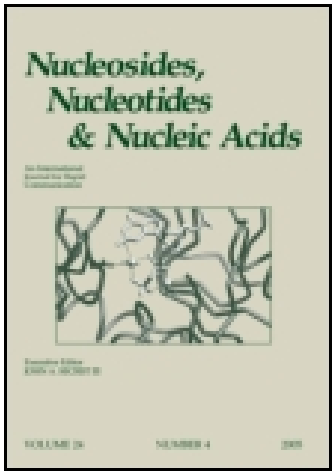

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An Improved Method for the Preparation of 4-Cyano-2-butenyl-deoxyribonucleosidephosphoramidites

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AN IMPROVED METHOD FOR THE PREPARATION OF 4-CYANO-2-BUTENYL-DEOXYRIBONUCLEOSIDEPHOSPHORAMIDITES.

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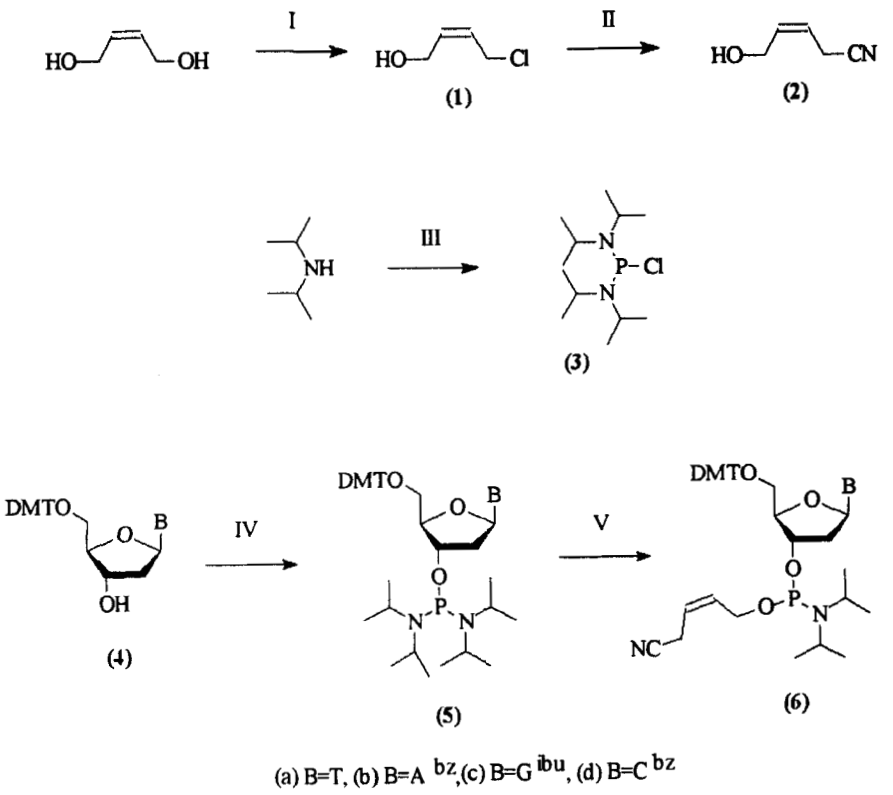
ABSTRACT An improved alternative synthesis of 4-cyano-2-butenyldeoxy nucleoside-phosphoramidites in >100g quantities is described via reaction of the phosphordiamidites with 4-cyano-2-buten-1-ol.

Currently, many pharmaceutical companies are investing significant effort into the synthesis of potential antisense therapeutic oligonucleotides[1]. In order to achieve a cost-effective synthetic route and to improve the stability of the resultant oligonucleotide, investigations continue into a range of protecting groups for the base[2], sugar[3] and internucleotidic phosphate linkage[4].

As part of our studies in this area, we recently had cause to synthesise deoxyribonucleoside-4-cyano-2-butenyl protected phosphoramidites as reported[4]. Our attempts to repeat this approach, although partially successful on a 5g scale, met with significant difficulties upon scale-up to >100g quantities and consequently, an alternative approach was sought. In our hands, the problem was the preparation and isolation of the cyanobutenylphosphitylating agent in sufficient quality and quantity.

Our exploration of alternative methods led us to consider the versatility of the phosphordiamidites[5](**5**), a class of compounds that have been used in the preparation of deoxynucleoside phosphoramidites[6] and deoxydinucleoside phosphoramidites[7], as a precursor to the cyanobutenylphosphoramidites (**6**). This approach has the added advantage of generating the deoxynucleoside phosphordiamidite (**5**) suitable for reaction, *in situ*, with



(a) B=T, (b) B=A ^{bz}, (c) B=G ^{ibu}, (d) B=C ^{bz}

FIG. 1: I) $SOCl_2$, Pyr, Et_2O, 0°C; II) KCN, NaI, MeCN, 20°C; III) PCl_3, DCM, -60°C; IV) DIPA, (3), DCM, 20°C; V) Tetrazole, (2), DCM, 20°C

4-cyano-2-buten-1-ol **(2)**. The chemical synthesis of the 4-cyano-2-butenylphosphoramidites **(6)** from the phosphordiamidite synthons is described.

4-Cyano-2-buten-1-ol **(2)** was prepared by methods previously reported i.e. monohalogenation[8] of 2-butene-1,4-diol followed by cyanation[4] of the resulting 4-chloro-2-buten-1-ol **(1)**. Bisdiisopropylaminochlorophosphine **(3)** was prepared by adding a solution of phosphorus trichloride in dichloromethane dropwise to a stirred solution of diisopropylamine (6.0 equiv.) in dichloromethane. The reaction was carried out at -60 °C. Once the addition of phosphorus trichloride was complete, the cooling bath was removed and the reactants stirred at room temperature over night. Diisopropylamine hydrochloride was removed by filtration and the product used without further purification.

5'-O-Dimethoxytritylthymidine[9] **(4a)** in dichloromethane was treated with diisopropylamine (1.5 equiv.) and bisdiisopropylaminochlorophosphine **(3)** (1.1 equiv.).

After stirring at room temperature for 1.5 hours TLC (5% methanol/dichloromethane) indicated complete conversion of **(4a).** 4-Cyano-2-butene-1-ol **(2)** (1.1equiv.) and tetrazole (0.25 equiv.) were added. TLC (diethyl ether) after 2.5 hours showed incomplete reaction. Further tetrazole (0.25 equiv.) was added and the reactants stirred overnight. After the usual aqueous work up the product was purified by chromatography on silica gel using a gradient of ethyl acetate in hexane (N.B. all solvents contained 1.0% triethylamine). Yield = 58%. The remaining three phosphoramidites **(6b-d)** were prepared in a similar manner in 42%, 40% and 41% yields respectively, the spectroscopic data was as reported[4].

In summary, this method provides an improved alternative route for the synthesis of 4-cyano-2-butenyl protected phosphoramidites and allows the preparation of the title compounds in >100g quantities.

REFERENCES

1 S.M. Freier, K.H. Altmann, *Nucleic Acid Research,* **1997,** *25*, 4429.
2 M.P. Reddy, N.B. Hanna, F. Farooqui, *Nucleosides and Nucleotides,* **1997,** *16*, 1589.
3 L. Beigelman, A. Karpeisky, J. Matulic-Adamic, P. Haeberli, D. Sweedler, N. Usman, *Nucleic Acid Research,* **1995,** *23*, 4434.
4 V.T. Ravikumar, Z.S. Cheruvallath, D.L. Cole, *Tetrahedron Letters,* **1996,** *37*, 6643.
5 G. Beaton, W.K.-D. Brill, A. Grandas, Y.-X. Ma, J. Nielsen, E. Yau, M. H. Caruthers, *Tetrahedron,* **1991,** *47*, 2377.
6 S.L. Beaucage, *Tet. Lett.*, **1984,** 25, 375; A.D. Barone, J.-Y. Tang, M.H. Caruthers, *Nucleic Acid Research,* **1984,** *12*, 4051.
7 J.E. Marugg, A. Burik, M. Tromp, G.A. van der Marel, J.H. van Boom, *Tetrahedron. Letters,* **1986,** *27*, 2271; B. Uznanski, A. Wilk, W.S. Stec, *Tetrahedron Letters,* **1987,** *28*, 3401.
8 J. Cologne, G. Poilane, *Bull. Soc. Chim. Fr.*, **1955,** 953.
9 F.Morvan, B.Rayner, J-L. Imbach. *In Methods in Molecular Biology, Protocols for Oligonucleotides and Analogs.* Edited by: S. Agarawal; Humana Press Inc., Totowa, New Jersey, ***1993;*** Vol. *20*, 261-283.