Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 8173–8175

TETRAHEDRON LETTERS

New environmentally friendly solvent free synthesis of dihydropyrimidinones catalysed by *N*-butyl-*N*,*N*-dimethyl-α-phenylethylammonium bromide☆

K. Rosi Reddy, Ch. Venkateshwar Reddy, M. Mahesh, P. V. K. Raju and V. V. Narayana Reddy*

Organic Chemistry Division II, Indian Institute of Chemical Technology, Hyderabad 500 007, India

Received 26 June 2003; revised 21 August 2003; accepted 1 September 2003

Abstract—*N*-Butyl-*N*,*N*-dimethyl-α-phenylethylammonium bromide catalyzes efficiently the three component condensation reaction of an aromatic aldehyde, a β-keto ester and urea/thiourea under solvent free conditions at 100°C to afford the corresponding dihydropyrimidinone in high yield.

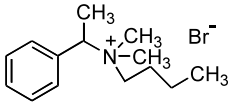
Dihydropyrimidinones and their derivatives have attracted great attention recently in synthetic organic chemistry due to their pharmacological and therapeutic properties such as antibacterial and antihypertensive activity as well as behaving as calcium channel blockers, α-1a-antagonists[1] and neuropeptide Y (NPY) antagonists.[2] The biological activity of some alkaloids isolated recently has been attributed to a dihydropyrimidinone moiety.[3] The first procedure to these compounds reported by Biginelli[4] more than a century ago makes use of the three component, one-pot condensation of a β-ketoester, an aldehyde and urea under strongly acidic conditions.[5] However this method suffers from low yields in the case of substituted aromatic and aliphatic aldehydes.[6] Owing to the versatile biological activity of dihydropyrimidinones, development of an alternative synthetic methodology is of paramount importance.

This has led to the development of several new synthetic strategies involving combinations of Lewis acids and transition metal salts, e.g. BF_3–OEt_2,[7] montmorillonite (KSF)[8] polyphosphate esters[9] and reagents like $InCl_3$,[10] LiBr,[11] TMSCl/NaI,[12] $LaCl_3{\cdot}7H_2O$,[13] $CeCl_3{\cdot}7H_2O$,[14] $Mn(OAc)_3{\cdot}2H_2O$,[15] which give better yields of dihydropyrimidinones.

Most of these reagents are expensive. More recently Ahmad Shabani et al.[16] reported ammonium chloride as catalyst for this transformation under solvent-free conditions. Despite being described as a catalyst, ammonium chloride is used in molar equivalents with respect to the reactant (0.5:1.0). This prompted us to seek an alternative and solvent-free method of synthesis of these biologically significant compounds. Our efforts in evaluating a new class of trialkylammonium halides as phase transfer catalysts for the synthesis of homochiral synthetic pyrethroids, culminated in the identification of a new catalyst, *N*-butyl-*N*,*N*-dimethyl-α-phenylethylammonium bromide **I**, as an efficient PTC for alkylation, esterification, etc.[17]

Herein we wish to report the utilization of **I** as a catalyst in the one-pot, three-component Biginelli's reaction under solvent-free conditions. This method (Scheme 1) not only preserved the simplicity of Biginelli's one-pot procedure but also remarkably improved the yields (>86%) of dihydropyrimidinones in shorter reaction times (20–60 min) as against the longer reaction times required for other catalysts.

Three sets of experiments were conducted simultaneously using salt **I** or ammonium bromide as the catalyst, or neat, with no catalyst, at the same temperature and time. The results obtained are summarized in Table 1.



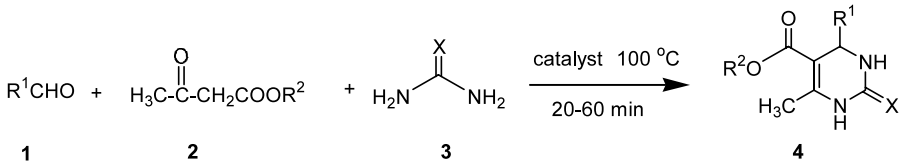
I

Keywords: *N*-butyl-*N*,*N*-dimethyl-α-phenylethylammonium bromide; β-ketoesters; Biginelli reaction; dihydropyrimidinones.

☆ IICT Communication No. 030610.

* Corresponding author. Fax: +91-40-27160387; e-mail: vaddu@iict.res.in

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.09.030



Scheme 1.

The three-component, cyclocondensation reaction may be performed under relatively simple reaction conditions by heating together the three components, an aldehyde, β-ketoester and urea/thiourea, in the ratio of 1:1:3 and the catalyst (0.35–0.50 mol%), to 100°C with stirring.[18] After the completion of the reaction, as indicated by TLC, the reaction mixture was poured onto crushed ice from which the dihydropyrimidinones were isolated by filtration and recrystallised from methanol/ethanol as indicated in Table 1.

The results presented in the Table indicate the scope and generality of the method, which is efficient, not only for urea or thiourea, but also for aliphatic as well as aromatic aldehydes. An important feature of this method is that electron releasing or withdrawing groups give excellent yields in high purity. It is pertinent to note that catalyst **I** gave consistently higher yields with aliphatic aldehydes, cf. entry **4u** as against the moderate yields[19] reported earlier.

Most of the catalysts used for preparation of dihydropyrimidinones are halogen containing Lewis acids. The present results indicate that the halide present in the catalyst may be playing a crucial role in these transformations and may assume significance in the wake of the large number of publications which have appeared recently for the synthesis of dihydropyrimidinones by modified Biginelli reactions using heavy metal halide catalysts. Maybe there is some doubt as to whether the reaction is catalyzed by Lewis acids via metal ion coordination or simply by the halide ions. Moreover, the reaction proceeds neat on prolonged reaction times without using solvents.

In conclusion, *N*-butyl-*N*,*N*-dimethyl-α-phenylethylammonium bromide has proved to be a catalyst for the synthesis of dihydropyrimidinones in excellent yields, with short reaction times, under solvent-free reaction conditions.

Table 1. *N*-Butyl-*N*,*N*-dimethyl-α-phenylethylammonium bromide-catalyzed formation of dihydropyrimidinones

Product (**4**)[a]	R^1	R^2	X	Time (min)	Yield (%)[b]			Melting point (°C)	
					A	B	C	Found[c]	Reported
4a	C_6H_5	C_2H_5	0	20	96	81	73	201	202.4[7]
4b	4-$CH_3C_6H_4$	C_2H_5	0	61	97	86	85	170	172[7]
4c	4-HOC_6H_4	C_2H_5	0	55	98	86	77	228	227–229[22]
4d	4-$CH_3OC_6H_4$	C_2H_5	0	45	96	88	75	202	201–202[7]
4e	4-ClC_6H_4	C_2H_5	0	25	87	81	72	210	213–215[7]
4f	2,5-$(CH_3O)_2C_6H_3$	C_2H_5	0	35	93	84	84	212	–
4g	3-$(C_6H_5O)C_6H_4$	C_2H_5	0	60	97	92	84	192	194[23]
4h	4-$NO_2C_6H_4$	C_2H_5	0	45	98	89	83	208	207–208[22]
4i	2-$NO_2C_6H_4$	C_2H_5	0	65	99	85	82	210	206–208[15]
4j	4-HO, 3-$CH_3OC_6H_3$	C_2H_5	0	35	96	91	73	233	232–233[4]
4k	3,4-$(CH_3O)_3C_6H_3$	C_2H_5	0	35	97	93	72	177	178[20]
4l	4-BrC_6H_4	C_2H_5	0	60	92	87	75	197	–
4m	C_6H_5	CH_3	0	30	98	87	81	210	209–212[7]
4n	4-$CH_3C_6H_4$	CH_3	0	60	98	85	80	203	204[21]
4o	4-ClC_6H_4	CH_3	0	40	97	86	79	205	204–207[7]
4p	4-HOC_6H_4	CH_3	0	45	99	90	80	230	–
4q	C_6H_5	C_2H_5	S	53	93	77	75	209	208–210[21]
4r	CH_3-$(CH_2)_5$	C_2H_5	0	55	93	86	75	152	151–152[20]
4s	CH_3-$(CH_2)_4$	C_2H_5	0	65	92	79	66	154	152–154[24]
4t	CH_3-$(CH_2)_8$	C_2H_5	0	65	91	78	68	170	–
4u	CH-$(CH_3)_2$	C_2H_5	0	25	86	64	52	170	170–172[22]

A: New catalyst (100°C).
B: NH_4Br (100°C).
C: Neat (100°C).
[a] All products were characterized by ^1H NMR, IR and mass spectroscopy
[b] Isolated and unoptimised yields
[c] Compounds **4a**–**l** recrystallised in ethanol. Compounds **4m**–**u** recrystallised in methanol and melting points were determined on a EDMUND BUHLER instrument and are uncorrected.

Acknowledgements

K.R.R. is thankful to the Director, IICT, for financial support. M.M. and Ch.V.R. thank the CSIR, New Delhi, for the award of fellowships.

References

1. (a) Atwal, K. S.; Rovnyak, G. C.; O'Reilly, B. C.; Schwartz, J. *J. Org. Chem.* **1989**, *54*, 5898–5907; (b) Kappe, C. O.; Fabian, W. M. F.; Semones, M. A. *Tetrahedron* **1997**, *53*, 2803–2816.
2. (a) Atwal, K. S.; Rovnyak, G. C.; Kimball, S. D.; Floyd, D. M.; Moreland, S.; Swanson, B. N.; Gougoutas, J. Z.; Schwartz, J.; Smillie, K. M.; Malley, M. F. *J. Med. Chem.* **1990**, *33*, 26292635; (b) Rovnyak, G. G.; Kimball, S. D.; Beyer, B.; Cucinotta, G.; DiMarco, J. D.; Gougoutas, J. Z.; Hedberg, A.; Malley, M. F.; McCarthy, J. P.; Zhang, R.; Moreland, S. *J. Med. Chem.* **1995**, *38*, 119–203 and references cited therein.
3. Snider, B. B.; Shi, Z. *J. Org. Chem.* **1993**, *58*, 3828–3839.
4. Biginelli, P. *Gazz. Chem. Ital.* **1893**, *23*, 360.
5. Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937–6963.
6. Barluenga, J.; Tomas, M.; Ballesteros, A.; Lopez, L. A. *Tetrahedron Lett.* **1989**, *30*, 4573–4576.
7. Hu, E. H.; Sidler, D. R.; Dolling, U. H. *J. Org. Chem.* **1998**, *63*, 3454–3457.
8. Bigi, F.; Carloni; Frullanti, B.; Maggi, R.; Sartori, G. *Tetrahedron Lett.* **1999**, *40*, 3465–3468.
9. Kappe, C. O.; Falsone, S. F. *Synlett* **1998**, 718–720.
10. Ranu, B. C.; Harja, A.; Jano, U. *J. Org. Chem.* **2000**, *65*, 6270–6272.
11. Partha, P. B.; Sunil, G.; Dipak, P.; Jagir, S. S. *Chem. Lett.* **2002**, *10*, 1038–1039.
12. Sabitha, G.; Kiran Kumar Reddy, G. S.; Srinivas Reddy, Ch.; Yadav, J. S. *Synlett* **2003**, 858–860.
13. Lu, J.; Bai, Y; Wang, Z; Yang, B; Ma, H. *Tetrahedron Lett.* **2000**, *41*, 9075–9078.
14. Subhas Bose, D.; Fatima Liyakat; Hari Babu, M. *J. Org. Chem.* **2003**, *68*, 587–590.
15. Kumar, K. A.; Kasthuraiah, M.; Reddy, C. S.; Reddy, C. D. *Tetrahedron Lett.* **2001**, *42*, 7873–7875.
16. Shaabani, A.; Bazgir, A.; Teimouri, F. *Tetrahedron Lett.* **2003**, *44*, 857–859.
17. Venkateshwar Reddy, Ch.; Mahesh, M.; Raju, P. V. K.; Narayana Reddy, V. V. *Synth. Commun.* **2002**, *32*, 2797–2802.
18. **General procedure for the preparation of *N*-butyl-*N*,*N*-dimethyl-α-phenylethylammonium bromide-catalyzed synthesis of dihydropyrimidinones 4**: A mixture containing the β-ketoester (10 mmol), aldehyde (10 mmol), urea or thiourea (30 mmol) and quaternary ammonium bromide salt (0.35 mol%) was heated at 100°C for the appropriate time as mentioned in Table 1. After completion of the reaction, as indicated by TLC, the reaction mixture was poured onto crushed ice, filtered and recrystallized from ethanol or methanol to afford pure product.
Spectroscopic data: **4f**: mp 212°C; ^{1}H NMR (80%$CDCl_3$+DMSO-d_6) δ 1.1 (t, $J=7.7$ Hz, 3H, OCH_2CH_3), 2.3 (s, 3H, 6-CH_3), 3.7 (s, 3H, 5′-OCH_3), 3.8 (s, 3H, 2′-OCH_3), 4.0 (q, $J=7.7$ Hz, 2H, OCH_2 CH_3), 5.57 (s, 1H, 4-H), 5.9 (s, br, 1H, 3-NH, D_2O exchangeable), 6.57 (d, $J=2.8$ Hz, 6′-H), 6.68 (dd, $J=2.8$, 8.2, 1H, 4′-H), 6.78 (d, $J=8.2$ Hz, 1H, 3′-H), 8.85 (s, br, 1H, 1-NH, D_2O exchangeable). FABMS: m/z (%) 321 (80) (M^+), 291 (22), 275 (16), 247 (14), 183 (16), 136 (100). IR (KBr) $\nu=3250$, 3190, 3000, 1700, 1650 cm^{-1}.
4l: mp 197°C; ^{1}H NMR (80%$CDCl_3$+DMSO-d_6) δ 1.19 (t, $J=7.0$ Hz, 3H, OCH_2CH_3), 2.21 (s, 3H, 6-CH_3), 3.9 (q, $J=7.0$ Hz, 2H, OCH_2CH_3), 5.18 (s, 1H, 4-H), 7.05 and 7.4 (ABq, $J=8.05$ Hz, 4H, 2′, 6′-H and 3′, 5′-H), 7.4 (s, br, 1H, 3-NH D_2O exchangeable), 8.9 (s, br, 1H, 1-NH, D_2O exchangeable). EIMS: m/z (%) 340 (12) (M^+), 309 (45), 183 (100), 169 (95), 137 (75). IR (KBr) $\nu=3210$, 3100, 2910, 1690, 1610 cm^{-1}.
4p: mp 230°C; ^{1}H NMR (80%$CDCl_3$+DMSO-d_6) δ 2.21 (s, 3H, OCH_2CH_3), 3.7 (s, 3H, $COOCH_3$), 5.05 and 5.07 (ss, 1H, 4-H), 5.2 (s, br, 1H, 3-NH, D_2O exchangeable) 6.6 (d, $J=8.3$ Hz, 2H, 3′, 5′-H), 6.9 (d, $J=8.3$ Hz, 2H, 2′, 6′-H Ar), 7.18 (s, br, 1H, OH D_2O exchangeable), 8.85 (s, br, 1H, 1-NH, D_2O exchangeable). EIMS: m/z (%) 262 (100) (M^+), 217 (75), 183 (50), 155 (40), 7.7 (30). IR (KBr) $\nu=3520$, 3230, 3150, 1705, 1690 cm^{-1}.
19. Lu, J.; Ma, H. *Synlett* **2000**, *1*, 63–69.
20. Yadav, J. S.; Reddy, B. V. S.; Reddy, K. B.; Raj, K. S.; Prasad, A. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1939–1941.
21. Fu, N. Y.; Yuan, Y. F.; Cao, Z.; Wang, S. W.; Wang, J. T.; Peppe, C. *Tetrahedron* **2002**, *58*, 4801–4807.
22. Folkers, K.; Harwood, H. J.; Johnson, T. B. *J. Am. Chem. Soc.* **1932**, *54*, 3751.
23. Yadav, J. S.; Subba Reddy, B. V.; Srinivas, R.; Venugopal; Ramalingam, T. *Synthesis* **2001**, *9*, 1341–1345.
24. Yadav, J. S.; Reddy, B. V. S.; Reddy, E. J.; Ramalingam, T. *J. Chem. Res. (S)* **2000**, 354–355.