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A traceless solid-phase synthesis of pteridines

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Abstract—The linking of pyrimidines to polystyrene supports via either a 2- or 4-thioether provides access to pteridines through solid-phase synthesis. Oxidative cleavage (dimethyldioxirane) followed by nucleophilic substitution by amines, azide, or water completes a traceless synthesis of pteridines.

1. Introduction

Solid-phase synthesis is well established as a major contributor to the discovery of novel biologically active compounds. Although deriving originally from oligopeptide synthesis many methods have now been described for the synthesis of heterocyclic systems.[1] Recent emphasis has been on so-called 'traceless linkers' to join the desired synthetic intermediates and products to the solid support so that cleavage can be accomplished without leaving a residue or trace of the linker. In that context, sulfur linkers have been attractive for heterocyclic synthesis because, if placed in a position adjacent to a pyridine-like nitrogen atom, they can be cleaved by nucleophilic aromatic substitution[2–5] using amines, with or without activation of the linker by oxidation to the corresponding sulfone, or by reductive cleavage using Raney nickel.[5] The only report so far of a pteridine synthesis by solid-phase methods has been a non-traceless synthesis of tetrahydropterins based upon Wang resin supported amino acid chemistry.[6] In view of the immense biological importance of pteridines and their derivatives, it is important that a flexible solid-phase methodology be available for their synthesis. Our long term aim, therefore was to develop a traceless synthesis of purines, pteridines, and related heterocyclic compounds of relevance to the study of pteridine biosynthesis and metabolism. In doing this, we were concerned to achieve the maximum possible versatility in terms of the heterocyclic systems accessible and the largest possible number of points of diversity. The substitution chemistry of pyrimidines is such that a linker could in principle equally be placed at the 2- or 4-positions thereby giving access to variations in structure at either site. In pyrimidines and derivatives, structural variation was planned for five sites (2, 4, 6, 7 and 8) and in purines and derivatives for five sites also (2, 4, 7, 8 and 9). Thus, in principle the full exploitation of this strategy would allow for the preparation of highly diverse libraries of natural product analogues. Some of the chemistry supporting this challenge has been described in previous papers.[7–9] However, as is well known, heterocyclic compounds are prone to substantial changes in reactivity due to substituent effects with the outcome that several approaches are necessary to tackle the broad challenge outlined above and that there are limitations in what can be achieved. The target of this study leading to a traceless synthesis is summarised in Figure 1 and the standard reaction scheme is shown in Figure 2.

2. Ring synthesis on solid supports

Synthesis of pteridines using linkage through 2- and 4-thioethers was investigated. For linking the pyrimidine through 2-sulfanyl ethers, two chloromethyl resins were used. Type A was a polystyrene resin cross linked with 2% divinylbenzene with a high loading of 6.05 mmol g^{-1} (courtesy of Professor David Sherrington, Strathclyde). Type B was a commercially available resin (Novabiochem) with lower cross linking (1%) and lower

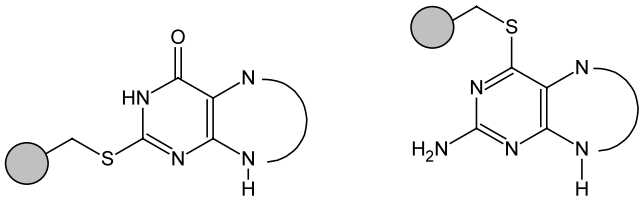

Figure 1. Targets for solid-phase synthesis of pteridines.

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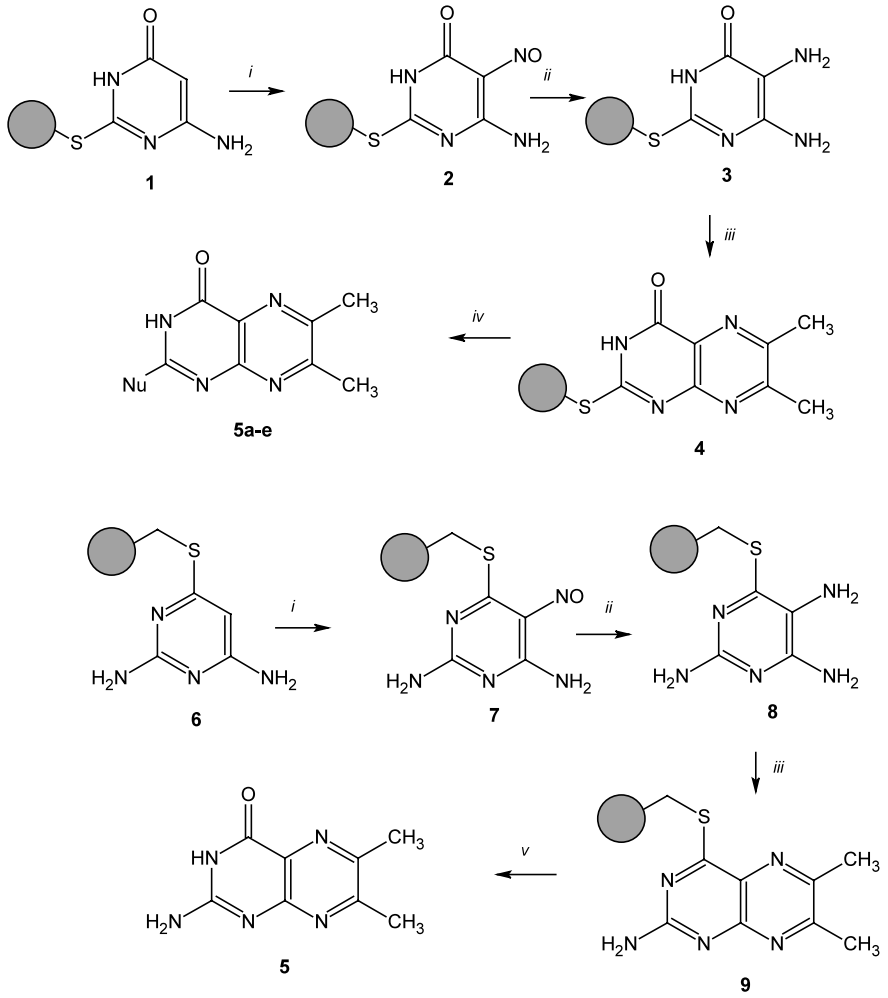

Figure 2. Reaction scheme for the synthesis of pteridines on polystyrene supports. **5a** Nu = OH, **b** Nu = NH_2, **c** Nu = $NHCH_2CH{=}CH_2$, **d** Nu = pyrrolidin-1-yl, **e** Nu = N_3. *Reagents and conditions*: (*i*) $NaNO_2$/HOAc, aq. DMF, rt 24 h; (*ii*) NaS_2O_4, aq. DMF, 40°C, 20 h; (*iii*) biacetyl (5 equiv.), DMF, 80°C 18 h; (*iv*) DDO (>4 equiv.) in acetone, rt, 4–10 h, then NuH in DMF (Nu as above); (*v*) DDO (5 equiv.) in acetone, rt 8 h, then H_2O.

loading (1.94 mmol g^{-1}). Although the loading and physical properties of solid supports can be very important in the success of solid-phase synthesis, in practice, there was no significant difference in handling between the two resins in our hands but higher reaction yields were usually obtained with of resin Type B. The resins were loaded with 6-amino-2-sulfanylpyrimidin-4(3*H*)-one by stirring in suspension in DMSO in the presence of potassium iodide and potassium hydroxide. For linkage through 4-sulfanyl ethers, a commercially available thiol-functionalised Merrifield type resin (Novabiochem) was used; this material was 1% cross-linked and had a loading of 4 mmol g^{-1}. Although the thioethers have attractive properties as traceless linkers, preliminary solution chemistry showed that the replacement of the 2-amino substituent normally found in pteridine synthesis by a thioether greatly reduced the reactivity of the pyrimidine to electrophilic substitution at C-5. Surprisingly, carbon electrophiles such as bromoesters and dicarbonyl compounds with acid catalysis failed to react. On the other hand, nitrosation was successful and in good yield (**2** >97%). Reduction with sodium dithionite (**3** ~80%) and subsequent cyclisation with biacetyl were also efficient (**4** >95%). With 2-amino-4-sulfanyl ethers, nitrosation at C-5 was also successful to give **7** but attempted alkylation with ethyl bromoacetate led to reaction on the 2-amino substituent leading to the formation of imidazopyrimidines. Completion of the synthesis of the pteridine ring (via **8** to **9**) occurred in similar yield to that for the 2-thioether link. These results essentially restricted the application of such thioether linkers to compounds having a nitrogen substituent at C-5 of the pyrimidine, namely pteridines and purines.

Since the full range of target compounds for the ultimate use of this methodology included highly substituted pteridines with oxidisable substituents, such as might interact strongly with enzymes of the folate and tetrahydrobiopterin pathways,[7,8] a mild, non-oxidative cleavage was sought. Treatment of resins loaded with pyrimidines with cyanogen bromide following standard peptide chemistry protocols released product in low yield.[9] However, the isolated products proved to be

mixtures of complex structures which appeared according to mass spectroscopy to comprise derivatives formed by both aryl and alkyl substitution reactions. Direct cleavage by ammonia and amines was also investigated.[2–4] 2-Amino **5b**, 2-allylamino **5c**, and 2-pyrrolidin-1-yl **5d** derivatives were all isolated and identified but the harsh reaction conditions (sealed tube at 180°C for **5b** and hot DMF for **5c** and **d**) led to low yields (~5%) and substantial decomposition. Cleavage with oxidative activation therefore seemed essential. This is in contrast with related syntheses of pyrimidine derivatives in which the ring bore strongly electron withdrawing substituents that would facilitate nucleophilic substitution[2,3] and emphasises for a second time the substantial changes in reactivity that can be observed with apparently innocuous changes of substituent. Recent work on the synthesis of pyrimidine libraries without electron withdrawing substituents has confirmed the importance of oxidative cleavage.[10]

Using the Type A resin, cleavage with *m*-chloroperbenzoic acid in dichloromethane led directly to the pteridinedione **5a** (R = OH),[11] which was isolated and fully characterised. The cleavage took place in 25% yield from the resin bound final product. This is equivalent to 18% yield overall based upon the initial loading of the resin. Indeed the pteridinedione was the only product obtained if conditions for oxidation and cleavage were not anhydrous. Cleavage of product from resin Type B was therefore investigated using dimethyldioxirane (DDO) in acetone solution over 4–10 h at room temperature. Subsequent addition of a nucleophile (primary or secondary amine or azide ion) allowed 2-substitution to be demonstrated. Cleavage by oxidation and subsequent addition of a nitrogen nucleophile was also more effective than direct nucleophilic cleavage. Thus, **5c** was obtained from cleavage of resin **4** (Type-B) using DDO and allylamine (34%), **5d** from cleavage of resin **4** (Type-B) using DDO and pyrrolidine (42%), **5e** from cleavage of resin **4** (Type-B) using DDO and sodium azide (41%). Consistent with the solution phase results,[7,8] this method was more efficient, the pteridine (**5a**, R = OH) being obtained in 45% yield on cleavage equivalent to 27% yield overall.

Whilst hydrolytic cleavage was a limitation at C-2, it could be turned to advantage by linking through C-4 thioethers; at C-4, the naturally occurring oxo group would then arise. Again consistent with the solution-phase experience,[7,8] cleavage by oxidation followed by displacement with water gave the highest yield of the pteridine **5e**; cleavage occurred in 50% yield which indicates 38% overall yield from the loaded resin. Since the solution chemistry of pteridinyl-4-sufanyl ethers with respect to nucleophilic substitution a C4 paralleled closely that of the 2-isomer, 4-amino and -azido pteridines will be accessible through the oxidation with DDO and nucleophilic displacement.

3. Conclusion

In this paper we have described, using the pteridindione **5a** and the pterin **9** as examples, a prototype solid-phase methodology for the synthesis of pteridines. The unexpected substantial changes in reactivity caused by substituent effects mean that there are clear limitations in the ability of this methodology with respect to cyclisation using carbon electrophiles at C5 of pyrimidine substrates and more work will be required to solve this problem. The exemplification of this prototype methodology for a range of heterocyclic products is now in hand.

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11. Data for compounds prepared: **5a** mp >260°C. δ_H (DMSO-d_6) 2.50 (3H, s, C(9)H_3), 2.52 (3H, s, C(10)H_3), 11.47 (1H, br s, N(1)H), 11.65 (1H, br s, N(3)H). δ_C (DMSO-d_6) 22.05 (C-9), 23.05 (C-10), 124.64 (C-4a), 148.12 (C-6), 148.94 (C-2), 150.78 (C-8a), 158.58 (C-7), 161.94 (C-4). λ_{max} (MeOH) 275, 207 nm; **5b** mp >260°C. δ_H (TFA) 2.89 (3H, s, C(10)H_3), 2.91 (3H, s, C(9)H_3). δ_C(TFA) 21.75 (C-10), 23.81 (C-9), 124.30 (C-4a), 148.15 (C-8a), 154.11 (C-2), 157.38 (C-6), 161.40 (C-4), 167.96 (C-7). ν_{max} (KBr) 3265, 2842, 1689, 1547, 1519, 1389, 1179, 686, 517 cm^{-1}; **5c** mp >240°C. δ_H (DMSO-d_6) 2.48

(3H, s, C(13)H_3), 2.49 (3H, s, C(12)H_3), 3.99 (2H, s, C(9)H_2), 5.12 (1H, d, $J=10.2$, 1×C(11)H_2), 5.22 (1H, d, $J=17.2$, 1×C(11)H_2), 5.90–5.97 (1H, m, C(10)H), 6.72 (1H, br s, NH), 11.17 (1H, br s, N(3)H). δ_C (DMSO-d_6) 21.69 (C-12) 22.91 (C-13), 42.83 (C-9), 115.93 (C-11), 126.35 (C-6), 135.28 (C-10), 147.5 (C-4a), 152.16 (C-7), 156.6 (C-8a), 158.73 (C-2), 161.12 (C-4); **5d** mp >240°C. δ_H (DMSO-d_6) 1.92 (4H, t, $J=6.5$, C(10)H_2, C(11)H_2), 2.48 (3H, s, C(14)H_3), 2.50 (3H, s, C(13)H_3), 3.50 (4H, t, $J=6.5$, C(9)H_2, C(12)H_2), 11.34 (1H, br s, N(3)H). ν_{max} (KBr) 3440, 3159 (NH), 2962 (CH), 1685 (C=O), 1605, 1559, 1520,1396, 1270, 984, 821, 732 cm^{-1}. λ_{max} (MeOH) 358, 286, 228 nm; **5e** mp >240°C. δ_H (DMSO-d_6) 2.30 (3H, s, C(9)H_3), 2.35 (3H, s, C(10)H_3), 11.90 (1H, s, N(3)H). ν_{max} (KBr) 3380 (NH), 2137 (N≡N), 2041, 1605, 1448, 1206, 641 cm^{-1}. λ_{max} (MeOH) 342, 266, 205 nm.