SHORT PAPER

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One-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones using cadmium sulfate as catalyst

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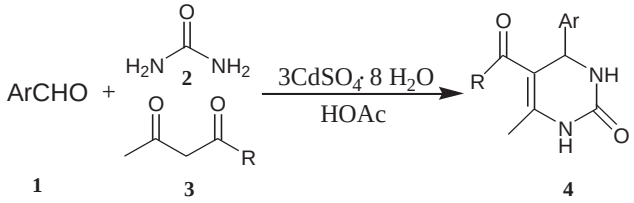
A simple effective synthesis of 3,4-dihydropyrimidin-2(1*H*)-one derivatives from aromatic aldehydes, 1,3-dicarbonyl compounds and urea in glacical acetic acid using cadmium sulfate as catalyst is described and compared with the classical Biginelli reaction conditions, this new method has the advantage of excellent yields (83–94%) and short reaction time (2-4 h).

Keywords: 3,4-dihydropyrimidin-2(1H)-ones, cadmium sulfate

Dihydropyrimidinones[1] (DHPMs, Biginelli compounds) are an important class of compounds which are becoming interesting due to their therapeutic and pharmacological activities. For example, DHPMs (a Biginelli series) and their derivatives exhibit attractive pharmacological profiles for serving as the integral backbones of several calcium channel blockers, antihypertensive agents, alpha-la-antagonists and neuropeptide Y (NPY) antagonists.[2] In addition, several alkaloids containing the dihydropyrimidinone-5-carboxylate motifs have been isolated from marine sources which show interesting biological properties.[3]

Because of the importance of the DHPMs, much work on improving their synthesis has been actively pursued for several decades.[4–11] Among the improved synthetic methods is the use of $BF_3{\cdot}OEt_2$ as promoter as reported by Hu and Sidler.[12] Later on, Kappe and co-workers further improved this reaction by employing microwave irradiation in the presence of PPE to give higher chemical yields of dihydropyrimidinone products.[13] Recently, several other methods including the use of lanthanide compounds,[14-15] several other Lewis acids[16-17] and metal Iron and Ni compounds[18-19] have also been reported to overcome the drawback of the classical Biginelli reaction. Very recently, we found that the Biginelli reaction can occur more smoothly upon irradiation by microwaves in the presence of ferric chloride as the catalyst.[20] In this paper, we report a new method, using cadmium sulfate as catalyst and glacial acetic acid instead of alcohol as solvent. Compared with the classical method, the new protocol is more efficient. The yields were higher and the reaction times were shorter. The ratio of aldehydes, 1,3-dicarbonyl compounds, urea and cadmium sulfate can be controlled as 1:1:1.2:0.25 (Scheme 1). The results are listed in Table 1.



1 3 4

Scheme 1

Table 1 $3CdSO_4{\cdot}8H_2O$ catalysed synthesis of dihydropyrimidinones

Entry	Ar	R	Yield/%		Mp/°C	
			A[a]	B[b]	Found	Reported
4a	C_6H_5	OEt	94	78	202–203	202–203[19]
4b	2–ClC_6H_4	OEt	91	51	215–217	215–218[13]
4c	3,4–$OCH_2OC_6H_3$	OEt	87	49	186–187	187–188[19]
4d	4–$NO_2C_6H_4$	OEt	89	58	207–208	207–208.5[19]
4e	4–$NMe_2C_6H_4$	OEt	86	–	257–258	256–257[19]
4f	2–OHC_6H_4	OEt	83	19	202–203	201–203[19]
4g	2,4–$(Cl)_2$–C_6H_3	OEt	92	69	248–250	249–250[19]
4h	4–ClC_6H_4	OEt	94	56	214–215	213–215[19]
4i	4–OHC_6H_4	OEt	89	67	228–230	227–229[19]
4j	4–$NO_2C_6H_4$	Me	92	–	227–229	230[15]
4k	4–$OCH_3C_6H_4$	Me	93	–	165–168	168–170[15]
4l	4–$NO_2C_6H_4$	OMe	92	41	237–238	235–237[12]
4m	4–$OCH_3C_6H_4$	OMe	94	28	193–196	192–194[12]
4n	4–ClC_6H_4	OMe	92	56	206–208	204–207[12]
4o	4–FC_6H_4	OMe	89	–	193–195	192–194[15]
4p	2–$NO_2C_6H_4$	OMe	91	–	280–282	–
4q	2–NO_2–5–Cl–C_6H_3	OMe	90	–	290–292	–

[a]Method A: new reaction conditions (cat. $3CdSO_4{\cdot}8H_2O$ in glacial acetic acid at 100°C for 2–4 h).
[b]Method B: classical Biginelli conditions (cat. HCl in EtOH, reflux 18h).

Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a FT IR-8101 spectrometer. ^{1}H NMR spectra were measured on a Bruker DPX 300MHz spectrometer using TMS as internal standard, DMSO-d_6 as solvent. Elemental analyses were carried out on a Perkin-Elmer 2400II elemental analyser.

General procedure

A dry 100 ml flask was charged with aromatic aldehyde (3 mmol), 1,3-dicarbonyl compound (3 mmol), urea (3.6 mmol), $3CdSO_4{\cdot}8H_2O$ (0.75 mmol), in glacial acetic acid (10 ml) and was heated to 100°C. The mixture was kept stirring at 100°C for 2–4 h (followed by TLC) before being cooled to room temperature. The mixture was then poured into 50 ml ice-water. The solid product was filtered, washed with water and ethanol (95%), and subsequently dried and recrystallised from ethanol to give the pure product.

All the products (except **4p** and **4q**) are known compounds which were characterised by m.p., IR, ^{1}H NMR spectral data and elemental analysis. Data of **4p**: m.p. 280–282°C; IR (KBr): 3359, 3232, 3108, 2954, 1702, 1644, 1530 cm^{-1}; ^{1}H NMR (DMSO-d_6): 9.38 (br s, 1H, NH), 8.12 (m, 2H, aromH), 7.91 (br s, 1H, NH), 7.63 (m, 2H, aromH), 5.29 (d, 1H, *J*=3.06 Hz, CH), 3.53 (s, 3H, CH_3OCO), 2.27 (s, 3H, CH_3); Anal. Calc. for $C_{13}H_{13}N_3O_5$: C, 53.61; H, 4.50; N, 14.43. Found: C, 53.56; H, 4.31; N, 14.40%. Data of **4q**: m.p. 290–292°C; IR (KBr): 3359, 3233, 3119, 2953, 1703, 1644, 1572, 1530 cm^{-1}; ^{1}H NMR (DMSO- d_6): 9.45 (br s, 1H, NH), 7.95 (s, 1H, aromH), 7.92 (br s, 1H, NH), 7.54 (m, 2H, aromH), 5.80

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(d, 1H, *J*=2.70 Hz, CH), 3.39 (s, 3H, CH_3OCO), 2.26 (s, 3H, CH_3); Anal. Calc. for $C_{13}H_{12}ClN_3O_5$: C, 47.94; H, 3.71; N, 12.90. Found: C, 47.80; H, 3.52; N, 12.76%.

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References

1 P. Biginelli, *Gazz. Chim. Ital*., 1893, **23**, 360.
2 K.S. Atwal, B.N. Swanson, S.E. Unger, D.M. Floyd, S. Moreland, A. Hedberg and B.C. O'Reilly, *J. Med. Chem*., 1991, **34**, 806. G.C. Rovnyak, K.S. Atwal, A. Hedberg, S.D. Kimball, S. Moreland, J.Z. Gougoutas, B.C. O'Reilly, J. Schwart and M.F. Malley, *J. Med. Chem.*, 1992, **35**, 3254. G.J. Grover, S. Dzwonczyk, D.M. Mcmullen, C.S. Normadinam, P.G. Slenph and S.J. Moreland, *J. Cardiovase. Pharmacol.*, 1995, **26**, 289.
3 B.B. Snider and Z.P. Shi, *J. Org. Chem.*, 1993, **58**, 3828. and references therein.
4 B.C. O'Reilly and K.S. Atwal, *Heterocycles*, 1987, **26**, 1185.
5 K.S. Atwal, B.C. O'Reilly, J.Z. Gougoutas and M.F. Malley, *Heterocycles*, 1987, **26**, 1189.
6 K.S. Atwal, G.C. Rovnyak, B.C. O'Reilly and J. Schwartz, *J. Org. Chem*., 1989, **54**, 5898.
7 R. Gupta, A.K. Gupta, S. Paul and P.L. Kachroo, *Ind. J. Chem.*, 1995, **34B**, 151.
8 P. Wipf and A. Cunningham, *Tetrahedron Lett*., 1995, **36**, 7819.
9 A. Studer, S. Hadida, R. Ferrito, S.Y. Kim, P. Jeger, P. Wipf and D.P. Curran, *Science*, 1997, **275**, 823.
10 A. Studer, P. Jeger, P. Wipf and D.P Curran, *J. Org. Chem*., 1997, **62**, 2917.
11 F. Bigi, S. Carloni, B. Frullanti, R. Maggi and G. Sartori, *Tetrahedron Lett.*, 1999, **40**, 3465.
12 E.H. Hu, D.R. Silder and U.H. Dolling, *J. Org. Chem*., 1998. **63**. 3454.
13 C.O. Kappe, D. Kumar and R.S. Varma, *Synthesis*, 1999, 1799.
14 L. Jun, B. Yinjuan, W. Zhenjun, Y. Bingqin and M. Huairang, *Tetrahedron Lett*., 2000, **41**, 9075.
15 M. Yun, Q. Changtao, W. Liming and Y. Ming, *J. Org. Chem*., 2000, **65**, 3864.
16 B.C. Ranu, A. Hajra and U. Jana, *J. Org. Chem*., 2000, **65**, 6270.
17 K. Ramalinga, P. Vijayalakshmi and T.N.B. Kaimal, *Synlett*., 2001, 863.
18 L. Jun and M. Huairang, *Synlett*., 2000, 63.
19 L. Jun and B. Yinjuang, *Synthesis*, 2002, **4**, 466.
20 T. Shujiang, Z. Jianfeng, C. Peijun, W. Hai and F. Juncai, *Synth. Commun*., 2002, **32**, 147.