Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 2757–2758

TETRAHEDRON
LETTERS

One-pot synthesis of dihydropyrimidinones catalysed by lithium bromide: an improved procedure for the Biginelli reaction

Gourhari Maiti,[a,]* Pradip Kundu[a] and Chandrani Guin[b]

[a]*Department of Chemistry, Jadavpur University, Jadavpur, Calcutta 700 032, India*
[b]*Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta 700 032, India*

Received 17 September 2002; revised 5 December 2002; accepted 13 December 2002

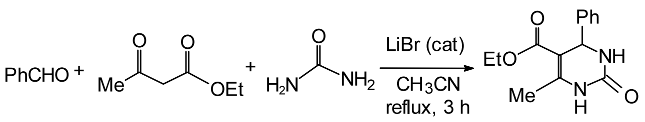
Abstract—LiBr catalyses efficiently the three component condensation reaction of an aldehyde, a β-ketoester and urea in refluxing acetonitrile to afford the corresponding dihydropyrimidinones in high yield. © 2003 Published by Elsevier Science Ltd.

4-Aryldihydropyrimidinones (denoted as Biginelli compounds) are known to exhibit a wide range of biological activities[1] such as antiviral, antitumour, antibacterial and anti-inflammatory actions. Many of them are pharmacologically important since they behave as calcium channel blockers, antihypertensive agents and α_1-1-a-antagonists.[2] Biological activities of some marine alkaloids isolated recently have been attributed to the presence of a dihydropyrimidinone moiety.[3] The simple and direct method for the synthesis of dihydropyrimidinones reported first by Biginelli in 1893, involves the one-pot condensation of an aldehyde, a β-ketoester and urea under strongly acidic conditions,[4] suffers from low yields of products in the cases of substituted aromatic and aliphatic aldehydes.[5] Subsequent multi-step syntheses[6] afford somewhat higher yields but these do not have the simplicity of the original one-pot Biginelli protocol. The art of performing efficient chemical transformations, which involve the coupling of three or more components in a single operation by catalytic means avoiding stoichiometric toxic reagents, large amounts of solvents and extensive purification techniques, represents a fundamental target of modern organic synthesis. So, the Biginelli reaction continues to merit attention to discover a simple, milder and efficient one-pot procedure for the synthesis of dihydropyrimidinones.

Recently, several improved procedures have been reported[7] using Lewis acids as well as protic acids as promoters. However in spite of their potential utility, many of these methods involve expensive reagents, stoichiometric amounts of catalysts, strongly acidic conditions, long reaction times, unsatisfactory yields, and incompatibility with other functional groups. Therefore, the development of a neutral alternative would extend the scope of the Biginelli reaction. LiBr is a unique mild Lewis acid which has a wide variety of utility in different chemical transformations[8] such as Friedel–Crafts acylation, the preparation of acylals, transesterification, rearrangement of epoxides, the Knovenagel condensation, etc. We wish to report here a simple and efficient method for the synthesis of dihydropyrimidinones using LiBr as catalyst.

As a representative example, the reaction of benzaldehyde (1.0 mmol), ethyl acetoacetate (1.2 mmol) and urea (1.2 mmol) in the presence of 10 mol% LiBr in refluxing acetonitrile (5 ml) for 3 h furnished the corresponding dihydropyrimidinone[9] in 92% yield (Scheme 1). Thus, a series of dihydropyrimidinones and thioderivatives were prepared in good yields as summarised in Table 1.

Aromatic aldehydes, carrying either electron-withdrawing or electron-donating substituents, afforded high yields of products with high purity. Furfural, an acid sensitive aldehyde, worked well without formation of any side product. Another important feature of this procedure is the survival of a variety of functional groups such as ether, nitro, hydroxy, halides, unsatura-



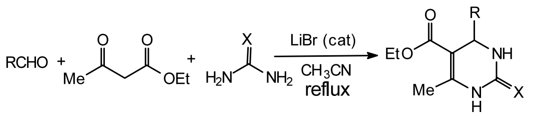
Scheme 1.

Keywords: dihydropyrimidinones; lithium bromide; Biginelli reaction.

* Corresponding author. E-mail: ghmaiti123@yahoo.com

0040-4039/03/$ - see front matter © 2003 Published by Elsevier Science Ltd.
doi:10.1016/S0040-4039(02)02859-9

Table 1. LiBr-catalysed formation of dihydropyrimidinones and thio-derivatives



Entry	R	X	Time (h)	Yield (%)
1	C_6H_5	O	3.0	92
2	4-(MeO)C_6H_4	O	3.25	94
3	3,4-$(MeO)_2C_6H_3$	O	3.0	93
4	4-(HO)-3-(MeO)C_6H_3	O	3.0	91
5	4-(Cl)C_6H_4	O	4.5	86
6	4-(O_2N)C_6H_4	O	5.0	93
7	3-(HO)C_6H_4	O	5.0	88
8	2-(HO)C_6H_4	O	4.75	82
9	1-Naphthyl	O	3.5	94
10	*n*-Pentyl	O	4.0	72
11	2-Furfuryl	O	4.5	85
12	3,4-Methylenedioxyphenyl	O	3.5	91
13	Cinnamyl	O	5.0	81
14	C_6H_5	S	3.0	85
15	4-(MeO)C_6H_4	S	3.5	88
16	3,4-Methylenedioxyphenyl	S	3.5	87
17	4-(Cl)C_6H_4	S	4.0	81

tion, etc, under the reaction conditions. Thiourea has been used with similar success to provide the corresponding thio-derivatives of dihydropyrimidinones which are also of much interest with respect to their biological activities. This method utilises readily available low cost reagents affording high yields of dihydropyrimidinones, in short reaction times, for a variety of compounds.

In conclusion, we have developed a new methodology for the synthesis of dihydropyrimidinones by three-component condensation in one pot using a catalytic amount of LiBr. Mild reaction conditions, elevated product yields, enhanced reaction rates, compatibility with various functional groups and a simple experimental procedure are the main advantages of this improved procedure over existing ones for the synthesis of various dihydropyrimidinones as well as the thio-derivatives.

Acknowledgements

We thank Professor S. C. Roy, Indian Association for the Cultivation of Science, Calcutta for his constant encouragement and kind help. Thanks are also due to Jadavpur University, Calcutta for financial assistance.

References

1. Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937–6963 and references cited therein.
2. (a) Atwal, K. S.; Rovnyak, G. C.; O'Reilly, B. C.; Schrartz, J. J. *J. Org. Chem.* **1989**, *54*, 5898–5907; (b) Kappe, C. O.; Fabian, W. M. F.; Semones, M. A. *Tetrahedron* **1997**, *53*, 2803–2816.
3. Snider, B. B.; Shi, Z. J. *J. Org. Chem.* **1993**, *58*, 3828–3839.
4. Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360–461.
5. (a) Folkers, K.; Johnson, T. B. *J. Am. Chem. Soc.* **1934**, 1180–1185; (b) Folkers, K.; Harwood, H. J.; Johnson, T. B. *J. Am. Chem. Soc.* **1932**, *54*, 3751–3758; (c) Wipf, P.; Conningham, A. *Tetrahedron Lett.* **1995**, *36*, 7819–7822.
6. (a) Atwal, K. S.; O'Reilly, B. C. *Heterocycles* **1987**, *26*, 1185–1188; (b) Atwal, K. S.; O'Reilly, B. C.; Gougoutas, J. Z.; Malley, M. F. *Heterocycles* **1987**, *26*, 1189–1192; (c) Shutalev, A. D.; Kishko, E. A.; Sivova, N.; Kuznetsov, A. Y. *Molecules* **1998**, *3*, 100.
7. (a) Hu, E. H.; Sidler, D. R.; Dolling, U. H. *J. Org. Chem.* **1998**, *63*, 3454–3457; (b) Kappe, C. O.; Falsone, S. F. *Synlett* **1998**, 718–720; (c) Ranu, B. C.; Hajra, A.; Jana, U. *J. Org. Chem.* **2000**, *65*, 6270–6272; (d) Lu, J.; Ma, H. *Synlett* **2000**, 63–64; (e) Bigi, F.; Carloni, S.; Frullanti, B.; Maggi, R.; Sartori, G. *Tetrahedron Lett.* **1999**, *40*, 3465–3468.
8. (a) Ono, F.; Negoro, R.; Sato, T. *Synlett* **2001**, 1581–1583; (b) Pushin, A. N.; Tkachenoko, S. E.; Martynov, I. V. *Dokl. Akad. Nauk SSSR* **1988**, *299*, 154–158; (c) Firouzabadi, H.; Iranpoor, N.; Karimi, B. *Synthesis* **1999**, 58–60; (d) Seebach, D.; Thaler, A.; Blaser, D.; Ko, S. Y. *Helv. Chim. Acta* **1991**, *74*, 1102–1118; (e) Prajapati, D.; Lekhok, K. C.; Sandhu, J. C.; Ghosh, A. C. *J. Chem. Soc., Perkin Trans. 1* **1996**, 959–960.
9. **Typical procedure**: A solution of ethyl acetoacetate (156 mg, 1.2 mmol), veratraldehyde (166 mg, 1.0 mmol) and urea (72 mg, 1.2 mmol) in acetonitrile (5 ml) was heated under reflux in the presence of a catalytic amount of LiBr (9 mg, 10 mol%) for 3 h (completion of the reaction was monitored by TLC). The reaction mixture was then poured onto crushed ice and the solid product separated was filtered and recrystallised from methanol to afford ethyl 4-(3,4-dimethoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (entry 3, Table 1). Mp 176°C, IR (KBr), ν_{max}: 3251, 3116, 1722, 1708, 1641 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz) δ 1.21 (t, $J=7.0$ Hz, 3H), 2.26 (s, 3H), 3.70 (s, 6H), 4.01 (q, $J=7.0$ Hz, 2H), 5.13 (d, $J=3.2$ Hz, 1H), 6.74 (dd, $J=8.3$, 1.9 Hz, 1H), 6.85 (d, $J=1.9$ Hz, 1H), 6.90 (d, $J=8.3$ Hz, 1H), 7.67 (s, 1H, NH), 9.14 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 14.94, 18.53, 54.30, 56.22, 60.20, 100.43, 111.21, 112.53, 118.77, 138.03, 148.86, 148.89, 149.25, 153.20, 166.39. MS *m*/*z* (%) 321 (86) (M^++1), 320 (65), 291 (41), 183 (100), 154 (97), 136 (87), 107 (54). All other products were characterised by spectral (NMR and IR) data and by comparison with those of authentic samples and also by the mixed-melting points with the authentic samples.