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Short Communication

Ionic Liquid Promoted One-Pot Three-Component Reaction: Synthesis of Annulated Imidazo[1,2-*a*]azines Using Trimethylsilylcyanide

Ahmad Shaabani* and **Ali Maleki**

Department of Chemistry, Shahid Beheshti University, Tehran, Iran

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Summary. Imidazo[1,2-*a*]azine derivatives are synthesized by a one-pot three-component reaction of an 2-aminoazine, an aldehyde, and trimethylsilylcyanide in the presence of 1-*n*-butyl-3-methylimidazolium bromide as a recoverable ionic liquid, in moderate to excellent yields with relatively short reaction times.

Keywords. Ionic liquid; 1-*n*-Butyl-3-methylimidazolium bromide; Multi-component reaction; Trimethylsilylcyanide; 3-Aminoimidazo[1,2-*a*]azine.

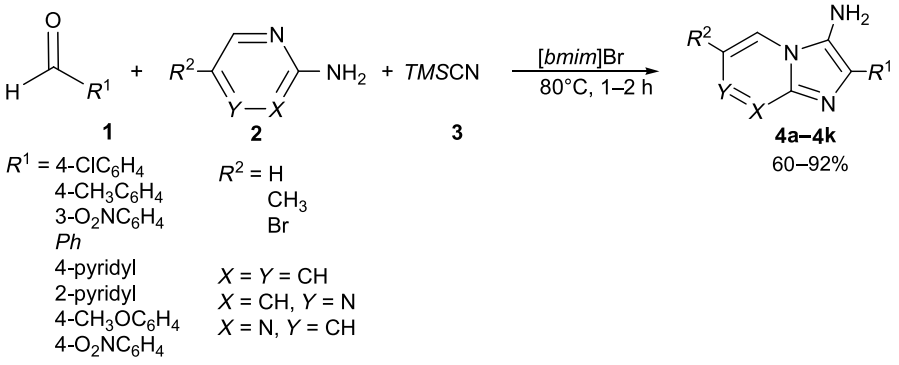
Introduction

Imidazo[1,2-*a*]pyridines have emerged as versatile biologically active compounds spanning applications in anti-inflammatory [1a, 1b] and antibacterial agents [1c], as inhibitors of gastric acids secretion [1d], as calcium channel blockers [1e], and in antiulcer based therapies [1f].

The classical synthesis of imidazo[1,2-*a*]azines involves the condensation of α-haloketones with 2-aminoazines [2]. Being only a two-component condensation, this reaction is less suitable for the generation of a large ensemble of compounds.

Several isocyanide-based multi-component reactions (MCRs) have been reported for the synthesis of these compounds by the condensation of an aldehyde, an isocyanide, and a 2-aminoazine in the presence of strong protic (*Ac*OH, $HClO_4$) [3–6] or *Lewis* acids ($Sc(OTf)_3$) [5, 6]. However, these reactions require long times for completion and isolation and recovery procedures are complicated.

* Corresponding author. E-mail: a-shaabani@cc.sbu.ac.ir



Scheme 1

The synthesis of imidazo[1,2-*a*]pyridines has been reported to proceed under microwave irradiation in the presence of montmorillonite K_{10} [7] or Sc(O*Tf*)$_3$ [8], however, special instrumentation is required.

Very recently, *Hulme* has discovered a convenient route for the synthesis of 3-aminoimidazo[1,2-*a*]azines *via* the application of trimethylsilylcyanide (**3**), as a non-classical isocyanide equivalent [9]. Reactions were performed in methanol by microwave irradiation and catalysis by Sc(O*Tf*)$_3$ with isolated yields in the 30–70% range. In spite of their potential utility and novelity of this approach the yields are relatively low and it requires an expensive catalyst and special instrumentation.

During recent years, ionic liquids have attracted interest as environmentally benign reagents due to their favorable properties, and a variety of catalytic reactions have been successfully described using ionic liquids [10]. The solvophobic properties of ionic liquids are able to generate an internal pressure and promote the association of the reactants in a solvent cavity during the activation process and thus accelerate the reaction. This property of ionic liquids is very efficient for multicomponent reactions in which the entropy of reaction is decreased for the transition state.

In connection with our previous work using ionic liquids as reaction media and our interest in multi-component reactions [11], we now report herein the facile synthesis of 3-aminoimidazo[1,2-*a*]pyridines **4**, 3-aminoimidazo[1,2-*a*]pyrazines **4**, and 3-aminoimidazo[1,2-*a*]pyrimidines **4** by a one-pot three-component condensation of an aldehyde **1**, a 2-aminoazine **2**, and trimethylsilylcyanide **3**, as an isocyanide equivalent, in the presence of 1-*n*-butyl-3-methylimidazolium bromide ([*bmim*]Br) as a promoter under classical heating conditions in high yields with rather short reaction times (1–2 h) (Scheme 1).

Results and Discussion

In order to optimize the reaction conditions, we conducted the condensation of 4-chlorobenzaldehyde (1 mmol), 2-amino-5-methylpyridine (1 mmol), and **3** (1.2 mmol) with stirring under heating conditions at 80°C in various solvents and ionic liquids. The results showed that the efficiency and the yield of the reaction in [*bmim*]Br was higher than those obtained in other solvents, such as

Table 1. Synthesis of 3-aminoimidazo[1,2-*a*]azines in the presence of [*bmim*]Br at 80°C

Product	R^1	R^2	*X*	*Y*	Time/h	Yield/%[a]
4a	4-ClC_6H_4	*Me*	CH	CH	1	92 (90, 86, 85, 80)[b]
4b	4-$CH_3C_6H_4$	*Me*	CH	CH	1.2	87
4c	3-$O_2NC_6H_4$	*Me*	CH	CH	1.2	85
4d	*Ph*	*Me*	CH	CH	1.5	77
4e	4-pyridyl	*Me*	CH	CH	2	80
4f	2-pyridyl	*Me*	CH	CH	2	62
4g	*Ph*	Br	CH	CH	1.5	83
4h	4-$CH_3OC_6H_4$	H	N	CH	2	60
4i	4-$O_2NC_6H_4$	H	N	CH	2	75
4j	4-$CH_3OC_6H_4$	H	CH	N	1.5	72
4k	4-$O_2NC_6H_4$	H	CH	N	1.5	84

[a] Isolated yield; [b] the same ionic liquid was used for all of the five runs

*Me*OH, *Et*OH, CH_2Cl_2, and toluene and other ionic liquids like [*bmim*]PF_6 and [*bmim*]BF_4.

To illustrate the need of the ionic liquid for these reactions an experiment was conducted in the absence of an ionic liquid. The yield in this case was only 5% after heating at 80°C for 3 h. Obviously, the ionic liquid is an important component of the reaction.

One of the advantages of ionic liquids is their ability to function as a recyclable reaction medium. We were able to separate [*bmim*]Br from the reaction medium easily by washing with water and evaporating the solvent under vacuum, and we could reuse it for subsequent reactions (Table 1, Entry 1).

Further, we examined the effect of a variety of aldehydes and aminoazines in this reaction. The results reported in Table 1 show that in all cases the products were obtained efficiently. It is worth mentioning that the reaction conditions are attractive: they are mild (approximately neutral conditions at 80°C in common vessels for 1–2 h) and only a slight excess of reagent 3 is required (1.2 mmol). Thus, this process could be also interesting for large-scale synthesis.

In conclusions, we report a useful method for the synthesis of 3-aminoimidazo[1,2-*a*]azine derivatives *via* a one-pot three-component condensation reaction of 2-aminoazines, aldehydes, and **3** (as an isocyanide equivalent) using the ionic liquid [*bmim*]Br as a promoter in moderate to excellent yields with relatively short reaction times.

Experimental

Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were recorded on a FT-IR 102MB BOMEM apparatus. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^1H and ^{13}C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz. ^1H and ^{13}C NMR spectra were obtained on solutions in $CDCl_3$ and *DMSO*-d_6. All chemicals were obtained from Fluka, Merck, and Aldrich and were used without purification. All products (except **4d**) are new compounds, which were identified by IR, ^1H and ^{13}C NMR spectral data, and mass spectroscopy.

General Procedure

A mixture of 1 mmol 2-aminoazine and 1 mmol aldehyde in the presence of 0.3 g [*bmim*]Br in a screw-capped vial was stirred for 15 min. Then 0.15 cm^3 **3** (1.2 mmol) were added and the reaction was heated at 80°C for 45 min. After completion of the reaction (monitoring by TLC, ethyl acetate/*n*-hexane, 3/1), the reaction mixture was cooled to room temperature and washed with H_2O. The solid residue was crystallized from ethyl acetate to obtain the pure product **4**. The ionic liquid was recovered by evaporation of the filtrate in vacuum.

2-(4-Chlorophenyl)-6-methylimidazo[1,2-a]pyridin-3-amine (**4a**, $C_{14}H_{12}ClN_3$)

White solid (0.24 g, 92%), mp 248–250°C (dec); IR (KBr): $\bar{\nu} = 3350$, 3285, 2923, 1661, 1611, 1480, 1320 cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.32$ (s, CH_3), 5.48 (br, NH_2), 7.19 (d, $J = 8.4$ Hz, H–*Ar*), 7.42 (d, $J = 8.4$ Hz, H–*Ar*), 7.50 (d, $J = 6.4$ Hz, 2H–*Ar*), 7.97 (d, $J = 6.4$ Hz, 2H–*Ar*), 8.23 (s, H–*Ar*) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 18.30$, 114.54, 121.17, 122.07, 122.78, 127.55, 128.16, 128.99, 129.22, 131.59, 136.98, 148.73, 155.85 ppm; MS (EI, 70 eV): m/z (%) = 258 ($M^+ + 1$, 75), 257 (M^+, 100), 93 (64), 92 (35), 65 (35), 39 (20).

6-Methyl-2-p-tolylimidazo[1,2-a]pyridin-3-amine (**4b**, $C_{15}H_{15}N_3$)

Yellow solid (0.21 g, 87%), mp 230°C (dec); IR (KBr): $\bar{\nu} = 3352$, 3290, 2925, 1661, 1612, 1481, 1322 cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.88$ (s, CH_3), 2.35 (s, CH_3), 3.67 (br, NH_2), 7.01–7.14 (m, 7H–*Ar*) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 16.58$, 18.23, 112.35, 123.62, 125.36, 126.30, 127.25, 129.63, 133.17, 134.25, 136.12, 147.29, 152.06 ppm; MS (EI, 70 eV): m/z (%) = 238 ($M^+ + 1$, 68), 237 (M^+, 100), 93 (45), 65 (44), 39 (27).

6-Methyl-2-(3-nitrophenyl)imidazo[1,2-a]pyridin-3-amine (**4c**, $C_{14}H_{12}N_4O_2$)

Yellow solid (0.23 g, 85%), mp 220–223°C (dec); IR (KBr): $\bar{\nu} = 3350$, 3280, 2923, 1665, 1535, 1485, 1356, 1320 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 2.35$ (s, CH_3), 3.25 (br, NH_2), 7.04 (d, $J = 9.2$ Hz, H–*Ar*), 7.47 (d, $J = 9.2$ Hz, H–*Ar*), 7.63 (dd, $J = 8.0$, 8.0 Hz, H–*Ar*), 7.98 (s, H–*Ar*), 8.22 (d, $J = 8.0$ Hz, H–*Ar*), 8.63 (d, $J = 8.0$ Hz, H–*Ar*), 8.75 (s, H–*Ar*) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 16.45$, 116.20, 121.23, 121.38, 121.70, 122.20, 125.70, 128.35, 129.43, 132.76, 133.12, 135.60, 140.36, 148.32 ppm; MS (EI, 70 eV): m/z (%) = 269 ($M^+ + 1$, 35), 268 (M^+, 100), 92 (65), 65 (38), 39 (23).

6-Methyl-2-phenylimidazo[1,2-a]pyridin-3-amine (**4d**, $C_{14}H_{13}N_3$)

White solid (0.18 g, 77%), mp 250°C (dec); IR (KBr): $\bar{\nu} = 3352$, 3275, 2927, 1667, 1625, 1472, 1333 cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.35$ (s, CH_3), 5.44 (br, NH_2), 7.21–7.72 (m, 5H–*Ar*), 7.45 (d, $J = 7.6$ Hz, H–*Ar*), 7.96 (d, $J = 7.6$ Hz, H–*Ar*), 8.26 (s, H–*Ar*) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 17.80$, 112.28, 114.34, 121.20, 122.87, 126.64, 127.74, 127.37, 129.54, 132.48, 136.77, 144.48 ppm; MS (EI, 70 eV): m/z (%) = 224 ($M^+ + 1$, 65), 223 (M^+, 100), 92 (72), 65 (55), 39 (23).

6-Methyl-2-(pyridin-4-yl)imidazo[1,2-a]pyridin-3-amine (**4e**, $C_{13}H_{12}N_4$)

Yellow solid (0.18 g, 80%), mp 182–185°C; IR (KBr): $\bar{\nu} = 3338$, 3254, 2927, 1659, 1586, 1482, 1340 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 2.39$ (s, CH_3), 3.42 (br, NH_2), 7.03 (d, $J = 9.2$ Hz, H–*Ar*), 7.44 (d, $J = 9.2$ Hz, H–*Ar*), 7.85 (s, H–*Ar*), 8.05 (d, $J = 5.8$ Hz, 2H–*Ar*), 8.64 (d, $J = 5.8$ Hz, 2H–*Ar*) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 18.42$, 116.75, 120.32, 120.83, 122.16, 126.55, 128.26, 133.12, 140.79, 142.30, 148.24 ppm; MS (EI, 70 eV): m/z (%) = 225 ($M^+ + 1$, 57), 224 (M^+, 100), 92 (78), 65 (46), 39 (34).

6-Methyl-2-(pyridin-2-yl)imidazo[1,2-a]pyridin-3-amine (**4f**, $C_{13}H_{12}N_4$)

Yellow solid (0.14 g, 62%), mp 201–204°C; IR (KBr): $\bar{\nu} = 3336$, 3252, 2927, 1657, 1585, 1487, 1342 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 2.35$ (s, CH_3), 3.43 (br, NH_2), 7.10 (d, $J = 9.2$ Hz, H–*Ar*), 7.46 (d, $J = 9.2$ Hz, H–*Ar*), 7.82 (s, H–*Ar*), 7.52–8.57 (m, 4H–*Ar*) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 18.43$, 116.85, 118.92, 119.85, 120.16, 121.32, 122.16, 125.64, 131.26, 137.12, 137.85, 148.65, 157.11 ppm; MS (EI, 70 eV): m/z (%) = 225 ($M^+ + 1$, 46), 224 (M^+, 100), 92 (66), 65 (44), 39 (28).

6-Bromo-2-phenylimidazo[1,2-a]pyridin-3-amine (**4g**, $C_{13}H_{10}BrN_3$)
Yellow solid (0.14 g, 60%), mp 230°C (dec); IR (KBr): $\bar{\nu} = 3340$, 3260, 2930, 1660 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 4.72$ (br, NH_2), 7.23–8.45 (m, 8H–*Ar*) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 106.65$, 117.59, 123.13, 125.32, 127.03, 127.77, 128.66, 128.64, 133.36, 136.86, 139.52 ppm; MS (EI, 70 eV): m/z (%) = 288 ($M^+ + 1$, ^{81}Br, 28), 286 (M^+, ^{79}Br, 30), 158 (66), 156 (75), 76 (25).

2-(4-Methoxyphenyl)imidazo[1,2-a]pyrimidin-3-amine (**4h**, $C_{13}H_{12}N_4O$)
Yellow solid (0.14 g, 60%), mp 212–214°C (dec); IR (KBr): $\bar{\nu} = 3337$, 3256, 2935, 1658, 1467, 1352 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 3.85$ (s, OCH_3), 4.25 (br, NH_2), 7.14 (d, $J = 8.9$ Hz, 2H–*Ar*), 7.66 (d, $J = 8.9$ Hz, 2H–*Ar*), 7.88–8.46 (m, 3H–*Ar*) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 55.30$, 114.54, 120.17, 122.17, 124.78, 128.84, 135.28, 136.24, 148.73, 157.85, 161.14 ppm; MS (EI, 70 eV): m/z (%) = 241 ($M^+ + 1$, 46), 240 (M^+, 100), 112 (35), 93 (35), 39 (20).

2-(4-Nitrophenyl)imidazo[1,2-a]pyrimidin-3-amine (**4i**, $C_{12}H_9N_5O_2$)
Yellow solid (0.19 g, 75%), mp 215–218°C (dec); IR (KBr): $\bar{\nu} = 3330$, 3252, 1672, 1547, 1358 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 4.35$ (br, NH_2), 7.67 (d, $J = 9.02$ Hz, 2H–*Ar*), 8.14 (d, $J = 9.02$ Hz, 2H–*Ar*), 7.38 (dd, $J = 7.15$ Hz, $J = 7.15$ Hz, H–*Ar*), 8.76 (d, $J = 7.15$ Hz, 2H–*Ar*) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 120.65$, 121.57, 122.37, 128.48, 135.68, 136.28, 138.24, 148.33, 148.62, 158.85 ppm; MS (EI, 70 eV): m/z (%) = 256 ($M^+ + 1$, 42), 255 (M^+, 100), 134 (44), 122 (25), 93 (35), 46 (30).

2-(4-Methoxyphenyl)imidazo[1,2-a]pyrazin-3-amine (**4j**, $C_{13}H_{12}N_4O$)
Yellow solid (0.17 g, 72%), mp 205–207°C (dec); IR (KBr): $\bar{\nu} = 3330$, 3253, 2931, 1653, 1464, 1340 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 3.86$ (s, OCH_3), 4.36 (br, NH_2), 7.01 (d, $J = 8.5$ Hz, 2H–*Ar*), 7.33 (d, $J = 8.5$ Hz, 2H–*Ar*), 8.42–8.46 (m, 3H–*Ar*) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 55.63$, 114.54, 120.47, 122.15, 124.68, 128.35, 135.32, 136.24, 143.24, 144.73, 161.24 ppm; MS (EI, 70 eV): m/z (%) = 241 ($M^+ + 1$, 35), 240 (M^+, 100), 112 (31), 93 (42), 39 (36).

2-(4-Nitrophenyl)imidazo[1,2-a]pyrazin-3-amine (**4k**, $C_{12}H_9N_5O_2$)
Yellow solid (0.21 g, 84%), mp 230–232°C (dec); IR (KBr): $\bar{\nu} = 3335$, 3250, 1674, 1537, 1353 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 4.25$ (br, NH_2), 7.73 (d, $J = 9.14$ Hz, 2H–*Ar*), 8.22 (d, $J = 9.14$ Hz, 2H–*Ar*), 8.58–8.66 (m, 3H–*Ar*) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 120.15$, 121.67, 122.23, 128.42, 135.58, 136.48, 139.24, 143.21, 144.33, 148.62 ppm; MS (EI, 70 eV): m/z (%) = 256 ($M^+ + 1$, 46), 255 (M^+, 100), 134 (34), 122 (35), 93 (32), 46 (20).

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