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Short Communication

One-Pot Three-Component Synthesis of 3-Aminoimidazo[1,2-*a*]pyridines and -pyrazines in the Presence of Silica Sulfuric Acid

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Summary. The synthesis of 3-aminoimidazo[1,2-*a*]pyridines and 3-aminoimidazo[1,2-*a*]pyrazines through a condensation reaction of 2-aminopyridine or 2-aminopyrazine, aldehyde, and alkyl or aryl isocyanide in high yields at room temperature in the presence of silica sulfuric acid is described.

Keywords. Multi-component reaction; Isocyanide; 3-Aminoimidazo[1,2-*a*]pyridine; 3-Aminoimidazo[1,2-*a*]pyrazine; Silica sulfuric acid.

Introduction

The imidazo[1,2-*a*]pyridine and imidazo[1,2-*a*]pyrazine moieties constitute a class of biologically active compounds that are potentially anti-inflammatory [1], antibacterial agents [2], inhibitors of gastric acids secretion [3], calcium channel blockers [4], and sedative-hypnotic drugs, such as *Zolpidem* and *Alpidem* [5].

The conventional two-component synthesis of imidazo[1,2-*a*]pyridines and imidazo[1,2-*a*]pyrazines, requires lachrymatory α-haloketones and the corresponding 2-aminopyridines [6], which restricts the generation of a diverse ensemble of these molecules. Among the existing multi-component reactions (MCRs) available, one involves the condensation of an aldehyde, an isocyanide, and a 2-aminopyridine in the presence of homogeneous protic acids, such as *Ac*OH, $HClO_4$, and the *Lewis* acid $Sc(OTf)_3$ [7]. In spite of their potential utility, these catalysts present limitations due to the use of toxic and corrosive reagents, the tedious work-up procedure, and the necessity of neutralization of the strong acid media producing

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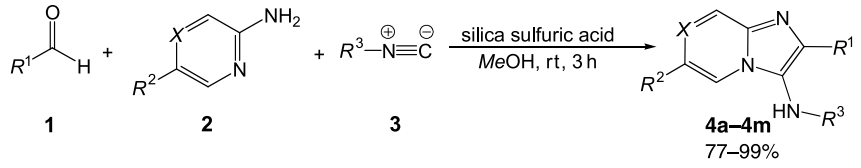

Scheme 1

undesired washes and long reactions times. For example, in the case of Sc(O*Tf*)$_3$, the reaction mixture was agitated for 72 h at ambient temperature, and then it was allowed slowly to adsorb onto Dowex 50WX 2-200, a strongly acidic cation exchange resin.

The syntheses of imidazo[1,2-*a*]pyridines and imidazo[1,2-*a*]pyrazines have also been reported under microwave irradiation in the presence of solid acid, montmorillonite K_{10} [8], and the *Lewis* acid Sc(O*Tf*)$_3$ [9], but they require special instrumentation.

Therefore, the discovery of a novel and an inexpensive solid acid catalyst under classical conditions, which can be easily separated, reused, and does not become contaminated by the products, is of importance in synthetic organic chemistry.

In connection with our previous work using silica sulfuric acid [10] and other solid acid catalysts in organic transformations [11] and our interest in isocyanide-based MCRs [12], we wish to report the synthesis of 3-aminoimidazo[1,2-*a*]pyridines and 3-aminoimidazo[1,2-*a*]pyrazines by the three-component condensation of an aldehyde **1**, 2-amino-5-methylpyridine, 2-amino-5-bromopyridine or 2-aminopyrazine **2**, and isocyanide **3** in the presence of catalytic amounts of silica sulfuric acid at room temperature (Scheme 1).

Results and Discussion

The reaction of aldehyde with 2-amino-5-methylpyridine, 2-amino-5-bromopyridine, or 2-aminopyrazine and isocyanide afforded 3-aminoimidazo[1,2-*a*]pyridine and 3-aminoimidazo[1,2-*a*]pyrazine ring systems in the presence of silica sulfuric acid as a promoter in excellent yields.

To explore the scope and limitations of this reaction, we have extended it to various substituted benzaldehydes in the presence of 2-amino-5-methylpyridine, 2-amino-5-bromopyridine, or 2-aminopyrazine and alkyl or aryl isocyanides. As indicated in Table 1, the reaction proceeds efficiently in all cases.

In order to optimize the reaction conditions, we conducted this reaction with solvents and under solvent-free conditions. The results showed that the efficiency and the yield of the reaction in *Me*OH were 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 silica sulfuric acid for these reactions, an experiment was conducted in which the reaction of *p*-methylbenzaldehyde and 2-amino-5-methylpyridine with cyclohexyl isocyanide was studied in the absence of silica sulfuric acid. The yield of product was only 35% at room temperature after 12 h. Obviously, the silica sulfuric acid is an important component of the reaction.

In conclusions, we developed a synthesis of 3-aminoimidazo[1,2-*a*]pyridines and 3-aminoimidazo[1,2-a]pyrazines *via* the condensation of an aldehyde, 2-amino-5-

Table 1. Synthesis of 3-aminoimidazo[1,2-*a*]pyridines and -pyrazines in the presence of silica sulfuric acid

Product	R^1	R^2	R^3	X	Yield/%
4a	*Ph*	Br	Cyclohexyl	CH	(98, 95, 92, 90, 85)[a]
4b	*Ph*	*Me*	Cyclohexyl	CH	95
4c	4-$CH_3C_6H_4$	*Me*	Cyclohexyl	CH	99
4d	4-$CH_3OC_6H_4$	H	Cyclohexyl	N	90
4e	4-ClC_6H_4	*Me*	Cyclohexyl	CH	85
4f	3-$O_2NC_6H_4$	*Me*	Cyclohexyl	CH	90
4g	4-pyridyl	*Me*	Cyclohexyl	CH	91
4h	*Ph*	Br	*tert*-Butyl	CH	97
4i	*Ph*	*Me*	*tert*-Butyl	CH	99
4j	4-$CH_3C_6H_4$	*Me*	*tert*-Butyl	CH	98
4k	4-$CH_3OC_6H_4$	H	*tert*-Butyl	N	85
4l	*Ph*	*Me*	2,6-$(Me)_2C_6H_3$	CH	77
4m	4-$CH_3C_6H_4$	*Me*	2,6-$(Me)_2C_6H_3$	CH	81

[a] The same catalyst recovered and reused for each of the five runs

methylpyridine, 2-amino-5-bromopyridine, or 2-aminopyrazine, and alkyl or aryl isocyanide in the presence of the silica based solid acid catalyst. Solid acids are environmentally friendly with respect to corrosiveness, safety, waste, and ease of separation and recovery. Thus, replacement of liquid acids with solid acids is desirable in the chemical industry.

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. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz. ^{1}H and ^{13}C NMR spectra were obtained on solutions in $CDCl_3$ and *DMSO*-d_6. 2-Amino-5-methylpyridine, 2-amino-5-bromopyridine or 2-aminopyrazine, isocyanides, and aldehydes were purchased from Fluka and Merck and used without purification.

All products (except **4d** and **4k**) are known compounds [12 g], which were characterized by melting point, IR, ^{1}H and ^{13}C NMR spectral data, and mass spectroscopy.

General Procedure

To a solution of 1 mmol 2-aminoazine, 1.2 mmol aldehyde, and 1.1 mmol alkyl or aryl isocyanide in methanol (4 cm^3) was added a catalytic amount of 0.11 g silica sulfuric acid prepared according to Ref. [10]. The resulting mixture was stirred for 3 h at room temperature. After completion of the reaction, as indicated by *TLC* (ethyl acetate/*n*-hexane, 2/1), the solid catalyst was separated by filtration. The solvent was evaporated under reduced pressure and after washing the residue with ethyl acetate the products were obtained.

N-Cyclohexyl-2-(4-methoxyphenyl)imidazo[1,2-a]pyrazin-3-amine (**4d**, $C_{19}H_{22}N_4O$)

Yellow crystals (0.290 g, 90%); mp 198–199°C (dec); IR (KBr): $\bar{\nu} = 3225$, 2910, 1636, 1603 cm^{-1}; MS: m/z (%) = 322 ($M^+ + 1$, 21), 321 (M^+, 62), 319 (75), 209 (100), 92 (64), 65 (50), 55 (36), 31 (29); ^{1}H NMR ($CDCl_3$): $\delta = 1.12$–1.76 (m, 5CH_2–cyclohexyl), 3.04 (m, CH–N–cyclohexyl), 3.84

(s, OCH_3), 3.80–3.90 (bs, NH), 6.95–8.96 (m, H–Ar) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 24.88$, 25.33, 34.11 (C–cyclohexyl), 55.34 (OCH_3), 56.23 (CH–N–cyclohexyl), 114.24, 117.73, 123.59, 126.74, 128.61, 129.05, 134.61, 139.61, 140.86, 160.51 (C–Ar) ppm.

N-tert-Butyl-2-(4-methoxyphenyl)imidazo[1,2-a]pyrazin-3-amine (**4k**, $C_{17}H_{20}N_4O$)
Yellow crystals (0.25 g, 85%); mp 165–168°C (dec); IR (KBr): $\bar{\nu} = 3275$, 2850, 1644, 1606 cm^{-1}; MS: m/z (%) = 296 ($M^+ + 1$, 19), 295 (M^+, 32), 209 (100), 92 (67), 65 (34), 57 (23); ^1H NMR (*DMSO*-d_6): $\delta = 1.04$ (s, $C(CH_3)_3$), 3.79 (s, OCH_3), 3.84 (bs, NH), 6.89 (d, $J = 8.6$ Hz, H–Ar), 7.94 (d, $J = 8.6$ Hz, H–Ar), 7.99–9.17 (m, H–Ar) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 30.34$ ($C(CH_3)_3$), 55.26 ($C(CH_3)_3$), 57.27 (OCH_3), 113.95, 117.44, 123.30, 126.45, 128.33, 129.69, 134.32, 139.32 140.58, 160.26 (C–Ar) ppm.

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