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Catalyst-free three-component reaction between 2-aminopyridines (or 2-aminothiazoles), aldehydes, and isocyanides in water

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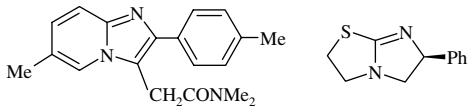
Abstract—A catalyst-free and convenient protocol is described for the preparation of 3-aminoimidazo[1,2-*a*]pyridines and 5-aminoimidazo[2,1-*b*][1,3]thiazoles via three-component reactions between 2-aminopyridines or 2-aminothiazoles, aldehydes, and isocyanides in water in good to excellent yields.

Water is a desirable solvent for chemical reactions because it is safe, non-toxic, environmentally friendly, readily available, and cheap compared to organic solvents.[1] Although enzymatic processes in Nature occur in aqueous environment by necessity, water has been avoided as a solvent for common organic reactions due to poor solubility and, in some cases, the instability of organic reagents or reaction intermediates in aqueous solutions. Since the pioneering studies on Diels–Alder reactions by Breslow,[2] there has been increasing recognition that organic reactions can proceed well in aqueous media and offer advantages over those occurring in organic solvents, such as rate enhancement and insolubility of the final products that facilitates their isolation.[1]

Imidazo[1,2-*a*]pyridines have been shown to possess antibacterial, antifungal, anthelmintic, antiviral, antiprotozoal, antiinflammatory, anticonvulsant, anxiolytic, hypnotic (e.g., Zolpidem, Fig. 1), gastrointestinal, antiulcer, and immunomodulatory activities.[3,4] Compounds containing the imidazo[2,1-*b*][1,3]thiazole skeleton have been used as anthelmintic agents, antihypertensives, anti-inflammatories, immunosuppressive agents, fungicides, herbicides, antitumor agents, and cardiotonic agents.[5,6] Levamisole (Fig. 1) has potential uses in such diverse disease areas as recurring infections, immune deficiency states, allergic and gastrointestinal disorders, and rheumatic diseases.[7]



Zolpidem Levamisole

Figure 1. Examples of pharmacologically important fused bicyclic imidazoles.

Multi-component reactions (MCRs) are useful for the construction of diverse chemical libraries of 'drug-like' molecules. The isocyanide-based MCRs are especially important in this area.[8] In 1998, new variants of the Ugi MCR[9] were described by Blackburn,[10] Bienaymé,[11] and Groebke[12], which enabled the ready synthesis of imidazo[1,2-*a*]azines. The reactions of an aldehyde, an isocyanide, and a 2-aminoazine in methanolic solution containing $Sc(OTf)_3$,[10] perchloric acid[11], or glacial acetic acid[12] as catalyst were performed at room temperature. However, these reactions required long times for completion and the reaction work-ups were complicated. The reaction has also been carried out under microwave irradiation in the presence of a solid acid, Montmorillonite K10,[13] and $Sc(OTf)_3$,[14] however, special instrumentation is required. This reaction was also performed using a nonpolar solvent[15] and in the presence of an ionic liquid.[16] Most of the above mentioned syntheses involve harsh or environmentally hazardous reaction conditions.

Keywords: Imidazo[1,2-*a*]pyridines; Imidazo[2,1-*b*][1,3]thiazoles; Isocyanides; Three-component reactions; Catalyst-free synthesis in water.
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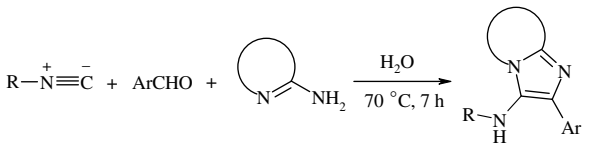
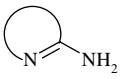
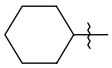
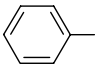
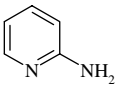
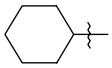
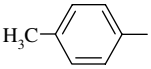
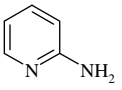
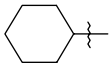
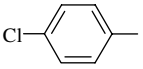
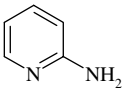
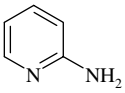
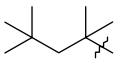
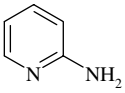
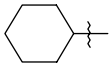
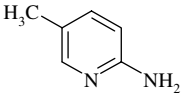
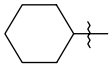
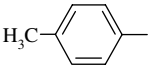
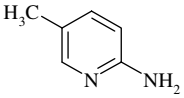
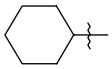
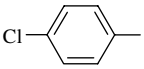
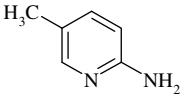
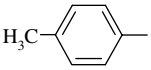
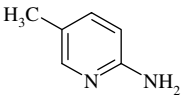
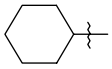
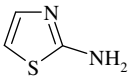
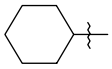
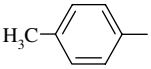
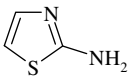
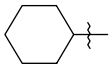
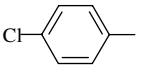
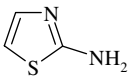
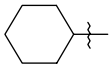
Table 1. Catalyst-free synthesis of imidazo[1,2-*a*]pyridines and imidazo[2,1-*b*][1,3]thiazoles in water



1 **2** **3** **4**

Entry	R	Ar		% Yield of **4**[a]
a				94
b				92
c				97
d				91
e				90
f				92
g				93
h				96
i				90
j				87
k				85
l				90
m				85

[a] Isolated yield.

Due to the unique pharmacological properties of imidazo[1,2-*a*]pyridines and imidazo[2,1-*b*][1,3]thiazoles, the development of synthetic methods, enabling easy access to these fused heterocycles, are desirable.[3,5,17] Herein, a catalyst-free and convenient protocol for the preparation of these heterocycles is described using 2-aminopyridine or 2-aminothiazole as the amine component with different aldehydes and isocyanides.

Thus, a mixture of isocyanide **1**, aldehyde **2**, and amine **3** were condensed at 70 °C in water to produce the corresponding fused aminoimidazoles **4** in 85–97% yields (Table 1). All the reactions went to completion within 7 h.[18] ^{1}H NMR analysis of the reaction mixtures clearly indicated the formation of the corresponding 3-aminoimidazo[1,2-*a*]pyridines or 5-aminoimidazo[2,1-*b*][1,3]thiazoles **4a**–**m** in good to excellent yields. Any product other than **4** could not be detected by NMR spectroscopy. The structures of the isolated products were confirmed by NMR spectroscopy, mass spectrometry, and elemental analysis.[18]

In conclusion, we have reported a convenient, simple, efficient, and environmentally friendly approach for the three-component condensation reaction of 2-aminopyridines or 2-aminothiazoles, aldehydes, and isocyanides resulting in the formation of imidazo[1,2-*a*]pyridines or imidazo[2,1-*b*][1,3]thiazoles. To the best of our knowledge, this is the first report on the catalyst-free synthesis of these fused aminoimidazoles in water.

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18. The procedure for the preparation of 2-(4-chlorophenyl)-3-cyclohexylaminoimidazo[1,2-*a*]pyridine **4c** is described as an example: A mixture of 2-aminopyridine (0.094 g, 1 mmol), 4-chlorobenzaldehyde (0.141 g, 1 mmol), and cyclohexyl isocyanide (0.131 g, 1.2 mmol) in H_2O (2 mL) was stirred at 70 °C for 7 h, then the heterogeneous reaction mixture was cooled to room temperature. Water was separated by suction and the residue was crystallized from acetone to give **4c** as colorless crystals, mp 179–181 °C. MS, *m/z* (%): 327 ($M^{+\ 37}$Cl, 22), 325 ($M^{+\ 35}$Cl, 57), 242 (100), 215 (79), 137 (4), 78 (65), 55 (8). Anal. Calcd for $C_{19}H_{20}ClN_3$ (325.84): C, 70.04; H, 6.19; N, 12.90. Found: C, 69.9; H, 6.3; N, 12.7. ^{1}H NMR (300.1 MHz, DMSO-d_6): δ 1.04–1.75 (10H, m, $CH(CH_2)_5$), 2.80 (1H, m, $NCH(CH_2)_5$), 4.83 (1H, d, $J = 5.6$ Hz, NH), 6.88 (1H, t, $J = 6.7$ Hz, CH), 7.17 (1H, dd, $J = 8.6$ Hz and $J = 7.0$ Hz, CH), 7.45 (1H, d, $J = 8.6$ Hz, CH), 7.46 (2H, d, $J = 7.9$ Hz, 2 CH), 8.24 (2H, d, $J = 7.9$ Hz, 2 CH), 8.30 (1H, d, $J = 6.8$ Hz, CH). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 23.48, 24.39 and 32.53 (3 CH_2), 55.50 (NHCH), 110.46, 115.79, 122.45 and 123.06 (4 CH), 125.03 (C), 127.05 and 127.25 (2 CH), 130.21, 132.52, 132.66 and 139.58 (4C). *5-Cyclohexylamino-6-(4-methylphenyl)imidazo[2,1-b][1,3]thiazole* (**4k**): colorless crystals, mp 134–135.5 °C. MS, *m/z* (%): 311 (M^+, 64), 228 (88), 201 (100), 119 (14), 91 (18), 69 (8), 55 (10). Anal. Calcd for $C_{18}H_{21}N_3S$ (311.45): C, 69.42; H, 6.80; N, 13.49. Found: C, 69.4; H, 6.9; N, 13.3. ^{1}H NMR (300.1 MHz, DMSO-d_6): δ 1.05–1.77 (10H, m, $CH(CH_2)_5$), 2.29 (3H, s, CH_3), 2.80 (1H, m, $NCH(CH_2)_5$), 4.58 (1H, d, $J = 5.8$ Hz, NH), 7.12 (1H, d, $J = 4.0$ Hz, CH), 7.16 (2H, d, $J = 7.8$ Hz, 2 CH), 7.71 (1H, d, $J = 4.0$ Hz, CH), 7.97 (2H, d, $J = 7.8$ Hz, 2 CH). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 19.76 (CH_3), 23.48, 24.46 and 32.45 (3 CH_2), 55.78 (NHCH), 110.87, 117.28 and 124.34 (3 CH), 126.74 (C), 127.71 (CH), 131.32, 133.85, 134.25 and 142.37 (4 C).