Pergamon

Tetrahedron Letters 43 (2002) 6169–6171

TETRAHEDRON LETTERS

Microwave-assisted solid-phase synthesis (MASS) of 2,6,9-trisubstituted purines

Richard E. Austin, John F. Okonya, Daniel R. S. Bond and Fahad Al-Obeidi*

Selectide, A Subsidiary of Aventis Pharmaceuticals Inc., 1580 E. Hanley Blvd, Tucson, AZ 85737, USA

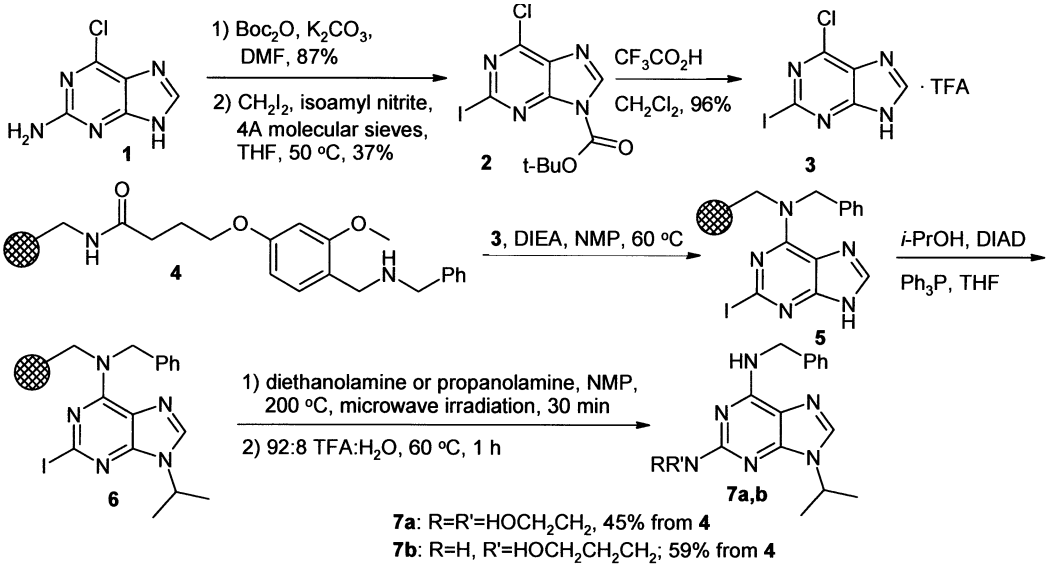
Received 13 June 2002; revised 24 June 2002; accepted 28 June 2002

Abstract—In an attempt to discover a high-throughput method for the synthesis of 2,6,9-trisubstituted purines, it was found that microwave irradiation was beneficial in accelerating the nucleophilic displacement of halogens by amines at the C-2 position of the purine nucleus. A method for microwave-assisted solid-phase synthesis (MASS) of 2,6,9-trisubstituted purines is presented.

1. Introduction

Purines have received much attention recently owing to their ubiquity and ability to mediate biological processes. The facility of protocols for synthesizing substituted purines has attracted chemists interested in preparing collections of these molecules.[1–10] A common theme among published sequences for preparing purine derivatives substituted at the C-2 position by amine displacement of a halogen is long reaction times. In considering an approach to the synthesis of 2,6,9-trisubstituted purines, it was this challenge that would be our focus.

The use of microwave irradiation as an alternative mode of heating reaction mixtures has been observed to dramatically reduce reaction times and affect product ratios and yields.[11] Although the source of the enhancements observed by employing microwave irradiation techniques has been debated,[12] this mode of heating has



Scheme 1.

* Corresponding author.

0040-4039/02/$ - see front matter
PII: S0040-4039(02)01271-6

been applied to resin bound molecules with positive results relative to conventional heating techniques.[13–18] We wish to report the results of our investigation of the synthesis of 2,6,9-tribsubstituted purines on solid phase employing microwave irradiation to enhance observed reaction rates.

2. Results and discussion

As a scaffold, we chose a 2,6-dihalopurine. Early experiments had indicated that the relative reactivities of 2-halopurines, toward nucleophilic displacement by aliphatic amines, followed the order of I>F>Cl under microwave irradiation.[19] The requisite 2-iodosubstituted scaffold was available in multi-gram quantities in three steps from 2-amino-6-chloropurine (Scheme 1).[20]

As examples, two closely related literature compounds were prepared to highlight the contribution of microwave irradiation to increase the efficiency of displacement of the C-2 iodo substituent by aliphatic amines.[21] The resin we employed was AMEBA-linked polystyrene that had undergone reductive amination to deliver **4**.[22] The loading of **4** was determined by coupling Fmoc-B-Ala to an aliquot of the resin and measuring Fmoc release upon treatment with piperidine. A stoichiometric portion of the scaffold **3** was added to the resin in NMP with DIEA and heated at 60°C for 7 hours to deliver **5**. Mitsunobu alkylation with isopropyl alcohol was achieved in the presence of diisopropyl azodicarboxylate and triphenylphosphine in THF to provide **6**. The key displacement of the C-2 iodine was accomplished under microwave irradiation[23] for 30 minutes with either diethanolamine or propanolamine to deliver, after release from the resin, the known compounds **7a**[24] and **7b**.[25] HPLC analysis of the crude products indicated that both displacements had gone to completion and the purities were 77% and 89%, respectively, for **7a** and **7b**. These materials were purified to homogeneity by flash chromatography to provide the pure products in good yield. To compare conventional heating techniques in the acceleration of C-2 displacements analogous to the transformation of **6** to **7**, long reaction times of up to 48 hours are typical.[3,6,26]

As a result of this investigation, we produced a large collection of 2,6,9-trisubstituted purines employing microwave irradiation in a parallel fashion to affect C-2 halogen displacement with aliphatic amines. Purities for these molecules are typically greater than 75% and isolated yields range from 30% to 80%.[19]

References

1. Nugiel, D. A.; Cornelius, L. A. M.; Corbett, J. W. *J. Org. Chem.* **1997**, *62*, 201–203.
2. 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.
3. Fiorini, M. T.; Abell, C. *Tetrahedron Lett.* **1998**, *39*, 1827–1830.
4. Chang, Y.-T.; Gray, N. S.; Rosania, G. R.; Sutherlin, D. P.; Kwon, S.; Norman, T. C.; Sarohi, R.; Leost, M.; Meijer, L.; Schultz, P. G. *Chem. Biol.* **1999**, *6*, 361–375.
5. Legraverend, M. O.; Ludwig, O.; Bisagni, E.; Leclerc, S.; Meijer, L.; Giocanti, N.; Sadri, R.; Favaudon, V. *Bioorg. Med. Chem.* **1999**, *7*, 1281–1293.
6. Dorff, P. H.; Garigipati, R. S. *Tetrahedron Lett.* **2001**, *42*, 2771–2773.
7. Brill, W. K.-D.; Riva-Toniolo, C. *Tetrahedron Lett.* **2001**, *42*, 6515–6518.
8. Brun, V.; Legraverend, M.; Grierson, D. S. *Tetrahedron Lett.* **2001**, *42*, 8161–8164.
9. Ding, S.; Gray, N. S.; Ding, Q.; Schultz, P. G. *Tetrahedron Lett.* **2001**, *42*, 8751–8755.
10. Ding, S.; Gray, N. S.; Ding, Q.; Wu, X.; Schultz, P. G. *J. Comb. Chem.* **2002**, *4*, 183–186.
11. Krstenansky, J. L.; Cotterill, I. *Curr. Opin. Drug Discovery Dev.* **2000**, *3*, 454–461.
12. Camelia, G.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, *27*, 213–223.
13. Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2002**, *4*, 95–105.
14. Hoel, A. M. L.; Nielsen, J. *Tetrahedron Lett.* **1999**, *40*, 3941–3944.
15. Larhed, M.; Lindeberg, G.; Hallberg, A. *Tetrahedron Lett.* **1996**, *37*, 8219–8222.
16. Yu, H.-M.; Chen, S.-T.; Wang, K.-T. *J. Org. Chem.* **1992**, *57*, 4781–4784.
17. Combs, A. P.; Saubern, S.; Rafalski, M.; Lam, P. Y. S. *Tetrahedron Lett.* **1999**, *40*, 1623–1626.
18. Larhed, M. G.; Lindeberg, G.; Halberg, A. *Tetrahedron Lett.* **1996**, *37*, 8219–8222.
19. Unpublished results.
20. *Synthesis of* ***3***. Boc anhydride (164 g, 750 mmol) was added to a slurry of 2-amino-6-chloropurine (101 g, 600 mmol) and K_2CO_3 (99 g, 720 mmol) in DMF (600 mL) at room temperature. The mixture was stirred overnight. Added 1 L water and stirred for 1 h. The precipitate was removed by filtration, triturated with diethyl ether, filtered again, and air-dried to recover the Boc protected purine (140 g, 520 mmol, 87%) as a white solid. The Boc protected purine (53.8 g, 200 mmol) was dissolved in a solution of dry THF (1 L) and CH_2I_2 (168 mL, 2.08 mmol). 4 Å molecular sieves (40 g) were added and the mixture heated to 50°C under nitrogen. Isoamyl nitrite (84 mL, 620 mmol) was added and the mixture stirred overnight. The reaction mixture was filtered and concentrated under reduced pressure to a thick syrup. The material was loaded directly onto a large flash column and eluted with 95:5 toluene:EtOAc to recover **2** (27.9 g, 73 mmol, 37%) as a light brown solid. The iodinated purine **2** (54.2 g, 143 mmol) was dissolved in CH_2Cl_2 (700 mL). Trifluoroacetic acid (4.3 mL, 56 mmol) was added at 24 h intervals for 3 days (12.9 mL TFA total). The resulting precipitate was removed by filtration (36.4 g, 92.3 mmol). The filtrate was concentrated under reduced pressure and the resulting solid triturated with 2:1 hexane:diethyl ether. The second crop (17.9 g, 45.4 mmol) was recovered by filtration. The total yield of **3** was 54.3 g (138 mmol, 96%).

21. *Scaffold coupling*. Resin **4** (553 mg, 0.60 mmol/g, 0.332 mmol) was treated with a solution of 6-chloro-2-iodopurine (**3**, 131 mg, 0.332 mmol) and DIEA (177 μL, 0.995 mmol) in *N*-methylpyrrolidinone (NMP, 5 mL). The mixture was heated at 60°C for 7 h. The resin was washed five times with DMF, five times with THF, and dried under vacuum to provide **5**. *Mitsunobu alkylation*. To a solution of triphenylphosphine (435 mg, 1.66 mmol) in THF (6 mL) was added diisopropyl azodicarboxylate (DIAD, 327 μL, 1.66 mmol) followed by isopropyl alcohol (127 μL, 1.66 mmol). The solution was added to the resin. After 24 h, the resin washed four times with DMF, three times with THF, three times with MeOH, and dried under vacuum to provide **6**. *Nucleophilic displacement and release*. Resin **6** was placed in a Teflon reaction vessel. The resin was covered with a 1 M solution of amine (10 μL per mg of resin). The mixture was heated in a microwave oven[23] to a temperature of 200°C for a period of 30 min. The resin was washed four times with DMF, three times with THF, three times with MeOH, and dried under vacuum. The final products were released from the resin by cleavage with 92:8 TFA:water at 60°C. The products were extracted using a 50:30:20 mixture of water:THF:MeOH. And purified by normal phase flash chromatography, eluting with a 95:5 mixture of CH_2Cl_2:7 N NH_3 in MeOH. The final products **7a** and **7b** exhibited spectral and mass data consistent with their structures.
22. Austin, R. E.; Waldraff, C. A.; Al-Obeidi, F. *Tetrahedron Lett*. **2002**, *43*, 3555–3556.
23. CEM Corporation, PO Box 200, Matthews, NC 28106, USA.
24. Verdugo, D. E.; Cancilla, M. T.; Ge, X.; Gray, N. S.; Chang, Y.-T.; Schultz, P. G.; Negishi, M.; Leary, J. A.; Bertozzi, C. R. *J. Med. Chem*. **2001**, *44*, 2683–2686.
25. Otyepka, M.; Krystof, V.; Havlicek, L.; Siglerova, V.; Strnad, M.; Koca, J. *J. Med. Chem*. **2000**, *43*, 2506–2513.
26. Gray, N. S.; Kwon, S.; Schultz, P. G. *Tetrahedron Lett*. **1997**, *38*, 1161–1164.