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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 1345–1348

Solid supported synthesis of structurally diverse dihydropyrido[2,3-*d*]pyrimidines using microwave irradiation

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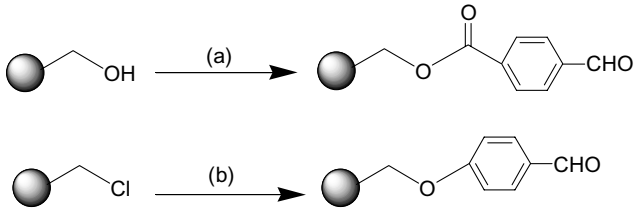
Received 27 October 2004; revised 14 December 2004; accepted 21 December 2004
Available online 11 January 2005

Abstract—We have synthesized a library of 16 dihydropyrido[2,3-*d*]pyrimidines in high yields (82–92%) on solid support using microwave irradiation.

The versatility of uracil derivatives for the synthesis of nitrogen-containing heteroaromatic species of biological importance has been well documented.[1] Pyrazolopyridines,[2] pyrimidopyrimidines,[3] pyridopurines,[4] pyrazolopyrimidines[5] and xanthine derivatives[6] have all been prepared by functionalization of these important heterocyclic building blocks, the structures of which are interesting in their own right, as well as being biologically active pyrimidine nucleosides.[7] The diverse range of biological activities (antitumour, anticancer, anti-inflammatory and CNS depressant activities) have stimulated considerable interest in the synthesis of dihydropyrido[2,3-*d*]pyrimidines via new and efficient routes. To accelerate a drug discovery program, combinatorial chemistry is recognized as a very powerful tool. The main attraction of combinatorial chemistry is the rapid synthesis of libraries of structurally related compounds, which is of great value for the identification, development and optimization of lead compounds. Solid supported synthesis is the core technology for generating combinatorial libraries of compounds due to the advantages of this technique over traditional solution approaches. For example, solid supported reactions are easier to work-up and as these reactions proceed to completion (by using high quantities of the other reactants), purification of the products are easy. The main disadvantage of solid supported reactions is the longer reaction times required in spite of using excess reactants (2–3 times), often taking 2–3 times longer to reach completion in comparison to solution phase reactions. This disadvantage can be overcome by using microwave irradiation instead of traditional heating. For example, reactions which require 8–10 h of heating by conventional methods and take 24–30 h heating in solid supported reactions, can occur within 3–5 min using microwave irradiation. Due to this advantage and parallel to the developments in combinatorial and solid phase organic synthesis, microwave enhanced synthesis has attracted a great deal of attention in recent years. During the past decade a number of reports[8] have been published that advocate the advantages and uses of microwave irradiation in organic synthesis. Dramatic increases in rates, yields and purities of products have frequently been observed with this nonconventional and energy efficient heating method. It is therefore surprising that the combination of solid phase synthesis and microwave heating[9] has so far not received much attention.



Scheme 1. Reagents and conditions: (a) 4-carboxybenzaldehyde, DIC, DMAP, NMP, MW, 15 min; (b) 4-hydroxybenzaldehyde, NaH, NMP, MW, 15 min.

Keywords: Dihydropyrido[2,3-*d*]pyrimidines; Solid support; Microwave irradiation.
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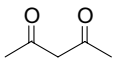
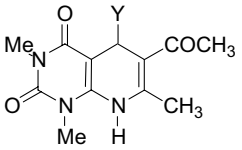
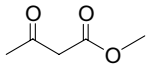
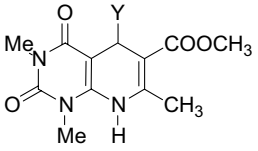
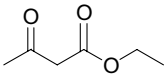
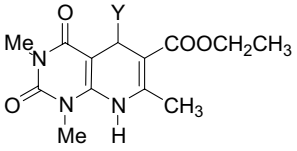
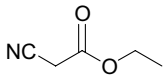
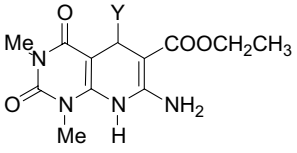
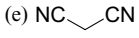
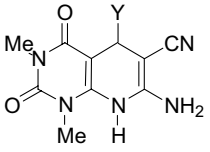
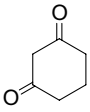
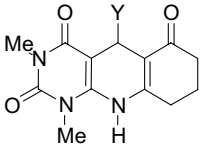
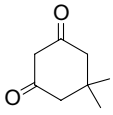
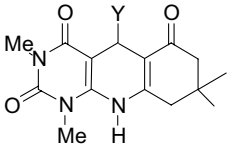
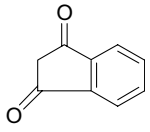
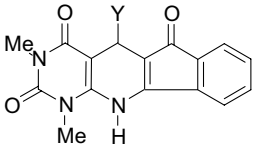
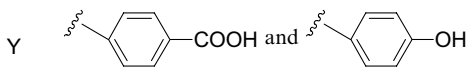
doi:10.1016/j.tetlet.2004.12.109

Table 1. Structures of the active methylene compounds and reaction products

Active methylene compounds	Products
(a) 	
(b) 	
(c) 	
(d) 	
(e) 	
(f) 	
(g) 	
(h) 	



In this communication, we describe the combination of solid support and microwave techniques to synthesize structurally diverse dihydropyrido[2,3-*d*]pyrimidines in high yields (82–92%). The synthesis of dihydropyrido[2,3-*d*]pyrimidines using 6-amino-1,3-dimethyluracil was reported by Kajino and Meguro,[10] but as a one-pot, three-component cyclocondensation reaction, suffering from very poor yields and limited substrate tolerance. We had earlier synthesized dihydropyrido[2,3-*d*]-pyrimidines in high yields and in one pot using conventional methods.[11]

As part of our ongoing program devoted to the synthesis of diverse heterocycles of biological interest,[12] we concentrated our investigations on dihydropyrido[2,3-*d*]pyrimidines due to their broad range of biological activities. Previously we have reported solid supported synthesis of quinolones,[13] substituted pyrimidines[14] and pyrimido-[4,5-*d*]pyrimidines.[15]

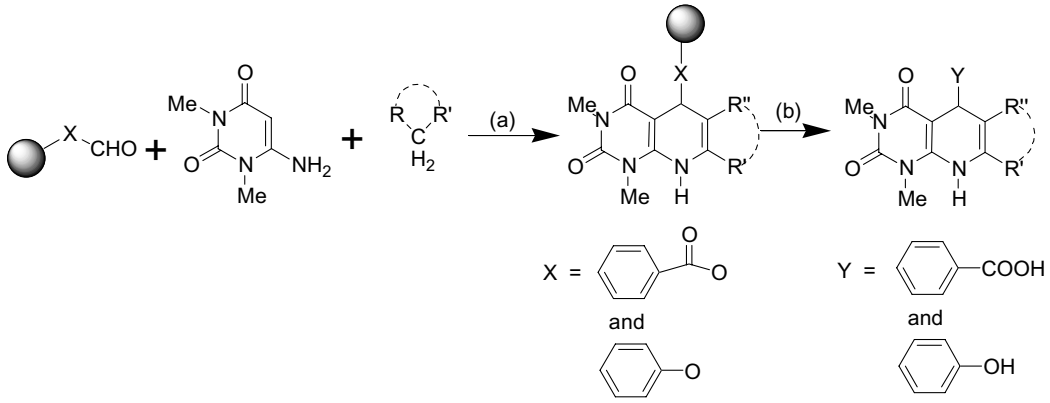
The resin-bound aldehydes were attached to Wang and Merrifield resins by condensing with 4-carboxybenzaldehyde and 4-hydroxybenzaldehyde, respectively (Scheme 1). 4-Carboxybenzaldehyde was loaded on Wang resin in the presence of DIC (1,3-diisopropylcarbodiimide) and DMAP (4-dimethylaminopyridine) in NMP (1-methyl-2-pyrrolidinone) according to a reported method.[16] The resin was heated in a domestic microwave oven at 180 W for 60×15 s with manual agitation during the intervals. 4-Hydroxybenzaldehyde was loaded on Merrifield resin by irradiation in a similar manner in the presence of NaH and NMP.

The resin-bound aldehydes were irradiated in the presence of 6-amino-1,3-dimethyluracil and compounds having an active methylene group (Table 1) in acetic acid for 60×4 s with manual agitation between each irradiation. The resin was then filtered off and washed thoroughly with DMF (3×10 mL), MeOH (3×10 mL) and CH_2Cl_2 (3×10 mL), dried under reduced pressure and used directly for the next step. The products were cleaved from the resin in high yields (82–92%) with 50% TFA and CH_2Cl_2. The solvent was evaporated and the products were recrystallized either from methanol or from chloroform and hexane. The structures were confirmed from IR, mass and NMR spectroscopic data.[17] The structures of the active methylene compounds and their corresponding products are shown in Table 1 (Scheme 2).

In conclusion, we have synthesized structurally diverse dihydropyrido[2,3-*d*]pyrimidines by three-component reactions in high yields (82–92%) on solid support using microwave irradiation. The use of microwave irradiation greatly reduced the time of reaction on solid support leading to rapid access to heterocyclic compounds.

Acknowledgements

A.A. thanks the Council of Scientific and Industrial Research (India) for the award of fellowship. We are



Scheme 2. Reagents and conditions: (a) acetic acid, MW, 60×4 s; (b) TFA–CH_2Cl_2 1:1, 30 min, rt.

also thankful to S.A.I.F., CDRI, Lucknow for providing spectroscopic data. C.D.R.I. communication no. 6683.

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17. Y = $4OHC_6H_4$ (a) MS 342 (M+1); mp 180–182 °C; IR (KBr) 3420, 2953, 1709, 1682, 1502, 1388 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 7.19 (d, 2H, $J = 8.5$ Hz), 6.74 (d, 2H, $J = 8.5$ Hz), 5.00 (s, 1H), 3.48 (s, 3H), 3.21 (s, 3H), 2.43 (s, 3H), 2.15 (s, 3H); ^{13}C (50 MHz) 199.5, 161.5, 158.5, 150.8, 142.0, 141.8, 137.1, 128.6, 128.2, 113.7, 91.5, 37.4, 29.8, 28.7, 28.2, 19.8. (b) MS 358 (M+1); mp 244–246 °C; IR (KBr) 3424, 2958, 1735, 1654, 1514, 1384 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6, 200 MHz) δ (ppm) 7.15 (d, 2H, $J = 8.4$ Hz), 6.68 (d, 2H, $J = 8.4$ Hz), 5.04 (s, 1H), 3.62 (s, 3H), 3.47 (s, 3H), 3.25 (s, 3H), 2.42 (s, 3H); ^{13}C (50 MHz) 171.9, 165.8, 159.9, 155.4, 48.6, 147.6, 141.8, 132.8, 119.3, 110.1, 95.3, 55.2, 40.6, 34.1, 32.2, 21.9. (c) MS 372 (M+1); mp 240–242 °C; IR (KBr) 3450, 2932, 1732, 1648, 1512, 1378 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6, 200 MHz) δ (ppm) 7.20 (d, 2H, $J = 8.4$ Hz), 6.68 (d, 2H, $J = 8.4$ Hz), 5.06 (s, 1H), 4.08 (q, 2H, $J = 7.0$ Hz), 3.49 (s, 3H), 3.27 (s, 3H), 2.46 (s, 3H), 1.21 (t, 3H, $J = 5.95$ Hz); ^{13}C (50 MHz) 172.3, 166.7, 160.7, 156.4, 149.1, 148.6, 142.9, 133.9, 120.1, 111.3, 96.2, 64.9, 41.7, 34.9, 33.1, 23.8, 19.3. (d) MS 373 (M+1); mp 230–232 °C; IR (KBr) 3426, 3340, 2952, 1740, 1686, 1522, 1396 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6, 200 MHz) δ (ppm) 7.16 (d, 2H, $J = 8.4$ Hz), 6.70 (d, 2H, $J = 8.4$ Hz), 5.01 (s, 1H), 4.06 (q, 2H, $J = 6.9$ Hz), 3.48 (s, 3H), 3.21 (s, 3H), 1.26 (t, 3H, $J = 4.5$ Hz); ^{13}C (50 MHz) 172.1, 166.5, 160.5, 156.3, 154.7, 149.2, 148.6, 133.8, 120.1, 111.3, 96.2, 64.9, 41.7, 34.9, 33.2, 23.8. (e) MS 326 (M+1); mp 210–212 °C; IR (KBr) 3426, 3342, 2952, 2195, 1712, 1678, 1554, 1374 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6, 200 MHz) δ

(ppm) 7.17 (d, 2H, $J = 8.5$ Hz), 6.68 (d, 2H, $J = 8.5$ Hz), 5.03 (s, 1H), 4.8 (s, 2H, NH_2), 3.48 (s, 3H), 3.24 (s, 3H); ^{13}C (50 MHz) 161.5, 160.8, 158.5, 150.8, 142.0, 137.1, 128.6, 128.2, 118.4, 113.7, 71.5, 37.4, 29.8, 28.7. (f) MS 354 (M+1); mp decomposes at 250 °C; IR (KBr) 3425, 2912, 1706, 1682, 1512 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6, 200 MHz) δ (ppm) 7.11 (d, 2H,$J = 8.5$ Hz), 6.69 (d, 2H, $J = 8.5$ Hz), 4.95 (s, 1H), 3.48 (s, 3H), 3.25 (s, 3H), 2.63 (t, 2H, $J = 4.8$ Hz), 2.37 (t, 2H, $J = 4.8$ Hz), 2.03 (m, 2H). ^{13}C (50 MHz) 199.9, 166.5, 161.7, 154.3, 153.9, 148.7, 142.6, 133.4, 120.3, 118.4. 96.6, 55.4, 45.5, 38.5, 35.5, 33.2, 19.2. (g) MS 382 (M+1); mp 238–240 °C; IR (KBr) 3430, 2924, 1712, 1668, 1540 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6, 200 MHz) δ (ppm) 7.17 (d, 2H, $J = 8.2$ Hz), 6.69 (d, 2H, $J = 8.2$ Hz), 5.08 (s, 1H), 3.47 (s, 3H), 3.24 (s, 3H), 2.57 (s, 2H), 2.48 (s, 2H), 1.06 (s, 3H), 0.94 (s, 3H). ^{13}C (50 MHz) 200.7, 166.6, 160.7, 156.3, 154.7, 148.9, 142.5, 133.9, 120.0, 118.1. 96.9, 55.8, 45.5, 38.5, 35.5, 34.6, 33.2, 32.2, 18.4. (h) MS 388 (M+1); mp >250 °C; IR (KBr) 3442, 2942, 1708, 1658, 1568 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6, 200 MHz) δ (ppm) 7.88 (d, 1H, $J = 8.2$ Hz), 7.50–7.60 (m, 3H), 7.18 (d, 2H, $J = 8.2$ Hz), 6.76 (d, 2H, $J = 8.2$ Hz), 5.00 (s, 1H), 3.46 (s, 3H), 3.24 (s, 3H). ^{13}C (50 MHz) 189.4, 161.5, 158.5, 150.8, 142.0, 141.8, 137.1, 136.3, 134.6, 132.4, 128.6, 127.8, 126.6, 126.2, 113.7, 61.5, 50.6, 37.4, 29.8, 28.7.