Pergamon

Tetrahedron Letters 42 (2001) 8165–8167

TETRAHEDRON LETTERS

Cyclin-dependent kinase (CDK) inhibitors: development of a general strategy for the construction of 2,6,9-trisubstituted purine libraries. Part 2

Virginie Brun, Michel Legraverend* and David S. Grierson

Laboratoire de Pharmacochimie, UMR 176 CNRS-Institut Curie, Bât 110 Centre Universitaire, 91405, Orsay, France

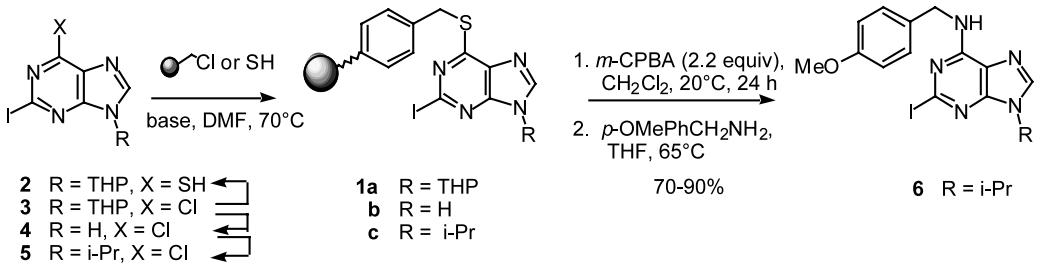
Received 2 August 2001; accepted 13 September 2001

Abstract—Purine bound resins **1a–c** were obtained by the reaction of 6-thiopurines **2** or 6-chloropurines **3–5** with Merrifield-Cl or -SH resins (DMF, 70°C, base). *S*-Oxidation of resins **1c** and reaction of the desired sulfone with *p*-methoxybenzylamine to give **6**, proved effective for release of the purine from the resin and simultaneous C-6 substitution. Reaction of resin **1c** with pyrrolidine and pyrrolidine-2-methanol prior to *S*-oxidation led to the C-2 amine substituted resin bound purines **8** and **9**. Activation of sulfur in these intermediates, followed by reaction with $Ar–CH_2–NH_2$ gave the 2,6,9-trisubstituted purines **10–14** in 42–60% yields.

The development of potent and specific inhibitors of cyclin dependent kinases (CDKs) is a current challenge with potentially important applications for such molecules as biochemical probes for the study of the different phases of the cell cycle and as therapeutic agents.[1] In the preceding communication we outlined the principle behind a solid-phase synthesis strategy for the construction of 2,6,9-trisubstituted purine libraries based upon the reactivity of a 6-thio substituted purine intermediate connected to the resin support via the sulfur atom.[2–8] The basic tenet is that the low reactivity of the purine C_6–S bond will provide the possibility to introduce a wide variety of functionality at the N-9 and C-2 positions prior to reaction at C-6. Subsequent activation of the sulfur atom (oxidation, alkylation, etc.) then opens the way to concomitant introduction of a substituent (nucleophile) at C-6 and cleavage of the trisubstituted purine product from the resin. In this way, full advantage is taken of solid-phase synthesis to introduce functionality at all three centers of interest in the purine ring.

Having demonstrated the efficacy of this strategy in solution, it remained to determine whether the sequence of operations could be effected on solid support. In this communication we describe the results of experiments to optimize both the loading of purine derivatives onto a Merrifield type resin, as well as the cleavage of the corresponding 6-sulfone linked purines from this resin through reaction with amine nucleophiles. We further describe the construction of a small, but representative 2,6-diaminopurine library of potential CDK inhibitors.

To prepare the resin bound purine **1a**, the reaction of 6-thiopurine **2** with Merrifield-Cl resin at 70°C in DMF was examined in initial experiments using either KOtBu or NaH as base (Scheme 1). Under these mild conditions it was found that the loading yield (determined by



Scheme 1. See preceding paper for reaction conditions of **3–5**, Ref. 10 for **2** and Ref. 11 for **3**.

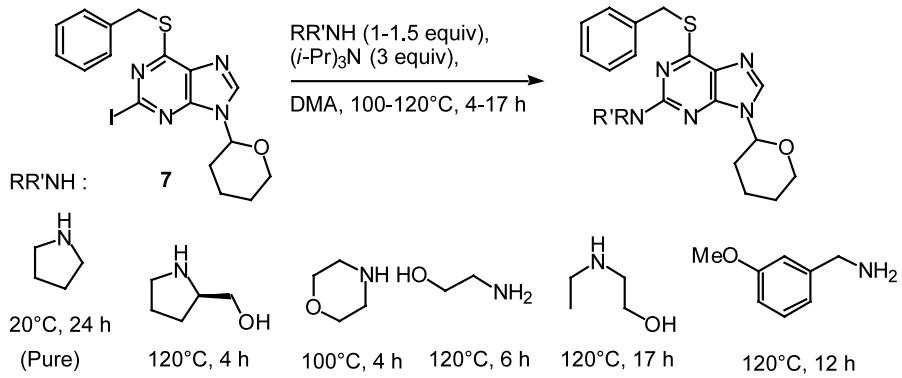
* Corresponding author. Fax: 33 (0) 169 86 30 85; e-mail: michel.legraverend@curie.u-psud.fr

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01752-X

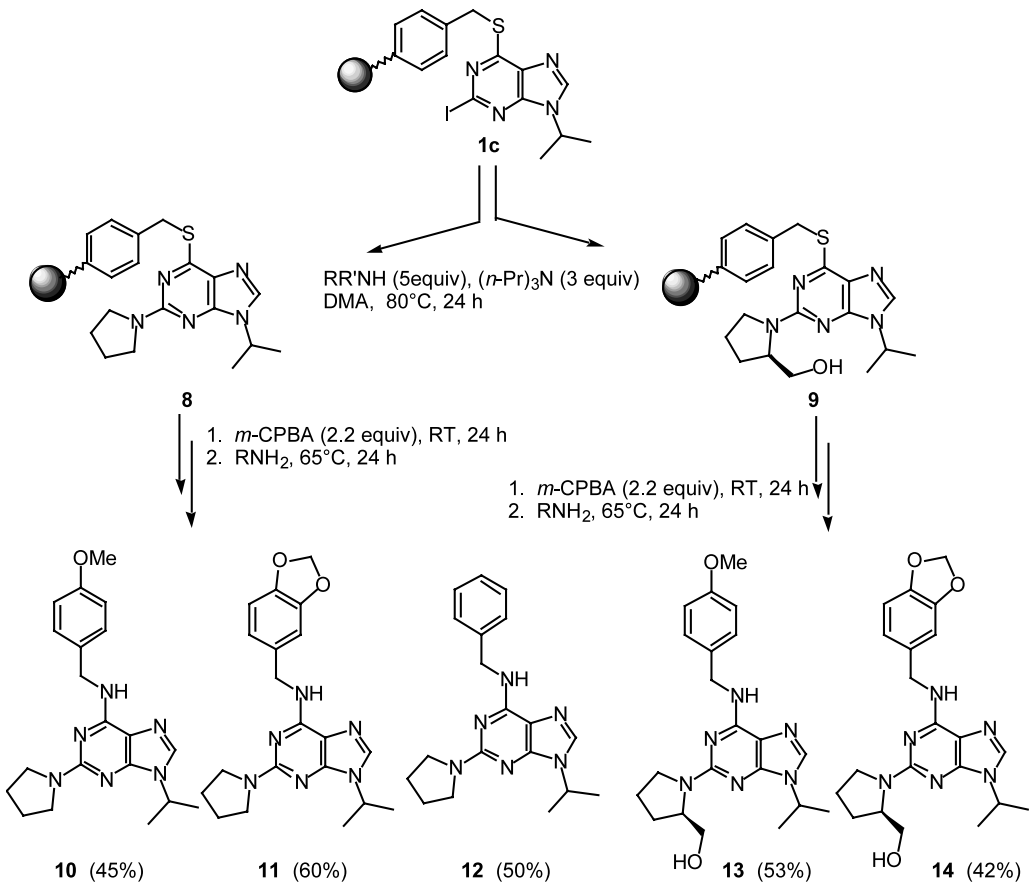
microanalysis; % nitrogen) varied little (87–95%) with mesh size (400–500 μm→35–75 μm) and loading capacity (1 or 2 mmol/g). The best results were obtained using the smaller 35–75 μm resin at 1 mmol/g charge capacity, and KOtBu base. Identical loading yields were obtained under these conditions in the reaction of 6-chloropurine **3** with Merrifield-SH resin. Somewhat lower loadings (75%) were observed for the attachment of compounds **4**, and **5** onto the Merrifield-SH resin.[7]

The efficiency of the release of the purine from resin **1c** was then evaluated following the two-step protocol developed in solution (*S*-oxidation/nucleophilic displacement). Note that longer reaction times (16–24 h) were employed for each step to ensure complete transformation. The yield for product **6** (after column chromatography) was in the 70–90% range (approx. 50% overall yield for loading and release operations).

The 2-iodo-9-(*iso*-propyl)purine containing resin **1c** was used to subsequently measure the efficiency with which amine substituents could be introduced at C-2 of the purine ring while it is bound to the support. As heating to 100–150°C for extended periods is often required to effect exchange of the halogen atom in 2-chloro or 2-iodopurine derivatives by an amine nucleophile there was some concern that the reaction of purine **1c** with amines may be accompanied by significant decomposition of the resin. To get an idea as to what conditions would be required, a series of different amines were first reacted with the 6-benzylthiol-2-iodopurine **7**[9] (Scheme 2). It was found that it was necessary to heat at 120°C



Scheme 2.



Scheme 3.

for only short time periods for the cyclic amines and ethanolamine, whereas heating up to 17 and 12 h, respectively, was needed for *N*-ethylethanolamine and *m*-methoxybenzylamine. Most interesting, it was found that the reaction with pyrrolidine as solvent occurred readily at room temperature!

Pyrrolidine-2-methanol and pyrrolidine were selected for reaction with resin **1c**. In separate experiments the resin was heated at 80°C for 24 h in dimethylacetamide (solvent) containing 5 equiv. of the respective amine and 3 equiv. of tri-*n*-propylamine. After washing, the resin bound purine was treated with 2.2 equiv. of *m*-CPBA in CH_2Cl_2 at room temperature for 24 h, and the derived sulfone was then reacted with $ArCH_2NH_2$ (5 equiv.) in THF at 65°C for 24 h. The released trisubstituted purine products **10**–**14** were isolated pure by silica-gel column chromatography. As can be seen, the overall yields for the four operations are good (45–60%), indicating that the I→ amine exchange reaction was efficient, and that little if any competing oxidation (*N*-oxide formation) of the pyrrolidine nitrogen in intermediates **8** and **9** occurred. It is probable that the isolated product yields could be further improved by treatment of the crude product mixture containing the excess amine with a formyl scavenger resin before (or instead of) chromatography (Scheme 3).

It was thus shown that a small library of 2,6,9-trisubstituted purines could be prepared via solid-phase organic synthesis using the 6-thiopurine bound Merrifield resin. Current efforts are being directed to increase the scope of amine substituents that can be introduced at C-2. Modern Pd(0) coupling methodology is playing an important role in this work, and as described in the following communication, the nature of the linker joining the purine to the resin is also a crucial factor.[9]

Acknowledgements

This work has been generously financed by ARC (Association pour la Recherche sur le Cancer, Grant no. 5713), and by an MENRT scholarship for V.B.

References

1. Sielecki, T. M.; Boylan, J. F.; Benfield, P. A.; Trainor, G. L. *J. Med. Chem.* **2000**, *43*, 1–18.
2. Norman, T. C.; Gray, N. S.; Koh, J. T.; Schultz, P. G. *J. Am. Chem. Soc.* **1996**, *118*, 7430–7431.
3. Nugiel, D. A.; Cornelius, L. A. M.; Corbett, J. W. *J. Org. Chem.* **1997**, *62*, 201–203.
4. Dorff, P. H.; Garigipati, R. S. *Tetrahedron Lett.* **2001**, *42*, 2771–2773.
5. Brill, W. K.-D.; Riva-Toniolo, C.; Müller, S. *Synlett* **2001**, 1097–1100.
6. Schow, S. R.; Mackman, R. L.; Blum, C. L.; Brooks, E.; Horsma, A. G.; Joly, A.; Kerwar, S. S.; Lee, G.; Shiffman, D.; Nelson, M. G.; Wang, X.; Wick, M. M.; Zhang, X.; Lum, R. T. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2697–2702.
7. Fréchet, J. M.; de Smet, M. D.; Farrall, M. J. *Polymer* **1979**, *20*, 675–680.
8. Brun, V.; Legraverend, M.; Grierson, D. S. *Tetrahedron Lett.* **2001**, *42*, 8161–8164.
9. Brun, V.; Legraverend, M.; Grierson, D. S. *Tetrahedron Lett.* **2001**, *42*, 8169–8171.
10. Compound **2**: mp >250°C. ^{1}H NMR (DMSO-d_6) δ 1.3–2.3 (m, 6H, $H_{2',3',4'}$); 3.5–3.8 (m, 1H, $H_{5'}$); 3.8–4.0 (m, 1H, $H_{5'}$); 5.3–5.5 (m, 1H, $H_{1'}$); 7.96 (s, 1H, H_8); 10.7 (s broad, 1H, NH or SH). MS (CI/NH_3) m/z 279 (M-THP)$^+$; m/z 385 (MH+NH_3)$^+$; m/z 386 and 387.
11. Compound **3**: mp 120°C; ^{1}H NMR (DMSO-d_6) δ 1.55–2.2 m, 6H, $H_{2,3,4}$); 3.6–3.85 (dt, 1H, J=3.61 and 10.29 Hz, $H_{5'}$); 4.05–4.2 (m, 1H, $H_{5'}$); 5.6–5.8 (dd, 1H, J= 2.06 and 9.81, $H_{1'}$); 8.21 (s, 1H, H_8). MS (CI/NH_3) m/z 365 (MH)$^+$; m/z 364 (M)$^+$; m/z 366 (M+2)$^+$.