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AN EFFICIENT THREE-COMPONENT ONE-POT SYNTHESIS OF PYRIMIDOBENZIMIDAZOLE DERIVATIVES

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Abstract

A simple, clean and convenient one pot method has been developed for the synthesis of pyrimido[1,2-a]benzimidazole derivatives by the multicomponent reaction of cyclic ketone (1) aminobenzimidazole (2) and malononitrile (3) in the presence of ammonia as a mild, cheap, efficient, commercially available, environmentally benign, non-toxic base in aqueous ethanol medium. The simple work-up procedure and good to very good yield in short time are some of the important features of this protocol. The chemical structures of the synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis.

Keywords : pyrimido[1,2-a]benzimidazole, one-pot synthesis, aqueous ammonia

Introduction

Multicomponent reactions have offered many fascinating and challenging transformations in organic synthesis[I-VII]. The atom-economy, operational simplicity convergent character, structural diversity, and complexity of the molecules are the major advantages associated with multicomponent reactions. These multicomponent reactions are developing as a powerful tool in the synthesis of biologically important compounds[VIII,IX].

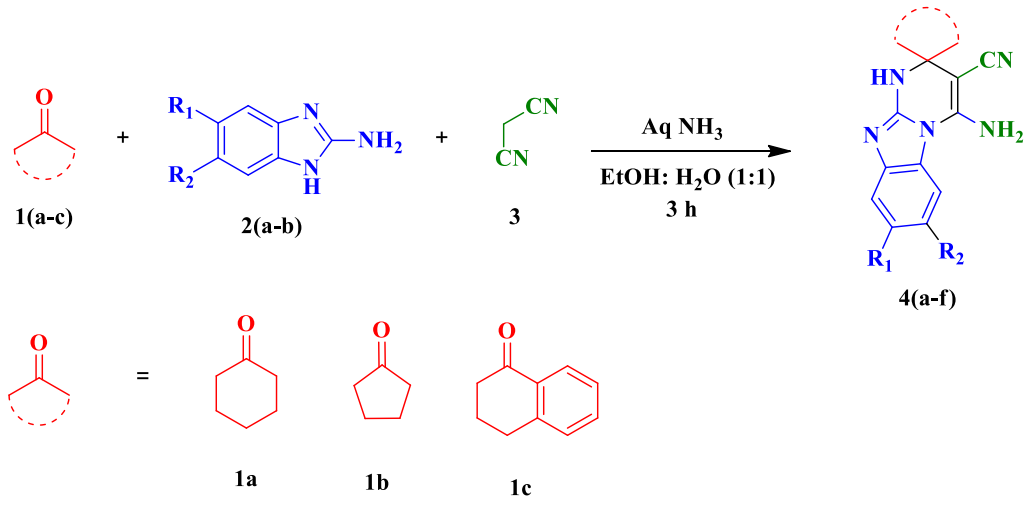
The formation of heterocyclic compounds is a very significant task in organic synthesis, mainly because they are present in numerous biologically active compounds and in several natural products[X]. Nitrogen-containing heterocyclic systems have a diverse spectrum of pharmacological properties. Different heterocyclic moiety's can be incorporated to produce molecules with enhanced biological properties.

Molecules containing the benzimidazole heterocycle which exhibit selective antibacterial activity[XI]. Presence of benzimidazole ring in numerous compounds is an important structural element for their biological and medical applications. For example benzimidazoles are widely spread in antiulcer, antihypertensive, antiviral, antifungal, anticancer, and antihistaminic medicines, among others[XII-XIV]. In recent years, benzimidazole compounds have emerged as a hot research topic due to their varied biological activities. Indeed, benzimidazole is a privileged scaffold in medicinal chemistry and agrochemistry.

Several commercial fungicides containing the benzimidazole scaffold have been launched or announced[XV,XVI]. Pyrimido[1,2-a]benzimidazoles represent core structures that are useful templates for the design of a variety of biologically active compounds[XVII]. Despite their importance from pharmacological and synthetic points of view, few methods for the preparation of pyrimido[1,2-a]benzimidazoles have been reported. However, these protocols suffer some drawbacks such as long reaction times, expensive reagents, use of toxic organic solvents, difficulties in the preparation of the catalyst, non-recoverability of the catalyst, and tedious work-up procedures. Moreover, most of them lack selectivity[XVIII-XXV]. Herein we report a new methodology for the synthesis of pyrimido[1,2-a]benzimidazoles using ammonia and inexpensive starting materials 2-aminobenzimidazole, malononitrile, and carbonyl compounds in ethanol (**Scheme 1**).

Results and Discussion

The synthesis of pyrimido[1,2-a]benzimidazole derivatives was carried out by the multicomponent reaction of carbonyl compounds (1) 2-aminobenzimidazole (2) and malononitrile (3) in the presence of ammonia in aqueous ethanol (**Scheme 1**).



Scheme 1: Synthesis of pyrimido[1,2-a]benzimidazole derivatives

Initially, the one-pot reaction of ketone (1) aminobenzimidazole (2) and malononitrile (3) was conducted in different solvents such as dichloromethane, toluene, acetonitrile, ethanol, water and aqueous ethanol (1:1) in the presence of ammonia (Table 1) at different temperatures. Considering the yield, aqueous ethanol was found to be most effective at 80^{o}C (**Table 1, Entry 5**). Using other solvents, the reaction time was longer and the yield was less. To further optimize the reaction conditions, a variety of parameters such as effect of amount of solvent, amount of base, reaction temperature and time were investigated to achieve optimal conditions. The results revealed that a 1:1:1 mole ratio of ketone (1) aminobenzimidazole and malononitrile (3) in 20 mL of aqueous ethanol at 90^{o}C in 4h in 10 mmol of catalyst was found to be optimum to achieve highest yield of pyrimido[1,2-a]benzimidazole **4a** (**Table 3, Entry 5**).

Table 1. Optimization of reaction medium

Entry	Solvent	Temp ^{o}C	Time (h)	Yield[a] (%)
1	Dichloromethane	38	10	Trace
2	Acetonitrile	78	10	4
3	Ethanol	80	10	12
4	Toluene	80	10	5
5	Water/Ethanol (1:1)	80	6	60
6	Water	80	10	58
7	Water	100	6	57

[a]Isolated yields

Table 2: Optimization of the reaction medium **4a**.

Entry	EtOH/Water (1:1) (ml)	Base (mmol)	Time (h)	Temperature (ºC)	Yield (%)[a]
1	30	15	3	75	60
2	25	10	3	75	63
3	20	10	3	75	68
4	15	10	3	75	61
5	20	10	3	79	82
6	20	10	3	70	69
7	20	10	4	79	60
8	20	5	4	70	62
9	20	10	4	40	10
10	20	10	4	55	59
11	20	10	4	60	61
12	20	10	4	65	63

a isolated yields

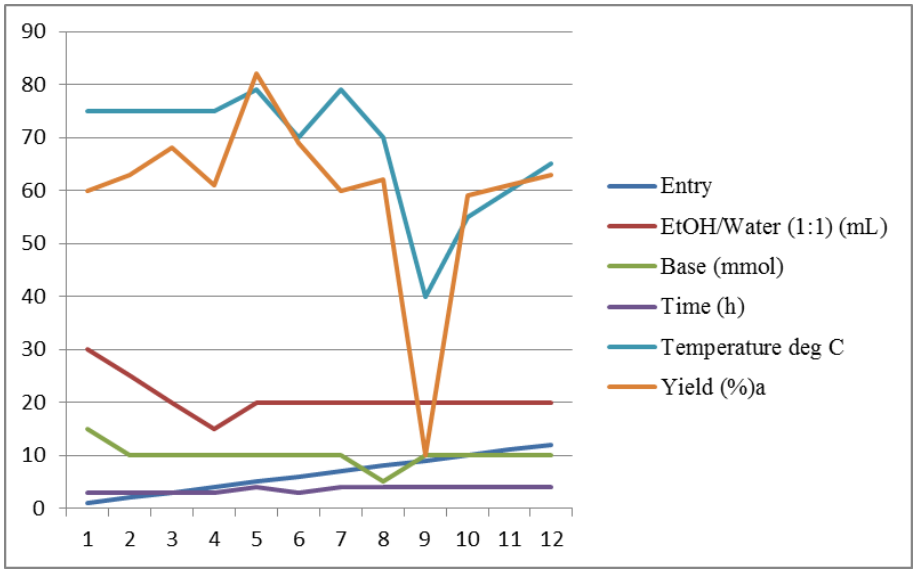


Fig 1: Optimization of the reaction medium **4a**

The substrate scope was then explored with different carbonyl components such as cyclohexanone (1a), cyclopentanone (1b) and tetralone(1c) and the results are presented in Table 3. The reaction has gone smoothly with cyclohexanone (Table 3, entry 1).

Table 3. Synthesis of pyrimido[1,2-a]benzimidazole derivatives [a]**4(a-f)**.

Entry	Product	Ketone	R_1	R_2	Time (h)	Yield[b] (%)
1	4a	1a	H	H	3	84
2	4b	1b	H	H	3	83
3	4c	1c	H	H	3	82
4	4d	1a	CH_3	CH_3	3	73
5	4e	1b	CH_3	CH_3	3	67
6	4f	1c	CH_3	CH_3	3	83

[a]Reaction of aminobenzimidazole**2**(10 mmol)**,**malanonitrile**3**(10mmol) with various ketones**1** (10 mmol) in the presence of ammonia in aqueous ethanol.
[b]Isolated yields.

The structure of the products **4(a-f)** were confirmed by IR, ^{1}H NMR, ^{13}CNMR and Mass. IR spectra of **4a** showed prominent sharp NH stretching in region 3360-3140 (NH & NH_2) cm^{-1} and showed strong absorption band at 2170 cm^{-1} indicating the presence of CN group. The ^{1}H NMR spectrum **4a** exhibited 7.91 ppm for NH and multiplet at 7.32-7.87 ppm for 4H Ar-H, singlet 2H at 5.75 ppm. Moreover **4a** also exhibited five multiplet at1.90 ppm, 1.92ppm, 2.13ppm, 2.35ppm, 2.47ppm for -CH_2-CH_2-CH_2-CH_2-CH_2-. The ^{13}C spectra of **4a** showed characteristic peaks of C-SP^3 at 20.3, 22.5, 29.5, 32.6, 35.6, 51.5 and 147.8, 169.4 ppm(C=N, C-NH_2).

Experimental

All the chemicals were purchased from commercial supplier used without further purification. Melting points were measured in open glass capillaries using a Perfit melting-point apparatus and are uncorrected. The progress of the reaction was monitored by thin-layer chromatography (TLC) using silica-gel precoated aluminium sheets (60 F254, Merck). Visualization of spots was effected by exposure to ultraviolet light (UV) at 365 and 254nm, iodine vapors. Recrystallization was achieved with ethanol. IR spectra (tmax, cm^-1) were recorded on Perkin-Elmer FT-IR spectrophotometer using KBr discs. ^{1}H NMR and ^{13}C NMR spectra in $CDCl_3$ as solvent were recorded on a Bruker 400-MHz with tetramethylsilane (TMS) as internal standard. The chemical shifts are expressed in (ppm) downfield from TMS. The abbreviations s, d, t, and m in ^{1}H spectra refer to singlet, doublet, triplet, and multiplet respectively.

General procedure for the synthesis of pyrimido[1,2-a]benzimidazole derivatives 4(a-f)

In a 50 ml round bottom flask mixture of ketone **1**(10 mmol), aminobenzimidazole **2** (10 mmol), malononitrile **3**(10 mmol) and ammonium (25%) were taken in 20 ml aqueous ethanol (1:1). The reaction mixture was allowed to stir magnetically at 80^{o}C. The progress of the reaction was monitored by TLC. After completion of the reaction, mass was cooled to room temperature and solid was filtered. Filtered solid was recrystallized from ethanol.

Spectral characterization data for 4(a-f)

4-amino-1*H*-spiro[benzo[4,5]imidazo[1,2-a]pyrimidine-2,1'-cyclohexane]-3-carbonitrile (4a) Half-white solid; m.p : 238 ^{o}C; IR (KBr) cm^{-1} : 3360-3140 (NH& NH2), 2170 (CN),1640 (C=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 1.90 (2H, m, CH_2), 1.92 (2H, m, CH_2), 2.13

(1H, m, CH_2), 2.35 (2H, m, CH_2), 2.47 (2H, m, CH_2), 5.75 (2H, s, NH_2), 7.32-7.87 (4H, m, Ar-H), 7.91 (1H, s, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm)20.3, 22.5, 29.5, 32.6, 35.6, 51.5, 70.7, 117.5, 118.9, 125.7, 130.9, 134.7, 138.4, 141.6, 147.8, 169.4;Anal. Calcd. For $C_{16}H_{17}N_5$: C, 68.79; H, 6.13; N, 25.07; Found: C, 68.19; H, 6.23; N, 25.01; MS (*m/z*): 280.14 $[M+H]^+$.

4-amino-1*H*-spiro[benzo[4,5]imidazo[1,2-a]pyrimidine-2,1'-cyclopentane]-3-carbonitrile (4b) : Half-white solid; m.p : 171 ^oC; IR (KBr) cm^{-1} : 3470-3240 (NH & NH2), 2180 (CN),1620 (C=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 1.89 (2H, m, CH_2), 2.04 (2H, m, CH_2), 2.33 (2H, m, CH_2), 2.57 (2H, m, CH_2), 5.60 (2H, s, NH_2), 7.01-7.57 (4H, m, Ar-H), 7.62 (1H, s, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm)21.2, 23.7, 28.5, 31.8, 38.9, 55.2, 74.7, 114.9, 119.7, 128.4, 131.9, 133.1, 140.4, 145.3, 150.4, 172.0;Anal. Calcd.for $C_{16}H_{17}N_5$: C, 67.90; H, 5.70; N, 26.40; Found: C, 67.80; H, 5.71; N, 26.42; MS (*m/z*): 266.13$[M+H]^+$.

4-amino-7,8-dimethyl-1H-spiro[benzo[4,5]imidazo[1,2-a]pyrimidine-2,1'-cyclohexane]-3-carbonitrile (4d) : White solid; m.p : 206 ^oC;IR (KBr) cm^{-1} : 3380-3140 (NH & NH2), 2190 (CN),1630 (C=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm). 1.44 (2H, m, CH_2), 1.59 (2H, m, CH_2),1.78 (2H, m, CH_2), 2.13 (1H, m, CH_2), 2.32 (2H, m, CH_2), 2.48 (6H, s, CH_3), 5.45 (2H, s, NH_2), 7.22-7.72 (2H, m, Ar-H), 7.85 (1H, s, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm)19.2, 21.5, 22.8, 24.75, 32.7, 36.9, 60.2, 74.9, 115.8, 123.7, 126.9, 128.5,134.9, 138.7, 141.7, 155.6;Anal. Calcd. for $C_{16}H_{17}N_5$, 70.33; H, 6.89; N, 22.78; Found: C, 70.13; H, 6.29; N, 22.71;MS (*m/z*): 308.17$[M+H]^+$.

4-amino-7,8-dimethyl-1*H*-spiro[benzo[4,5]imidazo[1,2-a]pyrimidine-2,1'-cyclopentane]-3-carbonitrile (4e) : White solid; m.p : 218 ^oC;IR (KBr) cm^{-1} : 3480-3260 (NH & NH2), 2170 (CN),1610 (C=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 1.82 (2H, m, CH_2), 2.07 (2H, m, CH_2), 2.21 (6H,s, CH_3), 2.38 (2H, m, CH_2), 2.64 (2H, m, CH_2), 5.65 (2H, s, NH_2), 7.15-7.72 (4H, m, Ar-H), 7.84 (1H, s, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm)19.8, 23.2, 29.7, 34.6, 60.2, 74.6, 117.3, 121.6, 124.2, 127.5,131.3, 135.7, 142.1, 150.9, 172.7;Anal. Calcd. for $C_{16}H_{17}N_5$: C, 69.60; H, 6.53; N, 23.87; Found: C, 69.60; H, 6.53; N, 23.87;MS (*m/z*): 294.16 $[M+H]^+$.

Conclusion

In conclusion, we have described an efficient and simple procedure for the synthesis of pyrimido[1,2-a]benzimidazoles from cyclic ketone, aminobenzimidazole and malononitrile *via* a three-component one-pot reaction. These methods have some advantages such as green pathways, easy workup, utilization of a metal-free catalyst, good yields, and wide applicability.

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