http://dx.doi.org/10.5012/bkcs.2012.33.2.377

Silica-gel Catalyzed Facile Synthesis of 3,4-Dihydropyrimidinones

Sameer Agarwal,[†,*] Umesh Aware,[†] Amit Patil,[†] Vinita Rohera,[†,‡] Manjunath Ghate,[‡] Mukul Jain,[†] and Pankaj Patel[†]

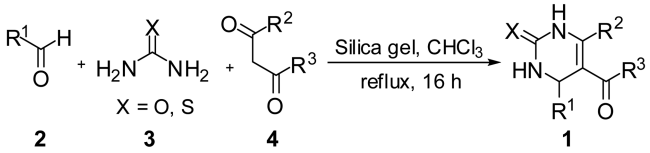
[†]*Zydus Research Centre, Sarkhej-Bavla N.H. 8A, Moraiya, Ahmedabad-382213, India*
[*]*E-mail: sameeragarwal@zyduscadila.com*
[‡]*Institute of Pharmacy, Nirma University, S. G. Highway, Ahmedabad-382481, India*
Received November 7, 2011, Accepted November 29, 2011

Key Words : Biginelli reaction, 3,4-Dihydropyrimidinones, Silica-gel, Multi-component reaction

The pyrimidinone ring is a basic substructure of numerous biologically active alkaloids and pharmaceutical products.[1] These cores are regarded as one of the most important groups of drug-like scaffolds.[2] 3,4-dihydropyrimidinones above are known to exhibit variety of pharmacological activity such as calcium channel modulation, mitotic kinesin Eg5 inhibition, antiviral, anti-inflammatory, antibacterial activity, *etc*.[3]

The Biginelli reaction[4] is a well-known, simple and straightforward procedure for the synthesis of 3,4-dihydropyrimidinones (3,4-DHPMs) by the three-component condensation of an aldehyde, β-ketoester and urea, under strongly acidic conditions. A recent article shows the interest of the synthetic chemists in order to find better and more selective catalysts for the synthesis of 3,4-DHPM under Biginelli reaction conditions.[5] Most of the methods are based on Brønsted or Lewis acid type catalysts. Probably, the most effective methods involve the reagent(s), which are stoichiometric dehydrating agents in the presence of protic or Lewis acids.[6] However, most of these methods use expensive reagents, strongly acidic conditions, require long reaction times, harsh conditions, give unsatisfactory yields and suffer from cumbersome work up and difficult product isolation. Subsequent multi-step syntheses produced somewhat higher yields but lacked the simplicity of the one-pot, one-step synthesis.[7] In the recent years, catalysts, which are recyclable and capable of performing the reaction under mild condition, have gained particular attention.[8] Since then, there was a need to find catalysts, which are capable to perform reaction under milder reaction conditions.

We wished to develop a direct and experimentally convenient one-pot condensation reaction for the construction of 3,4-DHPMs, without using strong acid catalysis. In this communication, we disclose a simple but effective protocol for Biginelli reaction that produces high yields of 3,4-DHPMs in presence of silica-gel while preserving the original one-pot strategy. Silica gel is a mild Lewis acid. The reactivity of silica gel and the effect of solvent, time and temperature



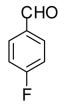
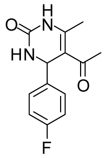
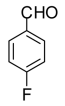
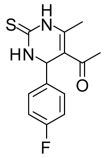
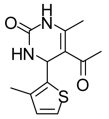
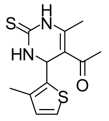
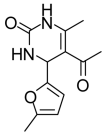
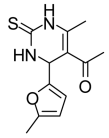
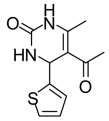
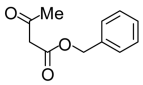
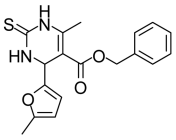
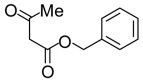
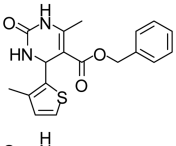
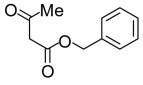
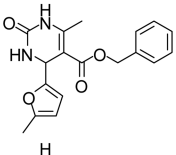
Scheme 1. Synthesis of substituted 3,4-dihydropyrimidinones.

were explored using the model reaction between aryl or aliphatic aldehyde **2**, urea or thiourea **3** and 1,3-dicarbonyl **4** which gave product **1** in excellent yield (Scheme 1). The reaction was found to be complete within 16 h in boiling chloroform in the presence of silica gel. Filtration, washing of the silica gel and removal of solvent produces essentially pure 3,4-DHPMs without any further purification. The scope of the methodology was demonstrated as a variety of 1,3-dicarbonyl compounds and various aryl or aliphatic aldehydes proved effective with this protocol (Table 1).[9] An optimization of the reaction conditions has not been carried out for each case. However, all compounds were formed in good yields (74-94%) and with high purity > 95%. It is noteworthy that acid sensitive reactants thienyl and furyl carbaldehydes, and conjugated double bonds of α,β-unsaturated aldehydes are tolerated in this reaction, resulting in formation of desired 3,4-DHPMs in high yields.

The choice of solvent is also extremely important. An extensive variation of solvent and silica-gel catalyst ratio for condensation of the aldehyde **2j**, urea and β-keto-ester **4j** to 3,4-dihydropyrimidinone **1j** demonstrated that the reaction works best using 10-fold of silica gel in dry chloroform (Table 2, Entries 1-3). The residual ethanol present in commercial chloroform inhibits the reaction, and, also, addition of water inhibits the reactions (Entries 4 and 5), whereas drying the silica gel at elevated temperature *in vacuo* increases the activity of the catalyst. The reaction does not occur in solvents that reduce the activity of silica gel such as methanol and THF (Entries 7 and 8) but does so in less Lewis basic solvents like toluene and ethyl acetate (Entries 9 and 10). In absence of silica-gel, formation of desired product was not detected (Entry 11). The use of silica sulfuric acid catalyst has been reported previously for the synthesis of 3,4-dihydropyrimidinones,[10] but these conditions would still not be effective as they require sulfuric acid. It has been reported[11] and also observed by us that the presence of mineral acids decreased reaction yield appreciably.

In conclusion, we have developed a mild and highly effective procedure for the one-pot synthesis of substituted dihydropyrimidinones in high yields using silica gel as a green, highly efficient and recyclable heterogeneous catalyst. Our approach can be applied to the preparation of a wide range of synthetic analogues for structure-activity studies. Investigations in this direction are ongoing.

Table 1. Synthesis of substituted 3,4-dihydropyrimidinones

Entry	Aldehyde, **2**	Urea, **3**	Dinone, **4**	Product, **1**	Yield (%)[a]
a					93
b					86
c					88
d					80
e					91
f					84
g					87
h					80
i					82
j					94
k					74

[a]Isolated yield.

Acknowledgments. We thank management of Zydus Research Centre, Cadila Healthcare Limited for encouragement and analytical department for support.

Table 2. Variation of solvent and silica-gel catalyst ratio for condensation of the aldehyde **2j**, urea and β-keto-ester **4j** to 3,4-dihydropyrimidinone **1j**

Entry	C/S[a]	Solvent	**1j**, Yield (%)[b]
1	10	dry $CHCl_3$	94
2	30	dry $CHCl_3$	78
3	5	dry $CHCl_3$	63
4	10	commercial $CHCl_3$	21
5	10	$CHCl_3/H_2O$ (10:1)	-
6	10	EtOH	23
7	10	MeOH	Trace
8	10	THF	Trace
9	10	PhMe	38
10	10	EtOAc	47
11	Nil	dry $CHCl_3$	-[c]

[a]Silica catalyst-to-substrate ratio by mass. [b]Isolated yield. [c]92% starting material (**2j**) was recovered.

References

1. Heys, L.; Moore, C. G.; Murphy, P. J. *Chem. Soc. Rev.* **2000**, *29*, 57.
2. Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043.
3. (a) Hang, Y.; Yang, F.; Zhu, C. *J. Am. Chem. Soc.* **2005**, *127*, 16386. (b) Mayer, T. U.; Kapoor, T. M.; Haggarty, S. J.; King, R. W.; Schreiber, S. L.; Mitchison, T. J. *Science* **1999**, *286*, 971. (c) Kapoor, T. M.; Mayer, T. U.; Coughlin, M. L.; Mitchison, T. J. *J. Cell Biol.* **2000**, *150*, 975.
4. (a) Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360. (b) Kappe, C. O. *J. Org. Chem.* **1997**, *62*, 720.
5. Litvić, M.; Večenaj, I.; Ladišić, Z. M.; Lovrić, M.; Vinković, V.; Filipan-Litvić, M. *Tetrahedron* **2010**, *66*, 3463.
6. (a) Kappe, C. O.; Falsone, S. F. *Synlett* **1998**, 718. (b) Zhu, Y.; Pan, Y.; Huang, S. *Synth. Commun.* **2004**, *34*, 3167. (c) Shen, Z. L.; Xu, X. P.; Ji, S. J. *J. Org. Chem.* **2010**, *75*, 1162.
7. (a) Atwal, K. S.; O'Reilly, B. C.; Gougoutas, J. Z.; Malley, M. F. *Heterocycles* **1987**, *26*, 1189. (b) Wipf, P.; Cunningham, A. *Tetrahedron Lett.* **1995**, *36*, 7819.
8. (a) Pisani, L.; Prokopcová, H.; Kremsner, J. M.; Kappe, C. O. *J. Comb. Chem.* **2007**, *9*, 415. (b) Stadler, A.; Kappe, C. O. *J. Chem. Soc., Perkin. Trans. 1* **2000**, 1363. (c) Salim, S. D.; Akamanchi, K. G. *Catalysis Commun*. **2011**, *12*, 1153.
9. ***General procedure for the silica gel catalyzed synthesis of 3,4-dihydropyrimidinones*:** To a solution of the aldehyde **2** (1.0 eq.), urea or thiourea **3** (1.0 eq.) and 1,3-dicarbonyl **4** (1.0 eq.) in anhydrous chloroform was added silica gel (10 fold). Silica gel (100-200 mesh) was pre dried at 200 ºC for 2 h *in vacuo*. The reaction mixture was heated at reflux temperature under nitrogen atmosphere for 16 h. The reaction mixture was then cooled and the solvent was removed under reduced temperature. The resulting slurry was filtrated at ambient temperature over a short path of silica (*n*-hexane-EtOAc) and removal of the solvent provided the 3,4-dihydropyrimidinones **1**. Spectral data of *benzyl 6-methyl-4-(5-methylfuran-2-yl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1j**)*: White powder; mp 145 ºC. IR (KBr): ν = 579, 692, 731, 779, 1020, 1088, 1179, 1231, 1319, 1427, 1647, 1720, 1941, 3115, 3252 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 9.26 (s, 1H), 7.73 (br s, 1H), 7.35-7.29 (m, 3H), 7.27-7.24 (m, 2H), 5.95 (dd, *J* = 0.8, 2.0 Hz, 1H), 5.90 (d, *J* = 2.8 Hz, 1H), 5.17 (d, *J* = 3.2 Hz, 1H), 5.11 (d, *J* = 12.8 Hz, 1H), 5.03 (d, *J* = 12.8 Hz, 1H), 2.25 (s, 3H), 2.20 (s, 3H). ^{13}C NMR and DEPT (100 MHz, DMSO-d_6): δ 13.33 (CH_3), 17.78 (CH_3), 47.66 (CH), 64.75 (CH_2), 96.42 (C), 106.08 (CH), 106.32 (CH), 115.19 (CH), 127.40 (CH), 127.68 (CH), 128.27 (CH), 129.32 (CH), 136.63 (C), 150.04 (C), 150.70 (C), 152.24 (C), 154.21 (C). 164.78 (C). MS (EI): *m/z* (%) = 326.9 (30) $[M+H]^+$, 349.1 (100) $[M+Na]^+$. HPLC (% Purity) = 96.31%. Anal. ($C_{18}H_{18}N_2O_4$) Calcd.: C, 66.25; H, 5.56; N, 8.58. Found: C, 65.85; H, 5.75; N, 8.08.
10. Salehi, P.; Dabiri, M.; Zolfigol, M. A.; Fard, M. A. B. *Tetrahedron Lett.* **2003**, *44*, 2889.
11. Hu, E. H.; Sidler, D. R.; Dolling, U.-H. *J. Org. Chem.* **1998**, *63*, 3454.