RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2014, **4**, 30229

Facile synthesis of imidazo[1,2-*a*]pyridines *via* a one-pot three-component reaction under solvent-free mechanochemical ball-milling conditions†

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Received 26th June 2013
Accepted 27th June 2014

DOI: 10.1039/c3ra43221a

www.rsc.org/advances

In this work, 3-aminoimidazo[1,2-*a*]pyridine derivatives have been synthesized by a one-pot three-component condensation reaction of 2-aminopridines, aldehydes and isocyanides under solvent-free mechanochemical ball-milling conditions in good to excellent yields at room temperature. This efficient protocol has many noticeable advantages such as mild reaction conditions, high yields, high atom economy, short reaction times and simple separation.

Introduction

Nowadays, research in science and technology is focusing more and more on clean, safe and inexpensive processes. In this regard, the chemical industry and academics are developing solvent-free reactions as one of the most important principals of the "green chemistry" approach. They have several advantages in comparison with traditional reactions using organic solvents, like reduction of organic solvent disposal, enhanced reaction rates, greater selectivity and the easy work-up procedures.[1]

Mechanochemical techniques like grindstone and ball-milling could be used in various organic syntheses for the grinding of materials into fine particles and the preparation or modification of organic and inorganic solids. Recently, due to this ability, some examples of using ball-mill in organic synthesis have been reported.[2–4]

Multicomponent reactions (MCRs) are introduced as an efficient strategy in synthetic organic chemistry because of their valued features such as atom economy, straightforward reaction design, simple purification of products, rapid generation of molecular complexity, diversity-oriented synthesis, and construction of chemical libraries of drug-like molecules with target-oriented functionalities.[5–7]

Imidazo[1,2-*a*]azines have shown a broad range of pharmacological and biological activities such as antibacterial,[8a] antidiabetic,[8b] antifungal,[8c] anthelmintic,[8d] antiviral,[8e] antiprotozoal,[8f] anti-inflammatory,[8g] anticonvulsant,[8h] anxiolytic (Alpidem) and hypnotic (Zolpidem),[8i] immunomodulatory (Kifunensine),[8j] antiulcer agents (Zolmidine, Necopidem and Saripidem),[8k,8l] anti-HIV,[9] and interesting fluorescence properties (Fig. 1).[10]

The first synthesis of imidazo[1,2-*a*]azines through MCRs was described in 1998.[11] It can be classified as an extension of the well-known Ugi-MCR[12] including a reaction among an aldehyde, an isocyanide, and a 2-aminoazine. Since then, in the literature, this reaction has been reported in the presence of various catalysts.[13] However, some of these methods have deficiencies such as the requirement of expensive and excess amounts of catalyst, using toxic solvents, difficulties in work-up procedure, harsh reaction conditions and special instrumentation. Therefore, the design and development of new approaches for this reaction is of prime importance.

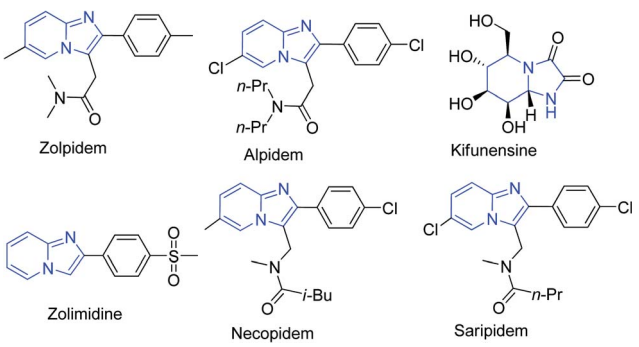

Fig. 1 The structure of some important drugs containing the imidazopyridine cores.

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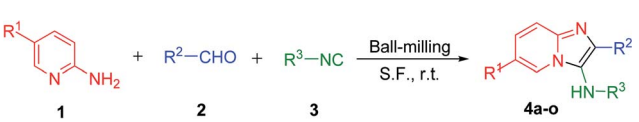
† Electronic supplementary information (ESI) available: Melting points and CHN analysis data of the products and copies of spectral analysis of 4-(6-bromo-3-(cyclohexylamino)imidazo[1,2-*a*]pyridin-2-yl)-2-methoxyphenol (**4o**). See DOI: 10.1039/c3ra43221a



Scheme 1 One-pot synthesis of 3-aminoimidazo[1,2-*a*]pyridine.

Table 1 Synthesis of 3-aminoimidazo[1,2-*a*]pyridines under ball-milling conditions

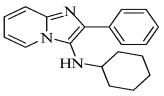
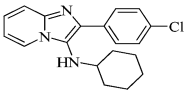
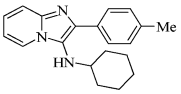
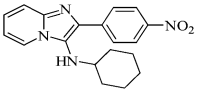
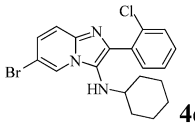
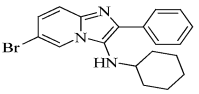
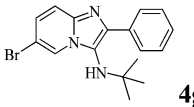
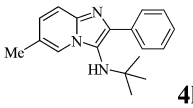
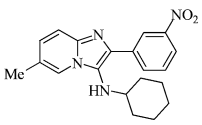
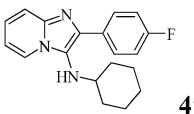
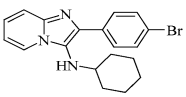
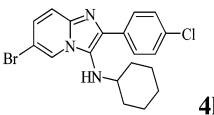
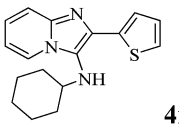
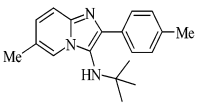
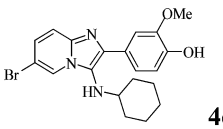
Entry	R^1	R^2	R^3	Product	Time (min)	Isolated yield (%)
1	H	C_6H_5	Cyclohexyl	 **4a**	20	90
2	H	*p*-ClC_6H_4	Cyclohexyl	 **4b**	15	90
3	H	*p*-MeC_6H_4	Cyclohexyl	 **4c**	20	90
4	H	*p*-$NO_2C_6H_4$	Cyclohexyl	 **4d**	15	96
5	Br	*o*-ClC_6H_4	Cyclohexyl	 **4e**	20	96
6	Br	C_6H_5	Cyclohexyl	 **4f**	15	98
7	Br	C_6H_5	*tert*-Butyl	 **4g**	20	90
8	CH_3	C_6H_5	*tert*-Butyl	 **4h**	25	90
9	CH_3	*m*-$NO_2C_6H_4$	Cyclohexyl	 **4i**	20	95
10	H	*p*-FC_6H_4	Cyclohexyl	 **4j**	15	98
11	H	*p*-BrC_6H_4	Cyclohexyl	 **4k**	15	95
12	Br	*p*-ClC_6H_4	Cyclohexyl	 **4l**	15	92
13	H	*o*-thienyl	Cyclohexyl	 **4m**	45	70

Table 1 (*Contd.*)

Entry	R^1	R^2	R^3	Product	Time (min)	Isolated yield (%)
14	CH_3	*p*-MeC_6H_4	*tert*-Butyl	 **4n**	25	80
15	Br	*m*-MeO-*p*-OH-C_6H_3	Cyclohexyl	 **4o**	25	86

In connection with our interest in MCRs,[13c,13h–j,14] wish to report the synthesis of 3-aminoimidazo[1,2-*a*]pyridines **4a–o** by a one-pot three-component reaction of 2-aminopyridines **1**, aldehydes **2** and isocyanides **3** under solvent-free ball-milling conditions at room temperature (Scheme 1). To the best of our knowledge, this work is the first example of using mechanochemical activation as an easy-to-handle process for the synthesis of variously substituted imidazo[1,2-*a*]pyridines through an isocyanide-based MCR.

Results and discussion

In the first step, to find the best reaction conditions for the synthesis of 3-aminoimidazo[1,2-*a*]pyridine derivatives, the one-pot three-component condensation of 2-aminopyridine **1** (1 mmol), benzaldehyde **2** (1 mmol) and cyclohexyl isocyanide **3** (1 mmol) was examined under various reaction conditions. The results showed that the efficiency and the yield of the reaction under solvent-free conditions were higher than those obtained in the presence of solvents.[13]

The scope and efficiency of the process was investigated under optimized conditions and the results are summarized in Table 1. For this purpose, a broad range of structurally diverse aldehydes bearing electron-releasing or electron-withdrawing substituents, 2-aminopyridines and isocyanides were successfully condensed *via* a one-pot reaction.

As shown in Table 1, all of the reactions proceeded efficiently and the desired products were produced in good to excellent yields in relatively short reaction times. Aromatic aldehydes bearing electron-withdrawing groups (Entries 4 and 9) reacted at a faster rate in comparison to those substituted with electron-releasing groups such as CH_3 or heteroaromatic thiophene moieties (Entries 3, 14, 15 and 13, respectively). Guaiacol as a specific aldehyde was also examined in this reaction and gave good yield (Entry 15). Furthermore, halogen bearing aldehydes gave suitable reaction yields in reasonable times (Entries 2, 5, 10–12). In addition, diversity and scope of the other components of this reaction were examined. In this order, 2-amino-5-bromopyridine (Entries 5–7, 12 and 15) and *tert*-butyl isocyanide (Entries 7, 8 and 14) were used and they gave excellent results, as predicted.

Experimental section

General

All chemicals were purchased from Merck, Aldrich or Fluka chemical companies; and have been used as received. Ball mill apparatus was Retsch MM2000 model having 20 mL iron cell and two iron balls of 12 mm diameter at a frequency of 20 Hz was used for protection reactions. Melting points were measured on an Electrothermal 9200 apparatus and are uncorrected. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu FT-IR 8400s spectrometer. The ^{1}H NMR spectra were recorded at 500 MHz on Bruker DRX-500 Avance spectrometer. The ^{13}C NMR spectra were recorded at 125 MHz on Bruker DRX-500 Avance spectrometer; chemical shifts (δ scale) are reported in parts per million (ppm). The elemental analyses were performed with an Elementar Analysensysteme GmbH VarioEL. Known compounds were characterized by elemental analyses and comparison of the melting points with those of authentic samples.

General procedure for the preparation of (4a–o)

A mixture of 2-aminopyridine (1 mmol), aldehyde (1 mmol), isocyanide (1 mmol) and PTSA (15 mol%) were poured in a 10 mL stainless steel double-walled ball mill beaker for the appropriate time according to Table 1. After completion of the reaction, as indicated by TLC (EtOAc–*n*-hexane, 2 : 1), the reaction mixture was washed with H_2O (2 × 10 mL) and the solid product was filtered and then crystallized from hot water to obtain the pure product.

4-(6-Bromo-3-(cyclohexylamino)-2,3-difydroimidazo[1,2-*a*]-pyridin-2-yl)-2-methoxyphenol (4o). Cream powder (86%); mp: 234–236 °C; IR (KBr): 3300 (OH), 3296 (NH), 3080, 2923, 2852, 1652. ^{1}H NMR (500 MHz, DMSO-d_6): δ_H (ppm) 1.01–1.65 (10H, m, $5CH_2$ of cyclohexyl), 2.82 (1H, m, CH of cyclohexyl), 3.79 (3H, s, OMe), 4.73 (1H, br s, NH), 6.78–7.60 (4H, m, H-Ar), 7.70 (1H, s, H-Ar), 8.40 (1H, s, H-Ar), 9.02 (1H, s, OH). ^{13}C NMR (125 MHz, DMSO-d_6): 24.6, 25.4, 33.5, 55.5, 56.4, 105.3, 110.4, 115.4, 117.6, 119.5, 122.9, 125.1, 125.6, 126.0, 135.8, 138.6, 146.0, 147.4. MS, *m*/*z* (%): 417 (M^+ + 1, ^{81}Br), 415 (M^+ + 1, ^{79}Br), 332, 305, 156, 55.

Conclusion

In summary, we have introduced an efficient and green approach for the synthesis of 3-aminoimidazo[1,2-*a*]pyridines *via* condensation reaction of 2-aminopyridines, aldehydes and isocyanides under solvent-free mechanical ball-milling conditions in good to excellent yields at room temperature. This protocol for the preparation of synthetically, biologically and pharmaceutically relevant imidazopyridine derivatives includes some important aspects like the easy work-up procedure, high atom economy, and mild reaction conditions. Furthermore, the reaction has been shown to display good functional group tolerance and product isolation is very straightforward and is the first introduction of ball-milling process in isocyanide-based MCRs.

Acknowledgements

The authors gratefully acknowledge financial support from the Iran National Science Foundation (INSF) and the Research Council of Iran University of Science and Technology. The authors would like to thank Dr M. R. Naimi-Jamal for Ball mill apparatus.

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