Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 49–51

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

# Highly Versatile Solid Phase Synthesis of Biofunctional 4-Aryl-3,4-dihydropyrimidines Using Resin-Bound Isothiourea Building Blocks and Multidirectional Resin Cleavage†

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Received 8 September 1999; accepted 14 October 1999

**Abstract**—A series of pharmacologically active, functionalized 4-aryl-3,4-dihydropyrimidine-5-carboxylates (DHPMs) are prepared by a versatile novel solid phase approach. In the key step, a polymer-bound thiouronium salt is condensed with unsaturated β-ketoesters. The resulting polymer bound 1,4-dihydropyrimidines are cleaved from the resin employing multidirectional resin cleavage strategies. 

The generation of combinatorial libraries of heterocyclic compounds by solid phase synthesis is of great interest for accelerating lead discovery and lead optimization in pharmaceutical research.[1,2] Multicomponent reactions (MCRs) leading to heterocycles are particularly useful for the creation of diverse chemical libraries, since the combination of $n \geq 3$ small molecular weight building blocks in a single operation leads to high combinatorial efficiacy.[1–4] Therefore, solid phase modifications of MCRs are rapidly becoming the cornerstone of combinatorial synthesis of small-molecule libraries.[1–6] One such MCR that has attracted considerable attention in recent years is the Biginelli reaction, which involves the one-pot cyclocondensation of a β-ketoester with an aryl aldehyde and an urea derivative (Scheme 1).[7] The resulting 4-aryl-3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) **2** exhibit a broad range of biological effects,[7] and have recently emerged as e.g. antihypertensive agents (SQ 32,926),[8–10] $\alpha_{1a}$ adrenergic antagonists (SNAP 6552),[11] and neuropeptide Y antagonists.[12] In recent years, several combinatorial protocols based on the classical three-component Biginelli condensation have been advanced,[13–17] employing e.g. solid phase,[13,14] or fluorous phase[15] reaction conditions. In these procedures, however, the urea component is linked to the solid (or fluorous) support via the amide nitrogen, which invariably leads to the formation of *N*1-functionalized, so far pharmacologically inactive, DHPMs of type **1** (Scheme 1).[13–15]

We now disclose a novel solid phase strategy towards DHPMs, that not only allows the synthesis of the desired *N*1-unsubstituted DHPM derivatives, but also should provide for the generation of the pharmacologically attractive *N*3-acylated analogues of type **2** (i.e. SQ 32,926,[8–10] SNAP 6552[11]).

The overall synthetic strategy for the synthesis of DHPMs **7**–**12** is outlined in Scheme 2. Treatment of resin-bound 4-(benzyloxy)-benzyl chloride (**4**, Wang equivalent) with excess thiourea in *N*-methyl-2-pyrrolidinone (NMP) at 75 °C furnished polymer bound thiouronium salt **5** in quantitative yield (FTIR).[20,21] Subsequent condensation of **5** with enones **3a**–**e** (1.5–2.5 equiv) was performed in NMP at 90 °C for 16 h in the presence of $Cs_2CO_3$ (1.5 equiv) to furnish polymer bound 1,4-dihydropyrimidines **6a**–**e**. The direct three component condensation of β-ketoester, aryl aldehyde and thiouronium salt **5** proved less attractive due to the formation of various side products.

In order to obtain the desired dihydropyrimidin-2(1*H*)-ones **7a**–**d** the corresponding polymer-bound 1,4-dihydropyrimidines **6a**–**d** were exposed to a dioxane/ethanol/AcOH/water mixture (cleavage condition A) which effectively liberated the products from the resin in a hydrolytic manner. DHPMs **7a**–**d** were obtained in 61–77% yield (over 3 steps, based on initial Cl loading of **1**, see Table 1) and showed >95% purity by $^1$H NMR

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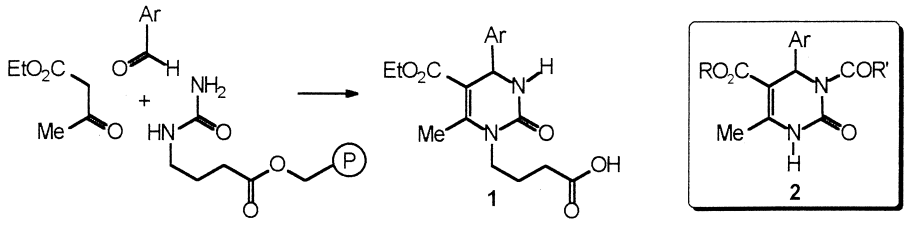
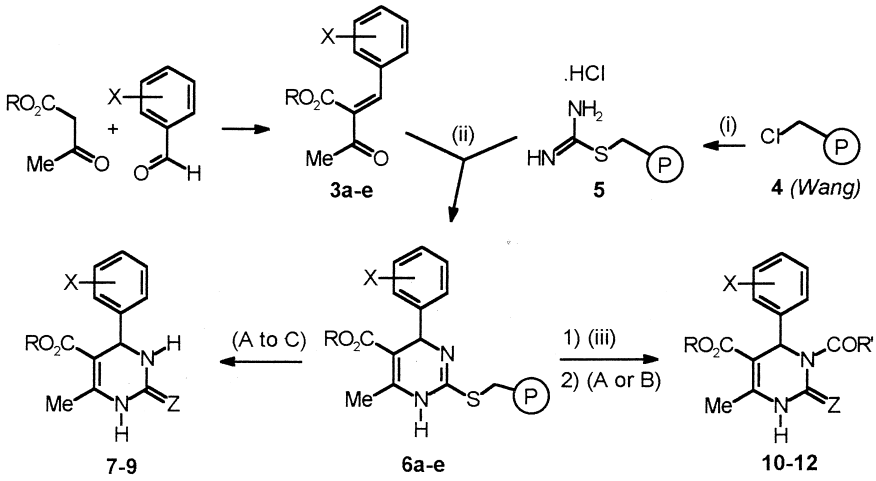
†Synthesis and reactions of Biginelli compounds, part 17; part 16 see Kappe, C. O.; Kumar, D.; Varma, R. S. *Synthesis* **1999**, pp. 1799–1803.

0960-894X/00/$ - see front matter 
PII: S0960-894X(99)00572-7



**Scheme 1.**



**Scheme 2.** Reagents and conditions:[24] (i) thiourea, NMP, 75 °C, 16 h; (ii) NMP, $Cs_2CO_3$, 90 °C, 16 h; (iii) Cl-COR′, pyridine, $CH_2Cl_2$, 0 °C→rt, 6 h; (A) dioxane, ethanol, AcOH, $H_2O$, reflux, 16 h; (B) TFA, EtSH, $CH_2Cl_2$, rt, 16 h; (C) dioxane, MeCN, $NH_4OAc$, reflux, 8 h.

**Table 1.** Preparation of 4-aryldihydropyrimidines (DHPMs) **7–12**[a]

| DHPM | Enone **3**[b] | *X* | *R* | *Z* | *R′* | Cleavage | Yield[c] |
|---|---|---|---|---|---|---|---|
| **7a** | **3a** | H | Et | O | | A | 71 |
| **8a** | **3a** | H | Et | S | | B | 66 |
| **7b** | **3b** | 3-$NO_2$ | Et | O | | A | 68 |
| **8b** | **3b** | 3-$NO_2$ | Et | S | | B | 62 |
| **7c** | **3c** | 2,3-$Cl_2$ | Et | O | | A | 65 |
| **8c** | **3c** | 2,3-$Cl_2$ | Et | S | | B | 63 |
| **7d** | **3d** | 2-$CF_3$ | Et | O | | A | 61 |
| **8d** | **3d** | 2-$CF_3$ | Et | S | | B | 59 |
| **9** | **3a** | H | Et | NH[d] | | C | 62 |
| **10b** | **3b** | 3-$NO_2$ | Et | O | OEt | A | 55[e] |
| **11b** | **3b** | 3-$NO_2$ | Et | S | OEt | B | 41[e] |
| **12e** | **3e** | 3-$NO_2$ | *i*-Pr | O | $NMe_2$ | A | 49[e] |

[a]DHPMs **7**, **8**, **10–12** were fully characterized by $^1$H NMR spectroscopy and identified by comparison with authentic materials (refs 8–10, 18, 19 and 23). Spectral and analytical data for **9** are given in ref 21.
[b]Enones were prepared by standard Knoevenagel condensation of the corresponding aryl aldehydes and β-ketoesters.
[c]Isolated yields.
[d]Isolated as crystalline acetate salt.
[e]After purification by silica gel flash chromatography.

analysis. As a consequence of using the acid labile Wang linker the corresponding dihydropyrimidine-2(1*H*)-thiones **8a–d** could also be accessed from **6a–d** in similar yields and purities by a benzylic-type cleavage using TFA/EtSH/$CH_2Cl_2$ cleaving conditions[19] (cleavage condition B, see Table 1). In addition, ammonolysis of **6a** with excess $NH_4OAc$ in dioxane/MeCN (cleavage condition C) provides an easy entry to the 2-imino-3,4-dihydropyrimidine analogue **9** in 62% overall yield (obtained as a crystalline acetate salt). The combination of the isothiourea moiety with the Wang linker, therefore, provides the opportunity to carry out multidirectional resin cleavage[22] from a common polymer-bound intermediate using different cleavage conditions. Therefore, in the final cleavage step an additional element of diversity is incorporated (i.e. $Z$ = O, S, NH in DHPMs **7–12**) which multiplies the number of DHPMs that can be generated by three.

Another important feature of this solid phase protocol is that polymer-bound 1,4-dihydropyrimidines of type **6** (i.e. **6b,e**) can be regioselectively acylated at the *N*3 position with electrophiles such as ethyl chloroformate or *N*,*N*-dimethylcarbamoyl chloride.[23] In this way, an additional element of diversity can be introduced onto the pyrimidine scaffold, making pharmacologically attractive target molecules of type **2**[7–12] accessible. The acylations are conveniently carried out in $CH_2Cl_2$ solution at rt using a 2-fold excess of the electrophile in the presence of pyridine (2 equiv) as a base. Subsequent cleavage from the resin leading to DHPMs **10b** and **12e** could be achieved using cleavage conditions A, although here 48 h were necessary to completely liberate the desired compounds from the resin. As expected, cleavage using conditions B (for **6b**) proceeded smoothly and provided the corresponding sulfur analogue **11b**. For N3-acylated DHPMs **10–12** the purity of the crude materials was 75–85% ($^1$H NMR) and, therefore, further purification had to be carried out by flash chromatography (overall yield over 4 steps 41–55%, see Table 1).

In conclusion, we have developed a highly versatile and general solid phase protocol for the synthesis of functionalized 4-aryl-3,4-dihydropyrimidines. This approach is particularly atttractive for the preparation of the pharmacologically active *N*3-acylated analogues of type **2** and should be useful for the generation of targeted libraries of this heterocyclic scaffold. A key feature in this method is the multidirectional cleavage of the thiouronium-derived Wang linker. By choosing individual building blocks and cleaving strategies, a high degree of molecular diversity can be achieved in a small number of steps.

## Acknowledgements

This work was supported by the Austrian Academy of Sciences (APART 319) and the Austrian Science Fund (FWF, Project P-11994-CHE).

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24. Typical procedure: A mixture of resin bound 4-(benzyloxy)-benzyl chloride (**4**, 500 mg, 1.10 meq/g, Fluka) and thiourea (200 mg, 2.63 mmol) in anhydrous NMP (5 mL) was heated at 75 °C for 16 h. The resin was successively washed with NMP (2×5 mL), THF (3×5 mL), MeOH (3×5 mL), and $CH_2Cl_2$ (3×5 mL), and subsequently dried under high vacuum for 10 h. The resulting resin **5** was treated with NMP (5 mL), enone **3a** (218 mg, 1.00 mmol), and $Cs_2CO_3$ (260 mg, 0.80 mmol) at 90 °C for 16 h. The resin was washed with NMP (2×5 mL), MeOH (3×5 mL), $H_2O$ (3×5 mL), MeOH (3×5 mL), and air-dried to give polymer-bound dihydropyrimidine **6a**. This material was then treated (cleavage conditions A) with a mixture of dioxane (5 mL), ethanol (5 mL), AcOH (1 mL), and water (1 mL) at reflux temperature for 16 h. The cleaved material was isolated by filtration and the resin rinsed with ethanol (2×5 mL); the solvent was removed in vacuo and the resulting solid triturated with water. The solid product was collected by filtration and dried to give **7a** (102 mg, 71% based on Cl loading of **4**) in >95% purity ($^1$H NMR). A second batch of the resin bound dihydropyrimidine **6a** (see above) was treated with a mixture (cleavage condition C) of dioxane (4 mL), MeCN (4 mL) and $NH_4OAc$ (385 mg, 5 mmol) at reflux temperature for 8 h. The hot mixture was filtered from the resin and evaporated in vacuo. Trituration with $H_2O$ left DHPM **9** as a crystalline acetate salt in 62% yield and > 95% purity ($^1$H NMR), mp. 230 °C dec.; $^1$H NMR (DMSO-$d_6$): 1.09 (t, $J$=7.5 Hz, 3H), 1.72 (s, 3H), 2.28 (s, 3H), 3.98 (q, $J$=7.5 Hz, 2H), 5.23 (s, 1H), 7.19–7.38 (m, 5H); $^{13}$C NMR (DMSO-$d_6$): 14.1, 19.2, 23.9, 52.1, 59.1, 99.8, 126.3, 127.5, 128.5, 144.5, 151.0, 153.5, 165.4, 175.4; calcd for $C_{16}H_{21}N_3O_4$: C, 60.18; H, 6.63; N, 13.16. Found: C, 60.26; H, 6.65; N, 13.00. MS (EI): $m/z$=259.