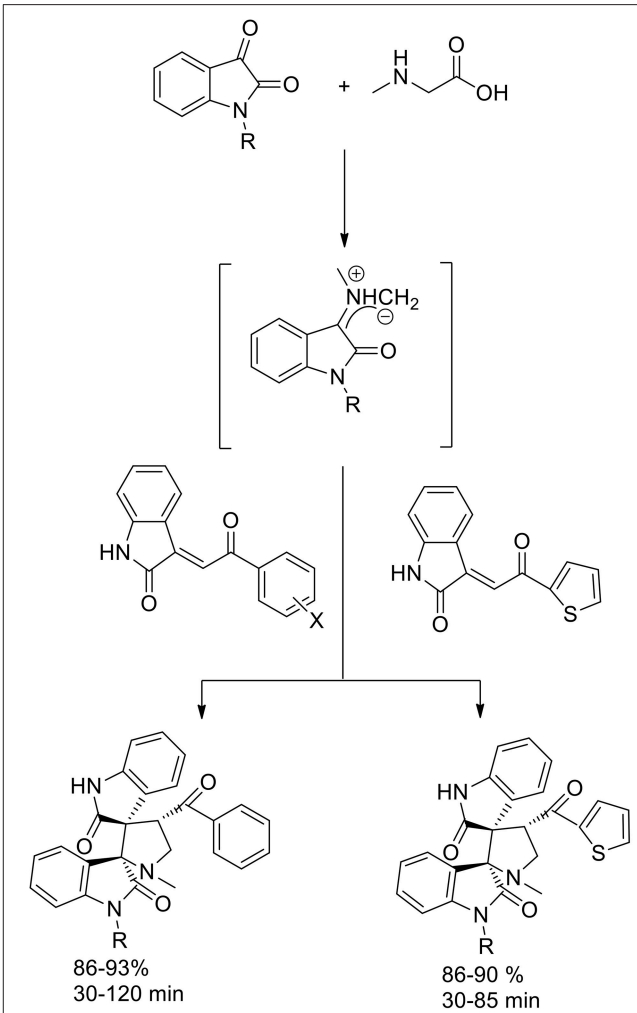
SCHEME 4 | Synthesis of 9-arylmethylene-10-anthrone and following 1,3-dipolar cycloaddition to bis-spiro compound.

reaction was proved as regioselective. The reaction showed high tolerance toward substituted benzaldehyde and electron donating as well as electron-withdrawing substituents at *ortho, meta,* and *para* positions gave satisfactory yields. ^{1}H-,^{13}C-, and 2D-NMR spectroscopy was exploited to elucidate the stereochemistry of the final product and unambiguously the stereochemistry was confirmed using a single crystal X-Ray diffraction study.

Also Jain et al. (2012) reported the enhancement in yield and rate due to the use of ionic liquid in 1,3-dipolar cycloaddition reaction *via* the generation of azomethine ylides from isatin and sarcosine (**Scheme 5**) to synthesize dispiropyrrolidine-bisoxindole. The dipolarophile employed was the olefin obtained by Knoevenagel condensation of isatin and un/substituted acetophenones and 2-acetylthiophene. In presence of [bmim]PF_6, the azomethine ylides approached the dipolarophiles regioselectively and excellent yields in short reaction times were obtained. Furthermore, there was no need for further purification processes, such as column chromatography, and the products were characterized by spectroscopic and analytical studies.

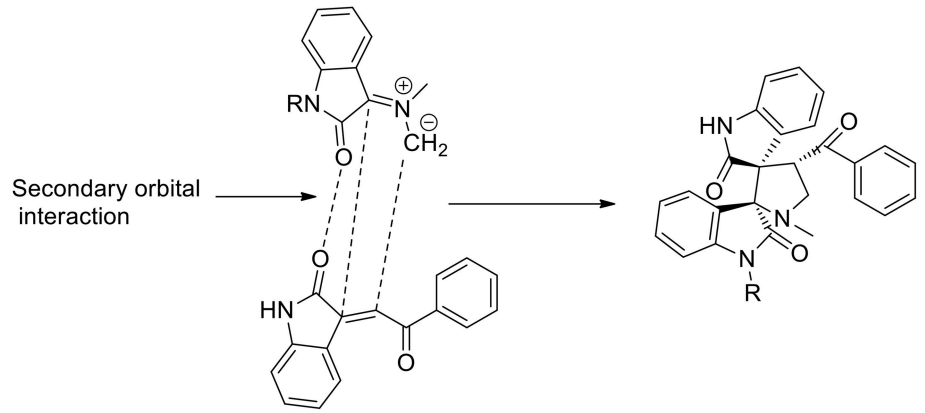
The stereoselectivity of the 1,3-dipolar cycloaddition is governed by both the orientation at which the dipole and dipolarophile approached and the conformation of the ylide. In the mentioned study, the authors hypothesize that constraints dictate that only one specific isomer can be involved in the transition state of the cycloaddition reaction. As described in the **Scheme 6**, the reaction occurs through one of the ylide geometries therefore its addition to dipolarophiles takes place under the control of relative stereochemistry at the spiro center. The formation of sterically hindered ylide was not obtained owing to steric repulsion between the oxindole carbonyl group and the methyl group of sarcosine. Ionic liquid recyclability was proved by the authors.

The parallel synthesis of novel molecular frameworks has been greatly enhanced by the discovery of the synergy between microwave irradiation and ionic liquid. Being a heterocycle of immense importance because of its potential biological activity, 1,3-dipolar cycloaddition under MW irradiation in ionic liquid has been explored for facilitating accelerations in drug discovery. Kumar et al. (2015) have studied the molecular recognition of

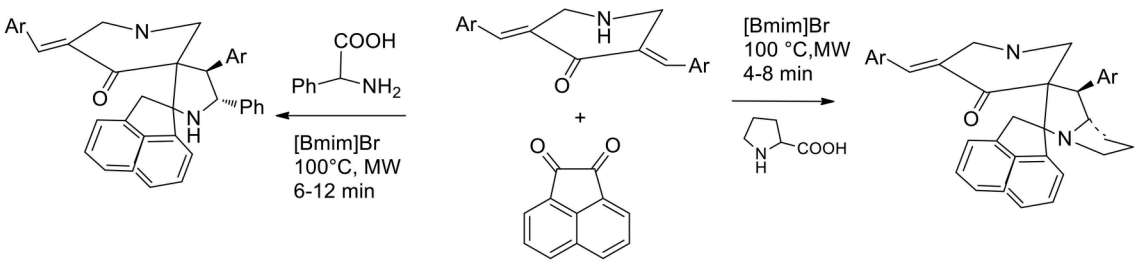


SCHEME 5 | Synthesis of dispiropyrrolidine derivatives.

cage compounds and attempted the incorporation into their structure or a second cavity that can participate in structure recognition. 1,3- dipolar cycloaddition between *N*-unsubstituted



SCHEME 6 | Schematic representation of plausible secondary orbital interaction of azomethine ylide.



SCHEME 7 | Synthetic route of diazapoycyclic cage compounds.

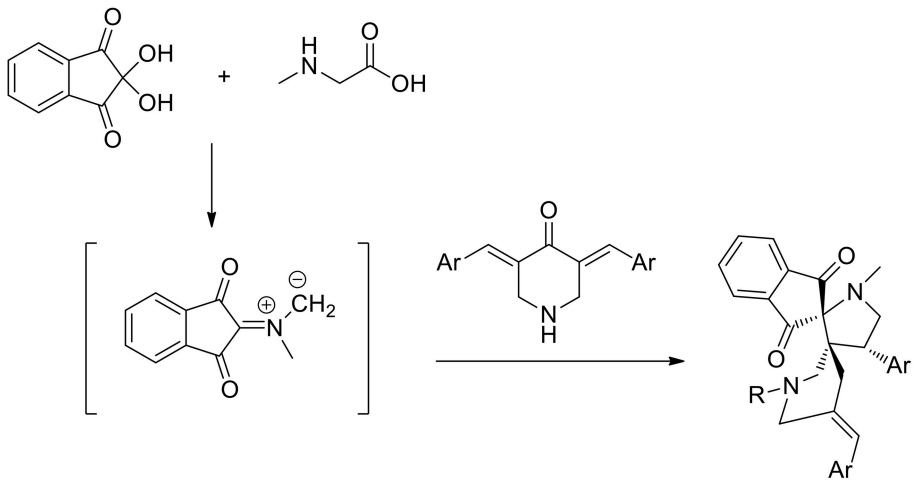
3,5-*bis*[(E)-arylmethylidene]tetrahydro- 4(1H)-pyridinones and azomethine ylides was exploited for the synthesis of novel diazahexa- and diazaheptacyclic ring. Azomethine ylides were generated *in situ* from acenaphthenequinone and α-amino acids (initially, proline and then phenylglycine). Initially the authors performed the reaction under conventional conditions and methanol, ethanol, ethanol−1,4-dioxane mixture (1:1 v/v), and 1,4-dioxane were employed in refluxing to afford the heptacyclic cage structure in 72, 60, 70, and 69% yields, respectively. When the reaction was performed in [bmim]Br at 100°C, the desired product was recovered in 81% yield in 20 min. The synergic effected of MW irradiation and ionic liquid was proved when an equimolar mixture of the starting materials in [bmim]Br was subjected to MW irradiation at 100°C for 4 min. The cage compound was recovered in 85% yield after purification by extraction and crystallization. The ionic liquid [bmim]Br was dried under reduced pressure after product extraction and its recyclability was investigated in successive syntheses of the cage compound, revealing that its efficacy was not particularly reduced in the three subsequent runs (**Scheme 7**).

Recently guanidine ionic liquids (GILs) have also emerged and have been efficiently used, as new-generation ionic liquids, in several reactions (Henry reaction, aldol reaction, Heck reaction etc.). The preparation of novel dispiropyrrolidine derivatives under green conditions was studied by Dandia et al. (2012) exploiting the task-specific ionic liquid 1,1,3,3-tetramethylguanidine acetate [TMG][Ac] as the reusable solvent in a 1,3-dipolar cycloaddition. The reaction was carried out in the presence of an equimolar mixture of sarcosine, ninhydrin, and 1-benzyl/methyl-3,5-bis[(E)-arylidene]-piperidin-4-one and at 80°C in 1,1,3,3- tetramethylguanidine acetate [TMG][Ac] for 3–6 h and the desired products were in good yields (86–92%). When different solvents were compared, the authors employed ethanol, methanol, dioxane, acetonitrile, and toluene, as well as several ionic liquids, including [bmim] BF_4 and [bmim]Cl. All these solvents were found to give comparatively low product yields (42–82% yield compared to 86–89 of ionic liquids in more than 5 h) and [TMG][Ac] was the best solvent, giving higher yields and shorter reaction times (92% yield in 3 h). A single regioisomer was isolated in all cases (**Scheme 8**).

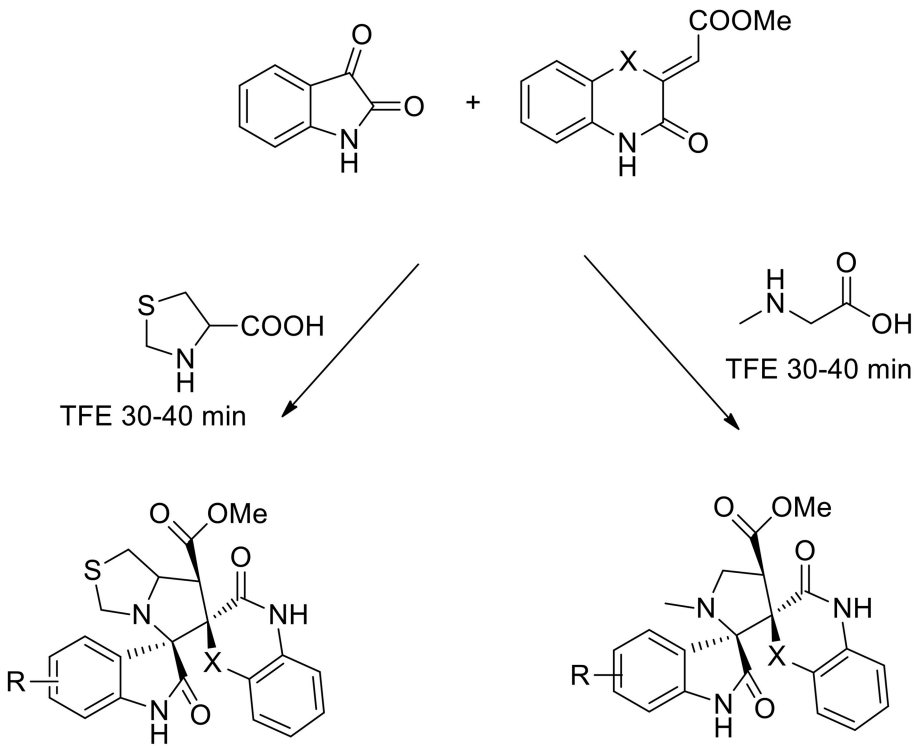
1,3-DIPOLAR CYCLOADDITION IN FLUORINATED SOLVENTS

2,2,2-trifluoroethanol is considered an ideal solvent and co-solvent because of its high ionizing power and strong hydrogen bond-donating ability, which provide good catalytic potential in a variety of organic transformations.

The use of 2,2,2-trifluoroethanol as a recoverable greener solvent was explored by Dandia, to obtain a series of novel



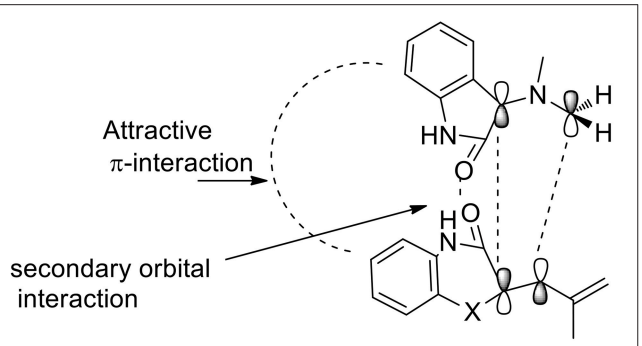
SCHEME 8 | Synthesis of dispiropyrrolidine derivatives.



SCHEME 9 | Synthesis of benzo[1,4]oxazine (X = O) and benzo[1,4]thiazine (X = S) based dispiroheterocycles *via* azomethine ylides.

efficiently regio- and stereoselective dispiropyrrolidinyl/thiapyrrolizidinyl hybrid molecules via the 1,3-dipolar cycloaddition of a benzo[1,4]oxazine-derived dipolarophile, isatin and sarcosine/1,3-thiazolane-4-carboxylic acid (Dandia et al., 2015). The dipolarophile was synthesized under catalyst-free conditions from o-aminophenol and dimethyl acetylene dicarboxylate (DMAD) in good yields. The authors studied the cycloaddition reaction in different solvents (ethanol, methanol, acetonitrile, 1,4-dioxane, hexafluoro isopropanol, 2,2,2-trifluoroethanol, and toluene). The best results were obtained using 2,2,2-trifluoroethanol, which gave a single regioisomer in a higher yield and a shorter reaction time than the other solvents (92% yield). The reaction was complete in 30 min vs. the 6 h requested in presence of different solvents (**Scheme 9**).

The 1,3-dipolar cycloaddition reactions proceeded in a concerted manner, meaning that the reaction is stereospecific.



SCHEME 10 | Plausible transition state.

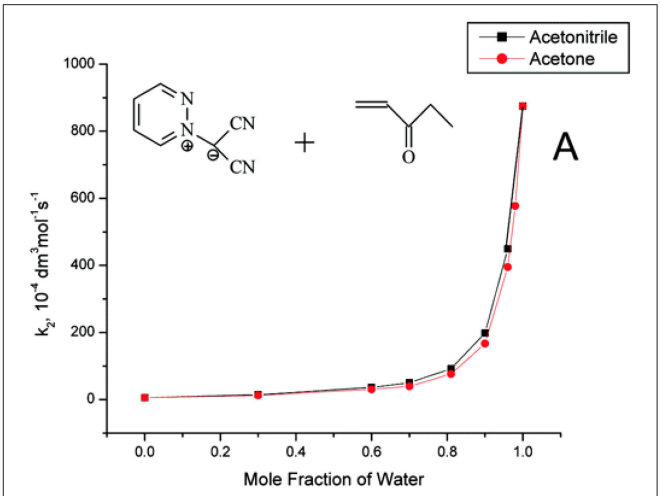


FIGURE 1 | Reprinted with permission from Butler et al. (2004). Copyright (2018) American Chemical Society.

In this case, the stereochemistry of alkene benzo[1,4]oxazine would influence the stereochemistry at positions 3 and 4. As described by the authors, the formation of only one diastereomer is explained by the plausible transition state (**Scheme 10**) which is somewhat promoted by a π-interaction between the aromatic rings as well as the secondary orbital interaction (SOI) between the ylide and the orbitals of the dipolarophile's carbonyl group.

1,3-DIPOLAR CYCLOADDITION IN WATER

The use of water in organic synthesis has stimulated several applications. Despite water's unique properties, it is still not commonly used as most organic compounds do not dissolve in water, meaning that a cosolvent is needed to increase solubility. This choice tends to diminish the advantages of low cost, no-toxicity, ease workup, and product isolation in water. Therefore, organic synthesis in aqueous media includes a large number of reactions that are performed both in homogeneous and in heterogeneous conditions (Chanda and Fokin, 2009).

As described by Sharpless et al. in their study of pericyclic cycloaddition, such reactions often benefit from working in water even when the organic reactants are insoluble in the aqueous phase. In fact, this substantial rate acceleration can be due to "on water" conditions that are created when insoluble reactants are stirred in an aqueous suspension (Narayan et al., 2005). This concept has been studied and applied to several different reactions. Even when the rate acceleration is negligible, this approach can still be considered successful as it makes product isolation easier and improves safety thanks to water's high redox stability and heat capacity.

Useful information derived from comparative studies of 1,3-dipolar cycloaddition reactions in organic solvents and water. The introduction of water as a cosolvent in cycloaddition reactions in organic solvents, such as acetonitrile and acetone, gave remarkable exponential rate increases as the solvent mixture approached pure water (Butler et al., 2004). Reactions of methyl vinyl ketone, ethyl vinyl ketone, and but-3-yn-2-one with pyridazine dicyanomethanide 1,3-dipole, which is soluble in water, display rate enhancements on changing from MeCN to H_2O (**Figure 1**). As observed in pericyclic cycloadditions, such as the Diels Alder reaction, the rate enhancement may be due to: (a) hydrophobic effects, which aggregate the organic reactants; (b) a lowering of the activation energy by special hydrogen bonding in the transition state; and (c) the fact that the cycloaddition transition state in water has higher polarity than its analog in organic solvents and, consequently, displays increased solvation stabilization in water (Butler et al., 2002).

The vast literature on the use of nitrones in the preparation of bioactive compounds pays testament to their huge synthetic potential. 1,3-dipolar nitrone-olefin cycloaddition has been used to obtain isoxazolidines, and even more complex bi- or tri-cyclic isoxazolidines, of biological interest and others that are useful synthetic intermediates for target molecules (De March et al., 1999; Fisera, 2007; Molteni, 2016). The fact that the formation of nitrones is due to the dehydration reactions of substituted hydroxylamine and carbonyl compounds drove A. Chatterjee et al. to explore the formation of nitrones in aqueous media using surfactants. As depicted in **Figure 2**, the micelles are hydrophobic and protect water-labile molecules from hydrolytic decomposition (Chatterjee et al., 2003).

The authors started with a model reaction between phenyl hydroxylamine and various aldehydes, in which cetyl trimethylammonium bromide (CTAB) showed better performance than sodium dodecyl sulfate (SDS) in preparing nitrones. This is presumably due to stronger binding with the substrate. Interestingly, no reaction was observed when the reaction was performed in water in the absence of a surfactant or neat. The same procedure was therefore used to obtain a stereoselective intramolecular nitrone cycloaddition (Chatterjee and Bhattacharya, 2006). Furanoside-5-aldehydes derivatives were reacted with phenyl hydroxylamine to form the corresponding nitrones in aqueous media and the reaction was catalyzed by a surfactant at room temperature. The nitrone intermediate underwent stereoselective intramolecular cycloaddition as described in **Scheme 11**. Interestingly, the authors observed the formation of only one of the four possible

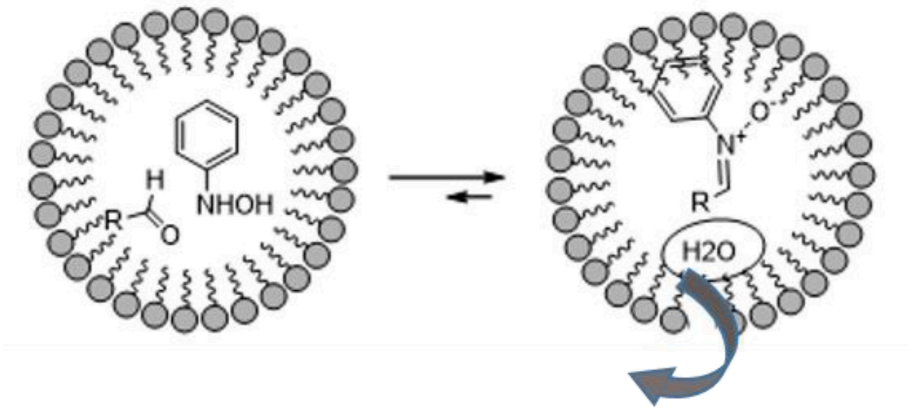
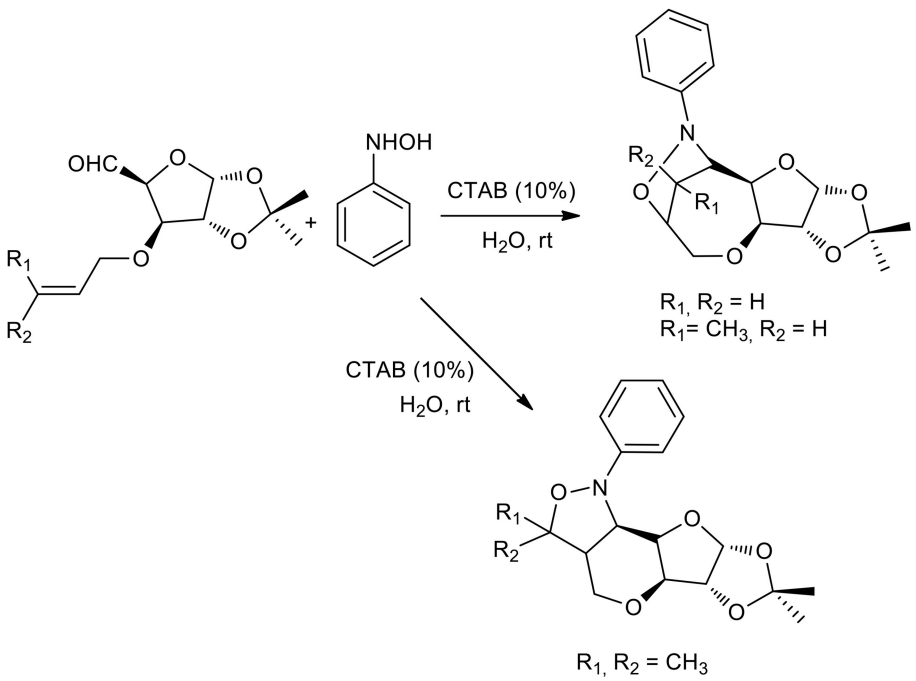


FIGURE 2 | Schematic representation of nitrones synthesis in micelle.



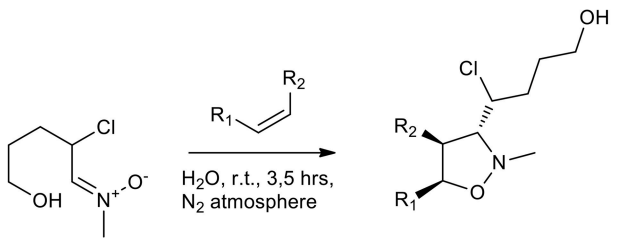
SCHEME 11 | 1,3-dipolar cycloaddition with furanoside-5-aldehydes derivatives and phenyl hydroxylamine.

isomers in these surfactant-mediated intramolecular nitrone cycloadditions. The nitrones of 3-O-allyl glucofuranose produce bridged isoxazolidines-oxepanes, as do the nitrones of crotyl derivatives. By contrast, nitrones of prenyl derivatives produce pyrans. This may be due to methyl-methyl steric repulsion restricting the formation of the oxepane skeleton.

Several other attempts to perform 1,3-dipolar cycloadditions in the presence of previously synthesized nitrones have been performed in water without the addition of a surfactant. *N*-methyl-α-chloro nitrone reacted quickly with ethyl acrylate, styrene and three different maleimides (*N*-methyl/phenyl/cyclohexyl) (**Scheme 12**). Yields were in the range of 91–97% and the ratio *anti/syn* was 7:3 in average (Chakraborty et al., 2010, 2012).

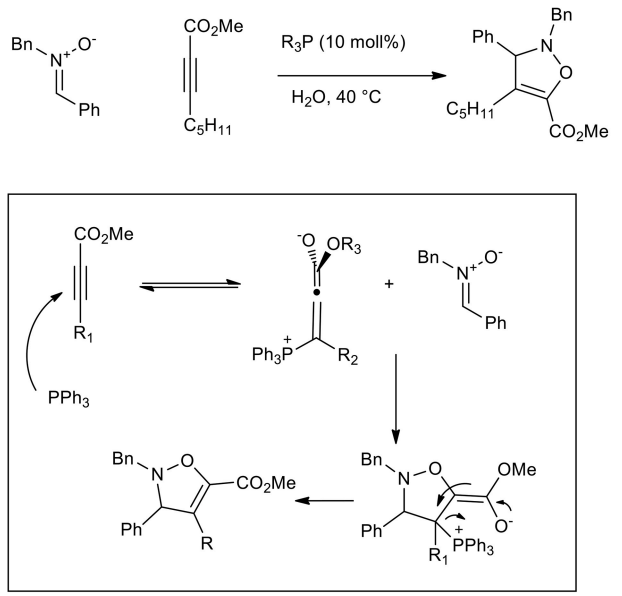
The 1,3-dipolar cycloaddition of nitrones in water has also been used to react two free sugar derivatives to produce pseudo-disaccharides, which bear imino-galactofuranose and galactofuranose units, in a 51% yield (Liautard et al., 2008). The reaction exploited the reactivity of water soluble nitrones with high enantioselectivity.

Triphenylphospine and tertiary amines can be used to activate conjugated carbonyl alkynes toward 1,3-dipolar cycloaddition. In fact, β-phosphonium (or ammonium) allenolates perform as reactive dipolarophiles in aqueous 1,3-dipolar cycloadditions



R_1, R_2 = CON(Me)CO
R_1, R_2 = CON(Ph)CO
R_1, R_2 = CON(CyHex)CO
R_1 = CO_2Et, R_2 = H
R_1 = Ph R_2 = H

SCHEME 12 | 1,3-dipolar cycloaddition of *N*-methyl-α-chloronitrone.



SCHEME 13 | Dipolar cycloaddition of β-phosphonium (or ammonium) allenolates to obtain isoxazolidine derivatives.

and have been used to give 2,3-dihydroisoxazole (**Scheme 13**) (Gonzalez-Cruz et al., 2006). The reaction increased the reaction yield up to 68% when LiCl was used and interestingly only one regioisomer was isolated, while no reaction was observed in toluene and DCM. By comparison with tertiary amines, PPh_3 showed the best catalytic activity in the presence of aromatic nitrone (68% yield vs. 59%), while quinuclidine was more active with aliphatic nitrones. As has already been reported, reagents solubility in water is not required as they react in suspension ("on water").

A catalytic amount of γ-cyclodextrin (γ-CD) has been used by G. Floresta et al., to produce 3,5-diarylisoxazolidines via the 1,3-dipolar cycloaddition of several *p*-substituted nitrones, styrenes and cinnamate derivatives (Floresta et al., 2017). The cyclodextrin cavity acted as a reactor and heating at 100°C for 8–12 h gave a set of derivatives in good yields with moderate to excellent diastereoselectivity. Interestingly, β-CD was inactive as a nano-reactor, while γ-CD was found to efficiently form inclusion complexes. The formation of the complex was confirmed by HR FT-ICR MALDI-MS Studies and NMR spectra. The authors rationalized by an *in silico* study the cycloaddition process and an E-*endo* transition state and that the cis major adduct is the more reactive rotamer of the nitrone. The calculation suggests that the transition stage is positioned within the CD reactor, as depicted in **Scheme 14**.

In 2008, an interesting publication demonstrated the influence that the solvent can have on the production of isoxazolidine. Alkenylazaarenes were utilized as dipolarophiles for the preparation of 4-substituted and 5-substituted isoxazolidines with nitrones giving high regioselectivity under a range of reaction conditions. Reaction in water under microwave in a sealed vessel gave in high to excellent yields only 5-substituted isoxazolidines, while the 4-substituted analogs were obtained as the major products when a Lewis acid, TMSOTf, was used as the catalyst in DCM at room temperature (**Scheme 15**) (Tong et al., 2018).

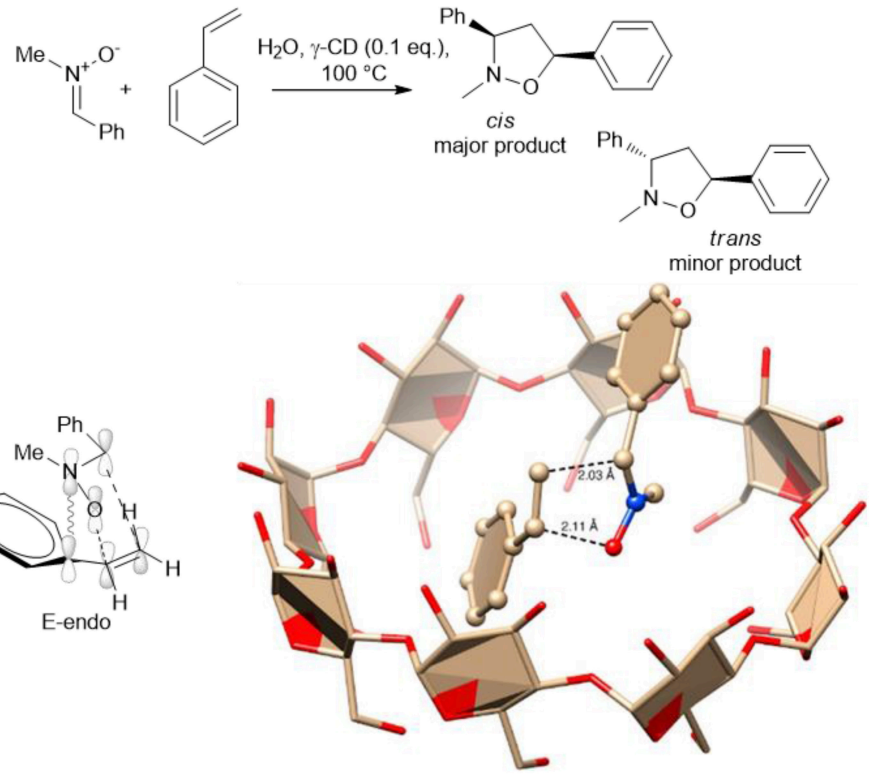
Oxindole derivatives that bear a spirocyclic quaternary stereocentre at the C3 position are interesting heterocyclic motifs generally found in a number of natural products and drugs.

Several green approaches for the synthesis of spiro-indole have been described as occurring in the presence of water as a solvent. Despite the common use of halogenated organic solvents, the "on-water" generation of carbonyl ylides using carbenoids was described in 2015 (Muthusamy and Ramkumar, 2015). The proposed synthesis catalyzed by rhodium(II) acetate dimer, afforded spiro-oxiranes from carbonyl ylide dipoles and diazoamides (3-diazooxindoles) (**Scheme 16**). Spiro-dioxolanes were obtained with complete diastereoselectivity when carbonyl ylides were obtained using aromatic aldehydes with electron-withdrawing substituents, while with electron-donating substituents the 1,3-dipolar cycloaddition reactions were observed.

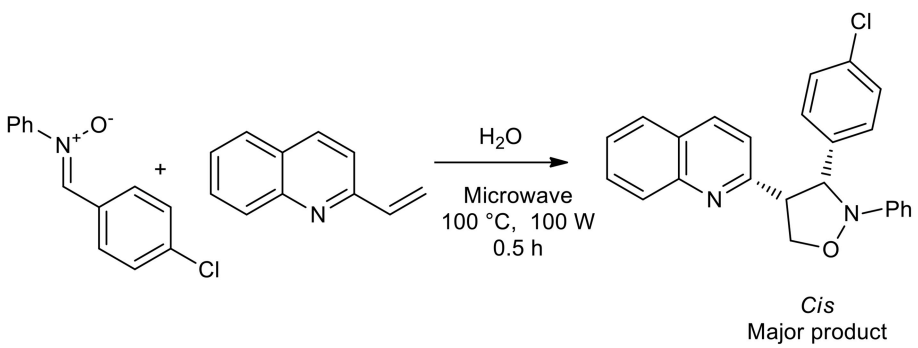
The reaction afforded *cis* products in both the spiro-oxirane and spiro-dioxolane syntheses. In the presence of 1.2 equivalents of aromatic aldehyde, the acyclic carbonyl ylide underwent the intermolecular stereoselective dipolar cyclization in a particular conformation, which involved an intramolecular hydrogen bond, to give epoxides (**Scheme 17**). When an excess of aldehyde was used (4 equivalents), the reaction happened "on water" as the nucleophilic addition of water was not observed to occur. Nevertheless, the free interfacial-water OH groups may stabilize the possible transition state.

A three-component, 1,3-dipolar cycloaddition of *in situ* generated azomethine ylides from isatin derivatives and benzylamine, with benzylideneacetone can be employed to give spiro-pyrrolidine-oxindoles (Peng et al., 2014). This reaction can be performed in water to give the desired product in a 23% yield and a 68:32 regioisomeric ratio.

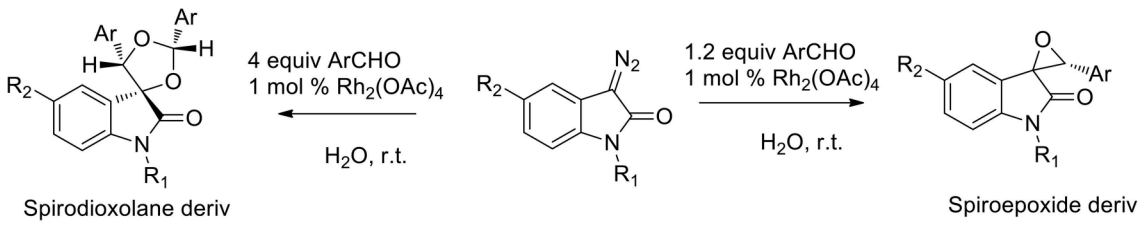
The use of Lewis acids, such as Ceric Ammonium Nitrate (CAN) or TiO_2, in the formation of spirooxindoles in water has been investigated, giving excellent results (**Scheme 18**)



SCHEME 14 | Schematic representation of synthesis of 3,5-diarylisoxazolidines via the 1,3-dipolar cycloaddition in presence of γ-CD and plausible transition stage to obtain the major E-*endo* derivative. The image was reprinted adapted with permission from Floresta et al. (2017). Copyright (2018) American Chemical Society.

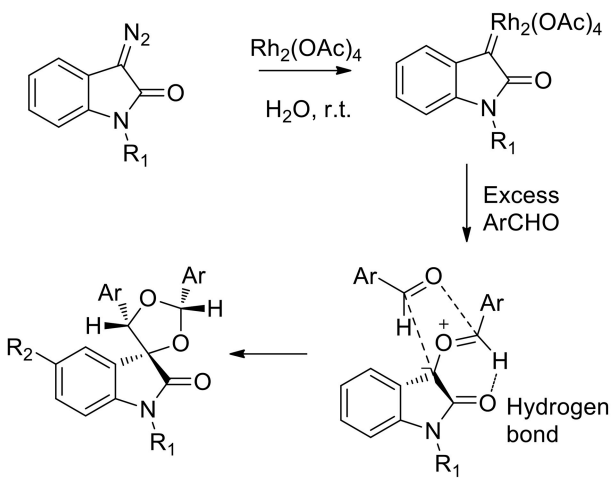


SCHEME 15 | Synthesis of 5-substituted isoxazolidines with nitrones in water under microwave irradiation.



SCHEME 16 | Schematic representation of spiro-indole synthesis from 3-diazooxindole derivatives.

(Ramesh et al., 2016, 2018). The 1,3-dipolar cycloaddition was performed with 1 mol% of CAN in 2 h, while the reaction was complete after 30 min when heterogeneous TiO_2 nanoparticles were used. Both reactions showed excellent regioselectivity and stereoselectivity, and the TiO_2 nanocatalyst was reused 5 times without losing catalytic activity. 20 different spirooxindole-pyrrolidines were obtained, in 65–90% yields with CAN and the reaction showed increased average yield in the presence of TiO_2.

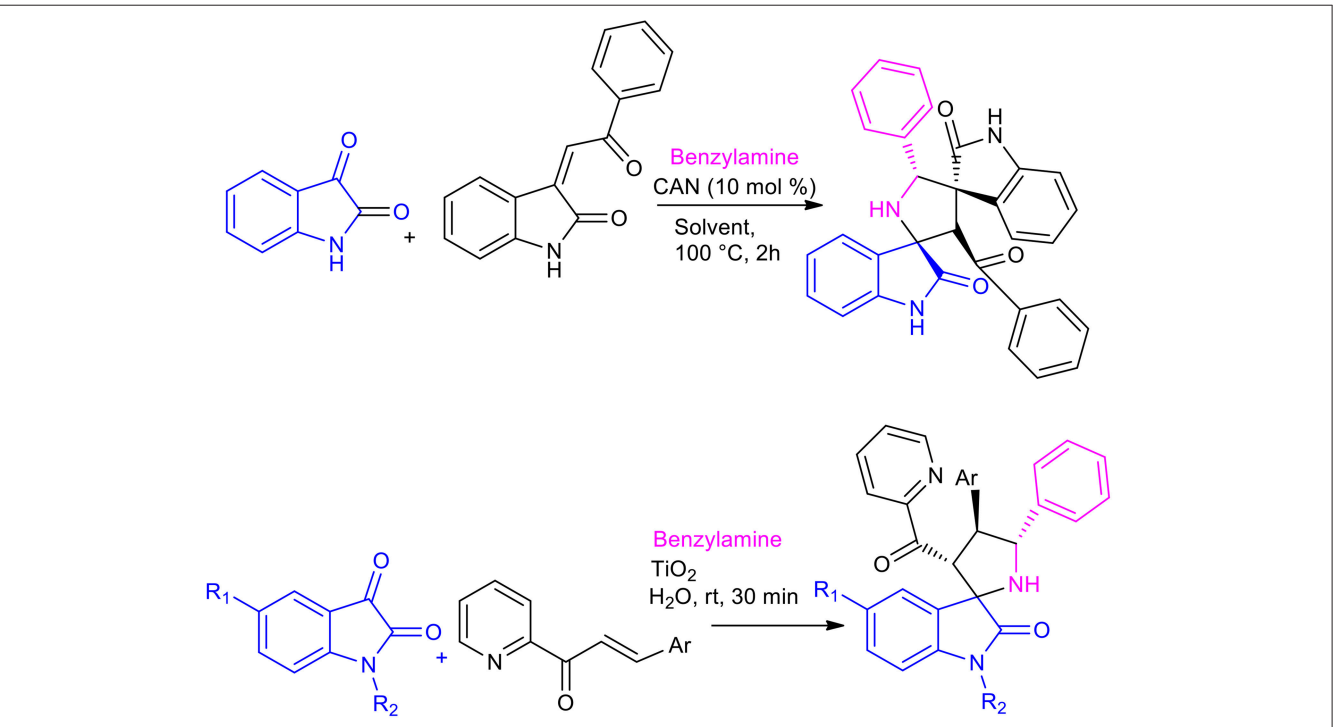


SCHEME 17 | Proposed mechanism.

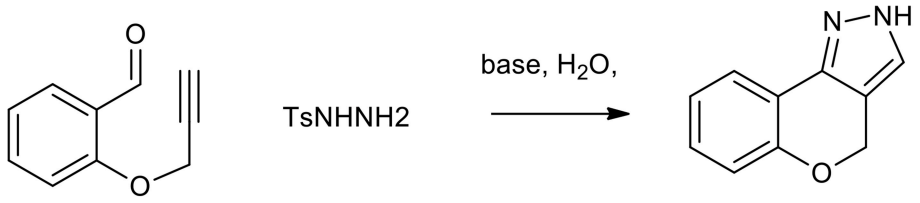
Diazoalkanes can be generated from the decomposition of tosylhydrazones and are efficient 1,3-dipoles exploitable for the synthesis of several nitrogen containing heterocycles (Munro and Sharp, 1984). An intramolecular 1,3-dipolar cycloaddition strategy for rapid access to pyrazoles or triazoles makes use of the *in situ* generated diazomethanes, in a two-step sequence, in which diazomethanes undergo smooth cycloaddition with alkyne or nitrile moieties (Padwa and Ku, 1980). As described in **Scheme 19**, this process can be used as a step-economical route to benzopyranopyrazole from propargylated salicylaldehydes and tosyl hydrazone. This reaction, which is usually performed in DMF, can be performed in water with K_2CO_3, providing excellent yields (more than 80%).

ORGANO-CATALYZED AND CATALYST-FREE 1,3-DIPOLAR-CYCLOADDITION

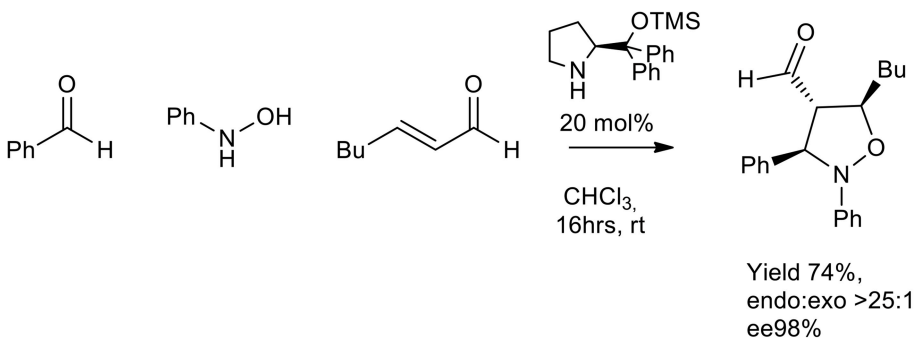
A novel organocatalytic asymmetric 1,3-dipolar addition has been proposed by MacMillan, that explored the synthesis of oxazolidine starting from nitrones and α,β- unsaturated aldehydes (Jen et al., 2000). In the presence of different chiral imidazolidinone·HCl the reaction between crotonaldehyde and *N*-benzyl phenyl nitrone showed moderate to high yield (45–77%) and *ee* (42–93%); when a Brønsted acid was added as co-catalyst, the efficient iminium activation could increase yield (98%) and *ee* (94%).



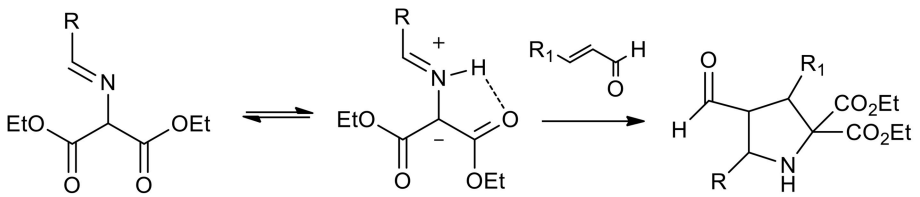
SCHEME 18 | Synthesis of spiroindole by 1,3-dipolar cycloaddition with TiO_2 in water and with CAN in solvent.



SCHEME 19 | Synthesis of benzopyranopyrazole from propargylated salicylaldehydes and tosyl hydrazine.



SCHEME 20 | Enantioselective synthesis of substituted isoxazolidine.



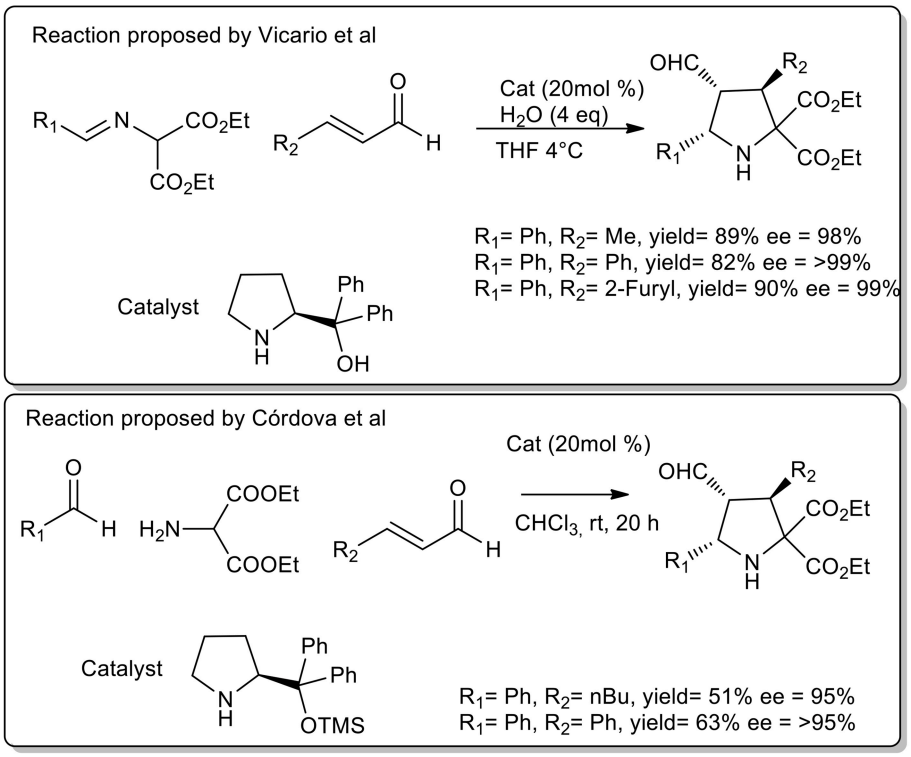
SCHEME 21 | Schematic representation of iminoesters as the precursors of stabilized azomethine ylides.

In 2007 Córdova et al. proposed an enantioselective organocatalyzed synthesis of substituted oxazolidine. *N*-arylhydroxylamines, aldehydes, and α,β-unsaturated aldehydes were reacted in the presence of a chiral organic catalyst. The *in-situ* generated nitrone reacted with activated enal, in chloroform or THF at room temperature (16 h) to give the isoxazolidine as a single diastereomer (>25:1 *endo:exo*). TMS protected diarylprolinol gave *ee* % up to 98% (**Scheme 20**) (Rios et al., 2007).

Organo-catalyzed (3+2) dipolar cycloadditions of azomethineylide with various dipolarophiles has been the object of intense investigation. Several publications studied iminoesters as the precursors of stabilized azomethine ylides, because, as described in the scheme, they can undergo thermal tautomerism to produce azomethine ylides (**Scheme 21**).

Vicario et al. observed that cycloaddition of imine and crotonaldehyde catalyzed diphenylprolinol provided a single *endo* isomer with excellent enantioselectivity (Vicario et al., 2007). The authors highlighted the fundamental role of free OH groups on the catalyst and the acceleration rate by water addition. The optimized protocol was performed at 4°C in THF. Similarly, Cordoba et al. proposed the synthesis of pyrrolidine in $CHCl_3$, at room temperature with protected prolinol. As described in **Scheme 22**, a slightly lower yield and selectivity were observed (Ibrahem et al., 2007).

An elegant example of 1,3-dipolar cycloaddition in asymmetric catalysis has been published by the Córdova group, which proved that a hydrogen bond donating network with a co-catalyst was to direct the cycloaddition by locking the conformation of the intermediate so to achieve a highly selective reaction (Lin et al., 2011). This dynamic one pot reaction was directed to cycloaddition in THF or DMF and the presence of hydrogen bond donating molecules such as oximes was favorable for the acceleration of the reaction when the substrate was cyanoacetate or α-cyanoglycine. Compared to the previously described approach, this one pot reaction generated four contiguous chiral centers including a quaternary carbon. As described in the scheme, the proposed mechanism involves the prototropy of the imine cyanoglycine so that the H bond activate the iminium salt and lock is conformation as **1** (see **Scheme 23**)



SCHEME 22 | Enantioselective synthesis of substituted pyrrolidines.

stereoselective ccloaddition from the Re face of intermediate **3** by and *endo* mechanism.

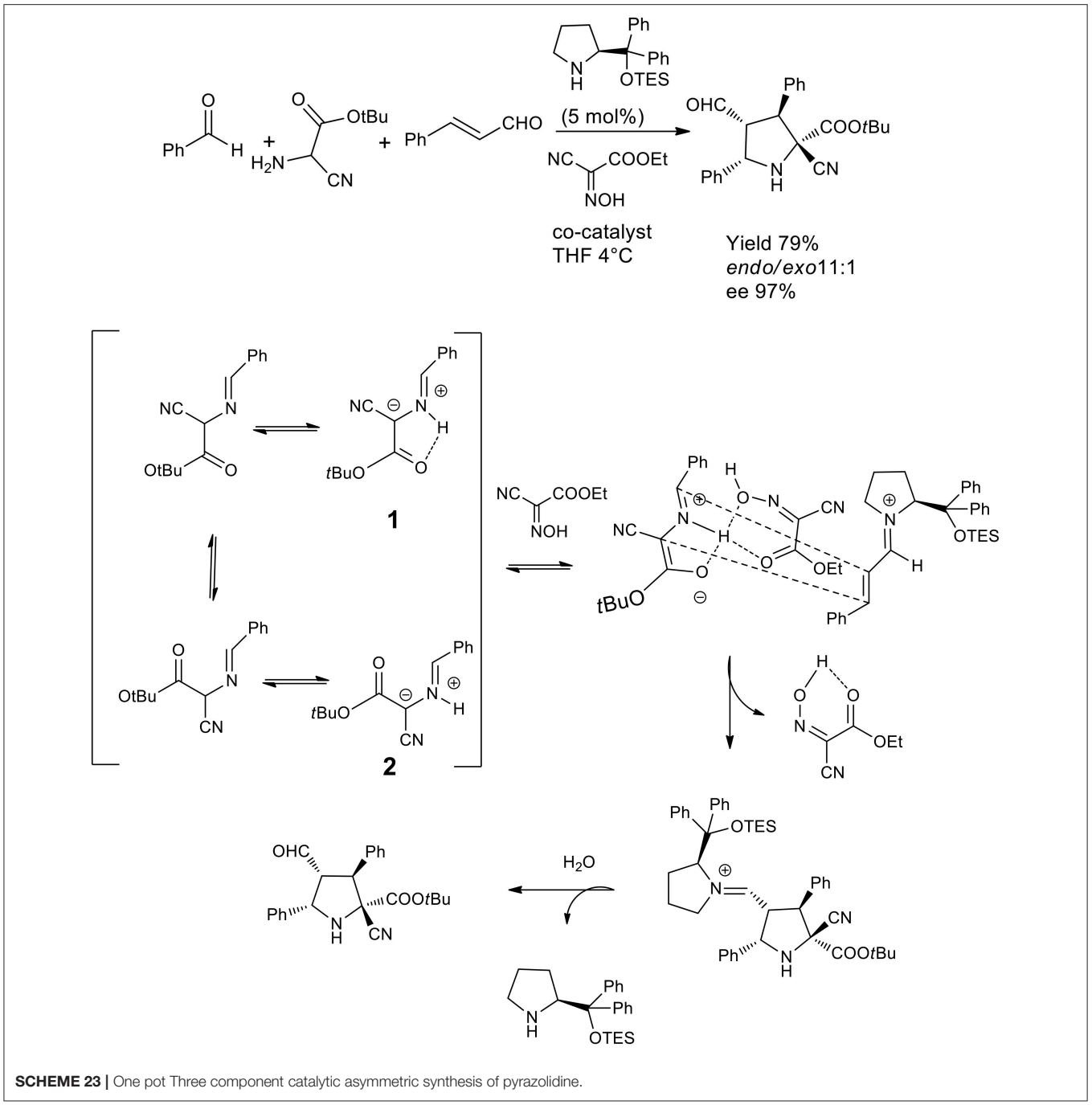
Another recent approach to activate different dipolarophiles other than unsaturated aldehydes was pursued by Chen et al. and chiral phosphoric acids were successfully exploited to obtain pyrrolidine or spirooxindole (Chen et al., 2009; Chang et al., 2016). Excellent yield and enantioselectivity were obtained in DCM at room temperature with chiral sterically hindered phosphoric acids for the imine activation (see **Scheme 24**).

Pyrazoles are known to be potent insecticides and herbicides, and have been also studied for their anti-tumor, anti-inflammatory, anti-microbial and anti-psychotic properties. Diazo compounds may react with alkynes to provide efficient synthesis of pyrazole via 1,3-dipolar cycloaddition. The 1,3-dipolar cycloaddition of alkynes to electron-rich diazo compounds has been described, whereas the intermolecular 1,3-dipolar cycloaddition of alkynes with electron-poor diazocarbonyl compounds is much less often reported because of the to the high HOMO–LUMO energy difference between alkynes and diazocarbonyl compounds. In presence of Lewis acid or transition metals LUMO of the alkyne dipolarophiles is lowered. Wang et al. (2013) developed an organocatalytic inverse-electron-demand [4+2] cycloaddition between diazoacetates and various carbonyl compounds. Secondary amines we employed as "green promoters," to catalyze the cycloaddition reaction and produce the target pyrazole ring (**Scheme 25**). Pyrrolidine was selected as the most effective catalyst and DMSO as best solvent for this transformation. The optimized protocol was performed in DMSO at room temperature with 10 mol% of pirrolidine and a 1:2 ratio of diazoacetates and carbonyl compounds.

When the reaction was performed with unsymmetrical cyclic ketones, high levels of regioselectivity were achieved. Nonetheless, the authors discovered that in the reaction between diazoacetates and aldehydes, it performed better in presence of acyclic secondary diethyl amine catalysis. Moderate-to-excellent yields of the corresponding adducts were obtained also varying the side-chain of the carbonyl group.

The hypothesis of selective C-H_1 bond-breaking was confirmed by a deuterium labeling experiment. The enamine-promoted cycloaddition reaction with α-deuterated benzyl diazoacetate yielded the final compound without any deuterium being incorporated into the pyrazole ring, which supports the hypothesis of a selective C-H_1 bond breaking. The authors supposed that the C-H_1 bond is activated by the adjacent electron-withdrawing ester group, toward the selective cleavage over the C-H_2 bond. The final product derived from an elimination step followed by tautomerization (**Scheme 26**).

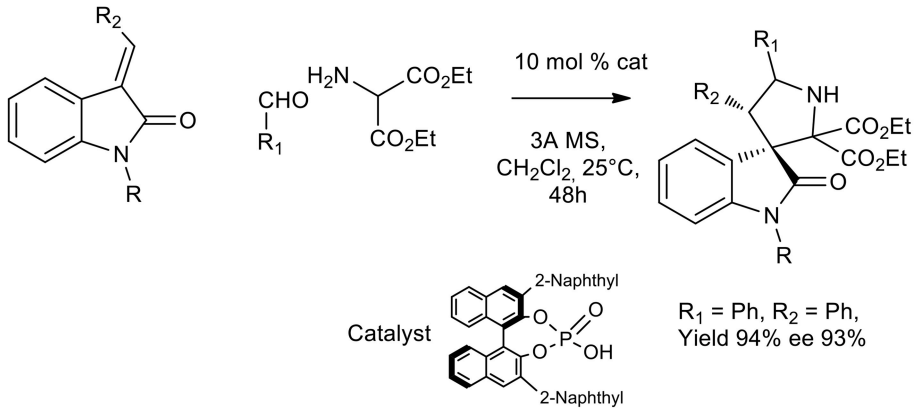
Liu et al. (2017) have presented the first catalyst-free 1,3-dipolar cycloaddition of C,N-cyclic azomethine imines and 3-nitroindoles to prepare highly functionalised, five-ring-fused tetrahydroisoquinolines, which feature an indoline scaffold with excellent diastereoselectivity. The reaction performed the



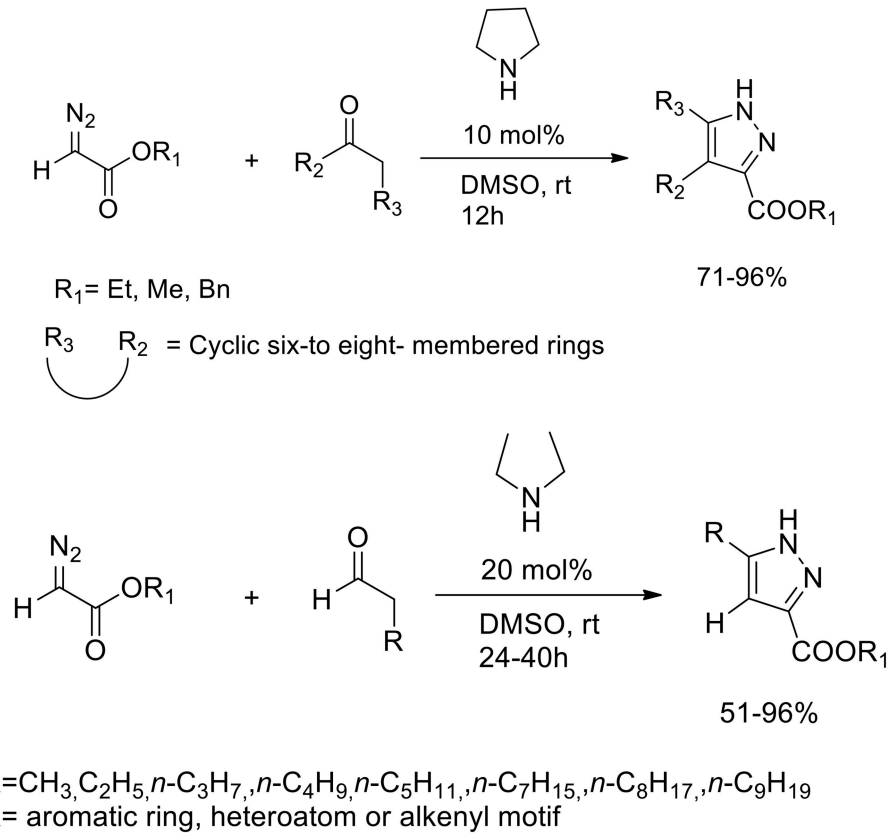
SCHEME 23 | One pot Three component catalytic asymmetric synthesis of pyrazolidine.

use of catalysts or additives and more than 95% yield was obtained in EtOAc (**Scheme 27**). In the presence of 20 mol% $Cu(OTf)_2$ in $CHCl_3$ the cycloaddition reaction afforded the corresponding product with only 23% conversion after 24 h at room temperature. When $Ni(OAc)_2{\cdot}4H_2O$ was used in $CHCl_3$, the conversion was enhanced to 89%. *N*-tosyl and *N*-alkoxycarbonylated protected, 3-nitroindoles performed very well giving in high yields the corresponding cycloadducts. Because of its reduced electrophilicity *N*-Methyl-protected 3-nitroindole failed to undergo the transformation. The versatility of this method was demonstrated with a list of structurally different C,N-cyclic azomethine imines.

1,2,3-triazoles have a wide range of applications as potential bioactive compounds and are often used in drugs synthesis. A general and efficient method for their fabrication came in the early 2000s with the novel concept of "click" chemistry and the Cu-catalyzed alkyne–azide cycloaddition reaction provides the regioselective formation of 1,4-disubstituted 1,2,3-triazoles. The metallo-catalyzed alkyne–azide cycloaddition reaction for the formation of 1,5-disubsituted 1,2,3-triazoles



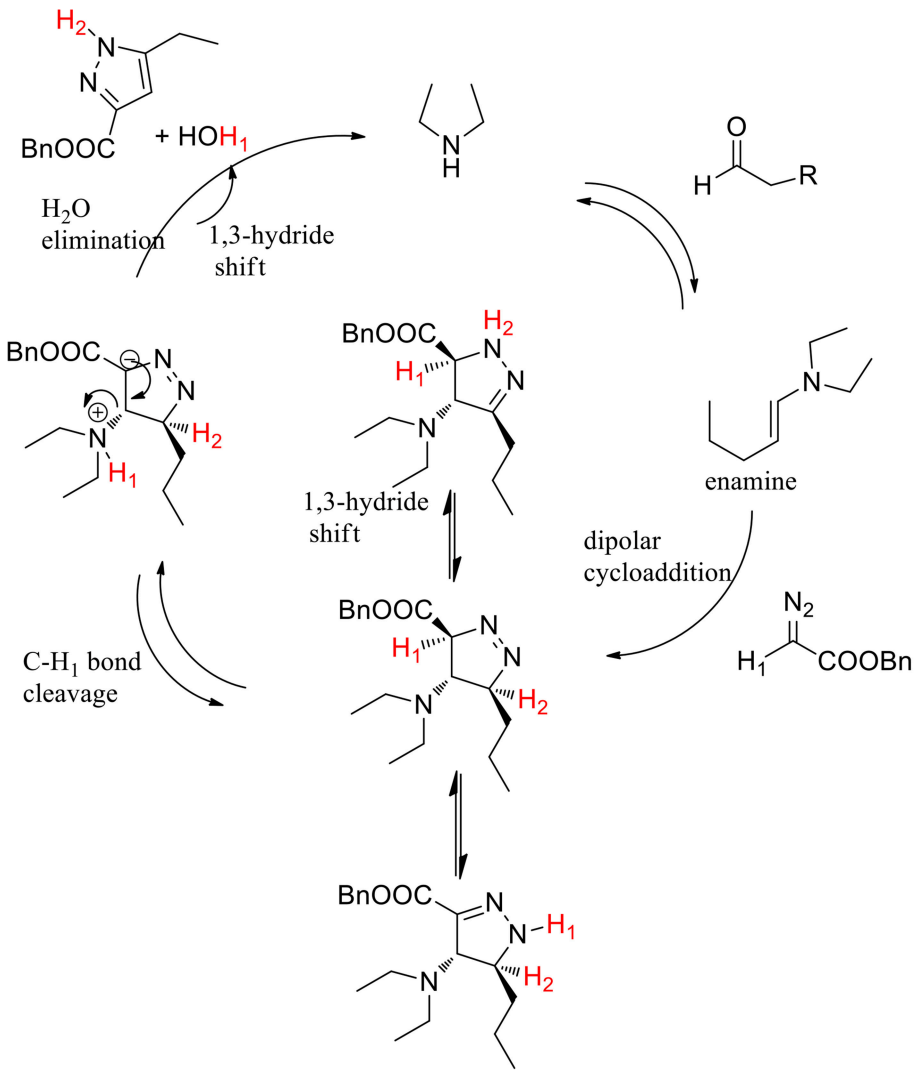
SCHEME 24 | Organocatalytic synthesis of spiro[pyrrolidin-3,3′-oxindoles].



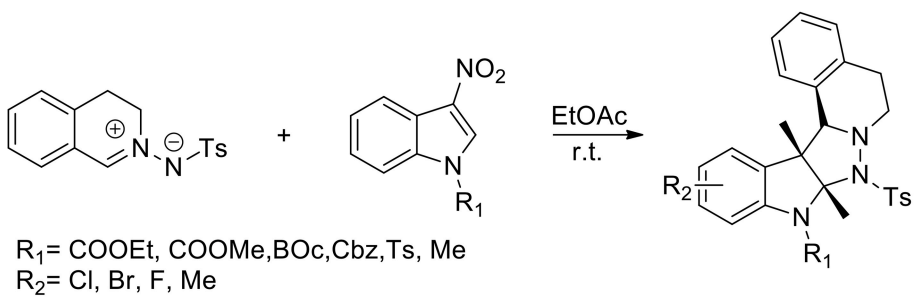
SCHEME 25 | Polysubstituted pyrazoles synthetic route from diazoacetates and carbonyl compounds.

was published later. However, the reactions mentioned above have made use of heavy metals, which has limited their practical applications.

Alternative synthetic pathways for 1,2,3-triazoles have also been developed and 1,2,3 triazoles have freely been obtained from a combination of azides with a range of reaction partners: e.g., cycloadditions of either β-keto esters or nitriles to azides catalyzed by secondary amines (Costa et al., 2017), cycloaddition of a triple domino sequence of reactions between azide, amine, and 5-bromo-2-furylcarbinol (Yang et al., 2015), the reaction of enols and enamines with azides (Blastik et al., 2018), nitro methylene-based three-component synthesis (Thomas et al.,



SCHEME 26 | Postulated reaction pathway.



SCHEME 27 | Synthesis of polycyclic tetrahydroisoquinoline derivatives.

2014), and others. However, these methods entail the use of organic azides or sodium azides, which are difficult to handle and toxic, particularly on a large scale. In a 2017 review, Ahmed (Ahmed et al., 2017) presented some less well-known synthetic protocols for 1,2,3-triazoles under azide-free and metal-free environments (**Figure 3**).

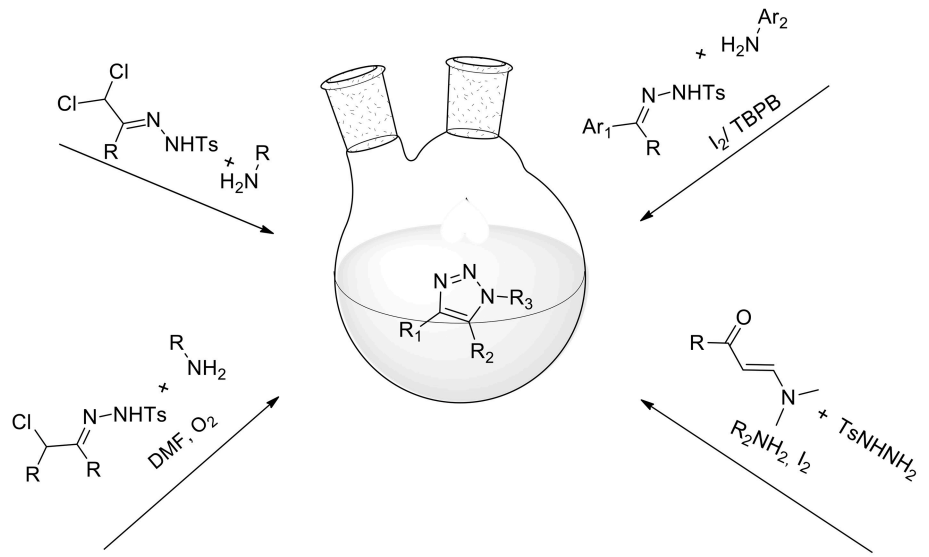
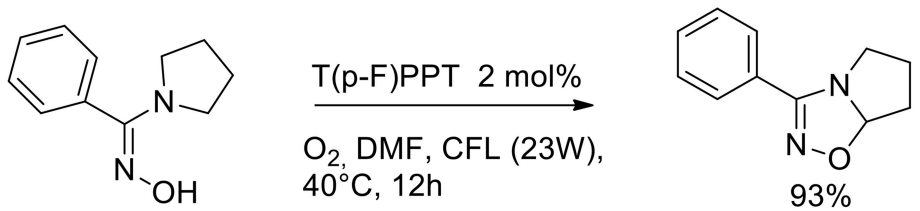


FIGURE 3 | "Metal-free" and "azide-free" syntheses of triazoles.



SCHEME 28 | Synthesis of bicyclic 1,2,4-oxadiazolines.

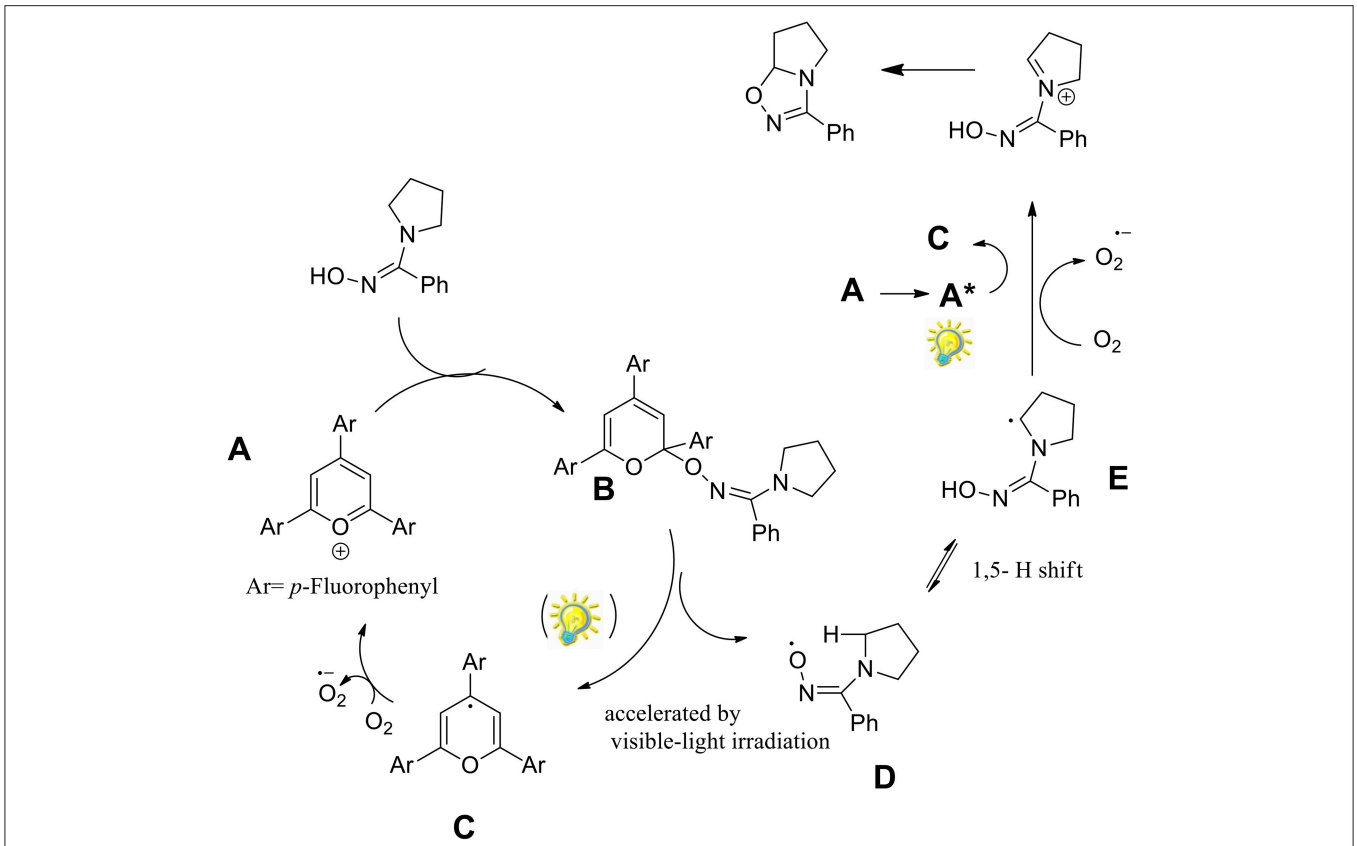
LIGHT INDUCED

The importance of aza-heterocycles relates to their presence as natural products, drugs and biologically relevant compounds. A variety of methods have been developed for the synthesis of 1,2,4-oxadiazolines, and these are typically carried out via the [4+2] cycloaddition of an imine with a nitrile oxide (generated *in situ* from hydroxamoyl chloride or nitroalkane). The design of a new synthetic path of 1,2,4-oxadiazolines, especially greener methods, is highly desirable because many of these methods suffer from one or more drawbacks. Soni et al. (2018) have very recently presented a greener method for the synthesis of 1,2,4-oxadiazolines via an intramolecular oxidative cyclisations of amidoximes in the presence of an organocatalyst and molecular oxygen. The authors optimized the reaction conditions to give 3-phenyl- 5,6,7,7a-tetrahydropyrrolo[1,2-d][1,2,4]oxadiazole from phenyl(pyrrolidin- 1-yl)methanone oxime, which was used as a model substrate. The optimized conditions involved 2 mol% of an organophotocatalyst, 2,4,6-tris(4-fluorophenyl)pyrylium tetrafluoroborate [T(p-F)PPT] at a 0.2 M concentration in DMF under an atmosphere of molecular oxygen. Visible-light irradiation was provided by a compact fluorescent lamp (CFL, 23 W). Organophotocatalyst can reduce the drawbacks of transition metals related to toxicity and the low residues admitted in pharmaceutical products (**Scheme 28**).

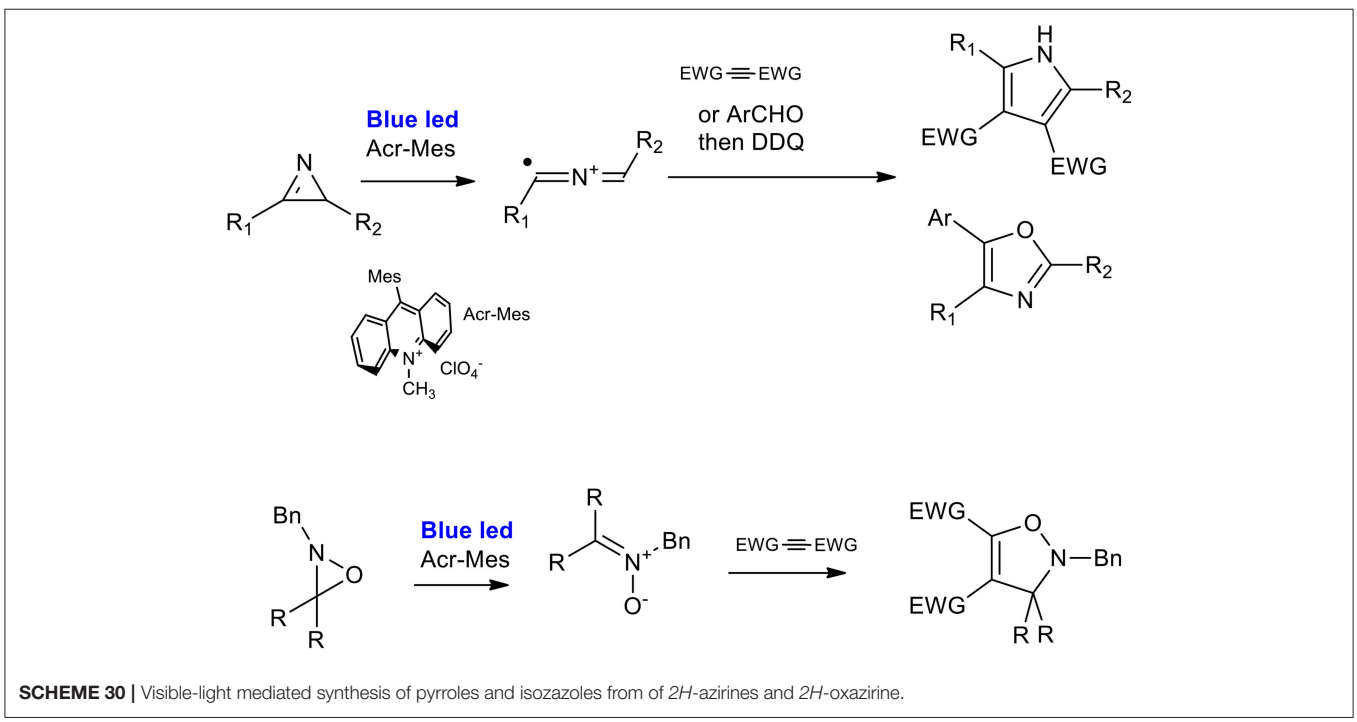
The authors investigated several pyrrolidinyl oxime derivatives both with electron-withdrawing and electron-donating substituents, for the oxidative cyclization to 1,2,4-oxadiazolines with a mechanism as proposed in **Scheme 29**.

It was observed that triphenylpyrylium (TPP) derivatives were the only effective photocatalysts among those examined, with conversion even in absence of light. As described in the **Scheme 29**, the reaction begins with the nucleophilic addition to the triphenylpyrylium ion (A) toward intermediate B. Molecular oxygen provides the oxidation of C by regenerates catalyst A. The iminyloxyl radical D undergoes an intramolecular 1,5- hydrogen atom transfer (HAT) to the radical E, which is then oxidized to the iminium ion F. The final 1,2,4-oxadiazoline is generated by intramolecular cyclization of F.

Visible-light-driven photoredox catalysis is attracting interest because of its inherent features of green chemistry and sustainability. In addition to a number of radical reactions,



SCHEME 29 | Plausible mechanism for the synthesis of 1,2,4-oxadiazolines.



SCHEME 30 | Visible-light mediated synthesis of pyrroles and isozazoles from of *2H*-azirines and *2H*-oxazirine.

several [2+3] cycloaddition applications have been described in the existing literature (Narayanam and Stephenson, 2011; Nakajima et al., 2016; Staveness et al., 2016; Savateev and Antonietti, 2018).

2*H*-azirines can react with activated alkynes or aldehydes to produce polysubstituted pyrroles or 2,5-dihydrooxazole, respectively, under very mild reaction conditions (visible-light irradiation, metal-free, and room temperature). As described by Xuan et al., the optimized procedure is catalyzed by 9-mesityl-10-methyl-acridinium perchlorate in dichloroethane under irradiation from a 3 W white LED light. Excellent results were obtained when a range of substituted 2H-azirines were reacted with dimethyl but-2-yne-dioate (Xuan et al., 2014). 2*H*-Azirines reacted with aldehydes in the presence of Li_2CO_3. This was done to avoid the oxidation of aldehydes to carboxylic acids, and 2,3-dichloro5,6-dicyano-1,4-benzoquinone (DDQ) was added to the reaction system in order to perform the one pot synthesis of oxazole. The applicability of the reactions was demonstrated using a panel of 12 2,4,5 trisubstituted oxazoles, giving yields in the 40–80% range (**Scheme 30**) (Zeng et al., 2015).

The ring-opening of 2*H*-oxazirine has been described as occurring via visible-light-mediated photoredox-catalyzed single-electron transfer (SET), giving nitrone precursors. The 1,3-dipolar cycloaddition was therefore used for the synthesis of 4-isoxazolines. 9-mesityl-10-methyl-acridinium perchlorate was the strategic choice of catalyst because of its high oxidizing power (+2.06 V). The [3 + 2] cycloaddition reaction of oxaziridine with dimethyl acetylenedicarboxylate gave very good results when performed in CH_3CN in the presence of water, used as an additive, and a large set of 4-isoxazolines was synthesized with a good average yield.

The first attempt to describe the mechanism of pyrrole cyclization focused on a radical cycloaddition of the intermediate 2-azaallenyl radical cation, which was in equilibrium with a 1,3-radical-cationic species. Subsequently, the publication mentioned the synthesis of the dihydroisoxazole by an hypothesis of a polar cycloaddition. In fact, the authors proposed the single-electron reduction of the nitrone radical to a nitrone species.

AUTHOR CONTRIBUTIONS

All the authors contributed equally to the review preparation. GC supervised the work and edited the final version.

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Gas-Phase Conversion of 1,3-Dithiolane-2-Thione Into 1,3-Dithiolan-2-One Over Molybdenum Trioxide

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Gas-phase reaction of 1,3-dithiolane-2-thione over molybdenum trioxide supported on pumice stone results in efficient conversion into 1,3-dithiolan-2-one. The solid reagent is regenerated on exposure to air and thus acts as a catalyst for the overall conversion of the thione and oxygen from the air into the ketone and sulfur dioxide. The process can be carried out under either dynamic vacuum or atmospheric pressure flow conditions and using a solid reagent prepared either by physical mixing of MoO_3 with the support or by solution impregnation, with an isolated yield of up to 67% obtained.

Keywords: oxidation, gas-phase reaction, thione, flow chemistry, green chemistry

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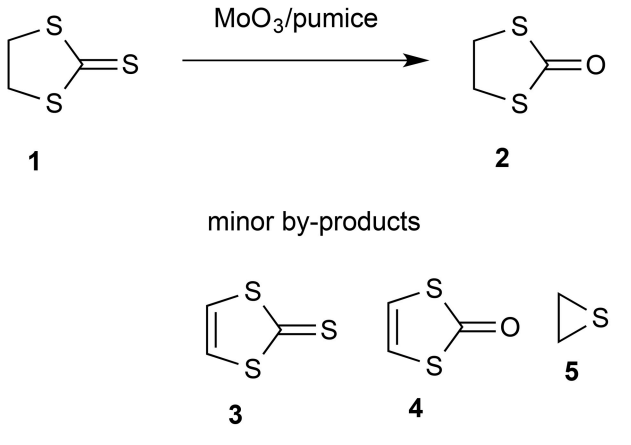
INTRODUCTION

There has been considerable recent interest in the use of flash vacuum pyrolysis (FVP) for the synthesis of heterocyclic compounds (Aitken and Boubalouta, 2015) and there have been occasional reports of its use in synthesis of pharmaceutical agents (Horn and Gervay-Hague, 2009) and natural products (Harras et al., 2017). The inherently clean conditions where each substrate molecule reacts during a brief "contact time" in the hot zone in the absence of solvents, reagents, or products and the products are then rapidly condensed in a cold trap at cryogenic temperatures can lead to high yields of otherwise inaccessible products. An extra dimension to the normal FVP through an empty tube is added by using a tube packed with a solid reagent or catalyst and such "vacuum gas-solid reactions" (Denis and Gaumont, 1997) have been successful in various areas. Among these is the use of solid bases such as potassium t-butoxide, potassium hydroxide, and sodium carbonate to bring about elimination reactions (Guillemin and Denis, 1988; Guillemin et al., 1988; Aitken et al., 1999) and metals such as magnesium (Aitken et al., 1997a,b, 2002, 2017; Aitken and Oyewale, 2015), zinc (Chapman et al., 1976; Rozsondai et al., 1989) and silver (Binnewies et al., 1984) to bring about dehalogenation. Solid catalysts such as zeolites and barium tungstate can also profoundly influence the product distribution in gas-phase processes involving reactive intermediates (Moyano et al., 2007, 2010; Lener et al., 2013). Attracted by a brief thesis report that FVP over molybdenum trioxide was effective in dehydrogenating tetrahydroquinolines and -isoquinolines to the fully aromatic heterocycles (McDougald and McNab, 2000), we have shown that this system is effective in aromatizing a range of partly hydrogenated heterocycles. In the course of this study we examined 1,3-dithiolane-2-thione **1**. Preliminary experiments established that there was no significant dehydrogenation but instead exchange of the exocyclic sulfur for oxygen

to give 1,3-oxathiolan-2-one **2** (**Scheme 1**). We therefore sought to optimize this transformation.

The starting thione **1** is readily available, having first been prepared at a very early date by reaction of sodium trithiocarbonate with 1,2-dibromoethane (Husemann, 1862). Later and more convenient preparations include reaction of 1,2-dichloroethane with carbon disulfide in the presence of a base (Coltof, 1940) or with sodium trithiocarbonate under phase-transfer conditions (Degani et al., 1986) and, most convenient and economical on an industrial scale, base-induced reaction of carbon disulfide and ethylene oxide (Culvenor et al., 1946). The product **2** is also well known and, after some initial confusion with the isomeric 1,3-oxathiolane-2-thione structure (Husemann, 1863), its identity was firmly established by the end of the 19th century (Miolati, 1891; Busch and Lingenbrink, 1900). Most significantly for the current project, the conversion of **1** into **2** has been achieved using a variety of reagents but most of these are highly toxic or hazardous and lead to formation of harmful waste. A clean method using air as the ultimate oxidant would therefore be highly desirable and fulfill many of the requirements for a "green chemistry" process. By way of contrast, the existing methods include stoichiometric use of mercuric acetate (Challenger et al., 1953), mercuric oxide/acetic anhydride (Overberger and Bonsignore, 1958), polymer-supported selenoxide and telluroxide reagents (Hu et al., 1986), dimethyl sulfate followed by acid hydrolysis (Degani et al., 1994), epoxycyclohexane (Barbero et al., 1996) and potassium permanganate under phase transfer conditions (Aitken et al., 1997c). Compound **2** is long known to be a convenient precursor for synthesis of the useful unsaturated heterocycles **3** and **4** (Mayer and Gebhardt, 1964), and there have been various recent applications of the product **2** including as a component of the electrolyte in high-temperature batteries (Ihara et al., 2008), as a key intermediate in the chemical recycling of waste polycarbonate (Hata et al., 2003), and as a precursor for binuclear iron-sulfur carbonyl complexes (Lagadec et al., 1987; Xiao et al., 2017).



SCHEME 1 | Gas-phase conversion of **1** into **2** with minor by-products also identified.

RESULTS AND DISCUSSION

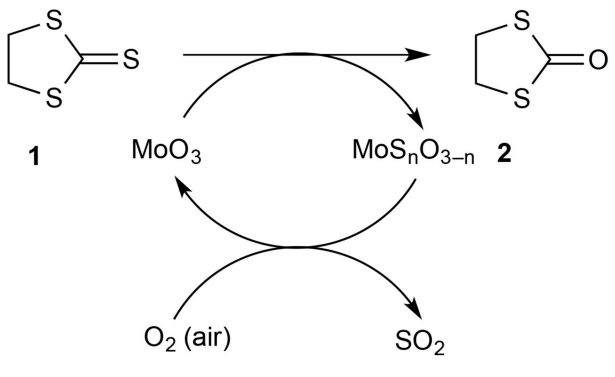
Molybdenum trixode is a readily available and thermodynamically stable material that has found use as a catalyst in many large-scale catalytic processes (Sebenik et al., 2012). Significantly for what follows, it is manufactured by roasting the ore molybdenite (MoS_2) in air at 600°C. For our studies, we used pumice stone as an inert support material. This is a readily available mineral whose surface properties have been studied in detail (Brito et al., 2004) and which has recently found use as a catalyst support for oxidative waste water treatment (Alver and Kilic, 2018). The solid reagent for our studies was prepared either by directly shaking a mixture of commercially available pumice stone chips (BET surface area 2.2 m^2g^{-1}) with finely powdered MoO_3 or by the solution impregnation method which has been commonly used to prepare supported MoO_3 catalysts (Hu and Wachs, 1995; Chary et al., 2004; Rathod et al., 2014). In this the pumice stone chips were stirred in an aqueous solution of ammonium molybdate at 80°C for 5 h. The mixture was then evaporated to dryness and the residual solid first dried at 100°C and then calcined at 500°C in air.

Initial studies quickly established that for effective reaction, the molybdenum trioxide should be evenly dispersed on a large amount of the solid support which filled the reaction tube (**Table 1**). For example while a packing of 1.25 g MoO_3 on 5 g pumice gave only 11% conversion, this was raised to 96% using a packing of 0.77 g MoO_3 on 50 g pumice (runs 1 and 2). Varying the temperature (runs 3–6) showed that for high conversion a temperature of at least 450–500°C was required. However, when a larger scale run was carried out at 500°C a problem became apparent as, despite a high degree of conversion, only 15% isolated yield was obtained. This was due to decomposition of product **2** under the conditions used, something that was readily confirmed by passing **2** through pumice at 450°C and 10^{-2} Torr which resulted in only 24% recovery with 76% decomposition into gases and other volatile products such as thiirane **5** which was detected by NMR in some runs. Therefore, a slightly lower reaction temperature may be preferable as the lower conversion is more than made up for by the lower extent of product decomposition leading to a higher isolated yield.

We were keen to evaluate the capacity of our solid-supported reagent and estimate how much of the MoO_3 was available for reaction. For this, the same tube of reagent was used repeatedly in the hope of exhausting the reagent and eventually observing a drop in conversion. However, this did not happen and this led to the realization that the reagent was being regenerated by exposure to air between runs. This was easily demonstrated by conducting successive runs on a 500 mg scale and leaving the hot reagent bed exposed to air for 30 min between runs giving 76 then 77% conversion. However, when a run was done as quickly as possible after the previous one with minimal exposure of the reagent to air in between, a drop in conversion to 20% was observed (run 8). A conventional run after this with exposure of the reagent to air saw a return to 74% conversion. A useful qualitative indicator for the state of the reagent bed was its color: the initially pure white solid became bright greenish-yellow upon partial sulfurization and then returned to white after

regeneration in air. The fact that the partly sulfurized MoO_3 is reconverted to MoO_3 on exposure to air at 500°C should come as no surprise since this is essentially the process by which it is manufactured from molybdenite ore (MoS_2). This has the important consequence that the process for converting **1** into **2** can in principle be catalytic in MoO_3 with oxygen of the air as the ultimate oxidant and the eliminated sulfur ending up as SO_2 which could be readily trapped from the gas phase if desired (**Scheme 2**).

We now turned to the solution impregnation method to prepare the solid reagent/catalyst and as expected this gave significantly better results. Predictably, decreasing the reaction temperature from 500°C to 300°C resulted in progressively lower conversion (runs 9–12), but this was accompanied by less product decomposition leading to higher isolated yields particularly at 400°C which at 67% gave the highest isolated yield in the current study. A second reagent sample prepared by the impregnation method but using ten times more ammonium molybdate gave excellent conversion at 400°C (run 13) but unfortunately this was accompanied by significant decomposition leaving an isolated yield of only 42%. When this high molybdenum catalyst was used for a large-scale preparation at atmospheric pressure, both the conversion and isolated yield were poorer and slight traces of both the dehydrogenation products 1,3-dithiole-2-thione **3** and 1,3-dithiol-2-one **4** were evident (run 14).



SCHEME 2 | Conversion of **1** into **2** with air regeneration of the catalyst.

Since we were well aware that the requirement for high vacuum is problematic for scaling up any flow process, we decided to examine this reaction under atmospheric pressure flow conditions. Using a stream of nitrogen as carrier gas and the solid catalyst prepared by impregnation, the conversion and isolated yield were found to be optimal at a furnace temperature of 300°C with 53% isolated yield and poorer results were obtained at either 250°C or 350°C (runs 15–17).

In conclusion, we have demonstrated that molybdenum trioxide supported on pumice stone is an effective reagent for the gas-phase conversion of dithiolanethione **1** into the corresponding dithiolanone **2** under both FVP and atmospheric pressure flow conditions. To maximize the isolated product yield it may be desirable in each case to operate at somewhat below the temperature of maximum conversion so that product loss by decomposition is minimized. As a bonus, the supported reagent is fully regenerated on exposure to air and may thus act as a catalyst with overall consumption of oxygen from the air and production of sulfur dioxide in the course of converting **1** into **2**. Further applications of gas-phase reactions over supported

TABLE 1 | Results for gas-phase conversion of 1,3-dithiole-2-thione into 1,3-dithiol-2-one over molybdenum trioxide.

Run	Quantity of 1 (mg)	Temperature (°C)	Pressure (Torr)	Reagent preparation	Starting material %	Product 2 %	Isolated yield %
1	40	550	10^{-2}	A	89	11	—
2	32	550	10^{-2}	B	4	96	—
3	42	350	10^{-2}	B	64	36	—
4	35	400	10^{-2}	B	35	65	—
5	35	450	10^{-2}	B	19	81	—
6	43	500	10^{-2}	B	8	92	—
7	498	500	10^{-2}	B	12	88	15
8*	500	500	10^{-2}	B	80	20	—
9	40	500	10^{-2}	C	4	96	8
10	40	450	10^{-2}	C	9	91	62
11	30	400	10^{-2}	C	28	72	67
12	40	300	10^{-2}	C	32	68	39
13	77	400	10^{-2}	D	0.4	99.6	42
14	2020	400	760	D	40	60	19
15	52	250	760	C	59	41	15
16	34	300	760	C	31	69	53
17	46	350	760	C	24	76	12

Reagent preparation: A = MoO_3 (1.25 g) shaken with pumice (5 g); B = MoO_3 (0.77 g) shaken with pumice (50 g); C = pumice (50 g) impregnated with MoO_3 from ammonium molybdate (0.91 g); D = pumice (50 g) impregnated with MoO_3 from ammonium molybdate (9.1 g).

** Run conducted immediately after previous one with no exposure of reagent to air in between.*

molybdenum trioxide in heterocyclic chemistry will be reported shortly.

EXPERIMENTAL

Preparation of Chemicals

1,3-dithiolane-2-thione **1** was prepared by the literature method (Culvenor et al., 1946) involving reaction of ethylene oxide with carbon disulfide and potassium hydroxide in methanol and was obtained as yellow crystals, mp 36–37°C. ^{1}H NMR ($CDCl_3$) δ = 4.00 (s); ^{13}C NMR ($CDCl_3$) δ = 228.8 (C = S), 43.7 (CH_2).

1,3-dithiolan-2-one **2** for reference was prepared by the literature method (Aitken et al., 1997c) involving $KMnO_4$ oxidation of **1** under phase transfer conditions and was obtained as pale yellow crystals, mp 35–36°C. ^{1}H NMR ($CDCl_3$) δ = 3.72 (s); ^{13}C NMR ($CDCl_3$) δ = 198.5 (C=O), 36.2 (CH_2).

Pyrolysis Equipment and Reaction Procedure

Gas phase reactions were carried out using a horizontal quartz reaction tube (30 × 2.5 cm) heated in a Carbolite Eurotherm laboratory tube furnace MTF-12/38A, the temperature being measured by a pt/pt-13% Rh thermocouple located at the center of the furnace. The reaction tube was packed with the solid reagent (50 g) sandwiched between plugs of glass wool. For vacuum experiments the system was connected via a *U*-shaped cold trap to an Edwards model E2M5 high capacity rotary oil pump giving pressures of 10^{-3}–10^{-2} Torr and the starting material was volatilized by external heating of the inlet tube. For atmospheric pressure experiments the starting material was volatilized by external heating of the inlet tube and carried through the reaction tube by a slow flow of nitrogen gas to a U-shaped cold trap.

Preparation of Solid Reagent/Catalyst

Finely powdered molybdenum (VI) oxide was obtained from Acros Organics and granular pumice stone was obtained from Fluka with grain size 4–6 mm. The BET surface area of the latter as determined by porosimetry was 2.2 m^2g^{-1}. The preparation of the supported reagent/catalyst was done in two separate ways. In the first, the finely powdered MoO_3 (0.77 g) was shaken in a bottle with pumice stone chips (50 g) until the two solids were intimately mixed and the pumice was evenly coated with MoO_3. In the second method, ammonium molybdate tetrahydrate (0.91 g) was stirred with pumice stone chips (50 g) in water (250 mL) at 80°C for 5 h. The mixture was then evaporated using a rotary evaporator and the resulting solid was first dried in an oven at 100°C for 16 h and then calcined by heating in the reaction tube at 500°C under slight vacuum for 5 h. Before use the reaction tube packed with solid reagent/catalyst was heated to 500°C open to the air for 30 min to drive off adsorbed moisture.

Analysis of Products

This was performed using NMR. The product was dissolved out from the cold trap using $CDCl_3$ and the ratio of starting material **1** to product **2** was determined by integration of the ^{1}H NMR signals at δ 4.00 and 3.72, respectively. Confirmation of the identity of the products was obtained by ^{13}C NMR and comparison with the literature data (Poleschner et al., 1981). Typical ^{1}H and ^{13}C NMR spectra are shown in the **Supplementary Material** and trace components also evident there (**Table 1**, run 14) are 1,3-dithiole-2-thione **3** (δ_H 7.18, δ_C 129.3) and 1,3-dithiol-2-one **4** (δ_H 6.83, δ_C 118.2). In some experiments thiirane **5** (δ_H 2.39, δ_C 18.1) was also observed.

AUTHOR CONTRIBUTIONS

TC and MA carried out the experimental work and processed the results. RA conceived the study, analyzed and interpreted the results and wrote the paper.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2019.00204/full#supplementary-material

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REVIEW
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Dialkyl Carbonates in the Green Synthesis of Heterocycles

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This review focuses on the use of dialkyl carbonates (DACs) as green reagents and solvents for the synthesis of several 5- and 6-membered heterocycles including: tetrahydrofuran and furan systems, pyrrolidines, indolines, isoindolines, 1,4-dioxanes, piperidines, and cyclic carbamates. Depending on the heterocycle investigated, the synthetic approach used was different. Tetrahydrofuran systems, pyrrolidines, indolines, isoindoline, and 1,4-dioxanes were synthesized using dimethyl carbonate (DMC) as sacrificial molecule ($B_{Ac}2/B_{Al}2$ mechanism). Cyclic carbamates, namely 1,3-oxazin-2-ones, were prepared employing DACs as carbonylating agents, either by $B_{Ac}2/B_{Al}2$ mechanism or through a double $B_{Ac}2$ mechanism. Piperidines were synthetized taking advantage of the anchimeric effect of a new family of dialkyl carbonates, i.e., mustard carbonates. Finally, in the case 5-hydroxymethylfurfural (HMF), DMC has been employed as efficient extracting solvent of this extensively investigated bio-based platform chemical from the reaction mixture. These synthetic approaches demonstrate, once again, the great versatility of DACs and their—yet to be fully explored—potential as green reagents and solvents in the synthesis of heterocycles.

Keywords: heterocycles, green synthesis, cyclization, dialkyl carbonates, green chemistry

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INTRODUCTION

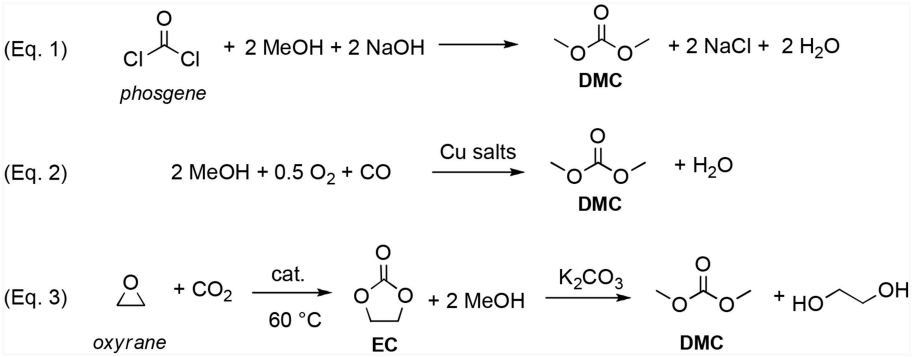
Dialkyl carbonates (DACs) are well-known and extensively exploited safe, green reagents and solvents. In particular, dimethyl carbonate (DMC)—the smallest organic carbonate—encompasses the following desirable features of a green compound (Tundo and Selva, 2002; Tundo et al., 2018):

Green Synthesis

DMC was initially produced by reaction of phosgene with methanol in basic conditions (Equation 1; **Scheme 1**). However, this process caused also the formation of a considerable amount of NaCl that had to be disposed of (Shaikh and Sivaram, 1996).

The main turning point in DACs exploitation was the development by Enichem (Romano et al., 1979) and UBE (Nishihira et al., 1993), of a greener synthesis of DMC, based on the catalytic oxidative carbonylation of methanol with oxygen (Equation 2; **Scheme 1**). As a result, since the middle 80's, DMC was produced in a commercial scale and started to be investigated as reagent and solvent in several industrial processes.

Over the years, numerous other green approaches to DMC were reported including alcoholysis of urea (Ball et al., 1980; Wang et al., 2005; Wu et al., 2012) and direct conversion of CO_2 and methanol into DMC employing inorganic and organic dehydrating agents (Yamazaki et al., 1979; Hoffman, 1982; Zhang et al., 2011; Fan et al., 2012). Nowadays DMC is mainly produced by insertion of CO_2 into oxyrane to give ethylene carbonate (EC), which—by reaction with methanol



SCHEME 1 | Syntheses of DMC. Via phosgene (Equation 1); by catalytic oxidative carbonylation of methanol (Equation 2); by CO_2 insertion into oxyrane (Equation 3).

in basic conditions—generates DMC and ethylene glycol (Equation 3; **Scheme 1**) (Kondoh et al., 1995; Miyaji et al., 2007; He et al., 2014; Wang et al., 2014; Martín et al., 2015).

No Toxicity

DACs display only low (eco)toxicity and are completely biodegradable. In particular, DMC is classified as a flammable liquid that does not smell (methanol-like odor) and does not have irritating or mutagenic effects by either contact or inhalation (Lamoureux and Agüero, 2009). As a result, DMC is a safe to handle compound and a very efficient alternative to chlorine reagents, as it can replace toxic methyl halides and dimethyl sulfate in alkylation reactions and phosgene in alkoxycarbonylation reactions. Furthermore, it can be employed as a substituted of halogenated solvents as dichloromethane and chloroform.

Numerous Applications as a Solvent

Dialkyl carbonates offer numerous vantages as solvents since they are stable under ambient conditions and available in large amounts at low prices. Besides DACs polarity and boiling points can be easily tuned by varying length and nature of the alkyl groups.

DACs are considered aprotic highly dipolar solvents like DMSO or DMF, although they show (except DMC) only limited miscibility with water.

The use of organic carbonates as solvents for electrochemical applications has been extensively investigated especially as a non-aqueous electrolyte. Furthermore, their use in extractive procedures is also well-established. In recent years, DACs are also started to be investigated as possible alternatives to replace VOCs and as co-solvents in cleaning processes and in cosmetics (Schmeidl, 1990; Rüsch gen. Klaas and Warwel, 2001; Su et al., 2009; Schfäfner et al., 2010; Olschimke et al., 2012; Tannir et al., 2012; Huang et al., 2015).

Versatility as Green Reagent

DACs are versatile reagents that can be employed both in alkylation (instead of alkyl halides) and alkoxycarbonylation reactions (instead of phosgene) (Climent et al., 2011; Tundo et al., 2018). In general, organic carbonates chemistry follows the Pearson's Hard-Soft Acid-Base (HSAB) theory (Pearson, 1963). In presence of a base and at $T < 90°C$, a DAC can react with a hard nucleophile at the sp^2 carbonyl moiety via bimolecular base-catalyzed acyl-cleavage ($B_{Ac}2$) substitution (Equation 1; **Scheme 2**) (Tundo et al., 2009; Grego et al., 2012). On the other hand, if the reaction is conducted at $T > 150°C$, DACs generally react—as alkylating agents—with a soft nucleophile at the saturated sp^3 carbon via bimolecular base-catalyzed alkyl-cleavage ($B_{Al}2$) substitution (Equation 2; **Scheme 2**) (Tundo et al., 2009; Aricò and Tundo, 2016b). DACs reactivity has been investigated with numerous monodentate and bidentate nucleophiles (Rosamilia et al., 2008a,b; Fiorani et al., 2018) in batch as well as in continuous-flow apparatus (Tundo et al., 2010c; Grego et al., 2013).

Another example of DACs versatility is the use of DMC for biocatalytic synthesis of glycerol carbonate. In this catalytic route glycerol was reacting with DMC in the presence of lipase under solvent-free conditions (Tudorache et al., 2012; Cushing and Peretti, 2013).

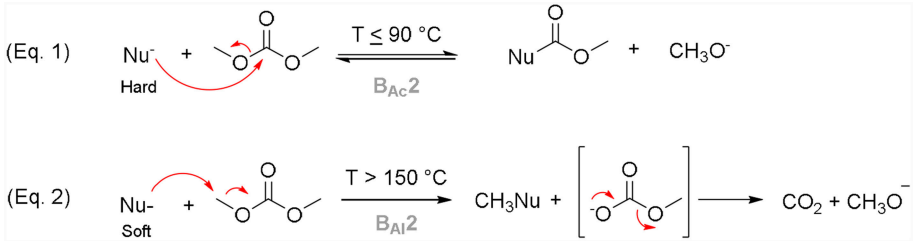
However, HSAB theory is not exhaustive in explaining all the features of DACs reactivity. The use of DACs in the preparation of heterocyclic compounds is a poignant example in which factors, such as entropic or anchimeric effects may drive the reaction mechanism. In this prospect, the purpose of this review is to report the use of DACs as efficient reagents and solvents in the green synthesis of five- and six-membered heterocycles.

The versatility of the organic carbonates is pivotal in these cyclization reactions, inasmuch, depending on the target heterocycle, DACs may be used as sacrificial molecule, carbonylating agent, reaction media, promoter of ring expansion or transposition reactions.

5-MEMEBERED HETEROCYCLES

Tetrahydrofuran and Furan Systems

Tetrahydrofuran systems are incorporated as structural subunits in numerous natural and synthetic compounds, such as muscarine (Matsumoto et al., 1969), lithospermic acid (Wang and Yu, 2011), obtusafuran, kadsurenone (Benbow and Katoch-Rouse, 2001), polyether antibiotics (Westley, 1982), inostamycins (Imoto et al., 1990), etc.



SCHEME 2 | DMC reactivity according to the HSAB theory.

The simplest method for the synthesis of tetrahydrofurans is via acidic cyclodehydration of 1,4-diols, i.e., the preparation of tetrahydrofuran from 1,4-butanediol (Olah et al., 1981; Pinkos et al., 2004; Mitsudome et al., 2012). In the literature, there are reported several other synthetic approaches to cyclic ethers, such as cyclization or cycloaddition reaction. These procedures generally employ heavy metals (Sharma et al., 2002; Shibata et al., 2005; Panda and Sarkar, 2008; Gadda et al., 2010; Tsui et al., 2012) or chlorine chemistry in the form of leaving groups, i.e., tosylate, mesylate etc. (Grubb and Branchaud, 1997; Lindner and Rodefeld, 2001; Adaligil et al., 2007).

Advances in the research of greener approaches to heterocyclic structures have been achieved by using alternative reagents. In this view, it has been reported that 5-membered cyclic ethers can be easily synthesized starting from1,4-diols by DMC chemistry in mild conditions and high yield. In particular, tetrahydrofuran (THF) was synthesized in a quantitative yield by reacting 1,4-butanediol with DMC (10.0 mol eq.) using a stoichiometric excess of a strong base, such as NaOMe or *t*-BuOK (2.0 mol eq.) and heating this solution to reflux for 4 h (Equation 1; **Scheme 3**) (Aricò et al., 2012c).

The cyclization of 1,4-butanediol **1** to THF **2** can be ascribed to the versatility of the DMC as reagent, that operates as a sacrificial molecule (Equation 1; **Scheme 3**). In fact, most likely, the cyclization mechanism comprises of the 1,4-diol methoxycarbonylation by a $B_{Ac}2$ mechanism, followed by an intramolecular cyclization thorough a $B_{Al}2$ mechanism with the release of the methylcarbonate anion as leaving group (Cyclization mechanism, **Scheme 3**).

Several other substrates were tested so to investigate the general applicability of this synthetic approach. 2-Methyl tetrahydrofuran **4** was prepared from 1,4-pentanediol **3**, in high yield under similar conditions, although a quantitative conversion required an excess of base (3 mol eq.) to cope with the lower reactivity of secondary alcohols (Equation 2; **Scheme 3**). In another example, the reaction performed using 2,5-hexandiol **5** (mixture of stereoisomers) gave the corresponding cyclic ether **6** only in traces (<5%); the substrate conversion was moderate even after 24 h (Equation 3; **Scheme 3**). In this case, even by using an excess of base (3.0 mol eq.), the cyclization was hindered by the reduced reactivity of secondary alcohols, both in the methoxycarbonylation step and in the nucleophilic substitution reaction. This latter result demonstrates that the DMC-based cyclization reaction requires to take place at least one primary alcohol incorporated in the starting diol. In fact, *cis*-1,4-but-2-ene diol **7** underwent fast and quantitative cyclization reaction (Equation 4; **Scheme 3**). In this case study, the formation of the related 2,5-dihydrofuran **8** is probably aided by the favorable *cis* position of the primary alcohol moieties; as a matter of fact, when the reaction was performed with a catalytic amount of sodium methoxide (5 mol %) the cyclic compound still formed in appreciable yield (30% yield).

The reactivity of 1,4-diols bearing aromatic moieties, i.e., 1,2-dihydroxymethyl benzene **11** and 2-hydroxyethyl phenol **9** was also reported. 2-Hydroxyethyl phenol **9** demonstrated to be a very reactive 1,4-diol, in fact, 2,3-dihydrobenzofuran **10**, was the only product formed even in the presence of substoichiometric amount (0.5 mol eq.) of a base (Equation 5; **Scheme 3**).

1,2-Bis(hydroxymethyl)benzene **11** also led to the quantitative formation of phthalan **12** under similar reaction conditions (Equation 6; **Scheme 3**).

Some preliminary computational studies on this DMC-based cyclization reaction were then carried out. It was showed that after methoxycarbonylation of one hydroxy groups (reactivity order: primary alcohol > secondary alcohol > tertiary alcohol) the pathway leading to the cyclic ethers was the most energetically favored (Aricò et al., 2012c, 2018b).

This *in silico* evidence confirmed the proposed two-step mechanism for the DMC-assisted cyclization (**Scheme 3**) involving the methoxycarbonylation of the less hindered alcohol via $B_{Ac}2$, followed by an intramolecular alkylation reaction via $B_{Al}2$. The former step follows the HSAB theory, while the latter is promoted by high entropic effects leading to ring closure.

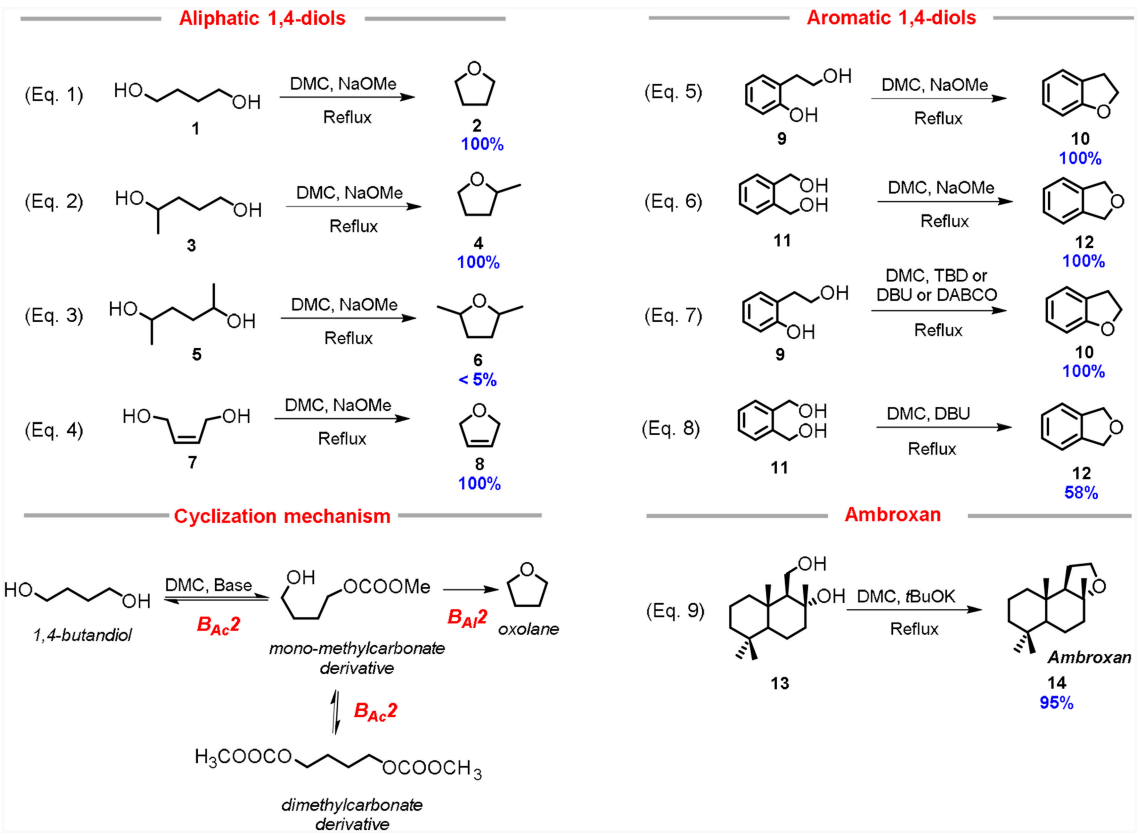
Recent investigations by our research group showed that a nitrogen bicyclic base is effective for the one-pot synthesis of heterocycles from aromatic 1,4-diols also when used in a catalytic amount (Aricò et al., 2015a). Nitrogen bicyclic bases, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO) and triazabicyclodecene (TBD) demonstrated to enhance the reactivity of DMC in methoxycarbonylation reaction by $B_{Ac}2$ mechanism (Carafa et al., 2011; Quaranta et al., 2014).

In the case of 2-hydroxyethyl phenol **9**, the DMC-mediated cyclization reaction was promoted by a catalytic amount of several nitrogen bicyclic bases, i.e., DBU, DABCO, and TBD. All those bases resulted efficient catalysts when used in 5% mol eq., providing quantitative conversion and selectivity toward the 2,3-dihydrobenzofuran **10** (Equation 7; **Scheme 3**) Furthermore, it

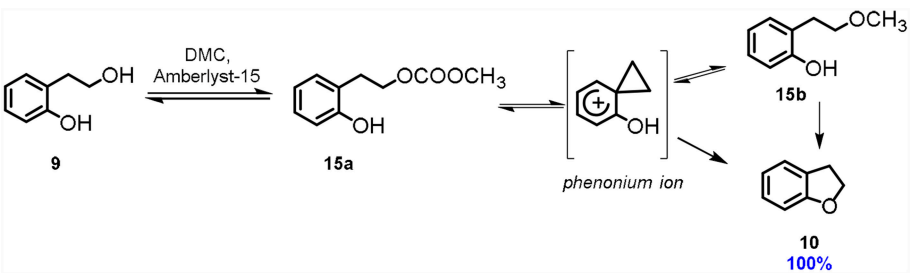
was possible to perform the cyclization in almost neat conditions by reducing the DMC consumption up to 4.0 mol eq. relative to the starting 1,4-diol (Aricò et al., 2015a).

The cyclization of 1,2-bis(hydroxymethyl)benzene **11** was then tested in similar reaction conditions, however none of the bicyclic nitrogen bases led to the quantitative synthesis of the related cyclic, 1,3-dihydroisobenzofuran **12**. The best yield (58%) was achieved employing DBU as catalyst (Equation 8; **Scheme 3**). This result is probably due to the lower acidity of the hydroxy group incorporated into the substrate **11** compared to the more reactive phenol unit of the previously investigated 2-(2-hydroxyethyl)phenol **9** (Aricò et al., 2015a).

An interesting application of the DMC-mediated cyclization reaction is the preparation of ambroxan **14**, also called (-)-norlabdane oxide, by using as starting reagent amberlyn diol **13** (Equation 9; **Scheme 3**). Ambroxan is used for providing



SCHEME 3 | Synthesis of 5-membered aliphatic and aromatic heterocycles via DMC chemistry. Reaction conditions: (Equation 1): **1**: NaOMe: DMC in 1.0: 2.0: 4.0 molar ratio in ACN, $T = 60°C$, $t = 4$ h; (Equation 2): **3**: NaOMe: DMC in 1.0: 3.0: 4.0 molar ratio in ACN, $T = 70°C$, $t = 6$ h; (Equation 3): **5**: NaOMe: DMC in 1.0: 3.0: 4.0 molar ratio in ACN, $T = 70°C$, $t = 24$ h; (Equation 4): **7**: NaOMe: DMC in 1.0: 2.0: 4.0 molar ratio in ACN, $T = 70°C$, $t = 4$ h; (Equation 5): **9**: NaOMe: DMC 1.0: 2.0: 4.0 molar ration in ACN, $T = 70°C$, $t = 2$ h; (Equation 6): **11**: NaOMe: DMC in 1.0: 2.0: 4.0 molar ratio in ACN, $T = 70°C$, $t = 4$ h; (Equation 7): **9**: DMC: base 1.00: 4.00: 0.05 molar ratio, $T = 90°C$, $t = 8$ h; (Equation 8): **11**: DMC: DBU 1.0: 8.0: 1.0 molar ratio, $T = 90°C$, $t = 24$ h; (Equation 9): Amberlyn **13**: *t*BuOH: DMC in 1.0: 2.0: 30.0 molar ratio, $T = 90°C$, $t = 3$ h.



SCHEME 4 | Cyclisation via phenonium ion. Reaction conditions: **9**: DMC 1.0: 60.0 molar ratio, Amberlyst-15 (100% w/w referred to **9**), $T = 90°C$, $t = 48$ h.

ambergris-type odors to perfumes, since the natural ambergris is no longer available (Steenkamp and Taka, 2009; Bevinakatti et al., 2013). Results showed that amberlyn diol **13** cyclized quantitatively to ambroxan within only 3 h, using two equivalents of potassium *tert*-butoxide in an excess of DMC (used as reagent and solvent). The amount of DMC could be reduced without affecting the outcome of cyclization as confirmed by performing the reaction in THF in the presence of three equivalents of DMC. Furthermore, it is noteworthy that the reaction via DMC preserves the chiral integrity of the starting material in the product.

In conclusion, it could be stated that, compared to commonly used chlorine-based procedure, the synthesis of heterocycles incorporating a tetrahydrofuran unit via DACs chemistry and under basic conditions is high-yielding, does not require chlorine chemicals or inorganic acids and the products can be isolated without employing any time-consuming purifications. This procedure can be considered of general application, since it has been proven efficient for aliphatic and aromatic 1,4-diols. The only limitation is that the starting diols should incorporate at least one primary hydroxy group, in order to render the cyclization effective.

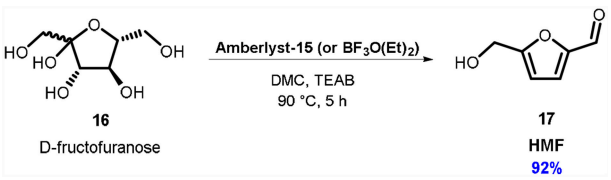
A different synthetic approach to 2,3-dihydrobenzofuran **10** via DMC chemistry was reported using acidic conditions, instead of basic ones (Aricò et al., 2018b). Several acids, organic and inorganic, have been tested for the cyclization of 2-(2-hydroxyethyl)phenol **9**. Among them, the exchange resin Amberlyst-15 resulted by far the most efficient. 2-(2-Hydroxyethyl)phenol **9** is an interesting substrate, as the 2-hydroxyethyl moiety is located in *ortho* position to the aromatic hydroxy group and thus it is capable of promoting the phenonium ion formation (**Scheme 4**).

Theoretical calculations suggested that the most favorable reaction pathway is the formation of a phenonium ion via DMC chemistry that is then converted into the 2-(2-methoxyethyl)phenol **15b**. 2,3-Dihydrobenzofuran **10** is finally formed via intramolecular cyclization of this intermediate.

It is noteworthy that in this peculiar acid catalyzed cyclization reaction, DMC is used as solvent, methoxycarbonylation agent as well as the leaving group promoting the phenonium ion formation.

Another interesting example of green synthesis of furan system via DMC chemistry is the preparation of bio-based platform molecule 5-hydroxymethylfurfural **17** (HMF). HMF is an archetype of the widely investigated furan-based platform molecules (Bozell and Peterson, 2010; Ruppert et al., 2012). This compound has found numerous applications as a building block in the synthesis of chemicals, materials, bio-based polymers and fuels (Mika et al., 2018). As a result, numerous synthetic procedures to HMF have been reported in the literature, which mostly rely upon the acid-catalyzed triple dehydration of D-fructose (Karinen et al., 2011; Qiao et al., 2015).

Compared to several of these preparations of HMF, the DMC-based one uses only commercially available materials and had a very simple work-up (**Scheme 5**). In the best-found reaction conditions, D-fructose **16** (1.0 eq. mol) was dissolved in a solvent system consisting in a mixture of DMC and TEAB (99:1 mol ratio) in the presence of Amberlyst-15 or Lewis acid $BF_3O(Et)_2$ (10% weight) as a catalyst (Musolino et al., 2018).



SCHEME 5 | Conversion of D-fructose **16** into HMF **17**. Reaction condition: **16**: TEAB: DMC in 1.00: 0.17: 16.80 molar ratio, Ambelyst-15 or $BF_3O(Et)_2$ (10% w/w referred to D-fructose), $T = 90°C$, $t = 5$ h.

In this novel reaction media, TEAB favors the dissolution of D-fructose, meanwhile DMC acts as an efficient extraction solvent. As a result, HMF **17** can be recovered as a pure product from the reaction mixture in > 90% yield by simple evaporation of the DMC. Large-scale preparations of HMF (up to 20 grams of D-fructose) were also conducted, without affecting the almost quantitative yield of this synthetic approach.

Materials efficiency performance of the HMF preparation via DMC was also taken into consideration; E-factor and PMI green metrics were calculated. The results were compared to literature reports for the same dehydration reaction, where selection criteria included isolation of HMF and the reaction scale was at least one-gram. In fact, although in the literature there are reported numerous synthetic procedures to HMF, most of them relies upon analytic techniques, such as high performance liquid chromatography (HPLC), for determining HMF yield. This is due to the difficult separation of the product from the reaction mixture and to the well-know HMF instability (Musolino et al., 2018). To the best of our knowledge, the synthetic procedure using DMC as extracting solvent resulted so far, the most convenient among the ones investigated. However, it should be pointed out, that, due to its complexity, there is still much room for improvement in terms of E-factor contributors for this reaction.

Cyclic Sugars: Isosorbide and Isomannide

Over the last 10 years, anhydro sugar alcohols held a top position in the biorefinery development. Among them, isosorbide **18** and isomannide **19** both encompass all of the desired criteria for a bio-based platform. In fact, these compounds have found many applications in food industry, pharmaceutical field, and biopolymer preparation (Bozell and Peterson, 2010).

Furthermore, alkyl derivatives of isosorbide **18**, such as dimethyl isosorbide have been investigated as potential substitutes of high-boiling solvents, such as dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) (Aricò et al., 2017).

Isosorbide **18** is also well-known for having a high and unexpected reactivity, probably due to its peculiar open-book configuration formed by two *cis*-fused tetrahydrofuran rings, where the four oxygens incorporated in the structure are in β-position to each other. The configuration of the two hydroxy groups—one *endo* (2-position) directed toward the V-shaped

cavity, and the second *exo* (5-position) pointing outside of the sugar cavity (**Figure 1**)—has been showed to influence the reactivity of isosorbide **18**. In fact, isoidide **20** and isomannide **19** (**Figure 1**), that incorporate either *exo* or *endo* hydroxy groups, showed a diverse reactivity.

Isosorbide and its epimer isomannide are industrially synthesized from their parent alcohols D-sorbitol **17** and D-mannitol respectively by a double dehydration reaction, using different types of catalysts (Rose and Palkovits, 2012). The actual synthetic approach to cyclic sugar isosorbide is focused on less toxic and easy to recover heterogeneous acidic catalysts, such as mixed oxides, phosphated or sulphated oxides, sulphonic resins, and bimetallic catalysts (Aricò and Tundo, 2016a). However, despite these new and promising methodologies, the main issue remains the separation and purification of isosorbide from the reaction mixture that might contain elimination products or other cyclization intermediates, such as 1,4-sorbitan derivatives.

In this prospect, a DMC-based synthetic approach has been exploited to achieve isosorbide (**Figure 2**). The idea was to employ DMC as a dehydrating agent in mild reaction conditions (Tundo et al., 2010a). In a first set of experiments, D-sorbitol **17** was dissolved in DMC (20 mol eq.) and reacted at 90°C using an excess of strong base (2.0 mol eq.), i.e., sodium methoxide. In these conditions, isosorbide **18** was isolated only in modest yield

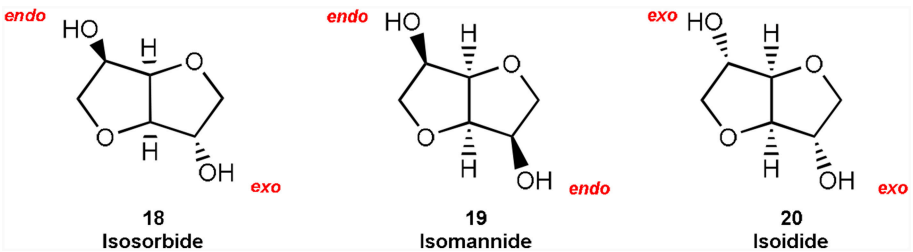
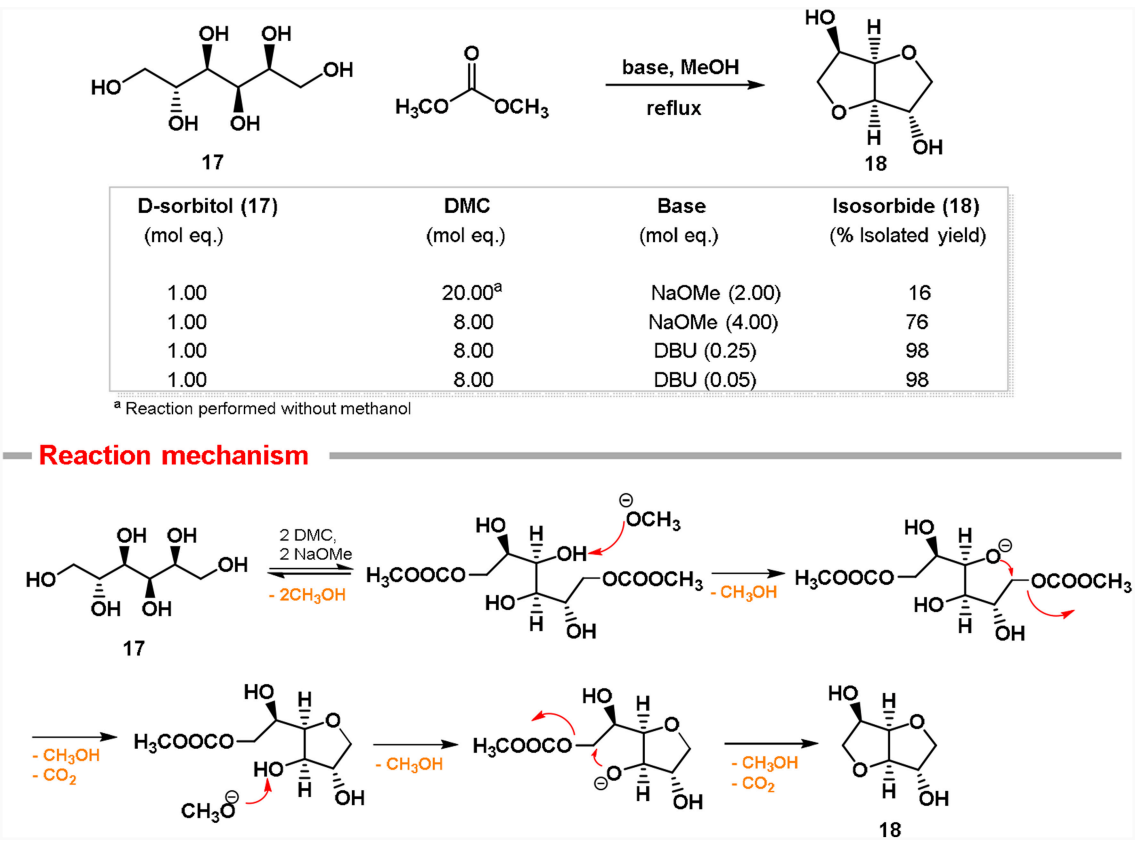


FIGURE 1 | Chemical structure of isosorbide and its epimers isomannide and isoidide.



D-sorbitol (17) (mol eq.)	DMC (mol eq.)	Base (mol eq.)	Isosorbide (18) (% Isolated yield)
1.00	20.00[a]	NaOMe (2.00)	16
1.00	8.00	NaOMe (4.00)	76
1.00	8.00	DBU (0.25)	98
1.00	8.00	DBU (0.05)	98

[a] Reaction performed without methanol

FIGURE 2 | Conversion of D-sorbitol **17** into isosorbide **18** via DMC chemistry.

(16%), as once it is formed, it further reacted with DMC leading to the formation of its methoxycarbonyl and methyl derivatives. In order to prevent further reactions, methanol was added to the reaction mixture as a co-solvent. By using this synthetic procedure, the numerous equilibria that affect the reaction can be efficiently shifted toward the isosorbide formation, preventing any by-products production. The best result, i.e., 76% isolated yield of isosorbide, was achieved when an excess of NaOMe was employed (4.0 mol eq.). The use of an excess of base has to be ascribed to the complexity of this one-pot double cyclization reaction that requires two equivalents of base for each tetrahydrofuran formed (see reaction mechanism in **Figure 2**).

Recently, we also reported that bicyclic nitrogen base DBU can be used in the high-yielding synthesis of isosorbide via DMC chemistry. The main advantage of this synthetic approach is that DBU works efficiently in substoichiometric amount (0.25 mol eq.) (Aricò et al., 2015a). In these reaction conditions, isosorbide can be isolated as a pure compound by a simple filtration on a silica pad, followed by DMC evaporation. Even when the amount of DBU was reduced to 5% mol eq., the wanted cyclic sugar was still formed in a quantitative yield.

This synthetic approach can be also employed for the cyclization of D-mannitol into isomannide **19**. It is noteworthy that both anhydro sugars isosorbide and isomannide are formed at low temperature (90°C) through a one-pot double cyclization reaction, thus the amount of DBU is 2.5% mol eq. for each tetrahydrofuranic cycle formed and in turn it can be considered as a catalytic amount.

Compared to previous works reported in the literature on isosorbide and isomannide preparation (Bozell and Peterson, 2010), the DMC-based synthetic methodology is one-pot, environmentally friendly (DMC can be eventually recycled), does not require any purification, allows very pure products and does not affect the chiral integrity of the substrates. To the best to our knowledge, the DMC-based approach is the highest yielding preparation reported so far for cyclic sugars.

Pyrrolidines, Indolines and Isoindolines

Five-membered *N*-heterocycles are present in numerous natural products, i.e., vitamins, hormones, and alkaloids (Padwa and Bur, 2004). As an example, pyrrolidines are often incorporated as key units in pharmaceuticals, herbicides, pesticides and dyes (Katritzky et al., 2010).

Similarly, to the 5-membered *O*-heterocycles above discussed, pyrrolidine systems can be synthesized employing DMC as a sacrificial molecule (Aricò et al., 2012b). In this view, both aliphatic and aromatic substrates have been investigated.

Preliminary experiments were conducted on 4-amino-1-butanol **21** using DMC as solvent and reagent in the presence of several catalysts (10% mol eq.); examples include metallic homogenous catalysts (Entry 1-2; **Table 1**), alkali and heavy metal basic carbonates (Entry 3-5; **Table 1**), strong bases (Entry 6-7; **Table 1**) and hydrotalcites (Entry 8; **Table 1**). All the reactions were carried out in autoclave at 180°C and they resulted in the formation of the wanted *N*-methoxycarbonyl pyrrolidine **22** in good yield (up to 62%) when cesium carbonate was used as a base (Entry 4; **Table 1**).

TABLE 1 | Synthesis of *N*-methoxycarbonyl pyrrolidine using different bases/catalysts[a].

Entry	Base/catalyst	eq	*N*-methoxycarbonyl pyrrolidine 22 (%)[b]
1	$ZnO(Ac_2)$	0.1	35
2	$SnOBu_2$	0.1	28
3	K_2CO_3	0.1	49
4	Cs_2CO_3	0.1	62
5	$(ZnCO_3)_2{\cdot}[Zn(OH)_2]_3$	0.1	39
6	MeONa	0.1	46
7	*t*BuOK[c]	0.5	76[d]
8	HT KW2000[e]	n.a.	48

[a] *Reaction conducted in autoclave heating to 180°C for 3 h;* [b] *Yields calculated by GC;* [c] *Reaction conducted in a autoclave heating to 160°C for 3 h;* [d] *Yield calculated by NMR;* [e] *10% in weight.*

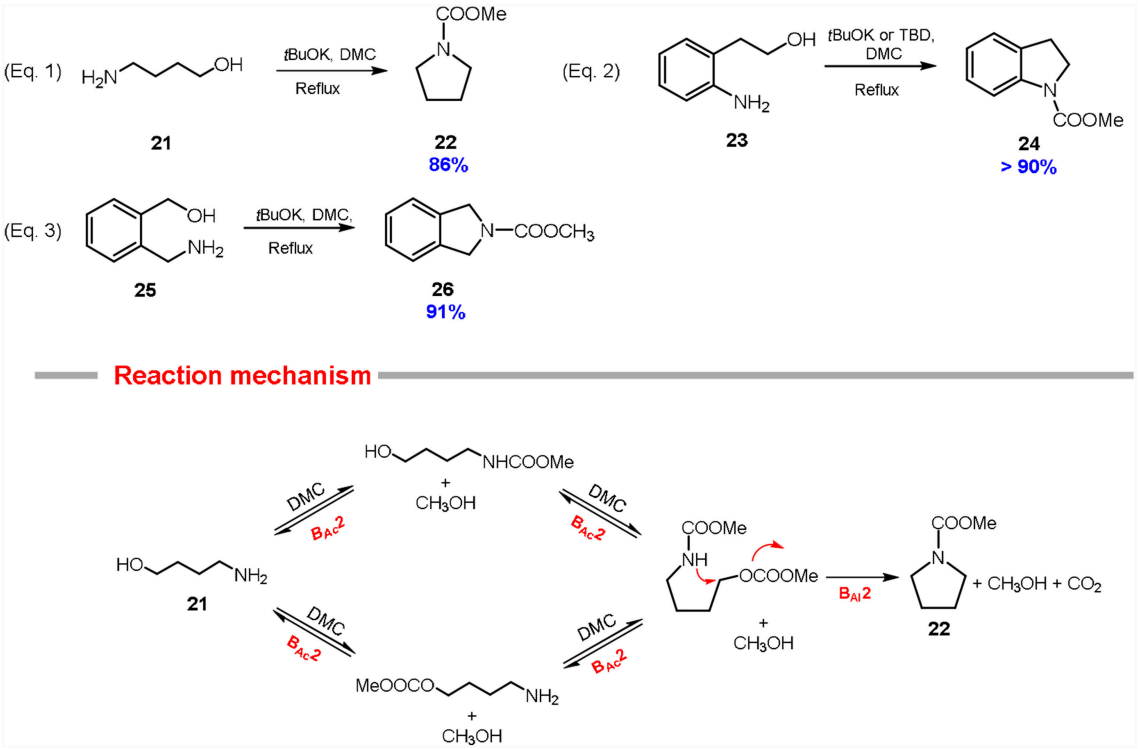
This cyclization reaction was also investigated at the reflux temperature of DMC (90°C), resulting in a high-yielding synthesis of the related pyrrolidine **22** (i.e., 86% isolated yield), although, in this case, an excess of potassium *tert*-butoxide (2.0 mol eq.) was required (Equation 1; **Scheme 6**).

The synthesis of pyrrolidine system via DMC chemistry is a remarkable example of Hard-Soft Acid-Base theory. In fact, the starting substrate includes two different nucleophiles, a primary amine and a primary alcohol capable to discriminate between the two electrophilic centers of the DMC to form the related pyrrolidine **22** in a one-pot cyclization. Most probably, the 4-amino-1-butanol **21** firstly undergoes carboxymethylation at the hydroxy (or the amine) group, then also the amine (or the hydroxy) group is carboxymethylated ($B_{Ac}2$). As a consequence, the amino group of the so formed carbamate is softer in character and it undergoes fast alkylation to give selectively the carboxymethyl pyrrolidine. The formation of the cyclic compound is favored also because all the methoxycarbonylation reactions are equilibria, meanwhile the final cyclization reaction is kinetically driven (Reaction mechanism; **Scheme 6**).

2-(2-Aminophenyl)ethanol **23** and 2-(aminomethyl)benzyl alcohol **25** were also tested as substrates for the preparation of the related *N*-carboxymethyl indoline **24** and *N*-carboxymethyl isoindoline **26**, respectively (Equations 2, 3; **Scheme 6**). In particular, 2-(2-aminophenyl)ethanol **23** readily cyclized in high yield (> 90%) either at reflux temperature (90°C) in the presence of an excess of potassium *tert*-butoxide (2.5 mol eq.) or in autoclave (180°C) with a substoichiometric amount of the same base (0.1 mol eq.) (Equation 2; **Scheme 6**).

In addition, *N*-carboxymethyl indoline **24** can be obtained in quantitative yield (97%) at 90°C also employing a substoichiometric amount of TBD (0.5 mol eq.), although the reaction required 21 hours to reach the completion (Equation 2; **Scheme 6**) (Aricò et al., 2015a).

2-(Aminomethyl)benzyl alcohol **25** was efficiently converted into *N*-carboxymethyl isoindoline **26** (Equation 3; **Scheme 6**) in excellent yield (91%) when the reaction was conducted at reflux temperature in the presence



SCHEME 6 | Preparation of pyrrolidine **22**, indoline **24** and isoindoline **26** via DMC chemistry. Reaction conditions: Equations 1, 3: substrates **21** and **25** (1.0 eq) were reacted with DMC (60.0 eq) and *t*BuOK (2.0–2.5 eq, at 90°C for 6 h. Equation 2: substrates **23** (1 eq) were reacted with DMC (60 eq) and *t*BuOK (2.5 eq) or TBD (0.5 eq), at 90°C for 6–21 h.

of potassium *tert*-butoxide (2.5 mol eq.) and in a good yield (71%) when the cyclization was performed in autoclave using a substoichiometric amount of the same base (10% mol eq.).

Cyclisation of aliphatic and aromatic 1,4-amminoalcohols via DACs chemistry represents a good example of green chlorine-free approach to the related 5-membered-nitrogen heterocycles. These syntheses resulted overall high yielding, although the complexity of the substrates incorporating two different nucleophilic groups led to the use of an excess of base. Furthermore, the reaction mechanism has yet investigated in detail.

6-MEMBERED HETEROCYCLES

1,4-Dioxanes

The synthesis of six-membered heterocycle 2,3-dihydrobenzo[b]-[1,4]dioxine **28** was recently reported using DMC. Benzodioxanes are key structural units in numerous pharmaceuticals; examples include piperoxan, fluparoxan, and americanol A (Bao et al., 2008; Bagnoli et al., 2013). Isovanillyl sweetening agents also incorporate a 2,3-dihydro-1,4-benzodioxane unit. In addition, this ring is included in numerous natural products, such as silybin, isosilybin, haedoxan A, and eusiderin.

In particular 2,3-dihydrobenzo[b]-[1,4]dioxine **28** can be easily prepared starting from commercially available 2-(2-hydroxyethoxy)phenol **27** by employing DMC both as reagent and reaction solvent in the presence of stoichiometric amounts of DBU, DABCO or TBD (**Scheme 7**) (Aricò et al., 2015a).

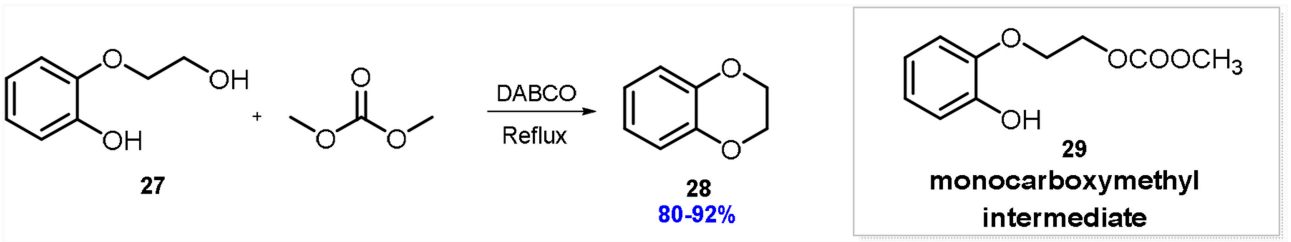
Among the organocatalysts investigated, DABCO (1.0 eq. mol) resulted very efficient (reaction time 2 h) in promoting the cyclization even when it was used in catalytic amounts (5% mol eq.). In fact, in the latter conditions 2,3-dihydrobenzo[b]-[1,4]dioxine **28** was isolated in 83% by simple removal of the exceeding solvent and without the use of any time-consuming column chromatography.

On the other hands, the reactions in the presence of DBU or TBD required longer reaction time and the experiment conducted in the presence of DBU showed lower selectivity toward the cyclic product, due to the presence of a reaction intermediate, the methoxycarbonyl derivative (**Scheme 7**).

The synthesis of 1,4-dioxan via DMC chemistry is an extension of the work reported on 5-membered cyclic compounds and it shows that the use of DMC as a sacrificial molecule in cyclization reaction can be employed also to more complex structures.

Piperidines

The preparation of piperidine via DACs chemistry is mostly related to our recent studies on mustard carbonates



SCHEME 7 | Preparation of 2,3-dihydrobenzo[b]-[1,4]dioxine **28** via DMC chemistry. Reaction conditions: **29**: DMC: DABCO in 1.00: 8.00: 0.05–1.00, at 90°C for 2–15 h.

(Aricò and Tundo, 2016c). These compounds are carbonate analogs of mustard gases, which are well-known vesicant and blistering agents used in several chemical warfares (Wang et al., 2012).

It has been discovered that the substitution of the mustard gas chlorine atom with a carbonate moiety via DACs chemistry resulted in molecules showing a similar reactivity and kinetic behavior of their chlorine homologs, without sharing their toxicological profile (Aricò et al., 2012a) (**Figure 3**).

Sulfur and nitrogen mustard carbonates reactivity was investigated in the presence of numerous nucleophiles, both in autoclave at 180°C in absence of any base (Aricò et al., 2013) and in neat at 150°C using a substoichiometric amount of a K_2CO_3 as a base (Aricò et al., 2014). Reaction mechanism, effect of the leaving group and kinetics confirmed that these compounds retain the anchimeric effect of their mustard gas analogs (Aricò et al., 2016a). Besides, nitrogen mustard carbonates have also been used in the synthesis of azacrowns and polycarbonates (Aricò et al., 2015b).

Two possible synthetic methodology for the synthesis of piperidines have been reported employing nitrogen-mustard carbonates: (i) by reaction of a symmetrical mustard carbonate with a CH_2-acidic compound or (ii) via ring expansion reaction of a pyrrolidine-based carbonate (**Scheme 8**).

In the first case a methylene acidic molecule, i.e., phenylsulfonyl acetonitrile **30** was reacted with a symmetrical nitrogen mustard carbonate, namely bis-*N,N*-[(2-methylcarbonate)ethyl]-methylamine **31**, in an autoclave at 180°C in the absence of any base (Equation 1; **Scheme 8**). Surprisingly, the substrate underwent a double intermolecular cyclization ($B_{Al}2$) leading to the formation of a 4-substituted piperidine **32** as the major product (Aricò et al., 2013). The pure piperidine can be isolated by a quick column chromatography in 60% yield. This reaction is a remarkable example of an intermolecular cyclization proceeding through a double alkylation reaction. Although several other substrates have been then exploited—i.e., phenylacetonitrile, bis(phenylsulfonyl)methane, 1,3-cyclohexanedione, ethyl acetoacetate, dimethyl malonate, etc.–, high selectivity toward the related piperidines was achieved only with phenylsulfonyl acetonitrile **30**.

The second approach to obtain a piperidine ring is related to the preparation of optically active 3-substituted piperdines, that are very common building blocks both in natural and bioactive compounds (Viegas et al., 2004; Castro et al., 2008).

A pyrrolidine-based mustard carbonate **33** (PMC) was prepared by reaction of (*S*)-1-methyl-2-pyrrolidinemethanol with DMC. The resulting compound was enantiomerically pure as confirmed by NMR investigation with a europium shift reagent.

The reaction of PMC **33** with a generic nucleophile, such as phenol **35a**, can lead to three products, i.e., a substituted (*S*)-pyrrolidine (**36a**) and the two enantiomers of a piperidine (**37a**) formed via ring expansion (Equation 2; **Scheme 8** and Entry 1; **Table 1**). In fact, the stereogenic center of the pyrrolidine can be affected only by the nucleophilic attack on the more sterically hindered tertiary carbon of the bicyclic aziridinium intermediates (Aricò et al., 2018a).

Experiments were conducted with different substrates, such as phenol (**35a**), *p*-bromo (**35b**) and *p*-nitro (**35c**), *p*-cyanophenol (**35d**), 2-naphthol (**35e**) (**Table 2**). It was reported that less acidic nucleophiles, i.e. phenol **35a**, *p*-bromophenol **35b**, and 2-naphthol **35e** led mainly to substituted pyrrolidines **36a**, **36b,** and **36e,** respectively (Entry 1, 2, and 5; **Table 2**), whereas more acidic ones, *p*-nitro **35c** and *p*-cyanophenol **35d** formed preferably the related 3-substituted piperidines **37c** and **37d**. These results were ascribed to the fact that less acidic nucleophiles follow a kinetically controlled mechanism; on the other hand, more acidic substrates undergo a thermodynamically controlled mechanism, leading to the ring expansion reaction of the starting pyrrolidine.

The observed ring expansion of *N*-alkylated prolinols in the presence of acidic substrates is generally highly stereoselective: the resulting optically active 3-piperidines were achieved in high yields (up to 89% for *p*-nitrophenol **35c**). X-ray diffraction analyses demonstrated that this reaction is stereoselective with inversion of configuration. It is remarkable that this reaction is the first example of ring expansion of *N*-alkylated prolinols based on carbonate chemistry.

In both the reported examples for the preparation of piperidine via DACs chemistry, it is evident that the cyclization is driven by the presence of the anchimeric effect of the mustard carbonate and by the ability of the methoxycarbonate moiety to act as an efficient leaving group. The yield of the cyclization depends on the substrate employed. Further investigations are needed to increase the greenness of these reaction as in selected

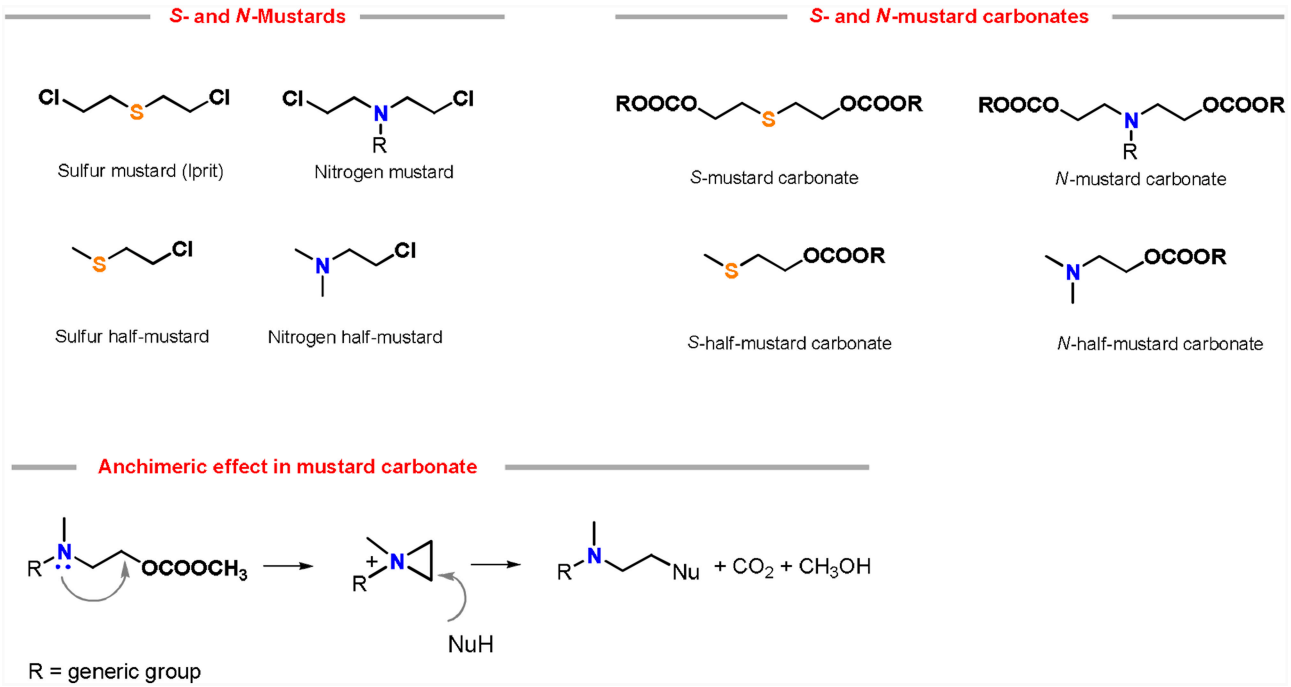
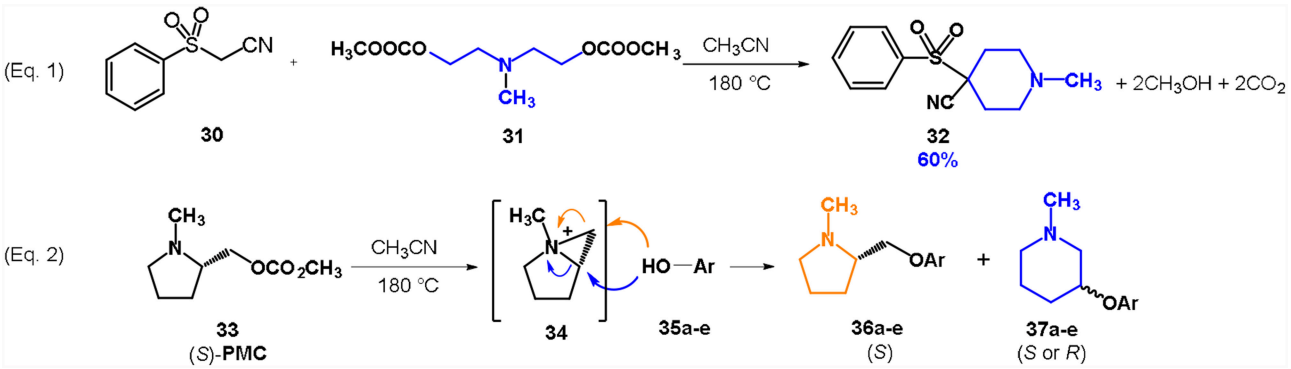


FIGURE 3 | Chemical structures of mustard gases and their analog carbonates. Reactivity of nitrogen mustard carbonates in the presence of a nucleophile (NuH) via anchimeric effect.



SCHEME 8 | Preparation of piperidines via DACs chemistry by reaction of a symmetrical mustard carbonate with a CH_2-acidic compound (Equation 1) or via ring expansion reaction of a pyrrolidine-based carbonate (Equation 2). Reaction conditions of Equation 1: **31**: **32** in 1: 1 molar ratio, in ACN, heated in a autoclave to 180°C for 7 h.

examples, a column chromatography was required to isolate the resulting piperdines.

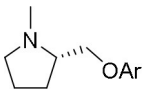
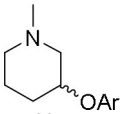
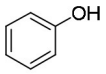
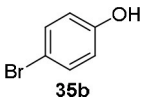
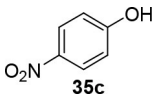
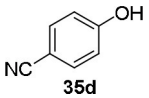
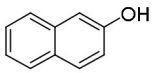
Cyclic Carbamates

Six-membered cyclic carbamates have numerous applications as pharmaceuticals, due to their biological activity mostly related to treatment of diseases connected to kinases activity (Hongqi and Gongchao, 2016). However, these cyclic carbamates also found application as herbicides with excellent crop-weed selectivity (Hino et al., 2009) and as monomers for the preparation of hyperbranched polyamines (Voit and Lederer, 2009) and polyurethane by cationic ring-opening polymerization (ROP) (Kreye et al., 2013).

Most of the synthetic routes to 1,3-oxazinan-2-ones involves phosgene or its derivatives (Murdock, 1968), alkyl halide chemistry (Trifunovic et al., 2010) and isocyanate compounds (Shibata et al., 1989). In the literature, there are also other procedures that generally require complex starting materials or multiple-step pathways, in order to achieve the final product (Mangelinckx et al., 2010).

Over the years, DACs chemistry has demonstrated to be very efficient for the preparation of differently substituted 1,3-oxazinan-2-ones. As an example, the reaction of primary amines

TABLE 2 | Pyrrolidine ring expansion by reaction with different nucleophiles[a].

Entry	Nucleophile	Yield (%)	
		 **36a–e**	 **36a–e**
1	 **35a**	46	32
2	 **35b**	56	37
3	 **35c**	11	89
4	 **35d**	23	56
5	 **35e**	35	23

[a] *Reaction conditions:* ***33***: ***35a-e*** *in 1: 1 molar ratio, in ACN heated in a autoclave to 180°C for 5–24 h.*

38a-c with a dimethylcarbonate derivative of 1,3- propanediol **40** in the presence of a strong base led the formation of 6-memebered cyclic carbamates **39a-c** (Equation 1; **Scheme 9**).

In the best-found reaction conditions, a mixture of an amine (**38a-c**), dimethylcarbonate derivative of 1,3-propandiol **40** and potassium *tert*-butoxide (1:1:1 mol ratio) were reacted at 90°C to give the wanted 1,3-oxazinan-2-one (**39a-c**) (McElroy et al., 2012). Several amines were used as substrates including aniline **38a** benzylamine **38b** and phenylhydrazine **38c** leading to the formation of the related cyclic carbamate **39a-c** in modest yield (27–53%).

Attempts to achieve 1,3-oxazinan-2-ones **39a-d** through a one-pot synthesis were then conducted by reacting an amine **38a-d**, a 1,3-diol **41** and a dialkyl carbonate in the presence of a strong base (Equation 2; **Scheme 9**). In a typical procedure, benzylamine **38b** was reacted with 1,3-propandiol **41** in the presence of different DACs to give the related 1,3-oxazinan-2-one **39b** (McElroy et al., 2012). The plan was to perform the cyclization reaction in one-step by synthesizing the dialkylcarbonate derivative of 1,3-propandiol *in-situ*, through a cascade reaction. Following this procedure, six membered cyclic carbonates formed with modest yield (21-57%), depending on the substrate, the DAC used and the nature of the diol.

It was found that the more hindered the diol used, the lower the yield of 1,3-oxazinan-2-one. Conversely, a very high level of selectivity was achieved when a 1,3-diol with both primary functionalities were employed. It can be concluded that for cyclization to occur, a primary CH_2 functionality (in α to the carbonate) must be present.

Regarding the effect of the DAC used, it was observed that the yield of cyclization increases by increasing the steric hindrance of the dialkyl carbonate used in the reaction. When DMC or diethylcarbonate (DEC) were employed, 3-benzyl-1,3-oxazinan-2-one **39b** was isolated in 21 and 36% yield respectively. Instead, when the reactions were carried out employing more sterically hindered diisoproprylcarbonate (DiPrC) or methyl *tert*-butyl methylcarbonate (M*t*BuC), the oxazinanone was isolated in higher yields (47 and 57% respectively).

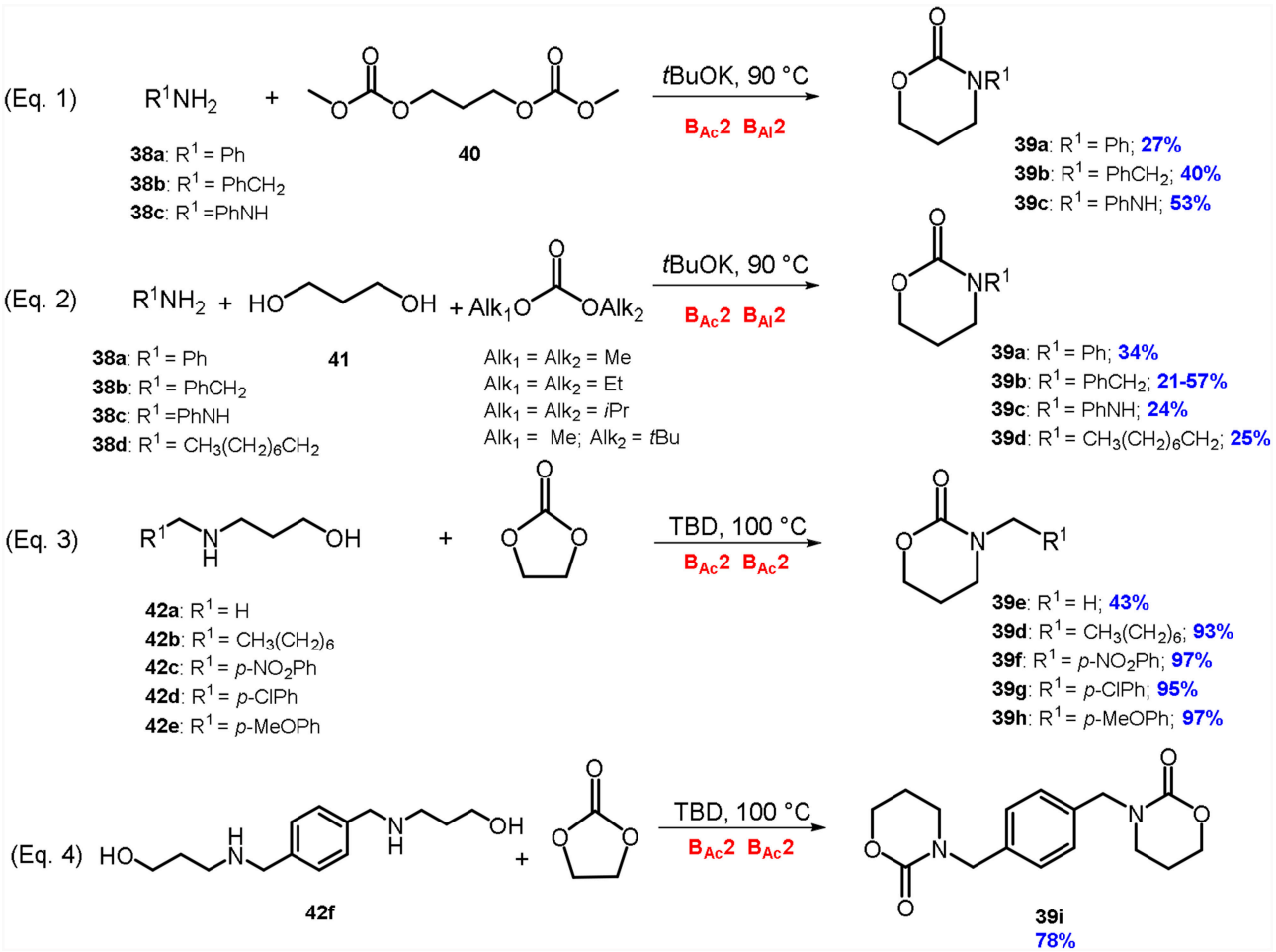
These results are in good accordance with our previous investigations comparing the reactivity of amines and alcohols with DACs. The reaction of an amine with a sterically hindered DAC leads to the related carbamate in high yield as more hindered alkoxides resulted to be better leaving groups (Tundo et al., 2010b). Conversely, when an alcohol is reacted with a DAC in basic conditions the trend of the leaving group is almost the opposite of that observed with an amine (Tundo, McElroy and Aricò, 2012).

The general applicability of the one-pot synthesis to 1,3-oxazinan-2-ones, was studied employing several nucleophiles i.e., aniline **38a**, phenylhydrazine **38c,** and *n*-octylamine **38d**. Results showed a higher reactivity of the aromatic substrates.

The above discussed DACs-based synthetic approaches to cyclic carbamate (Equation 1-2; **Scheme 9**) were identified by EATOS software and Andraos spreadsheets analysis as the most promising on the basis of their low environmental impact (Toniolo et al., 2014). However, it should be mentioned that in both procedures, the formation of cyclic carbamates occurs together with several concurrent reactions leading to numerous by-products, such as aromatic carbamates, aromatic ureas and aliphatic and aromatic carbonates. Therefore, although cyclic carbamates are achieved as major products, a purification by column chromatography on silica gel is needed to isolate them.

Recently, our research group has reported a simpler and high yielding approach to cyclic carbamates **39d-i** by reaction of 3-amino-1-propanols **42a-f**, easily prepared by reductive amination, with ethylene carbonate, in the presence of catalytic amount (up to 5% mol eq.) of bicyclic nitrogen base TBD (Equation 3-4; **Scheme 9**). The procedure resulted in a general application for the synthesis of aliphatic and aromatic 1,3-oxazin-2-ones (Aricò et al., 2016b). In fact, several *N*-substituted 1,3-aminopropanols **42b-f** were synthesized and investigated as substrates; the related 1,3-oxazin-2-one derivatives **39d** and **39f-i** were achieved in good yield, without any further purification (78-98%). Noteworthy, this synthetic approach proved to be effective also in the synthesis of an aryl bis(1,3-oxazinan-2-one). This compound was achieved by a double intermolecular cyclization and isolated as a pure product in 78% yield (Equation 4; **Scheme 9**).

Compared to other previously reported DACs-based reactions, this intermolecular cyclization follows a double $B_{Ac}2$ reaction mechanism, instead of a $B_{Ac}2$ followed by a $B_{Al}2$ mechanism. Furthermore, the ethylene carbonate has a double



SCHEME 9 | Synthesis of 1,3-oxazin-2-ones via DACs chemistry by reaction of: an amine with a dicarbonate derivative of 1,3-diols (Equation 1), an amine with a 1,3-diol and a dialkyl carbonate (Equation 2), 3-amino-1-propanols with ethylene carbonate (Equation 3); synthesis of an aryl bis(1,3-oxazinan-2-one) (Equation 4). Reaction conditions: Equation 1: **38a-c**: **40**: *t*BuOK in 1.0: 1.0: 1.0 molar ratio, at $T = 90°C$ for 2 h; Equation 2: **38a-d**: **41**: DAC: *t*BuOK in 1.0: 1.0: 2.0: 3.0 molar ratio, at $T = 90°C$ for 2 h; Equations 3, 4: **42a-f**: EC: TBD in 1.0: 1.0: 0.2 molar ratio, at $T = 100°C$, for 5–97 h.

role being employed both as solvent and reagent in the synthesis of the related cyclic carbamate.

The main advantages of this synthetic approach are: simple work-up of the reactions, high yield, sustainable reaction conditions, general application and absence of by-products formation.

CONCLUSIONS

The synthesis of heterocycles via DACs chemistry is a striking example of the versatility of this class of compounds. Following are reported the main results for each class of heterocycles investigated via DACs chemistry.

5- and 6-Membered *O*-Heterocycles

In the best-found reaction conditions, aliphatic and aromatic 1,4-diols gave the related heterocycles by reaction with DMC at reflux temperature (90°C) in the presence of catalytic amounts of superbases DBU or TBD. The cyclization reaction proceeds via $B_{Ac}2$ mechanism followed by an intramolecular alkylation, i.e., $B_{Al}2$ mechanism.

This green approach to synthesize tetrahydrofuran systems does not use any additional solvent other than the selected DAC and the wanted cyclic products can be isolated as pure by a simple filtration on a silica pad.

6-member *O*-heterocycle 1,4-benzodioxane was also prepared in quantitative yield by a similar approach demonstrating the possibility to use this methodology with more complicated substrates.

In this view, industrially relevant compounds, isomannide, isosorbide, and ambroxan were achieved in quantitative yield starting from D-mannitol, D-sorbitol and amberlyn diol respectively via DMC-promoted cyclization. Besides, in all cases, the chiral integrity of the substrate was preserved.

In a specific case, the synthesis of 2,3-benzofuran, the cyclization reaction was conducted in acidic conditions. In this

case DMC acts as methoxycarbonylation agent and leaving group in the intramolecular cyclization, which is promoted by the formation of a phenonium ion.

5-(Hydroxymethyl)Furfural

In the case of bio-based platform chemical HMF, DMC was used as a very efficient extracting solvent, leading to one of the very few procedure in which HMF can be easily separated from the reaction mixture and isolated as a pure product (92% isolated yield). This synthetic approach was evaluated according to several green metrics and resulted the most promising in terms of mass consumption.

5-Membered *N*-Heterocycles

Pyrrolidines, indolines, and isoindolines were also achieved using DMCs as sacrificial molecules. In this case, the starting substrates—1,4-aminoalcohols–incorporates two different nucleophilic groups, thus the cyclization requires an excess of a base and, for specific products, the products purification is also necessary.

Piperidines

For this class of heterocycles the DACs-based synthetic approach took advantage of the anchimeric effect of a new family of compounds, named mustard carbonates. In particular, 4-substituted piperidines were prepared by reaction of compounds including acidic CH_2 groups, in the presence of a symmetrical nitrogen mustard carbonate. However, it should be mentioned that this synthetic approach resulted high yielding only in the case of phenylsulfonyl acetonitrile.

Optically active 3-piperidines can be efficiently synthesized via ring expansion of methylcarbonate derivatives of *N*-alkylated prolinols in the presence of acidic phenols. In this synthetic approach, the anchimeric effect of the prolinol derivative is pivotal for the high yielding ring expansion reaction (up to 89 % for *p*-nitrophenol). It should be mention that in some cases the heterocycle purification was necessary.

6-Membered Cyclic Carbamates

Numerous examples of 1,3-oxazinan-2-ones were synthesized via DACs employing different synthetic approaches, such as by reaction of an amine with a dicarbonate derivative of 1,3-diols or by reaction of an amine with a 1,3-diol and a dialkyl carbonate. These two methodologies are based upon a $B_{Ac}2$ mechanism followed by an intramolecular alkylation reaction ($B_{Al}2$ mechanism). Despite being identified by EATOS software and Andraos spreadsheets analysis as the most promising cyclic carbamate preparation, both procedures lead to the formation of numerous by-products. Recently a more efficient and greener procedure was reported and it was based upon the reaction of easily prepared *N*-substituted 3-amino-1-propanol derivatives with ethylene carbonate. In this preparation EC is used as a carbonylating agent and the 6-membered cyclic carbamates are formed via a double $B_{Ac}2$ mechanism.

In conclusion, over the last 10 years several examples of green synthesis of heterocycles have been reported via DACs chemistry. It is noteworthy that, in these cyclizations, DMC or other DACs act as reaction media and as a sacrificial molecule, similarly to chlorine compounds. Although chlorine compounds employed in cyclization reactions generally are effective at lower temperature, in the case of DMC (as an example), the intrinsic toxicity of chlorine-based molecules is avoided since at the end of the reaction DMC is fully converted into methanol and CO_2.

FUTURE PERSPECTIVES

The green synthesis of heterocycles via DACs chemistry is still relatively new and unexplored, thus in the near future, it is expected that DACs might be employed for the preparation of more complex cyclic compounds. Future exploitations might include heterocycles incorporating more heteroatoms, such as benzoxazine and benzothiazine. It would be also interesting to extend DACs-based heterocyclic to the synthesis to seven- and eight-membered heterocycles to prove the robustness of this approach.

Finally, an example of macrocycle preparation via DACs chemistry has already been explored (Aricò et al., 2015b) and new investigations in the preparation of macromolecules could also take in consideration.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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