One-step Chemical Synthesis of Ribonucleosides bearing a Photolabile Ether Protecting Group

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Summary Ribonucleosides bearing a photolabile protecting function, the *o*-nitrobenzyl group, which may be cleaved without affecting either purine or pyrimidine bases, have been produced in one step from unprotected ribonucleosides.

THE chemical synthesis of sequence-defined oligoribonucleotides requires ribonucleoside intermediates bearing a protecting group on the 2′-OH which is stable to the conditions for internucleotide bond formation but labile under conditions which do not permit 3′ → 2′ phosphate migration. The benzyl group has been suggested as meeting these requirements,[1,2] but catalytic hydrogenolysis of pyrimidine ribonucleoside 2′-*O*-benzyl ethers without concomitant reduction of the 4,5 double bond is difficult.[2] The *o*-nitrobenzyl group has been used in oligosaccharide synthesis, but these derivatives have been very difficult to prepare.[3] We now report a one-step preparation from unprotected ribonucleosides of 2′-*O*-(*o*-nitrobenzyl) ethers and subsequent photolytic cleavage under conditions which do not affect the purine or pyrimidine bases.

Treatment of a methanolic solution of the ribonucleoside (adenosine, inosine, cytidine or uridine) with *o*-nitrophenyl diazomethane in 1,2-dimethoxyethane in the presence of $SnCl_2 \cdot 2H_2O$ gave mixtures of 2′- and 3′-*O*-(*o*-nitrobenzyl) ribonucleosides in 74—87% yield. Direct crystallization (adenosine) or dry-column chromatography using Woelm neutral alumina (inosine, cytidine, uridine) afforded the 2′-*O*-(*o*-nitrobenzylribonucleosides) in 37—46% yield based on starting ribonucleoside (the cytidine derivative was initially crystallized as its HCl salt). These compounds were identified by elemental analysis and by the u.v. and ^{1}H n.m.r. methods previously developed for *O*-benzylribonucleosides.[2]

Ease of photolytic removal of the *o*-nitrobenzyl group was evaluated with all of the 2′-derivatives prepared in this study. Photolysis was carried out in MeOH–DMF (2:1) for 60 min (adenosine), in MeOH for 70 min (uridine), 105 min (inosine) or 60 min (cytidine), using a quartz vessel in a Rayonet photoreactor (350 nm). After silica gel chromatography the isolated yields of chromatographically pure (t.l.c.) nucleosides were essentially quantitative. No evidence for other ribose containing compounds was found using the sensitive anisaldehyde–sulphuric acid reagent of Stahl.[4]

Evaluation of the protected nucleosides in oligoribonucleotide synthesis is in progress and will be reported in detail elsewhere.

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[1] C. B. Reese and D. R. Trentham, *Tetrahedron Letters*, 1965, 2459.
[2] L. F. Christensen and A. D. Broom, *J. Org. Chem.*, 1972, **37**, 3398.
[3] U. Zehavi, B. Amit, and A. Patchornik, *J. Org. Chem.*, 1974, **39**, 192.
[4] E. Stahl and U. Kaltenbach, *J. Chromatog.*, 1961, **5**, 351.