Bio-compatible and efficient catalytic synthesis of 3, 4-dihydropyrimidin-2(*1H*)-ones and thiones in acidic medium

T. Durai Ananda Kumar[a,b], P. Soumya[a], C.V.S. Subrahmanyam[a,c] and K. Satyanarayana[d]

[a]*Department of Pharmaceutical Chemistry, Gokaraju Rangaraju College of Pharmacy, Hyderabad, 500 090, Andhra Pradesh, India.*

[b]*Research and Development Cell, JNT University, Hyderabad, 500 072, Andhra Pradesh, India.*

[c]*Faculty of Pharmacy, Osmania University, Hyderabad, 500 007, Andhra Pradesh, India*

[d]*R & D, Natco Pharma Ltd, Sanath Nagar, Hyderabad, 500 080, Andhra Pradesh, India.*

Abstract

A biocompatible, efficient and versatile PTC mediated synthesis of DHPMs is described in this communication. Excellent yield, short reaction path and easier isolation of products are the significant features of this protocol. All the biginelli products reported in this article require shorter reaction time (40-70 min). Application of this methodology for the large scale preparation was evaluated and found good.

Key words: Biginelli reaction; 3, 4-Dihydropyrimidin-2(*1H*)-ones; Phase transfer catalysts

Address for correspondence:

Sr Asst. Professor, Department of Pharmaceutical Chemistry, Gokaraju Rangaraju College of Pharmacy, Hyderabad, 500 090, Andhra Pradesh, India.
Tel: +91 98668 52707,
Mail ID: anandurai78@gmail.com

Introduction

Condensation of three or more reactants in a single event is termed as multi component condensation (MCC).[1] Biginelli reaction is most recognized MCCs generates 3, 4-dihydropyrimidin-2-one /2-thione (DHPMs) by condensing aldehyde, β-ketoester and urea / thiourea with catalytic amount of hydrochloric acid.[2] Biginelli DHPMs were reported as potent calcium channel blockers,[3] antihypertensives,[4] mitotic kinesin Eg5 inhibitors,[5] antivirals,[6] antibacterials,[7] analgesics,[8] anti-inflammatory agents[9] and antioxidants.[10] Conventional biginelli synthesis suffers with long reaction time (24-36 h), loss of sensitive functional groups and low yields.[11]

Several methods were developed to overcome the potential drawbacks mentioned above includes lewis acids,[12] bronsted acids,[13] metal salts,[14] ionic liquids,[15] polymers,[16] and solid supports.[17] Lewis acids ($InCl_3$, LiBr), bronsted acid-$KHSO_4$ and polymer amberlyst-15 causes skin irritation and eye irritation. BF_3OEt_2 and $CdCl_2$ are carcinogenic in nature, while $Ln(OTf)_3$, $InCl_3$ and $ZrCl_4$ are expensive and eco pollutants.

These facts demand the bio-compatible catalyst for the synthesis of DHPM. In search of an environmentally benign catalyst, phase transfer catalysts (PTC) were identified as an alternative. PTCs utility in the yield improvement reactions of medicinally important molecules is documented in literature.[18]

Prompted by these facts, we attempted the PTC mediated synthesis of 3, 4-dihydropyrimidin-2-ones/2-thiones (scheme-1). To the best of our knowledge, there is no report focusing on the study of effect of various parameters in the biginelli reaction. After many trials, the reaction conditions were optimized and applied for various aryl aldehydes. We envisioned the effect of two different PTCs (TBAB and BTEAC), reaction path and reaction medium. Among two catalysts tested, BTEAC was found to be high yielding catalyst (BTEAC>TBAB) with shorter reaction path. The solvent free reaction rendered excellent yield compared to other solvents examined. The utility of this protocol for the industrial scale preparation was also examined by conducting the reaction on large scale.

EXPERIMENT

Melting points were determined in DBK program melting point apparatus, expressed in ˚C and are uncorrected. Reactions were monitored by thin layer chromatography using aluminium backed plates coated with silica gel 60 F_{254}. The chromatograms were visualized under UV light (254 and 366 nm) and by staining with iodine. The IR spectra were recorded on Schimadzu IR affinity-1 spectrophotometer using DRS 8000 and expressed in cm^{-1}. ^1H NMR spectra was recorded on Advance 300 MHZ NMR spectrophotometer. The chemical shifts were reported as parts per million (δ ppm), using tetramethylsilane as an internal standard and deuterated chloroform as solvent.

Optimization of reaction conditions

The model reaction of cyclo-condensation of benzaldehyde (10 mmol), ethyl acetoacetate (20 mmol) and urea (20 mmol) was optimized. The impact of solvents (H_2O/ CH_3OH/ C_2H_5OH/ CH_3COCH_3 / $CH_3COOC_2H_5$ / THF) and catalysts (TBAB / BTEAC, 5, 10 and 15 mol%) in the reaction rate was investigated. The solvent free reaction also conducted to explore the impact of solvents. The condensation of multi fold concentrations of reactants (1-15 fold scale) was effected in view of investigating the scope of the protocol in large scale preparation.

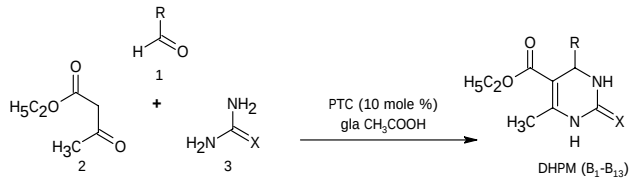
Typical procedure for the preparation of 3, 4-dihydropyrimidine-2-ones / 2-thiones (B_1-B_{13})

A mixture of aryl aldehyde **1** (10 mmol), ethyl acetoacetate **2** (20 mmol), ammonium acetate **3** (20 mmol) and PTC (TBAB / BTEAC, 10 mol%) was heated at 120°C with stirring (neat reaction) for appropriate time. After completion of the reaction (TLC monitoring), ethanol (2 mL) and crushed ice (10 g) were added to the mixture and kept aside for 1hr. The precipitated product was filtered and purified by recrystallization from ethanol. All the products are known and were identified by comparing with their reported m.p.

FT-IR and ^{1}H NMR data of compounds B_1 and B_2

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(*1H*)-one (B_1): FT-IR (KBr cm^{-1}): 3412, 3229, 1710, 1639; ^{1}H NMR (300 MHz): δ (ppm): 8.89 (s, 1H, NH), 7.34 (s, 1H, Ar), 7.12-7.23 (m, 5H, Ar), 5.18 (s, 1H, CH), 3.93 (q, J=6.88 Hz, 2H, CH_2CH_3), 2.22 (s, 3H, CH_2CH_3), 1.07 (s, 3H, CH_3).

5-Ethoxycarbonyl-6-methyl-4-(4-methoxy phenyl)-3,4-dihydropyrimidin-2(*1H*)-one (B_2): FT-IR (KBr cm^{-1}): 3238, 3113, 1700, 1637; ^{1}H NMR (300 MHz): δ (ppm): 8.39 (s,1H, NH), 7.23 (d, J=8.53 Hz, 2H, Ar), 6.84 (d, J=8.53 Hz, 2H, Ar), 5.94 (s, 1H, Ar), 5.94 (s, 1H, CH), 4.10 (d, J=6.88 Hz, 2H, CH_2CH_3), 3.78 (s, 3H, OCH_3), 2.32 (s, 3H, CH_2CH_3), 1.16 (s, 3H, CH_3).



Scheme-1: PTC mediated synthesis of biginelli compounds (B_1-B_{13}).

Results and discussion

Condensation of benzaldehyde, ethyl acetoacetate and urea to compound B_1 was considered as a model reaction for optimization purpose. The reactions were performed by varying parameters such as different solvents, changing reaction time and catalyst loading. Initial studies were focused on the effect of different solvents (H_2O, CH_3OH, C_2H_5OH, CH_3COOH, CH_3COCH_3, $CH_3COOC_2H_5$, and THF) and the results were summarized in Table 1. Solvent free reaction afforded higher yield of compound B_2 (67% with TBAB, 83% with BTEAC, Table 1, entry 8). Acetic acid reaction offered comparatively higher yield (Table 1, entry 5), however, reactions with ethanol, methanol and acetone led to lower yields (Table 1, entries 2-4) and reactions in water, ethyl acetate and THF did not succeed (Table 1, entries 1, 6, 7).

Table 1: Investigation of effect of different solvents

Entry	Solvent	Yield (%)	
		TBAB	BTEAC
1	Water	0	0
2	Methanol	15	20
3	Ethanol	20	30
4	Acetone	10	12
5	Acetic acid	67	78
6	Ethyl acetate	0	0
7	THF	0	0
8	Neat reaction	75	86

Further the study was focused on the effect of different concentrations of catalysts. Both the PTCs generated higher yields of compounds B_1 and B_2 in 10 mol% concentration (Table 2, entry 2) and no significant yield improvement were observed with increase in concentration.

Considering the overall effects of solvents, reaction path and catalyst loading, the optimum condition for the condensation was considered as use of BTEAC (10 mol%) and acetic acid as medium.

Table 2: Investigation of effect of catalyst loading

Entry	Catalyst loading (mol %)	Yield (%)	
		TBAB	BTEAC
1	5	39	55
2	10	67	83
3	15	57	61

Table 3: BTEAC promoted synthesis of 3, 4-dihydropyrimidin-2(*1H*)-ones/thiones [B_1-B_{13}].

Cmpd	Substitution		Yield (%)	m.p (°C)	
Code	R	X		Observed	Reported [Reference]
B_1	C_6H_5	O	83	200-202	202-204 [19]
B_2	p-OCH_3-C_6H_4	O	80	198-200	199-201 [19]
B_3	C_6H_5	S	66	208-210	208-209 [17]
B_4	p-OCH_3-C_6H_4	S	68	148-150	150-152 [19]
B_5	p-Cl-C_6H_4	O	71	210-211	210-212 [19]
B_6	p-Cl-C_6H_4	S	65	178-180	180-182 [19]
B_7	p-OH-C_6H_4	O	75	223-225	225-226 [12]
B_8	p-OH-C_6H_4	S	42	190-192	193-194 [13]
B_9	o-NO_2-C_6H_4	O	70	208-210	206-208 [17]
B_{10}	o-NO_2-C_6H_4	S	43	188-190	190-192 [17]
B_{11}	3,4,5$(OCH_3)_3$-C_6H_2	O	92	191-193	180-182 [20]
B_{12}	2,4$(Cl)_2$-C_6H_3	O	95	238-240	238-240 [17]
B_{13}	3-OCH_3,4-OH-C_6H_3	O	49	229-231	231-232 [12]

m.p: Melting point; BTEAC: Benzyl Tri Ethyl Ammonium Chloride

The substrate scopes of this optimized condition were explored by utilizing this approach in the formation of biginelli compounds B_2-B_{13} with varying reaction duration (Table 3). The utility of this reaction in industrial scale preparations was evaluated by large scale preparation (Table 4).

Table 4: Large scale preparation of B_1

Entry	Reactants	Yield (%)
1	1 Fold	83
2	2 Fold	78
3	5 Fold	73
4	10 Fold	69
5	15 Fold	63

1 fold: benzaldehyde-7.5mmol; ethyl acetoacetate-7.5 mmol; urea-9 mmol; acetic aci- 8 ml; BTEAC-10 mol%

All the biginelli products reported in this communication require shorter reaction time (40-70 min). The desired products were obtained in good to excellent yields. The reactions worked well with electron donating and electron withdrawing aryl aldehydes as well as heterocyclic ones.

Conclusion

Our new eco benign approach reported here in involves the use of BTEAC for the biginelli condensation (neat reaction). Shorter reaction time, high yields and simple isolation (non-chromatographic method) are the significant features of this protocol. This newer protocol will find application in pharmaceutical industries for the synthesis of medicinally important DHPMs.

References

1. Kalinski, C.; Lemoine, H.; Schmidt, J.; Burdack, C.; Kolb, J.; Umkehrer, M.; Ross, G. *Synthesis* **2008**, 24, 4007.

2. Biginelli, P. *Gazz. Chim. Ital.* **1893,** 23, 360.

3. Rovnyak, G.C.; Kimball, S.D.; Beyer, B.; Cucinotta, G.; Dimarco, J.D.; Gougoutas, J.; Hedberg, A.; Malley, M.; McCarthy, J.P.; Zhang, R.; Moreland, S. *J. Med. Chem*. **1995**, 38, 119.

4. Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M; Moreland, S.; Hedberg, A.; O'Reilly, B. *J. Med. Chem.* **1991**, 34, 806.

5. Kappe, C. O. Shishkin, O. V.; Uray, G.; Verdino, P. *Tetrahedron* **2000**, 56, 1859.

6. Kappe, C. O. *Eur. J. Med. Chem.* **2000**, 35, 1043.

7. Chitra, S.; Devanathan, D.; Pandiarajan, K. *Eur. J. Med. Chem.* **2010**, 45, 367.

8. Chikhale, R.V.; Bhole, R.P.; Khedekar, P. B.; Bhusari, K. P. *Eur. J. Med. Chem.* **2009**, 44, 3645.

9. Amir, M.; Javed, S. A.; Kumar, H. *Acta. Pharm*. **2008**, 58, 467.

10. Ismaili, L.; Nadaradjane, A.; Nicod, L.; Guyon, C.; Xicluna, A. *Eur. J. Med. Chem*. **2008**, 43, 1270.

11. Ahmed, B.; Khan, R. A.; Habibullah.; Kashari, M. *Tetrahedron Lett*. **2009**, 50, 2889.

12. Lu, J.; Bai, J. *Synthesis* **2002**, 4, 466.

13. Reddy, C. V.; Mahesh, M.; Raju, P. V. K.; Babu, T. R.; Reddy, V. V. N. *Tetrahedron Lett*. **2002**, 43, 2657.

14. Tu, S.; Fang, F.; Zhu, S.; Li, T.; Zhang, X.; Zhuang, Q. *J. Heterocycl. Chem*. **2004**, 41, 253.

15. Ma, Y.; Qian, C.; Wang, L.; Yang, M. *J. Org. Chem.* **2000**, 5, 3864.

16. Kappe, C. O.; Kumar, D.; Varma, R. S. *Synthesis* **1999**, 10, 1799.

17. Bigi, F.; Carloni, S.; Frullanti, B.; Maggi, R.; Sartori, G. *Tetrahedron Lett.* **1999**, 40, 3465.

18. Tamaddon, F.; Razmi, Z.; Jafari, A. A. *Tetrahedron Lett.* **2010**, 51, 1187.

19. Heravi, M. M.; Derikvand, F.; Bamoharram, F. F. *J. Mol. Catal. A: Chem.* 2005; 242: 173.

20. Gangadasu, B.; Narender, P.; Raju, B. C.; Rao, V. J. *Indian J. Chem*. **2006**, 45B, 1259.