Polyethylene Glycol Promoted Synthesis of Pyrimido[1,2-a]benzimidazole and Pyrano[2,3-c]pyrazole Derivatives in Water

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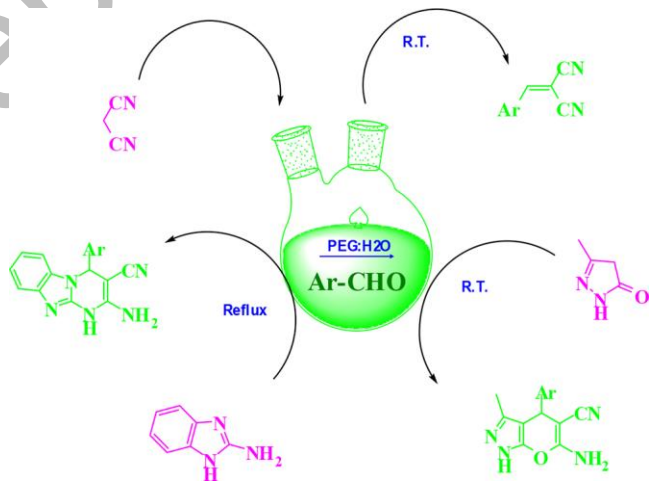
Abstract

Synthesis of pyrimido[1,2-*a*]benzimidazole and pyrano[2,3-c]pyrazole derivatives were achieved using polyethylene glycol (PEG-400) as promoting reaction medium in water under catalyst-free conditions at reflux and room temperature respectively. The structure of pyrimido[1,2-*a*]benzimidazole was confirmed using ^{1}HNMR, ^{13}CNMR, DEPT and HMBC experiments. The promising point for present methodology are efficiency, generality, high yield, short reaction time, cleaner reaction profile, ease of product isolation, simplicity, potential of recycling reaction medium and finally agreement with green chemistry protocols.

Graphical Abstract



KEYWORDS: Catalyst-free synthesis, pyrimido[1,2-a]benzimidazole, PEG-Water, pyrano[2,3-c]pyrazole

1. INTRODUCTION

The discovery of new synthetic methodologies that facilitate the preparation of organic compound is a focal point of research activity in field of modern organic, bio-organic and medicinal chemistry [1]. Benzimidazole is a class of heterocyclic aromatic organic compound which share a fundamental structural characteristic of six membered benzene fused to the 4 and 5-position of five membered imidazole ring system. The heterocyclic benzimidazole scaffold is a useful structural motif for the development of molecules of pharmaceutical or biological interest. In 1872, Hobrecker reported the first benzimidazole synthesis of 2,5- and 2,6-dimethylbenzimidazole and he never suspected that benzimidazole scaffold would become such a preeminent structure [2]. The interest in benzimidazole chemistry has been spawned by the discovery of N-ribosyl-dimethyl benzimidazole. The N-ribosyl-dimethyl benzimidazole was found to be most prominent benzimidazole compound in nature serves as an axial ligand for cobalt in vitamin B12 [3]. Over the years of active research, benzimidazole and its derivatives have evolved as important privileged structures in medicinal chemistry encompassing a diverse range of biological activities including antiparasitic (specifically anthelmintics, e.g., albendazole, mebendazole), Antiulcer (proton pump inhibitors (PPIs), e.g., omeprazole), antihypertensive (angiotensin II receptor blockers, e.g., candesartan, telmisartan), antihistaminic (H1-receptor antagonists, e.g., Bilastine), anti-cancer (nitrogen mustard alkylating agents, e.g., bendamustine), antiemetic/antipsychotics (e.g., droperidol) [4-6].

The fused pyrimido[1,2-a]benzimidazole ring system with phenyl sulfonyl moiety exhibited comparable analgesic and anti-inflammatory activity to indomethacin [7] and The tricyclic benzimidazole compounds having potent anti-inflammatory activity comparable to standard ibuprofen [8-10]. A number of drugs like albendazole, mebendazole, thiabendazole as anthelmintics; omeprazole, lansoprazole, pantoprazole as proton pump inhibitors; astemizole as antihistaminic; enviradine as antiviral; candesarten cilexitil and telmisartan as antihypertensive contains benzimidazole were already well established and successfully used in the treatment of multiple ailments. Therefore development of an efficient, one pot and chemo selective procedure synthesis of pyrimido[1,2-a]benzimidazole in green reaction medium without catalyst is of considerable interest. PEGs are green, non-volatile, recyclable, stable to acid, base, and also to high temperature. Recently reported in many reactions, PEG and its aqueous solutions were acting as promoting reaction medium [11-16]. Here we were report a facile and convenient way to create diversely substituted medicinally privileged 2-amino pyrimido[1,2-a]benzimidazole and pyrano[2,3-c]pyrazole scaffold. The new simple green non catalytic multicomponent process in PEG-Water as a solvent can produce an effective transformation of aromatic aldehyde, malononitrile and 2-amino benzimidazole into heterocyclic pyrimido[1,2-a]benzimidazole at reflux without addition of catalyst.

2. RESULT AND DISCUSSION

A catalyst free condensation of p-chloro benzaldehyde, 2-amino benzimidazole and malononitrile were studied in different solvents at various temperature conditions. It was observed that only trace amount of product formed in DMF, DMSO and Toluene while it

furnished moderate yield in water. In polyethylene glycol reaction proceeded at reflux giving 60% yield. We observed that knoevenagel condensation requires more time (~2 h) in PEG 400 so only small amount of water in PEG is essential to catalyze knoevenagel condensation with faster rate. The best results were obtained in PEG: Water (8:2) by optimizing reaction conditions at different PEG: water ratio shown in table 1. Interestingly we found that knoevenagel condensation proceeds within 5-10 min in presence of PEG: water. Water catalyses knoevenagel condensation [17, 21] and hence cyclocondensation reaction completes within 6 h with good to excellent yields. Initially all starting materials were soluble in aqueous PEG solution so at the start of the reaction a solution was observed to be nearly transparent. Almost all products were found to be insoluble in PEG solution, so with the progress of reaction products sediments slowly from reaction mixture. Due to high hydrophilicity of PEG, separation of the products from reaction mixture could be realized by adding water. This simple procedure allowed easy scale up of our methodology. We extended the reaction towards synthesis of pyrano[2,3-c]pyrazole Surprisingly we found that the reaction completes within short reaction time without use of catalyst at room temperature.

All synthesized compounds were characterised by IR, ^{1}H and ^{13}CNMR and Mass spectroscopy and found to be well matching with that reported in the literature [18-20]. We observed that aldehydes having electron donating or electron withdrawing groups does not affect reaction rate considerably. However steric effect from the substrate had a major impact on the overall yield of product (**Table 2** entry 4e and 4g). After reaction, the polyethylene glycol was easily separated from the reaction medium by washing with

distilled water (PEG is soluble in water). The washed PEG is distilled under vacuum to recover solvent for reuse in subsequent reactions. After three successive runs, recycled PEG showed no loss of efficiency with regard to reaction time and yield.

3. CONCLUSION

The new, simple, green and non-catalytic multicomponent process offers a facile and convenient way to create substituted medicinally relevant pyrimido[1,2-a]benzimidazoles and its derivatives approved basis for the generation of molecules having promising biological activity. The promising point for present methodology are efficiency, generality, high yield, short reaction time, cleaner reaction profile, ease of product isolation, simplicity, potential of recycling reaction medium and finally agreement with green chemistry protocols, making it a useful and attractive process for the synthesis of pyrimido[1,2-a]benzimidazole derivatives. Application of PEG-water as a solvent system not only makes product separation much easier, but also shows higher environmental compatibility and sustainability due to the avoidance of quenching steps, reduced reliance on toxic organic solvents and minimization of waste and convenience of non-catalytic chain 'green' processes in water. Therefore this type of MCR brings us a closer to the notion of 'ideal synthesis' [11].

4. EXPERIMENTAL

All chemicals were obtained from commercial suppliers and were used without further purification. Melting points were determined in open capillaries and were uncorrected. All reactions were monitored by thin layer chromatography (TLC) with 0.2

mm Merck silica gel F_{254} plates. NMR spectra were recorded on Bruker Avance III FT NMR at 400 MHz spectrometer in DMSO-d_6 using TMS as internal standard (chemical shifts are expressed as δ values relative to TMS as internal standard). IR spectra were recorded on a Perkin Elmer FTIR spectrophotometer.

General one-pot procedure for synthesis of pyrimido[1,2-a]benzimidazoles : A mixture of aldehyde (1 mmol), 2-amino benzimidazole (1 mmol) and malononitrile (1 mmol) in PEG 400 (4 ml) and water (1 ml) solution were refluxed for 6-8 h. The progress of reaction was monitored by TLC using petroleum ether: ethyl Acetate (6:4) as solvent system. After completion of the reaction, H_2O (200 ml) was added and stirred for 2-3 h, the solid product separate out which was filtered to give the corresponding product with high purity without the need of column chromatography for purification.

General one-pot procedure for synthesis of pyrano[2,3-c]pyrazole derivatives: A mixture of ethyl acetoacetate (1.2 mmol) and hydrazine hydrate (1.2 mmol) was taken in dry reaction flask, The flask was stirred till the solid separate out within 1-2 min. To this flask Aldehyde (1 mmol), malononitrile (1 mmol) and PEG 400 (4 ml): water (1 ml) solution was added and continued the stirring for 2-3 h at room temperature. The progress of reaction was monitored by TLC using petroleum ether: ethyl Acetate (6:4) as solvent system. After completion of the reaction the reaction mass was poured over ice, 200 ml water was added to solution and solution was stirred for 2 hr. The obtained solid was filtered, washed with water and crude solid was crystallized from methanol.

SUPPORTING INFORMATION

Supplementary material, which includes some of the scan copies of IR, 1H-NMR, ^{13}CNMR and Mass analysis, for this article can be accessed on the publisher's website

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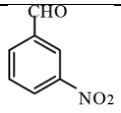
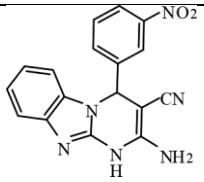
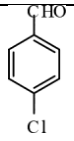
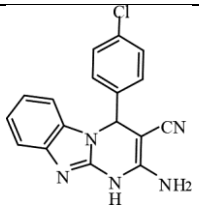
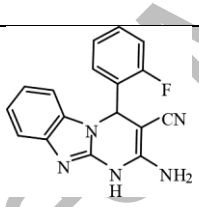
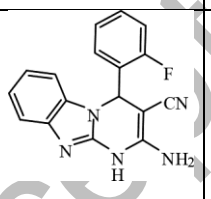
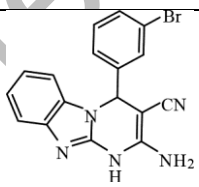
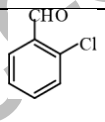
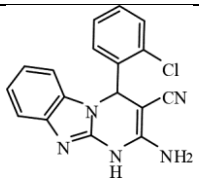
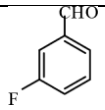
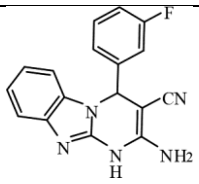
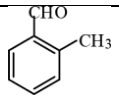
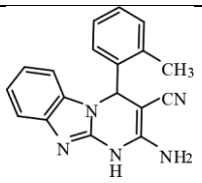
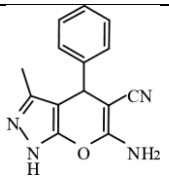
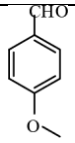
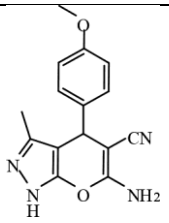
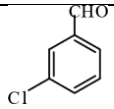
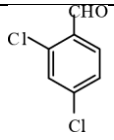
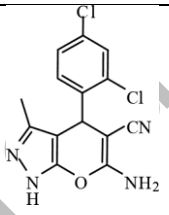
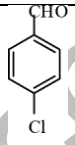
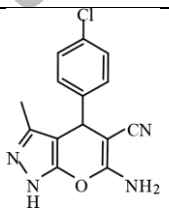
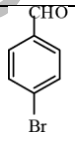
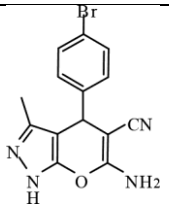
Table 1 Optimisation of reaction conditions for a catalyst-free synthesis of 4b in different solvent and at temperature conditions respectively.

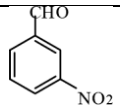
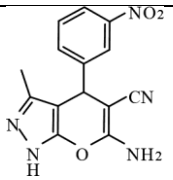
Entry	Solvent	Temp (^{o}C)	Time(h)	Yield (%)[b]
1	Toluene	90	7	Trace
2	DMF	90	7	Trace
3	DMSO	90	7	Trace
4	Water	90	7	60
5	PEG-600	reflux	7	65
6	PEG: Water (5:5)	reflux	7	74
7	PEG: Water (7:3)	reflux	7	80
8	**PEG: Water (8:2)**	reflux	7	**86**
9	PEG: Water (9:1)	reflux	7	82

Reaction Condition: p-chloro benzaldehyde (1 mmol), 2-amino benzimidazole (1 mmol) and malononitrile (1 mmol), Solvent (5 ml), [b] isolated yield.

Table 2 The reaction between aromatic aldehyde, 2-amino benzimidazole / (Ethyl acetoacetate and hydrazine hydrate) (1mmol each) and malononitrile in PEG: Water at reflux and room temperature respectively.

Entry	Aldehyde	Product[a]	Time (hr)	Yield (%)[b]	Ref
1			7	84	18
2			7	86	18
3			7.5	75	18
4			7	80	18
5			7.5	72	18
6			7.5	80	18

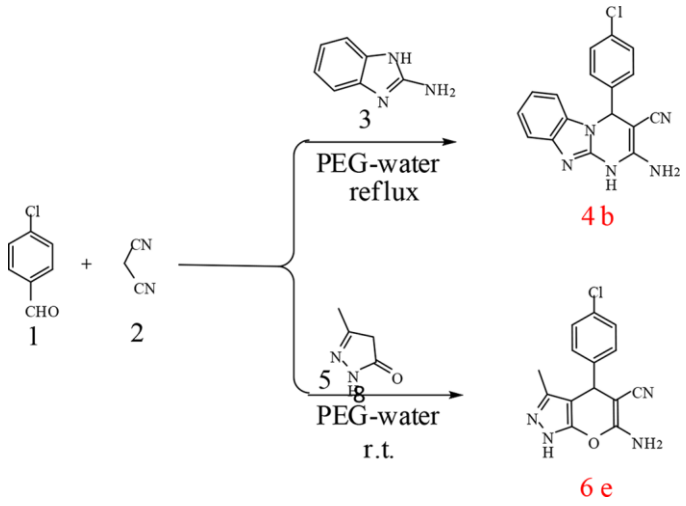
7			2.0	77	18
8			2.0	90	19
9			2.0	91	19
10			2.0	88	19
11			2.5	81	20
12			2.0	86	19
13			2.0	87	19

14			2.5	80	20

Reaction Condition: Aromatic aldehyde (1 mmol), 2-amino benzimidazole / (Ethyl acetoacetate and hydrazine hydrate) (1 mmol each) and malononitrile (1 mmol) in PEG: Water (4:1) at reflux.

[a]All the products are known and were identified by their comparison of their IR and NMR spectra [18-20], [b] isolated Yields.

Scheme 1 A catalyst-free synthesis of 4b and 6e using PEG-H_2O as aqueous reaction medium.



Scheme 2 A catalyst-free synthesis of pyrimido[1,2-a]benzimidazole and pyrano[2,3-c]pyrazole derivatives using PEG-H_2O as aqueous reaction medium.