Notes

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Method for the Cleavage of Osmate Esters

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Osmate esters obtained in the oxidation of alkenes with osmium tetroxide have been cleaved with reagents such as strong aqueous base and mannitol,[1] refluxing aqueous alcoholic sodium sulfite[2] or bisulfite,[3] and hydrogen sulfide.[4] This communication describes a method for the smooth transformation of osmate esters to *cis*-glycols under mild conditions which avoid the often troublesome separation of product from osmium or its inorganic derivatives.

In this modified technique an osmate ester which is prepared in pyridine is stirred at room temperature for 5 to 30 minutes with a solution of sodium bisulfite and aqueous pyridine. The clear orange solution which results contains the *cis*-glycol and a soluble osmium salt. Extraction of the aqueous pyridine solution with chloroform yields a colorless chloroform and pyridine solution which contains only the *cis*-glycol. By this method 3β-hydroxyandrost-5-en-17-one, 17-vinyltestosterone, and ouabagenin tetraacetate have been oxidized to glycols in crude yields of 86, 72, and 81%, respectively.

EXPERIMENTAL

General procedure. A 3.9-mmol. sample of the alkene to be oxidized was dissolved in 15 ml. of pyridine and stirred with 1.0 g. (3.94 mmol.) of osmium tetroxide for an appropriate time. To this mixture was added with stirring a solution of 1.8 g. of sodium bisulfite, 30 ml. of water, and 20 ml. of pyridine. The ratio of sodium bisulfite, and water, and pyridine in the final mixture should be about 2:30:35. When a clear orange solution was obtained (5 to 30 min.), it was extracted thoroughly with chloroform. The chloroform extract was dried over potassium carbonate or sodium sulfate and evaporated to dryness *in vacuo* to yield the product.

3β,5α,6α-Trihydroxyandrostan-17-one.[5] A solution of 1.14 g. (3.9 mmol.) of 3β-hydroxyandrost-5-en-17-one, 1.0 g. (3.94 mmol.) of osmium tetroxide and 15 ml. of pyridine was stirred for 2 hr. The mixture was then stirred for 5 min. with a solution of 1.8 g. of sodium bisulfite, 30 ml. of water, and 20 ml. of pyridine. The orange solution which was obtained was extracted with one 150-ml. and two 50-ml. portions of chloroform. The combined organic extract was dried over potassium carbonate and evaporated to dryness *in vacuo*. The crude crystalline product was triturated with ethyl acetate, collected by filtration, and dried. It weighed 1.05 g. (86%) and melted at 240–243°.

17,20ε,21ε-Trihydroxy-17α-pregn-4-en-3-one.[6] A solution of 3 g. (9.65 mmol.) of 17-vinyltestosterone, 3.0 g. (11.8 mmol.) of osmium tetroxide and 60 ml. of pyridine was stirred in the dark for 20 hr. To the mixture was added with stirring a solution of 5.6 g. of sodium bisulfite, 90 ml. of water, and 45 ml. of pyridine. The solution was then extracted thoroughly with chloroform. The chloroform extract was washed with water, dilute hydrochloric acid, water, and aqueous sodium bicarbonate, dried over sodium sulfate, and evaporated to dryness *in vacuo*. Crystallization of the residue from methanol yielded 2.5 g. (72%) of product which melted at 186–193°.

1β,3β,5β,11α,14,19,20ε,22ε-Octahydroxycardanolide-1,3,11,-19-tetraacetate. A solution of 2.2 g. (3.25 mmol.) of ouabagenin-1,3,11,19-tetraacetate,[7] 1.0 g. (3.94 mmol.) of osmium tetroxide and 20 ml. of pyridine was stirred for 1 day. The mixture was then stirred for 30 min. with a solution of 1.8 g. of sodium bisulfite, 30 ml. of water, and 15 ml. of pyridine. The solution was extracted thoroughly with chloroform. The chloroform extract was washed with water, dilute hydrochloric acid, water, and aqueous sodium bicarbonate, dried over sodium sulfate, and evaporated to dryness *in vacuo*. Crystallization of the residue from ethyl acetate yielded a crude product which melted at 285–290° and weighed 1.7 g. (81%). An analytical sample prepared by crystallization of the crude product from methanol melted at about 318°.

Anal. Calcd. for $C_{31}H_{44}O_{14}$: C, 58.11; H, 6.92. Found: C, 57.86; H, 7.07.

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Aliphatic Nitriles from Alkyl Chlorides

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The preparation of nitriles by the reaction of primary alkyl halides with alkali metal cyanides is an old and well known procedure. However, alkyl chlorides, except for benzyl- or allyl-type compounds, have not been used very frequently because of excessive reaction times required with the aqueous alcohol solvent usually used for this type reaction.[1] Other solvent systems, such as ethylene glycol monomethyl ether[2] or polyethylene glycol,[3]

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(2) O. W. Cass, *Chem. Eng. News*, **32**, 2197 (1954).

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TABLE I

Reaction of Alkyl Chlorides with Sodium Cyanide in DMSO

	Reaction Time, Min.	Product	Yield, %	B.P., Mm.	n_D^{25}
1,2-Dichloroethane	20	Succinonitrile	56	114 (3.4)	—
1,3-Dichloropropane	30	Glutaronitrile	67	101–102 (1.5)	1.4339
1,4-Dichlorobutane	30	Adiponitrile	88	115 (0.7)	1.4369
1,5-Dichloropentane	30	Pimelonitrile	75	149 (1.0)	1.4398
1-Chlorobutane	20	Valeronitrile	93	139	1.3949
1-Chloropentane	20	Capronitrile	97	80 (48)	1.4050
1-Chlorohexane	20	Heptanenitrile	91	96–97 (50)	1.4125
1-Chlorodecane	20	Hendecanenitrile	94	87–88 (1.2)	1.4314
2-Chlorobutane	180	2-Cyanobutane	69	125–126	1.3873
2-Chlorooctane	60	2-Cyanooctane	70	88 (12)	1.4179

have recently been disclosed which permitted the use of primary chlorides in the preparation of nitriles in reasonable reaction times, but no mention has been made of the use of secondary chlorides.

It has now been found that both primary and secondary alkyl chlorides react with sodium cyanide in dimethyl sulfoxide solvent to give high yields of the corresponding nitrile in shorter reaction times than have been obtained with bromides or iodides in aqueous alcohol solvent. Both mono- and diprimary alkyl chlorides react in thirty minutes or less while secondary chlorides require one to 3 hours depending on the boiling point of the chloride. The yield of secondary nitrile by this method far exceeds the 25–30% yield generally given for the displacement of secondary halides by cyanide.[1] Table I shows the reaction times and the yields of nitriles from a number of representative chlorides.

EXPERIMENTAL

Starting materials. Dimethyl sulfoxide, obtained from the Stepan Chemical Co., was dried over calcium hydride before use. Reagent grade sodium cyanide was dried at 110° overnight and stored in a tightly stoppered bottle. Failure to dry the sodium cyanide sometimes caused the reaction mixtures to become very dark in color. The alkyl halides were all Eastman Kodak Co. White Label grade and were used as received.

Procedure for primary chlorides. Dry sodium cyanide (30 g.) was added to 150 ml. of dimethyl sulfoxide in a flask fitted with a stirrer, reflux condenser, dropping funnel, and thermometer. The thick slurry was heated on a steam bath to 90° and the steam bath was then removed. The halide (0.5 mol. of monochloride or 0.25 mol. of dichloride) was slowly added to the stirred mixture causing the temperature to increase immediately. The rate of addition was such that the temperature of the reaction did not go above about 160°. After all the halide was added (about 10 min.) the mixture was stirred for 10 min. more, or until the temperature dropped below 50°. In the preparation of mononitriles, the reaction mixture was then poured into water and the product extracted with chloroform or ethyl ether. The extract was washed several times with saturated sodium chloride solution, dried over calcium chloride, and the product distilled.

With the dinitriles a slightly different procedure was used due to their water solubility. After the reaction had cooled, 150 ml. of chloroform was added to the flask and this mixture was then poured into saturated salt solution. Enough water was added to dissolve precipitated salt and the chloroform layer was separated. The aqueous layer was extracted once with chloroform. The combined extracts were then washed twice with salt solution, dried, and distilled.

Secondary chlorides. With a low-boiling chloride such as 2-chlorobutane, a stirred slurry of 30 gm. of sodium cyanide in 150 ml. of dimethyl sulfoxide was heated to 90° with a heating mantle and 0.5 mol. of the chloride was slowly added over a period of 30 min. The temperature of the refluxing reaction mixture slowly increased as nitrile was formed. Refluxing continued as the temperature slowly rose to 150° after 3 hr. reaction time. The flask was then cooled and the reaction mixture worked up in the same way as for the primary nitriles. With 2-chloroöctane, the sodium cyanide–dimethyl sulfoxide slurry was heated to 130° and 0.5 mol. of the chloride added. The reaction mixture was maintained at 135–145° for 1 hr., then cooled, and the product isolated.

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Reactions of Ethyl Isobutenyl Ether

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The ready availability of ethyl isobutenyl ether[1] prompted our investigation of some of its reactions.

The acid-catalyzed addition of ethyl orthoformate[2] to ethyl isobutenyl ether gave dimethylmalonaldehyde tetraethyl acetal in good yield. Although the dimethylmalonaldehyde bis(2,4-dinitrophenylhydrazone) could be obtained in the usual manner from the acetal, repeated attempts to obtain the free aldehyde by hydrolysis failed; either the acetal was recovered or the hydrolytic cleavage products of the aldehyde, formic acid, and isobutyraldehyde were obtained.

The acid-catalyzed addition of diethyl acetals to ethyl isobutenyl ether occurred smoothly,

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