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PEG-1500 in water: A green, recyclable catalyst for the one-pot synthesis of imidazo[1,2-a]pyrimidines under microwave irradiation

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Abstract: polyethylene glycol (PEG-1500) is used as a convenient, green and recyclable catalyst for the one-pot synthesis of different derivatives of imidazo[1,2-a]pyrimidines from the reaction of 2-aminopyrimidines, aromatic ketones and N-bromosuccinimide under microwave irradiation in water. The main advantage of this protocol is significantly reduced reaction time under mild condition and relatively higher yield.

Keywords: Imidazo[1,2-a]pyrimidines; PEG-1500; one-pot; Microwave irradiation.

1. INTRODUCTION

Imidazo[1,2-a]pyrimidine derivatives attracted great deals of interest due to wide application in medicinal chemistry such as, antibiotic,¹ and antianexia,² gastrointestinal diseases,³ in addition they possess an antagonistic activity against that of purines,⁴ high-affinity GABAA agonists with good oral bioavailability in rat and dog, inhibitors of wnt/ β -catenin signaling⁵ and bone resorption inhibitor YM 529 was efficacious in phase-III clinical trial for the treatment of osteoporosis.⁶ Different methods have been reported for the synthesis of Imidazo[1,2-a]pyrimidines from the reaction of 2-aminopyrimidine

with the α -bromoacetophenones and hypervalent iodine.⁷⁻⁹ in solvents such as DMF,¹⁰ water,¹¹ ethanol,¹² some bridgehead azaheterocycles have been prepared in solvents like, β -cyclodextrin, PEG-400 as a reaction medium.¹³ Denis S. Ermolatev developed new protocol for the Synthesis of Substituted 2-Aminoimidazoles from 2-Aminopyrimidines and Pd(0)-Mediated Microwave-Assisted Arylation of 2-Substituted Imidazo[1,2-a]pyrimidines.^{14,15} But these methods have different disadvantages like, expensive starting material, low yield, use of lachrymatics and expensive α -haloketones and tedious workup procedures.

Herein, We have developed a versatile, environmentally benign, one-pot protocol for the synthesis of 2-arylimidazo[1,2-a]pyrimidines by cyclocondensation of in-situ generated α -bromoacetophenones and 2-amino-pyrimidine using PEG-1500 in water as a greener reaction medium under microwave irradiation.

Scheme

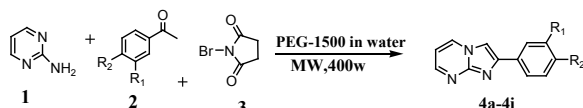


Fig.1 one-pot synthesis of 2-arylimidazo[1,2-a]pyrimidines

2. RESULTS AND DISCUSSION

The earlier reported methods for the synthesis of imidazo[1,2-a]pyrimidines involved refluxing 2-amino pyrimidines and α -haloketones in organic solvents, ^{8,9,10} but most of them used α -haloketones, toxic catalyst as well as volatile organic solvents. Considering the hazardous effect of α -halo ketones and volatile organic solvent, it prompted our interest to design environmentally benign route for the synthesis of imidazo[1,2-a]pyrimidines. Initially we have carried out reactions of acetophenones, NBS and 2-amino pyrimidines in PEG-1500-water at room temperature but it require more time [4-6hr.] hence we tried same reaction under microwave irradiation, the product obtained with excellent yield in minimum reaction time. To checked the validity of this method a number of imidazo[1,2-a]pyrimidine derivatives have been synthesized and the results are shown in (table 1). It was observed that Electron withdrawing groups present on the substrate increases the rate of reaction and yield of the imidazo[1,2-a]pyrimidines. The mechanism for this method showed in figure 2.

Mechanism of the reaction:

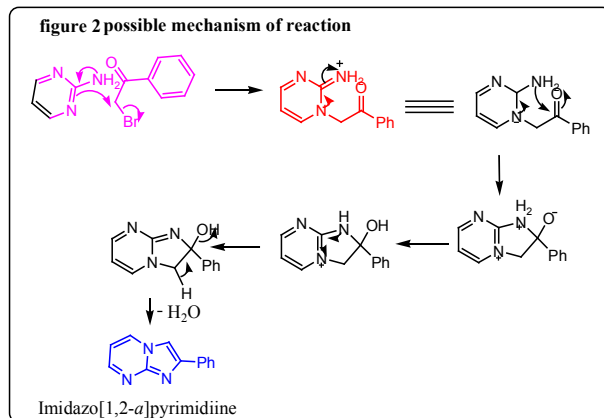


Table 1 Evaluation of compounds (4a-4j)^a

Product	Time (Min.)	Temp. (°C)	YIELD ^b %	M.P (°C)	LIT. M.P. (°C)
	8	80	84	189-191	190-192 ³⁰
	7	80	89	270-271	266-268 ³⁰
	7	80	87	215-218	218-221 ³⁰
	6	80	89	232-231	236-238 ³⁰
	8	85	84	191-194	188-190 ³⁰
	8	85	82	232-235	236-238 ³⁰
	5	80	89	370	>370 ³⁵
	9	85	86	145-148	145-147 ¹²
	6	85	89	226-229	228 ¹²

^aReaction condition: 1) acetophenones (0.5mmol), 2-aminopyrimidine (0.5mmol), NBS (0.5mmol), at 80°C for 30min.; ^bIsolated yield.

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 Microwave Chemistry Technology Co.Ltd.) used for irradiation at 400 watt power. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. ^1H NMR and ^{13}C NMR was determined in CDCl_3 solvent on a Bruker AC 300 MHz Spectrometer.

General one-pot procedure for the synthesis of 2-arylimidazo[1,2-a]pyrimidines(4a-4j)

1gm of PEG-1500 dissolve in 10 ml water and stirred for 10 minutes and to this solution, mixture of Acetophenones (5 mmol) and NBS (5 mmol) was added and irradiated for 5 min. at 400 watt power at 80-90°C. The formation of α -bromoacetophenone was monitored by TLC. After completion of bromination, 2-amino pyrimidine (5mmol) was added to the reaction mixture and reaction mass was further irradiated for 3-5 min at same reaction condition. After completion of the reaction, the reaction mass was poured in ice cold water and extracted with Ethyl acetate. solid product obtained recrystallised with proper solvent.

Characterization data of 2-phenylimidazo[1,2-a]pyrimidines(4a-4f)

2-Phenylimidazo[1,2-a]pyrimidine (4a). ^1H NMR (300 MHz, CDCl_3 + $\text{DMSO}-d_6$): δ 6.79-6.82 (m, 1H), 7.32-8.01 (m, 5H), 7.74 (s, 1H), 8.25-8.45 (m, 1H), 8.49-8.53 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 107.91, 108.52, 126.12, 127.13, 128.91, 129.14, 133.66, 139.03, 148.81, 153.11; IR (KBr) cm^{-1} : 1694, 1592, 1074, 769; ES-MS (m/z): 195 $[\text{M}+\text{H}]^+$; HRMS-EI: found: 195.0789, calculated: 195.0794. spectra data was consistent with previous literature report. [8]

2-(4-Chlorophenyl)-imidazo[1,2-a]pyrimidine (4b). ^1H NMR (300 MHz, CDCl_3): δ 6.87-6.90 (m, 1H), 7.45-7.84 (m, 4H), 7.86 (s, 1H), 8.39-8.45 (m, 1H), 8.51-8.54 (m, 1H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 108.11, 109.22, 128.13, 129.55, 132.54, 133.65, 134.21, 139.51, 148.47, 153.21; IR (KBr) cm^{-1} : 1615, 1076, 745, 679; ES-MS (m/z): 229 $[\text{M}+\text{H}]^+$; HRMS-EI: found: 206.1093, calculated: 206.1094; Anal. Calcd for $\text{C}_{12}\text{H}_8\text{ClN}_3$: C, 62.75; H, 3.51; N, 18.30. Found: C, 62.81; H, 3.42; N, 18.23. spectra data was consistent with previous literature report. [8]

2-(4-Bromophenyl)-imidazo[1,2-a]pyrimidine (4c). ^1H NMR (300 MHz, CDCl_3): δ 6.89-6.95 (m, 1H), 7.55 (d, 2H, J 8.4 Hz), 7.86 (s, 1H), 7.94 (d, 2H, J 8.5 Hz), 8.52-8.54 (m, 1H), 8.84 (dd, 1H, J 6.9, 2.1 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 108.49, 109.87, 125.73, 130.17, 133.33, 134.01, 134.95, 136.93, 149.41, 152.95; IR (KBr) cm^{-1} : 1631, 764, 507; ES-MS (m/z): 275 (Br79), 277 (Br81), $[\text{M}+\text{H}]^+$; HRMS-EI: found: 272.9909, calculated: 272.9901. spectra data was consistent with previous literature report. [8]

2-(4-Fluorophenyl)-imidazo[1,2-a]pyrimidine (4d). ^1H NMR (300 MHz, CDCl_3): δ 6.91-6.96 (m, 1H), 7.41-7.78 (m, 4H), 7.99 (s, 1H), 8.33-8.46 (m, 1H), 8.55-8.58 (m, 1H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 108.51, 109.96, 127.56, 130.81, 132.97, 134.84, 135.20, 139.55, 148.61, 153.11; IR (KBr) cm^{-1} : 1641, 1096, 755; ES-MS (m/z): 214 $[\text{M}+\text{H}]^+$; spectra data was consistent with previous literature report. [8,9]

2-(4-Methoxyphenyl)-imidazo[1,2-a]pyrimidine(4e). ^1H NMR (300 MHz, CDCl_3): δ 3.75 (s, 3H-OCH₃) 6.77-6.79 (dd, 1H), 6.88-6.93 (d, 2H), 7.56 (s, 1H), 7.93-7.98 (d, 2H), 8.35-8.38 (dd, 1H), 8.40-8.43 (dd, 1H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 55.36 (OCH₃), 106.51, 108.96, 114.56, 124.51, 127.97, 133.14, 145.20,

149.25, 149.61, 160.11; IR (KBr) cm^{-1} : 13132, 1615, 1515; ES-MS (m/z): 225 $[\text{M}+\text{H}]^+$; spectra data was consistent with previous literature report. [8,9]

2-(3-Nitrophenyl)-imidazo[1,2-a]pyrimidine(4f). ^1H NMR (300 MHz, CDCl_3): δ 6.84-6.91 (m, 1H), 7.49-7.62 (m, 4H), 7.92 (s, 1H), 8.51-8.56 (m, 1H), 8.74-8.79 (m, 1H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 107.51, 109.46, 120.98, 123.54, 130.97, 131.14, 133.20, 133.65, 147.64, 148.21, 149.11, 153.11; IR (KBr) cm^{-1} : 1589, 1513, 1342; ES-MS (m/z): 240 $[\text{M}+\text{H}]^+$; spectra data was consistent with previous literature report. [8,9]

4. CONCLUSION

In conclusion, we have described an efficient one-pot route for the synthesis of 2-aryl imidazo[1,2-a]pyrimidine using PEG-1500 as catalyst in water as a reaction medium. The important features of this procedure are rapid, simple, no need of column chromatography and yield are relatively high.

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