Available online at www.sciencedirect.com
SCIENCE DIRECT
Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 16 (2006) 2463–2466

A practical and green approach towards synthesis of dihydropyrimidinones: Using heteropoly acids as efficient catalysts

Ezzat Rafiee* and Hadi Jafari

Department of Chemistry, Faculty of Science, Razi University, Kermanshah 67149, Iran

Received 4 January 2006; revised 20 January 2006; accepted 23 January 2006
Available online 7 February 2006

Abstract—A simple and green chemistry procedure for the synthesis of dihydropyrimidinones using heteropoly acid mediated cyclocondensation reaction is described. This method provides an efficient and much improved modification of the original Biginelli reaction reported in 1893, in terms of high yields, and short reaction times. It has the ability to allow a wide variety of substitutions in all three components.

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry.[1–6] In a time when a premium is put on speed, diversity and efficiency in the drug discovery process,[4,5] MCR strategies offer significant advantages over conventional linear-type syntheses.[1–6] In such reactions, three or more reactants come together in a single reaction vessel to form new products that contain portions of all the components. The search and discovery for new MCRs on one hand,[7] and the full exploitation of the already known multicomponent reactions on the other hand, is therefore of considerable current interest. One such MCR that belongs to the latter category is the Biginelli; dihydropyrimidine (DHPM) synthesis.

3,4-Dihydropyrimidin-2(1*H*)-ones, named Biginelli compounds, are known to exhibit a wide range of biological activities such as antiviral, antitumour, antibacterial and anti-inflammatory actions.[6,8,9] More recently, appropriately functionalized DHPMs have emerged as potent calcium channel blockers,[10] antihypertensive agents,[11] α_{1a} adrenergic antagonists[12] neuropeptide Y (NPY) antagonists.[13] Several marine alkaloids containing the DHPM core unit have shown interesting biological properties. In particular, batzelladine alkaloids have been found to be potent HIV gp-120-CD4 inhibitors.[14]

The Biginelli reaction, first reported more than a century ago and recently reviewed,[8] involves the acid-catalyzed cyclocondensation reaction of ethyl acetoacetate, benzaldehyde and urea. A number of synthetic procedures based on the modifications of the classical Biginelli's approach have been developed during past few years.[6,8] Basically, these methods are all similar, using different Lewis acid catalysts.[15–29] Obviously, many of these catalysts and solvents are not acceptable in the context of green synthesis. Thus, as a part of our programme towards green synthesis,[30] and continuing our studies on the application of heteropoly acids (HPAs) in organic synthesis,[31] our new approach reported herein involves the use of HPAs as catalysts for the synthesis of DHPMs.

Heteropoly acids have been extensively studied as acid catalysts for many reactions and found industrial applications in several processes.[32] The Keggin-type HPAs typically represented by the formula $H_{8-x}[XM_{12}O_{40}]$, where X is the heteroatom (e.g., P^{5+} or Si^{4+}), x is its oxidation state and M is the addenda atom (usually Mo^{6+} or W^{6+}), are the most important catalysts, especially $H_3PW_{12}O_{40}$ (PW), $H_3PMo_{12}O_{40}$ (PMo) and $H_4SiW_{12}O_{40}$ (SiW).[33] They are more active than the conventional catalysts, such as mineral acids, ion-exchange resins, zeolites, SiO_2/Al_2O_3 and H_3PO_4/SiO_2.[32,34] HPAs have several advantages over liquid acid catalysts,

Keywords: Dihydropyrimidinones or thiones (DHPMs); Heteropoly acid; Multicomponent reactions (MCR); Biginelli reaction.
* Corresponding author. Tel./fax: +98 831 4274559; e-mail: e.rafiei@razi.ac.ir

0960-894X/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2006.01.087

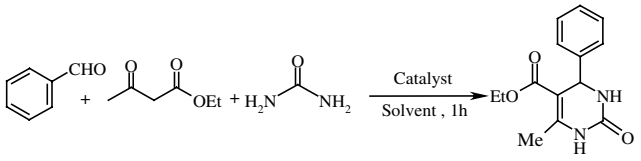
including being noncorrosive and environmentally benign. Thus, they present fewer disposal problems and more economically and environmentally attractive.[35] Furthermore, HPA catalysis lacks side reactions, such as sulfonation, chlorination, etc., that frequently occur with mineral acids.

Recently, our own work found HPAs to be very efficient catalyst for three-component coupling reactions.[31] We wish to report here another remarkable catalytic activity of HPAs for the one-pot condensation of 1,3-dicarbonyl compound (**1**), aldehyde (**2**) and urea or thiourea (**3**) to DHPMs (**4**).

After some experimentation with respect to the catalytic amount of several HPAs (Table 1, entries 2–10), different solvents (Table 1, entries 10–13) and reaction temperature (Table 1, entry 14), the optimal conditions have been established.[36] However, in the absence of HPA, the reaction did not yield the desired product (Table 1, entry 1).

To study the generality of this process, a variety of substituted aromatic, carrying either electron-donating or -withdrawing substituents, aliphatic and heterocyclic aldehydes were examined (Table 2). Many of the pharmacologically relevant substitution patterns on the aromatic ring could be introduced with high efficiency. Aliphatic aldehydes such as propanal and pentanal also reacted well (Table 2, entries 12–14). Such aldehydes normally show extremely poor yields in the Biginelli reaction. It is interesting to note that in the case of the acid-sensitive aldehydes such as furfural and cinnamaldehyde, DHPMs were achieved in excellent yields without the formation of any side products, which are normally observed in the presence of protic acids (Table 2, entries 15–17). Furthermore, the experimental results showed that besides ethyl acetoacetate, acetylacetate and methyl acetoacetate could also be used, and the

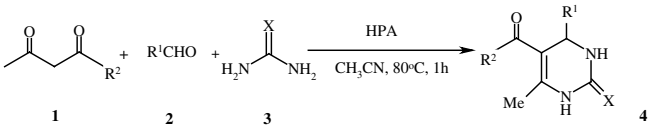
Table 1. Effect of catalysts under different reaction conditions for condensation of benzaldehyde, ethyl acetoacetate and urea

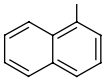


Entry	Catalyst (mol %)	Temperature (°C)	Solvent	Yield[a] (%)
1	—	80	CH_3CN	0[b]
2	PMo (5)	80	CH_3CN	70
3	PMo (10)	80	CH_3CN	89
4	PMo (8)	80	CH_3CN	87
5	SiW (2)	80	CH_3CN	79
6	SiW (5)	80	CH_3CN	93
7	SiW (8)	80	CH_3CN	95
8	PW (2)	80	CH_3CN	81
9	PW (8)	80	CH_3CN	95
10	PW (5)	80	CH_3CN	92
11	PW (5)	80	C_2H_5OH	53
12	PW (5)	80	$C_6H_5CH_3$	41
13	PW (5)	80	$CHCl_3$	59
14	PW (5)	rt	CH_3CN	68

[a] Isolated yield.
[b] After 10 h.

Table 2. Heteropoly acids catalyzed synthesis of dihydropyrimidin-2(1*H*)-ones and thiones (DHPMs)



Entry	R^1	R^2	X	Yield[a] (%)			Ref.[e]
				PW[b]	PMo[c]	SiW[d]	
1	C_6H_5	OEt	O	92	87	93	25
2	3-$NO_2C_6H_4$	OEt	O	89	80	90	25
3	4-$NO_2C_6H_4$	OEt	O	90	86	91	25
4	4-$CH_3OC_6H_4$	OEt	O	96	91	92	25
5	2-ClC_6H_4	OEt	O	91	89	89	25
6	3-ClC_6H_4	OEt	O	90	90	87	25
7	4-ClC_6H_4	OEt	O	91	87	92	25
8	4-$CH_3C_6H_4$	OEt	O	95	92	94	25
9	2-HOC_6H_4	OEt	O	52	57	60	19
10	3-HOC_6H_4	OEt	O	73	70	71	25
11	4-$N(Me)_2$–C_6H_4	OEt	O	94	90	96	19
12	C–C_6H_{11}	OEt	O	68	61	65	20
13	*n*-C_3H_7	OEt	O	57	55	54	19
14	*n*-C_5H_{11}	OEt	O	50	47	52	20
15	PhCH=CH	OEt	O	90	89	88	25
16		OEt	O	95	90	91	25
17		OEt	O	93	91	92	25
18		OEt	O	77	79	70	19
19	C_6H_5	OMe	O	93	85	86	25
20	3-ClC_6H_4	OMe	O	88	83	90	18
21	4-ClC_6H_4	OMe	O	90	85	91	22
22	4-$CH_3OC_6H_4$	OMe	O	97	90	95	25
23	4-$NO_2C_6H_4$	OMe	O	75	69	73	25
24	4-$CH_3C_6H_4$	OMe	O	96	94	96	25
25	4-$N(Me)_2$–C_6H_4	OMe	O	88	80	82	26
26	C_6H_5	Me	O	93	89	90	21
27	4-$CH_3OC_6H_4$	Me	O	91	87	86	21
28	4-$NO_2C_6H_4$	Me	O	71	70	72	21
29	C_6H_5	OEt	S	94	86	91	25
30	4-$CH_3OC_6H_4$	OEt	S	97	91	93	25
31	3-HOC_6H_4	OEt	S	71	68	62	29
32	4-ClC_6H_4	OEt	S	85	81	80	25
33	4-$NO_2C_6H_4$	OEt	S	86	80	87	25
34	4-$CH_3C_6H_4$	OEt	S	96	93	94	25
35		OEt	S	89	85	84	25

[a] Isolated yield.
[b] The mole ratio of aldehyde to dicarbonyl compound to urea or thiourea to PW is 1:1:1.5:0.05.
[c] The mole ratio of aldehyde to dicarbonyl compound to urea or thiourea to PMo is 1:1:1.5:0.08.
[d] The mole ratio of aldehyde to dicarbonyl compound to urea or thiourea to SiW is 1:1:1.5:0.05.
[e] Products were characterised by comparison of their spectroscopic data with those reported in the literature.

corresponding DHPMs were produced in high to excellent yields (Table 2, entries 19–28). Thiourea has been used with similar success to provide the corresponding dihydropyrimidin-2(1*H*)-thiones which are also of much interest with regard to biological activity[8] (Table 2, entries 29-35). Noteworthy is the recently identified lead compound, monastrol (Table 2, entry 31), of a new class of anticancer agents that act as cell division (mitosis) blockers.[37] Thus, variations in all three compounds have been accommodated very comfortably. It is pleasing to observe the remarkable stability of a variety of functional groups such as ether, nitro, hydroxyl, halides, heterocyclic moieties and conjugated C=C double bond under the reaction conditions. The authors investigated the mechanism of the Biginelli reaction in the literature[38] and proposed an *N*-acyliminium ion formed in situ by reaction of the aldehyde with urea as the key intermediate.

In conclusion, this report discloses a simple modification of the Biginelli DHPM synthesis. Excellent yields, enhanced reaction rates, compatibility with various functional groups, environmentally friendly procedure, timesaving process, low cost and easy availability of the catalyst are some of the salient features of this reaction. This procedure will offer an easy access to substituted dihydropyrimidin-2(1*H*)-ones and thiones with different substitution patterns in high to excellent yields.

Acknowledgments

The authors thank the Razi University Research Council and Kermanshah Refinery Company for support of this work.

References and notes

1. Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123.
2. Tietze, L. F.; Lieb, M. E. *Curr. Opin. Chem. Biol.* **1998**, *2*, 363.
3. Dax, S. L.; McNally, J. J.; Youngman, M. A. *Curr. Med. Chem.* **1999**, *6*, 255.
4. Plunkett, M.; Ellman, J. A. *New Drugs Sci. Am.* **1997**, 276.
5. Schreiber, S. L. *Science* **2000**, *287*, 1964.
6. Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879.
7. Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, *3*, 366.
8. Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937.
9. Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043.
10. Rovnyak, G. C.; Kimball, S. D.; Beyer, B.; Cucinotta, G.; Dimarco, D. J.; Gougoutas, J.; Hedberg, A.; Malley, M.; McCarthy, J. P.; Zhang, R.; Moreland, S. *J. Med. Chem.* **1995**, *38*, 119.
11. (a) Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O'Reilly, B. C. *J. Med. Chem.* **1991**, *34*, 806; (b) Grover, G. J.; Dzwomczyk, S.; McMullen, D. M.; Normadinam, C. S.; Sleph, P. G.; Moreland, S. J. *J. Cardiovasc. Pharmacol.* **1995**, *26*, 289.
12. (a) Silder, D. R.; Larsen, R. D.; Chartrain, M.; Ikemote, N.; Roerber, C. M.; Taylor, C. S.; Li, W.; Bills, G. F. PCT Int. WO 99 07695; (b) Kappe, C. O.; Fabian, W. M. F.; Semones, M. A. *Tetrahedron* **1997**, *53*, 2803.
13. Bruce, M. A.; Pointdexter, G. S.; Johnson, G. PCT Int. Appl. WO 98 33791.;
14. Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; Debrossi, C.; Mai, S.; Truneh, A.; Faulkner, D. J.; Carte, B.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westley, J. W.; Potts, B. C. M. *J. Org. Chem.* **1995**, *60*, 1182; (b) Rama Rao, A. V.; Gujar, M. K.; Vasudevan, J. *J. Chem. Soc., Chem. Commun.* **1995**, 1369; (c) Snider, B. B.; Chen, J.; Patil, A. D.; Freyer, A. *Tetrahedron Lett.* **1996**, *37*, 6977.
15. Bose, D. S.; Sudharshan, M.; Chavhan, S. W. *ARKIVOC* **2005**, 228.
16. Russowsky, D.; Lopes, F. A.; da Silva, V. S. S.; Canto, K. F. S.; Montes D'Oca, M. G.; Godoi, M. N. *J. Brazil. Chem. Soc.* **2004**, *15*, 165.
17. Reddy, Y. T.; Rajitha, B.; Reddy, P. N.; Kumar, B. S.; Rao, V. P. *Synth. Commun.* **2004**, *34*, 3821.
18. Paraskar, A. S.; Dewkar, G. K.; Sudalai, A. *Tetrahedron Lett.* **2003**, *44*, 3305.
19. Lu, J.; Bai, Y. *Synthesis* **2002**, 466.
20. Yadav, J. S.; Reddy, B. V. S.; Srinivas, R.; Venugopal, C.; Ramalingam, T. *Synthesis* **2001**, 1341.
21. Ma, Y.; Qian, C.; Wang, L.; Yang, M. *J. Org. Chem.* **2000**, *65*, 3864, and references cited therein.
22. Hu, E. H.; Sidler, D. R.; Dolling, U. H. *J. Org. Chem.* **1998**, *63*, 3454.
23. Ranu, B. C.; Hajra, A.; Jana, U. *J. Org. Chem.* **2000**, *65*, 6270.
24. Reddy, C. V.; Mahesh, M.; Raju, P. V. V. K.; Babu, T. R.; Reddy, V. V. N. *Tetrahedron Lett.* **2002**, *43*, 2657.
25. Fu, N. Y.; Yuan, Y. F.; Cao, Z.; Wang, S. W.; Wang, J. T.; Peppe, C. *Tetrahedron* **2002**, *58*, 4801.
26. Bose, D. S.; Fatima, L.; Mereyala, H. B. *J. Org. Chem.* **2003**, *68*, 587.
27. Ramalinga, K.; Vijayalakshmi, P.; Kaimal, T. N. B. *Synlett* **2001**, 863.
28. Kappe, C. O.; Kumar, D.; Varma, R. S. *Synthesis* **1999**, 1799.
29. Salehi, P.; Dabiri, M.; Zolfigol, M. A.; Bodaghi Fard, M. A. *Tetrahedron Lett.* **2003**, *44*, 2889.
30. (a) Rafiee, E.; Tangestaninejad, S.; Habibi, M. H.; Mikhani, V. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3611; (b) Kozhevnikova, E. F.; Rafiee, E.; Kozhevnikov, I. V. *Appl. Catal., A* **2004**, *260*, 25; (c) Rafiee, E.; Tangestaninejad, S.; Habibi, M. H.; Mikhani, V. *Bull. Korean Chem. Soc.* **2004**, *25*, 599; (d) Rafiee, E.; Tangestaninejad, S.; Habibi, M. H.; Mikhani, V. *Synth. Commun.* **2004**, *34*, 3673.
31. Rafiee, E.; Tork, F.; Joshaghani, M. *Bioorg. Med. Chem. Lett.*, **2006**, *16*, 1221.
32. (a) Kozhevnikov, I. V. *Chem. Rev.* **1998**, *98*, 171; (b) Okuhara, T.; Mizuno, N.; Misono, M. *Adv. Catal.* **1996**, *41*, 113; (c) Kozhevnikov, I. V.. In *Catalysis for Fine Chemicals, Catalysis by Polyoxometalates*; Wiley: Chichester, 2002; Vol. 2,, Chapter 7 (d) Misono, M. *Chem. Commun.* **2001**, 1141.
33. (a) Kozhevnikova, E. F.; Quartararo, J.; Kozhevnikov, I. V. *Appl. Catal., A* **2003**, *245*, 69; (b) Firouzabadi, H.; Jafari, A. A. *J. Iran. Chem. Soc.* **2005**, *2*, 85, and references cited therein; (c) Firouzabadi, H.; Iranpoor, N.; Jafari, A. A. *Synlett* **2005**, 299; (d) Moffat, J. B. *The Surface and Catalytic Properties of Heteropolyoxometalates*; Kluwer: New York, 2001.
34. (a) Tiofeeva, M. N.; Dimidov, A. V.; Kozhevnikov, I. V. *J. Mol. Catal.* **1993**, *79*, 21; (b) Drago, R. S.; Dias, J. A.; Maier, T. *J. Am. Chem. Soc.* **1997**, *119*, 7702.
35. Izumi, Y.; Urabe, K.; Onaka, M. *Zeolite Clay and Heteropoly Acids in Organic Synthesis*; Kodansha/VCH: Tokyo, 1992.

36. Typical procedure for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and -thiones: a mixture containing an appropriate β-dicarbonyl compound (2 mmol), corresponding aldehyde (2 mmol), urea or thiourea (3 mmol) and appropriate amount of catalyst (Table 2) in acetonitrile (5 mL) was stirred rapidly and heated at 80 °C in a preheated oil bath for one hour (completion of the reaction was monitored by TLC). The reaction mixture was then filtered to remove the catalyst, and the filtrate was poured into crushed ice. Stirring was continued for several minutes. The solid product was filtered, washed with cold water (2× 30 mL) and recrystallized from ethyl acetate/*n*-hexane or ethanol to afford pure product. All products were identified by comparing their spectral and physical data with those for authentic samples.
37. Mayer, T. U.; Kapoor, T. M.; Haggarty, S. J.; King, R. W.; Schreiber, S. L.; Mitchison, T. J. *Science* **1999**, *286*, 971.
38. (a) Sweet, F.; Fissekis, J. *J. Am. Chem. Soc.* **1973**, *95*, 8741; (b) Folkers, K.; Johnson, T. B. *J. Am. Chem. Soc.* **1933**, *55*, 3784; (c) Kappe, C. O. *J. Org. Chem.* **1997**, *62*, 7201; (d) Kappe, C. O.; Falsone, S. F. *Synlett* **1998**, 718.