BIGINELLI REACTIONS IN MOLTEN AMMONIUM BROMIDES

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Abstract:3,4-Dihydropyrimidin-2(1H)-ones were synthesized in good yields by solvent-free one-pot three-component Biginelli condensation in the presence of molten tetrabutylammonium bromide or ammonium bromide as catalyst,irrespective of the presence of electron donating or electron withdrawing groups aromatic aldehydes.

INTRODUCTION

The Biginelli reaction was first reported more than a century ago (1) and involved the synthesis of 3,4-dihydropyrimidin-2(1H)-one (DHPM) by a very simple one-pot condensation reaction of benzaldehyde 1, urea 2 and ethyl acetoacetate 3 in ethanol. This reaction played an important role in organic and medicinal chemistry due to the importance of the resulting dihydropyrimidinone products. However, this one-pot, one-step protocol often provides only low to moderate yields of the desired target molecules 4, in particular when substituted aromatic or aliphatic aldehydes are employed. In the past decade, it was demonstrated that these dihydropyrimidine derivatives exhibited important pharmacological properties (2), for example, by serving as the integral backbones of several calcium channel blockers, antihypertensive agents, α-1a-antagonists and neuropeptide Y (NPY) antagonists. In addition, several marine alkaloids containing the dihydropyrimidinone-5-carboxylate motifs also showed interesting biological activities (3-5). Therefore, the discovery of milder and practical routes for the synthesis of dihydropyrimidin-2(1H)-ones by the Biginelli reaction continues to attract the attention of researchers. The development of several new synthetic strategies have, therefore, being developed, for example, lewis acid (6), fluoroboric acid (7), molybdophosphoric acid (8), potassium hydrogen sulfate (9), p-toluenesulfonic acid (10), boric acid (11), lanthanide triflate (12), bismuth(III) nitrate (13), iodine (14), CuI (15), clay catalysis (16), fluorapatite (17) and phase transfer catalyst (18a,b) and have been found to be effective. However, some of these methods require the use of unfriendly or expensive reagents, stoichiometric amounts of catalysts, strongly acidic conditions and incompatibility with other functional groups. The Biginelli reaction can occur more smoothly under microwave irradiation heat in the 3 presence of ferric chloride or TsOH as the catalyst and dry acetic acid (19) and using room temperature ionic liquids (20).

In the recent past, tetrabuthylammonium bromide (TBAB) is emerging as an effetive phase transfer catalyst for various organic reactions. We sought to explore the possibilty of TBAB as catalyst for Biginelli reaction. In this paper, we describe a

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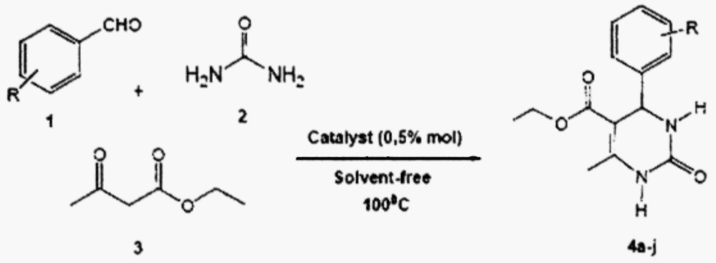
general and practical route for the Biginelli cyclocondensation reaction using TBAB and NH4Br as catalysts under solvent-free condition and a comparative study has been carried out for evaluation of the catalysts (scheme 1).



Scheme 1.Biginelli reaction

RESULTS AND DISCUSSION

The results described in the table 1 indicate the scope and generality of the method, which is very efficient. Use of just 0.5% mol of TBAB or NH4Br is sufficient to push the reaction into completion with good yield. In this series it is also described a new dihydropyrimidin-2(1H)-one carrying a sulfonyl group 4f that is commonly present in many compounds having pharmacological activities.

Table 1. NH4Br and TBAB catalyzed Biginelli reactions under solvent-free condition[a,b]

Entry	R-CHO	Urea	DHPM	Catalyst	Yieldc (%)
1.	4-Br-C6H4	O	4a	TBAB	80
2.	3-Cl-C6H4	O	4b	TBAB	76
3.	3-F-C6H4	O	4c	TBAB	77
4.	4-NO2-C6H5	O	4d	TBAB	85
5.	4-N(CH3)2-C6H4	O	4e	TBAB	54
6.	4-SO2CH3-C6H4	O	4f	TBAB	72
7.	4-CF3-C6H4	O	4g	TBAB	68
8.	3,4-OCH2OC6H3	O	4h	TBAB	66
9.	4-NO2-C6H5	S	4i	TBAB	80
10.	3-Cl-C6H4	S	4j	TBAB	73
11.	4-Br-C6H4	O	4a	NH4Br	85
12.	3-Cl-C6H4	O	4b	NH4Br	92
13.	3-F-C6H4	O	4c	NH4Br	83
14.	4-NO2-C6H	O	4d	NH4Br	97
15.	4-N(CH3)2-C6H4	O	4e	NH4Br	79
16.	4-SO2CH3-C6H4	O	4f	NH4Br	90
17.	4-CF3-C6H4	O	4g	NH4Br	85
18.	3,4-OCH2OC6H3	O	4h	NH4Br	80

19.	4-NO2-C6H5	S	4i	NH4Br	91
20.	3-Cl-C6H4	S	4j	NH4Br	88

[a] Reaction condition: aromatic aldehyde (5 mmol), urea (or thiourea) (15 mmol), ethylacetoacetate (5 mmol) and catalyst (0,5% mol) at 100^{0}C by 1 h.

[b] All products were characterized by FT-IR, ^{1}H NMR and their melting points in comparison with literature. For 4f see note 21.

[c] Isolated yields.

Our results using TBAB gave moderate to good yields (entries 1-10), while using NH4Br as catalyst gave excellent yields (entries 11-20). The new DHPM 4f was characterized by 1H NMR, 13C NMR and IR (21).

A similar but more expensive reagent benzyltriethylammonium chloride (TEBA) was previously reported in the Biginelli reaction yielding also good results [20b]. Other similar systems have previously been reported (20c) to be useful in Biginelli reaction but in principle the present systems appears to be more tolerant (and cheap) to a variety of substrates. The reaction can be carried out in a one-pot fashion in the presence of a catalytic (sub-stoichiometric) amount of NH4Br or TBAB under solvent-free conditions. This method not only preserved the simplicity of Biginelli's onepot procedure but also remarkably improved the yields of dihydropyrimidinones in shorter reaction times compared previous methods. However, since the behavior of these salts as ionic liquids was considered by Calo and coworkers (20d) care must be taken when analyzing the present results.

The results presented in the table 1 demonstrated that as TBAB as NH4Br were very satisfactory in the utilized conditions, furnishing DHPMs with good to high yields, independent of the functional groups. The novel DHPM 4f (entries 6 and 14) was obtained with good yield when utilized TBAB and high yield with NH4Br. To test the effect of catalyst in solvent, Biginelli reaction of 4-nitrobenzaldehyde, 3-chlorobenzaldehyde and piperonal at the same condition was carried out using water as solvent and TBAB as phase transfer catalyst. The results obtained were unsatisfactory leading the formation of the respective DHPMs in lower yields.

Kappe reported that the mechanism of the reaction may proceed through the formation of an imine intermediate formed by reaction of the aldehyde with urea, wich is the key rate-determining step (22). The formed iminium ion added to ethyl acetoacetate in the presence of TBAB-catalyst or NH4Br-catalyst producing an open chain ureide followed by cyclization and dehydration would afford the dihidropyrimidinone.

CONCLUSION

In summary, we have developed a simple and efficient method for the direct preparation of substituted dihydropyrimidinones using molten tetrabuthylammonium bromide or ammonium bromide as reaction media in good yields from readily available starting materials with good tolerance to different functional groups. In particular, aromatic aldehydes containing electron withdrawing or electron donating groups can be used in this protocol.

EXPERIMENTAL

Syntheses of 3,4-dihydropyrimidin-2(1H)-ones were carried out with two different catalysts under solvent-free condition. Initially, the reaction was carried out using TBAB as catalyst with aromatic aldehydes, urea or thiourea and ethyl acetoacetate. The same condition was employed to NH4Br.

2.1 Procedure for synthesis of 3,4-dihydropyrimidin-2(1H)-ones using catalyst under solvent-free

In a 25 ml round bottom flask, aromatic aldehyde (5 mmol), urea (or thiourea) (15 mmol), ethyl acetoacetate (5 mmol) and the catalyst (0,5% mol) were mixed in a one-pot condensation employing heat at 1000C for 1 h. After the reaction was completed, the reaction mixture was poured into ice water. The crude product was further purified by recristallization from ethanol to afford pure dihydropyrimidinones **4aj**.

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REFERENCES

1 P. Biginelli, Gaz. Chim. Ital. 23, 360 (1893).

2 C. O. Kappe, Acc. Chem. Res. 33, 879 (2000).

3 M. Gartner, N. Sunder-Plassmann, J. Seiler, M. Utz, I. Vernos, T. Surrey, A. Giannis, Chem. BioChem. 6, 173 (2005).

4 C. D.Cox, M. J. Breslin, B. J. Mariano, P. J. Coleman, C. A. Buser, E. S. Walsh, K. Hamilton, H. E. Huber, N. E. Kohl, M. Torrent, Y. Yan, L. C. Kuo, G. D. Hartman, Bioorg. and Med. Chem. Lett. 15, 2041 (2005).

5 C. O. Kappe, Eur. J. Med. Chem. 35, 1043 (2000).

6 J. Li, S. Wang, G. Chen, T. Li, Curr. Org. Synth. 2, 415 (2005).

7 W. Chen, S. Qin, J. Jin, Catal. Commun. 8, 123 (2007).

8 M.M. Heravi, K. Bakhtiari, F. F. Bamoharram, Catal.Commun.7, 373 (2006).

9 S. G. Tu, F. Fang, S. Zhu, T. Li, X. Zang, O. Zhuang, Synlett 537 (2004).

10 A. K. Bose, M. S. Manhas, S. Pednekar, S. N. Ganguly, H. Dang, W. He, A. Mandadi, Tetrahedron Lett. 46, 1901 (2005).

11 S. Tu, F. Fang, C. Miao, H. Jiang, Y. Feng, D. Shi, X. Wang,Tetrahedron Lett. 44, 6153 (2003).

12 Y. Ma, C. Qian, L. Wang, M. Yang, J. Org. Chem. 65, 3864 (2000).

13 M. A. Chari, D. Shobha, T. K. Kumar, P. K. Dubey, Arkivoc (xv), 74 (2005).

14 R. S. Bhosale, S. V. Bhosale, S. V. Bhosale, T. Wang, P. K. Zubaidha, Tetrahedron Lett. 45, 9111 (2004).

15 H. R. Kalita, P. Phukan, Catal. Commun. 8, 179 (2007).

16 V. F. Ferreira, M. C. B. V. Souza, R. S. Rianelli, F. C. Silva, O. A. C. Antunes, Recent Advances in Clay-Catalyzed Synthesis of Heterocycles, Ed., Focus in Catalysis Research, New Science Publishers, NY, 2005, pp 147- 175.

17 H. E. Badaoui, F. Bazi, R. Tahir, H. B. Lazrek, S. Sebti, Catal. Commun. 6, 455 (2005)

18 (a) K. R. Reddy, C. V. Reddy, M. Mahesh, P. V. K. Raju, N. Reddy, Tetrahedron Lett. 44, 8173 (2003). (b) E. S. Putilova, G. V. Kryshtal', G. M. Zhdankina, N. A. Troitskii, S. G. Zlotin, Russian, J. Org. Chem. 41, 512 (2005).

19 Microwave-assisted Biginelli reactions:(a) V. R. Choudhray, V. H. Tillu, V. S. Narkhede, H. B. Borate, R. D. Wakharkar, Catal. Commun. 4, 449 (2003). (b) J. Wannberg, D. Dallinger, C. O. Kappe, M. J. Larhed, Comb. Chem. 7, 574

(2005). (c) J. Legeary, J. J. V. Eynde, J. P. Bazureau, Tetrahedron 61, 12386 (2005). (d) M. S. Manhas, S. N. Ganguly, S. Mukherjee, A. K. Jain, A. K. Bose, Tetrahedron Lett. 47, 2423 (2006). (e) S. J. Tu, J. F. Zhou, P. J. Cai, H. Wang, J. C. Feng, Synth. Commun. 32, 147 (2002). (f) M. Kidway, S. Saxena, R. Mohan, R. Venkataramanan, J. Chem. Soc., Perkin Trans. 1, 1845 (2002).

20 (a) J. Peng, Y. Deng, Tetrahedron Lett. 42, 5917 (2001). (b) D. S. Bose, M. Sudharshan, S. W. Chavhan, Arkivoc (iii), 228 (2005). (c) A. Shaabani, A. Bazgir, S. Arab-Ameri, Phosphurus, Sulphur and Silicon 179, 2169 (2004). (d) V. Calo, A. Nacci, A. Monopoli, S. Laera, N. Cioffi, J. Org. Chem. 68, 2929 (2003).

21 All products (except 4f) are known compounds, characterized by mp, IR and 1H NMR spectral data. 4f : mp 207-2080C. IR cm-1 3315, 3103, 2926, 1718, 1697, 1650, 1308, 1146. 1H NMR (DMSO-d6) δ 1.06 (t, 3 H), 3.25 (s, 3 H), 3.50 (s, 3 H), 4.01 (q, 2 H), 5.24 (s, 1 H), 7.41 (d, 2 H), 7.59 (d, 2 H), 9.31 (s, 2 H). 13C NMR (DMSO-d6) δ14.1, 17.9, 18.6, 43.6, 53.8, 59.4, 98.5, 127.3, 139.7, 149.2, 150.3, 151.9, 165.2.

22 C. O. Kappe, S. F. Falsone, Synlett, 718 (1998).

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