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Vanadium(III) chloride catalyzed Biginelli condensation: solution phase library generation of dihydropyrimidin-(2*H*)-ones☆

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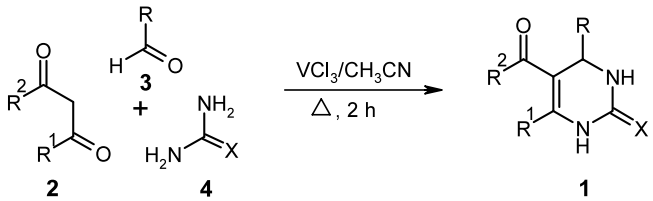
Abstract—The three component condensation of an aldehyde, a β-keto ester and urea (thiourea) in the presence of a catalytic amount of VCl_3 is disclosed for the solution phase synthesis of dihydropyrimidinones. The ease of synthesis and work-up allowed the parallel synthesis of a 48-membered library of dihydropyrimidinones quickly and efficiently in good yields.

Combinatorial chemistry is playing an increasingly important role as one of the tools of modern medicinal chemistry for the rapid discovery of new leads.[1] The preparation of libraries of small organic molecules is a rapidly evolving area of research.[2] Recently much attention has been devoted towards dihydropyrimidine derivatives due to their significant therapeutic and medicinal properties.[3] Several marine alkaloids having the dihydropyrimidinone core unit were found to show interesting biological activities such as antiviral, antitumor, antibacterial and anti-inflammatory activities.[4] In particular, the batzelladine alkaloids have been found to be potent HIV gp-120-CD4 inhibitors.[5] Many functionalised derivatives are used as calcium channel blockers, antihypertensive agents and α-1a antagonists.[6] Therefore, the preparation of this heterocyclic core unit has gained much importance. The simple and direct method originally reported by Biginelli[7] involves the one-pot condensation of a β-keto ester with an aldehyde and urea under strongly acidic conditions but often suffers from low yields when substituted aromatic and aliphatic aldehydes are employed. This has led to the disclosure of several improved procedures using strong Lewis acids such as $BF_3{\cdot}Et_2O$, protic acids such as HCl, and AcOH as additives; many other reagents[8] have also been employed, including ionic liquids, for the synthesis of these derivatives. More recently KSF has been employed for this[9] transformation but requires long reaction times (10–48 h) to obtain good yields. Most of these methods use expensive reagents, strongly acidic conditions, require long reaction times, give unsatisfactory yields and involve difficult product isolation. To the best of our knowledge, there is no report on the synthesis of a dihydropyrimidine library in solution phase.

In this communication, we disclose a simple but effective modification of the Biginelli reaction that produces high yields of dihydropyrimidinones using a catalytic amount of VCl_3 while preserving the original one-pot strategy. Vanadium(III) chloride is relatively unexplored as a reagent in organic synthesis.[10] The reactivity of VCl_3 and also the effect of solvent, time and temperature on the Biginelli reaction was explored using the model reaction between **2a**, **3a** and **4A** which gave product **1aA** (Scheme 1). The reaction was found to be complete within 2 h in refluxing acetonitrile and the product precipitated from the reaction mixture on cooling to room temperature. A catalytic amount of VCl_3 was sufficient to push the Biginelli reaction forward. To demonstrate the advantages of this procedure, we carried out the synthesis of a 48-compound library in a



Scheme 1.

Keywords: Biginelli condensation; VCl_3; dihydropyrimidin-2(1*H*)-ones; parallel synthesis.

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Table 1. A 48-membered library of dihydropyrimidinones[a,b]

Aldehyde 3 / β-Ketoester 2	a	b	c	d	e	f	g	h	i	j	4
a	**1aA** (96) **1aB** (92)	**1bA** (90)	**1cA** (90)	**1dA** (90) **1dB** (85)	**1eA** (87)	**1fA** (88)	**1gA** (92) **1gB** (86)	**1hA** (92)	**1iA** (85	**1jA** (87)	**A**
b	**1kA** (92) **1kB** (85)	**1lA** (88)	**1mA** (65)	**1nA** (87) **1nB** (80)	**1oA** (85)	**1pA** (86)	**1qA** (90)	**1rA** (86)	**1sA** (82)	**1tA** (80)	**B**
c	**1uA** (85) **1uB** (80)	**1vA** (88)	**1wA** (86) **1wB** (82)	**1xA** (82)		**1yA** (80)	**1zA** (82)	**1aaA** (85)			
d	**1abA** (80)	**1acA** (85)		**1adA** (80)		**1aeA** (85)	**1afA** (82)	**1agA** (88)			
e	**1ahA** (90)		**1aiA** (85)	**1ajA** (82)				**1akA** (86)			
f	**1alA** (86)		**1amA** (82)			**1anA** (75)	**1aoA** (85)				

[a] yields are reported in parenthesis
[b] all products were characterized by ^{1}H NMR, IR and mass spectroscopy and known compounds by comparison with reported data

parallel fashion using a Multiple synthesizer[11] in 4 sets of reactions (Table 1). For this purpose 12 reaction vessels were charged with different mixtures of substrates and a catalytic amount of VCl_3 was added to each vessel which were then heated at acetonitrile reflux temperature for 2 h after which the completed reactions were taken out of the reaction block (see experimental procedure[12]). On cooling to room temperature the products precipitated out. The reaction mixtures were then poured onto crushed ice, and the solid product separated, filtered and recrystallized. In order to increase diversity, 6 different ketoesters or 1,3-dicarbonyl substrates, 10 different aldehydes and urea or thiourea were used. The scope of the methodology was demonstrated as a variety of 1,3-dicarbonyl compounds proved effective with this protocol. Similarly, the condensation reactions were repeated three times with different combinations. All 48 compounds were formed in good yields (80–96%) and with high purity >95%. Due to short reaction times, high yields and easy work-up procedures combined with the use of the Multiple synthesizer, it was also possible to synthesize the 48 compounds within a few hours.[13]

Under these conditions, the yields were significantly increased, and the reaction time was shortened to 2 h. Most importantly, aromatic aldehydes possessing either electron-donating or electron-withdrawing substituents all reacted well, giving good to excellent yields using the Multiple synthesizer. Dimedone **2d**, a symmetrical dione also reacted efficiently with aldehydes and urea under the present reaction conditions to afford good yields of products. In the presence of a catalytic amount of VCl_3, the condensation of unsymmetrical diones such as 4-hydroxycoumarins **2e** and **2f** with aldehydes and urea proceeded smoothly to give the corresponding dihydropyrimidines in good yields in 2 h (see Table 1).

In summary, a novel solution phase procedure for the preparation of dihydropyrimidinones has been reported. The short reaction times, simple work-up and isolation of the products in high yields with high purities make this approach a feasible and attractive protocol for the generation of dihydropyrimidinone libraries as is demonstrated in Table 1.

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References

1. (a) Gordan, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med Chem.* **1994**, *37*, 1385; (b) Moos, W. H.; Green, G. D.; Pavia, M. R. In *Ann. Rep. Med Chem*; Bristol, J. A., Ed.; Academic: San Diego, 1993; Vol. 28, pp. 315–324; (c) Ecker, D. J.; Crooke, S. T. *Biotechnology* **1995**, *13*, 351; (d) Virgilio, A. A.; Ellman, J. A *J. Am. Chem. Soc.* **1994**, *116*, 11580; (e) Freier, S. M.; Konings, D. A. M.; Wyatt, J. R.; Ecker, D. J. *J. Med. Chem.* **1995**, *38*, 344; (f) Gordeev, M. F.; Gordon, E. M.; Patel, D. V. *J. Org. Chem.* **1997**, *62*, 8177.
2. (a) Bunin, B. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 10997; (b) Yu, K.-L.; Deshpande, M. S.; Vyas, D. M. *Tetrahedron Lett.* **1994**, *35*, 8919; (c) Smith, P. W.; Lai, J. Y. Y. Q.; Whittington, A. R.; Cox, B.; Houston, J. G.; Stylli, C. H.; Banks, M. N.; Tiller, P. R. *Bioorg.*

Med. Chem. Lett. **1994**, *4*, 2821; (d) Kick, E. K.; Ellman, J. A. *J. Med. Chem.* **1995**, *38*, 1427; (e) Holmes, C. P.; Jones, D. G. *J. Org. Chem.* **1995**, *60*, 2318; (f) Murphy, M. M.; Schullek, J. R.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 5381.

3. (a) Review: Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043; (b) Kappe, C. O.; Fabian, W. M. F. *Tetrahedron* **1997**, *53*, 2803; (c) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937.
4. (a) Snider, B. B.; Shi, Z. *J. Org. Chem.* **1993**, *58*, 3828 and references cited therein; (b) Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 2657 and references cited therein.
5. Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; Debrosse, C.; Mai, S.; Trunch, A.; Faulkner, D. J.; Carte, B.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westley, J. W.; Ports, B. C. M. *J. Org. Chem.* **1995**, *6*, 1182.
6. (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) 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.; Mallay, M. F. *J. Med. Chem.* **1990**, *33*, 2629.
7. Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360.
8. (a) $BF_3{\cdot}OEt_2$: Hu, E. H.; Sidler, D. R.; Dolling, U.-H. *J. Org. Chem.* **1998**, *63*, 3454; (b) HCl: Lu, J.; Ma, H. R. *Synlett* **2000**, 63; (c) $La(OTf)_3$: Ma, Y.; Qian, C.; Wang, L.; Yang, M. *J. Org. Chem.* **2000**, *65*, 3864; (d) $LiClO_4$: Yadav, J. S.; Reddy, B. V. S.; Srinivas, R.; Venugopal, C.; Ramalingam, T. *Synthesis* **2001**, 1341; (e) $FeCl_2$. $NiCl_2$: Lu, J.; Bai, Y. *Synthesis* **2002**, *4*, 466; (f) $LaCl_3.7H_2O$: Lu, J.; Bai, Y.; Wang, Z.; Yang, B.; Ma, H. *Tetrahedron Lett.* **2000**, *41*, 9075; (g) $InCl_3$: Ranu, B. C.; Hajra, A.; Jana, U. *J. Org. Chem.* **2000,** *65*, 6270; (h) $Bi(OTf)_3$: Adapa, S. R.; Alam, M. M.; Varala, R. *Synlett* **2003**, 67; (i) ionic liquids: Peng, J.; Deng, Y. *Tetrahedron Lett.* **2001**, *42*, 5917.
9. Bigi, F.; Carloni, S.; Frullanti, B.; Maggi, R.; Sartori, G. *Tetrahedron Lett.* **1999**, *40*, 3465.
10. (a) Ho, T-L.; Olah, G. A. *Synthesis* **1977**, *11*, 171 and references cited therein; (b) Inokuchi, T.; Kawafuehi, H.; Torii, S. *Synlett* **1992**, 510.
11. The table top organic synthesizer 'Carousel' stirring hot plate was used. The 48 compounds were synthesized in 4 operations, each time 12 reactions were conducted.
12. **Typical general experimental procedure**: A solution of an aldehyde (4.7 mmol), β-dicarbonyl compound (4.7 mmol) and urea or thiourea (7 mmol) in acetonitrile (10 ml) was heated under reflux in the presence of a catalytic amount of vanadium(III) chloride (10 mol%) for 2 h (TLC) (1–12 samples placed in a multiple synthesizer). The reaction mixture was then poured onto crushed ice and the solid product separated was filtered and recrystallized. The same procedure was repeated 3 more times by placing 12 samples at a time in a multiple synthesizer to provide a 48 compound library of dihydropyrimidin-(2*H*)-ones.
13. NMR data for selected compounds: **1aB**: mp 206–207°C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.15 (t, 3H, $J=7.0$ Hz), 2.30 (s, 3H), 4.05 (q, 2H, $J=7.0$ Hz), 5.22 (d, 1H, $J=3.5$ Hz), 7.20–7.38 (m, 5H, ArH), 9.30 (brs, NH), 9.95 (brs, NH). IR (KBr): ν 1585, 1672, 3100, 3185, 3338. **1jA**: mp 195–196°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.75 (d, 3H, $J=6.2$ Hz), 0.90 (d, 3H, $J=6.2$ Hz), 1.25 (t, 3H, $J=7.0$ Hz), 1.75 (m, 1H), 2.25 (s, 3H), 4.00 (t, 1H, $J=3.5$ Hz), 4.05 (q, 2H, $J=8.5$ Hz), 7.00 (brs, NH), 8.80 (brs, NH). IR (KBr): ν 1650, 1700, 3109, 3245. **1abA**: mp 167–169°C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.00 (s, 6H), 2.00–2.38 (m, 4H), 5.25 (brs, 1H, NH), 5.40 (brs, 1H, NH), 6.08 (d, 1H, $J=8.8$ Hz), 7.00–7.38 (m, 5H, Ar). IR (KBr): ν 1610, 1685, 3095, 3100. Anal. calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.31; H, 6.89; N, 10.10. **1agA**: mp 153–154°C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 0.98 (s, 6H), 2.05–2.40 (m, 4H), 5.38 (brs, 1H, NH), 6.03 (d, 1H, $J=8$ Hz), 6.70 (d, 1H, $J=4$ Hz, NH), 6.82–7.30 (m, 9H, Ar). IR (KBr): ν 1605, 1690, 3090, 3110. Anal. calcd for $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.12; N, 7.73. Found: C, 73.04; H, 6.28; N, 7.92. **1alA**: mp 224–226°C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.40 (s, 3H), 6.30 (s, 1H), 7.08–7.40 (m, 8H), 7.70 (brs, 2H, NH). IR (KBr): ν 1565, 1670, 3105, 3095. Anal. calcd for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15. Found C, 70.75; H, 4.45; N, 8.95.