Pergamon

Tetrahedron Letters 43 (2002) 2657–2659

TETRAHEDRON LETTERS

Zirconium(IV) chloride catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones†

Ch. Venkateshwar Reddy, M. Mahesh, P. V. K. Raju, T. Ramesh Babu and V. V. Narayana Reddy*

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

Received 28 November 2001; revised 3 January 2002; accepted 6 February 2002

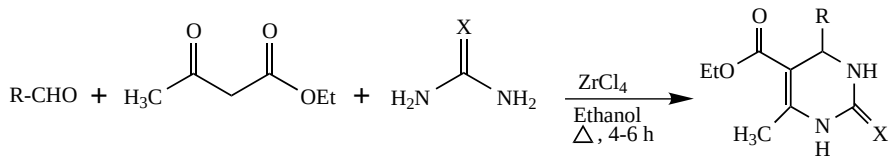
Abstract—Zirconium tetrachloride catalyzes efficiently the three component condensation reaction of an aromatic aldehyde, a β-ketoester and urea in refluxing ethanol to afford the corresponding dihydropyrimidinone in high yield.

Many dihydropyrimidinones (DHPMs) and their derivatives are pharmaceutically important as calcium channel blockers, antihypertensive agents and α_1-1-a-antagonists.[1] The biological activity of some alkaloids isolated recently has been attributed to the dihydropyrimidinone moiety.[2] The simple and direct method for the synthesis of dihydropyrimidinones reported by Biginelli in1893, involves the one-pot condensation of an aldehyde, a β-ketoester and urea under strongly acidic conditions.[3] However, this method suffers from low yields especially in the case of aliphatic and substituted aromatic aldehydes. This has led to the development of multistep synthetic strategies that produce somewhat better yields but lack the simplicity of the one-pot, one-step synthesis.[1,4,5]

Thus, Biginelli's reaction for the synthesis of dihydropyrimidinones has received renewed interest and several improved procedures have recently been reported.[3b,6] The use of zirconium(IV) chloride as an efficient Lewis acid for various transformations such as electrophilic amination of activated arenes,[7] transthioacetylization of acetals,[8] deoxygenation of heterocyclic-*N*-oxides,[9] reduction of nitro compounds,[10] conversion of carbonyl compounds to 1,3-oxathiolanes[11] and Friedel–Crafts reactions has been well documented in the literature.

Herein we wish to report a simple and efficient method for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones using zirconium tetrachloride as the catalyst. The reaction of benzaldehyde, ethyl acetoacetate and urea in the presence of 10 mol% zirconium(IV) chloride in refluxing ethanol gave the corresponding dihydropyrimidinone in 90% yield.[15] This one-pot synthesis is novel in the sense that it preserves the simplicity of Biginelli's one-pot reaction and improves the yields to an extent of 83–96% (Scheme 1).

It is interesting to note that when ethyl trifluoroacetoacetate is used as the β-ketoester in this synthesis, the hexahydropyrimidine (Scheme 2), considered to be an intermediate in the Biginelli reaction, was isolated in very good yields. This confirms the earlier report by



1 **2** **3** **4 a-m**

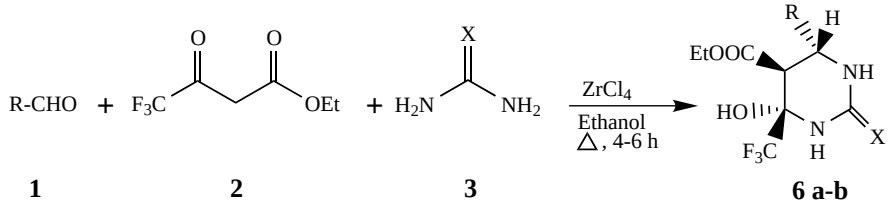
Scheme 1.

Keywords: zirconium tetrachloride; β-ketoesters; Biginelli reaction; dihydropyrimidinones.

* Corresponding author. Fax: 91-40-7160757; e-mail: vaddu@iict.ap.nic.in

† IICT Communication No. 011112.

0040-4039/02/$ - see front matter
PII: S0040-4039(02)00280-0



Scheme 2.

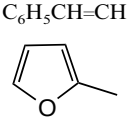
Kappe et al.[14] that in the ^{1}H NMR spectrum of **6b** the doublets at δ 2.91 and 4.71 with a coupling constant of 11.0 Hz are assignable to the 4-H and 5-H protons which are *trans* to each other. The isolation and characterization of this intermediate (**6b**) for the first time assumes significance in terms of confirming the mechanism of the reaction. It may be presumed that the OH group at C-6 may be *cis* to 5-H, thereby the elimination of water requires drastic conditions.

The three component condensation reactions proceeded smoothly in refluxing ethanol and were completed within 4–6 h. Many pharmacologically important moieties may be substituted on the aromatic ring with high efficiency under the zirconium tetrachloride catalyzed conditions. Aromatic aldehydes carrying either electron-donating or withdrawing substituents afforded high yields of products in high purity. Acid sensitive aldehydes such as furfural worked well without the formation of any side products. Besides its simplicity and mild reaction conditions, this method is effective for the preparation of DHPMs. Another important feature of this procedure is the survival of a variety of functional groups such as ether, nitro, hydroxy, halides, etc., under the reaction conditions. The advantage of the $ZrCl_4$ for this reaction lies in its simplicity. This method utilizes readily available reagents at low cost and also affords high yields of DHPMs in short reaction times.

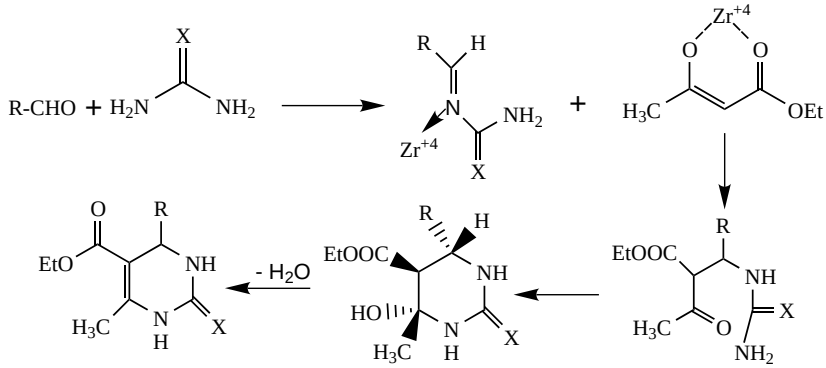
Thus, this procedure offers easy access to substituted dihydropyrimidinones with a variety of substitution patterns. Among the various solvents such as acetonitrile, methanol, THF and ethanol used for the transformation, ethanol and methanol were found to be the best. The results summarized in Table 1 reveal the scope and generality of the reaction with respect to various aldehydes, β-ketoesters and urea or thiourea. It is presumed that the reaction may proceed through the imine intermediate formed from the aldehyde and urea, stabilized by the zirconium ion followed by the addition of the β-ketoester enolate and cyclodehydration to afford the dihydropyrimidine (Scheme 3).

In conclusion, we have developed a simple and general method for the synthesis of dihydropyrimidinones using the inexpensive and easily available zirconium tetrachloride as catalyst. The method offers several advantages including high yields, short reaction times and a simple experimental workup procedure, which makes it a useful process for the synthesis of dihydropyrimidinones.

Table 1. $ZrCl_4$ catalyzed formation of dihydropyrimidinones

Product[a] (**4**)	R	X	Time (h)	Yield[b] (%)	Melting point (°C)	
					Observed	Reported
4a	C_6H_5	O	4	90	200–202	202[12]
4b	4-(Me)-C_6H_4	O	4	88	169–171	172[6]
4c	4-(OMe)-C_6H_4	O	5	97	198–200	201[12]
4d	4-(OH)-C_6H_4	O	5	98	198–200	–
4e	4-(Cl)-C_6H_4	O	6	95	210–212	212[12]
4f	4-(NO_2)-C_6H_4	O	6	88	206–208	209[12]
4g	4-(NMe_2)-C_6H_4	O	6	90	229–232	–
4h	4-(F)-C_6H_4	O	5	95	173–176	175[12]
4i	3-(OPh)-C_6H_4	O	4	96	192–194	194[13]
4j	C_6H_5CH=CH	O	6	83	229–232	232[13]
4k		O	6	84	203–205	205[13]
4l	C_6H_5	S	5	90	190–192	–
4m	4-(OH)-C_6H_4	S	4	95	193–194	–
6a	C_6H_5	O	6	80	160–162	–
6b	4-(OH)-C_6H_4	O	5	85	186–188	–

[a] All products were characterized by ^{1}H NMR, IR and mass spectroscopy.
[b] Isolated and unoptimized yields and melting points are uncorrected.



Scheme 3.

Acknowledgements

Ch.V.R. and M.M. are thankful to the Director, IICT, for financial support.

References

1. (a) Atwal, K. S.; Rovnyak, G. C.; O'Reilly, B. C.; Schwartz, J. *J. Org. Chem.* **1989**, *54*, 5898; (b) Kappe, C. O.; Fabian, W. M. F.; Semones, M. A. *Tetrahedron* **1997**, *53*, 2803.
2. Snider, B. B.; Shi, Z. *J. Org. Chem.* **1993**, *58*, 3828.
3. (a) Biginelli, P. *Gazz. Chem. Ital.* **1893**, *23*, 360; (b) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937.
4. Barluenga, J.; Thomas, M.; Ballesteros, A.; Loez, L. A. *Tetrahedron Lett.* **1989**, *30*, 4573.
5. O'Reilly, B. C.; Atwal, K. S. *Heterocycles* **1987**, *26*, 1185.
6. Ramalinga, K.; Vijayalaxmi, P.; Kaimal, T. N. B. *Synlett* **2001**, *6*, 863.
7. Lenarsic, R.; Kocevar, M.; Polanc, S. *J. Org. Chem.* **1999**, *64*, 2558.
8. Firouzabadi, H.; Iranpoor, N.; Karimi, B. *Synlett* **1999**, *3*, 319 and 321.
9. Chary, K. P.; Mohan, G. H.; Iyengar, D. S. *Chem. Lett.* **1999**, *12*, 1339.
10. Chary, K. P.; Ram, S. R.; Mohan, G. H.; Iyengar, D. S. *Synlett* **2000**, *5*, 683.
11. Karimi, B.; Seradj, H. *Synlett* **2000**, *6*, 805.
12. Ma, Y.; Qian, C.; Wang, L.; Yang, M. *J. Org. Chem.* **2000**, *65*, 3864.
13. Yadav, J. S.; Subba Reddy, B. V.; Srinivas, R.; Venugopal, C.; Ramalingam, T. *Synthesis* **2001**, *9*, 1341.
14. Kappe, C. O.; Falsone, S. F. *Synlett* **1998**, 718.
15. **General procedure for the $ZrCl_4$ catalyzed synthesis of pyrimidinones 4**: A mixture containing an appropriate β-ketoester (5 mmol), corresponding aldehyde (5 mmol), urea or thiourea and $ZrCl_4$ (10 mol%) in ethanol (15 ml) was refluxed for 4 h. After completion of the reaction, as indicated by TLC, the solvent was removed under reduced pressure to yield a solid, which was washed thoroughly with water, filtered and recrystallized from ethanol to afford pure product.

Spectroscopic data. **4d**: Mp 198–200°C; ^{1}H NMR (DMSO-d_6): δ 1.18 (t, $J=7.5$ Hz, 3H, CH_3), 2.28 (s, 3H, CH_3), 4.0 (q, $J=7.5$ Hz, 2H, -OCH_2), 5.18 (s, 1H), 6.7 (d, $J=8.9$ Hz, 2H, Ar), 7.09 (d, $J=8.9$ Hz, 2H, Ar), 7.25 (s, 1H), 8.95 and 9.0 (2s, 2H, brs. NH). EIMS: m/z (%)=276 (10) (M^+), 248 (100), 231 (28), 204 (80), 168 (87), 136 (48). IR (KBr): $\nu=3520$, 3230, 3150, 1705, 1690 cm^{-1}. Anal. calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.83; N, 10.17. Found: C, 60.81; H, 5.78; N, 10.11.

4g: Mp 229–232°C; ^{1}H NMR (DMSO-d_6): δ 1.20 (t, $J=7.6$ Hz, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.87 (s, 6H, $N(CH_3)_2$), 4.0 (q, $J=7.6$ Hz, 2H, -OCH_2), 5.18 (s, 1H, CH), 6.62 (d, $J=9.1$ Hz, 2H, Ar), 7.19 (d, $J=9.1$ Hz, 2H, Ar), 8.90 and 8.95 (2s, 2H, brs. NH). EIMS: m/z (%)= 303 (75) (M^+), 274 (100), 257 (15), 230 (78), 155 (20). IR (KBr): $\nu=3200$, 3100, 1700, 1685 cm^{-1}.

4l: Mp 190–192°C; ^{1}H NMR (DMSO-d_6): δ 1.19 (t, $J=7.3$ Hz, 3H, CH_3), 2.27 (s, 3H, CH_3), 4.08 (q, $J=7.3$ Hz, 2H, -OCH_2), 5.22 (s, 1H, CH), 7.23 (m, 5H, Ar), 9.25 and 9.9 (2s, 2H, 2brs. NH). EIMS: m/z (%)=276 (65) (M^+), 237 (45), 204 (100), 172 (35), 142 (20). IR (KBr): $\nu=3259$, 3195, 3100, 1710, 1690 cm^{-1}.

4m: Mp 193–194°C; ^{1}H NMR (DMSO-d_6): δ 1.18 (t, $J=7.5$ Hz, 3H, CH_3), 2.25 (s, 3H, CH_3), 4.0 (q, $J=7.5$ Hz, 2H, -OCH_2), 5.10 (s, 1H, CH), 6.65 (d, $J=9.1$ Hz, 2H, Ar), 7.00 (d, $J=9.1$ Hz, 2H, Ar), 9.10 (br. s, 1H, OH), 9.15 and 9.8 (2br. s, 2H, NH). EIMS: m/z (%)=292 (25) (M^+), 264 (28), 220 (20), 200 (15), 142 (25), 50 (100). IR (KBr): $\nu=3450$, 3190, 3040, 1705, 1650 cm^{-1}.

6a: Mp 160–162°C; ^{1}H NMR (DMSO-d_6): δ 0.85 (t, $J=7.5$ Hz, 3H, CH_3), 3.10 (d, $J=11.5$ Hz, 1H, CH), 3.88 (q, $J=7.5$ Hz, 2H, -OCH_2), 4.86 (d, $J=11.5$ Hz, 1H), 5.70 (br. s, 1H, NH), 5.72 (br. s, 1H, NH) 6.30 (s, 1H, OH), 7.36 (s, 5H, Ar). EIMS: m/z (%)=332 (80) (M^+), 285 (20), 269 (75), 241 (100), 237 (72), 142 (25). IR (KBr): $\nu=3450$, 3210, 1700, 1690 cm^{-1}.

6b: Mp 186–188°C; ^{1}H NMR (DMSO-d_6): δ 0.92 (t, $J=7.3$ Hz, 3H, CH_3), 2.92 (d, $J=11$ Hz, 1H), 3.86 (q, $J=7.3$ Hz, 2H, -OCH_2), 4.74 (d, $J=11$ Hz, 1H, CH), 6.65 (s, 1H), 6.70 (d, $J=8.25$ Hz, 2H, Ar), 6.96 (d, NH), 7.16 (d, $J=9.1$ Hz, 2H, Ar), 9.10 (s, 1H, NH). EIMS: m/z (%)=348 (75) (M^+), 288 (30), 272 (70), 244 (100), 224 (65). IR (KBr): $\nu=3410$, 3250, 3195, 1710, 1695 cm^{-1}.