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An Efficient and Green Microwave Assisted One Pot Synthesis of Azaindolizines in PEG-400 and Water

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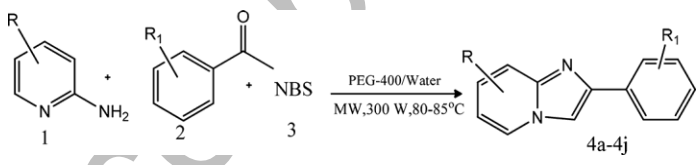
Abstract

A facile, convenient, environmentally benign and one pot synthesis of Imidazo[1,2-a]pyridines from 2-aminopyridines and in-situ generated phenacyl bromides under microwave irradiation in PEG-400 and water (1:2) has been developed. The developed protocol provides the better alternative to the existing method as it involves utilization of in-situ generated α-bromoacetophenones and avoids the use of lachrymatric α-haloketones as well as volatile toxic organic solvents and to reduced reaction time to obtained excellent yield.

GRAPHICAL ABSTRACT



KEYWORDS: Imidazo[1,2-a]pyridines; 2-aminopyridines; PEG-400-water, Microwave irradiation; NBS.

1. INTRODUCTION

Theazaindolizines (bridgehead azaheterocycles)containing imidazole ring systems have several valuable diversified pharmaceutical activity and are used as hypotensive,[1]

antiulcer[2] andanxiolytic agents[3] in addition to bradycardic,[4] antiasthmatic,[5] antimicrobial,[6] as HIF-1αprolyl hydroxylase inhibitors,[7] cytoprotective[8]. Imidazo[1,2-a]pyridines that directly Interact with Hepatitis CNS4B[9] and imidazo[1,2-a]pyridine ring can be considered a biosimilar "aza-indole" analogue. Functionalized imidazo[1,2-a]pyridines and other imidazo-fused heterocycles are prevalent structural motifs in biologically active and pharmaceutically important compounds[10-14]. Inrecent years, N-bromosuccinimide (NBS) emerged as a brominating agents gaining popularity in organic synthesis due to user friendly and easy to handle.[15] Microwave irradiation has emerged as a powerful and well controlled heating source for various organic reactionsduetoits reduced reaction times and enhanced yields.[16]

Water acts as an environmentally benign, readilyavailable, non-toxic, non-flammable and economically affordable solvents in organic chemistry. PEG-400 is non-toxic, easily available, inexpensive, non-ionic liquid medium of low volatility, thermally stable, reusable and also are phase transfer catalyst.[17]A number of methods have been reported for the synthesis of this important framework; the most exploited one involves 2-aminopyridine and as starting material. The main part of the protocols involves initial coupling reactions between endocyclic nitrogen of 2-aminopyridine and various reagents, such as α-halo carbonyl compounds,[18]diazoketones,[19]oxothioamide,[20]1,2-diols,[21]imidazo[1,2-a]pyridines. But these methodshavelacuna as difficulty to obtain starting materials, lowyields, use of lachrymatric α-halo ketones and tedious workup procedures. Herein,we have developed a versatile,environmentally benign, convenient protocol for theone-pot synthesis of different derivatives of imidazo[1,2-a]pyridines from

cyclocondesation of in-situ generated α-bromoacetophenones and 2-aminopyridines in PEG-400 and water(1:2) as a greener medium for getting high yield. In order to generate α-bromo ketones in-situ we have carried out selective bromination of substituted acetophenones with N-bromosuccinimide in PEG-400 and water(1:2) irradiated at 85^0c.[22] Main advantage of this protocol is no need to isolate in situ generated lachrymatric α-bromo ketones and yields are relatively high.

2. RESULT AND DISCUSSION

The earlier reported methods for the synthesis of imidazo[1,2-a]pyridines involved refluxing 2-amino pyridines and α-halo ketones in organic solvents. But α-halo ketones are unstable and lachrymatric and difficult to handle it. Considering the hazardous effect of α-halo ketones and volatile organic solvents prompted us to design new and green methods for the synthesis of imidazo[1,2-a]pyridines. For the fate of proposal, we have carried out reactions of acetophenones, NBS and 2-amino pyridines in water but reaction not occurred without addition of PEG-400. In this protocol we used PEG-400 at a catalytic amount and water as a solvent under microwave irradiationto obtained high yield. We have optimized reaction condition under different proportion of PEG-400 and water as a reaction medium and temperature was maintained at 80-85 throughout the reaction. It was observed that when we used PEG-400/water in 1:2 proportion product obtained with higher yield (entry 3 table 1) comparatively the yield obtained by using PEG-400/water in 1;3 proportion and PEG-400 alone (entry 2&1 table 1). To establish the generality and scope of the method given in this report, acetophenones carrying different functional groups such as EDG and EWG were subjected to study their reaction

with 2-amino pyridine and NBS in PEG-400/water in 1:2 proportion and number of (imidazo[1,2-a]pyridines) derivatives have been synthesized and The results are presented in (Table 2),andIt was observed that electrons withdrawing group present on the substrate increases the rate of reaction and yield of the imidazo[1,2-a]pyridines.(Table 2).Plausible mechanism for the reaction has been depicted in Figure 2. Initially NBS released bromine as cation in the presence of water and enol form of acetophenones attacked on bromine to generate α-bromoacetophenones and The main part of the mechanism involves initial coupling reactions between endocyclic nitrogen of 2-aminopyridine and α-bromoacetophenonesand followed by cyclisation to formed imidazo[1,2-a]pyridines.

Plausible Mechanism of the Reactions

3. EXPERIMENTAL DETAILS

All the chemicals and solvents were of AR grade and used without further purification. Melting points were determined in open capillary tubes and are uncorrected. Microwave synthesizer (MAS-II**) Sineo Technology Limited**, **China** used for irradiation at 300 watt. Formation of the compoundswere checked by TLC on aluminium sheets silica gel 60 F254 plates of 0.5 mm thickness. IR spectra were recorded on Shimadzu FT-IR-8400Instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique.^{1}H NMR and ^{13}C NMR was determined in DMSO-d6 solvent on a Bruker AC 400 MHz Spectrometer.

General Procedure for Preparation of Substituted Imidazo[1,2-A]Pyridines(4a-4j)

A mixture. of aromatic acetophenones (5 mmol), NBS (5.5 mmol), in PEG-400 and water (1:2) 5 ml irradiated for 30 min.at 300 watt power at 80-85^{o}C.The formation of α-bromoacetophenone was monitored by TLC. Aftercompletion of bromination2-amino pyridine (5mmol) was added to reaction mixture and reaction mass was further irradiated for 3-5 min.at 300 watt powerat 80-85^{o}C. The progress of reaction was monitored by Thin layer chromatography (TLC). After completion of reaction 10ml of ethyl acetate were added and stirred for 20 min. this process repeated twice. The combined Ethyl acetate phase was removed under reduced pressure to obtain imidazo[1,2-a]pyridines(4a-j).

Spectral Data of Some Selected 2-Phenyl Imidazo[1,2-A]Pyridines (4a-4d)

2-Phenylimidazo[1,2-A]Pyridine (4a)

M.P. 133^{O}C; 134LIT.[38]MP (^{O}C); ^{1}H NMR (300 MHz, DMSO-d6): δ 6.83-6.89 (m, 1H), 7.11-7.24 (m, 1H), 7.29-7.33 (m, 1H), 7.41-7.44 (m, 2H), 7.57 (d, 1H, J 6.9 Hz), 7.94-7.85 (m, 2H), 8.41 (s, 1H), 8.49-8.54 (m, 1H); ^{13}C NMR (50 MHz, DMSO-d6): δ 107.32, 113.10, 115.89, 127.49, 128.13, 129.71, 129.92, 130.51, 134.12, 144.52; IR (KBr) cm-1: 1637, 769; ES-MS (m/z): 195 [M+H]+; HRMS-EI: found: 194.0837, calculated: 194.0843.spectra data was consistent with previous literature report. [38]

2-(4-Chlorophenyl)-Imidazo[1,2-A]Pyridine (4b)

M.P. 157^{O}C 157-159;LIT. [38]MP (^{O}C);^{1}H NMR (300 MHz, CDCl3): δ 6.79-6.91 (m, 1H), 7.25-7.31 (m, 1H), 7.35 (d, 2H, J 8.5 Hz), 7.59 (d, 1H, J 9.0 Hz), 7.74 (s, 1H), 7.79 (d,

2H, J 8.5 Hz), 8.2(d, 1H, J 6.8 Hz); ^{13}C NMR (50 MHz, CDCl3): δ 109.23 (CH), 111.51 (CH), 113.73 (CH), 125.12 (CH), 126.21 (CH), 128.61 (CH), 129.55 (CH), 131.76 (C), 134.37 (C), 142.46 (C), 145.19 (C); IR (KBr) cm-1: 1633, 760, 675; ES-MS (m/z): 229 [M+H]+; HRMS-EI: found: 228.0451, calculated: 228.0455. spectra data was consistent with previous literature report. [38]

2-(4-Bromophenyl)-Imidazo[1,2-A]Pyridine (4c)

M.P. 214-215^{O}C; 215-216;LIT.[38]MP (^{O}C); ^{1}H NMR (300 MHz, CDCl3): δ 6.38-6.48 (m, 1H), 6.63-6.71 (m, 2H), 7.41 (d, 1H, J 9.0 Hz), 7.53 (d, 2H, J 8.3 Hz), 7.63 (d, 2H, 7.5 Hz), 7.76 (s, 1H), 8.14 (d, 1H, J 6.3 Hz); ^{13}C NMR (75 MHz, CDCl3+DMSO-d6): δ 108.53, 112.56, 116.34, 125.67, 127.63, 130.12, 133.21, 135.12, 135.45, 143.19, 146.42; IR (KBr) cm-1: 1637, 760, ES-MS (m/z): 274(Br79), 275 Br80) [M+H]+; HRMS-EI: found: 271.9947, calculated: 271.9950.spectra data was consistent with previous literature report. [38]

2-(4-Methoxyphenyl)-Imidazo[1,2-A]Pyridine (4d)

M.P. 131^{O}C; 132;LIT.[38] MP (^{O}C); ^{1}H NMR (300 MHz, DMSO-d6): δ 3.73 (s, 3H), 6.51-6.89 (m, 1H), 7.17 (d, 2H, J 8.2 Hz), 7.25-7.32 (m, 1H), 7.51 (m, 1H), 7.81(d, 2H, J 8.2 Hz), 8.24 (s, 1H), 8.49-8.51 (m, 1H); ^{13}C NMR (75 MHz, CDCl3+DMSO-d6): δ 59.12, 109.11, 113.16, 115.22, 118.41, 119.11, 127.20, 129.43, 131.51, 134.32, 145.54, 161.32; IR (KBr) cm-1: 1639, 765 ES-MS (m/z): 225 [M+H]+; HRMS-EI: found: 224.0947, calculated:. 224.0950.spectra data was consistent with previous literature report. [38,37]

4. CONCLUSION

We have developed facile, one pot,environmentally benign convenient protocol for thesynthesis of 2-phenylimidazo[1,2-a]pyridines from cyclocondesation of in-situ generated α-bromoacetophenones and 2-aminopyridines in PEG-400 and water(1:2) as a greener medium. Main advantage of this method over other prevailing methods is no need to isolate lachrymatric α-bromoketones, low cost, environmentally benign and yield relatively high.

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SUPPORTING INFORMATION

Supplementary data (full experimental procedures and (^{1}H and ^{13}C NMR and HRMS Spectral data) associated with this article can be found via the ‘‘Supplementary Content’’ section of this article’s webpage.

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Table 1. Optimization of reaction medium.

Solvent	Proportion	Temp. (^{O}C)	Yield %
Water only	-	80-85	0
PEG-400	-	80-85	45
PEG+Water	1:2	80-85	80-89
PEG+Water	1:3	80-85	60-65

[a]isolated yield

Table 2. Evaluation of compounds (4a-4j)[a]

Product	R	R'	Reaction time in min.	Temp. (^{O}C)	YIELD %
4a	H	H	32	80	84
4b	H	4-Cl	31	80	84
4c	H	4-Br	31	80	84
4d	H	4-OCH_3	32	80	86
4e	H	4-CH_3	33	85	84
4f	6-Cl	H	31	85	86
4g	6-Br	H	32	85	86
4h	6-Cl	4-OCH_3	32	80	85
4i	6-CH_3	4-CH_3	35	85	89
4j	6-Br	4-Cl	31	85	84

[a]Reaction condition:1)acetophenones(0.5mmol),2-amino pyridine(0.5mmol),NBS(0.5mmol), (PEG-400/water in (1:2) ratio.

2) [a]isolated yield

Figure 1. One pot Synthesis of Imidazo[1,2-a]pyridine

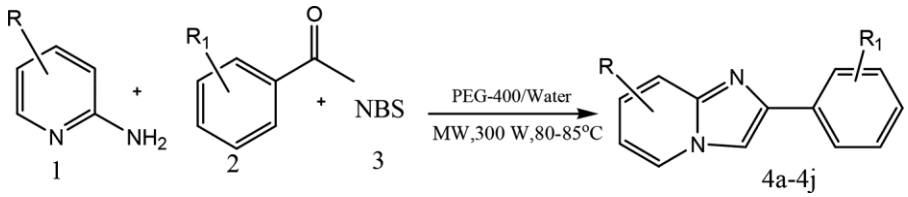

Figure 2. Mechanism of one-pot synthesis of imidazo[1,2-a]pyridines