Microwave-Assisted, One-Pot Three Component Synthesis of 2-Phenyl *H*-imidazo[1,2-*a*]pyridine

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Received 5 November 2011; Accepted 7 January 2012

Abstract: A novel synthesis of 2-phenylH-imidazo[1,2-*a*] pyridines is described from a one-pot, three-component reaction between pyridine, guanidine (urea or thiourea) and α -bromoketones under microwave irradiation and solvent-free conditions in excellent yields.

Keywords: Three-component reaction, Pyridine, Microwave-assisted reaction, Solvent-free.

Introduction

One-pot multicomponent reactions have emerged as an effective tool for atom economic and benign synthesis by virtue of their convergence, productivity, facile execution, and generation of highly diverse and complex products from easily available starting materials.¹ Green chemistry emphasizes the need for environmentally clean synthesis, which involves improvement in selectivity, high atom efficiency, elimination of hazardous reagents, and easy separation with recovery and reuse of reagents.² In the meantime, the utility of microwave energy in synthetic organic chemistry has been increasingly recognized as compared with conventional heating. Reactions promoted by microwave irradiation (MWI) have shown an environmental friendly nature, greater selectivity, and enhanced reaction rate. Therefore, the MWI-mediated multicomponent reaction has constituted an especially attractive synthetic strategy for the rapid and efficient library generation.³

Imidazo[1,2-*a*] pyridines have received considerable interest from the pharmaceutical industry because of their interesting therapeutic properties,⁴ including antibacterial,⁵ antifungal,⁶ antiviral,⁷ antiulcer,⁸ and anti-inflammatory behavior.⁹ They have also been characterized as selective cyclin-dependent kinase inhibitors,¹⁰ calcium channel blockers,¹¹ β -amyloid formation inhibitors,¹² and benzodiazepine receptor agonists.¹³ Drug formulations containing imidazo[1,2-*a*] pyridines such as alpidem (anxiolytic), zolpidem (hypnotic), and zolimidine (antiulcer) are currently available (Scheme 1). Different synthetic pathways have been used to prepare substituted imidazo[1,2-*a*] pyridines, either from the imidazole or from the pyridine nucleus.¹⁴ Further, they have been obtained by cyclocondensation of 2-aminopyridines with substituted phenacylbromides of α -bromoacetophenones in poor yields.¹⁵ 2-substituted-imidazo[1,2-*a*] pyridines have been synthesized by cyclocondensation of alkynyl(phenyl)iodonium salts with 2-aminopyridine easily in CHCl_3 under reflux in the presence of K_2CO_3 .¹⁶ Other methodologies included treating 2-aminopyridines with α -tosyloxyketones,¹⁷ a polymer supported [hydroxy(sulfonyloxy)i]benzene with ketones or alcohols,¹⁸ α -diazoketones,¹⁹ and propargyl bromide.²⁰ Although these methods are suitable for certain synthetic conditions sometimes, however, some of these procedures are associated with one or more disadvantages such as high cost, use of stoichiometric and even excess amounts of reagents or catalysts, long reaction time, hazardous organic solvents, low yield, special apparatus and drastic reaction conditions, which leaves scope for further development of new environmentally clean syntheses. Thus, there is an increasing need for improved and newer methods of synthesis of imidazo[1,2-*a*] pyridines.

Scheme 1. Biologically relevant imidazo[1,2-*a*]pyridines.

In this Letter, we report a novel and efficient method for the synthesis of 2-phenyl/*H*-imidazo[1,2-*a*] pyridine **4** via the coupling of pyridine **1**, phenacylbromide **2** and guanidine (urea or thiourea) **3** under microwave irradiation²¹ (Scheme 2).

Experimental

Chemicals and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Microwave assisted reactions were carried out in microwave oven (ETHOS 1600, Milestone) with a power of 600 W specially designed for organic synthesis. Column chromatography were performed on silica Gel (0.015-0.04 mm, mesh-size 60) and TLC on precoated plastic sheets (25 DC_{UV-254}), respectively. Melting points were measured on Barnstead Electrothermal melting point apparatus and were not corrected. IR spectra were measured on aq Shimadzu FT-IR-4300 spectrophotometer as KBr discs. ¹H NMR and ¹³C NMR spectra were determined in CDCl₃ on a Bruker 500 spectrophotometer and chemical shifts were expressed in ppm downfield from tetramethylsilane.

General Procedure

A mixture of pyridine (**1**, 0.16 g, 2 mmol) and phenacylbromide (**2**, 0.4 g, 2 mmol) was irradiated with microwaves at 100 °C for 1 min. After nearly complete conversion to N-Phenacylpyridinium bromides, as was indicated by TLC, guanidine hydrochloride (**3**, 0.19 g, 2 mmol) was added to reaction mixture and it was irradiated at 150 °C for a further 2-3 min with a power of 600 W (ETHOS 1600, Milestone). Then the reaction mixture was cooled to room temperature and the residue was purified by column chromatography (1:2 n-hexane–EtOAc as eluent, Merck silica gel 60 mesh).

2-Phenylimidazo[1,2-a]pyridine (**4a**)

White powder; mp 133-134 °C (lit. 131-133)¹⁹; $\nu_{\max}$ (KBr): 2926, 2855, 1741, 1625, 1515, 1465, 1370, 1269, 1205, 1145, 1080, 1032, 690 cm^{-1} ; δ_{H} (500 MHz, CDCl_3): 8.10 (d, J = 6.75 Hz, 1H), 7.95 (d, J = 7.8 Hz, 2H), 7.85 (s, 1H), 7.64 (d, J = 9.11 Hz, 1H), 7.42 (t, J = 7.31 Hz, 2H), 7.32 (d, J = 7.4 Hz, 1H), 7.19 (t, J = 7.20 Hz, 1H), 6.77 (t, J = 6.75 Hz, 1H); δ_{C} (125 MHz, CDCl_3): 145.9, 145.8, 133.9, 128.7, 128, 126.2, 125.7, 124.7, 117.7, 114.4, 108.3.

2-(4-Chlorophenyl)imidazo[1,2-a]pyridine (**4d**)

White powder; mp 208-209 (lit. 208) [18]; $\nu_{\max}$ (KBr): 2920, 1650, 1470, 1370, 1260, 1200, 1085, 1015, 950, 840, 740, 600, 514; cm^{-1} ; δ_{H} (500 MHz, CDCl_3): 8.10 (d, J = 6.78 Hz, 1H), 7.90 (d, J = 8.18 Hz, 2H), 7.84 (s, 1H), 7.60 (d, J = 9.12 Hz, 1H), 7.40 (d, J = 8.18 Hz, 2H), 7.20 (t, J = 7.15 Hz, 1H), 6.78 (t, J = 6.70 Hz, 1H); δ_{C} (125 MHz, CDCl_3): 145.8, 144.7, 133.7, 132, 129, 127, 125.2, 125, 118, 112.8, 108.2.

Results and Discussion

The applied solvent free reaction proceeds in 3-4 minutes to give products with high yields. The scope and generality of this procedure is illustrated with respect to various phenacylbromides and pyridines. The results are presented in Table 1. The structures of the products were established by ^1H NMR, ^{13}C NMR spectroscopy and by comparison of their spectral data and melting point values with those of the authentic samples reported in the literature.

Scheme 2

The proposed mechanism of the cyclization step has been outlined in Scheme 3. Accordingly, nucleophilic attack of pyridine **1** to phenacyl bromide **2** produces charged species of **5** that subsequently reacts with urea **3** to produce adduct **6** that undergoes cyclization by elimination of HBr to produce **7**. At the end of process aromatization of product **4** is obtained by elimination of formamide.

Table 1. Synthesis of products **4** under microwave irradiation.

4	Ar	R	X	Time (min)	Yield (%)	M.P (°C)	Lit mp(°C)
a	C ₆ H ₅	H	O	7	79	133-134	131-133 ¹⁹
b	C ₆ H ₅	H	S	9	75		
c	4-MeOC ₆ H ₄	H	O	5	80	134-135	133-134 ¹⁷
d	4-ClC ₆ H ₄	H	O	6	82	208-209	208 ¹⁸
e	2,4-Cl ₂ C ₆ H ₃	H	S	7	85	182-184	181-182 ²²
f	4-FC ₆ H ₄	H	O	7	80	170-172	169 ²⁴
g	4-NO ₂ C ₆ H ₄	H	O	6	82	267-269	269 ²⁴
h	4-MeC ₆ H ₄	H	S	8	85	137-138	137 ²³
i	C ₆ H ₅	CH ₃	O	5	85	169-171	172-173 ²⁵ , 163 ²⁴
j	4-ClC ₆ H ₄	CH ₃	S	5	78	242-244	240-242 ²³
k	4-ClC ₆ H ₄	CH ₃	O	8	85		
l	4-BrC ₆ H ₄	CH ₃	S	8	80	215-217	216-217 ²⁵

Scheme 3

Conclusion

In conclusion, we have presented a new and efficient one-pot synthesis of the 2-phenyl *H*-imidazo[1,2-*a*]pyridine ring systems in good yields. In addition to its simplicity and solvent free conditions, this method provides high yields of products making it a useful and

attractive strategy for the preparation of biologically relevant imidazo[1,2-*a*]pyridines in a single step operation.

Acknowledgments

Support of this investigation by the Islamic Azad University Tehran south branch through grant is gratefully acknowledged.

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