Journal of Mechanical Research and Application (JMRA), Vol. 14 No.3, 1403 (2024),24-31

JMRA
Journal of Mechanical Research and Application
ISSN: 2251-7383, eISSN: 2251-7391

A Novel Microwave-Assisted, One-Pot Three Component Synthesis Based Upon Environmentally Protection Principles

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Abstract: In this research, a new synthesis method of 2-phenylH-imidaze(1,2-a] pyridines is, obtained ¡ from a one-pot, three-component reaction between pyridine, urea (or guanidine) and a-bromoketones under microwave irradiation by observing the obvious principles of fluid mechanics and solvent-free conditions in excellent yields. One-pot multicomponent reactions have been disclosed as an effective instrument for atom economic and fluid mechanics obvious synthesis principles with regards to their convergence, productivity, and generation of highly diverse and complex products from easily available starting materials.

Green chemistry in relationship with fluid mechanics obvious principles emphasizes the importance for environmentally clean and safe synthesis, which contains high atom efficiency, elimination of dangerous chemicals, and easy separation with recovery and reuse of chemicals. In this way, 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 environmentally friendly nature, greater selectivity, and enhanced reaction rate. Therefore, the MWI-mediated multicomponent reaction has erected a specific attractive synthetic strategy for the fast and efficient library generation.

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

Introduction

In recent years, Imidazo[1,2-α] pyridines have received considerable interest from the pharmaceutical industry because of their interesting therapeutic properties, (1-3), including antibacterial, (5) antifungal, (6) antiviral, (7), antiulcer, (8) and anti-inflammatory behavior. (9)

The recent researchers 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-α] pyridines such as alpidem (anxiolytic), zolpidem (hypnotic), and zolimidine (antiulcer) are currently available (Scheme 1). various synthetic pathways have been used to synthesize substituted imidazo[1,2-α] pyridines, either from the imidazole or from the pyridine nucleus (14). progress in selectivity, high atom efficiency, elimination of dangerous chemicals, and easy separation with recovery and reuse of chemicals (2). In this way, the utility of microwave energy in synthetic organic chemistry has been increasingly recognized as compared with conventional heating (4). Reactions promoted by microwave irradiation (MWI) have shown an environmentally friendly nature, greater selectivity, and enhanced reaction rate (11,12). Therefore, the MWI-mediated multicomponent reaction has erected a specific attractive synthetic strategy for the fast and efficient library generation (3).

Imidazo[1,2-α] 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-α] pyridines such as alpidem (anxiolytic), zolpidem (hypnotic), and zolimidine (antiulcer) are currently available (Scheme 1).

various synthetic pathways have been used to synthesize substituted imidazo[1,2-α] pyridines, either from the imidazole or from the pyridine nucleus (14). Further, they have been obtained by cyclocondensation of 2-minopyridines with substituted phenacylbromides of α-bromoacetophenones in poor yields (15). 2-substituted-imidazo[1,2-α] 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)iodo]

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, dangerous organic solvents, low yield, which leaves scope for further development of new environmentally clean syntheses (22). Therefore, there is an increasingly necessity for advanced and newer routes of synthesis of imidazo[1,2-α] pyridines (21).

Scheme 1. Biologically related formulas imidazo[1,2-a]pyridines

Scheme 1. States the chemical formulas imidazo[1,2-a] pyridines based upon biological aspects.

In this manuscript, we are decided to introduce a new and efficient method for the synthesis of 2-phenylH- imidazo[1,2-α] pyridine 4 via the coupling of pyridine 1, phenacyl bromide 2 and guanidine (urea or thiourea) 3 under microwave irradiation based upon the principles of fluid mechanics (21). (Scheme 2).

Experimental

Reagents 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 was performed on silica Gel (0.015-0.04 mm, mesh-size 60) and TLC on

precoated plastic sheets (25 DCUV-254), respectively. Melting points were measured on Barnstead Electrothermal melting point apparatus and were not corrected. IR spectra were measured on Shimadzu FT-IR-4300 spectrophotometer as KBr discs. 1H NMR and 13C NMR spectra were determined in $CDCl_3$ on a Brucker 500 spectrophotometer and chemical shifts were expressed in ppm downfield from tetramethylsilane.

General Procedure

A mixture of pyridine (1, 0.24 g, 3 mmole) and phenacyl bromide (2, 0.6 g, 3 mmole) was irradiated with microwaves at 100 °C for 1 min. After nearly complete conversion to N- Phenacyl pyridinium bromides, as was indicated by TLC, urea hydrochlolride (3, 0.34 g, 3 mmole) was added to reaction mixture and it was irradiated at 155 °C for a further 5-7 min with a power of 600 W (ETHOS 1600, Milestone). Then the reaction mixture was cooled to room

temperature and the residue were 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; vmax (KBr): 2927, 2855, 1742, 1626, 1514,

1466, 1371, 1268, 1204, 1144, 1081, 1033, 691 cm-1; δH (500 MHz, CDCl3): 8.10 (d, J =

6.77 Hz, 1H), 7.95 (d, J = 7.79 Hz, 2H), 7.85 (s, 1H), 7.64 (d, J = 9.18 Hz, 1H), 7.42 (t, J =

7.36 Hz, 2H), 7.32 (d, J = 7.6 Hz, 1H), 7.19 (t, J = 7.21 Hz, 1H), 6.77 (t, J = 6.77 Hz, 1H);

δc (125 MHz, CDCl3): 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)

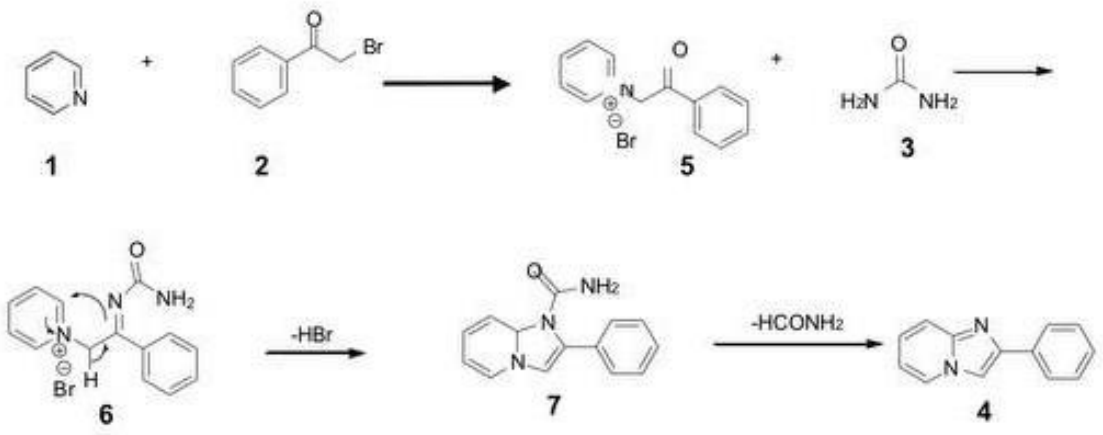
White powder; mp 208-209 (lit. 208) [18]; vmax (KBr): 2922, 1651, 1471, 1372, 1261, 1201,

1084, 1014, 951, 841, 741, 601, 515; cm-1; δH (500 MHz, CDCl3): 8.10 (d, J = 6.78 Hz, 1H),

7.90 (d, J = 8.19 Hz, 2H), 7.84 (s, 1H), 7.60 (d, J = 9.13 Hz, 1H), 7.40 (d, J = 8.19 Hz, 2H), 7.20 (t, J = 7.16 Hz, 1H), 6.78 (t, J = 6.71 Hz, 1H); δc (125 MHz, CDCl3): 145.7, 144.6, 133.8, 131, 128, 126, 125.1, 126, 119, 112.7, 108.3.

Results and Discussion

The applied solvent free reaction advances in 10-8 minutes to provide products with high yields. The scope and generality of this procedure is expressed with respect to different phenacyl bromides and pyridines. The results are inserted in Table 1. The structures of the products were drawn by ^{1}H NMR, ^{13}C NMR spectroscopy and by comparison of their spectral data and melting point data with those of the genuine samples cited in the literature.

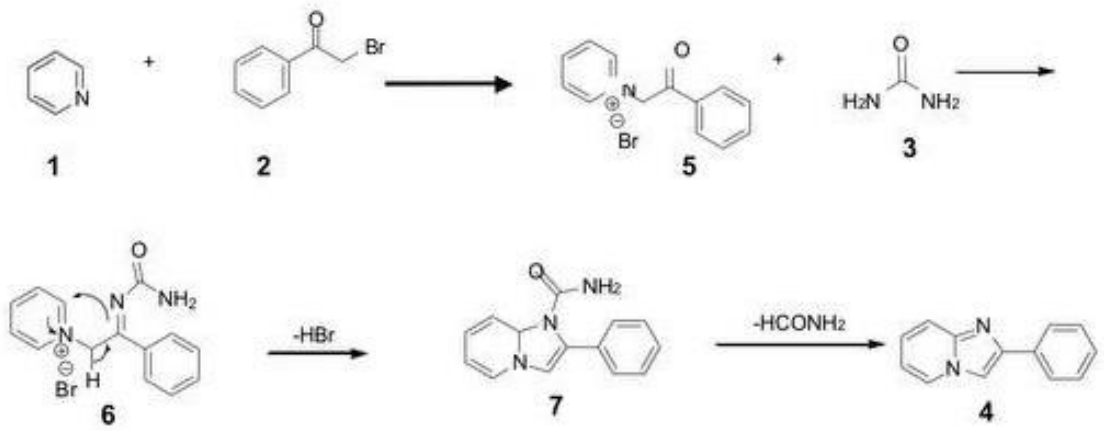


Scheme 2. A chemical reaction under microwave irradiation based upon the principles of fluid mechanics

The suggested mechanism of the cyclization step has been inserted in Scheme 3. In accordance with that, nucleophilic attack of pyridine 1 to phenacyl bromide 2 products charged species of that subsequently reacts with urea 3 to produce adduct 4 that undergoes cyclization by elimination of HBr to product 5. Finally, product 6 is achieved 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_6H_5	H	O	7	79	133-134	131-133[19]
b	C_6H_5	H	S	9	75		
c	4-$MeOC_6H_4$	H	O	5	80	134-135	133-134[17]
d	4-ClC_6H_4	H	O	6	82	208-209	208[18]
e	2,4-$Cl_2C_6H_3$	H	S	7	85	182-184	181-182[22]
f	4-FC_6H_4	H	O	7	80	170-172	169[24]
g	4-$NO_2C_6H_4$	H	O	6	82	267-269	269[24]
h	4-MeC_6H_4	H	S	8	85	137-138	137[23]
i	C_6H_5	CH_3	O	5	85	169-171	172-173[25], 163[24]
j	4-ClC_6H_4	CH_3	S	5	78	242-244	240-242[23]
k	4-ClC_6H_4	CH_3	O	8	85		
l	4-BrC_6H_4	CH_3	S	8	80	215-217	216-217[25]



Scheme 3. The suggested mechanism of the cyclization step

Conclusion

In conclusion, we have presented a new and efficient one-pot synthesis of the 2-phenyl H-imidazo[1,2-α] 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-α] pyridines in a single step operation.

Acknowledgments

Suitable support of this research by the Islamic Azad University Tehran south branch through grant is gratefully acknowledged.

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