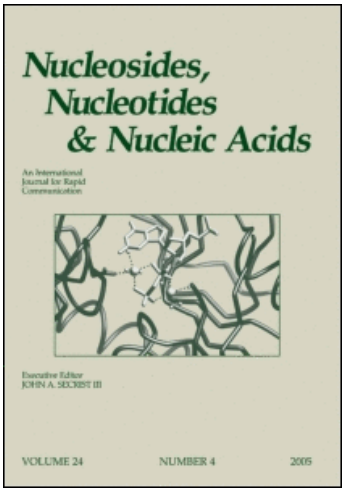


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

2'-OH Protection by the p-Nitrophenylethylsulfonyl (NPES) Group in Oligoribonucleotide Synthesis

R. Charubala[a]; W. Pfleiderer[a]
[a] Fakultät für Chemie, Universität Konstanz, Konstanz

To cite this Article Charubala, R. and Pfleiderer, W.(1987) '2'-OH Protection by the p-Nitrophenylethylsulfonyl (NPES) Group in Oligoribonucleotide Synthesis', Nucleosides, Nucleotides and Nucleic Acids, 6: 1, 517 — 520
To link to this Article: DOI: 10.1080/07328318708056273
URL: http://dx.doi.org/10.1080/07328318708056273

NUCLEOSIDES & NUCLEOTIDES, 6(1&2), 517-520 (1987)

2'-OH PROTECTION BY THE p-NITROPHENYLETHYLSULFONYL (NPES) GROUP IN OLIGORIBONUCLEOTIDE SYNTHESIS

R. Charubala and W. Pfleiderer
Fakultät für Chemie, Universität Konstanz, D-7750 Konstanz

Summary: The NPES group has been sucessfully applied for protection of the 2'-hydroxyl function in synthesizing the adenylate dimer ApA.

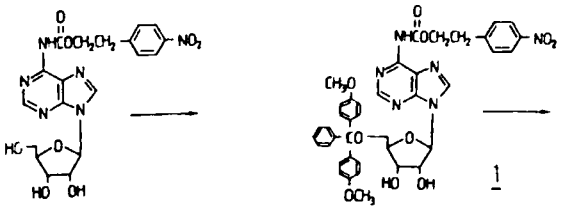
The protection of the 2'-hydroxyl function at the ribosyl moiety constituted an important step in designing a strategy for a multistep chemical synthesis of oligoribonucleotides. Several acid and base labile protecting groups (1) as well as the ones removable under neutral conditions (2) or by mild Lewis acids (3) and the fluoride ions (4) respectively are known.

Our investigations to find a suitable protecting group for the 2'-hydroxyl function in the ribo series were guided by the striking features of the p-nitrophenylethyl (NPE) and -p-nitrophenylethoxycarbonyl (NPEOC) residues as universal blocking groups (5,6) and led to the development of the p-nitrophenylethylsulfonyl (NPES) group (7), for 2'-protection, since it can be cleaved cleanly by a ß-elimination mechanism, in aprotic solvents.

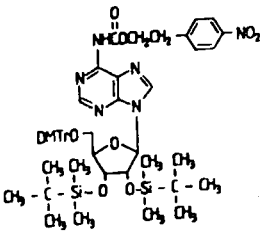
This paper describes the synthesis of three different dimers using the NPES group in the synthetic approach.

5'-O-Dimethoxytrityl-N^6-p-nitrophenylethoxycarbonyl-adenosine (1) was silylated with tert.butyldimethylsilyl chloride to give the 2'-O-silyl (2), 3'-O-silyl (3) and 2',3'-disilyl derivatives (4) in 33, 50 and 8 % yields respectively. Compound 3 was treated with p-nitrophenylethylsulfonyl chloride in pyridine at room temp. to give the 2'-sulfonated product 5 in 88 % yield. The 3'-O-silyl group was then cleaved with 0.5 M TBAF at -6°C to give the required compound 6 in a yield of 76 %.

Three different phosphoramidites were prepared in over 85 % yield from compound 6 using p-nitrophenylethyl-N,N-diisopropylamino phosphomonochloridite to give 7, ß-cyanoethyl-N,N-diisopropylamino phosphomonochloridite (8) to give 8 and p-nitrophenylethyl octahydro

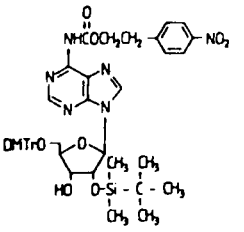


1



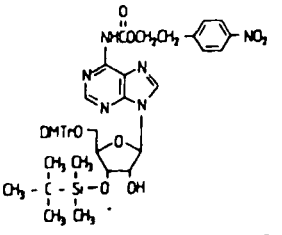
8%

4



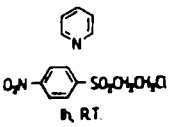
33%

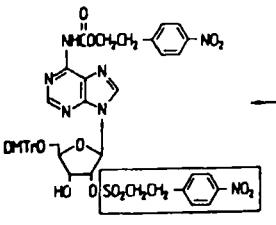
2



50%

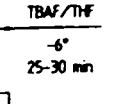
3

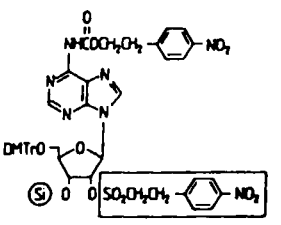




76%

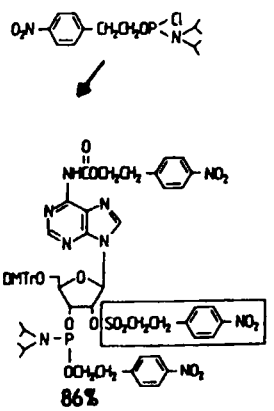
6





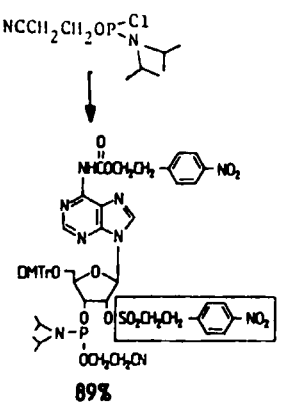
88%

5



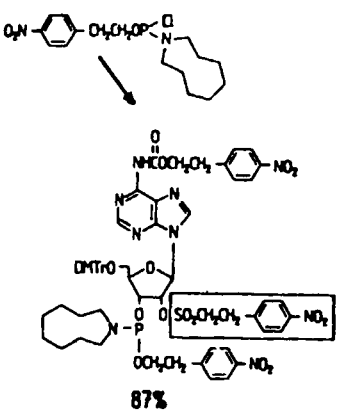
86%

7



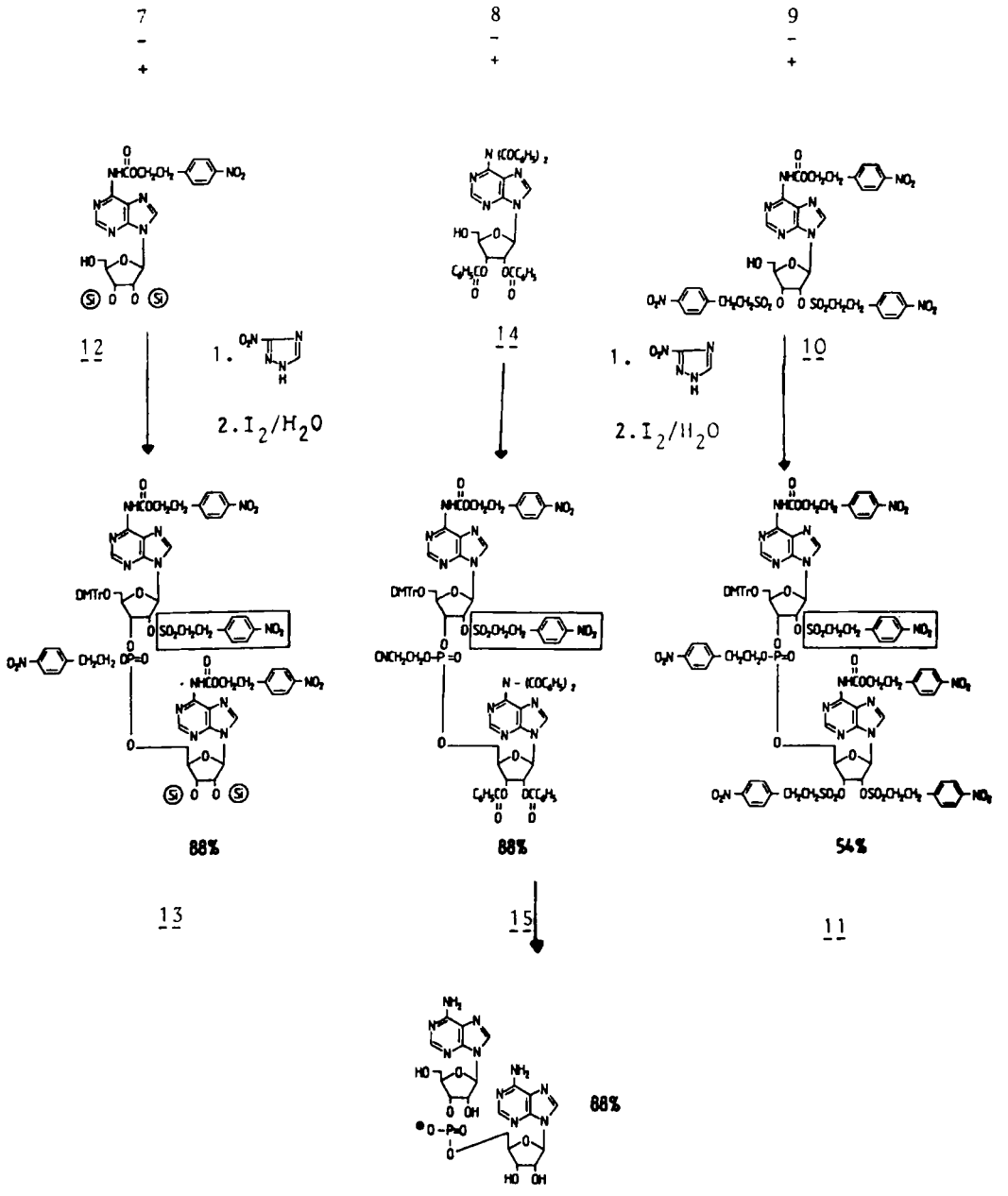
89%

8



87%

9



azoninophosphomonochloridite (9) to yield 9, respectively. Purification was done by column chromatography on silica gel, and characterization by ^{1}H and ^{31}P-NMR, UV and TLC analysis.

5'-O-DMTr-2'-O-NPES-N^6-NPEOC-adenosine-3'-p-nitrophenylethylphosphoroamidite 9 was condensed with N^6-NPEOC-2',3'-di-O-NPES-adenosine 10 in presence of 3-nitro-1,2,4-triazole in CH_3CN and

subsequent oxidation with iodine/H_2O gave the dimer 11 in only 55 % yield due to low solubility of the compound 10 under the applie reaction condition. The phosphoramidite 7 was condensed with N^6-NPEOC-2',3'-di-O-tert.butyldimethylsilyl-adenosine (12), and after oxidation led to the dimer 13 in 88 % yield. The phosphoramidite 8 was finally condensed with 2',3',N^6,N^6-tetrabenzoyladenosine (14) and gave after iodine oxidation the fully protected dimer 15 in 88 % yield. This compound was then subjected to DBU treatment to remove subsequently the cyanoethyl and p-nitrophenylethylsulfonyl and p-nitrophenylethoxycarbonyl groups. Conc. ammonia removed the benzoyl groups and finally 80 % AcOH deblocked the 5'-O-DMTr group to ApA. The crude dimer was purified by DEAE Sephadex column chromatography using a linear gradient of TEAB buffer. The purity of the compound was checked by TLC on cellulose, and PEI cellulose in different solvent systems, by HPLC which showed pure ApA without any trace of isomerisation. The yield of the deblocking step was 87 % after purification.

These results suggest that the NPES groups is a suitable protecting group for hydroxyl function in oligoribonucleotide synthesis. Further work is in progress and will be published very soon.

REFERENCES

1. C.B. Reese, Protection of Alcoholic Hydroxyl Groups and Glycol Systems in "Protective Groups in Organic Chemistry", ed. J.F.W. McOmie, Plenum 1973, 95;
2. J.B. Chattopadhyaya, C.B. Reese and A.R. Todd, J.C.S. Chem. Comm. 1979, 987;
3. E.J. Corey, J.L. Gras, P. Ulrich, Tetrahedron Lett. 1976, 809; M.D. Matteucci and M.H. Caruthers, Tetrahedron Lett. 1980, 3243;
4. K.K. Ogilvie, S.L. Beaucage, A.L. Schifman, N.Y. Theriault and K.L. Sadana, Can.J.Chem. 21, 2768 (1978);
5. E. Uhlmann and W. Pfleiderer, Helv.Chim. Acta 64, 1688 (1981);
6. F. Himmelsbach, B.S. Schulz, T. Trichtinger, R. Charubala and W. Pfleiderer, Tetrahedron 40, 59 (1984);
7. M. Pfister, Diplomarbeit, Universität Konstanz 1986;
8. M.W. Schwarz and W. Pfleiderer, Tetrahedron Lett. 1984, 5513;
9. N.D. Sinha, J. Biernat and H. Köster, Tetrahedron Lett 1983, 5843.