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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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. © 1999 Elsevier Science Ltd. All rights reserved.

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 ≥ 3 small molecular weight building blocks in a single operation leads to high combinatorial efficacy.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(1H)-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 α1a 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 phase15 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 N1-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 N1-unsubstituted DHPM derivatives, but also should provide for the generation of the pharmacologically attractive N3-acylated analogues of type 2 (i.e. SQ 32,926,8–10 SNAP 655211).

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 Cs2CO3 (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(1H)-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 1H NMR.

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As a consequence of using the acid labile Wang linker the corresponding dihydropyrimidine-2(1H)-thiones 8a–d could also be accessed from 6a–d in similar yields and purities by a benzylic-type cleavage using TFA/EtSH/CH₂Cl₂ cleaving conditions¹⁹ (cleavage condition B, see Table 1). In addition, ammonolysis of 6a with excess NH₄OAc 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 multi-directional resin cleavage²² 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 N₃ 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 7–12 accessible. The acylations are conveniently carried out in CH₂Cl₂ 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% (¹H 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 attractive for the preparation of the pharmacologically active N3-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

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References and Notes

7. For a review on DHPMs, see: Kappe, C. O. Tetrahedron 1993, 49, 6937.
24. Typical procedure: A mixture of resin bound 4-(benzyl oxy)-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 CH2Cl2 (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 Cs2CO3 (260 mg, 0.80 mmol) at 90°C for 16 h. The resin was washed with NMP (2×5 mL), MeOH (3×5 mL), H2O (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 (1 mL) at 80°C. The cleaved material was filtered 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 load of 4) in >95% purity (1H NMR). A second batch of the resin bound dihydropyrimidine 6a (see above) was treated with a mixture (cleavage condition C) of dioxane (4 mL), ethanol (5 mL), AcOH (1 mL), and water (1 mL) at reflux temperature for 8 h. The hot mixture was filtered from the resin and evaporated in vacuo. Trtitration with H2O left DHPM 9 as a crystalline acetate salt in 62% yield and >95% purity (1H NMR), mp. 230°C dec.; 1H NMR (DMSO-d6): 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); 13C NMR (DMSO-d6): 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; cdcl3 for C18H17N3O4C: 60.18; H: 6.63; N: 13.16. Found: C: 60.26; H: 6.65; N: 13.00. MS (EI): m/z = 259.