

ALKYL ORTHOFORMATES

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Orthoformic esters were first prepared by the Williamson synthesis, that is, the reactions of chloroform with alkali metal alkoxides (1). Later another method, Pinner's imidoester procedure, was developed. This involves reaction between a nitrile, hydrogen chloride, and alcohol in ether solution. The imidoester hydrochloride forms, precipitates out, and is collected and allowed to react with excess alcohol. The yields of alkyl orthoformate are excellent in this process but there are several drawbacks. The imidoester hydrochloride, which must be freed of excess hydrogen chloride, crystallizes very slowly at times and is very easily hydrolyzed. Also, the use of anhydrous solvent is required. This was ether in Pinner's original procedure but Copenhaver (2) has shown that certain other solvents give better results. Post (3) has summarized work on the Williamson and Pinner methods.

Pinner first attempted to perform the orthoester synthesis by carrying out the reaction between hydrogen cyanide, hydrogen chloride, and alcohol in one step with excess alcohol as solvent (4). He reported that his reaction mixtures exploded each time he tried this procedure. He gave no explicit description of experimental conditions but stated merely that a "great excess" of alcohol was used as solvent for the hydrogen cyanide and that gaseous hydrogen chloride was led into the mixture. In spite of "good external cooling", a violent reaction occurred each time after a period of introduction of hydrogen chloride. Since Pinner's time no one seems to have used the one-step approach. The imidoester method has been widely used, however.

We have found that one may easily prepare the lower alkyl orthoformates by one-step reactions between hydrogen cyanide, hydrogen chloride, and excess alcohol. If one passes hydrogen chloride slowly enough into a stirred and cooled (to room temperature) mixture of hydrogen cyanide and alcohol (procedure A), the reaction occurs smoothly. If the hydrogen chloride is introduced rapidly, however, a violent reaction takes place, as Pinner reported. Another procedure (B) is to dissolve the hydrogen chloride in cold alcohol and to add a cold solution of hydrogen cyanide in alcohol to this alcoholic hydrogen chloride. Surprisingly enough, there is no violent reaction even if the two solutions are mixed as fast as they can be poured together (in a few seconds).

An extensive series of runs has been made to determine the effects of various experimental variables. It does not seem worthwhile giving details of all of these experiments but the main conclusions can be stated. Some of the most successful experiments are described in the experimental section. The highest yield of methyl orthoformate was 55%.

In all of the work described here, hydrogen chloride was the only acid employed. Hydrogen cyanide and alcohol were always used in excess with reference

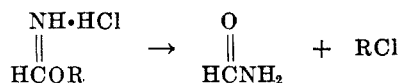
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to the hydrogen chloride. There are two reasons for keeping the amount of hydrogen chloride as the limiting factor. In the first place, hydrogen chloride reacts slowly with alcohols and the water formed in this manner will, of course, destroy an equivalent amount of ortho ester. Running the reaction with excess hydrogen cyanide ensures the consumption of hydrogen chloride before it can react appreciably with alcohol. A second reason for avoiding an excess of hydrogen chloride is that solutions containing free hydrogen chloride would be corrosive and troublesome in handling and distillation.

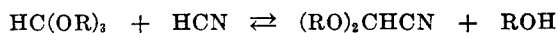
The yield of orthoformic ester increases with increasing molar ratio of hydrogen cyanide to hydrogen chloride. The rate of increase becomes small as the excess of hydrogen cyanide becomes large and is insignificant after a 400% excess of hydrogen cyanide has been attained. With increasing amount of hydrogen cyanide, more high-boiling by-products are formed, a good part of which are dialkoxyacetonitriles. These are formed by the acid-catalyzed reaction between orthoformic esters and hydrogen cyanide (5).

Methyl, ethyl, and butyl alcohols have been used successfully in the reaction. Presumably, any alcohol which is not too highly hindered and which does not react rapidly with hydrogen chloride may be used. Under comparable conditions, the yield of orthoformic ester is considerably lower with ethanol than with methanol. Butanol, however, gives nearly as good a yield of orthoformate as does methanol. Very likely, alcohols higher than butyl would also give fair yields. The yield of orthoformic ester increases with increasing molar ratio of alcohol to hydrogen chloride. Here, too, one encounters the law of diminishing returns—the yield of ortho ester increases very slowly after a 600% excess of alcohol has been reached. The amount of high-boiling by-product decreases with increasing excess of alcohol.

In the temperature range, 0–30°, the precise temperature employed has virtually no effect upon the yield. This statement applies only to the reaction between hydrogen cyanide, hydrogen chloride, and alcohol. When dissolving the hydrogen chloride in alcohol, it is very desirable to use low temperatures and thereby to minimize reaction between hydrogen chloride and alcohol. Formation of orthoformate appears to be complete within 24 hours and is probably complete within ten hours.



Several catalysts were studied with the hope of raising yields. Zinc chloride, mercuric chloride, or tetramethylammonium chloride, added to the reaction mixtures at the time of mixing, had a distinctly harmful effect upon the yield of methyl orthoformate. Boron trifluoride etherate, added 20 hours after the initial mixing, was also harmful. The harmful effect of catalysts added during the initial mixing, is probably of twofold origin. First, there may be a destruction of



the intermediate formimidate hydrochloride, yielding, for example, formamide and alkyl chloride. Secondly, there are undoubtedly increased amounts of dialkoxyacetoneitriles formed by reaction between the orthoester and excess hydrogen cyanide. This reaction takes place to a certain extent under any conditions, since it is catalyzed by ammonium chloride, but it is more powerfully catalyzed by zinc chloride. The negative effect of boron trifluoride etherate cannot be due to destruction of alkyl formimidate hydrochloride since, when this catalyst was added, the alkyl formimidate had already been converted to orthoformic ester. However, boron trifluoride can catalyze the formation of dialkoxyacetoneitriles. The addition of catalyst (zinc chloride) during the isolation step, when the excess hydrogen cyanide has been distilled off and before much of the excess alcohol has been removed, is beneficial. Under such conditions the formation of dialkoxyacetoneitrile is reversed and orthoformic esters are regenerated.

EXPERIMENTAL

Reagents. The hydrogen cyanide, stabilized with a trace of sulfur dioxide, was dried over Drierite. Methanol was dried by distillation from magnesium methoxide. Commercial anhydrous ethanol was employed. Butanol was dried with Drierite followed by distillation.

Methyl orthoformate. Experiment (1). A mixture of methanol (576 g., 18.0 moles) and hydrogen cyanide (162 g., 6.0 moles) was made up in a three-necked flask equipped with an air-tight stirrer, a gas introduction tube, and an outlet tube packed with Drierite. The mixture was stirred and held at 20–22° while anhydrous hydrogen chloride (73.5 g., 2.01 moles; measured by the gain in weight of the solution) was passed into the solution over a period of six hours (mode *A* of mixing). Ammonium chloride began to precipitate 3½ hours after the start of introduction of hydrogen chloride. The mixture then was allowed to stand at 20–22°. Forty-four hours after the start of the reaction, the mixture was chilled to 5°, filtered, and distilled to dryness through a Claisen head. The distillate was fractionated through a 4-ft. column, packed with ¼ inch stainless steel helices. A partial takeoff head maintained a reflux ratio of 20:1. This fractionation removed excess hydrogen cyanide, methyl formate, and most of the excess methanol. Complete separation of the methanol from the methyl orthoformate was not desired in this large column since some of the ortho ester would have been lost in wetting the packing. The residue was distilled through a 10-inch column packed with helices, giving 76.6 g. (35.9%) of methyl orthoformate, b.p. 102°, n_D^{25} 1.3770, and 19.0 g. of higher-boiling material. The literature (6) gives b.p. 103–105°, n_D^{20} 1.3793.

Experiment (2). Anhydrous hydrogen chloride (55.9 g., 1.53 moles) was dissolved in methanol (410 g.). The temperature of the mixture was held below 5° during this step which required 1.5 hours. An ice-cold mixture of hydrogen cyanide (202 g., 7.50 moles) and methanol (600 g.) then was added rapidly (within a minute) to the methanolic hydrogen chloride (mode *B* of mixing). The temperature of the mixture rose immediately to 9°, then slowly (over 1.5 hours) to room temperature. No cooling bath was used at this stage. When the mixture reached room temperature it was held at 21–25° by occasional application of an ice-bath. Ammonium chloride began to precipitate 3.5 hours after mixing. After 90 hours at 21–25°, the mixture was filtered, distilled, and fractionated in the manner described above. The yield of methyl orthoformate was 81.0 g. (50.2%) and 11.0 g. of high-boilers was obtained.

Experiment (3). This experiment was similar to the second experiment in that the same procedure was followed and the same molar ratio of HCN:alcohol:HCl (5:21:1) was employed. The exact quantities were 61 g. (1.67 moles) of hydrogen chloride, 225 g. (8.33

moles) of hydrogen cyanide, and 1120 g. (35.0 moles) of methanol. After the excess hydrogen cyanide had been distilled from the mixture, 0.5 g. of zinc chloride was added and the isolation was completed in the same manner. The yield of methyl orthoformate was 96.8 g. (54.7%); one gram of high-boiler was also isolated.

Ethyl orthoformate. This experiment is similar to experiment (2) above, with the following differences. Hydrogen chloride (36.5 g., 1.0 mole), hydrogen cyanide (81.0 g., 3.0 moles), and ethanol (414 g., 9.0 moles) were used and the alcoholic solutions were mixed at 24° in a period of less than a minute (mode B). After 44 hours at 24° the mixture was filtered, distilled to dryness, and fractionated through the 10-inch column described in experiment (1). Ethyl orthoformate (33.9 g., 22.9%), b.p. 147°, n_D^{25} 1.3900, was obtained, together with 33.0 g. of high-boiling byproducts. The literature (6) gives b.p. 145–147°, n_D^{20} 1.3922.

Butyl orthoformate. This experiment was similar to the preparation of ethyl orthoformate above, using 36.9 g. (1.01 moles) of hydrogen chloride, 81.0 g. (3.0 moles) of hydrogen cyanide, and 666 g. (9.0 moles) of butyl alcohol. The two solutions were mixed at 24° and allowed to stand at 24° for 66 hours. The mixture was filtered and distilled to dryness. Hydrogen cyanide, butyl formate, and butyl alcohol were distilled off through the 10-inch column described above. Distillation of the residue gave 98.6 g. (42.5%) of butyl orthoformate, b.p. 247°, n_D^{25} 1.4160. A high-boiling residue (32.1 g.) was also obtained. The literature (6) gives the b.p. 245–247°, n_D^{20} 1.4180.

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SUMMARY

Alkyl orthoformates may be prepared by one-step reactions between hydrogen chloride, hydrogen cyanide, and alcohol. The hydrogen chloride may be passed into a mixture of hydrogen cyanide and alcohol or alcoholic solutions of hydrogen chloride and hydrogen cyanide may be mixed. The second procedure is less apt to produce violent reactions.

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