Facile Conversion of Vinyl Azides to Ketones or Aldehydes[1]

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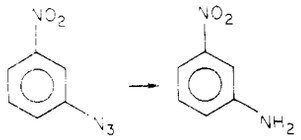
The azido group has found extensive utility in organic synthesis, especially when present as a substituent on an olefinic double bond.[2] While various reducing agents have been employed in the conversion of aliphatic and aromatic azides to the corresponding amines,[3] there have been few reports on the reduction of vinyl azides (primarily with zinc–acetic acid[4] or triphenyl phosphite[5]) which yield ketones, presumably via enamine derivatives.[6]

That the search for mild, convenient methods of reduction of azides is continuing is obvious from recent studies.[7,8] This prompts us to report our findings that vinyl azides are readily and cleanly converted at room temperature and in high yield to ketones or aldehydes according to Scheme I, namely, by reaction with sodium sulfide in methanol in the presence of a catalytic amount of triethylamine followed by workup with aqueous acid. The conversions can be carried out as a one-pot process, and the carbonyl compounds are purified by distillation or crystallization. The presence of triethylamine is helpful since in its absence somewhat lower yields of ketone or aldehyde were observed. The starting vinyl azides can be synthesized readily by general methods from alkenes or alkynes[9] as well as from triflones.[5] The formation of several types of ketones and aldehydes from vinyl azides is shown in Table I. The yields compare favorably to those obtained by using triphenyl phosphite.[5] The method is mild enough to permit reduction of an azide in the presence of a nitro group (cf. **3** → **4** in 64% yield) or of a carbonyl group.

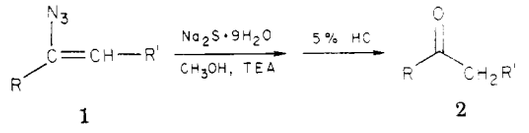


3 **4**

We found the Na_2S method, herein described, to be superior to Zn–HOAc (better yields) and to H_2S in CH_2Cl_2 and Et_3N (reproducibility and handling). For instance, hydrogen sulfide is a highly toxic gas, has a foul odor, and has apparently limited solubility in methylene chloride, so that H_2S needs to be constantly bubbled through the reaction mixture.[10] By contrast, commercially available $Na_2S{\cdot}9H_2O$ can be readily weighed and is sufficiently soluble in methanol[11] to allow the reaction to go to completion. Furthermore, unlike methanol, CH_2Cl_2 is not miscible with 5% hydrochloric acid, and this slows down the rate of hydrolysis in the second step of the procedure.

Though the mechanism of the Na_2S reduction has not been studied, a reasonable pathway may be one illustrated in Scheme II.[12] Indeed, at the end of the reaction and before addition of dilute acid, a precipitate of sulfur and/or polysulfides is present. Elemental sulfur was identified in some cases, and the polysulfide precipitate dissolves on addition of 5% HCl.

Scheme I



1 **2**

Scheme II

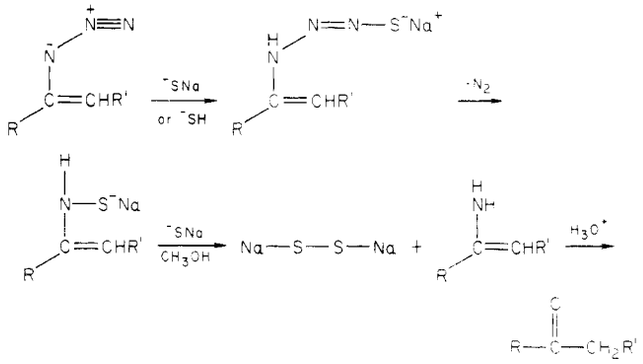
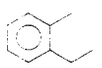


Table I. Conversion of Vinyl Azides 1 to Ketones or Aldehydes 2 by Means of $Na_2S{\cdot}9H_2O$ in Methanol in the Presence of Et_3N

ketone or aldehyde 2	yield, %	ketone or aldehyde 2	yield, %
R = Ph; R′ = H	91	R = R′ = 	88
R = Ph; R′ = CH_3	92		
R = *n*-Bu; R′ = H	90[a]	R = R′ = $(CH_2)_6$	85
R = H; R′ = *t*-Bu	82[a,b]	R = C(O)Ph; R′ = Ph	74

[a] The product is quite soluble in water, so care should be taken during the aqueous workup. [b] Identified by NMR and by the melting point of its hydrazone.

Experimental Section

General Methods. The starting vinyl azides were prepared by known methods.[9] The solvents and the triethylamine were distilled before use. $Na_2S{\cdot}9H_2O$ was obtained from Fischer Scientific Co.

The product ketones and aldehydes were identified by comparison of melting and boiling points and nuclear magnetic resonance and infrared spectra with authentic samples.

Synthesis of Ketones from Vinyl Azides. General Procedure. Vinyl azide (10 mmol) was added to a solution of 5 g

(1) Synthetic Methods 14. For paper 13 see A. Hassner and J. A. Soderquist, *J. Am. Chem. Soc.*, in press.

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(6) Attempts to hydrolyze vinyl azides to the corresponding carbonyl compounds with acid are only partially successful since in addition to ketones, amides were also produced via a Schmidt rearrangement of the protonated vinyl azide. For details see A. Hassner, E. S. Ferdinandi, and R. J. Isbister, *J. Am. Chem. Soc.*, **92**, 1672 (1970); J. B. Hendrickson and P. Skipper, *Tetrahedron*, **32**, 1627 (1976).

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(10) When H_2S was bubbled through the solvent system for 3 h and the stream discontinued immediately before the vinyl azides were added, large amounts of unreacted starting material were recovered after workup.

(11) No reaction was observed in a variety of other solvents such as pentane, acetonitrile, and methylene chloride, presumably because of the low solubility of sodium sulfide.

(12) Attack of nucleophiles on azides may lead to formation of triazenes, and even $SnCl_2$ reduction of aromatic azides gives aryltriazenes: O. Dimroth and K. Pfister, *Ber. Dtsch. Chem. Ges.*, **43**, 2757 (1910).

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(21 mmol) of $Na_2S \cdot 9H_2O$, 0.10 g of triethylamine (1 mmol), and 20 mL of reagent grade methanol which was stirred magnetically at room temperature.

The flask became warm during the addition, a white and yellow precipitate formed on the sides of the reaction vessel, and N_2 gas was evolved. The mixture was stirred for 18–24 h, and then 25 mL of 5% hydrochloric acid was added slowly. After the mixture was stirred for 3–12 h, during which time it became homogeneous and the white precipitate dissolved, 25 mL of diethyl ether was added and the mixture stirred for another 0.5 h.

The two layers were separated, and the aqueous layer was washed with two 25-mL portions of ether. The organic layers were combined and washed with two 25-mL portions of water and then with saturated sodium chloride solution.

The ether layer was dried with anhydrous magnesium sulfate and filtered, and the ether was removed under vacuum to give the crude ketone or aldehyde.

The products were further purified by distillation for liquids or crystallization for solids.

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Registry No. 1 (R = Ph; R′ = H), 16722-99-9; 1 (R = Ph; R′ = CH_3), 28022-21-1; 1 (R = Br; R′ = H), 34910-43-5; 1 (R = H; R = *t*-Bu), 40168-86-3; 1 (R, R′ = $-C_6H_4$-2-CH_2-), 16719-57-6; 1 (R = R′ = $(CH_2)_6$), 40934-24-5; 1 (R = C(O)Ph; R′ = Ph), 26087-01-4; **2** (R = Ph; R′ = H), 98-86-2; **2** (R = Ph; R′ = CH_3), 93-55-0; **2** (R = Bu; R′ = H), 591-78-6; **2** (R = H; R′ = *t*-Bu), 2987-16-8; **2** (R, R′ = $-C_6H_4$-2-CH_2-), 83-33-0; **2** (R = R′ = $(CH_2)_6$), 502-49-8; **2** (R = C(O)Ph; R′ = Ph), 23464-17-7.

Studies on Biologically Active Nucleosides and Nucleotides. 6. An Anodic Oxidation of 2′,3′-*O*-Isopropylideneuridine-5′-carboxylic Acid

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In recent years there has been a great deal of interest in the preparation of $C_{4'}$-substituted nucleosides. Much of this interest is a result of the isolation and structure identification of the nucleoside antibiotic nucleosidin, 4′-fluoro-5′-*O*-sulfamoyladenosine, which has a unique structure bearing a fluorine atom at $C_{4'}$ of the sugar moiety.[1] Synthetic methods developed for the introduction of various substituents at $C_{4'}$ thus far have included (a) prior construction of suitable carbohydrate derivatives followed by coupling with activated bases,[2] (b) the aldol coupling of nucleoside-5′-aldehydes,[3] and (c) the addition reaction to the exocyclic vinyl ether moiety of 4′,5′-unsaturated nucleosides.[4] Recently, a novel $C_{4'}$-alkylation has been developed by exploiting a "Claisen-type" rearrangement of an N-alkylated 4′,5′-enamine derivative of uridine.[5]

The reactions of suitably protected 4′,5′-unsaturated nucleosides with halogenating agents, e.g., *N*-bromosuccinimide,[4a,b] bromine,[4f] and iodine,[4d] in methanol have been shown to give 5′-halogeno-4′-methoxy nucleosides. In the addition reactions, when the opportunity exists for intramolecular participation by the C_2 carbonyl of the pyrimidine ring or N^3 of the adenine ring at $C_{4'}$, the formation of 2,4′-[4b,6] or N^3,4′-cyclo-5′-halogeno nucleosides[7] has been observed.

It has been well documented that the anodic oxidation of carboxylic acids substituted by the electron donating group in the α position generates carbonium ions which are stabilized by charge delocalization.[8] The resulting carbonium ions can undergo nucleophilic attack by alcoholic or carboxylic acid solvents to form ethers or esters, respectively.[8] We conceived that electrolysis of nucleoside-5′-carboxylic acid in these solvents might provide 4′-alkoxy, 4′-acyloxy, and 2(N^3),4′-cyclo nucleosides via intermediary 4′-carbonium ions. Such nucleosides, which lack the 4′-hydroxymethyl group, are of interest as intermediates for the derivatization at $C_{4'}$ and with respect to their possible biological activity. We report herein results on the anodic oxidation of 2′,3′-*O*-isopropylideneuridine-5′-carboxylic acid (**1**) in methanol and acetic acid. Very recently, while our study was in progress, the synthesis of aminocyclitol via anodic oxidation of uronic acid was reported.[9]

The carboxylic acid **1** was prepared from uridine-5′-carboxylic acid in a good yield by a modification of the procedure previously described.[10] The electrolysis of **1** in methanol was carried out in the presence of a catalytic amount of sodium methoxide at 5–10 °C, using a graphite anode–graphite cathode in a nondivided cell. After 1.4 times a theoretical amount of current was passed, a mixture of products was separated into three major fractions by chromatography on silicic acid. The first fraction contained a roughly equal (NMR) mixture of 1-[2,3-*O*-isopropylidene-4(*R*)-methoxy-β-D-erythrofuranosyl]uracil (**4**) and 1-[2,3-*O*-isopropylidene-4(*S*)-methoxy-β-D-erythrofuranosyl]uracil (**5**) in a combined yield of 35%. The methoxy nucleoside could be resolved into its diastereoisomers by fractional crystallization, **4** and **5** being isolated in yields of 4 and 11%, respectively. The structures of **4** and **5** were confirmed by NMR spectroscopy. The spectra of both **4** and **5** showed the presence of a methoxyl group and the expected downfield shift of the $C_{4'}$ proton relative to that of **1**. In compound **4** the value of $J_{3',4'}$ was 4 Hz, while compound **5** had $J_{3',4'}$ = 0 Hz. These values are consistent with the assigned orientations (cis for **4** and trans for **5**) of $C_{3'}H$ and $C_{4'}H$.[11] In addition, the reported coupling data[12] for vicinal hydrogens in the

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