Short Communication

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

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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 (1e),2,3 and recently 1-hydroxy-4-nitro-6-trifluoromethylbenzotriazole (1d).4 Phosphotriester derivatives of 1a,1 1b5 and 1c5 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 chemistry8,9 we needed an efficient way to synthesise 1d and 1e, and their corresponding phosphonium-based coupling reagents, 4-nitro-6-trifluoromethylbenzotriazol-1-yl oxotris(pyrrolidin-1-yl)phosphonium hexafluorophosphate (PyF-NOP, 2a, Fig. 1) and 4,6-dinitrobenzotriazol-1-yl oxotris(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’. 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.8,9,10,11 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.


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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-dinitrobenzotri fluoride (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-dinitrobenzotri fluoride was from Fluka. Picryl chloride was prepared by a published procedure.13 1H and 31P 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-dinitrobenzotri fluoride (1.35 g, 5 mmol) was suspended in a mixture of NaOAc·3H2O (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 (M+). NMR: δH (DMSO-d6) 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. C7H3F3N4O2: C, H, N.

N-(2,6-Dinitro-4-trifluoromethylphenyl)-N’-acetylhydrazine (6a). Recrystallisation of 5a prepared as described7 from glacial acetic acid gave 6a as yellow needles. M.p. 225.5–226°C. FAB+ MS: 309.0 (M+). NMR: δH (DMSO-d6) 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 C18H16F3N4O2: 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 NaHCO3 (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 P2O5 and recrystallised from dry acetonitrile to give anhydrous 1e as dark orange-brown crystals. Yield 0.50 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 (M+).

Anal. C6H3N3O4: C, H, N. NMR: δH (DMSO-d6) 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-(2,6-Trinitrophenyl)-N’-acetylhydrazine (6b). Recrystallisation of 5b prepared as described7 from glacial acetic acid gave 6b as orange needles. M.p. >210°C (decomp.) [lit. 214°C (decomp.)]. NMR: δH (CD3OD) 9.11 (s, 2 H, H3+H5), 2.08 (s, 3 H, CH3). TLC (CH3Cl2–MeOH; 95:5): Rf = 0.42. Anal. C8H2N4O2: C, H, N.

4,6-Dinitrobenzotriazol-1-yl-oxytris(pyrrrolidin-1-yl)phosphonium hexafluorophosphate (P2DNOP, 2b). 2b was made by the procedure given by Wijkmans et al.4 Yield 1.53 g (73%), 98% pure (31P NMR). Recrystallisation from acetone–ether gave 0.99 g (47%) of light yellow crystals. M.p. 139.5–141.5°C. Anal. C18H26F6N4O4P2: C, H, N. NMR: δH(acetone-d6) 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, CH2N), 2.03 (m, 12 H, CH2CH2N). δP(acetone-d6) –142.9 (septet, PF6), 33.3 (s, P+). FAB+ MS: 465.2 (M–PF6).

**References**


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