Heterocyclic Letters
Vol. 5 | No.4|637-643| Aug-Oct| 2015
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

DBU: AN EFFICIENT CATALYST FOR THE SYNTHESIS OF 5-UNSUBSTITUTED-3,4-DIHYDROPYRIMIDIN-2 (1 *H*)-ONE DERIVATIVES UNDER MICROWAVE IRRADIATION

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Abstract: In this research paper, we have furnished a useful catalytic application of 1,8-diazabicyclo[5,4,0] undec-7-ene (DBU) for one pot three component cyclocondensation of aromatic aldehydes, acetophenone and urea produces corresponding 4,6-diphenyl-3,4-dihydropyrimidine-2 (1*H*) one derivatives in excellent yields under microwave irradiation.

The reported protocol possesses many advantages over reported one such as mild reaction conditions, inexpensive catalyst, short reaction times and high yield of the products.

Keywords: DBU, 4,6-diphenyl-3,4-Dihydropyrimidine-2 (1*H*) one derivatives, Microwave irradiation.

Introduction

In recent year pyridimidone motif plays an important role in medicinal chemistry due to its wide range of biological properties.[i] Some of pyrimidone derivatives have emerged as internal backbones calcium-channel blockers antibatcterial and anti-inflammatory agent.[ii] Several alkaloids isolated from marine sources posses biological activities, molecular structure of which contains the dihydropyrimidone moiety. The betzelladine alkaloids have been found to be potent HIV gp-120-CD_4 inhibitors.[iii]

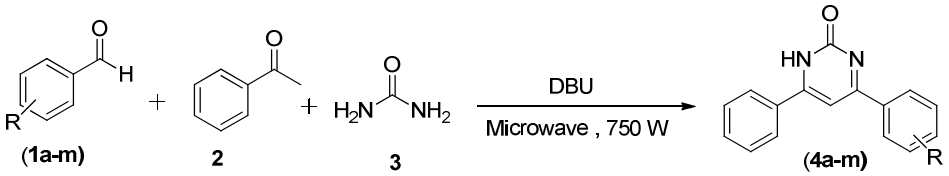
Synthesis of 4,6-diphenyl-3,4-dihydropyrimidine-2 (1*H*) one derivatives is achieved by cyclocondensation of aromatic aldehydes, aromatic ketone and urea. Literature survey reveals that, there are only few methods reported for the synthesis of 4,6-diphenyl-3,4-dihydropyrimidine-2 (1*H*) one derivatives such as using atomized Na metal,[iv] PPh_3,[v] Bi $(TFA)_3$ immobilized on [nbpy] $FeCl_4$,[vi] [BMIM] $[Bf_4]$,[vii] cyanouric trichloride/CF_3SO_3Zn.[viii-xi] and also by using Bronsted and Lewis acid,[xii-xx] Iodine,[xxi] CBSA-TMSCl,[xxii] NaOH,[xxiii] H_2NSO_3H, TMuCl.[xxiv]

Above reported methods suffering from various drawbacks which include harsh reaction conditions, low product yield, longer reaction times, using hazards solvents and catalysts. So, to overcome these drawbacks the development of new method for the synthesis of 4,6-diphenyl-3,4-dihydropyrimidine-2 (1*H*) one derivatives are still desirable.

1,8-diazabicyclo[5,4,0] undec-7-ene (DBU) act as base, catalyst, ionic liquid. There are various methods reported where DBU used as catalyst which includes synthesis of (*Z*)-

arylvinyl bromides,[xxv] spiro-2-amino-4*H*-pyrans, spiroacenaphthylenes, and spirooxindoles,[xxvi] 2*H*-1-benzopyrans,[xxvii] *N*-3 alkylation of 10 substituted isoalloxaines,[xxviii] hydroalkoxylation of activated alkenes and alkynes,[xxix] regiospecific and diastereoselective reaction of chiral *N*-(tert-butansufinyl) ketimines and α,β-unsaturated trifluromethyl ketones,[xxx] amides *via* aminolysis of methyl esters,[xxxi] aza-Michael additions of aromatic amines to α,β-unsaturated ketones,[xxxii] 3-benzylidenecyclohexenes.[xxxiii] Organic synthesis under microwave irradiation has advantage of shorter reaction time of using only small amount of energy.[xxxiv-xxxvii]

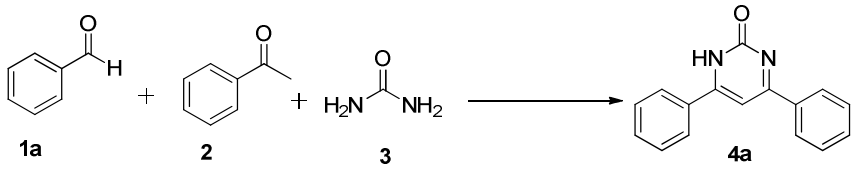
Owing to synthetic utility of DBU as catalyst and microwave irradiation, herein we wish to report a greener protocol for the synthesis of 4,6-diphenyl-3,4-dihydropyrimidine-2 (1*H*) one derivatives using DBU as catalyst under using microwave irradiation (**Scheme 1**).



Scheme 1 Synthesis of 4,6-diphenyl-3,4-dihydropyrimidine-2 (1*H*) one derivatives using DBU as catalyst under microwave irradiation.

Result and Discussion:

Initially, for the optimization of reaction condition the reaction of **1** benzaldehyde (1 mmol), **2** acetophenone (1 mmol) and **3** urea (1.5 mmol) to yield **4a** product was considered as model reaction (**Scheme 2**).



Scheme 2 Standard model reaction.

First the model reaction was carried out without catalyst under neat condition at 90 °C after 180 min. we found that reaction was not completed and gave 45 % yield of **4a** then, model reaction was carried out under neat condition with changing various catalysts (summarized in Table No.1). After screening of different catalysts for model reaction under neat condition, we found that by using DBU as catalyst under neat condition for model reaction (Entry 4 Table 1) we observed that the desire product **4a** was formed within 60 min with 80 % yield. Inspired with this result, we carried out model reaction using DBU as catalyst under microwave irradiation surprisingly, we found that within 8 min the desire product **4a** was formed with 96 % yield (Entry 5, Table No. 1).

Table 1 Optimization of catalysts for model reaction.

Entry	Catalyst 10 mol %	Conditions	Time (min)	% Yield[b]
1	None	Neat at 90 °C	120	30
		Microwave at 90°C,750W	15	40
2	Triethyl amine	Neat at 90 °C	120	45
		Microwave at 90°C,750W	15	55
3	Piperidine	Neat at 90 °C	120	43
		Microwave at 90°C,750W	15	46
4	Morpholine	Neat at 90 °C	120	43
		Microwave at 90°C,750W	15	54
5	DBU	Neat at 90 °C	120	80
		Microwave at 90°C,750W	8	96

The effect of temperature on model reaction was evaluated for that we, carried out model reaction with different temperature such as 50, 60, 70, 80 and 90 °C and 750 W. We found that at 90 °C and 750 W it gave 96 % yield within 8 min. Then we tested different microwave power on model reaction such as 500, 550, 600, 650, 700, 750, and 800 W. We found that 750 W is optimal power for model reaction (Entry 6, Table No. 2).

Table 2 Effect of different microwave irradiation powers on model reaction[a].

Entry	Power (W)	Time (min)	Yield[b] (%)
1	500	8	87
2	550	8	80
3	600	8	84
4	650	8	85
5	700	8	91
6	750	8	96
7	800	8	96

[a]Reaction conditions: Benzaldehyde (1 mmol), acetophenone (1 mmol), urea (1.5 mmol) and 10 mol % DBU under microwave irradiation at 90 °C, 750 MW. [b]Isolated yields.

In next step we screened out different solvents for model reaction after screening of solvent for model reaction. We observed that under solvent free condition it gave better result with respect to yield and time. (Entry 4, Table No. 2).

Table 2 screening of solvents for model reaction[a].

Entry	Solvent	Time (min)	yield[b]
1	Ethanol	15	67
2	DMF	15	57
3	toulene	15	46
4	Water	15	65
5	Neat	8	96

[a]Reaction conditions: Benzaldehyde (1 mmol), acetophenone (1 mmol), urea (1.5 mmol) and 10 mol % DBU under microwave irradiation at 90 °C, 750 MW. [b]Isolated yields.

Then we carried out the optimization of mol % of DBU such as 5, 10, 15, and 20 % for the model reaction, we found that 10 mol % of DBU was sufficient for the model reaction (Entry 2, Table No. 3).

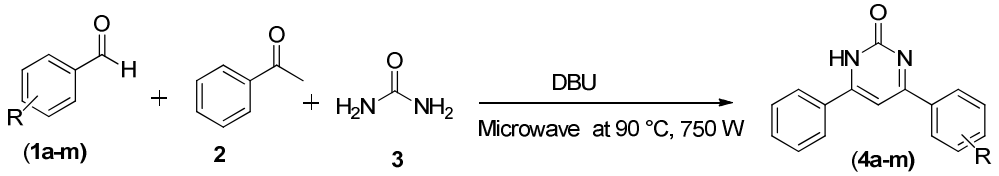
Table 3 Effect of mol % of DBU on model reaction[a]

Entry	Catalyst (Mol %)	Time (Min)	% Yield[b]
1	5	8	90
2	**10**	**8**	**96**
3	15	8	96
4	20	8	96

[a]Reaction conditions: Benzaldehyde (1 mmol), acetophenone (1 mmol) and urea (1.5 mmol) and 10 mol % DBU under microwave irradiation at 90 °C, 750 MW. [b]Isolated yields.

Then we carried out derivatives of 4,6-diphenyl-3,4-dihydropyrimidine-2 (1 *H*) one by changing the aromatic aldehydes we found that electron withdrawing or donating group on aromatic aldehyde did not effect on yield and time of product formation (summarized in Table 4)

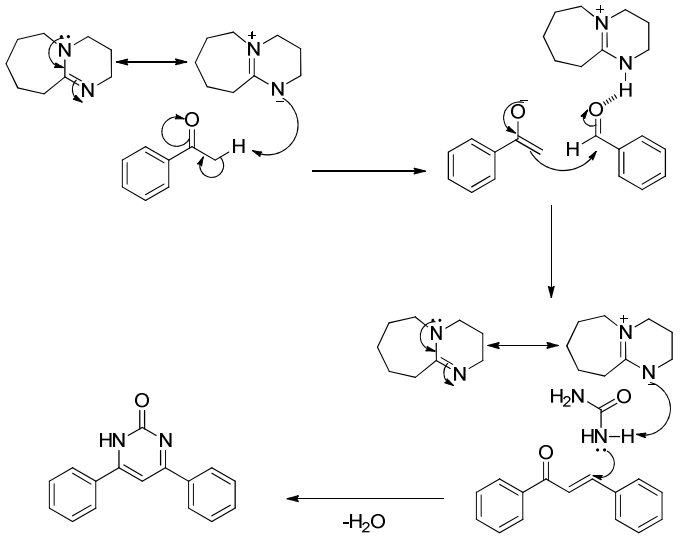
Table 4 DBU catalyzed synthesis of **4a-m**[a].



Entry	Product	R-aldehyde	Time (Min)	Yield[b]	Melting point (°C) Found	Reported
1	**4a**	C_6H_5	8	96	234-236	233-240[iv]
2	**4b**	4-Me-C_6H_4	9	94	288-290	287-290 [iv]
3	**4c**	4-Cl-C_6H_4	10	95	256-258	258-260[iv]
4	**4d**	4-HO-C_6H_4	9.5	95	258-260	260-263[iv]
5	**4e**	4-MeO-C_6H_4	12	94	259-261	258-260[iv]
6	**4f**	4-N,N-$(CH_3)_2$	11	93	288-290	290-293[iv]
7	**4g**	4-F- C_6H_3	8.5	94	157-159	159-161[xxiii]
8	**4h**	4-Br- C_6H_4	9	93	256-258	255-256 [xxiii]
9	**4i**	3-Cl- C_6H_4	11	91	208-210	210-212[xxiii]
10	**4j**	2-Cl-C_6H_4	10	92	218-220	220-223[xxiii]
11	**4k**	2,4-$(Cl)_2$-C_6H_3	12	94	220-224	223-225[xxiii]
13	**4l**	3,4-$(Cl)_2$-C_6H_3	10.5	91	>290	>290[xxiii]
14	**4m**	4(CH_3)CH-C_6H_4	12	90	286-288	287-288[xxiv]

[a]Reaction conditions: Benzaldehyde (1 mmol), acetophenone (1 mmol), urea (1.5 mmol) and 10 mol % DBU under microwave irradiation at 90 °C, 750 MW. [b]Isolated yields.

Lastly, we explore the mechanistic approach of DBU catalyzed synthesis of 4,6-diphenyl-3,4-dihydropyrimidine-2 (1 *H*) one derivatives (**Scheme 3**). DBU act as base catalyst and in first step it abstract the proton form acetophenone and enolate formation was take place then this enolate will reacted with aromatic aldehyde and forms chalcone then reaction of urea with chalcone was enhanced by DBU which lead to formation of desire products (**4a-4m**).



Scheme 3 Plausible mechanism for synthesis of 4,6-diphenyl-3,4-dihydropyrimidine-2 (1*H*) one derivatives.

Experimental

All chemical were purchased from Aldrich chemical company and used without further purification. Microwave synthesizer (STARSYNTH Microwave having maximum out-put power of 1200 W) has been used for microwave irradiation. ^{1}H NMR spectra were recorded on Bruker Advance 400, in DMSO in presence TMS as an internal standard.^{13}C NMR spectra recorded on Bruker DRX-300 in DMSO as solvent. Mass spectra were recorded on water UPLC TQD Mass spectrometer, showing $M^{+\cdot}$ peak. Melting points were recorded in open capillary method and are uncorrected.

General experimental procedure.

A mixture of aromatic aldehyde (1 mmol), acetophenone (1 mmol), urea (1.5 mmol) and 10 mol % of DBU was taken in 50 dm^3 two necked round bottom flask. Then the reaction mixture was subjected to microwave irradiation at 750 W for the indicated time to afford the corresponding 4,6-diphenyl-3,4-dihydropyrimidine-2 (1*H*) one derivatives (Table 1). The progress of the reaction was monitored by TLC, after completion of reaction the reaction mass was pour on crushed ice filtered and the obtained products were crystallized from ethanol.

Spectral data of representative compound **4c** is given here.

4c (4-(4-chlorophenyl)-6-phenylpyrimidin-2(1*H*)-one) Colour: white crystals, Yield: 95%, , M.p.: 256-258°C; **^{1}H NMR** (400 MHz, $CDCl_3$-, δ ppm): 2.49 (bs, S, 2H), 6.38-6.94 (m, , 5H, Ar-H), 7.07 7.27- (m, 5H, Ar-H). **^{13}C NMR** (75 MHz, DMSO): δ.79.02, 97.30, 126.9, 128.9, 128.7, 129.7, 134.3, 137.4, 138.3, 164.0,165.2. **Mass** EI-MS *m*/*z* cal. 284.07, *m*/*z* obs. $[M^{+\cdot}+H] = 285.09$.

Conclusion

We have developed an efficient protocol for the synthesis of 4,6-diphenyl-3,4-dihydropyrimidine-2 (1*H*) one derivatives *via* cyclocondensation of aromatic aldehydes, acetophenone and urea. This protocol having advantages such as use of small amount of catalyst, short reaction time, excellent yield of products and environmentally benign method.

Acknowledgements

One of the Authors, MSS is honored by CSIR, New Delhi, bestowing him Emeritus scientist position, hence we acknowledges the CSIR authorities. The DSK also thanks to Head, Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad for providing laboratory facilities. The scanning help received from SAIF, CDIR, Lucknow is gratefully acknowledged.

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Received on August17, 2015.