frontiers in Chemistry

ORIGINAL RESEARCH
published: 08 July 2019
doi: 10.3389/fchem.2019.00457

Development of Novel and Efficient Processes for the Synthesis of 5-Amino and 5-Iminoimidazo[1,2-*a*]imidazoles via Three-Component Reaction Catalyzed by Zirconium(IV) Chloride

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Specialty section:
This article was submitted to Organic Chemistry, a section of the journal Frontiers in Chemistry

Received: *14 March 2019*
Accepted: *07 June 2019*
Published: *08 July 2019*

Citation:
Driowya M, Guillot R, Bonnet P and Guillaumet G (2019) Development of Novel and Efficient Processes for the Synthesis of 5-Amino and 5-Iminoimidazo[1,2-a]imidazoles via Three-Component Reaction Catalyzed by Zirconium(IV) Chloride. Front. Chem. 7:457. doi: 10.3389/fchem.2019.00457

General and efficient approaches for the synthesis of new 5-amino and 5-iminoimidazo[1,2-*a*]imidazoles were developed through a three-component reaction of 1-unsubstituted 2-aminoimidazoles with various aldehydes and isocyanides mediated by zirconium(IV) chloride. The protocols were established considering the reactivity of the starting substrate, which varies depending on the presence of a substituent on the 2-aminoimidazole moiety. A library of new N-fused ring systems with wide structural diversification, novel synthetic, and potential pharmacological interest was obtained in moderate to good yields.

Keywords: multicomponent reactions, isocyanide Ugi reaction, zirconium(IV) chloride, catalysis, N-heterocycles, fused-ring systems, 2-aminoimidazole

INTRODUCTION

The development of innovative synthetic approaches that allow rapid access to a wide variety of new heterocyclic derivatives is of crucial interest. The use of multicomponent reactions (MCRs) offers significant advantages in organic synthesis, such as the combination of chemical transformations of three or more different starting materials in a one-pot procedure without isolating the intermediates (Dömling and Ugi, 2000; Dömling, 2006; Abdelraheem et al., 2017; Bariwal et al., 2018; Murlykina et al., 2018). In 1998, the groups of Groebke, Blackburn, and Bienayme simultaneously developed a new subclass of MCRs to produce a series of azine- and azole-fused aminoimidazoles, using diverse 2-aminoazines or 2-aminoazoles, aldehydes and isocyanides in the presence of Lewis or Brønsted acid catalysts (Bienayme and Bouzid, 1998; Blackburn, 1998; Groebke et al., 1998).

This reaction recently attracted much attention in organic and medicinal chemistry because of its simplicity, efficiency and the ability to generate diverse compound libraries (Devi et al., 2015; Kaur et al., 2016; Shaaban and Abdel-Wahab, 2016; Shaabani and Hooshmand, 2016).

The fused bicyclic 5-5 systems containing three nitrogen atoms with one in the bridgehead position are an important class of fused heterocyclic compounds in organic and medicinal chemistry due to their relevant biological properties, such as anti-cancer (Baviskar et al., 2011; Grosse et al., 2014; Sidduri et al., 2014; Meta et al., 2017), anti-viral (Elleder et al., 2012), anti-inflammatory (Bruno et al., 2007; Brullo et al., 2012), and anti-diabetic effects (Mascitti et al.). Our group has been involved over the last few years in the development of powerful tools for the synthesis of such systems (El Akkaoui et al., 2012; Grosse et al., 2012, 2013, 2014; Arnould et al., 2013; Tber et al., 2015a,b; Driowya et al., 2018). For instance, we very recently reported an efficient one-pot three component procedure for the synthesis of new functionalized imidazo[1,2-*b*]pyrazole derivatives in addition to a library of hitherto undescribed 7,7′-(substituted methylene)bis-imidazo[1,2-*b*]pyrazoles starting from 3-aminopyrazoles, various aldehydes and isocyanides, using a catalytic amount of perchloric acid or zirconium(IV) chloride (Driowya et al., 2018).

The imidazo-imidazole scaffolds hold a special place in this category, since they are found in compounds showing a wide range of pharmaceutical activities. In particular, they have been described as antifungal (Lila et al., 2003), antithrombotic (Imaeda et al., 2008; Fujimoto et al., 2009), anxiolytic and anti-depressive agents (Han et al., 2005; Tellew and Luo, 2008; Zuev et al., 2010). In addition, they have been reported as androgen receptor agonists and antagonists that are useful in the treatment of a variety of disorders (Zhang et al., 2006). Several synthetic methods based on multistep synthesis have been employed by our group and others to prepare these medicinally important N-fused imidazoles (Langer et al., 2001; Poje and Poje, 2003; Adib et al., 2008; Saima et al., 2012; Chen et al., 2013; Grosse et al., 2015; Castanedo et al., 2016; Loubidi et al., 2016; Kheder and Farghaly, 2017).

On the other hand, compounds containing an imidazo[1,2-*a*]imidazole moiety have been understudied (Compernolle and Toppet, 1986; Kolar and Tisler, 1995; Mas et al., 2002). Only one paper was found in the literature for the preparation of 5-aminoimidazo[1,2-*a*]imidazole compounds by MCRs starting from 1,5-disubstituted 2-aminoimidazoles (Pereshivko et al., 2013). However, the reported protocol gave poor to moderate yields and showed some limitations with 1-unsubstituted 2-aminoimidazole substrates. Hence, there is a need to develop a new, more efficient and general method for the preparation of these derivatives.

In this context, and in continuation of our ongoing search for innovative small molecules, we report herein novel and straightforward approaches for the synthesis of new series of 5-amino and 5-iminoimidazo[1,2-*a*]imidazoles starting from 1-unsubstituted 2-aminoimidazoles and using zirconium(IV) chloride as catalyst. To the best of our knowledge, this is the first report using 1-unsubstituted 2-aminoimidazoles in MCRs.

RESULTS AND DISCUSSION

In order to find a MCR protocol that can afford an efficient formation of 5-aminoimidazo[1,2-*a*]imidazoles, we initially performed a model reaction using ethyl 2-aminoimidazole-4-carboxylate **1** with benzaldehyde and *t*-octyl isocyanide under different conditions (**Table 1**). Two possible regioisomers can be formed in this case **4a** or **4a′** according on which side of the 2-aminoimidazole **1** that reacts.

In our last study, we showed that the Lewis acid zirconium(IV) chloride delivered an efficient catalytic effect for the MCR (Driowya et al., 2018). This catalyst was therefore chosen for the present optimization study.

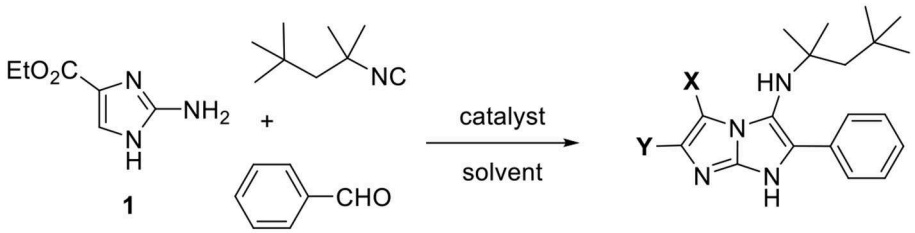
First, the reaction was carried out in methanol at room temperature in presence of 5 mol% of $ZrCl_4$, but unfortunately, no product was observed (entry 1). Poor yields of the expected product **4a** or **4a′** were obtained when the reaction was performed under heating in ethanol with either 5 or 10 mol% of $ZrCl_4$ (entries 2 and 3). The reaction time was significantly reduced to 10 min under MW irradiation at 140°C, and the yield was relatively improved to 38% (entry 4). The use of *n*-BuOH as solvent instead of EtOH under MW irradiation resulted in an improvement of the yield to 62% (entry 5), whereas the use of PEG-400 gave a moderate yield (entry 6). Interestingly, the reaction in PEG-400 under classical heating at 75°C during 4 h provided a very good yield (entry 7). Moreover, the optimal amount of catalyst (10 mol%) was confirmed, since the use of 5 mol% resulted in a lower yield (entry 8). Finally, replacing $ZrCl_4$ by other catalysts such as *p*-TsOH or $ZnCl_2$ was associated with a significant decrease in the yield of the product 5-aminoimidazo[1,2-*a*]imidazole **4a** or **4a′** (entries 9 and 10).

Hence, the optimized reaction conditions were found to be $ZrCl_4$ (10 mol%) as catalyst and PEG-400 as solvent with heating at 75°C during 4 h. This system was used before for the preparation of imidazo[1,2-*a*]pyridines (Guchhait and Madaan, 2009).

In order to disclose the structure of the formed regioisomer of this reaction, we carried out a single-crystal X-ray analysis of the product (**Figure 1**). The results reveal the formation of the regioisomer **4a**. The regioselectivity of this reaction can be explained by the presence of intermolecular hydrogen bonds on the ethyl 2-aminoimidazole-4-carboxylate **1**, orienting the synthesis toward the formation of only the regioisomer **4a**. Moreover, the structure of compound **4a** is stabilized by intramolecular N-H…O and intermolecular N-H...N interactions as observed in the crystalline structure (see the crystallographic section on the **Supplementary Material**).

With these reaction conditions in hand, we next explored the scope and limitation of our methodology with diverse 2-aminoimidazoles and isocyanides in the presence of a range of aldehydes as shown in **Table 2**. A large chemical library of 5-aminoimidazo[1,2-*a*]imidazole derivatives **4a–f** and **5a–i** was designed in generally good yields. The reactions proceeded well with both ethyl 2-aminoimidazole-4-carboxylate

TABLE 1 | Optimization of the reaction conditions.

Entry[a]	Catalyst (mol%)	Solvent	Temp (°C)	Heating method	Time	Yield (%)[b]
						
	4a (X = CO_2Et, Y = H) **4a'**(X = H, Y = CO_2Et)					
1	$ZrCl_4$ (5)	MeOH	r.t	–	14 h	0[c]
2	$ZrCl_4$ (5)	EtOH	80	Conventional	14 h	12[c]
3	$ZrCl_4$ (10)	EtOH	80	Conventional	14 h	18[c]
4	$ZrCl_4$ (10)	EtOH	140	MW	10 min	38
5	$ZrCl_4$ (10)	*n*-BuOH	140	MW	10 min	62
6	$ZrCl_4$ (10)	PEG-400	140	MW	10 min	31
7	**$ZrCl_4$ (10)**	**PEG-400**	**75**	**Conventional**	**4 h**	**77**
8	$ZrCl_4$ (5)	PEG-400	75	Conventional	6 h	55
9	p-TsOH (10)	PEG-400	75	Conventional	4 h	58
10	$ZnCl_2$ (10)	PEG-400	75	Conventional	7 h	23

[a] ***1*** *(1.0 mmol), benzaldehyde (1.1 mmol), t-octyl isocyanide (1.1 mmol), solvent (2 mL: entries 1–5; 1 mL: entries 6–10).*
[b] *Yield of isolated product.*
[c] *Starting materials were recovered.*
The bold values represent the optimized conditions.

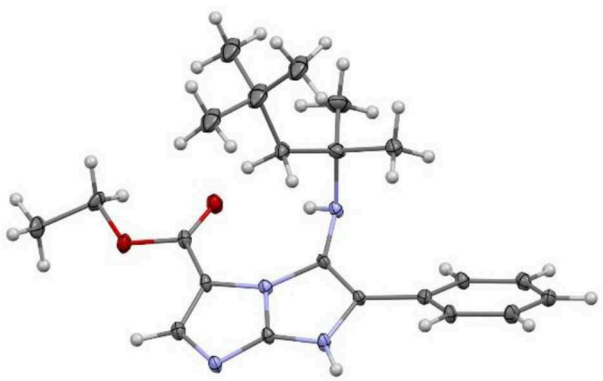


FIGURE 1 | ORTEP representation of compound **4a**.

1 and 4,5-dicyano-2-aminoimidazole **2**. Unfortunately, no reaction was observed when employing the unsubstituted 2-aminoimidazole **3** as substrate, which was recovered after purification.

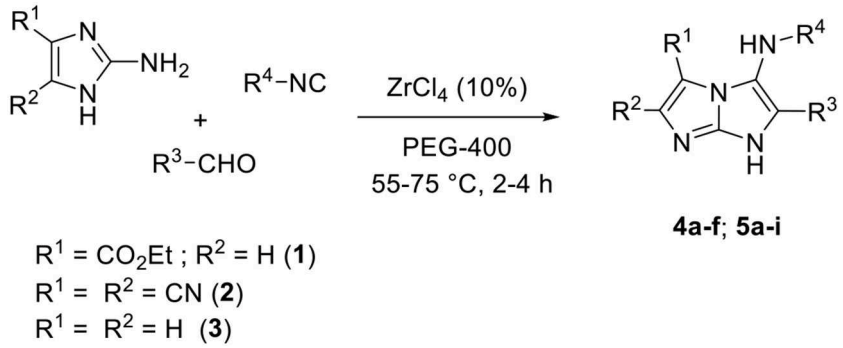
Moreover, the reaction occurred with electron-withdrawing and electron-donating substituents of the benzaldehydes, in addition to sterically hindered aldehydes (entry 9), aliphatic and heteroaromatic aldehydes (entries 12 and 13, respectively). However, a poor yield was obtained when using propionaldehyde (entry 12).

The impact of isocyanide on our reaction was also investigated; the *tert*-octyl isocyanide and *tert*-butyl isocyanide gave similar good results, whereas the cyclohexyl isocyanide showed slightly lower yields.

The MCR involving the unsubstituted 2-aminoimidazole **3** using our conditions did not yield any product. This can be explained by the poor reactivity of the starting substrate due to the absence of an electron-withdrawing group.

In order to find another strategy allowing us to synthetize 5-aminoimidazo[1,2-*a*]imidazoles starting from the unsubstituted 2-aminoimidazole **3**, we first carried out the condensation of the latter with *p*-anisaldehyde as a first step model reaction under different conditions (**Table 3**). The free amine **3** was prepared from the commercially available 2-aminoimidazole sulfate (see **Supplementary Material**). Initially, conventional or MW heating of the reaction in different solvents with $ZrCl_4$ (10 mol%) as catalyst provided the desired imine **6a** in poor yields (entries 1–4). The use of $ZnCl_2$ as catalyst furnished a very low yield (entry 5), while *p*-TsOH and $InCl_3$ gave slightly higher yields (entries 6 and 7). Very interestingly, using a reduced catalytic amount of $InCl_3$ (2 mol% instead of 10 mol%) under conventional or MW heating in ethanol produced a real improvement in terms of yield and reaction time (entries 9 and 11). This may explain the non-reactivity observed in the MCR

TABLE 2 | Synthesis of 5-aminoimidazo[1,2-*a*]imidazole derivatives **4a–f** and **5a–i**.

Entry[a]	R^1, R^2	R^3	R^4	Product	Yield (%)[b]
					
1	CO_2Et, H	C_6H_5	*t*-octyl	**4a**	77 (62)[c]
2	CO_2Et, H	4-$MeOC_6H_4$	*t*-octyl	**4b**	68
3	CO_2Et, H	4-ClC_6H_4	*t*-octyl	**4c**	56
4	CO_2Et, H	4-$CF_3C_6H_4$	*t*-octyl	**4d**	71
5	CO_2Et, H	C_6H_5	*t*-butyl	**4e**	74
6	CO_2Et, H	C_6H_5	cyclohexyl	**4f**	59 (50)[c]
7	CN, CN	C_6H_5	*t*-octyl	**5a**	67 (42)[c]
8	CN, CN	4-$MeOC_6H_4$	*t*-octyl	**5b**	65
9	CN, CN	2,4,6-$MeOC_6H_2$	*t*-octyl	**5c**	61
10	CN, CN	4-ClC_6H_4	*t*-octyl	**5d**	58
11	CN, CN	4-$CF_3C_6H_4$	*t*-octyl	**5e**	76
12	CN, CN	C_2H_5	*t*-octyl	**5f**	12 (5)[c]
13	CN, CN	3-Pyridyl	*t*-octyl	**5g**	79
14	CN, CN	4-ClC_6H_4	*t*-butyl	**5h**	60 (54)[c]
15	CN, CN	4-ClC_6H_4	cyclohexyl	**5i**	47
16	H, H	4-$MeOC_6H_4$	*t*-octyl	-	0 (0)[c]

[a] ***1***, ***2,*** *or* ***3*** *(1.0 mmol), aldehyde (1.1 mmol), isocyanide (1.1 mmol), $ZrCl_4$ (0.1 mmol), PEG-400 (1 mL), 75°C, 4 h (entries 1–6, 16) or 55°C, 2 h (entries 7–15).*

[b] *Yield of isolated product.*

[c] *Isolated yield using the conditions: $ZrCl_4$ (10 mol%), n-BuOH (2 mL), MW (140°C), 10 min.*

(**Table 2**, entry 16), because of the instability of the formed imine under such acidic conditions. However, the prolonged reaction time noted with $ZrCl_4$ (2 mol%) or when no catalyst was used, revealed the influence of $InCl_3$ on this condensation reaction (entries 8 and 10, respectively).

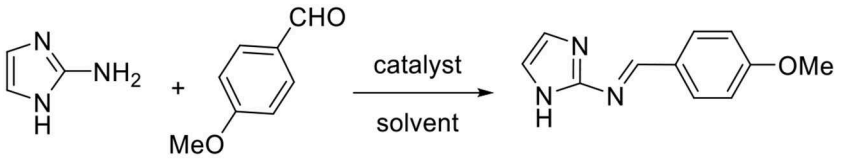
After developing these optimized conditions for the first reaction step, we next focused on finding the best conditions for the second step, which is based on the [4+1] cycloaddition reaction of the formed imine with an isocyanide.

The resulting imine **6a** was isolated and reacted with *tert*-octyl isocyanide under several catalytic conditions (**Table 4**). No reaction occurred when using the same conditions as for the condensation step (entry 1). Increasing the catalytic amount of $InCl_3$ to 10 mol% produced the desired product in poor yields with either conventional or MW heating methods (entries 2 and 3). It is interesting to note that the 5-aminoimidazo[1,2-*a*]imidazole product formed was unstable and underwent a dehydrogenation reaction *in situ* to generate the corresponding stable oxidized compound 5-iminoimidazo[1,2-*a*]imidazole **7a**. We already observed this type of oxidation in our previous work on the synthesis of imidazo[1,2-*b*]pyrazoles by MCRs (Driowya et al., 2018).

The use of other catalysts such as *p*-TsOH, $ZnCl_2$, and $ZrCl_4$ under microwave irradiation did not produce any significant improvement in the reaction yield (entries 4–6). However, using $ZrCl_4$ as catalyst and replacing EtOH by *n*-BuOH as solvent for the reaction showed a slight increase in the yield to 40% (entry 8), which was the optimum result obtained for this reaction. The same conditions used under conventional heating resulted in a significant decrease in the yield. The low yield and the difficulty of this reaction can be explained by the instability of the imine in the acid medium.

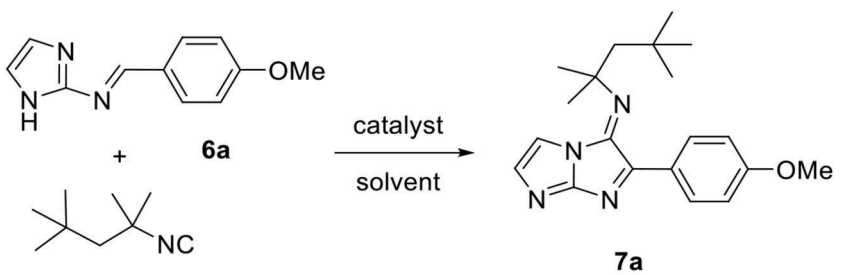
With these optimized conditions in hand, we succeeded in achieving the one-pot two-step procedure without isolating the imine by removing EtOH at the end of the first reaction step. The isolated product **7a** was obtained with a global yield of 32%. This protocol was next extended to the synthesis of series of 5-iminoimidazo[1,2-*a*]imidazoles **7a–i** starting from the unsubstituted 2-aminoimidazole and exploring a wide range of

TABLE 3 | Screening conditions for the synthesis of imine **6a**.

Entry[a]	Catalyst (mol%)	Solvent	Temp (°C)	Heating method	Time (h)	Yield (%)[b]
						
	3			**6a**		
1	$ZrCl_4$ (10)	PEG-400	75	Conventional	16	31
2	$ZrCl_4$ (10)	*n*-BuOH	140	MW	2	22
3	$ZrCl_4$ (10)	Toluene	110	Conventional	16	15
4	$ZrCl_4$ (10)	EtOH	80	Conventional	16	24
5	$ZnCl_2$ (10)	EtOH	80	Conventional	16	5
6	p-TsOH (10)	EtOH	80	Conventional	16	53
7	$InCl_3$ (10)	EtOH	80	Conventional	16	40
8	$ZrCl_4$ (2)	EtOH	80	Conventional	16	61
9	**$InCl_3$ (2)**	**EtOH**	**80**	Conventional	**2**	**78**
10	–	EtOH	80	Conventional	30	60
11	**$InCl_3$ (2)**	**EtOH**	**100**	**MW**	**1**	**75**
12	$InCl_3$ (2)	*n*-BuOH	100	MW	2	59

[a] ***3*** *(0.5 mmol), p-anizaldehyde (0.55 mmol).*
[b] *Yield of isolated product.*
The bold values represent the optimized conditions.

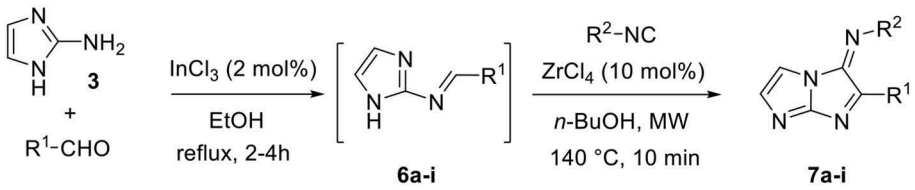
TABLE 4 | Screening conditions for the synthesis of 5-iminoimidazo[1,2-*a*]imidazole **7a**.

Entry[a]	Catalyst (mol%)	Solvent	Temp (°C)	Heating method	Time	Yield (%)[b]
						
	6a			**7a**		
1	$InCl_3$ (2)	EtOH	80	Conventional	14 h	0
2	$InCl_3$ (10)	EtOH	80	Conventional	6 h	<5
3	$InCl_3$ (10)	EtOH	140	MW	10 min	14
4	p-TsOH (10)	EtOH	140	MW	10 min	19
5	$ZnCl_2$ (10)	EtOH	140	MW	10 min	13
6	$ZrCl_4$ (10)	EtOH	140	MW	10 min	22
7	$ZrCl_4$ (10)	PEG-400	140	MW	10 min	26
8	**$ZrCl_4$ (10)**	*n*-BuOH	**140**	MW	**10 min**	**40**
9	$ZrCl_4$ (10)	*n*-BuOH	140	Conventional	3 h	<5
10	$ZrCl_4$ (5)	*n*-BuOH	140	MW	10 min	31
11	$InCl_3$ (10)	*n*-BuOH	140	MW	20 min	25

[a] ***6a*** *(0.2 mmol), tert-octyl isocyanide (0.22 mmol).*
[b] *Yield of isolated product.*
The bold values represent the optimized conditions.

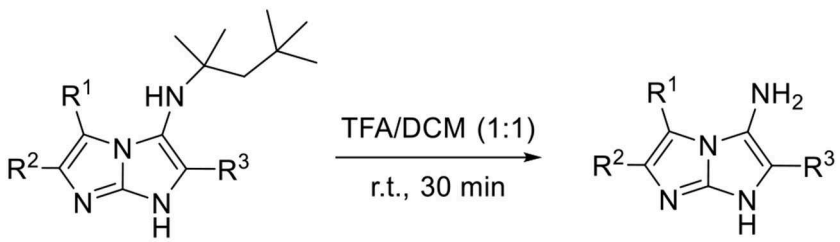
aldehydes and isocyanides (**Table 5**). As mentioned previously, the 5-aminoimidazo[1,2-*a*]imidazole products formed were unstable and led directly to the corresponding imine forms **7a–i**. Despite the low yields obtained, it was nevertheless possible

TABLE 5 | One-pot two-step synthesis of 5-iminoimidazo[1,2-*a*]imidazole derivatives **7a–i**.

Entry[a]	R^1	R^2	Product	Yield (%)[b]
				
1	4-$MeOC_6H_4$	*t*-octyl	**7a**	32
2	C_6H_5	*t*-octyl	**7b**	24
3	2,4,6-$MeOC_6H_2$	*t*-octyl	**7c**	35
4	4-ClC_6H_4	*t*-octyl	**7d**	19
5	4-$CF_3C_6H_4$	*t*-octyl	**7e**	13
6	C_2H_5	*t*-octyl	**7f**	16
7	3-Pyridyl	*t*-octyl	**7g**	12
8	4-$MeOC_6H_4$	*t*-butyl	**7h**	17
9	4-$MeOC_6H_4$	cyclohexyl	**7i**	10

[a]***3*** *(1.0 mmol), aldehyde (1.1 mmol), $InCl_3$ (0.02 mmol), EtOH (10 mL), 2–4 h (90°C); isocyanide (1.1 mmol), $ZrCl_4$ (0.1 mmol), n-BuOH (2 mL), 10 min (140°C).*
[b]*Yield of isolated product.*

TABLE 6 | Cleavage of the *t*-octyl group of the products **4a–d** and **5a–g**.

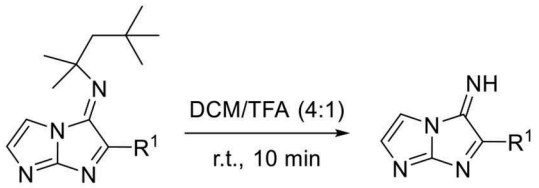
Entry[a]	R^1	R^2	R^3	Product	Yield (%)[b]
					
1	CO_2Et	H	C_6H_5	**8a**	70
2	CO_2Et	H	4-$MeOC_6H_4$	**8b**	74
3	CO_2Et	H	4-ClC_6H_4	**8c**	68
4	CO_2Et	H	4-$CF_3C_6H_4$	**8d**	65
5	CN	CN	C_6H_5	**9a**	59
6	CN	CN	4-$MeOC_6H_4$	**9b**	61
7	CN	CN	2,4,6-$MeOC_6H_2$	**9c**	32
8	CN	CN	4-ClC_6H_4	**9d**	57
9	CN	CN	4-$CF_3C_6H_4$	**9e**	79
10	CN	CN	C_2H_5	**9f**	41
11	CN	CN	3-Pyridyl	**9g**	26

[a]***4a–d***, ***5a–g*** *(0.2 mmol), DCM/TFA 1:1 (5 mL), r.t.*
[b]*Isolated yield.*

to produce the targeted compounds, which proved unsuccessful with the methods developed previously or with those cited in the literature.

The chemical space of our synthetized compounds was then enlarged, by removing the *tert*-octyl groups of 5-aminoimidazo[1,2-*a*]imidazoles **4a–d** and **5a–g** using TFA as cleavage agent in DCM and giving access to the primary amine compounds **8a–d** and **9a–g**, respectively, with yields ranging from 26 to 79% (**Table 6**). In a similar way, the primary imine imidazo[1,2-*a*]imidazoles **10a**, **10b**, **10d**, **10e,** and **10g** were

TABLE 7 | Dealkylation of the *t*-octyl group of the products **7a–g**.

Entry[a]	R^1	Product	Yield (%)[b]
			
	7a-g		**10a; 10b**; **10d** **10e**; **10g**
1	4-$MeOC_6H_4$	**10a**	74
2	C_6H_5	**10b**	85
3	2,4,6-$MeOC_6H_2$	–	–
4	4-ClC_6H_4	**10d**	82
5	4-$CF_3C_6H_4$	**10e**	63
6	C_2H_5	–	–
7	3-Pyridyl	**10g**	64

[a] ***7a–g*** *(0.15 mmol), DCM/TFA 4:1 (5 mL), r.t.*
[b] *Isolated yield.*

prepared in good yields from their corresponding Schiff base derivatives **7a, 7b, 7d, 7e,** and **7g** by deprotection of *tert*-octyl groups using the same conditions (**Table 7**). Unfortunately, the reaction was unsuccessful when the substituent R^1 was 2,4,6-trimethoxyphenyl (entry 3) or ethyl (entry 6).

CONCLUSION

In summary, we have designed highly efficient protocols of multicomponent isocyanide-based reactions catalyzed by zirconium(IV) chloride which offer the synthesis of a library of new functionalized 5-amino and 5-iminoimidazo[1,2-*a*]imidazoles in moderate to good yields. The optimized processes were successively applied to a large number of substituted (or unsubstituted) 2-aminoimidazoles, aldehydes and isocyanides. In addition, the use of inexpensive zirconium(IV) chloride as catalyst delivered an efficient catalytic effect for the reactions with a greater purity of isolated products compared to other catalysts.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript and/or the **Supplementary Files**.

AUTHOR CONTRIBUTIONS

MD designed and performed the experiments, then was responsible for writing the manuscript. RG realised the X-ray analysis for the compound **4a**. PB and GG directed the project and revised the manuscript.

ACKNOWLEDGMENTS

We acknowledge Région Centre-Val de Loire for financial support and Dr. Cyril Colas (ICOA, University of Orléans) for HRMS measurements of our products.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2019.00457/full#supplementary-material

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.