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.

EASTERN LABORATORY, EXPLOSIVES DEPARTMENT
E. I. DU PONT DE NEMOURS & CO., INC.
GIBBSTOWN, N. J.

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# Reactions of Ethyl Isobutenyl Ether

KENT C. BRANNOCK

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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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(1) (a) M. G. Voronkov, *J. Gen. Chem. U.S.S.R.*, (Eng. Transl.), **20**, 2060 (1950). (b) J. L. E. Erickson and M. Z. Woskow, *J. Org. Chem.*, **23**, 670 (1958).

(2) F. G. Young, U. S. Patent **2,556,312** (1949).

giving 1,1,3-triethoxy-2,2-dimethylalkanes in good yields. Because of the greater stability of ethyl isobutenyl ether, a much smaller excess of the acetal is required for optimum yields than when the vinyl ethers are used.[3] The 1,1,3-triethoxy-2,2-dimethylalkanes were easily hydrolyzed to the corresponding 3-ethoxy-2,2-dimethylalkanals which, in turn, were easily reduced to the 3-ethoxy-2,2-dimethyl-1-alkanols.

Ethyl isobutenyl ether underwent the Diels-Alder reaction with acrolein to give 2-ethoxy-3,4-dihydro-3,3-dimethyl-2H-pyran.[4]

Hydroformylation of ethyl isobutenyl ether gave two isomeric aldehydes. The major product was the expected 2-ethoxy-3-methylbutyraldehyde. The minor product was 4-ethoxy-3-methylbutyraldehyde, which must have arisen from a rearrangement of the double bond of the isobutenyl group.

## EXPERIMENTAL

*Ethyl isobutenyl ether.* The method used was essentially that of Voronkov,[1a] except that phosphoric acid was used as the catalyst.[5] Distillation of isobutyraldehyde diethyl acetal (441 g., 3 mol.) from 0.2 g. of 85% phosphoric acid through a 1-ft. Vigreux column at a rate that maintained a head temperature of 72–84° (flask temperature 113–150°) gave 408.5 g. of distillate. The distillate was washed once with a 500-ml. portion and twice with 250-ml. portions of 0.5% aqueous potassium carbonate solution to remove the ethyl alcohol. The remaining organic phase was dried over potassium carbonate and distilled to give 252 g. (84%) of ethyl isobutenyl ether, b.p. 91–92°, $n_{\mathrm{D}}^{20}$ 1.4081 (lit.[1a] b.p. 94°, $n_{\mathrm{D}}^{20}$ 1.4053; lit.[1b] b.p. 92–94°, $n_{\mathrm{D}}^{25}$ 1.4060).

*Dimethylmalonaldehyde tetraethyl acetal.* Ethyl isobutenyl ether (150 g., 1.5 mol.) was added over a 1-hr. period to ethyl orthoformate (296 g., 2 mol.) containing 5 ml. of boron trifluoride etherate. The temperature was maintained at 20–25° by cooling. The mixture was stirred for an additional 1.5 hr. and the catalyst was then neutralized by addition of excess potassium carbonate solution. The organic phase was separated and distilled to give, after removal of unreacted starting materials, 268 g. (72%) of dimethylmalonaldehyde tetraethyl acetal, b.p. 52°/2 mm., $n_{\mathrm{D}}^{20}$ 1.4192, and 20 g. of residue.

*Anal.* Calcd. for $C_{13}H_{28}O_4$: C, 62.9; H, 11.4. Found: C, 62.9; H, 11.5.

The acetal gave the very insoluble bis(2,4-dinitrophenylhydrazone), which was recrystallized from acetone; m.p. 260–261°.

*Anal.* Calcd. for $C_{17}H_{16}N_8O_8$: C, 44.4; H, 3.5. Found: C, 44.3; H, 3.7.

*Products from addition of isobutyraldehyde diethyl acetal to ethyl isobutenyl ether.* A. Ethyl isobutenyl ether (140 g., 1.4 mol.) was added over a 2.5-hr. period to isobutyraldehyde diethyl acetal (307 g., 2.1 mol.) containing 1.5 ml. of boron trifluoride etherate at 35–40°. Stirring was continued for 1 hr., and the catalyst was then neutralized by addition of excess potassium carbonate solution. The organic phase was separated and distilled to give, after removal of unused starting materials, 218 g. (63.5%) of 1,1,3-triethoxy-2,2,4-trimethylpentane, b.p. 53–54°/0.5–1 mm., $n_{\mathrm{D}}^{20}$ 1.4259.

*Anal.* Calcd. for $C_{14}H_{30}O_3$: C, 68.3; H, 12.3. Found: C, 68.1; H, 12.0.

B. A solution of 24 ml. of concentrated sulfuric acid in 1 l. of water was stirred for 16 hr. with 1,1,3-triethoxy-2,2,4-trimethylpentane (360 g., 1.46 mol.) at room temperature. The organic phase was taken up in ether and distilled to give 232.5 g. (92.5%) of 3-ethoxy-2,2,4-trimethylvaleraldehyde, b.p. 66–67°/7.5 mm., $n_{\mathrm{D}}^{20}$ 1.4262.

*Anal.* Calcd. for $C_{10}H_{20}O_2$: C, 69.7; H, 11.7. Found: C, 69.4; H, 11.7.

The 2,4-dinitrophenylhydrazone melted at 102–103°.

*Anal.* Calcd. for $C_{16}H_{24}N_4O_5$: C, 54.5; H, 6.9. Found: C, 54.4; H, 6.9.

C. Hydrogenation of the 3-ethoxy-2,2,4-trimethylvaleraldehyde over Raney nickel at 125° and 100 atm. gave 3-ethoxy-2,2,4-trimethyl-1-pentanol, b.p. 47–48°/0.5 mm., $n_{\mathrm{D}}^{20}$ 1.4370, in 92% yield.

*Anal.* Calcd. for $C_{10}H_{22}O_2$: C, 68.9; H, 12.7. Found: C, 69.1; H, 12.6.

*Products from addition of acetaldehyde diethyl acetal to ethyl isobutenyl ether.* A. In a manner similar to that described above, acetaldehyde diethyl acetal and ethyl isobutenyl ether gave 1,1,3-triethoxy-2,2-dimethylbutane, b.p. 77°/7 mm., $n_{\mathrm{D}}^{20}$ 1.4182, in 76% yield.

*Anal.* Calcd. for $C_{12}H_{26}O_3$: C, 66.0; H, 12.0. Found: C, 65.8; H, 11.9.

B. 3-Ethoxy-2,2-dimethylbutyraldehyde, b.p. 62–64°/23 mm., $n_{\mathrm{D}}^{20}$ 1.4133, was obtained in 87% yield.

*Anal.* Calcd. for $C_8H_{16}O_2$: C, 66.6; H, 11.2. Found: C, 66.5; H, 11.2.

The 2,4-dinitrophenylhydrazone melted at 116–118°.

*Anal.* Calcd. for $C_{14}H_{20}N_4O_5$: C, 51.8; H, 6.2. Found: C, 51.6; H, 6.3.

C. 3-Ethoxy-2,2-dimethyl-1-butanol, b.p. 128–130°/160 mm., $n_{\mathrm{D}}^{20}$ 1.4262, was obtained in 90% yield.

*Anal.* Calcd. for $C_8H_{18}O_2$: C, 65.7; H, 12.4. Found: C, 65.9; H, 12.5.

*Products from addition of benzaldehyde diethyl acetal to ethyl isobutenyl ether.* A. 1,1,3-Triethoxy-2,2-dimethyl-3-phenylpropane, b.p. 89–91°/0.5 mm., $n_{\mathrm{D}}^{20}$ 1.4770, was obtained in 77% yield using a 1:1 ratio of acetal to ether.

*Anal.* Calcd. for $C_{17}H_{28}O_3$: C, 72.8; H, 10.1. Found: C, 72.9; H, 10.0.

B. 3-Ethoxy-2,2-dimethylhydrocinnamaldehyde, b.p. 64°/0.5 mm., $n_{\mathrm{D}}^{20}$ 1.4950, was obtained in 92% yield.

*Anal.* Calcd. for $C_{13}H_{18}O_2$: C, 75.7; H, 8.8. Found: C, 75.6; H, 8.8.

The 2,4-dinitrophenylhydrazone melted at 134°.

*Anal.* Calcd. for $C_{19}H_{22}N_4O_5$: C, 59.1; H, 5.7. Found: C, 59.3; H, 5.9.

C. 3-Ethoxy-2,2-dimethyl-3-phenyl-1-propanol, b.p. 88°/1.3–1.4 mm., $n_{\mathrm{D}}^{20}$ 1.5022, was obtained in 89% yield.

*Anal.* Calcd. for $C_{13}H_{20}O_2$: C, 75.0; H, 9.7. Found: C, 75.5; H, 9.8.

*2-Ethoxy-3,4-dihydro-3,3-dimethyl-2H-pyran.* A mixture of ethyl isobutenyl ether (252 g., 2.52 mol.) and acrolein (168 g., 3 mol.) containing 0.2 g. of hydroquinone was heated for 3 hr. at 180° in an autoclave. Distillation of the reaction mixture gave, after removal of unreacted starting materials and a small amount of acrolein dimer, 212 g. (54%) of 2-ethoxy-3,4-dihydro-3,3-dimethyl-2H-pyran, b.p. 158°, $n_{\mathrm{D}}^{20}$ 1.4344.

*Anal.* Calcd. for $C_9H_{16}O_2$: C, 69.2; H, 10.3. Found: C, 69.3; H, 10.2.

The dihydropyran gave, by the usual procedure, the bis-(2,4-dinitrophenylhydrazone) of 2,2-dimethylglutaraldehyde, m.p. 237–239°.

*Anal.* Calcd. for $C_{19}H_{20}N_8O_8$: C, 46.7; H, 4.1. Found: C, 46.6; H, 4.1.

*Hydroformylation of ethyl isobutenyl ether.* A mixture of ethyl isobutenyl ether (136 g., 1.36 mol.) in 500 ml. of benzene and 10 g. of cobalt carbonyl was placed in an autoclave. Hydrogen was admitted to the autoclave to a pressure of 30 atm., and then hydrogen–carbon monoxide was admitted to a pressure of 100 atm. The temperature was raised to 130° and held for 1 hr. The reaction mixture was

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(3) R. I. Hoaglin and R. Hirsch, *J. Am. Chem. Soc.*, **71**, 3468 (1949); U. S. Patent **2,564,760** (1957).

(4) R. I. Longley, Jr., and W. S. Emerson, *J. Am. Chem. Soc.*, **72**, 3079 (1950).

(5) A. Duhamel, *Bull. soc. chim. France*, 156 (1956).

then steam-distilled. The organic phase was separated and then fractionated. Two well defined fractions were obtained. The first fraction (46 g., 27%), b.p. 137–138°, $n_D^{20}$ 1.4029, was 2-ethoxy-3-methylbutyraldehyde.

*Anal.* Calcd. for $C_7H_{14}O_2$: C, 64.6; H, 10.8. Found: C, 64.8; H, 10.9.

The 2,4-dinitrophenylhydrazone melted at 125–126°.

*Anal.* Calcd. for $C_{13}H_{18}N_4O_5$: C, 50.3; H, 5.8. Found: C, 50.1; H, 5.8.

The second fraction (21 g., 12%), b.p. 160–162°, $n_D^{20}$ 1.4132, was 4-ethoxy-3-methylbutyraldehyde.

*Anal.* Calcd. for $C_7H_{14}O_2$: C, 64.6; H, 10.8. Found: C, 64.9; H, 10.9.

The 2,4-dinitrophenylhydrazone, m.p. 48–50°, was very soluble and therefore difficult to purify.

*Anal.* Calcd. for $C_{13}H_{18}N_4O_5$: C, 50.3; H, 5.8. Found: C, 49.7; H, 6.1.

The structures of the two aldehydes were assigned on the basis of their nuclear magnetic resonance spectra. These spectra were in full agreement with the assigned structures and preclude the other possible isomer, ethoxypivalaldehyde.

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RESEARCH LABORATORIES
TENNESSEE EASTMAN CO.
DIVISION OF EASTMAN KODAK CO.
KINGSPORT, TENN.

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## Studies of Configuration. VI. *cis-* and *trans-*4-Methoxycyclohexanol[1,2]

DONALD S. NOYCE, GAR LOK WOO,
AND BARBARA R. THOMAS

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The isomeric mixture of the 4-methoxycyclohexanols is well known, having been prepared frequently by hydrogenation of hydroquinone monomethyl ether.[3] However, there are only three reports concerning individual isomers. In 1941, Ruggli, Leupin, and Businger[4] reported that 4-methoxycyclohexyl tosylate could be separated into a solid, m.p. 87°, and a liquid. They suggested the *trans*-configuration for the solid 4-methoxycyclohexaneacetic acid prepared by treatment of the tosylate with sodio diethylmalonate, but made no assignment to the 4-methoxycyclohexyl tosylate.

Almost simultaneously with our preliminary report on the solvolysis of the *cis-* and *trans*-4-methoxycyclohexyl tosylates, Henbest and Nichols[5] reported the 3,5-dinitrobenzoate of the *trans*-isomer.

We have reported the separation of the isomers through the acid phthalates and a preliminary correlation of the configuration with the known 1,4-dihydroxycyclohexane by partial methylation. In view of the very interesting behavior of the two isomers, it seemed essential to present a definitive proof of configuration. Such is the purpose of the present report.

The known *cis*-4-hydroxycyclohexanecarboxylic acid[6] (I) was converted by methylation with methyl iodide and silver oxide following the procedure used by Noyce and Denney[7] to methyl *cis*-4-methoxycyclohexanecarboxylate (II). Ample evidence is available to show that this reaction proceeds without jeopardizing the stereochemical integrity of the system. The ester II was hydrolyzed to *cis*-4-methoxycyclohexanecarboxylic acid (III), m.p. 54.5–55.7°. This material was shown to be identical, by mixed melting point and comparison of infrared spectra, with the isomer of 4-methoxycyclohexanecarboxylic acid assigned the *cis*-configuration by Noyce and Weingarten.[8] Thus, confirmation of the previous assignment on the basis of rearrangement behavior is obtained.

Treatment of *cis*-4-methoxycyclohexanecarboxylic acid with methyllithium afforded the ketone *cis*-4-methoxy-1-acetylcyclohexane (IV). This reaction has been shown by Dauben and Hoerger[9] to proceed without any inversion or epimerization adjacent to the carbonyl group. Treatment of the ketone with perbenzoic acid afforded *cis*-4-methoxycyclohexylacetate (V), a reaction shown to proceed with retention of configuration by Turner.[10] Hydrolysis of the acetate afforded *cis*-4-methoxycyclohexanol (VI), which was characterized by infrared spectra and preparation of derivatives. Each of the steps proceeded in satisfactory yield.

The second method which was used was the partial methylation of the known *trans*-1,4-dihydroxycyclohexane.[11] Unfortunately, the yield of the monomethyl ether was low (10%) and the more definitive sequence above was carried through.

The chemical transformations are summarized in Chart I, and the properties of derivatives of *cis-* and *trans*-4-methoxycyclohexanol are given in Table I.

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(1) A portion of this work has been published in preliminary form [D. S. Noyce and B. R. Thomas, *J. Am. Chem. Soc.*, **79**, 755 (1957)].

(2) Supported in part by the National Science Foundation (G-2387).

(3) For recent examples, see F. Hunziker, F. X. Mullner, and H. Schaltegger, *Helv. Chim. Acta,* **38**, 1943 (1955); D. Papa, F. J. Villani, and H. F. Ginsberg, *J. Am. Chem. Soc.*, **76**, 4446 (1954).

(4) P. Ruggli, O. Leupin, and A. Businger, *Helv. Chim. Acta*, **24**, 339 (1941).

(5) H. B. Henbest and B. Nichols, *Proc. Chem. Soc.*, 61 (1957); *J. Chem. Soc.*, 227 (1959).

(6) N. R. Campbell and J. H. Hunt, *J. Chem. Soc.*, 1379 (1950).

(7) D. S. Noyce and D. B. Denney, *J. Am. Chem. Soc.*, **76**, 768 (1954).

(8) D. S. Noyce and H. I. Weingarten, *J. Am. Chem. Soc.*, **79**, 3093 (1957).

(9) W. G. Dauben and E. Hoerger, *J. Am. Chem. Soc.*, **73**, 1504 (1951).

(10) R. B. Turner, *J. Am. Chem. Soc.*, **72**, 878 (1950).

(11) W. Nudenberg and L. W. Butz, *J. Am. Chem. Soc.*, **66**, 307 (1944).