An Efficient, Regioselective, Versatile Synthesis of N-Fused 2- and 3-Aminoimidazoles via Ugi-Type Multicomponent Reaction Mediated by Zirconium(IV) Chloride in Polyethylene Glycol-400

Sankar K. Guchhait,* Chetna Madaan

Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), S. A. S. Nagar (Mohali)-160062, Punjab, India
Fax +91(172)2214692; E-mail: skguchhait@niper.ac.in

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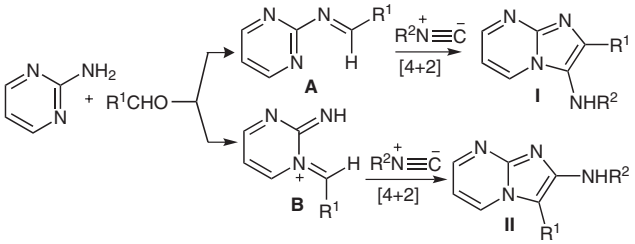
Abstract: An Ugi-type multicomponent reaction of heterocyclic amidines with aldehydes and isocyanides catalyzed by zirconium(IV) chloride in PEG-400 was developed. The protocol offers the rapid, environment friendly, regioselective and versatile synthesis of medicinally important N-fused 2- and 3-aminoimidazoles in good to high yields. The combination of catalyst and solvent, that was judiciously explored, was crucial for regioselectivity and versatility of the method.

Key words: multicomponent reaction, regioselective synthesis, N-heterocycles, zirconium(IV) chloride, polyethylene glycol

Nitrogen-fused imidazoles[1] have recently gained immense attention because of their wide range of pharmaceutical activities such as antibacterial,[2] antiviral,[3] antifungal[4] and anti-inflammatory[5] agents, selective CDK inhibitors,[6] GABA receptor agonists,[7] bradykinin B_2 receptor antagonists[8] and calcium channel blockers.[9] These classes of heterocycles are represented by launched drugs in market like zolimidine (antiulcer), zolpidem (hypnotic) and alpidem (anxiolytic). Significant approaches to the synthesis of N-fused imidazoles include coupling of 2-aminopyridines with α-halocarbonyl compounds,[10] [3+2]-cyclization of 2-aminopyridine with 1,2-bis(benzotriazolyl)-1,2-(dialkylamino)ethanes,[11] Ugi-type multicomponent reaction of heterocyclic 2-aminoazines with aldehydes and isocyanides,[12] five-step one-pot cascade reaction starting from pyridine[13] and Pd–Cu-catalyzed Sonogashira coupling followed by in situ heterocyclization.[14] As multicomponent reactions (MCRs)[15] offer key advantages of atom economy and feasibility of introducing maximum molecular diversity elements in a single chemical event, the MCR processes have received preferred attention in context of organic and medicinal chemist's perspective in drug discovery. But the versatile inefficiency of the MCR approaches for various heteroaromatic amidines and aldehydes leading to the diversity in products is of real concern. Additionally, regioselectivity problem of reaction in case of 2-aminopyrimidine, formation of side products, long reaction time and use of expensive Lewis acid e.g., $Sc(OTf)_3$ restrict the use of MCR methodologies in the synthesis of library of N-fused aminoimidazoles.

As a part of our research program focused on the synthesis of polycyclic heterocyclic compounds for drug discovery, we sought to develop a MCR protocol which would offer the efficient formation of library of versatile N-fused aminoimidazoles. Bradley[12f] reported that the reaction of 2-aminopyrimidines catalyzed by $Sc(OTf)_3$, $HClO_4$ or AcOH in MeOH formed a regioisomeric mixture of 2- and 3-aminoimidazo[1,2-*a*]pyrimidines (**I** and **II**, Scheme 1) in almost equimolar ratio, while ammonium chloride in toluene led the reaction to form only 3-aminoimidazo[1,2-*a*]pyrimidines (**II**) as developed by Krasavin.[12e] This regioselective variation in the reaction of 2-aminopyrimidine can be speculated, as proposed by Krasavin,[12e] that MeOH favors the formation of both of possible uncharged imine and ionic iminium intermediates (**A** and **B**, Scheme 1), while toluene being nonpolar solvent can stabilize only imine intermediate (**A**).



Scheme 1 Plausible mechanism[12e]

Additionally, nucleophilic solvents like methanol were found to promote the competitive side reaction of nucleophilic attack of 2-aminoazines as well as that of solvent itself on intermediates **A** and **B**. It is noteworthy that the use of nonpolar solvent like toluene in reaction requires longer time at high temperature. We reasoned that the polar protic but less nucleophilic solvent like polyethylene glycol could favor the formation of ionic iminium intermediate and avoid nucleophilic side reaction. Thus high regioselectivity and versatility of the reaction could be achieved if performed in PEG-400,[16] with use of suitable Lewis acid catalyst having high cationic charge potential. Zr^{4+}, with a high charge to size ratio (Z^2/r is 22.22 e^2m^{-10}) has strong coordinating ability, and thus $ZrCl_4$ shows high

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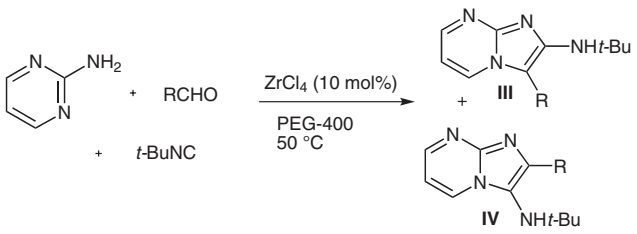
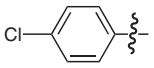
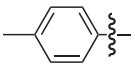
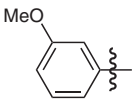
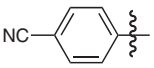
Table 1 Regioselective Synthesis of 2-Aminoimidazo[1,2-*a*]pyrimidines



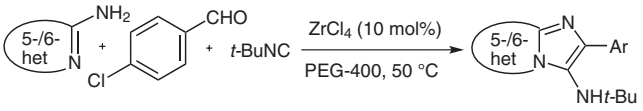
Entry	Substrate (R)	Time (h)	Isolated yield (%)	
			III	**IV**
1		1	83	9
2		2	80	10
3		1.5	78	11
4		2	84	7

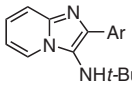
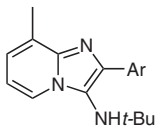
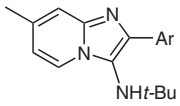
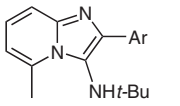
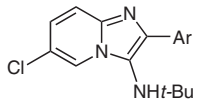
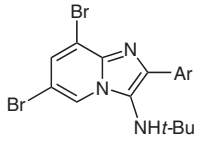
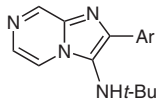
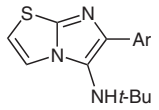
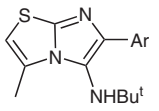
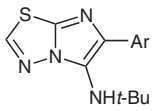
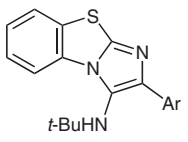
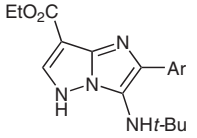
efficiency in catalytic activity.[17] Additionally, the inexpensiveness and ease and safety of handling of $ZrCl_4$ prompted us to choose it as catalyst for initial screening. Herein, we report the results of this study.

In the initial experiment, the reaction of 2-aminopyridine was carried out with 4-chlorobenzaldehyde and *tert*-butyl isocyanide catalyzed by $ZrCl_4$ (10 mol%) in PEG-400 as solvent at 50 °C. It provided *N*-*tert*-butyl-2-(4-chlorophenyl)imidazo[1,2-*a*]pyridin-3-amine in 85% isolated yield in 4.5 hours. This result incited us to investigate the reaction systematically to explore its potential utility. The use of $CeCl_3 \cdot 7H_2O$, $ZnClO_4 \cdot 6H_2O$ or $InCl_3$ as catalyst effected the reaction in comparatively lower yields. Polar aprotic solvent like acetonitrile led the reaction very slowly and the formation of side products was observed. $ZrCl_4$ was necessary as the reaction in PEG-400 without catalyst did not form product after five hours. A 10 mol% loading of $ZrCl_4$ gave the best result at optimal temperature and reaction time. The experimental procedure is very simple and straightforward.[18]

The optimized protocol was then tested for its regioselective efficiency. Very interestingly, 2-aminopyrimidine in this method catalyzed by $ZrCl_4$ in PEG-400 afforded the highly regioselective formation of 2-*tert*-butylaminoimidazo[1,2-*a*]pyrimidines **III** over 3-amino regioisomeric products **IV** in almost 8:1 ratio with high yields (Table 1). The reason for regioselective formation of products **III** can be speculated that PEG-400, being polar solvent, stabilizes preferentially the ionic iminium intermediate **B** and $ZrCl_4$ acting as Lewis acid of high cationic charge potential enhances the formation of pyrimidin-2(1*H*)-imine tautomeric form of 2-aminopyrimidine and thus intermediate **B**. The structures of 2- and 3-aminoimidazo[1,2-

Table 2 Synthesis of Versatile N-Fused 3-Aminoimidazoles Spanning Diverse Heterocyclic Amidines[a]



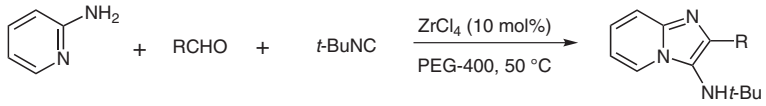
Entry	Product[b]	Time (h)	Yield (%)[c]
1		4.5	85
2		7	81
3		2	83
4		3	90
5		2.5	85
6		3.5	72
7		3	90
8		5	90
9		2	83
10		7	64
11		4.5	84
12		5	79

[a] Reaction conditions: heterocyclic amidines, aldehydes and isocyanides in equimolar ratio, $ZrCl_4$ (10 mol%), PEG-400, 50 °C.
[b] Ar = 4-chlorophenyl, and all products were characterized by ^1H NMR, ^{13}C NMR, IR, mass and elemental analyses.
[c] Isolated yields.

a]pyrimidines were characterized by their spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, mass and elemental analyses) which, along with R_f value in TLC, were identical with those of respective isomers prepared by reported method.[12f]

Splendidly, the scope of this protocol was extensively broad and versatile, spanning a wide range of heterocyclic 2-aminoazines, aldehydes and isocyanides. The heterocyclic azine used included 2-aminopyridine, 2-aminopyrazine, 2-aminothiazole, 2-aminothiadiazole, 2-aminobenzthiazole and 3-amino-1*H*-pyrazole (Table 2). The aldehydes comprised electron-rich, electron-poor, sterically hindered and metallocene-derived aromatic, heteroaromatic and aliphatic aldehydes (Table 3). The reactions of all heterocyclic amidines other than 2-aminopyrimidine (Tables 2 and 3) formed only one regioselective product, N-fused 3-aminoimidazoles, which are likely to be formed according to the reported MCR approaches. Less reactive amidines such as aminopyrazine, aminothiazole and aminothiadiazole in Ugi-type MCR in MeOH were reported to suffer from a competing reaction through nucleophilic attack of MeOH and amidine-amine on intermediate Schiff bases.[12a,e,f] Significantly, the reaction of these amidines in this process (Table 2, entries 8–11) afforded high yield of products suppressing side reactions, as reasoned. While glyoxylic acid was explored[19] to be an efficient formaldehyde equivalent in MCR to afford 2-unsubstituted 3-amino N-fused imidazoles, the reaction of formaldehyde in Ugi-type MCRs for their synthesis are reportedly scarce, and those reported are low yielding.[12d] Interestingly, the reaction of paraformaldehyde with 2-aminopyridine and *tert*-butyl isocyanide (Table 3, entry 11) in this method offered the product in 75% yield, and thus this protocol provides the convenient access of 2-unsubstituted 3-amino N-fused imidazoles. This process was quite general for isocyanides. The reaction of 2-aminopyridine and 4-chlorobenzaldehyde with *tert*-butyl, cyclohexyl and 1,1,3,3-tetramethylbutyl isocyanides afforded the corresponding products in 85%, 88% and 90% yield respectively. Significantly, the dealkylation of 1,1,3,3-tetramethylbutyl group of MCR product by TFA can convert it into the corresponding primary amine product, which can be as useful for further modification.[20] Functional groups on aromatic rings of aldehydes and heterocyclic amidines, such as methoxy, chloro, bromo, cyano, *N*,*N*-dimethyl and carboxyl were unaffected by the reaction conditions. This method was straightforward. Reactions were sufficiently fast and insensitive to oxygen and moisture. Preformation of imine was found to be unnecessary.

Table 3 Synthesis of Versatile N-Fused 3-Aminoimidazoles (Imidazo[1,2-*a*]pyridines) Spanning a Wide Range of Aldehydes[a,b]



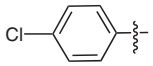
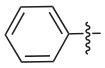
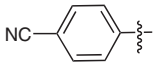
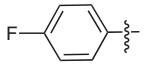
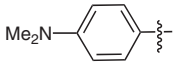
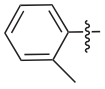
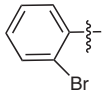
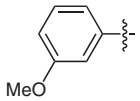
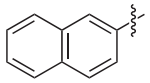
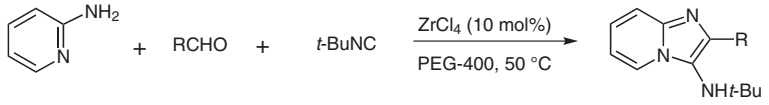
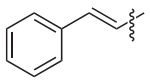
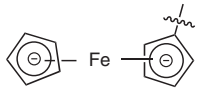
Entry	Substrate (R)	Time (h)	Yield (%)[c]
1		4.5	85
2		3	80
3		6	78
4		1.5	88
5		3	82
6		2	80
7		5	95
8		3.5	95
9		2.5	85

Table 3 Synthesis of Versatile N-Fused 3-Aminoimidazoles (Imidazo[1,2-*a*]pyridines) Spanning a Wide Range of Aldehydes[a,b] (continued)



Entry	Substrate (R)	Time (h)	Yield (%)[c]
10		1.5	88
11	$(CH_2O)_n$	5	75
12	C_3H_7–	2	92
13		2.5	89
14		2.5	81
15		2.5	83
16		1.5	86
17		2.5	78

[a] Reaction conditions: 2-aminopyridine, aldehydes and isocyanides in equimolar ratio, $ZrCl_4$ (10 mol%), PEG-400, 50 °C.
[b] All products were characterized by ^1H NMR, ^{13}C NMR, IR, mass and elemental analyses.
[c] Isolated yields.

In conclusion, we have developed a novel method with judicious choice of solvent and catalyst for the synthesis of N-fused 2- and 3-aminoimidazoles. This new protocol has enormous potential for preparing a large library of regioisomerically pure, versatile nitrogen-fused 2- and 3-aminoimidazoles in an expeditious and environmentally friendly way in good to excellent yields from readily accessible starting materials. Further investigation on use of this methodology in multistep synthesis of library of target molecules for drug discovery is ongoing.

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References and Notes

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(18) **Representative Experimental Procedure for the Synthesis of *N-tert*-Butyl-2-(4-chlorophenyl)imidazo[1,2-*a*]pyridin-3-amine (Table 2, entry 1)**: To a mixture of 2-aminopyridine (0.19 g, 2 mmol) and 4-chlorobenzaldehyde (0.28 g, 2 mmol) in PEG-400 (2 mL), *tert*-butyl isocyanide (0.17 g, 2 mmol) and $ZrCl_4$ (47 mg, 10 mol%) were added. The mixture was allowed to stir at 50 °C under open air. After completion of the reaction (4.5 h, monitored by TLC), the resulting mixture was extracted with EtOAc and washed with H_2O. The organic layer was dried over anhyd Na_2SO_4, filtered and concentrated under reduced pressure. The column chromatographic purification of crude product over silica gel (mesh size: 60–120) eluting with EtOAc–hexane (1:1.5) afforded *N-tert*-butyl-2-(4-chlorophenyl)imidazo-[1,2-*a*]pyridin-3-amine (0.48 g, 85%); white solid; mp 146–149 °C. MS (ESI): *m*/*z* = 300 [M + 1]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (s, 9 H), 3.00 (br, NH), 6.78 (t, *J* = 6.8 Hz, 1 H), 7.15 (t, *J* = 8.0 Hz, 1 H), 7.40 (d, *J* = 8.8 Hz, 2 H), 7.54 (d, *J* = 7.2 Hz, 1 H), 7.92 (d, *J* = 8.8 Hz, 1 H), 8.20 (d, *J* = 6.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.3 (3 × Me), 56.4 (C), 111.5 (CH), 117.3 (CH), 123.3 (CH), 123.4 (C), 124.3 (CH), 128.4 (2 × CH), 129.3 (2 × CH), 133.1 (C), 133.7 (C), 138.3 (C), 142.0 (C). IR (KBr): 3457, 2972, 1635, 1194, 770 cm^{-1}. Anal. Calcd for $C_{17}H_{18}ClN_3$: C, 68.11; H, 6.05; N, 14.02. Found: C, 67.89; H, 6.07; N, 13.99. All reactions (Tables 1– 3) were carried out following this procedure.

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