Acta Chemica Scandinavica, 1996: 50: 1171–1173
Printed in UK – all rights reserved

ACTA
CHEMICA SCANDINAVICA
ISSN 0904–213X

Short Communication

Improved Syntheses of 1-Hydroxy-4-nitro-6-trifluoromethylbenzotriazole and 1-Hydroxy-4,6-dinitrobenzotriazole

Jan Kehler, Ask Püschl and Otto Dahl*

Department of Chemistry, The H. C. Ørsted Institute, University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen, Denmark

Kehler, J., Püschl, A. and Dahl, O., 1996. Improved Syntheses of 1-Hydroxy-4-nitro-6-trifluoromethylbenzotriazole and 1-Hydroxy-4,6-dinitrobenzotriazole. – Acta Chem. Scand. 50: 1171–1173. © Acta Chemica Scandinavica 1996.

Coupling reagents which are phosphonium or uronium salts derived from 1-hydroxybenzotriazole (HOBt, **1a**, Fig. 1) are much used for peptide synthesis.[1] In order to increase the coupling rates for difficult couplings, electronegative groups have been introduced into the benzene ring of HOBt, e.g., 1-hydroxy-6-nitrobenzotriazole (**1b**),[2] 1-hydroxy-6-trifluoromethylbenzotriazole (**1c**),[2,3] and recently 1-hydroxy-4-nitro-6-trifluoromethylbenzotriazole (**1d**).[4] Phosphotriester derivatives of **1a**,[1] **1b**[5] and **1c**[5] have been used for oligonucleotide synthesis, and **1d** and 1-hydroxy-4,6-dinitrobenzotriazole (**1e**) have been tested for their properties as nucleophilic catalysts in oligonucleotide synthesis by the triester method.[6,7]

During our work on the preparation of oligonucleoside phosphorodithioates by triester chemistry[8,9] we needed an efficient way to synthesise **1d** and **1e**, and their corresponding phosphonium-based coupling reagents, 4-nitro-6-trifluoromethylbenzotriazol-1-yloxytris(pyrrolidin-1-yl)phosphonium hexafluorophosphate (PyF-NOP, **2a**, Fig. 1) and 4,6-dinitrobenzotriazol-1-yloxytris(pyrrolidin-1-yl)phosphonium hexafluorophosphate (PyDNOP, **2b**). **2a** has been described once,[4] and was prepared from **1d** which was 'readily accessible by a slight modification of the procedure of Reese and Pei-Zhuo'.[7] The dinitro analogue **2b** has not been described before. The nitro-trifluoromethyl-substituted compound **1d** has been described only once,[7] whereas several preparations of the dinitro compound **1e** have been published.[6,7,10,11] However, we were unable to obtain **1d** or **1e** by the procedure of Reese and Pei-Zhuo (Fig. 2, i–iii).[7] A closer investigation showed that the ring closure failed because the intermediate substituted 2-nitrophenylhydrazines (**5a**, **b**, Fig. 2) were *N*-acetylated during the prescribed recrystallization from acetic acid. This is similar to what is observed for 2,4-dinitrophenylhydrazine, which is *N*-acetylated even in aqueous acetic acid.[12] Since the preparation of the arylhydrazine

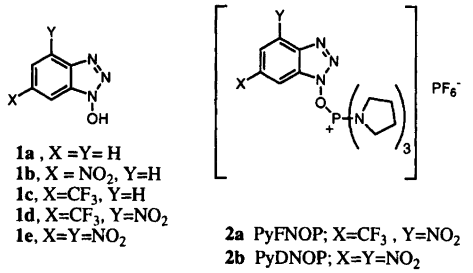

Fig. 1. Substituted 1-hydroxybenzotriazoles **1a–e** and the phosphonium-based coupling reagents **2a–b**.

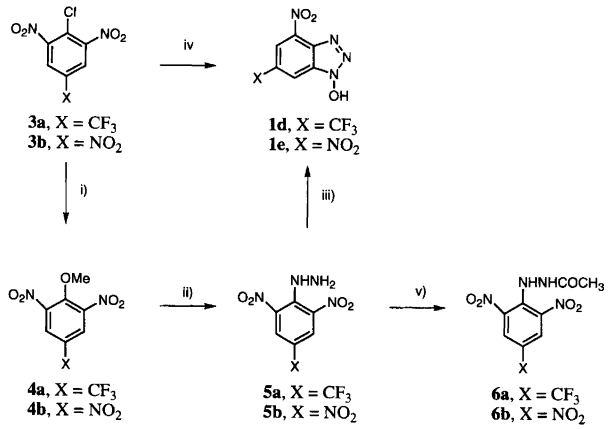

Fig. 2. Synthesis of 1-hydroxy-4-nitro-6-trifluoromethylbenzotriazole, **1d**, and 1-hydroxy-4,6-dinitrobenzotriazole, **1e**: (i) NaOMe, MeOH; (ii) hydrazine hydrate, EtOH; (iii) hydrazine hydrate, acetate-buffer, reflux; (iv) hydrazine hydrate, acetate-buffer (**1d**) or aq. $NaHCO_3$ (**1e**); (v) glacial acetic acid.

and the subsequent ring closure seemed to occur under similar conditions we decided to attempt a one-step preparation.

Here we describe convenient one-pot preparations of **1d** and **1e** from commercially available 4-chloro-3,5-dinitrobenzotrifluoride (**3a**) and the easily obtainable picryl chloride (**3b**), respectively, and the preparation of **2b**. The reactions are reliable and fast, and the yields of **1d** (64%) and **1e** (50%) are higher than those obtained by the previously published two- or three-step procedures.

Experimental

General. Acetonitrile and dichloromethane were dried over 4 Å molecular sieves. 4-Chloro-3,5-dinitrobenzotrifluoride was from Fluka. Picryl chloride was prepared by a published procedure.[13] ^{1}H and ^{31}P NMR spectra were recorded at 400 and 161.9 MHz, respectively, on a Varian XL-400 spectrometer.

1-Hydroxy-4-nitro-6-trifluoromethylbenzotriazole (**1d**). 4-Chloro-3,5-dinitrobenzotrifluoride (1.35 g, 5 mmol) was suspended in a mixture of $NaOAc \cdot 3H_2O$ (10.04 g, 74 mmol), glacial acetic acid (5.0 ml), water (20 ml) and ethanol (40 ml). Hydrazine monohydrate (1.0 ml, 20 mmol) was added dropwise and the suspension heated with stirring to reflux for 5 h under nitrogen. Activated charcoal (1 g) was added to the hot, homogeneous, red solution, and the mixture was filtered and evaporated *in vacuo*. The residue was dissolved in the minimum of water (30 ml), and 4 M HCl (20 ml) was added to precipitate the product. The mixture was cooled in an ice–water bath for 60 min, and the crystals were isolated by filtration and washed with cold 4 M HCl. Crude **1d** was recrystallized from aqueous trifluoroacetic acid (0.2 M, 40 ml) to give orange needles which were dried by evaporation twice from dry acetonitrile. Yield 800 mg (3.2 mmol; 64% of anhydrous **1d**); m.p. 181–182 °C (lit.[7] 163–164 °C). FAB$^+$MS: 249.1 (MH^+). NMR: δ_H (DMSO-d_6) 12.2–12.8 (br, 1 H, OH) 8.77 (d, J=2.0 Hz, 1 H, H5/H7) 8.53 (d, J=2.0 Hz, 1 H, H5/H7). Anal. $C_7H_3F_3N_4O_3$: C, H, N.

N-*(2,6-Dinitro-4-trifluoromethylphenyl)*-N′-*acetylhydrazine* (**6a**). Recrystallisation of **5a** prepared as described[7] from glacial acetic acid gave **6a** as yellow needles. M.p. 223.5–224 °C. FAB$^+$MS: 309.0 (MH^+). NMR: δ_H (DMSO-d_6) 10.23 (1 H, NH), 9.64 (1 H, NH), 8.30 (s, 2 H, H3+H5). Found: C 35.24; H 1.79; N 18.10. Calc. for $C_9H_7F_3N_4O_5$: C 35.08; H 2.29; N 18.18.

1-Hydroxy-4,6-dinitrobenzotriazole (**1e**). Picryl chloride **3b** (1.24 g, 5 mmol) was added to a solution of hydrazine hydrate (1.2 ml, 25 mmol) in 5% aqueous $NaHCO_3$ (80 ml) under nitrogen at 0 °C. When most of the picryl chloride had dissolved (15–30 min), the resulting dark red solution was stirred for 2 h at r.t. and then heated to 60 °C for 1 h under nitrogen. Activated charcoal (1 g) was added to the hot solution and the reaction mixture was filtered and cooled to 0 °C in an ice–water bath. The reaction mixture was acidified with 4 M HCl (40 ml) and the product, which precipitated as a light orange-brown powder, was isolated by filtration, dried over P_2O_5 and recrystallised from dry acetonitrile to give anhydrous **1e** as dark orange-brown crystals. Yield 0.56 g (50%), m.p. 197–198 °C (decomp). (lit.[7] 185–186 °C, lit.[11] 185–190 °C, lit.[10] 200–201 °C). FAB$^+$MS: 226.0 (MH^+). Anal. $C_6H_3N_5O_5$: C, H, N. NMR: δ_H (DMSO-d_6) 12.4 (br, 1 H, OH) 9.11 (d, J=2.0 Hz, 1 H, H5/H7), 8.89 (d, J=2.0 Hz, 1 H, H5/H7).

N-*(2,4,6-Trinitrophenyl)*-N′-*acetylhydrazine* (**6b**). Recrystallisation of **5b** prepared as described[7] from glacial acetic acid gave **6b** as orange needles. M.p. >210 °C (decomp.) [lit. 214 °C (decomp.)[14]]. NMR: δ_H (CD_3OD) 9.11 (s, 2 H, H3+H5), 2.08 (s, 3 H, CH_3). TLC (CH_2Cl_2–MeOH; 95:5): R_f=0.42. Anal. $C_8H_7N_5O_7$: C, H, N.

4,6-Dinitrobenzotriazol-1-yloxytris(pyrrolidin-1-yl)phosphonium hexafluorophosphate (PyDNOP, **2b**). **2b** was made by the procedure given by Wijkmans *et al.*[4] Yield 1.53 g (73%), 98% pure (^{31}P NMR). Recrystallisation from acetone–ether gave 0.99 g (47%) of light yellow crystals. M.p. 139.5–141.5 °C. Anal. $C_{18}H_{26}F_6N_8O_5P_2$: C, H, N. NMR: δ_H(acetone-d_6) 9.26 (d, J= 1.8 Hz, 1 H, H5/H7), 9.10 (d, J=1.8 Hz, 1 H, H5/H7), 3.62 (m, 12 H, CH_2N), 2.03 (m, 12 H, CH_2CH_2N). δ_P(acetone-d_6) −142.9 (septet, PF_6), 33.3 (s, P^+). FAB$^+$MS: 465.2 ($M-PF_6$).

References

1. Paquette, L. A., Ed., *Encyclopaedia of Reagents for Organic Synthesis*, Wiley, Chichester 1995, Vol. 4, p. 2752.
2. Høeg-Jensen, T., Olsen, C. E. and Holm, A. *J. Org. Chem. 59* (1994) 1257.
3. Wijkmans, J. C. H. M., Kruijtzer, J. A. W., van der Marel, G. A., van Boom, J. H. and Bloemhoff, W. *Recl. Trav. Chim. Pays-Bas 113* (1994) 394.
4. Wijkmans, J. C. H. M., Blok, F. A. A., van der Marel, G. A., van Boom, J. H. and Bloemhoff, W. *Tetrahedron Lett. 36* (1995) 4643.
5. de Vroom, E., Fidder, A., Marugg, J. E., van der Marel, G. A. and van Boom, J. H. *Nucleic Acids Res. 14* (1986) 5885.
6. Devine, K. G. and Reese, C. B. *Tetrahedron Lett. 27* (1986) 5529.
7. Reese, C. B. and Pei-Zhuo, Z. *J. Chem. Soc., Perkin Trans. 1* (1993) 2291.
8. Eldrup, A. B., Bjergårde, K., Felding, J., Kehler, J. and Dahl, O. *Nucleic Acids Res. 22* (1994) 1797.

9. Eldrup, A. B., Felding, J., Kehler, J. and Dahl, O. *Tetrahedron Lett. 36* (1995) 6127.
10. Takahashi, S., Yamamura, T., Kamo, M. and Satake, K. *Chem. Lett.* (1984) 127.
11. Huisgen, R. and Weberndörfer, V. *Chem. Ber. 100* (1967) 71.
12. Curtius, T. and Mayer, M. *J. Prakt. Chem. 76* (1907) 369.
13. *Vogel's Textbook of Practical Organic Chemistry*, 4th ed., Longman, London 1978, p. 731.
14. Giua, M. and Cherchi, F. *Gazz. Chim. Ital. 49* II (1919) 152.

Received March 18, 1996.