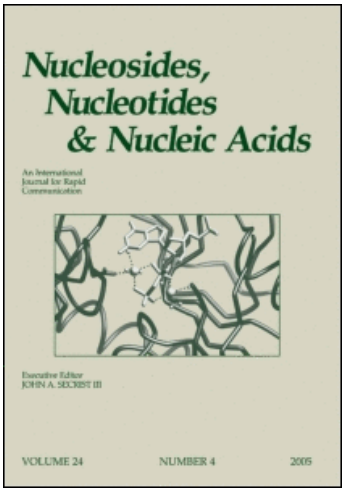

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THE 9-FLUORENYLMETHYLOXYCARBONYL (Fmoc) GROUP AS A 5'-O BASE LABILE PROTECTING GROUP IN SOLID SUPPORTED OLIGONUCLEOTIDE SYNTHESIS

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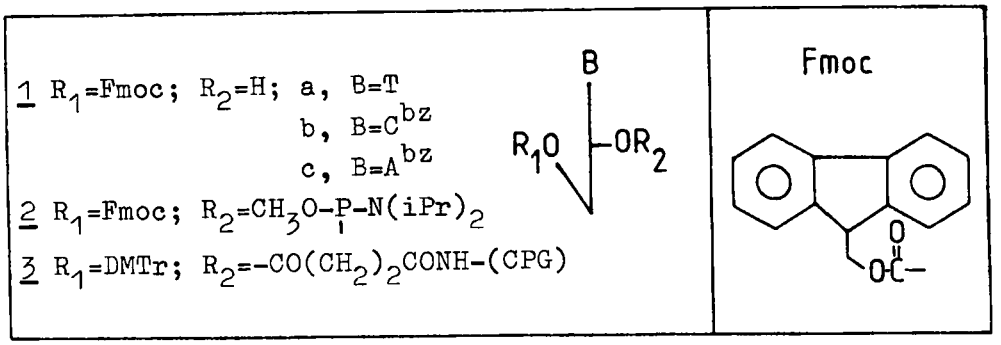
Abstract: The title strategy is discussed and applied to the synthesis of a short oligomer.

A recurrent problem in a standard type oligonucleotide synthesis is the depurination of N-protected dA during acidic removal of the 5'-O dimethoxytrityl (DMTr) group. Depurination can be kept to a minimum by a fine tuning of the acidic treatment and a pertinent choice of the aglycone protection. However, if it could be demonstrated that a base labile 5'-O protection is as easy and convenient to use as the DMTr group, one would get a useful alternative strategy. The base labile 5'-O Fmoc protection was used by Chattopadhyaya and al., in the context of a phosphotriester block synthesis in solution. The deprotection step (NEt_3, pyridine) was slow[1]. We however circumvented this problem, as described hereunder.

We first synthesized compounds 1a-c by acylation of dT, dC^{bz} and dA^{bz} by FmocCl in pyridine at r.t. (Yields 70-80% of pure 1a-c, devoid of contamination by the 3'-O Fmoc isomer). Compounds 2a-b were obtained by standard technics.



In acetonitrile/piperidine (95:5)(method A) and acetonitrile/morpholine (70:30)(method B), the deprotection of 1a was complete in less than 2 min. In acetonitrile/triethylamine (70:30)(method C), the deprotection time was 15 min. When method A or B (basic treatment: 3 min.) was applied to an otherwise classical solid supported synthesis of d(TpTpTpT), using 2a and CPG as support, an excellent

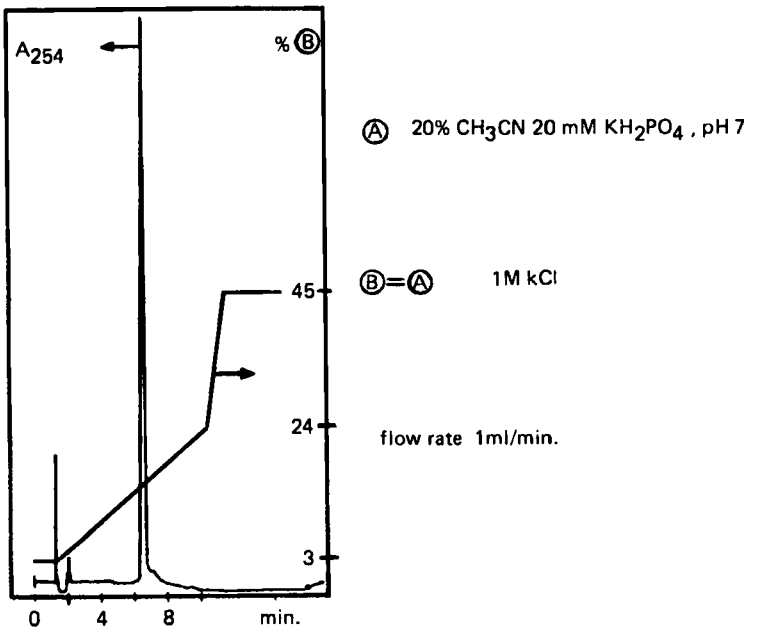


FIGURE 1

chromatographic trace of the fully deprotected tetramer was obtained (FPLC MonoQ HR5/5)(Figure). When, however, method C was used, truncated sequences and/or side products were observed. The rationale is probably that piperidine and morpholine (but not NEt_3) add to the very reactive dibenzofulvene generated by β-elimination.

The chemical stability of other functions in conditions of methods A and B was studied. The conjugate 3 was submitted to a 6 hrs treatment in the conditions of method A. No weakening of the DMTr loading of the CPG was observed. The succinate link with the support was thus not cleaved. Finally, the half-life of the very sensitive DMTr(dC^{bz}) synthon in the conditions of method A was more than 25 hrs.

We thus conclude that the Fmoc group is a promising candidate for the protection of the 5'-OH function of the building blocks engaged in a solid supported oligonucleotide synthesis.

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Gioeli, C. and Chattopadhyaya, J. B., J. Chem. Soc., Chem. Commun. 1982, 672.