Pergamon

Tetrahedron Letters 41 (2000) 8177–8181

TETRAHEDRON LETTERS

4,6-Dichloro-5-nitropyrimidine: a versatile building block for the solid phase synthesis of dihydropteridinones

Anthony D. Baxter, E. Andrew Boyd, Philip B. Cox,* Vincent Loh Jr., Claude Monteils and Andrew Proud

Discovery Division, Oxford Asymmetry International plc, 111 Milton Park, Milton, Abingdon, Oxon OX14 4RX, UK

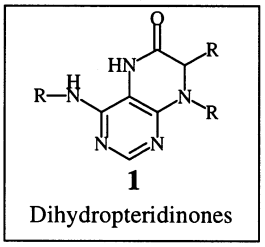
Received 22 June 2000; revised 17 August 2000; accepted 23 August 2000

Abstract

This letter describes a novel, flexible, solid phase route to pyrimidine-based heterocycles that utilises commercially available 4,6-dichloro-5-nitropyrimidine. This was exemplified by the synthesis of dihydropteridinones. © 2000 Elsevier Science Ltd. All rights reserved.

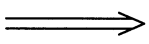
Keywords: combinatorial chemistry; solid phase synthesis; 4,6-dichloro-5-nitropyrimidine; dihydropteridinones.

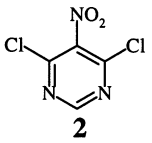
Combinatorial chemistry is recognised as a very powerful tool for the acceleration of the drug discovery process. The philosophy behind how combinatorial methods can be employed more effectively has become more refined to allow for such concepts as 'privileged structures'[1] and the synthesis of libraries that contain 'drug-like' characteristics, e.g. those that generally obey Lipinski's rules[2] and Rich's concept of resistance to hydrophobic collapse.[3]



1

Dihydropteridinones





2

4,6-Dichloro-5-nitropyrimidine

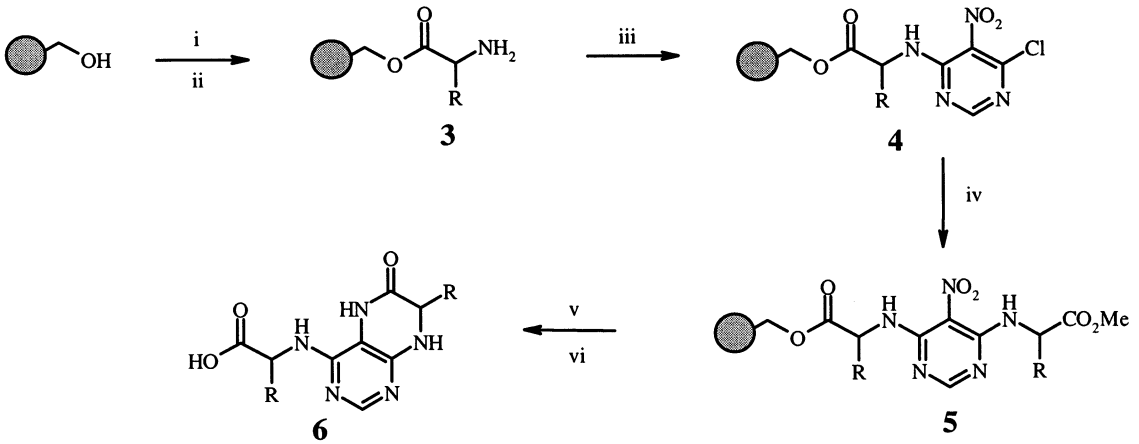
* Corresponding author. E-mail: pcox@oai.co.uk

PII: S0040-4039(00)01427-1

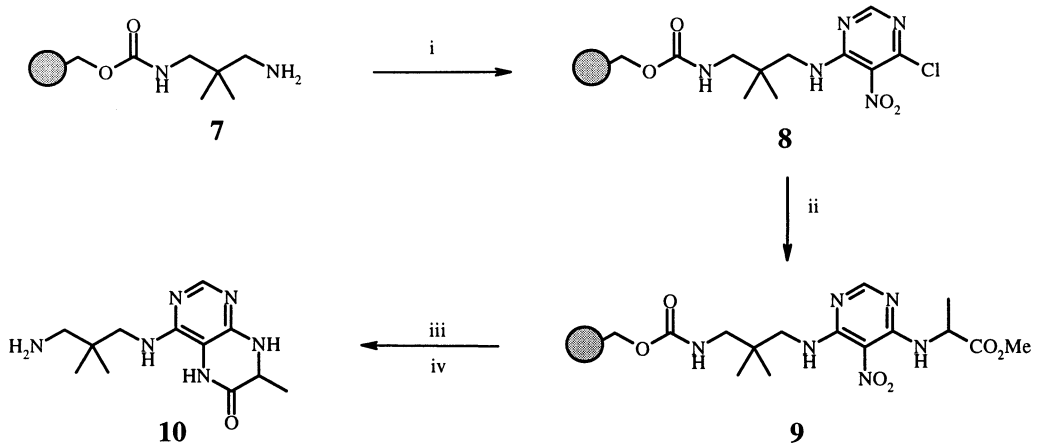
The design, and synthesis, of library scaffolds that possess 'drug-like' characteristics, and that are also amenable to parallel high throughput synthesis methods, remains a continuing challenge for the combinatorial chemist.[4] Recently, we embarked on a development programme for the solid phase parallel synthesis of the biologically interesting heterocycles, the dihydropteridinones **1**. The dihydropteridinones have a well exemplified history in the drug discovery arena[5] and as a chemical class, their structural rigidity, clog P, and range of H-bonding and accepting groups make them ideal templates upon which to base a discovery library. Furthermore, a solid phase synthetic route to such derivatives remains, as yet, unreported.

Our initial aim was to develop a flexible route that would allow for the synthesis of a wide structural range of compounds utilising one central pyrimidine building block. We envisaged that 4,6-dichloro-5-nitropyrimidine **2** would be a suitable candidate as it should be possible to differentially functionalise using sequential nucleophilic aromatic substitution (S_NAr)—first by substitution of the pyrimidine onto a resin bound amine, followed by further substitution with an amino acid methyl ester. Subsequent nitro-group reduction and concomitant cyclisation should then afford the required dihydropteridinone **1**.

After initial loading of Wang resin[6] with an Fmoc-protected amino acid and subsequent Fmoc removal, the resin-bound amine **3** was treated with three equivalents of 4,6-dichloro-5-nitropyrimidine,[7] in the presence of Hünigs base, to cleanly load the pyrimidine on resin[8] (Scheme 1). The resin-bound chloropyrimidine **4** was then further functionalised with a range of amino acid methyl esters and subsequently reductively cyclised, utilising tin(II) chloride,[9] and cleaved with TFA, to provide the desired dihydropteridinones **6** in good yield and purity.[10] In order to extend the diversity of this method we also explored the possibility of using diamine functionalised Wang resin **7** to form the corresponding amino dihydropteridinone **10** (Scheme 2).



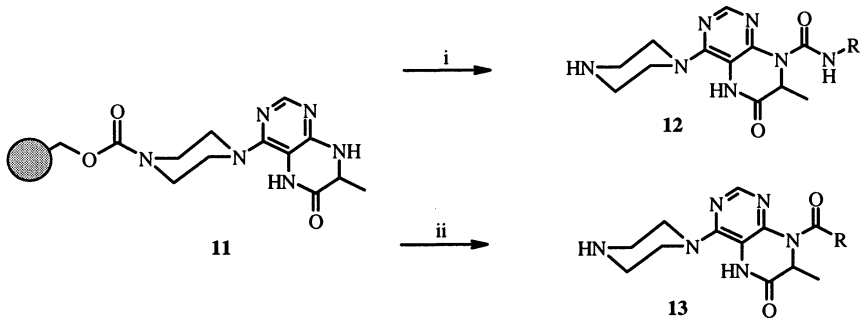
Scheme 1. Reagents: (i) FmocNHCHRCO$_2$H (3 equiv.), DIC (3 equiv.), DMAP (cat.), DMF (95%, by weight); (ii) piperidine/DMF (1:4 v/v); (iii) 2,6-dichloro-5-nitropyrimidine (3 equiv.), ^{i}Pr$_2$NEt (3 equiv.), DMF, 4 h, rt (75–90% by weight); (iv) HCl·NH$_2$CHRCO$_2$Me (5 equiv.), ^{i}Pr$_2$NEt (10 equiv.), DMF, 4 h, rt (75–90% by weight); (v) SnCl$_2$·H$_2$O, EtOH, DMF, 70°C, o/n; (vi) 50% TFA, DCM



Scheme 2. Reagents: (i) 4,6-dichloro-5-nitropyrimidine (3 equiv.), $^{i}Pr_2NEt$ (3 equiv.), DMF, 4 h, rt (75–90% by weight); (ii) $HCl{\cdot}NH_2CH(Me)CO_2Me$ (3 equiv.), $^{i}Pr_2NEt$ (3 equiv.), DMF, 4 h, rt (75–90% by weight); (iii) $SnCl_2{\cdot}H_2O$, EtOH, DMF, 70°C, 4 h; (iv) 50% TFA, DCM

Thus diamino Wang resin **7** was treated with 4,6-dichloro-5-nitropyrimidine using the same conditions as described earlier to provide the desired chloropyrimidine **8** on resin. Further aromatic substitution with alanine methyl ester hydrochloride then provided the fully substituted pyrimidine **9**. Cyclisation and cleavage proceeded smoothly to provide the desired dihydropteridinone **10** in good overall yield and purity (see entries 7 and 8 in Table 1).

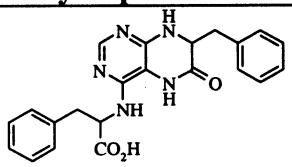
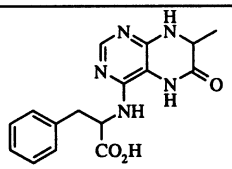
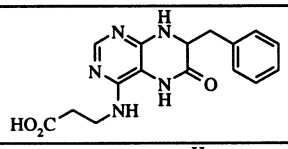
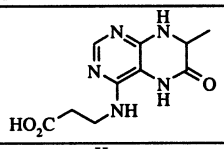
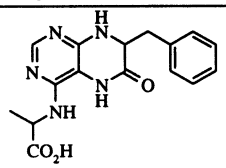
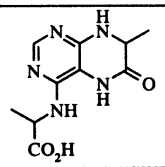
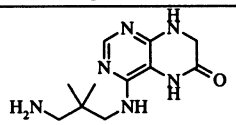
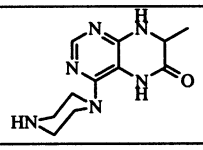
Further functionalisation of these compounds is also possible on the solid phase by treatment with isocyanates or acid chlorides to provide the corresponding ureas and amides in good yield and purity. As these heterocycles now incorporate three points of diversity, we are currently extending the scope of this chemistry in order to produce large numbers of these potentially biologically significant heterocycles (Scheme 3).



Scheme 3. Reagents: (i) RNCO, THF, rt, 16 h, TFA, DCM; (ii) RCOCl, $^{i}Pr_2NEt$ (3 equiv.), DCM, 16 h, rt, TFA, DCM

We have demonstrated that 4,6-dichloro-5-nitropyrimidine is an excellent building block for the assembly of dihydropteridinones on the solid phase. We are currently taking full advantage of the versatility of this compound by extending the chemistry to encompass the synthesis of purine analogues and other pyrimidine-based heterocycles; we will publish our findings forthwith.[11]

Table 1

Entry	Dihydropteridinones	Analysis	MS(ES$^+$)	Purity/Yield
1		LC, MS, LC/MS	M+H: 403.80	65%/45%
2		LC, MS, LC/MS	M+H: 328.05	61%/95%
3		LC, MS, LC/MS NMR	M+H: 328.05	85%/95%
4		LC, MS, LC/MS NMR	M+H: 252.18	70%/95%
5		LC, MS, NMR	M+H: 328.12	70%/45%
6		LC, MS, LC/MS	M+H: 252.06	70%/76%
7		LC, MS, NMR	M+H: 251.0	90%/84%
8		LC, MS, NMR	M+H: 249.00	95%/90%

Acknowledgements

We thank the Analytical Department at OAI for expert MS, LC, and LC/MS analysis. We also wish to thank Dr. C. Holyoke, Dr. S. Lee, and Dr. M. Howard of DuPont Agricultural Products for helpful discussions.

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4. For examples of comprehensive reviews on combinatorial and solid supported chemistry see: (a) Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *30*, 8135–8173. (b) Balkenhohl, F.; Bussche-Huennefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288–2337. (c) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, 449–472. (d) Terrett, N. K. *Combinatorial Chemistry*; Oxford University Press: Oxford, 1998. (e) Bunin, B. A. *The Combinatorial Index*; Academic Press: San Diego, 1998. (f) Obrecht, D.; Villalgordo, J. M. *Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries*; Elsevier Science Ltd: Oxford, 1998.
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6. Wang, S.-S. *J. Am. Chem. Soc.* **1973**, *95*, 1328–1333.
7. General experimental method for the coupling of amine (either resin-bound or in solution) with the chloropyrimidine (either resin-bound or in solution): the resin-bound amine or chloropyrimidine was pre-swollen in a minimum volume of DCM. A solution of amine or 4,6-dichloro-5-nitropyrimidine (3 equiv.) and Hünigs base (3 equiv.) in DCM (3×volume used to swell resin) was added, and the mixture agitated for 16 h. The reaction was then filtered and washed with equal volumes of DCM, methanol, DCM, methanol, DCM and ether. The resin was then dried in a stream of air for 15 min. A sample of resin was cleaved with 50% TFA in DCM for 1 h.
8. For some recent examples of S_NAr reactions on the solid phase see: Tumelty, D.; Schwartz, M. K.; Needels, M. C. *Tetrahedron Lett.* **1998**, *39*, 7467–7470. Lee, J.; Gauthier, D.; Rivero, R. A. *Tetrahedron Lett.* **1998**, *39*, 201–204; Mayer, J. P.; Lewis, G. S.; McGee, C.; Bankaitis-Davis, D. *Tetrahedron Lett.* **1998**, *39*, 6655.
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10. General experimental procedure for reductive cyclisation: tin(II) chloride dihydrate (4.8 g) was dissolved in oxygen free ethanol (10 ml) to this solution was added oxygen free DMF (20 mL). The resin bound methyl ester (1 equiv.) was suspended in the tin(II) chloride dihydrate solution (5 equiv.) and the mixture heated at 70°C with agitation for 16 h. The resin was filtered and washed with equal volumes of DMF, methanol, DCM, methanol, DCM and ether. The resin was then dried in a stream of air for 15 min. A sample of resin was cleaved with 50% TFA in DCM for 1 h.
11. Since the preparation of this manuscript, Gilbert and co-workers have published a procedure for the solid phase synthesis of purines that employs 4,6-dichloro-5-nitropyrimidine as a key building block: DiLucrezia, R.; Gilbert, I. H.; Floyd, C. D. *J. Comb. Chem.* **2000**, *2*, 249–253.