## Sugars with Potential Antiviral Activity. I. Conversion of Hydroxy Compounds to Nitriles

D. Brett, I. M. Downie, and J. B. Lee

*Department of Organic Chemistry, The University of Technology, Loughborough, Leics., England*

*Received July 18, 1966*

We have investigated a variety of methods for the introduction of amino groups into carbohydrates, and in the case of a primary terminal amino group (*i.e.*, $CH_2NH_2$) an obvious precursor was the nitrile. Nitriles of sugar acids are obtainable in several ways, for example, *via* the cyanohydrin reaction[1] or by dehydration of oximes[2]; in the former case chain extension is obtained.

The treatment of alkyl halides with sodium cyanide in ethanol[3] or other solvents[4] has been used to prepare nitriles in the aliphatic series, and sodium cyanide has also been used to convert sulfonate esters to nitriles.[5] When we carried out model experiments with alkyl halides, prior to using this reaction in the sugar series, we were unable to obtain reasonable yields using these conditions[3-5]; the use of aqueous solvents apparently resulted in considerable hydrolysis, while the insolubility of sodium cyanide in anhydrous organic solvents led to poor yields presumably since the reaction was heterogeneous. Since the preparation of halo deoxy sugars often involves several stages,[6] usually *via* the sulfonate esters,[7] use of the latter esters is superficially more attractive, but in our hands the yields in this modification were only moderate.[8] The use of aqueous systems is also undesirable with sugars since protecting groups may be removed with consequent losses in yield. Solvent effects are shown in Table I.

Table I

Solvent Effects in Conversion of Chloride into Nitrile[a]

| Compound: solvent | Time of reacn[a] | Yield, % |
|---|---|---|
| 2-Chlorobutane: ethanol | 70 | 24[b] |
| 2-Chlorobutane: aqueous methanol | 65 | 45[b] |
| 2-Chlorobutane: DMF | 40 | 18[c] |
| 2-Chlorobutane: acetone | 56 | 5[c] |
| 2-Chlorobutane: diglyme | 34 | 10[c] |
| 2-Chlorobutane: DMSO | 1.8 | 89 |
| 1-Chlorobutane: methanol | 48 | 45[b] |
| 1-Chlorobutane: DMSO | 0.2 | 92 |

[a] The reaction was followed by analysis of aliquots until no further significant nitrile formation was occurring. [b] Most of starting material reacted. [c] Most of starting material unreacted.

Sodium cyanide is reasonably soluble in anhydrous dimethyl sulfoxide, and using this solvent we obtained high conversions of alkyl chloride to nitrile. In applying this method in the sugar series it would be convenient to have a one-stage conversion of hydroxyl to nitrile; most methods of preparation of halo deoxy sugars require several stages, are time consuming, and yields can occasionally be poor.[6]

We found that rapid conversion of an alcohol to a nitrile was accomplished by treatment of a refluxing mixture of alcohol, carbon tetrachloride, and triphenylphosphine successively with dimethyl sulfoxide and sodium cyanide. A fairly vigorous reaction ensued, and from the mixture could be isolated the required nitrile in reasonable yield.

Solvents other than dimethyl sulfoxide gave poor or negligible yields under the same conditions. Exclusion of moisture from the reaction was important. Primary alcohols reacted more readily than secondary alcohols; the latter therefore required higher temperatures and longer reaction times. The use of carbon tetrachloride in the initial stage is essential, its replacement by other solvents leading to negligible conversion of alcohol to cyanide. While triphenylphosphine may be replaced by other phosphines, if no phosphine is added the reaction does not occur.

Examination of the stoichiometry of the reaction showed that maximum yields were obtained, under otherwise similar conditions, when equimolar quantities of alcohol and phosphine were used. The use of less than equimolar proportions of carbon tetrachloride also reduced the yield seriously, but excess of this solvent appeared to have little effect. Triphenylphosphine oxide was isolated from the final reaction mixture and chloroform was separated from the products of the initial reaction before addition of dimethyl sulfoxide and sodium cyanide. Since the presence of chloroform further reduced the temperature of reflux of the mixture, we found it advantageous in some cases, at the point of addition of dimethyl sulfoxide, to remove the chloroform formed from the mixture by distillation immediately prior to the addition of the sodium cyanide.

The variations in reaction rate which we observed with various primary and secondary alcohols suggest an SN2 rather than an SN1 process (tertiary alcohols dehydrate under these conditions.

The success of the method would appear to be the result of a rapid (2–3 min) transformation of alcohol to halide, with the formation only of inert by-products, permitting reaction *in situ*, hence reducing losses on work-up of halide.

Having established that reaction occurred smoothly with aliphatic alcohols (see the Experimental Section) we examined the reaction of the reagent with 1,2-O-isopropylideneglycerol and methyl 2,3,4-tri-O-acetyl-α-D-glucoside; the products were 2-deoxy-3,4-O-isopropylidenetetrononitrile and methyl 2,3,4-tri-O-acetyl-6-deoxy-α-D-*gluco*-hepturononitrile. The latter was obtained in 45% over-all yield. For comparison the compound was prepared using the standard method of halide introduction[9] followed by treatment with sodium cyanide–DMSO under similar conditions; only

---

[1] H. Kiliani, *Ber.*, **22**, 521 (1889); C. S. Hudson, O. Hartley, and C. B. Purves, *J. Am. Chem. Soc.*, **56**, 1248 (1934); W. Militzer, *Arch. Biochem.*, **21** 143 (1949); C. S. Hudson, *J. Am. Chem. Soc.*, **73**, 4498 (1951).

[2] B. Coxon and H. G. Fletcher, *ibid.*, **86**, 922 (1964); R. M. Hann and C. S. Hudson, *ibid.*, **59**, 1898 (1937); V. Dulofeu, *Advan. Carbohydrate Chem.*, **4**, 119 (1949).

[3] D. T. Mawry, *Chem. Rev.*, **42**, 189 (1948).

[4] A. Brandstrom, *Acta Chem. Scand.*, **10**, 1197 (1956); O. W. Cass, *Chem. Eng. News*, **32** (22), 2197 (1954).

[5] R. Grewe and H. Pachaly, *Ber.*, **87**, 46 (1954); R. Grewe and E. Nolte, *Ann.*, **575**, 1 (1952).

[6] *E.g.*, B. Helferich and A. Gnutchel, *Ber.*, **71**, 712 (1938); B. Helferich and E. Himmen, *ibid.*, **61**, 1825 (1928); A. B. Foster, W. G. Overend, and M. Stacey, *J. Chem. Soc.*, 974 (1951); V. M. Clark, A. R. Todd, and J. Zussman, *ibid.*, 2952 (1951).

[7] R. S. Tipson, *Advan. Carbohydrate Chem.*, **8**, 107 (1953).

[8] J. B. Lee, unpublished results.

[9] M. Zief and R. C. Hockett, *J. Am. Chem. Soc.*, **67**, 1267 (1945); *cf.* B. Helferich and E. Himmen, *Ber.*, **61**, 1825 (1928).

30% over-all yield was obtained, and considerably longer reaction times were involved.

### Experimental Section

Complete exclusion of moisture from apparatus and reagents is required for the best results. Dimethyl sulfoxide is dried by shaking with calcium chloride, filtration onto calcium hydride, and distillation of the filtered, dried solvent under vacuum. The usual precautions must be observed when handling cyanide.

Identity of materials with authentic samples was confirmed by comparison of the infrared and/or proton magnetic resonance spectra in addition to the usual physical constants (*i.e.*, boiling point or melting point, refractive index).

Some variation in technique is possible and examples are given of typical reactions.

**Valeronitrile.**—To a mixture of 9 ml of 1-butanol and 15 ml of carbon tetrachloride was added in one portion 22.5 g of triphenylphosphine. The mixture was heated on a steam bath until vigorous refluxing occurred. After several minutes a portion of 100 ml of dimethyl sulfoxide was added, the temperature of the solution was raised almost to 100°, and 5 g of sodium cyanide was added. After some time the reaction was allowed to cool, and the nitrile was isolated by diluting the mixture with dilute, aqueous sodium sulfate, extraction with chloroform, drying the washed chloroform layer, and fractionation. Valeronitrile was obtained as a colorless liquid, bp 135–138°, $n^{20}\text{D}$ 1.3967 (85% yield).

**2-Methyloctanonitrile.**—A mixture of 14 ml of 2-octanol, 15 ml of $CCl_4$, and 20 g of triphenylphosphine was heated on a steam bath under reflux for several minutes, 80 ml of dimethyl sulfoxide was then added, and the solution was distilled until a temperature of approximately 90° was obtained. The solution was then heated under reflux with portionwise addition of 4.7 g of sodium cyanide. Heating and stirring were continued for an additional 2 hr under reflux. The cooled solution was poured onto an ice plus aqueous ferrous sulfate solution, the combined mixture was extracted with chloroform (three 100-ml portions), and the dried extracts were fractionated under vacuum. 2-Methyloctanonitrile was obtained, bp 85–90° (water pump), $n^{20.5}\text{D}$ 1.4201 (70% yield). By similar methods 1-hexanol, 1-pentanol, 1-decanol, and 1-heptanol may be converted to the nitrile.

Production of chloroform in the reaction was confirmed as follows. A mixture of 10 ml of 1-pentanol, 25 ml of carbon tetrachloride, and 26 g of triphenylphosphine was heated under reflux. The mixture was then roughly fractionated and material of bp 58–68° was compared with solvent chloroform by gas-liquid partition chromatography and proton magnetic resonance. The material was mainly chloroform contaminated with some carbon tetrachloride and 1-chloropentane.

Production of triphenylphosphine oxide was confirmed by recrystallization of the reaction residues after removal of volatile material. The white, crystalline material, mp 148–150°, was identical in infrared spectrum and behavior on thin layer chromatography with that of authentic triphenylphosphine oxide, the melting point of which it did not depress.

**Methyl 2,3,4-Tri-O-acetyl-6-deoxy-α-D-glucohepturononitrile.**—A solution of 9.6 g of methyl 2,3,4-tri-O-acetyl-α-D-glucoside in 50 ml of carbon tetrachloride was heated under reflux with 7.9 g triphenylphosphine for 15 min and 100 ml of dimethyl sulfoxide was then added; solvent was removed on the steam bath until approximately 45 ml of distillate had collected, and a 2.5-g portion of sodium cyanide was then added. Heating was continued on the steam bath for 1.5 hr. The mixture was then poured onto ice (approximately 800 g) and set aside to reach room temperature. The solid was separated, washed several times with cold water, and then dissolved in boiling methanol and filtered while hot. The solvent was removed *in vacuo* and the residue was recrystallized from a little warm methanol. The product (4.5 g) was dissolved in chloroform and petroleum ether was added until a faint turbidity still persisted on heating the solution. On cooling, white crystals, mp 132–133°, $[\alpha]^{18}\text{D}$ +147° (*c* 0.7, $CHCl_3$), were obtained. These liberated ammonia with hot aqueous sodium hydroxide and showed no hydroxyl band in the infrared. Bands at 2215 and 1745 $cm^{-1}$ indicated nitrile and acetyl to be present.

*Anal.* Calcd for $C_{14}H_{19}NO_8$: C, 50.66; H, 5.67; N, 4.25. Found: C, 50.56; H, 5.78; N, 4.02.

**Registry No.**—Valeronitrile, 110-59-8; 7-butanol, 71-36-3; 2-methyloctanonitrile, 2570-96-9; 2-octanol, 123-96-6; 1-hexanol, 111-27-3; 1-pentanol, 71-41-0; 1-decanol, 112-30-1; 1-heptanol, 111-70-6; methyl 2,3,4-tri-O-acetyl-6-deoxy-α-D-glucohepturononitrile, 7432-71-5.

---

# Allene Chemistry. VI.[1] Reaction of Sodium Thiolates with Allene

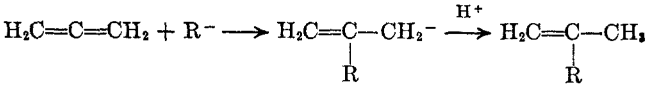
W. H. MUELLER AND K. GRIESBAUM

*Central Basic Research Laboratory,*
*Esso Research and Engineering Company, Linden, New Jersey*

*Received September 9, 1966*

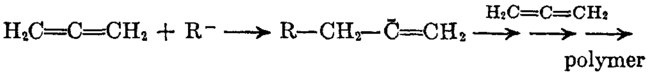
Considerable advances have been made during the past decade in the understanding of electrophilic and of free-radical addition reactions to allene.[2] In contrast, very little is known to date about the course of anionic additions to allene and to allenic systems in general.

In analogy with the well-documented facile addition of nucleophiles to acetylenes[3] and in line with the preferred formation of the least substituted carbanion intermediates in such reactions one might anticipate a preferential attack at the central sp carbon atom of allene to yield a vinylic monoadduct.



$$H_2C{=}C{=}CH_2 + R^- \longrightarrow H_2C{=}\underset{R}{\underset{|}{C}}{-}CH_2^- \xrightarrow{H^+} H_2C{=}\underset{R}{\underset{|}{C}}{-}CH_3$$

Such a preferred reaction course was indeed reported for the addition of ethanol to allene in the presence of potassium hydroxide.[4] The Ziegler-type polymerization of allene, on the other hand, which was also formulated as an anionic reaction was reported to follow precisely the opposite reaction path *via* a preferred terminal attack on allene.[5]



$$H_2C{=}C{=}CH_2 + R^- \longrightarrow R{-}CH_2{-}\bar{C}{=}CH_2 \xrightarrow{H_2C=C=CH_2} \longrightarrow \longrightarrow \text{polymer}$$

In the light of this apparent discrepancy we have undertaken a brief investigation of this reaction, using the strongly nucleophilic thiolate ions[6] as adding species. The freshly prepared sodium thiolates were in each case treated with a 100% molar excess of allene in methanol as a solvent at elevated temperatures (Table I) in pressure tubes. After arbitrary periods of reaction times the unreacted gases were withdrawn and analyzed, and the remaining liquid products were worked up as described in the Experimental Section.

It was a common feature of all of these reactions that the corresponding 2-propenyl sulfides (I) were formed in very high selectivities (~90%), along with

---

[1] For the previous report in this series, see K. Griesbaum, *Angew. Chem.*, **78**, 953 (1966); *Angew. Chem. Intern. Ed. Engl.*, **5**, 933 (1966).

[2] For leading references, see footnote 1.

[3] (a) W. E. Truce in "Organic Sulfur Compounds," Vol. I, N. Kharasch, Ed., Pergamon Press Inc., New York, N. Y., 1961, pp 112–120; (b) W. E. Truce, H. C. Klein, and R. B. Kruse, *J. Am. Chem. Soc.*, **83**, 4636 (1961).

[4] A. Fawórsky, *J. Prakt. Chem.*, [2] **44**, 208 (1891).

[5] W. P. Baker, Jr., *J. Polymer Sci.*, **A1**, 655 (1963).

[6] For a summary, see footnote 3 in ref 3a.