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SYNTHESIS OF[4+2] CYCLOADDITION REACTION BY USING BASE CATALYST UNDER ULTRASONIC IRRADIATION

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ABSTRACT

An efficient synthesis of substituted dihydropyrimidobenzimidazoles was achieved via (4+2) one pot three-components Povarov reaction using aromatic aldehydes, 2-amino-bezamidazole and maleic anhydride under piperidine base catalysis. The discovered methodology for the preparation of substituted dihydropyrimidobenzimidazoles offers several advantages over previous methods including mild reaction conditions, easy work-up, a wide range of applicability, less time consume and products in good yields.

KEYWORDS: Substituted dihydropyrimidobenzimidazoles, Aromatic Aldehyde**,** Povarov reaction, Ultra-sound irradiation.

INTRODUCTION

The Povarov(Aza-Diels-Alder) reaction is an inverse-electron-demand (4+2) cycloaddition reaction to synthesize natural products from diene and dienophile.[1,2] Dihydropyrimidobenzimidazoles derivatives are one of the most important classes of natural products exhibiting a wide spectrum of pharmaceutical properties.[3] It includesniciceptin/orphanin FQ receptor agonism[4], HIV-1 integrase inhabitation.[5] Aza-Diels-Alder reaction is a powerfuland efficientmethod for preparation of Dihydropyrimidobenzimidazoles.[6,8] Mostly, Schiff's bases (imines) derived from aromatic amines and aldehydes act as heterodienes and react with various dienophile in presence of

different acid catalysts like Rh(II)[9], $Yb(OTf)_3$[10], $TiCl_2$[11], $InCl_2$[12], BF_3. MeOH[13], $Al(OTf)_3$[14], $Sc(OTf)_3$[15] and phosphoric acid.[16] Literature surveyentails that Povarov reaction has been rarely carried out in a basic condition and Ultrasonic irradiation[17,18]. This hasencouraged investigatingthe base catalyzed Povarov reaction.

Thus, Piperidinecatalyzedto synthesis of Dihydropyrimidobenzimidazoles derivativesare reported by (4+2) cycloaddition reactionusing Ultrasonic irradiation.

MATERIAL AND METHODS

General

Ultrasonication was performed- 230 V AC, 50 Hz, liquid holding capacity 5.5 L and temperature at 70°C. The 100 mL Round Bottom reaction flasks with condenser attached to stand and reaction flasks were suspended at the center of bath. ^{1}H NMR spectra were recorded at (Bruker) 400 MHz in DMSO using TMS as an internal standard. ^{13}C NMR spectra measurements were performed at 100 MHz using TMS as an internal standard. All the compounds were identified by ^{1}H NMR and are in good agreement with those reported. IR spectroscopy was performed on a Perkin-Elmer FT-IR Spectrometer. Melting points were measured manually. TLC was conducted on standard conversion aluminum sheets pre-coated with 0.2 mm layer of silica gel. All reagents were commercially available.

General procedure for (4+2) cycloaddition reaction of the dihydropyrimidobenzimidazoles derivatives

For the Ultrasound-assisted method, a mixture of piperidine (10%, mol), isoniazide (0.1 mol), Aldehyde (0.1 mol) and Maleic anhydride (0.1 mol) inDCE as solvent (5 mL) was irradiated with Ultrasound (with a frequency of 50 Hz and power of 250 V AC) temperature at 70 °C for 2 hours. The reaction flasks were located at center of the bath with condensed assembly and the surface of the reactants was placed slightly lower than the water level in round bottom flask. The reaction progress was checked on TLC using ethyl acetate: hexane (5:5) as solvents. After the completion of reaction, the mixture was cooled at room temperature. Charged methanol (10 mL) was used for crystallization and then cooled at 22°C, stirred for 30 minutes. Filtered the product through G_1 sintered crucible with assembly and recrystallize by alcohol.

4-(4-methoxyphenyl)-5a,6-dicyclobenzo[4,5]imidazo[1,2-a]furo[3,4-e]pyrimidine-1,3(3a*H*,11a*H*)-dione (4a)-White crystal, m.p. 250-252^{o}C. FTIR (KBr cm^{-1}): 3250, 2803, 2190, 1667, 1629, 1594, 1471; ^{1}H NMR 400 MHz, DMSO) δ 9.90 (s, 1H, D_2O exchangeable NH), 6.13-7.94 (m, 8H,Ar), 3.80 (s, 1H), 3.1-3.2 (m, 1H), 2.6 (s, 3H), 2.3 (s, 1H), ^{13}C NMR (100 MHz, DMSO): 169.27, 168.52, 166.19, 151.64, 148.09, 137.05, 136.13, 132.72, 130.20, 129.86, 129.81, 129.67, 129.09, 123.0, 122.14, 113.86, 111.53, 80.0, 57.0, 47.0, 40.0-39.1.

4-(2,5-dimethoxyphenyl)-5a,6-dicyclobenzo[4,5]imidazo[1,2-a]furo[3,4-e]pyrimidine-1,3(3a*H*,11a*H*)-dione (4b)-White grey crystal, m.p. 168-170^{o}C. FTIR (KBr cm^{-1}): 3249, 2829, 2186, 1661, 1618, 159294, 1412; ^{1}H NMR 400 MHz, DMSO) δ 9.86 (s, 1H, D_2O exchangeable NH), 6.16-7.97 (m, 7H,Ar), 3.82 (s, 1H), 3.2 (m, 1H), 2.7 (s, 6H), 2.4 (s, 1H), ^{13}C NMR (100 MHz, DMSO): 170.00, 169.02, 160.19, 151.45, 150.09, 139.15, 132.13, 131.32, 130.22, 130.04, 129.96, 129.74, 129.09, 123.09, 121.94, 113.76, 111.57, 79.0, 56.90, 46.97, 38.91- 40.0.

4-(phenyl)-5a,6-dicyclobenzo[4,5]imidazo[1,2-a]furo[3,4-e]pyrimidine-1,3(3a*H*,11a*H*)-dione (4g)- White crystal, m.p. 245-248^{o}C. FTIR (KBr cm^{-1}): 3250, 2802, 2190, 1667, 1692, 1593, 1471; ^{1}H NMR 400 MHz, DMSO) δ 9.94 (s, 1H, D_2O exchangeable NH), 6.08-7.97 (m, 9H,Ar), 3.76 (s, 1H), 3.17 (m, 1H), 2.54 (s, 1H), ^{13}C NMR (100 MHz, DMSO): 170.35, 168.52, 164.75, 151.95, 147.46, 138.37, 132.12, 131.13, 130.65, 129.71, 129.57, 129.22, 128.29, 122.80, 121.60, 114.21, 111.54, 79.0, 46.97, 38.9-40.10.

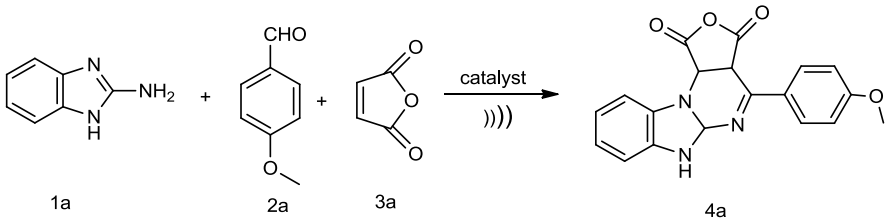
4-(4-chlorophenyl)-5a,6-dicyclobenzo[4,5]imidazo[1,2-a]furo[3,4-e]pyrimidine 1,3(3a*H*,11a*H*)-dione (4j)- White crystal, m.p. 215-218^{o}C. FTIR (KBr cm^{-1}): 3068, 2675, 2190, 1663, 1630, 1593, 1540; ^{1}H NMR 400 MHz, DMSO) δ 9.95 (s, 1H, D_2O exchangeable NH), 6.14-7.92 (m, 8H,Ar), 3.8 (s, 1H), 3.2-3.0 (m, 1H), 2.5 (s, 1H), ^{13}C NMR (100 MHz, DMSO): 170.35, 168.78, 164.60, 151.66, 147.46, 136.02, 131.16, 131.03, 130.02, 129.82, 129.60, 128.92, 128.42, 123.01, 121.45, 113.79, 111.42, 79.0, 44.40, 38.0-40.00.

4-(2,4-dichlorophenyl)-5a,6-dicyclobenzo[4,5]imidazo[1,2-a]furo[3,4-e]pyrimidine-1,3(3a*H*,11a*H*)-dione (4k)- Brownish white crystal, m.p. 180-184^{o}C. FTIR (KBr cm^{-1}): 3168, 2665, 2130, 1658, 1615, 1591, 1536; ^{1}H NMR 400 MHz, DMSO) δ 9.90 (s, 1H, D_2O exchangeable NH), 6.23-7.9 (m, 7H,Ar), 3.7 (s, 1H), 3.2-3.2 (m, 1H), 2.5 (s, 1H), ^{13}C NMR (100 MHz, DMSO): 170.30, 168.68, 163.90, 151.56, 146.40, 135.02, 131.26, 131.23, 131.02, 129.72, 129.60, 128.49, 128.43, 123.11, 121.53, 114.89, 112.00, 79.00, 44.35, 38.0-40.05.

4-(4-fluorophenyl)-5a,6-dicyclobenzo[4,5]imidazo[1,2-a]furo[3,4-e]pyrimidine-1,3(3a*H*,11a*H*)-dione (4m)- Greenish white crystal, m.p. 220-222^{o}C. FTIR (KBr cm^{-1}): 3246, 2900, 2190, 1667, 1630, 1594, 1571, 1447; ^{1}H NMR 400 MHz, DMSO) δ 9.0 (s, 1H, D_2O exchangeable NH), 6.10-7.95 (m, 8H,Ar), 3.7 (s, 1H), 3.2-3.0 (m, 1H), 2.5 (s, 1H), ^{13}C NMR (100 MHz, DMSO): 170.20, 168.53, 164.30, 151.61, 148.00, 138.00, 136.14, 131.00, 122.97, 122.00, 114.00, 111.52, 79.00, 44.53, 39.00-40.00.

RESULTS AND DISCUSSION

In our initial studies of the reaction mixture (2-amino-benzamidazole 4-methoxy benzaldehyde, maleic anhydride and 10 mol% of piperidine) was stirred at room temperature for 10 hours in CH3CN, EtOH, DCE and DCM solvents. Here (**4a**) product was not observed. Then same reactions were performed in reflux for 10 hours, here (**4a**) product was observed after 10 hours but only in EtOH and DCE solvents (Table 1).



Scheme 1.

Table 1: Optimization reaction conditions for solvents using Piperidine (10 mol%) Catalyzed (4+2) cycloaddition reaction.

Entry	Solvent	Temp (^{o}C)	Time (h)	Yield (%)
1	CH_3CN	RT	10	-
2	EtOH	RT	10	-
3	DCE	RT	10	-
4	DCM	RT	10	-
5	DCM	Reflux (110^{o}C)	06	-
6	EtOH	Reflux (110^{o}C)	06	65
7	DCE	Reflux (110^{o}C)	06	60
8	CH_3CN	Reflux (110^{o}C)	06	-
9	DCM	Irradiation(70^{o}C)	02	60
10	EtOH	Irradiation (70^{o}C)	02	-
11	DCE	Irradiation (70^{o}C)	02	80
12	CH_3CN	Irradiation (70^{o}C)	02	-
13	DCM	Irradiation (RT)	02	-
14	DCE	Irradiation (RT)	02	-

The reaction was carried out by the addition of 2-amino-benzamidazole (0.1 mol), 4-methoxy benzaldehyde (0.1 mol), Maleic anhydride (0.1 mol) and (10 mol%) piperidine catalyst (each solvent-5 mL).

Thus, we have performed under ultrasonic irradiation and observed effect. 2-amino-benzamidazole, 4-methoxy benzaldehyde, maleic anhydride with 10 mol% of piperidine catalyst at 70^{o}C temperature in DCE, DCM and EtOH for 02 hours;(**4a**) product observed only in DCE and DCM solvents. Further, decreasing the temperature from 70^{o}C to room temperature (for DCE and DCM solvents), (**4a**) product was not observed (Table 1).

Figure 1: Ultrasonic irradiator with condenser.

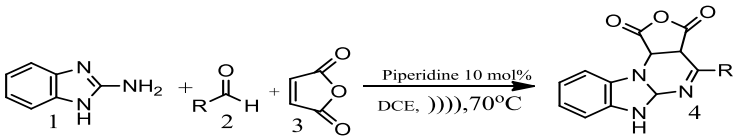
In order to observe the effect of piperidine on the reaction, variable amount of catalyst (Table 2) was experimented.

Table 2: Optimization of reaction conditions for piperidine catalyzed (4+2) cycloaddition reaction.

Entry	(mol %)	Time(h)	Yield (%)
1	5	02	40
2	10	02	80
3	15	02	83
4	20	02	84

The reaction was carried out by the addition of 2-amino-benzamidazole (0.1mol), 4-methoxy benzaldehyde (0.1 mol) and Maleic anhydride (0.1 mol) in DCM solvent under Ultrasound irradiation at 70^{o}C temperature.

Using piperidine catalyst this workreportsmild and efficient approach for the synthesis ofdihydropyrimidobenzimidazolederivatives (scheme 1), via (4+2) cycloaddition. This reaction gives good yield.



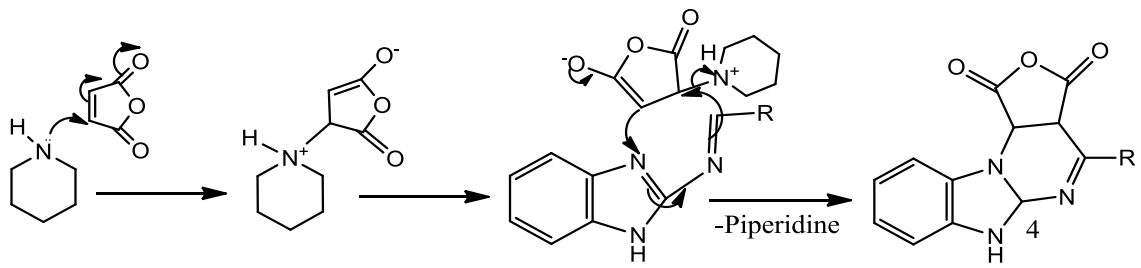
2a-l R=Ph **4a-l** R=Ph

Scheme 2

Table 3: (4+2) cycloaddition reaction of various dihydropyrimidobenzimidazoles derivatives catalyzed by piperidine.

Entry	R	Product	Time(min)	Yield(%)
1	4-$MeOC_6H_4$	4a	68	80
2	2,5- $MeO_2C_6H_3$	4b	30	74
3	3,4-$HO_2C_6H_3$	4c	60	77
4	3- HOC_6H_4	4d	32	78
5	4- CNC_6H_4	4e	52	73
6	4-HO-3-$MeOC_6H_3$	4f	48	71
7	ph	4g	53	75
8	3-BrC_6H_4	4h	63	79
9	4- HOC_6H_4	4i	72	69
10	4- ClC_6H_4	4j	69	78
11	2,4- $Cl_2C_6H_3$	4k	74	76
12	4- $NO_2C_6H_4$	4l	64	71
13	4- FC_6H_4	4m	79	77
14	2,3- $HO_2C_6H_3$	4n	50	74

The reaction was carried out by the addition of 2-amino-benzamidazole (0.1 mol), Aromatic aldehydes (0.1 mol), Maleic anhydride (0.1 mol) and (10 mol%) piperidine catalyst in DCM solvent (5 mL) at temperature 70^oC under irradiation.



Scheme 3. The proposed mechanism of piperidine catalyzed (4+2) cycloaddition reaction.

The above result showsthat 2-amino-benzamidazole, 4-methoxy benzaldehyde and maleic anhydride with 10 mol% of piperidine at 70^oC temperaturein DCE under Ultrasonic irradiation presents an efficient procedure in the terms of high yields and less time consuming.

With the optimal reaction condition, we then checked a variety of aromatic aldehydes in conventional and Ultrasound promoting catalytic cycloaddition reactions so as to form imines (formed in situ from aromatic aldehydes and 2-amino-benzamidazole in DCE as solvent).

Using piperidine catalyst, iminessmoothlycyclize with maleic anhydrideunder the ultrasonic irradiation to afforddihydropyrimidobenzimidazolesderivatives.

The products were purified by separation and recrystallization method and later identified by FTIR, ^{1}H NMR, and ^{13}C NMR spectroscopic data.

CONCLUSION

In conclude, we have discovered ahighly efficient one pot multicomponent (4+2) cycloaddition (Povarov) reaction with intermediate-imine and maleic anhydride catalyzed by piperidine under Ultrasonic irradiation. This cycloaddition reaction is rapid, environmental friendly, operationally simple and less time consuming.

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