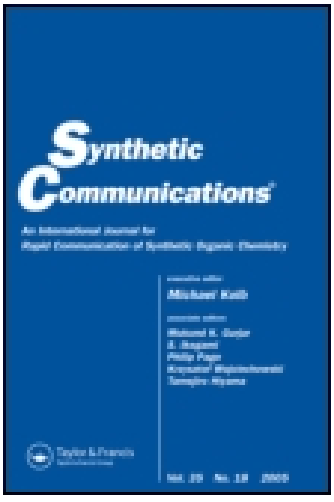

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Rapid Synthesis of 3-Aminoimidazo[1,2-a]Pyridines and Pyrazines

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Rapid Synthesis of 3-Aminoimidazo[1,2-*a*] Pyridines and Pyrazines

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Abstract: *p*-Toluenesulfonic acid catalyzed the one-pot, three-component synthesis of 3-aminoimidazo[1,2-*a*]pyridines and pyrazines through a condensation reaction of a 2-aminoazine, an aldehyde, and an isocyanide at room temperature. This methodology affords a number of 3-aminoimidazo[1,2-*a*]pyridines in reasonable yields and short reaction times without any significant optimization of the reaction conditions.

Keywords: 3-Aminoimidazo[1,2-*a*]pyridines, 3-aminoimidazo[1,2-*a*]pyrazines, isocyanide, *p*-toluenesulfonic acid

INTRODUCTION

Derivatives containing the imidazo[1,2-*a*]pyridine ring system have been shown to possess a broad range of useful pharmacological activities, including antibacterial, antifungal, anthelmintic, antiviral, antiprotozoal, anti-inflammatory, anticonvulsant, anxiolytic (Alpidem), hypnotic (Zolpidem), gastrointestinal, antiulcer (Zolmidine), and immunomodulatory (Kifunensine) activities.[1–4] They have also been shown to be selective cyclin-dependant kinase inhibitors, γ-aminobutyric acid (GABA) and benzodiazepine receptor agonists, and bradykinin B_2 receptor antagonists.[1–6] The classical synthesis of imidazo[1,2-*a*] annulated pyridines, pyrimidines, and

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pyrazines involves the condensation of α-haloketones with 2-aminopyridines, 2-aminopyrimidines, and 2-aminopyrazines, respectively.[7] However, this approach does not readily lend itself to a diversity-oriented synthesis.

A more versatile approach uses a three-component coupling involving the condensation of aldehydes, 2-aminopyridine, and isocyanides in the presence of acid catalysts. This robust approach allows for the preparation of a diverse range of products. However, it requires long reaction times (20–72 h).[8–11] The use of an ionic liquid such as 1-butyl-3-methylimidazolium bromide and a solid acid catalyst such as silica sulfuric acid have been reported for reducing reaction times.[12]

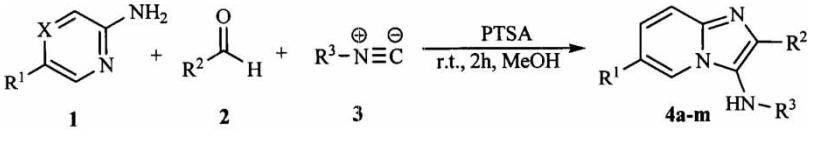
In connection with our previous work on the synthesis of 3-aminoimidazo[1,2-*a*]pyridines and pyrazines[12] and our interest in isocyanide-based multicomponent reactions (MCRs).[13] we report the synthesis of 3-aminoimidazo[1,2-*a*]pyridines and pyrazines **4** by three-component condensation of an 2-aminoazine **1**, an aldehyde **2**, and an isocyanide **3** in the presence of catalytic amounts of *p*-toluenesulfonic acid (PTSA) as an inexpensive catalyst in excellent yields in methanol at room temperature (Scheme 1).

RESULTS AND DISCUSSION

As indicated in Table 1, the reaction of aldehyde with 2-aminoazine derivatives and isocyanides afforded 3-aminoimidazo[1,2-*a*]pyridines and pyrazines in the presence of PTSA as a promoter in very high yields.

Limitations of this condensation reaction were further explored by extending the number of reactants. For this purpose, the reactivities of various aldehydes, constituted of either electron-donor or electron-acceptor groups, were examined. As indicated in Table 1, the reaction proceeds efficiently in all cases studied.

In conclusion, we have described a novel application of PTSA as a cheap catalyst for the one-pot preparation of 3-aminoimidazo[1,2-*a*]pyridines and pyrazines via condensation of an aldehyde, a 2-aminoazine, and an isocyanide in quantitative yields at room temperature. The reaction has been shown to display good functional group tolerance and is high yielding, and product isolation is very straightforward.



1 2 3 4a-m

Scheme 1.

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

Entry	R^1	R^2	R^3	X	Product	Yield (%)
1	Me	Ph	Cyclohexyl	CH	**4a**	97
2	Br	Ph	Cyclohexyl	CH	**4b**	94
3	H	Ph	Cyclohexyl	CH	**4c**	94
4	H	4-$CH_3OC_6H_4$	Cyclohexyl	CH	**4d**	93
5	Me	4-$CH_3OC_6H_4$	Cyclohexyl	N	**4e**	88
6	Me	3-$O_2NC_6H_4$	Cyclohexyl	CH	**4f**	92
7	H	4-ClC_6H_4	Cyclohexyl	CH	**4g**	90
8	Me	4-$CH_3C_6H_4$	Cyclohexyl	CH	**4h**	98
9	Me	4-pyridyl	cyclohexyl	CH	**4i**	91
10	Me	Ph	tert-Butyl	CH	**4j**	98
11	Br	Ph	tert-Butyl	N	**4k**	96
12	Me	4-$CH_3OC_6H_4$	tert-Butyl	N	**4l**	86
13	H	Ph	2,6-$(Me)_2C_6H_3$	CH	4**m**	88

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 $CDCl_3$. 2-Aminoazines, isocyanides, and aldehydes were purchased from Fluka and Merck and used without purification.

Typical Procedure for Preparation of 4a–m

Catalytic amounts of *p*-toluenesulfonic acid (0.1 g, 0.52 mmol) were added to a solution of 2-aminoazine (1.00 mmol), aldehyde 1.20 mmol), and isocyanide (1.10 mmol) in methanol (4 mL). The resulting mixture was stirred for 2 h at room temperature. After completion of the reaction, as indicated by thin-layer chromatography (TLC, ethyl acetate/*n*-hexane, 2:1), the solid product was separated by filtration followed by washing the residue with ethyl acetate to obtain the pure product.

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

Data

N-Cyclohexyl-2-phenylimidazo[1,2-*a*]pyridin-3-amine (**4c**). Yellow solid (0.27 g, 94%); mp 200–202 °C. IR (KBr) cm^{-1}: 3250, 2920,1602. MS m/z: 291 (M^+), 259, 158, 76. ^1H NMR ($CDCl_3$) $\delta = 1.15–1.97$ (10H, m, $5CH_2$ of cyclohexyl), 2.94 (1H, m, CH-N of cyclohexyl), 3.76 (1H, brs, NH), 7.06–8.15 (9H, m, H-Ar). ^{13}C NMR ($CDCl_3$) $\delta = 24.7$, 25.6, 34.1 (C-cyclohexyl), 56.8 (CH-N-cyclohexyl), 107.9, 117.7, 123.0, 125.2, 127.0, 127.7, 128.6, 128.6, 133.4, 135.9, 137.5 (C-Ar). Anal. calcd. for $C_{19}H_{21}N_3$: C, 78.32; H, 7.26; N, 14.42. Found: C, 78.29; H, 7.20; N, 14.35.

N-Cyclohexyl-2-(4-methoxyphenyl)*H*-imidazo[1,2-*a*]pyridin-3-amine (**4d**). Yellow solid (0.30 g, 93%); mp 152–154 °C. IR (KBr) cm^{-1}: 3251, 2925, 1605. MS m/z: 321 (M^+), 238, 211, 78, 55, 41. ^1H NMR ($CDCl_3$) $\delta = 1.17–1.83$ (10H, m, $5CH_2$ of cyclohexyl), 2.96 (1H, m, CH-N of cyclohexyl), 3.10 (1H, brs, NH), 3.87 (3H, s, OCH_3), 7.06–8.15 (8H, m, H-Ar). ^{13}C NMR ($CDCl_3$) $\delta = 24.8$, 25.7, 34.1 (C-cyclohexyl), 55.3 (OCH_3), 56.8 (CH-N-cyclohexyl), 111.7, 113.9, 116.8, 122.7, 124.1, 126.6, 128.3, 136.1, 141.2, 159.0 (C-Ar). Anal. calcd. for $C_{20}H_{23}N_3O$: C, 74.74;H, 7.21; N, 13.07. Found: C, 74.65; H, 7.15; N, 13.16.

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