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A MILD CONVERSION OF VICINAL DIOLS TO ALKENES. EFFICIENT TRANSFORMATION OF RIBONUCLEOSIDES INTO 2'-ENE AND 2',3'-DIDEOXYNUCLEOSIDES[1]

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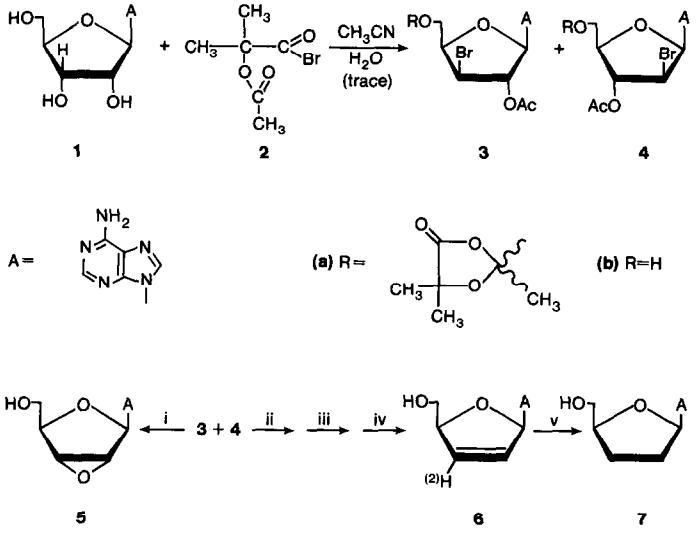
α-Acetoxyisobutyryl bromide in "moist" acetonitrile converted adenosine to trans-3'(2')-bromo-2'(3')-acetates with <3% glycosyl cleavage. This mixture was acetylated, treated with Zn/Cu/DMF, and deacylated to give 81% of the 2'-alkene.

The nucleoside antibiotics blasticidin S and mildiomycin have 2',3'-unsaturated pyranosyl sugar units and several related antibiotics have reduced 2',3'-dideoxy structures.[3] Renewed interest in efficient methods for the synthesis of 2',3'-unsaturated furanosyl nucleosides has been stimulated recently by the use of their reduced 2',3'-dideoxynucleoside 5'-triphosphates for DNA sequencing.[4]

Access to 2',3'-unsaturated nucleosides was attained originally using base-promoted elimination with 3'-O-sulfonyl esters of pyrimidine[5] and purine[6] 2'-deoxynucleosides. More recently methods have been reported for conversions of ribonucleosides to the 2'-enofuranosyl products.[7-10] However, overall yields from ribonucleosides (or 2'-deoxynucleosides) to the 2'-alkenes have been low to moderate. Very recently the Barton deoxygenation was employed to convert dithiocarbonate derivatives of the expensive 2'-deoxynucleosides to 2',3'-dideoxynucleosides in overall yields of 40-55%.[11] We now report a very mild reaction sequence for conversion of ribonucleosides to 2',3'-unsaturated nucleosides in ~80% yields. Hydrogenation of the adenine compound gave 2',3'-dideoxyadenosine in 89% for an overall yield of 72% from adenosine. Several model vicinal diols also were converted smoothly to akenes[12] by our two-stage sequence which employs readily available reagents and proceeds at room temperature.

A suspension of 267 mg (1 mmol) of adenosine (1) in 20 mL of dry acetonitrile was treated with 2 mL of acetonitrile/water (10:1)[12] and 0.6 mL (4 mmol) of α-acetoxyisobutyryl bromide[13] (2) and the mixture was stirred at room temperature (~22°C) for 1 h. A clear solution resulted after ~45 min and at ~50 min a fine precipitate began separating. Aqueous sodium bicarbonate solution was added and the solution was extracted with ethyl acetate. The organic phase contained two product bands (TLC). ^{1}H NMR analysis of the faster migrating major band indicated an ~9:1 mixture of the 2'-O-acetyl-3'-bromo-xylo

(3a) and 3'-O-acetyl-2'-bromo-arabino (4a) products protected at O5' as 2,5,5-trimethyldioxolan-4-on-2-yl ortho esters.[13] The slower minor band contained an ~9:1 mixture of the xylo (3b) and arabino (4b) isomers with free 5'-hydroxyl groups. Ultraviolet spectral analysis of the aqueous layer indicated ~2% of adenine. Treatment of the crude mixture (3, 4) from the combined organic phase with Amberlite IRA-400(OH^-) resin in dry methanol gave recrystallized 2',3'-anhydroadenosine[8a] (5) in 92% yield. This confirmed the efficient conversion of adenosine (1) to 3 + 4 and the minimal glycosyl cleavage.



(i) Amberlite IRA - 400(OH^-) resin/MeOH. (ii) Ac_2O/pyridine/DMAP. (iii) Zn/Cu/DMF. (iv) NH_3/MeOH. (v) H_2/5% Pd·C/98% EtOH.

Crude 3 + 4 was acetylated and the readily soluble amorphous glass was dissolved in 12 mL of DMF and stirred with freshly prepared zinc-copper couple for 1 h at room temperature. Filtration of the mixture using Celite, evaporation, deacylation with NH_3/MeOH, chromatography on a column of Dowex 1X2(OH^-) resin with water as eluant, and recrystallization from Et_2O/MeOH (diffusion)[8a] gave 189 mg (81% overall from 1) of 9-(2,3-dideoxy-β-D-glycero-pent-2-eno-furanosyl)adenine (6), mp 194-196°C (lit.[7] mp 194-195°C).

Hydrogenation of 1 mmol of 6 in 98% EtOH over 5% Pd·C gave 89% of recrystallized 2',3'-dideoxyadenosine (7), mp 185-187°C (lit.[6] mp 183-185°C). This conversion of 1 to 7 (72% overall) represents a substantial improvement in yields relative to previously reported routes.

The "abnormal" Mattocks reaction of diols with α-acetoxyisobutyryl halides was first applied to nucleosides by Moffatt and coworkers.[13] However, treatment of adenosine with the acid chloride at elevated temperature resulted in ~20% glycosyl cleavage. Use of the bromide at room temperature alleviated cleavage but resulted in formation of ~20% of 2',3',5'-tris-O-protected ortho ester by-products.[13] Extensive formation of the tris ortho ester by-products occurred with the acyl iodide generated in situ.[7,14]

The present use of "moist" acetonitrile with excess acyl bromide at room temperature effectively circumvents both the cleavage and ortho ester formation side reactions. Zinc-copper couple in non-aqueous sodium acetate/acetic acid at -10°C effected facile reductive elimination of bromide and acetate from nucleoside and model diol derived intermediates.[2,12] However, some glycosyl cleavage of the acid-labile unsaturated nucleosides occurred as well as simple reduction to give monodeoxy nucleoside by-products analogously to previous results with a chromous ion complex.[7] The Zn/Cu/DMF system at room temperature promotes smooth reductive elimination with insignificant simple reduction in the cases examined thus far.

Subjection of 3'-deuterioadenosine (1, 3'-^{2}H) to this sequence gave 9-(3-deuterio-2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)adenine (6, 3'-^{2}H). The lower field vinyl proton signal was absent from the ^{1}H NMR spectrum of this compound and the corresponding lower field vinyl carbon signal was depleted. Independent evaluation of a second purine nucleoside labeled with a 2'-deuterium corroborated the vinylic assignments of H2' and C2' to higher field in the 2',3'-unsaturated nucleosides. Reduction of 6 → 7 resulted in reversal to the usual lower field positions for H2',2" and C2' relative to H3',3" and C3'. These assignments correct previous NMR analyses[6,7,9a,15,16] that were based on analogy with the usual 2' < 3' ordering. From data presently available it appears that the general shift trend of H1' < H3' < H2' < H4' < H5',5" and C3' < C2' < C1' < C4' < C5' exists for the 2',3'-unsaturated nucleosides, although the close shifts for C1' (δ 138.2) and C4' (138.0) of 6 might be reversed with other related compounds.

The present sequence of treatment of ribonucleosides (and model diols) with α-acetoxyisobutyryl bromide followed by reductive elimination of the derived bromo acetates proceeds at room temperature to give high yields of the corresponding alkenes. Previously encountered problems of significant glycosyl cleavage, ortho ester by-product formation, and simple reduction to monodeoxy nucleosides are circumvented. Hydrogenation of the 2'-enofuranosyl compounds provides the 2',3'-dideoxynucleosides in good overall yields. A reversal of signal positions in the NMR spectra of the 2',3'-unsaturated nucleosides relative to ribonucleosides and 2',3'-dideoxynucleosides occurs with H2' and

C2' resonating at higher fields than H3' and C3'. Synthetic and spectroscopic details will be published in our full paper.

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1. (a) This contribution constitutes: Nucleic Acid Related Compounds. 46. (b) For the previous paper in this series see: F. Hansske and M. J. Robins, J. Am. Chem. Soc., in press.
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