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Ammonium chloride catalyzed one-pot synthesis of imidazo[1,2-*a*]pyridines

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Abstract Ammonium chloride as a very inexpensive and readily available reagent efficiently catalyzes one-pot, three-component *Groebke* condensation reactions of aldehydes, isocyanides, and 2-aminopyridines or 2-aminopyrimidines in methanol to afford the corresponding imidazo[1,2-*a*]pyridines in high yields at room temperature.

Keywords Imidazo[1,2-*a*]pyridine; Ammonium chloride; Three-component reaction; Isocyanide.

Introduction

Imidazo[1,2-*a*]pyridines show anticytomegalo-zoster and antivaricella-zoster virus [1a–e], antibacterial [1, 2] antiinflammatory, analgesic, antipyretic [3a–c], hypnoselective, and anxioselective activities [4]. They are α-amyloid formation inhibitors [5] and constitute a novel class of orally active nonpeptide bradykinin B2 receptor antagonists [6]. Several imidazo[1,2-a]pyridines already on the market include zolimidine (an antiulcer drug) [3c], zolpidem (ahypnotic drug), and alpidem (a nonsedative anxiolytic) [7]. Imidazo[1,2-a]pyrimidine structural moieties are also important as benzodiazepine receptor agonists [8], antiviral agents [1a], antibacterials [9], antifungal agents [10], and calcium channel blockers [11].

Recently, several synthesis methods for preparing these compounds based on multi-component reactions have been reported including classical conditions, with microwave irradiation and by using *Lewis* acids as well as protic liquid and solid acids promoters such as: scandium triflate [12], $ZnBr_2$ [13], $ZnCl_2$ [14], *Ts*OH [15], $HClO_4$ [16], HO*Ac* [17], montmorillonite K_{10} [18], cellulose sulfuric acid [19], and ionic liquid [20].

However, in spite of potential utility of aforementioned routes for the synthesis of imidazo[1,2-*a*]pyridine derivatives, many of these methods involve expensive reagents, strong acidic conditions, long reaction times, low yields, use of excess of reagents/catalysts, and use of toxic organic solvents. For example, in the case of $Sc(OTf)_3$, the reaction mixture was agitated for 72 h at ambient temperature, then it was allowed slowly to adsorb onto Dowex 50WX 2-200 strongly acidic cation exchange resin. The resin was washed with *Me*OH, CH_2Cl_2, and *Me*OH and finally the product was eluted using 2 *M* NH_3 in *Me*OH and the solvent evaporated.

Ammonium chloride as an inexpensive and readily available reagent has been used in various reactions. It effectively promotes the *Ugi* reaction [21], *Biginelli* reaction [22], *Claisen* rearrangement [23], isocyanide-based MCRs for the synthesis of 4-imino-4*H*-3,1-benzoxazines [24], tetrahydrofuro[2,3-*c*]pyridines [25], pyrrolo[3,4-*b*]pyridine-5-one [26], and diindolylmethanes [27]. So, it is used as promoter in the oxidation [28] or reduction of organic compounds [29].

The synthesis of imidazo[1,2-a]pyridine has also been reported in the presence of NH_4Cl under reflux

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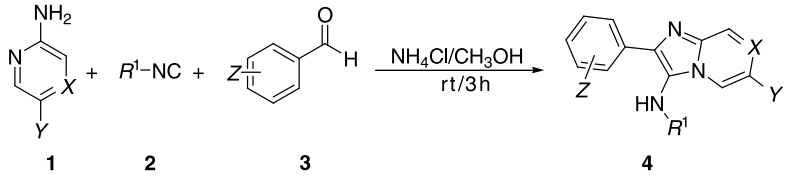

Scheme 1

conditions in toluene as a nonpolar aprotic solvent [30]. However, this required long reaction times (30 h) and gave unsatisfactory yields (49–66%) under reflux conditions.

A change of solvent can have drastic impact on kinetics or thermodynamic of a chemical reaction due to different stabilization of reagent, transition state or product by the solvent molecules. In some cases rate accelerations by a factor of up to 1×10^9 can be achieved solely by a solvent change [31]. Therefore, it is very important to select a suitable solvent in chemical synthesis.

In connection with our previous work on multicomponent reactions [32] and using ammonium chloride as a catalyst and co-reactant [28], we wish to report the results obtained from a study of the preparation imidazo[1,2-*a*]pyridine [19, 20] in the presence of NH_4Cl as a very inexpensive and easily available catalyst under neutral conditions in methanol within 3 h at room temperature (Scheme 1).

Results and discussion

As can be seen from Table 1, 2-aminopyridine or 2-aminopyrazine (**1**), and isocyanides **2** with various aromatic aldehydes **3**, carrying either electron-donating or electron-withdrawing substituents, gave the corresponding *N*-alkyl- or aryl-aminoimidazo[1,2-*a*]pyridine **4** under neutral conditions in good yields after 3 h.

Table 1 Condensation reaction of 2-aminopyridine or 2-aminopyrazine with aldehydes and isocyanides at room temperature

Entry	*X*	*Y*	R^1	*Z*	Product	Yield/%
1	CH	CH_3	cyclohexyl	H	**4a**	73
2	CH	CH_3	cyclohexyl	4-CH_3	**4b**	72
3	CH	CH_3	cyclohexyl	4-Cl	**4a**	86
4	CH	CH_3	cyclohexyl	3-NO_2	**4d**	67
5	CH	CH_3	*t-but*	H	**4e**	60
6	CH	CH_3	*t-but*	CH_3	**4f**	73
7	CH	*Br*	cyclohexyl	H	**4g**	85
8	CH	*Br*	cyclohexyl	4-CH_3	**4h**	87
9	CH	*Br*	cyclohexyl	4-Cl	**4i**	96
10	CH	*Br*	*t-but*	H	**4j**	80
11	N	H	cyclohexyl	4-OCH_3	**4k**	63
12	N	H	*t-but*	4-OCH_3	**4l**	58

In order to optimize the reaction conditions, we conducted this reaction with various solvents and under solvent-free conditions. The results showed that the efficiency and the yield of the reaction in *Me*OH was higher than those obtained in other solvents like *Et*OH, H_2O, and CH_3CN and under solvent-free conditions.

To illustrate the need of NH_4Cl for these reactions, an experiment was conducted in which the reaction of 4-methylbenzaldehyde and 2-amino-5-methylpyridine with cyclohexyl isocyanide was studied in the absence of NH_4Cl. The yield of product was only 10% at room temperature after 3 h. Obviously, the NH_4Cl is an important component of the reaction.

In conclusions, we developed the synthesis of 3-aminoimidazo[1,2-*a*]pyridines and 3-aminoimidazo[1,2-a]pyrazines *via* the condensation of an aldehyde, 2-amino-5-methylpyridine or 2-amino-5-bromopyridine or 2-aminopyrazine, and alkyl or aryl isocyanide in the presence of NH_4Cl as an inexpesive catalyst in methanol.

Experimental

Melting points were measured with an Electrothermal 9100 apparatus and are corrected. IR spectra were recorded with a Shimadzu IR-470 spectrometer. 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 with a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz. NMR spectra were obtained on solution in $CDCl_3$.

All the products (except **4h** and **4i**) are known compounds [19, 20, 32d], which were characterized by melting point, IR, ^1H, and ^{13}C NMR spectral data and mass spectroscopy.

General procedure

To a solution of 0.052 g ammonium chloride (1 mmol) in 4 cm^3 methanol was added 1.2 mmol isocyanide, 1.1 mmol aldehyde, and 1 mmol 2-aminoazine. The mixture was stirred for 3 h at room temperature. After completion of the reaction, as indicated by TLC (ethyl acetate:hexane, 2:1), the reaction mixture was diluted with 30 cm^3 water to afford the product as

a precipitate. The solid residue was filtered and crystallized from ethyl acetate to give products.

N-Cyclohexyl-6-methyl-2-p-tolylimidazo[1,2-a]pyridin-3-amine (**4h**, $C_{21}H_{25}N_3$)
White powder (0.333 g, 87%); mp 210–212°C; IR (KBr): $\bar{\nu} = 3442$ (NH), 3285, 2924, 1507 cm^{-1}; MS: m/z (%) = 385 ($M^+ + 2$, 60), 383 (M^+, 55), 302 (55), 300 (55), 275 (96), 273 (100), 158 (45), 156 (45); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.18$–1.78 (m, $5CH_2$ of cyclohexyl), 2.41 (s, CH_3), 2.96 (m, CH–N of cyclohexyl), 3.16 (bs, NH), 7.18 (d, $^3J_{HH} = 9.4$ Hz, H–*Ar*), 7.26 (d, $^3J_{HH} = 7.8$ Hz, H–*Ar*), 7.44 (d, $^3J_{HH} = 9.4$ Hz, H–*Ar*), 7.90 (d, $^3J_{HH} = 7.7$ Hz, H–*Ar*), 8.23 (s, H–*Ar*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.34$, 24.77, 25.67, 34.10, 56.83, 106.53, 117.81, 122.90, 124.88, 126.87, 127.27, 129.35, 130.85, 137.47, 139.69 ppm.

5-Bromo-N-cyclohexyl-2-(4-chlorophenyl)-imidazo[1,2-a]pyridin-3-amine (**4i**, $C_{19}H_{19}BrClN_3$)
White powder (0.387 g, 96%); mp 213–214°C; IR (KBr): $\bar{\nu} = 3256$ (NH), 2925, 2850, 1508 cm^{-1}; MS: m/z (%) = 405 ($M^+ + 2$, 90), 403 (M^+, 80), 322 (90), 321 (80), 295 (100), 293 (78), 158 (45), 156 (45); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.18$–1.81 (m, $5CH_2$ of cyclohexyl), 2.93 (m, CH–N of cyclohexyl), 3.14 (bs, NH), 7.19–4.45 (m, H–A), 7.97–8.22 (m, H–A) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 24.76$, 25.61, 34.14, 56.83, 106.95, 117.90, 122.91, 125.12, 127.87, 128.25, 128.78, 132.16, 133.49, 139.77 ppm.

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