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One-pot synthesis of imidazo[1,2-*a*]pyridines from benzyl halides or benzyl tosylates, 2-aminopyridines and isocyanides

Mehdi Adib *, Ehsan Sheikhi, Narjes Rezaei

School of Chemistry, University College of Science, University of Tehran, PO Box 14155-6455, Tehran, Iran

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ABSTRACT

A one-pot synthesis of imidazo[1,2-*a*]pyridines is described. Benzyl halides or benzyl tosylates are oxidized to aldehydes under mild Kornblum conditions which then undergo a three-component reaction with various 2-aminopyridines and isocyanides to afford the imidazo[1,2-*a*]pyridines in excellent yields.

Imidazo[1,2-*a*]pyridines are of interest because of the occurrence of their saturated and partially saturated derivatives in biologically active compounds. Compounds containing the imidazo[1,2-*a*]pyridine ring system have been shown to possess a broad range of useful pharmacological properties, including antibacterial, antifungal, anthelmintic, antiviral, antiprotozoal, antiinflammatory, anticonvulsant, anxiolytic, hypnotic (e.g., zolpidem, Fig. 1), gastrointestinal, antiulcer, and immunomodulatory activities.[1,2]

Several synthetic methods have been reported for the preparation of 2- or 3-substituted imidazo[1,2-*a*]pyridines with the majority relying on the condensation of 2-aminopyridine with α-bromoketones to form the five-membered cyclic system.[1,2] Particularly interesting are those structures that contain an amino group at C-2 or C-3. There are well established methods for the preparation of 3-aminoimidazo[1,2-*a*]pyridines; these include nitration at C-3 of the already formed heterocycle and subsequent reduction,[3] preparation from pyridinium fluorides,[4] Strecker-type reaction between 2-aminopyridines, a cyanide and a limited number of aldehydes,[5] or by use of benzotriazole as an auxiliary group.[6] Most of these methods involve three or more sequential synthetic steps, the use of harsh reaction conditions that give low yields, and in some cases, the use of hazardous or expensive starting materials.

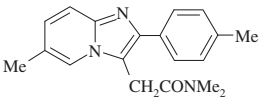

Figure 1. Zolpidem, a pharmacologically important imidazo[1,2-*a*]pyridine.

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.[7] In 1998, new variants of the Ugi MCR[8] were described by Blackburn,[9] Bienaymé,[10] and Groebke[11] which enabled simple syntheses of imidazo[1,2-*a*]azines. Reactions of an aldehyde, an isocyanide and a 2-aminoazine in methanolic solution containing a catalyst such as $Sc(OTf)_3$,[9] perchloric acid[10] or glacial acetic acid[11] were performed at room temperature. However, these methods required long reaction times and the work-ups were complicated. Imidazo[1,2-*a*]azine syntheses have also been carried out under microwave irradiation in the presence of a solid acid, Montmorillonite K10,[12] and $Sc(OTf)_3$,[13] and using a nonpolar solvent,[14] or in the presence of an ionic liquid.[15] Improved conditions have been reported in recent years.[16]

As part of our continuing efforts on the development of new routes for the preparation of biologically active heterocyclic compounds,[17] we have reported syntheses of imidazo[1,2-*a*]pyridines via microwave-assisted one-pot reaction of pyridines, α-bromoketones, and ammonium acetate,[18] reaction between 2-aminopyri-

* Corresponding author. Tel./fax: +98 21 66495291.
E-mail address: madib@khayam.ut.ac.ir (M. Adib).

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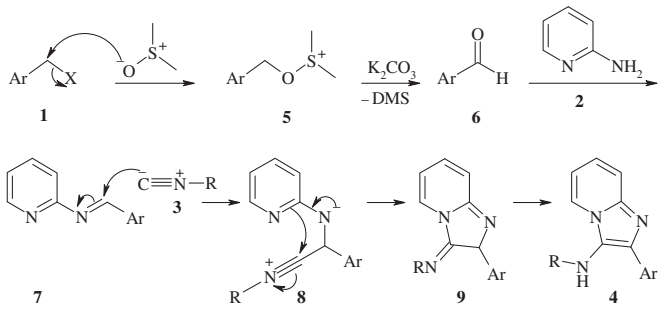
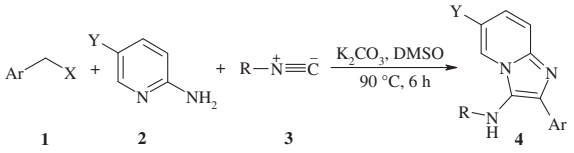


Scheme 1.

dines, benzaldehydes and imidazoline-2,4,5-trione under solvent-free conditions,[19] catalyst-free reaction between 2-aminopyridines, aldehydes and isocyanides in water,[20] and condensation of 2-aminopyridines and diaroylacetylenes.[21] Herein, we describe a novel and straightforward approach for the synthesis of imidazo[1,2-*a*]pyridines which involves an in situ oxidation–cyclocondensation sequence starting from benzyl halides or benzyl tosylates. This procedure develops the known reaction, while not limiting one of the substrates to an aldehyde.

Thus, under mild Kornblum oxidation conditions,[22] benzylic substrate **1** in DMSO in the presence of K_2CO_3 at 90 °C was converted into the corresponding aldehyde (Scheme 1). Subsequently,

Table 1
One-pot synthesis of imidazo[1,2-*a*]pyridines **4**



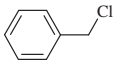
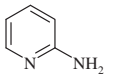
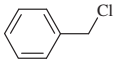
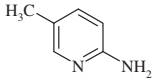
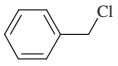
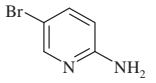
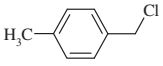
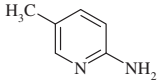
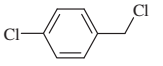
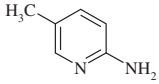
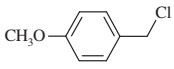
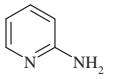
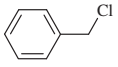
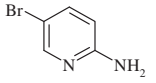
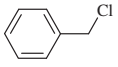
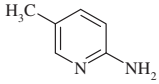
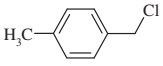
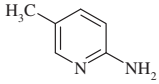
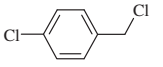
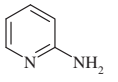
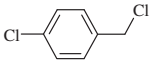
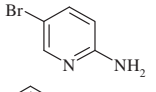
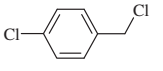
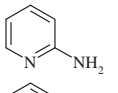
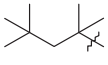
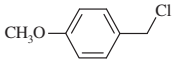
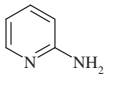
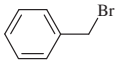
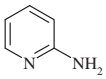
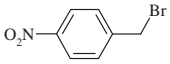
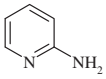
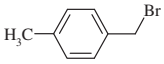
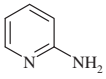
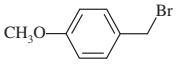
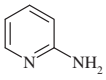
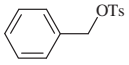
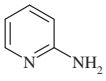
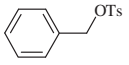
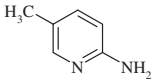
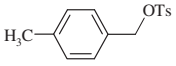
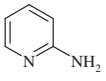
Entry	$ArCH_2X$	2-Aminopyridine	R	Yield[a] (%)	Mp (°C)
1				94	198–200[16h]
2				92	199–203 (dec)[15]
3				93	207–210 (dec)[15]
4				90	216–219 (dec)[15]
5				95	208–210 (dec)[15]
6				90	154[16e]
7				90	206–208 (dec)[15]
8				95	216–219 (dec)[15]
9				93	211–213[15]
10				94	148–150[16c]
11				92	174–176[24]
12				88	199–201[24]
13				93	127[24]

Table 1 (*continued*)

Entry	$ArCH_2X$	2-Aminopyridine	R	Yield[a] (%)	Mp (°C)
14				90	198–200[16h]
15				95	235–237
16				94	166–169
17				91	154[16e]
18				96	198–200[16h]
19				94	216–219 (dec)[15]
20				95	166–169

[a] Isolated yield.

the in situ prepared aldehyde was condensed with the 2-aminopyridine **2** followed by treatment with isocyanide **3** at 90 °C to produce the corresponding 3-alkylamino-2-arylimidazo[1,2-*a*]pyridine **4** in 88–96% yields (Table 1). All the reactions went to completion within 6 h.[23] ^{1}H NMR analysis of the reaction mixtures clearly indicated the formation of the corresponding 3-aminoimidazo[1,2-*a*]pyridines **4** in excellent yields. All the products were characterized by melting point determination and from ^{1}H and ^{13}C NMR spectral data.

Simple alkyl halides or alkyl tosylates were oxidized to the corresponding aldehydes in good yields, but these aldehydes, when treated with 2-aminopyridines and isocyanides resulted in complicated reaction mixtures.

A mechanistic rationalization for this reaction is provided in Scheme 1. Treatment of the benzylic substrate **1** with dimethyl sulfoxide yields an alkoxysulfonium ion **5** which, in the presence of K_2CO_3 undergoes elimination of dimethyl sulfide to form the corresponding aldehyde **6**. Next, the aldehyde undergoes condensation with the 2-aminopyridine **2** to give the imine intermediate **7**. This imine undergoes nucleophilic addition with the isocyanide **3** to form the isonitrilium intermediate **8**, which cyclizes into the imino intermediate **9**. This intermediate tautomerizes under the reaction conditions to afford the 3-alkylamino-2-arylimidazo[1,2-*a*]pyridine **4**.

In conclusion, we have developed a new and straightforward approach for the synthesis of imidazo[1,2-*a*]pyridines via a one-pot, three-component condensation reaction between 2-aminopyridines, benzyl halides or benzyl tosylates and isocyanides. The use of benzylic substrates in place of aldehydes and the excellent yields of the products are the main advantages of this reaction.

Acknowledgment

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References and notes

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23. The procedure for the preparation of 3-cyclohexylamino-2-phenylimidazo[1,2-*a*]pyridine (entry 1, Table 1) is described as an example: a mixture of benzyl chloride (0.126 g, 1 mmol) and K_2CO_3 (1.5 mmol) in DMSO (1 mL) was stirred for 4 h at 90 °C. Next, 2-aminopyridine (0.094 g, 1 mmol) and cyclohexyl isocyanide (0.120 g, 1.1 mmol) were added to the reaction mixture and stirring was continued at 90 °C for 2 h. The reaction mixture was cooled to room temperature and H_2O (3 mL) was added. Stirring was continued for 1 h at ambient temperature. The resulting white precipitate was filtered, washed with H_2O (2 × 2 mL), dried, and recrystallized from *n*-hexane/EtOAc (3:1)[25] to give 3-cyclohexylamino-2-phenylimidazo[1,2-*a*]pyridine as colorless crystals, mp 198–200 °C, yield: 0.274 g, 94%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.09–2.02 [10H, m, CH(CH_2)$_5$], 2.90–2.94 [1H, m, NC*H*(CH_2)$_5$], 4.65 (1H, d, *J* = 5.6 Hz, NH), 6.89 (1H, t, *J* = 6.7 Hz, CH), 7.16–7.89 (7H, m, 7CH) 8.30 (1H, d, *J* = 6.8 Hz, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 24.6, 25.4, 33.6, 56.9, 109.3, 116.4, 123.2, 124.9, 126.8, 127.5, 128.4, 128.7, 133.2, 137.1, 142.2. *3-tert-Butylamino-2-(4-chlorophenyl)imidazo[1,2-a]pyridine* (Entry 10, Table 1): colorless crystals, mp 148–150 °C, yield: 0.282 g, 94%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.04 [9H, s, C(CH_3)$_3$], 3.70 (1H, br s, NH), 6.82 (1H, t, *J* = 6.7 Hz, CH), 7.16 (1H, dd, *J* = 8.5, 7.1 Hz, CH), 7.42 (2H, d, *J* = 8.6 Hz, 2CH), 7.54 (1H, d, *J* = 7.2 Hz, CH), 7.92 (2H, d, *J* = 8.6 Hz, 2CH), 8.26 (1H, d, *J* = 6.8 Hz, CH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 30.7, 56.4, 110.9, 116.6, 123.1, 123.6, 124.6, 127.3, 127.9, 132.3, 132.9, 138.4, 141.1.
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25. All reactions (Table 1) were carried out following this procedure.