REVIEWS

Synthesis of Carboxylic and Carbonic Ortho Esters

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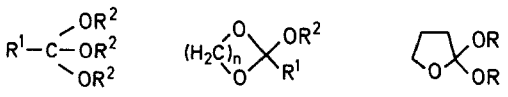
Methods of synthesizing ortho esters of carboxylic and carbonic acids are reviewed. Among the compounds discussed are acyclic orthocarboxylates and orthocarbonates and heterocyclic ortho esters having 1,3-dioxolane, 1,3-dioxan, furan, pyran, 2,6,7-trioxabicyclo[2.2.2]octane, 2,4,10-trioxaadamantane, and spirocyclic ring systems. Acyloxy orthoesters are also considered.

Es werden Methoden zur Herstellung von Orthocarbonsäure- und Orthokohlensäureestern beschrieben. Folgende Verbindungen werden abgehandelt: Acyclische Orthocarbonsäure- und Orthokohlensäureester, heterocyclische Orthoester mit 1,3-Dioxolan-, Furan-, Pyran-, 2,6,7-Trioxabicyclo[2.2.2]octan-, 2,4,10-Trioxaadamantan-Struktur sowie spirocyclische Ringsysteme. Acyloxy-orthocarbonsäureester werden ebenfalls besprochen.

Carboxylic ortho esters are substances having an orthoacyl carbon linked by oxygen bridges to three other carbons. They include acylic ortho esters (**1**), as well as a variety of heterocyclic substances such as the 2-alkoxy-1,3-dioxolanes (**2**, n = 2) and dioxanes (**2**, n = 3) and their derivatives, lactone acetals (e.g. **3**), 2,6,7-trioxabicyclo[2.2.2]octanes (**4**), and 2,4,10-trioxa-adamantanes (**5**). Carbonic ortho esters (orthocarbonates) are substances having four oxygen atoms linked to a single carbon atom (e.g., **1**, **2**, **4**, and **5**, $R^1 = OR^2$).



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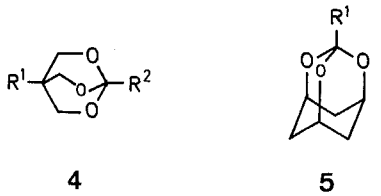


4 **5**

Ortho esters are reagents widely used in organic synthesis, and some of the cyclic ortho esters are useful intermediates for the protection of hydroxy and carboxyl groups during multi-step syntheses[1].

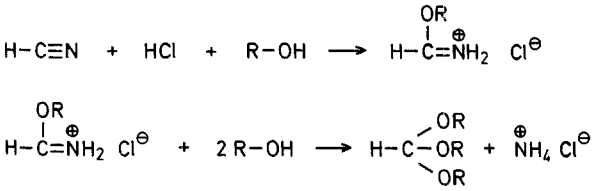
In the discussion which follows, syntheses of acyclic ortho esters are arranged according to the structure of the acid from which the ester is derived, while cyclic ortho ester syntheses are arranged according to the structure of the heterocyclic portion of the ester. For an exhaustive survey of syntheses and reactions of ortho esters, see reference 1.

[1] R. H. DeWolfe, "*Carboxylic Ortho Acid Derivatives*", Academic Press, New York, 1970.

1. Orthoformates

1.1. Orthoformates from Hydrogen Cyanide

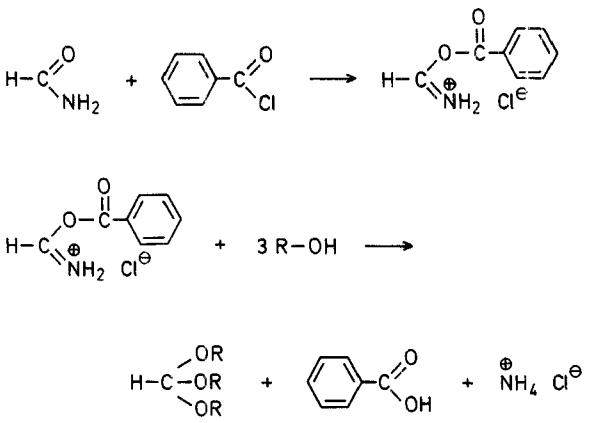
Trialkyl orthoformates were prepared by alcoholysis of the alkyl formimidate hydrochlorides formed by reaction of hydrogen cyanide with anhydrous hydrogen chloride and alcohols[2,3].



The toxicity of hydrogen cyanide, the exothermicity of the first step of the reaction, and the ready commercial availability of simple trialkyl orthoformates will deter most chemists from synthesizing orthoformates by this procedure or modifications[4–6] of it.

1.2. Orthoformates from Formamide

Trialkyl orthoformates may also be synthesized by reaction of alcohols and benzoyl chloride with formamide[7]. Presumably *O*-benzoylformimidate hydrochloride is an intermediate.



R = C_2H_5, *i*-C_3H_7, *n*-C_3H_7, *n*-C_4H_9

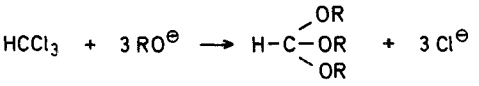
Triethyl Orthoformate:
To a stirred, cooled mixture of absolute ethanol (180 ml, 3 mol), formamide (46 g, 1 mol), and petroleum ether (b.p. 70–80°, 200 ml) is added dropwise benzoyl chloride (140.5 g, 1 mol) during 20 minutes. Stirring is continued at 30–40° for 1 hr, after which the mixture is allowed to stand at room temperature for 2 hr. The crystalline benzoic acid and ammonium chloride are filtered off and the filtrate is dropped into stirred, cooled 3 *N* sodium hydroxide solution (150 ml). The organic phase is separated, washed with water, and dried over anhydrous potassium carbonate. Fractional distillation gives triethyl orthoformate; yield: ~60 g (41%); b.p. 143–145°.

Tri-*n*-propyl and tri-*n*-butyl orthoformates are similarly prepared in 58% and 53% yields.

[2] A. Pinner, *Ber. dtsch. chem. Ges.* **16**, 325 (1883).
[3] A. Pinner, *Ber. dtsch. chem. Ges.* **16**, 1643 (1883).
[4] L. Claisen, *Ber. dtsch. chem. Ges.* **31**, 1010 (1898).
[5] H. Meerwein in Houben-Weyl "*Methoden der Organischen Chemie*" (E. Müller, Ed.), Vol. VI, part 3, Thieme, Stuttgart, 1965, p. 303.

1.3. Orthoformates from Trihalomethanes or Halomethyl Ethers

Chloroform reacts with alkoxides and with phenoxides to form trialkyl and triaryl orthoformates.



This reaction has been used to prepare a number of simple and mixed trialkyl orthoformates. The preparation of triethyl orthoformate in about 30% yield from chloroform, ethanol and sodium is described in "*Organic Syntheses*"[8]. A superior procedure for preparing trimethyl and triethyl orthoformates from chloroform and pre-formed alkoxides is described in the patent literature[9]. Tri-*t*-butyl orthoformate, the only tri-*t*-alkyl orthocarboxylate known, is obtained in low yield from the reaction of potassium *t*-butoxide with dichlorofluoromethane[10].

Triaryl orthoformates are by-products of Reimer-Tiemann syntheses of phenolic aldehydes. The best published procedure for the synthesis of triphenyl orthoformate from chloroform gave only a 15% yield, based on the amount of phenoxide used[11].

A more versatile reaction which affords a variety of simple and mixed triaryl orthoformates in 55–80% yields uses aryl dichloromethyl ethers as starting materials. The aryl dichloromethyl ethers are prepared from aryl formates, which are obtained in high yields by reactions of phenols with acetic formic anhydride.

Triphenyl Orthoformate[12]:
Phenyl formate is prepared[13] by mixing acetic anhydride (1 mol) and formic acid (1 mol), allowing the mixture to stand at 45° for 1 hr, cooling it, and adding pyridine (0.01 mol) and phenol (0.67 mol). After 24 hr at room temperature the acids and anhydrides are distilled from the mixture under reduced pressure and the product is purified by fractional distillation to obtain phenyl formate; yield: ~85%; b.p. 90°/30 torr.

Phenyl formate is converted to phenyl dichloromethyl ether[14] by adding it dropwise with stirring to an equimolar amount of phosphorus pentachloride. After one hour the mixture is fractionally distilled to give phenyl dichloromethyl ether; yield: 85%; b.p. 88–89° 13/torr.

[6] K. Sennewald, *German Patent (DBP)* 1812371 (1970); *C. A.* **73**, 44923 (1970).
[7] R. Ohme, E. Schmitz, *Liebigs Ann. Chem.* **716**, 207 (1968).
[8] W. Kaufmann, E. Dreger, "*Organic Syntheses*", Coll. Vol. I, Wiley, New York, 1941, p. 258.
[9] H. A. Weidlich, W. Schulz, *German Patent (DBP)* 919465 (1954); *C. A.* **52**, 14685 (1958).
[10] J. Hine, P. D. Dalsin, J. O. Schreck, *J. Org. Chem.* **34**, 3609 (1969).
[11] H. Baines, J. E. Driver, *J. Chem. Soc.* **125**, 907 (1924).
[12] J. W. Scheeren, J. J. H. Van Roy, A. P. M. Van der Veek, *Rec. Trav. Chim. Pays-Bas* **90**, 745 (1971).
[13] A. Van Es, W. Stevens, *Rec. Trav. Chim. Pays-Bas* **84**, 1247 (1965).
[14] D. H. Holsboer, J. W. Scheeren, A. P. M. Van der Veek, *Rec. Trav. Chim. Pays-Bas* **90**, 556 (1971).

A suspension of sodium phenolate is prepared by cautiously adding one equivalent of sodium to a solution of phenol in 1,2-dimethoxyethane. If necessary, dissolution of the sodium is completed by heating the mixture under reflux. The phenolate is prepared in 10% excess of the amount required to react with the dichloromethyl ether. Phenyl dichloromethyl ether is added dropwise to the stirred suspension of sodium phenoxide. After addition is complete the mixture is refluxed for half an hour, the solvent is distilled off under reduced pressure, and water and ether are added, with agitation, to the residue. The ether solution is washed several times with water and dried over anhydrous sodium sulfate. Evaporation of the ether yields practically pure triphenyl orthoformate; yield: ~80%; m.p. 74–75°.

By varying the structures of the phenols used in the first and third steps, this synthesis can be used to prepare most simple and mixed triaryl orthoformates.

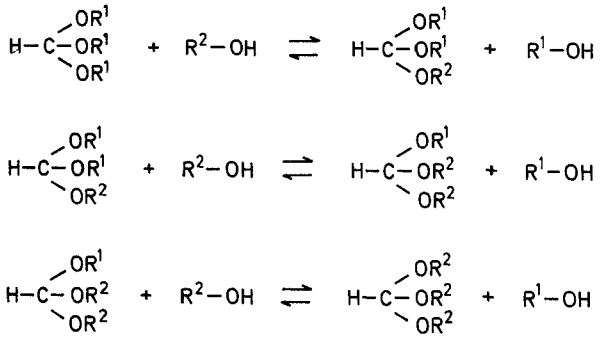
Triphenyl orthoformate may also be prepared by reaction of chlorodiphenoxymethane, a less readily available starting material, with phenol and pyridine in ether solution[15]. Chlorodiphenoxymethane is similarly converted to mixed aryldiphenyl and alkyldiphenyl orthoformates.

Trimethyl orthoformate, several dialkylmethyl orthoformates, and diphenylmethyl orthoformate were prepared by reaction of dichloromethyl methyl ether with sodium alkoxides and with sodium phenoxide[16].

1.4. Orthoformates from Other Trialkyl Orthoformates

1.4.1. Trialkyl Orthoformates by Transesterification

Trialkyl orthoformates undergo facile acid catalyzed transesterification.



If R^1OH is lower-boiling than R^2OH, the exchange equilibria may be displaced to the right by distilling the more volatile alcohol from the reaction mixture. With efficient fractionation it is often possible to obtain a high yield of the new orthoformate.

Transesterification of trimethyl and triethyl orthoformates occurs smoothly with most primary alcohols in the presence of trace amounts of hydrogen chloride or sulfuric acid. Transesterifications involving secondary alcohols generally occur slowly and sometimes yield only mixed ortho esters. Attempts to prepare tri-*t*-butyl orthoformate from triethyl orthoformate yielded only di-*t*-butylethyl orthoformate and *t*-butyldiethyl orthoformate[17].

[15] H. Scheibler, M. Depner, *J. Prakt. Chem.* **7**, 60 (1958).
[16] H. Gross, A. Rieche, *Chem. Ber.* **94**, 538 (1961).

Transesterifications with optically active alcohols give optically active orthoformates (e.g. tri-(*S*)-2-methylbutyl orthoformate[18] and tri-(*S*)-3-methyl-2-pentyl orthoformate[19]).

Tri-*n*-propyl Orthoformate[20,21]:
A flask containing a mixture of 1-propanol and triethyl orthoformate in a 4:1 molar ratio, plus 4 drops of conc. sulfuric acid per mol of orthoformate, is connected to an efficient fractionating column equipped with a total reflux condenser and a partial take-off head. The mixture is heated under reflux, and the theoretical amount of ethanol is removed at the still head in about three hours. The column is replaced with a short, insulated Vigreux column, and the excess propanol is distilled off. Fractionation of the residue at reduced pressure yields tri-*n*-propyl orthoformate; yield: ~95%; b.p. 106–108°/40 torr.

The above procedure is applicable to transesterifications with most other primary alcohols. In reactions using secondary alcohols, 1 g sodium per mol of orthoformate is added to the reaction mixture, after removal of the ethanol, to neutralize the acid and thus minimize decomposition of the product during the final distillation. Secondary alcohols require longer reaction times than primary alcohols. Trimethyl orthoformate is used as the starting material for triisopropyl orthoformate. Table 1 summarizes reported transesterification reactions.

Table 1. Trialkyl Orthoformates by Transesterification of Triethyl Orthoformate[20,21,22]

R in $HC(OR)_3$	Yield (%)	B.p.
$ClCH_2CH_2$—	88	163–165°/11 torr
n-C_3H_7—	95	106–108°/40 torr
$H_3CCHClCH_2$—	86	105–107°/0.5 torr
i-C_3H_7—	75[a]	65–66°/18 torr
n-C_4H_9—	92	132–133°/21.5 torr
i-C_4H_9—	86	118–120°/22 torr
s-C_4H_9—	87	115°/23 torr
n-C_5H_{11}—	80	135–137°/4 torr
i-C_5H_{11}—	95	105–106°/1.5 torr
n-C_6H_{13}—	87	152–153°/1.8 torr
c-C_6H_{11}—	44[b]	(m.p. 73–74°)

[a] Trimethyl orthoformate was the starting material.
[b] Diethylcyclohexyl orthoformate and ethyldicyclohexyl orthoformate were also isolated.

1.4.2. Orthoformates by Chemical Transformations of Alkoxy Substituents of Other Orthoformates

Trivinyl and triisopropenyl orthoformates have been prepared in yields of 72% and 80% by potassium

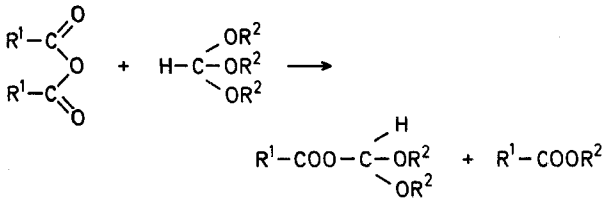
[17] R. P. Narain, R. C. Mehrotra, *Proc. Natl. Acad. Sci. India* **A 33**, 45 (1963).
[18] F. Piacenti, *Gazz. Chim. Ital.* **92**, 225 (1962).
[19] R. Rossi, P. Pino, F. Piacenti, L. Lardicci, G. Del Bino, *J. Org. Chem.* **32**, 842 (1967).
[20] R. M. Roberts, T. D. Higgins, P. R. Noyes, *J. Amer. Chem. Soc.* **77**, 3801 (1955).
[21] E. R. Alexander, H. M. Busch, *J. Amer. Chem. Soc.* **74**, 554 (1952).
[22] H. Stetter, E. Reske, *Chem. Ber.* **103**, 639 (1970).

t-butoxide promoted dehydrohalogenation of tri-2-chloroethyl orthoformate and tri-1-chloro-2-propyl orthoformate[22].

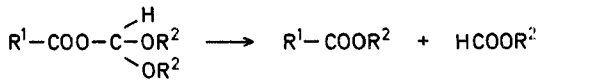
Trivinyl Orthoformate:
Into a 1 l 3-necked flask fitted with a reflux condenser, stirrer, and gas inlet tube is placed tri-2-chloroethyl orthoformate (200 g, 0.796 mol). The flask is flushed with dry nitrogen, and a nitrogen atmosphere is maintained during the dehydrohalogenation. The reaction flask is heated in a water bath while the first part of potassium *t*-butoxide [3.0 mol, a 25% excess, prepared by dissolving potassium (39.1 g) in anhydrous *t*-butyl alcohol (650 g), distilling off the alcohol at a bath temperature of 140°, finally under vacuum; it contains one mol of alcohol of crystallization] is introduced slowly, with stirring. When the mixture begins to boil, the heating bath is removed and the remainder of the butoxide is added at such a rate that the reaction mixture continues to boil. Then the mixture is stirred for half an hour, refluxed for one hour, allowed to cool, diluted with water to about 1 l, and extracted with ether. The ether solution is dried over anhydrous potassium carbonate, some anhydrous potassium carbonate and hydroquinone are added, and the solution is distilled to a pot temperature of 200°. The distillate is thoroughly washed with water to free it from *t*-butyl alcohol, dried over potassium carbonate, and redistilled from potassium carbonate and hydroquinone to yield trivinyl orthoformate; yield: ~81 g (72%); b.p. 141–141.5°.

1.4.3. Acyldialkyl Orthoformates

Acyldialkyl orthoformates (dialkoxymethyl carboxylates) are considerably more reactive than trialkyl orthoformates, and are the reagents of choice in numerous syntheses using orthoformates. They are formed by reactions of trialkyl orthoformates with carboxylic anhydrides.



Acyldialkyl orthoformates (e.g. diethoxymethyl acetate) needed in syntheses are often generated *in situ* by adding equimolar amounts of trialkyl orthoformate and acid anhydride to the reaction mixture. Attempts to isolate acyldialkyl orthoformates from reactions of orthoformates and anhydrides usually give low yields, since the products decompose at rates comparable to their rates of formation.



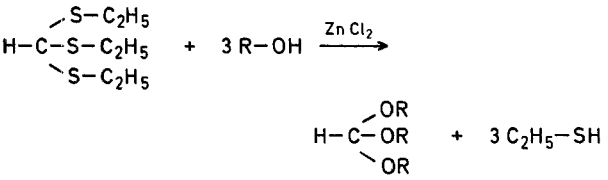
Improved yields of diethoxymethyl acetate, dimethoxymethyl acetate, and diethoxymethyl propionate are obtained by substituting acetic formic and propionic formic anhydrides for acetic anhydride and propionic anhydride[23].

Diethoxymethyl Acetate:
To a formic acetic anhydride reaction system, prepared by mixing acetic anhydride (110 g, 1.08 mol) with formic acid (55 g, 1.20 mol) is added triethyl orthoformate (148 g, 1.0 mol). The mixture is allowed to stand overnight at room temperature, then distilled at a pot temperature of 50° under an appropriate reduced pressure until no more ethyl formate and ethyl acetate pass over. The remaining liquid is fractionally distilled at reduced pressure to give diethoxymethyl acetate; yield: ~100 g (62%); b.p. 70°/15 torr.

Diethoxymethyl esters of propionic, butyric, isobutyric, valeric, pivalic, benzoic, and mesitoic acids were obtained in about 75% yields by distilling equimolar mixtures of the carboxylic acids and diethoxymethyl acetate under reduced pressure. Diethoxymethyl formate was prepared in 50% yield by reaction of formic acid with diethoxymethyl benzoate in pentane solution[23].

1.5. Orthoformates from Trithioorthoformates

Trialkyl orthoformates are obtained by zinc chloride catalyzed alcoholysis of triethyl trithioorthoformate[24].



This reaction provides a route to trialkyl orthoformates from alkyl formates or formic acid, since both formic acid and its esters are readily converted to trialkyl trithioorthoformates[25,26].

Triethyl Orthoformate from Triethyl Trithioorthoformate:
Triethyl trithioorthoformate is prepared from ethyl formate by saturating an ice-cooled mixture of ethanethiol and ethyl formate (in a molar ratio of 2:1) with anhydrous hydrogen chloride, allowing the mixture to stand overnight, separating the layers, extracting the aqueous layer with ether, washing the combined organic layer and ether extract successively with water, aqueous potassium hydroxide, and water, drying the ether solution over anhydrous magnesium sulfate, and fractionally distilling it to obtain the trithioortho ester; yield: ~76% (based on ethanethiol); b.p. 133°/21 torr.

A mixture of triethyl trithioorthoformate (98 g, 0.5 mol), and absolute ethanol (92 g, 2.0 mol) is refluxed with fused zinc chloride (2 g) in a flask fitted with a fractionating column having a total reflux-partial take-off head for 10 hours while about 90% of the theoretical amount of ethanethiol distills off at 35–37°. The remaining material is distilled to give of triethyl orthoformate; yield: ~49 g (66%); b.p. 144–146°.

Tributyl orthoformate is prepared similarly in about 46% yield.

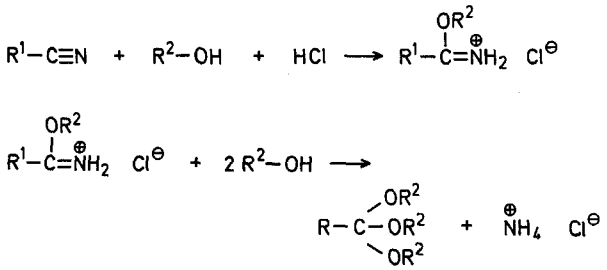
2. Other Aliphatic Ortho Esters

2.1. Synthesis of Ortho Esters from Nitriles

The most versatile method of preparing trialkyl orthocarboxylates is a two-step synthesis using nitriles as starting materials. This reaction, known

[23] J. W. Scheeren, W. Stevens, *Rec. Trav. Chim. Pays-Bas* **85**, 793 (1966).
[24] W. A. Mochel, C. L. Agre, W. E. Hanford, *J. Amer. Chem. Soc.* **70**, 2268 (1948).
[25] B. Holmberg, *Ber. dtsch. chem. Ges.* **40**, 1740 (1907).
[26] J. Houben, *Ber. dtsch. chem. Ges.* **45**, 2942 (1912).

as the Pinner synthesis[2,3], involves alcoholysis of the imidic ester hydrochlorides obtained by reaction of nitriles with alcohols and anhydrous hydrogen chloride.



The preparation and alcoholysis of imidic ester hydrochlorides are normally carried out separately.

2.1.1. Preparation of Imidic Ester Hydrochlorides

The conversion of aliphatic nitriles to imidate hydrochlorides is usually carried out at 0° or below in the presence of an inert diluent (chloroform, nitrobenzene, 1,4-dioxane, benzene, or – usually – diethyl ether), which is added to the reaction mixture to prevent the product from solidifying to an intractible cake. Aliphatic imidic ester hydrochlorides may be prepared by the procedures of McElvain and coworkers[27-32].

Ethyl Imidate Hydrochlorides:

To an ice-cooled solution of the nitrile (1 mol, distilled from phosphorus pentoxide) in anhydrous ethanol (1.1 mol), contained in a flask protected from the atmosphere, anhydrous hydrogen chloride is added until 1.1 mol has been adsorbed. The resulting solution is then allowed to stand at 0° (with careful exclusion of atmospheric moisture) for the time indicated in the third column of Table 2, after which anhydrous ether is added in the quantity shown in the fourth column. In the case of the more reactive nitriles (acetonitrile, chloroacetonitrile) it is necessary to add the ether to the alcohol solution of the nitrile **prior** to addition of the hydrogen chloride in order to prevent solidification of the reaction mixture before all of the hydrogen chloride has been added. Cooling to −30° results in immediate separation of the crystalline imidic ester hydrochloride. With the less reactive nitriles, the ethereal solution is allowed to stand at 0° overnight, after which it is cooled to −30° and the precipitated salt is collected by suction filtration. The salt is dried in a vacuum desiccator over dishes of solid potassium hydroxide and phosphorus pentoxide, after which it is triturated under sufficient cold (−40°) ether to cover it, and again filtered and dried in a desiccator. On standing a few more days in the refrigerator, the mother liquor usually yields a second crop of crystals. After the ether washing the salt does not give an acid reaction to moistened congo red paper, and is suitable for alcoholysis. Imidic ester hydrochlorides can be kept for several weeks if carefully protected from atmospheric moisture.

Methyl imidate hydrochlorides, which are formed more rapidly and in higher yields than their ethyl homologues[28-30], are prepared by essentially the same procedure.

The yield of aliphatic imidate hydrochlorides is influenced by steric hindrance in the nitrile. Ethyl isovalerimidate hydrochloride was obtained in only 30–40% yields under conditions which gave yields of 70% or more of unbranched ethyl imidate hydrochlorides[27], and 2,2-diphenyl-4-chlorobutyronitrile did not react with alcoholic hydrogen chloride in 44 days[33].

The rate of conversion of nitriles to imidate hydrochlorides is influenced by both steric and electronic factors. Rates of formation of ethyl imidate hydrochlorides decrease as the size of R in RCN increases.

Table 2. Preparation of Imidic Esters Hydrochlorides $[R^1C(OR^2)=NH_2]^{\oplus}Cl^{\ominus}$

R^1	R^2	Reaction time at 0°	Ratio alcohol/nitrile: ether[a]	Yield (%)	References
CH_3	C_2H_5	2 hr	1:0.5[b]	85–95	27
C_2H_5	C_2H_5	6 hr	1:4	85–95	27
n-C_3H_7	CH_3	2 days	1:3[b]	77	29
n-C_3H_7	C_2H_5	4 days	1:4	65–70	27
i-C_3H_7	CH_3	2 days	1:3[b]	99	28
i-C_3H_7	C_2H_5	4 days	1:4	70–90	27
n-C_4H_9	CH_3	2 days	1:3[b,c]	79	30
n-C_4H_9	C_2H_5	5 days	1:4	70–80	27
i-C_4H_9	C_2H_5	6 days	1:6	35–40	27
c-C_6H_{11}	CH_3	14 days	1:2	100	31
$C_6H_5CH_2$	CH_3	12 hr	1:1[b]	95	32
$C_6H_5CH_2$	C_2H_5	12 hr	1:1	75	32
$ClCH_2$	C_2H_5	—	1:8[b]	80–90	27

[a] Ratio by volume of alcohol/nitrile mixture to ether.
[b] The ether was added to the alcohol/nitrile mixture before the hydrogen chloride.
[c] Di-n-propyl ether was used as the diluent.

[27] S. M. McElvain, J. W. Nelson, *J. Amer. Chem. Soc.* **64**, 1825 (1942).
[28] S. M. McElvain, C. L. Aldridge, *J. Amer. Chem. Soc.* **75**, 3987 (1953).
[29] S. M. McElvain, D. H. Clemens, *J. Amer. Chem. Soc.* **80**, 3915 (1958).
[30] S. M. McElvain, R. E. Kent, C. L. Stevens, *J. Amer. Chem. Soc.* **68**, 1922 (1946).
[31] S. M. McElvain, R. E. Starn, *J. Amer. Chem. Soc.* **77**, 4571 (1955).
[32] S. M. McElvain, J. T. Venerable, *J. Amer. Chem. Soc.* **72**, 1661 (1950).
[33] F. E. King, K. G. Latham, M. W. Partridge, *J. Chem. Soc.* **1952**, 4268.

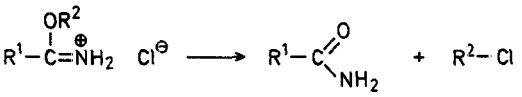
The conversion of acetonitrile to ethyl acetimidate hydrochloride requires about 2 hours, while the analogous reaction of propionitrile requires about 6 hours. One to several days is required to convert most higher aliphatic nitriles to ethyl imidate hydrochlorides[27].

Electron-withdrawing substituents in the nitrile appear to facilitate formation of the imidate hydrochloride, but interpretation of the limited data available is complicated by variations in concentrations of reactants and solvents used, and by the fact that the rates of crystallization of imidate hydrochlorides may be considerably slower than their rates of formation.

Chloroacetonitrile, malononitrile, succinonitrile and 4,4,4-trichlorobutyronitrile have been converted to ethyl imidate hydrochlorides in satisfactory yields[27,34]. However, attempts to convert dichloroacetonitrile, trichloroacetonitrile or nitroacetonitrile to the substituted methyl acetimidate hydrochlorides yielded only methyl chloride and substituted acetamides[35,36].

The conversion of benzonitriles to alkyl benzimidate hydrochlorides has not been investigated as systematically as analogous reactions of aliphatic nitriles. However, a few generalizations can be made. Although some *o*-substituted benzonitriles and some α-naphthonitriles cannot be converted to imidic ester hydrochlorides by Pinner's procedure[37,38], most *m*- and *p*-substituted benzonitriles can be converted to methyl and ethyl benzimidate hydrochlorides. Pinner[39] specified that stoichiometric amounts of alcohol and hydrogen chloride be used, and that reaction mixtures be kept cold until reaction is complete. However, satisfactory yields of most ethyl benzimidates are obtained if a chilled solution of the nitrile in a slight excess of ethanol (plus ether, benzene dioxane or chloroform, if the nitrile is insufficiently soluble in ethanol) is saturated with anhydrous hydrogen chloride and allowed to stand at room temperature until crystallization of the ethyl benzimidate hydrochloride is complete (usually 1–4 days)[40]. The preparation of methyl benzimidate hydrochlorides has also been described[41].

The most serious competing reaction in the synthesis of both aliphatic and aromatic imidate hydrochlorides is decomposition of the imidate salt to an alkyl chloride and an amide.



This reaction is minimized by carrying out the synthesis at a low temperature, and is troublesome only if the acyl substituent of the imidate is strongly electron-attracting.

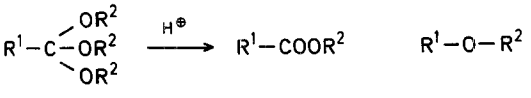
2.1.2. Alcoholysis of Imidic Ester Hydrochlorides

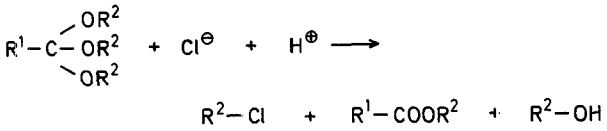
Imidic ester hydrochlorides are converted to ortho esters by reaction with alcohols. The simplest procedure, which is the preferred method for alcoholysis of imidate salts having electronegative acyl substituents (e.g., cyanoacetimidate hydrochlorides, phenylacetimidate hydrochlorides, chloroacetimidate hydrochlorides), involves dissolving the salt in an excess of the alcohol and allowing the mixture to stand at room temperature until no more ammonium chloride precipitates.

However, with simple aliphatic alkyl imidate hydrochlorides, this procedure is time consuming and frequently gives poor yields of the ortho ester. The time required for alcoholysis of these salts is greatly reduced, and yields are improved, if the alcoholysis is carried out in a refluxing mixture of the imidate hydrochloride, a five- to ten-fold excess of the alcohol, and diethyl ether.

Carboxamide formation is a serious competing reaction in the alcoholysis of imidate hydrochlorides having two or more α- and/or β-acyl substituents. These imidate salts frequently afford ortho esters in yields of 20–30% or less. Yields of trimethyl orthocarboxylates from sterically hindered methyl carboximidate hydrochlorides (methyl isobutyrimidate hydrochloride, for example) are significantly improved by substituting low-boiling petroleum ether for diethyl ether as the diluent.

Yields of ortho esters in imidate alcoholyses are also reduced by acid catalyzed reactions of the ortho esters with alcohols and chloride ion to form alkyl carboxylates, dialkyl ethers, and alkyl chlorides.



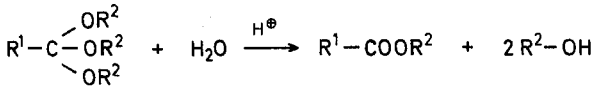


These side reactions cannot be avoided during the alcoholysis reaction, since they are catalyzed by unreacted imidate hydrochloride. Acid catalyzed decompositions of the ortho ester during work-up

[34] S. M. McElvain, J. P. Schroeder, *J. Amer. Chem. Soc.* **71**, 40 (1949).
[35] W. Steinkopf, *Ber. dtsch. chem. Ges.* **42**, 617 (1909).
[36] W. Steinkopf, W. Malinowski, *Ber. dtsch. chem. Ges.* **44**, 2898 (1911).
[37] G. T. Lander, F. T. Jewson, *J. Chem. Soc.* **83**, 766 (1903).
[38] A. Pinner, *Ber. dtsch. chem. Ges.* **23**, 2917 (1890).
[39] A. Pinner, "*Die Imidoaether und ihre Derivate*", Robert Oppheim, Berlin, 1892.
[40] R. H. DeWolfe, F. A. Augustine, *J. Org. Chem.* **30**, 699 (1965).
[41] H. Kwart, M. B. Price, *J. Amer. Chem. Soc.* **82**, 5123 (1960).

of the reaction mixture can be minimized by adding sufficient sodium alkoxide to neutralize acidic substances which remain in the reaction mixture after the ammonium chloride has been filtered off.

Ortho esters are destroyed by strong acids such as hydrogen chloride, and are extremely susceptible to acid-catalyzed hydrolysis.



It is therefore essential that the imidic ester hydrochloride be completely free of hydrogen chloride, that water-free alcohols and solvents be used, and that moisture be carefully excluded during the alcoholysis reaction.

Ortho esters are usually purified by fractional distillation at reduced pressures. In the few cases where the by-product alkyl carboxylates cannot be separated adequately from the ortho esters by distillation, they may be destroyed by treatment with sodium hydride[32] or aqueous alkali prior to isolation of the ortho ester.

Trialkyl Orthocarboxylates[27]:
The ethyl carboximidate hydrochloride and anhydrous ethanol, in a molar ratio of about 1:15, are placed in a flask fitted with a reflux condenser, an efficient stirrer, and a thermometer dipping into the reaction mixture. The mixture, carefully protected from atmospheric moisture, is stirred until the salt dissolves, and the quantity of anhydrous diethyl ether indicated in Table 3 is added. The resulting solution is refluxed (or kept at 40° if no ether was added) for the time indicated in Table 3. After this the reaction mixture is cooled to 0°, and the precipitated ammonium chloride is filtered off (250 ml of ether per mol of imidate are added before filtration if ether is not present during the alcoholysis). The filtrate is washed with an equal volume of 10% aqueous sodium carbonate, and then with saturated aqueous sodium carbonate. The washed solution is dried over anhydrous potassium carbonate and fractionally distilled at reduced pressure.

Trimethyl Orthoisobutyrate[28]:
Methyl isobutyrimidate hydrochloride and anhydrous methanol in a 1:3 molar ratio, and dry petroleum ether (b.p. 35°, 900 ml per mol of imidate), are placed in a flask fitted with a stirrer and a reflux condenser protected by a calcium chloride tube. The mixture is stirred at room temperature for two days, at the end of which time the lower layer of ammonium chloride is filtered off and the liquid is fractionally distilled. The excess methanol distills as an azeotrope with the petroleum ether at 27°. As the volume of the liquid is reduced, some isobutyramide crystallizes out. The mixture is again filtered and distillation resumed from a smaller flask containing about 2.5 g of sodium hydride per mol of imidate used, which removes the last traces of water, alcohol, and amide. The trimethyl orthoisobutyrate, b.p. 134–136°, is obtained in about 70% yield.

Ortho Esters Having Electronegative Acyl Substituents (e.g., Trialkyl Orthocyanoacetates and Trialkyl Orthophenylacetates)[32,34,42]:
The methyl or ethyl carboximidate hydrochloride is dissolved in a large excess of the appropriate anhydrous alcohol (about 300 ml of alcohol per mol of the phenylacetimidate hydrochloride, or about 1 l of alcohol per mol of the cyanoacetimidate hydrochloride), and the solution is allowed to stand at room temperature until precipitation of ammonium chloride is complete (1–2 days). A volume of ether equal to about half the volume of alcohol used is added to the suspension, and the ammonium chloride is filtered off. Enough of the appropriate sodium alkoxide is added to the filtrate to make it basic to phenolphthalein, and the ether and alcohol are removed at room temperature under reduced pressure. The concentrated solution is chilled in a dry ice-acetone bath, and the carboxamide which separates is filtered off. The filtrate is then fractionally distilled at reduced pressure to obtain the ortho ester in 45–65% yield:
trimethyl orthocyanoacetate, b.p. 98–102°/13 torr;
trimethyl orthophenylacetate, b.p. 72–76°/0.5 torr;
triethyl orthocyanoacetate, b.p. 83–84°/2 torr;
triethyl orthophenylacetate, b.p. 88–91°/0.1 torr.
(The crude trimethyl orthophenylacetate is treated with sodium hydride to remove methyl phenylacetate prior to the final distillation)[32].

The conversion of benzimidate hydrochlorides to trialkyl orthobenzoates has not received the careful scrutiny given aliphatic imidate hydrochloride alcoholyses by McElvain and co-workers (see above). Published procedures are sketchy, and reported yields are low.

In general, the alkyl benzimidate hydrochloride is dissolved in an excess of the anhydrous alcohol, and the reaction mixture is allowed to stand 10–30 days at room temperature. Filtering off the ammonium chloride and distilling the filtrate yields the trialkyl orthobenzoate, along with the alkyl benzoate. When the ordinary ester cannot be adequately separated from the ortho ester by fractional distillation, it may be removed by saponification, which leaves the ortho ester unchanged[41].

Orthobenzoates prepared from the imidate hydrochlorides include trimethyl[43] and triethyl[43,44] ortho-

Table 3. Alcoholysis of Ethyl Carboximidate Hydrochlorides to Triethyl Orthocarboxylates

R in $[RC(OC_2H_5)=NH_2]^{\oplus}Cl^{\ominus}$	Reaction time	Alcohol/ether ratio	Reaction temperature	Yield (%) of $RC(OC_2H_5)_3$	B.p.
CH_3	6	1:1	46°	75–78	144–146°/740 torr
C_2H_5	9	1:2	42°	75–78	70–72°/32 torr
n-C_3H_7	18	1:3	41°	60–63	58–59°/7 torr
i-C_3H_7	24	1:5	39°	27–30	50–51°/7 torr
n-C_4H_9	12	1:3	42°	59–61	49–50°/3 torr
i-C_4H_9	28	1:5	39°	21–23	57–59°/7 torr
$ClCH_2$	6	1:0	40°	70–73	68–70°/10 torr

[42] S. M. McElvain, C. L. Stevens, *J. Amer. Chem. Soc.* **68**, 1917 (1946).
[43] J. P. Vila, R. G. Jarque, *Anales fís. y quím. (Spain)* **40**, 248 (1944).

benzoates, trimethyl ortho-*p*-anisate[41], trimethyl ortho-*p*-toluate[41] and trimethyl ortho-*p*-nitrobenzoate[41].

2.1.3. A One-step Synthesis of Ortho Esters from Nitriles

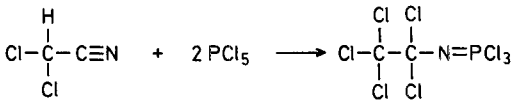
Triethyl orthoacetate and triethyl orthopropanoate have been prepared in good yields from the nitriles without isolating the imidate hydrochlorides[45].

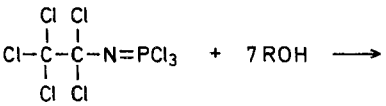
Triethyl Orthoacetate:
Dry hydrogen chloride (36.5 g, 1 mol) is added to a water-cooled mixture of acetonitrile (41 g, 1 mol), anhydrous ethanol (46 g, 1 mol), and anhydrous chloroform (35 ml). The temperature is allowed to rise to room temperature, and the mixture is allowed to stand, with occasional agitation, for 48 hours. Anhydrous ethanol (200 ml) is added, and the mixture is allowed to stand at room temperature for 2 days. Ammonium chloride is filtered off and washed with ethanol. The filtrate and washings are mixed with 5% aqueous sodium hydroxide (800 ml), and the product extracted with chloroform. Fractional distillation of the dried (anhydrous potassium carbonate) extract yields triethyl orthoacetate; yield: 96–127 g (59–78%); b.p. 70–80°/60 torr.

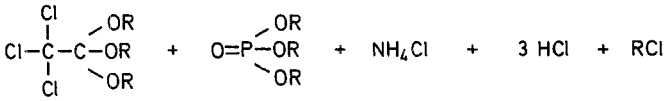
Triethyl orthopropanoate was prepared similarly in 40–50% yields.

2.1.4. Trialkyl Orthotrichloroacetates

Although trialkyl orthotrichloroacetates cannot be prepared from trichloroacetonitrile by the Pinner synthesis, they may be obtained by alcoholysis of pentachloroethylphosphorimidic trichloride, which may be prepared from dichloroacetonitrile.







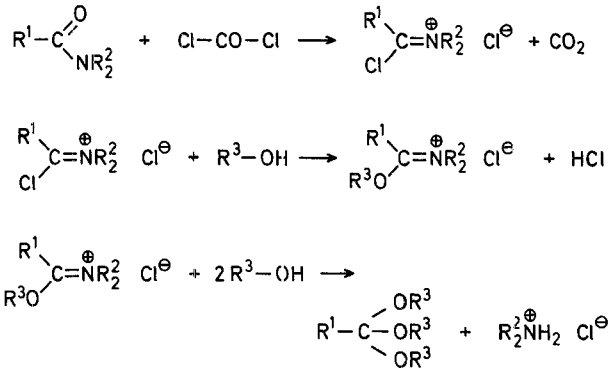
Triethyl Orthotrichloroacetate[46]:
Pentachloroethylphosphorimidic trichloride is obtained in 91% yield[47] by stirring a mixture of dichloroacetonitrile (27.5 g, 0.25 mol) and phosphorus pentachloride (104 g, 0.5 mol) for 8 hours while gradually increasing the temperature from 40° to 100°. The phosphorus trichloride is distilled from the mixture at reduced pressure, and a small amount of phosphorus pentachloride is filtered from the residue. Distillation of the filtrate gives pentachlorethylphosphorimidic trichloride; yield: ~80 g; b.p. 117 to 118°/5 torr.

A solution of the phosphorimidic trichloride (17.7 g, 0.05 mol) in benzene (20 ml) is added slowly with stirring to absolute ethanol (50 ml), and stirring is continued while the mixture is heated for two hours at 75–80°. The ammonium chloride is filtered off from the cooled mixture, the solvent is distilled off, and the residue is fractionally distilled to obtain triethyl orthotrichloroacetate; yield: 6.6 g, 50%; b.p. 101–102°/2 torr.

The trimethyl, tripropyl, and triphenyl esters were prepared similarly.

2.2. Ortho Esters from Amide Chlorides

Ortho esters can be prepared from *N,N*-disubstituted carboxamides via the amide chlorides.



This sequence provides a route to ortho esters from the corresponding carboxylic acids via amides of secondary amines. The parallel between the last two steps and the Pinner synthesis is obvious. The second and third steps may be carried out without isolating the alkyl imidium chloride.

Triethyl Orthopropanoate from 1-Propanoylpiperidine[48]:
The amide chloride of 1-propanoylpiperidine is prepared by adding phosgene (198 g, 2 mol) to a solution of the amide (141 g, 1 mol) in dry benzene (~500 ml) at room temperature, and allowing the mixture to stand 4–5 hours. The amide chloride is filtered off, washed with dry ether, and stored in a desiccator. Yield: 176–186 g, 90–95%; m.p. 82–85°. To a stirred, cooled (0°), suspension of the amide chloride (19.6 g, 0.10 mol) in dry ether (100 ml) is added anhydrous ethanol (14 g, 0.3 mol). The mixture separates into two phases. The ether layer is separated, and the residue is added dropwise to a solution of sodium (6.0 g) in anhydrous ethanol (150 ml). Then glacial acetic acid (20 ml) is added, and the mixture is allowed to stand at room temperature for 24 hours. The mixture is poured into an ice-aqueous sodium hydroxide suspension, the ortho ester is extracted with ether, the ether solution is dried over anhydrous potassium carbonate, and the triethyl orthopropanoate is isolated by fractional distillation; yield: 11 g, 62%; b.p. 158–163° (b.p. 60°/17 torr).

2.3. Ortho Esters from Other Ortho Esters

2.3.1. Ortho Esters by Transesterification

Transesterification, previously described for trialkyl orthoformates (section 1.4.1), has received little attention as a method of preparing other trialkyl orthocar-

[44] A. Kiprianov, Z. P. Suitnik, E. D. Suich, *Zh. Obshch. Khim.* **6**, 42 (1936).
[45] V. E. B. Filmfabrik Agfa Wolfen, *Belgian Patent* 617666 (1962); *C. A.* **58**, 12425 (1963).
[46] V. I. Shevchenko, A. A. Koval, *Zh. Obshch. Khim.* **38**, 22 (1968).
[47] V. I. Shevchenko, N. D. Bodnarchuk, A. V. Kirsanov, *Zh. Obshch. Khim.* **33**, 1342 (1963).
[48] H. Eilingsfeld, M. Seefelder, H. Weidinger, *Chem. Ber.* **96**, 2671 (1963).

boxylates. Tripropyl, tributyl, trihexyl and trioctyl orthopropanoates were prepared by phosphoric acid-catalyzed transesterification of triethyl orthopropanoate[49]. Tri-2-chloroethyl esters of orthoacetic, orthochloroacetic and orthovaleric acids are obtained in good yields by hydrogen chloride catalyzed transesterification of the triethyl orthocarboxylates with 2-chloroethanol[22,50].

Transesterification should be a generally applicable method of preparing ortho esters of higher-boiling primary alcohols from the corresponding trimethyl or triethyl orthocarboxylates. Transesterification of higher orthocarboxylates with secondary and tertiary alcohols would probably be even more severly limited by steric hindrance than analogous reactions of orthoformates.

2.3.2. Trialkyl Ortho-α-bromocarboxylates

α-Bromoortho esters, useful precursors of ketene acetals[51], are formed in high yields when trialkyl orthocarboxylates having at least one α-hydrogen are treated with bromine and pyridine.

Trimethyl Ortho-α-Bromovalerate[52]:
To a cooled mixture of trimethyl orthovalerate (162 g, 1 mol), dry pyridine (87 g, 1.1 mol), and carbon tetrachloride (150 ml) in a 1 l flask fitted with a stirrer and a dropping funnel is added, dropwise with stirring, a solution of bromine (160 g, 1 mol) in carbon tetrachloride (200 ml). The reaction mixture is allowed to come to room temperature toward the end of the bromine addition. When the addition is finished, the reaction mixture is warmed to 50°. The precipitated salts are then filtered off and washed with dry ether. Distillation of the combined filtrate and ether wash gives trimethyl ortho-α-bromovalerate: yield: ~190 g, 79%; b.p. 93–96°/14 torr.

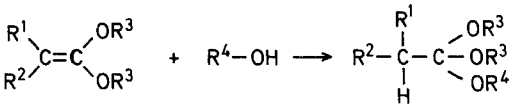
Similarly prepared are trimethyl[53] and triethyl[54] orthobromoacetates, triethyl ortho-α-bromopropanoate[51], trimethyl ortho-α-bromoisobutyrate[55], triethyl ortho-α-bromovalerate[55], trimethyl ortho-α-bromopelargonate[52], and trimethylortho-α-bromophenylacetate[42].

2.3.3. Synthesis of Ortho Esters by Modification of Acyl or Alkoxy Substituents of Other Ortho Esters

The ortho ester function is practically inert under alkaline and neutral conditions. This fact makes possible syntheses of ortho esters by chemical transformations of the acyl or alkoxy substituents of ortho ester precursors, under conditions which do not destroy the ortho ester function. Such transformations involve elimination, substitution, addition, oxidation, and reduction reactions, and are the basis for the use of the ortho ester function as a carboxyl and hydroxyl protecting group. Simple examples of this class of reactions are the synthesis of trimethyl ortho-4-chloro-3-butynoate by treatment of trimethyl ortho-4,4,4-trichlorobutyrate with sodium methoxide[34], the conversion of triethyl orthobromoacetate to triethyl orthoiodoacetate by reaction with ethanolic sodium iodide[54], and dehydrohalogenation of 2-chloroalkyl ortho esters to trivinyl orthocarboxylates. Trivinyl orthoacetate, trivinyl orthochloroacetate, and trivinyl orthovalerate were prepared by the procedure described in section 1.4.2, and trivinyl orthoacetate has also been prepared by dehydrohalogenation of divinyl-2-chloroethyl orthoacetate, obtained by addition of 2-chloroethanol to ketene divinylacetal[56].

2.4. Ortho Esters from Ketene Acetals

Alcohols and phenols add to ketene acetals to form simple and mixed orthocarboxylates.



The reaction is catalyzed by acids but occurs in their absence.

The reaction of alcohols with ketene acetals is not a practical method of synthesizing most ortho esters, since the ketene acetals are difficult to prepare and are often best prepared by dealcoholation of the desired ortho esters. In spite of this limitation, a number of ortho esters have been synthesized from ketene acetals, and several of them have been prepared in no other way. These include trimethyl orthodiphenylacetate[57], trimethyl orthodimethoxyacetate[58], triethyl ortho-3,3-diethoxypropanoate[59], and triphenyl orthoacetate[60] (see Scheme **A**).

2.5. Ortho Esters from Trihalomethyl Compounds or α-Haloethers

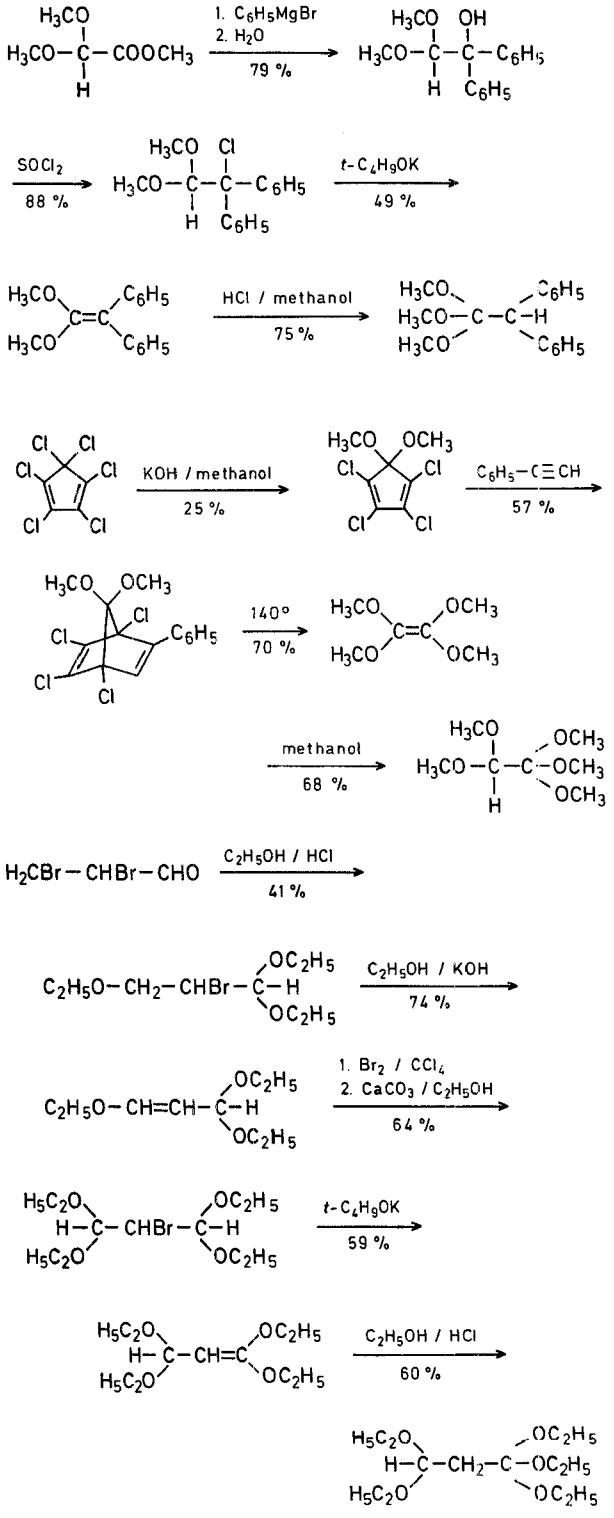
Although conversion of most trihalomethylalkanes to ortho esters is not feasible due to competing elimination reactions, triethyl ortho-2,3,3-trichloroacrylate[61] and trimethyl and triethyl ortho-4,4-dichloro-2,3,4-trifluorocrotonates[62] have been pre-

[49] B. A. Arbusov, E. K. Yuldasheva, *Dokl. Akad. Nauk SSSR* **70**, 231 (1950).
[50] J. Hebky, *Collect. Czech. Chem. Commun.* **13**, 442 (1948).
[51] P. M. Walters, S. M. McElvain, *J. Amer. Chem. Soc.* **62**, 1482 (1940).
[52] S. M. McElvain, R. E. Kent, C. L. Stevens, *J. Amer. Chem. Soc.* **68**, 1924 (1946).
[53] S. M. McElvain, H. I. Anthes, S. H. Shapiro, *J. Amer. Chem. Soc.* **64**, 2525 (1942).
[54] F. Beyerstedt, S. M. McElvain, *J. Amer. Chem. Soc.* **59**, 1237 (1937).
[55] S. M. McElvain, R. L. Clarke, G. D. Jones, *J. Amer. Chem. Soc.* **64**, 1966 (1942).
[56] S. M. McElvain, A. N. Bolstad, *J. Amer. Chem. Soc.* **73**, 1988 (1951).
[57] S. M. McElvain, S. B. Mirviss, C. L. Stevens, *J. Amer. Chem. Soc.* **73**, 3806 (1951).
[58] R. W. Hofmann, J. Schneider, H. Hauser, *Chem. Ber.* **99**, 1892 (1966).
[59] S. M. McElvain, L. R. Mirviss, *J. Amer. Chem. Soc.* **73**, 206 (1951).
[60] S. M. McElvain, B. Fajardo-Pinzón, *J. Amer. Chem. Soc.* **67**, 650 (1945).

pared by reactions of alkoxides with hexachloropropene and with 1,3,4,4-tetrachloro-1,2,3,4-tetrafluoro-1-butene.

Triethyl orthodichloroacetate is obtained in 43% yield by the action of refluxing alcoholic sodium ethoxide on ethyl 2,2-dichloro-1,1-difluoroethyl ether, prepared by addition of ethanol to 1,1-dichloro-2,2-difluoroethene[63].

Trialkyl orthobenzoates have been prepared in satisfactory yields by alcoholysis of the appropriate benzotrichlorides.

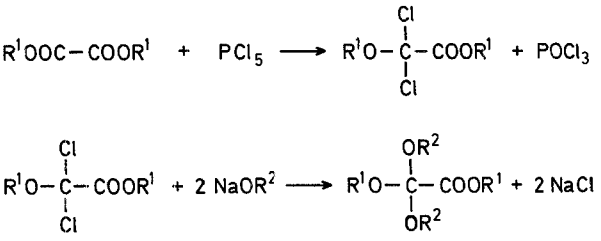


Scheme A

Trimethyl Orthobenzoate[32]:
A solution of sodium (75 g, 3.25 mol) in anhydrous methanol (1 l) is prepared in a 3-necked flask fitted with a stirrer, reflux condenser, and dropping funnel. The sodium methoxide solution is cooled to 0 °, and benzotrichloride (195.5 g, 1 mol) is added, dropwise, with stirring. After addition of the trichloride, stirring is continued for one hour, and the mixture is allowed to stand overnight at room temperature. The reaction mixture is then refluxed for 36 hours, after which it is cooled in an ice-bath and the sodium chloride is filtered off. The salt is washed with a small protion of dry methanol, which is combined with the filtrate. Fractional distillation of the solution gives trimethyl orthobenzoate; yield: 145 g (80%); b.p. 114–115 °/25 torr.

Triethyl orthobenzoate[64], trimethyl ortho-*p*-chlorobenzoate[41,65], and hexamethyl *m*- and *p*-diorthophthalates[66] have been prepared similarly.

Hemi-orthooxalates (alkyl trialkoxyacetates) are prepared by reaction of alcohols with alkoxydichloroacetates in the presence of alkoxides or pyridine. The alkoxydichloroacetates are obtained from dialkyl oxalates and phosphorus pentachloride[67–70].



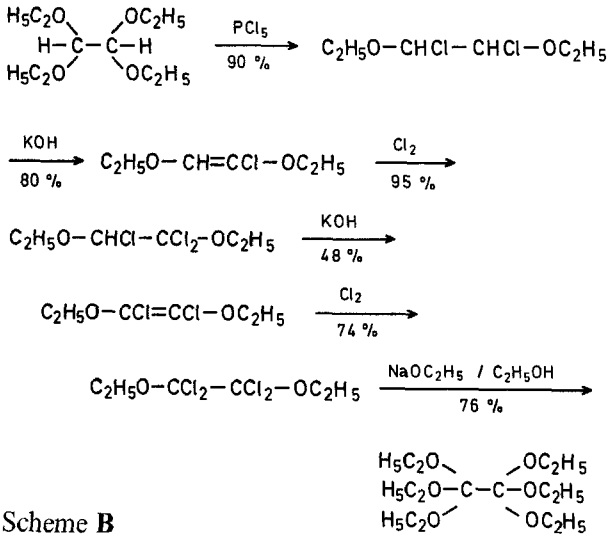
Ethyl triethoxyacetate[70]:
A mixture of diethyl oxalate (146 g, 1 mol) and phosphorus pentachloride (229 g, 1.1 mol) is heated at 100–110 ° for 10–15 hours with occasional stirring. Reduced pressure distillation of the mixture gives phosphorus oxychloride and ethyl ethoxydichloroace-

[61] A. Roedig, E. Degener, *Chem. Ber.* **86**, 1469 (1953).
[62] I. L. Knunyants, B. L. Dyatkin, L. S. German, E. P. Mochalina, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **1960**, 231.
[63] P. Tarrant, H. C. Brown, *J. Amer. Chem. Soc.* **73**, 1781 (1951).
[64] S. M. McElvain, H. I. Anthes, S. H. Shapiro, *J. Amer. Chem. Soc.* **64**, 2530 (1942).
[65] B. G. Ramsey, R. W. Taft, *J. Amer. Chem. Soc.* **88**, 3058 (1968).
[66] S. J. Lapporte, *J. Org. Chem.* **27**, 3098 (1962).
[67] R. Anschütz, *Liebigs Ann. Chem.* **254**, 31 (1889).
[68] R. Anschütz, J. Stiepel, *Liebigs Ann. Chem.* **306**, 8 (1899).
[69] E. Blaise, M. Maire, *Ann. Chim. (Paris)* [8] **15**, 564 (1908).
[70] R. G. Jones, *J. Amer. Chem. Soc.* **73**, 5168 (1951).

tate; yield: ~156 g, 78%; b.p. 75–82°/12 torr. The product is decanted from the small amount of phosphorus pentachloride which separates from it on cooling to 0°. It is essential that the pressure does not exceed 15 torr during the distillation.

In a flask provided with a stirrer, reflux condenser, and dropping funnel is placed ethyl ethoxydichloroacetate (100.5 g, 0.5 mol), absolute ethanol (55 g, 1.2 mol), and dry ether (175 ml). With stirring, dry pyridine (95 g, 1.2 mol) is dropped into the solution at such a rate that the mixture refluxes gently (about 1 hour). After several hours the pyridine hydrochloride is filtered off and washed with dry ether (100 ml). The ether is distilled from the combined filtrate and washings, and the residue is heated on a steam bath for about half an hour. The cooled liquid is washed with ice-cold 3*N* sulfuric acid (2 × 300 ml), then with aqueous sodium carbonate, and dried over anhydrous magnesium sulfate. Distillation gives ethyl triethoxyacetate; yield: ~85 g, 77%; b.p. 90–92°/8 torr.

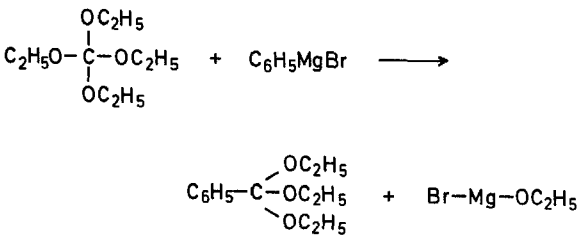
Hexaethyl orthooxalate (hexaethoxyethane) is obtained in 76% yield by heating 1,1,2,2-tetrachloro-1,2-diethoxyethane with sodium ethoxide and ethanol at 145° (Scheme **B**).



Scheme **B**

2.6. Orthocarboxylates from Orthocarbonates

Tschitschibabin synthesized triethyl orthobenzoate in good yield by allowing phenylmagnesium bromide to react with tetraethyl orthocarbonate[72]:



While he emphasized that short reaction times and relatively low reaction temperatures are essential if the reaction is to yield ortho esters rather than acetals, Tschitschibabin did not specify relative amounts or concentrations of reactants, or give detailed experimental procedures.

Although this reaction should be generally applicable, other workers have used it with mixed results. Iotsitch prepared triethyl orthophenylpropiolate by reaction of phenylethynylmagnesium iodide with tetraethyl orthocarbonate[73], but McElvain failed in attempts to prepare other trialkyl orthocarboxylates by Tschitschibabin's reaction[27]. It is perhaps significant that the successful examples of this synthesis involved Grignard reagents with electron attracting organic groups (which should reduce the extent of acetal formation by diminishing the nucleophilicity of the Grignard reagent and the reactivity of the initially formed orthocarboxylate).

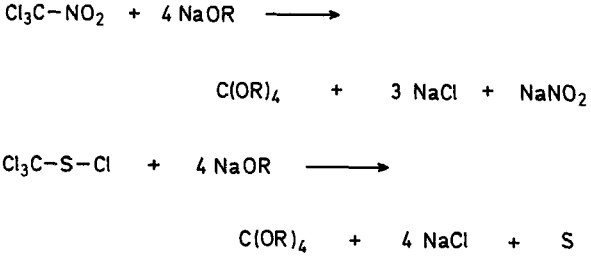
One published example of this reaction gives adequate experimental details. Similar procedures may work with other Grignard reagents.

Triethyl Ortho-3-butynoate[74]:
A solution of propargylmagnesium bromide (43 g, 0.30 mol) in anhydrous ether (160 ml) is dropped slowly into a chilled solution (−30°) of tetraethyl orthocarbonate (48 g, 0.25 mol) in ether (80 ml) in a flask filled with a nitrogen atmosphere. The temperature is then raised until, at about 25°, an exothermic reaction commences. External cooling is applied to prevent the temperature of the reaction mixture from rising above 30°. After 30 minutes the reaction mixture is hydrolyzed with saturated ammonium chloride solution. The ether solution is washed with water, dried over anhydrous magnesium sulfate, and fractionally distilled to obtain triethyl ortho-3-butynoate; yield: 17.3 g, 37% (based on tetraethyl orthocarbonate); b.p. 73–75°/10 torr.

3. Orthocarbonates

3.1. Orthocarbonates from Trihalomethyl Compounds and Halomethyl Ethers

Although tetraalkyl orthocarbonates, $C(OR)_4$, are not formed by reactions of alkoxides with carbon tetrachloride (orthoformates are obtained instead[75]), they may be prepared in satisfactory yields from alkoxides and chloropicrin or trichloromethanesulfenyl chloride (thiocarbonyl perchloride).



The preparation of tetraethyl orthocarbonate in 46 to 49% yields from chloropicrin is described in "*Organic Syntheses*"[76]. The same compound may be obtained in higher yields from trichloromethanesul-

[71] H. Baganz, K. E. Krüger, *Chem. Ber.* **91**, 807 (1959).
[72] A. E. Tschitschibabin, *Ber. dtsch. chem. Ges.* **38**, 561 (1905).
[73] J. I. Iotsitch, F. Kochelov, *Bull. Soc. Chim. Fr.* [4] **10**, 1308 (1911).
[74] R. Finding, U. Schmidt, *Angew. Chem.* **82**, 482 (1970); *Angew. Chem. Int. Ed.* **9**, 456 (1970).
[75] C. K. Ingold, W. J. Powell, *J. Chem. Soc.* **119**, 1228 (1921).
[76] J. D. Roberts, R. E. McMahon, "*Organic Syntheses*", Coll. Vol. III, Wiley, New York, 1963, p. 457.

fenyl chloride[77,78], which may be prepared from carbon disulfide[79], and is commercially available.

Tetraethyl Orthocarbonate:
An ethanolic sodium ethoxide solution is prepared by dissolving sodium (34.5 g, 1.5 mol) in absolute ethanol (1 l) in a flask fitted with a reflux condenser and a dropping funnel, and protected from atmospheric moisture. The resulting solution is cooled in an ice bath, and a solution of trichloromethanesulfenyl chloride (56 g, 0.3 mol) in dry ether (50 ml) is added at such a rate that the temperature of the reaction mixture does not rise above room temperature. The reaction mixture is allowed to stand overnight at room temperature, after which most of the alcohol is distilled off. The residue is poured into water and the suspension is extracted with ether. The ether extract is dried over anhydrous potassium carbonate and fractionally distilled to obtain tetraethyl orthocarbonate; yield: 44 g, 77%; b.p. 158–160°.

Tetramethyl, tetrapropyl, tetrabutyl, and tetraisobutyl orthocarbonates have been prepared similarly.

Tetraphenyl orthocarbonate has been prepared from phenol and dichlorodiphenoxymethane[80].

Tetraphenyl Orthocarbonate:
Dichlorodiphenoxymethane is prepared by heating diphenyl carbonate and phosphorus pentachloride (in a molar ratio of 1:1.3) in a sealed tube at 200° for 15 hours, and fractionally distilling the resulting mixture at reduced pressure with careful exclusion of moisture to obtain about a 60% yield, b.p. 183–187°/12 torr.

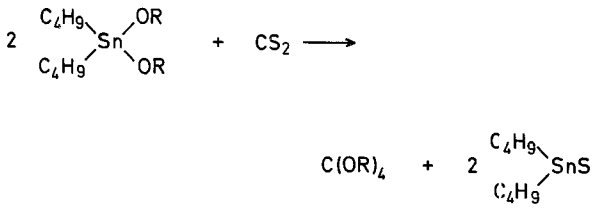
Dichlorodiphenoxymethane (0.5 mol per mol of phenol used) is added to a solution of phenol in about 5 times its volume of dry ether. The solution is warmed until no more hydrogen chloride is evolved. The ether is distilled off and the residue is triturated with water in a mortar, then recrystallized from aqueous ethanol to obtain tetraphenyl orthocarbonate; yield: ~80%; m.p. 97–98°.

3.2. Transesterification Reactions of Tetramethyl Orthocarbonate

Transesterification reactions of tetraalkyl orthocarbonates are more difficult to drive to completion than are analogous reactions of orthoformates. An attempt to prepare tetra-*n*-butyl orthocarbonate by acid catalyzed transesterification of the tetramethyl ester yielded only butyltrimethyl orthocarbonate, dibutyldimethyl orthocarbonate, and tributylmethyl orthocarbonate[81]. However, tetra-*n*-hexyl, tetra-*n*-octyl, tetra-*n*-nonyl, and tetra-*n*-decyl orthocarbonates were prepared by transesterification of the tetramethyl ester[82].

3.3. Tetraalkyl orthocarbonates from Dibutyltin Dialkoxides

Tetraalkyl orthocarbonates are formed in 80–95% yields by heating dibutyltin dialkoxides and carbon disulfide at 95–120° in a closed system[83].



R = CH_3, C_2H_5, n-C_3H_7, n-C_4H_9, n-C_6H_{13}

Tetramethyl Orthocarbonate from Dibutyldimethoxytin:
Dibutyldimethoxytin is prepared[84] by dissolving sodium (45.4 g, 1.98 mol) in absolute methanol (450 ml), cooling the solution to 0°, and adding a solution of dibutyltin dichloride (303.7 g, 1 mol) in absolute methanol (335 ml) to the stirred methoxide solution. Stirring is continued until the reaction mixture is neutral. The salt is filtered off, and the methanol is evaporated at 40° to give dibutyldimethoxytin; yield: 0.93 mol, 93%; b.p. 136 to 139°/1.2 torr.

Dibutyldimethoxytin (5.92 g, 0.02 mol) and carbon disulfide (1.2 ml) are mixed at room temperature, and the solid adduct which forms is heated at 100° for 5–10 hours in a sealed glass tube. The liquid reaction mixture is fractionally distilled to give tetramethyl orthocarbonate; yield: ~3 g, 95%; b.p. 114°.

4. Heterocyclic Ortho Esters

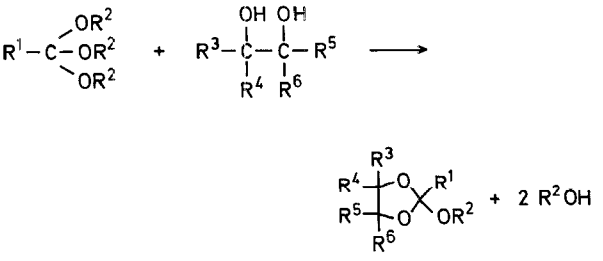
This section considers syntheses of some of the many classes of ortho esters whose orthoacyl carbons are incorporated in hetero rings.

4.1. 2-Alkoxy-1,3-dioxolanes and 2-Alkoxy-1,3-dioxanes

The largest groups of heterocyclic ortho esters are the 2-alkoxy-1,3-dioxolanes (**2**, n=2) and 2-alkoxy-1,3-dioxanes (**2**, n=3) and their derivatives. These substances are cyclic ortho esters of 1,2- and 1,3-diols, respectively. They are most conveniently prepared by transesterification of the diols with acyclic ortho esters. Other reactions may be used if a suitable ortho ester is not available for transesterification.

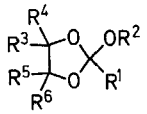
4.1.1. 2-Alkoxy-1,3-dioxolanes and 2-Alkoxy-1,3-dioxanes from Diols and Orthocarboxylates

Transesterification of *vic*-diols with trialkyl orthocarboxylates yields 2-alkoxy-1,3-dioxolanes. 2-Alkoxy-1,3-dioxanes are obtained similarly from 1,3-diols. The procedure is essentially that described for transesterification of orthoformates (see section 1.4.1): equimolar amounts of the ortho ester and diol, plus a catalytic amount of sulfuric acid, hydrogen chloride, or *p*-toluenesulfonic acid, are heated at reflux until the theoretical amount of alcohol has distilled off, and the residue is fractionally distilled to obtain the ortho ester (usually in high yield):



[77] J. M. Connolly, G. M. Dyson, *J. Chem. Soc.* **1937**, 827.
[78] H. Tieckelmann, H. W. Post, *J. Org. Chem.* **13**, 265 (1948).
[79] G. M. Dyson, "*Organic Syntheses*", Coll. Vol. I, 2nd Ed., Wiley, New York, 1951, p. 506.
[80] H. Gross, A. Rieche, E. Höft, *Chem. Ber.* **94**, 544 (1961).
[81] B. Smith, S. Delin, *Svensk. Kem. Tidskr.* **65**, 10 (1953).
[82] B. A. Arbusov, T. G. Shavsha, *Dokl. Akad. Nauk SSSR* **68**, 515 (1949).
[83] S. Sakai, Y. Kobayashi, Y. Ishii, *J. Org. Chem.* **36**, 1176 (1971).

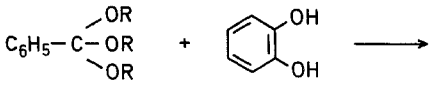
Table 4. 2-Alkoxy-1,3-dioxolanes Prepared by Transesterification Reactions

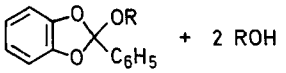


R^1	R^2	R^3	R^4	R^5	R^6	Yield (%)	References
H	CH_3,C_2H_5, C_3H_7,C_4H_9	H	H	H	H	60–90	85,86
H	C_2H_5	CH_3	H	H	H	59	85
H	C_2H_5	CH_2X(X=Cl,OAr)	H	H	H	—	87–89
H	C_2H_5	CH_3	H	CH_3	H	—	90
H	C_2H_5	$COOC_2H_5$	H	$COOC_2H_5$	H	—	91
H	C_2H_5	C_6H_5	H	C_6H_5	H	—	91
H	C_2H_5	CH_3	CH_3	CH_3	CH_3	95	90,91
CH_3	CH_3,C_2H_5	H	H	H	H	70	92,93
CH_3	CH_3,C_2H_5	CH_2X(X=Cl,Br,OAr)	H	H	H	70–75	89,94
C_2H_5	C_2H_5	*o*-CH_3—C_6H_4—OCH_2—	H	H	H	—	89
C_4H_9	CH_3	*o*-CH_3—C_6H_4—OCH_2—	H	H	H	—	89
C_6H_5	CH_3	H	H	H	H	60	95

2-Alkoxydioxolanes synthesized by this procedure are listed in Table 4.

Catechol reacts with trialkyl orthobenzoates to yield 2-phenyl-2-substituted benzodioxoles[95,96].





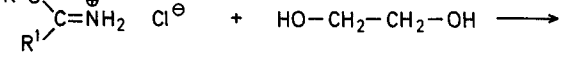
Other bicyclic ortho esters having 2-alkoxy-1,3-dioxolane rings are obtained by transesterification of *cis*- and *trans*-1,2-cyclohexanediols with triethyl orthoformate[91] and triethyl orthoacetate[97].

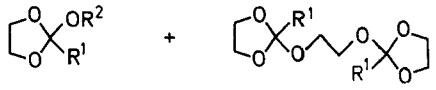
2-Alkoxy-1,3-dioxanes are obtained from 1,3-diols and trialkyl orthoformates[87,90]. *cis*-2-Hydroxymethylcyclohexanol reacts with triethyl orthoacetate to form *cis*-2-ethoxy-2-methyl-4,5-tetramethylene-1,3-dioxane[98,99].

2-Methoxy- and 2-ethoxy-1,3-dioxolanes undergo 2-alkoxy interchange when treated with alcohols in the presence of acid catalysts. 2-[2-Chloroethoxy]-[85,86], 2-menthyloxy-[86], and 2-bornyloxy-1,3-dioxolanes[86] were prepared in this manner, as were 2-butoxy-2-dichloromethyl-1,3-dioxolane[100] and 2-propoxy-2-trichloromethyl-1,3-dioxolane[101].

4.1.2. 2-Alkoxy-1,3-dioxolanes from Imidic Ester Hydrochlorides and Diols

2-Alkoxy-1,3-dioxolanes are the major products of reactions of imidate hydrochlorides with ethylene glycol. Some diortho ester is formed simultaneously.





This synthesis is useful if the corresponding acyclic ortho ester is not available for transesterification with the glycol[28,102].

2-Isopropyl-2-methoxy-1,3-dioxolane[102]:
Methyl isobutyrimidate hydrochloride (section 2.1.1) (1 mol, 137.5 g) and ethylene glycol (61.4 g, 0.99 mol) are placed in a

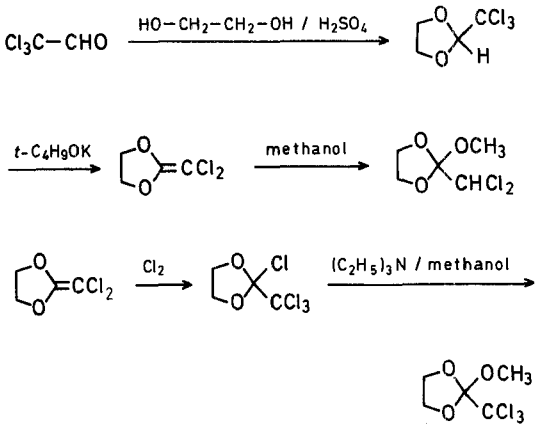
[84] G. P. Mack, E. Parker, *U.S. Patent* 2700675 (1955); *C. A.* **50**, 397 (1956).
[85] H. Baganz, L. Domaschke, *Chem. Ber.* **91**, 650 (1958).
[86] V. G. Mkhitaryan, *Zh. Obshch. Khim.* **10**, 667 (1940).
[87] R. A. Braun, *J. Org. Chem.* **31**, 1147 (1966).
[88] V. Petrow, O. Stephenson, A. M. Wild, *J. Pharm. Pharmacol.* **12**, 37 (1960).
[89] L. E. Tenenbaum, J. V. Scudi, *U.S. Patent* 2636884 (1953); *C. A.* **48**, 5227 (1954).
[90] R. C. Mehrotra, R. P. Narain, *Indian J. Appl. Chem.* **28**, 53 (1965).
[91] G. Crank, F. W. Eastwood, *Aust. J. Chem.* **17**, 1392 (1964).
[92] H. Meerwein, K. Bodenbenner, P. Borner, F. Kunert, K. Wunderlich, *Liebigs Ann. Chem.* **632**, 38 (1960).
[93] P. R. Story, M. Saunders, *J. Amer. Chem. Soc.* **84**, 4876 (1962).
[94] S. Winstein, L. Goodman, *J. Amer. Chem. Soc.* **76**, 4368 (1954).
[95] A. Rieche, E. Schmitz, E. Beyer, *Chem. Ber.* **91**, 1942 (1958).
[96] K. Dimroth, K. Schromm, *Angew. Chem.* **77**, 863 (1965); *Angew. Chem. Internat. Ed.* **4**, 873 (1965).
[97] S. Winstein, R. E. Buckles, *J. Amer. Chem. Soc.* **65**, 613 (1953).
[98] L. C. Dolby, C. N. Lieske, D. R. Rosencrantz, M. Schwartz, *J. Amer. Chem. Soc.* **85**, 47 (1963).
[99] O. J. Kovacs, G. Schneider, L. K. Lang, A. Apjok, *Tetrahedron* **23**, 4181 (1967).
[100] H. Meerwein, H. Sönke, *J. Prakt. Chem.* [2] **137**, 295 (1933).
[101] H. Meerwein, H. Sönke, *Ber. dtsch. chem. Ges.* **64**, 2375 (1931).
[102] S. M. McElvain, C. L. Aldridge, *J. Amer. Chem. Soc.* **75**, 3993 (1953).

flask fitted with a stirrer and protected from atmospheric moisture. The mixture is stirred for 10 minutes at room temperature, following which petroleum ether (b.p. 35°, 300 ml) is added and stirring is continued for 63 hours. The precipitated ammonium chloride is filtered off and washed with petroleum ether. The combined filtrate and washings are made basic by adding sodium methoxide (1.5 g). Filtration and fractional distillation of the filtrate gives 2-isopropyl-2-methoxy-1,3-dioxolane; yield: ~95 g, 66%; b.p. 60 to 66°/22 torr. Refractionation from over sodium hydride gives the pure compound, b.p. 160–160.5° at atmospheric pressure.

2-Cyclopentyl-2-methoxy-1,3-dioxolane and 2-cyclohexyl-2-methoxy-1,3-dioxolane were prepared similarly in 58% and 75% yields[31].

4.1.3. 2-Alkoxy-1,3-dioxolanes from Ketene Ethylene Acetals

2-Alkoxy-1,3-dioxolanes may be prepared by addition of alcohols to ketene ethylene acetals. The reaction is not often useful, since the ketene acetals are usually most conveniently prepared by dealcoholation of alkoxydioxolanes. It does, however, provide a route to 2-alkoxy-1,3-dioxolanes having electronegative substituents at the 2-position – compounds difficult to obtain from other starting materials. The synthesis of 2-dichloromethyl-2-methoxy-1,3-dioxolane and 2-methoxy-2-trichloromethyl-1,3-dioxolane from 2-dichloromethylene-1,3-dioxolane is illustrative:



2-Dichloromethylene-1,3-dioxolane[103]:
Equimolar amounts of ethylene glycol and chloral, plus 100 ml conc. sulfuric acid per mol of chloral, are mixed and heated two hours at 70°. The cooled mixture is poured over cracked ice and extracted with chloroform. The extract is washed with water, dried, and distilled to give 2-trichloromethyl-1,3-dioxolane; yield: ~63%; b.p. 85–86°/12 torr; m.p. 41–42°.

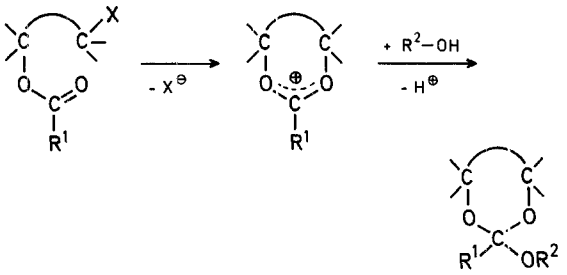
Equimolar amounts of 2-trichloromethyl-1,3-dioxolane and potassium *t*-butoxide in *t*-butyl alcohol (prepared by dissolving each mol of potassium in 820 ml of anhydrous alcohol at reflux) are mixed, and the *t*-butyl alcohol is slowly distilled from the mixture at atmospheric pressure to a final pot temperature of 160°. The mixture is fractionated at reduced pressure to obtain 2-dichloromethylene-1,3-dioxolane; b.p. 118–121°/21 torr.

2-Dichloromethyl-2-methoxy-1,3-dioxolane[103]:
2-Dichloromethylene-1,3-dioxolane reacts with an equimolar amount of methanol in the presence of a trace of hydrogen chloride to give 2-dichloromethyl-2-methoxy-1,3-dioxolane; yield: 83%; b.p. 69–70°/1.7 torr.

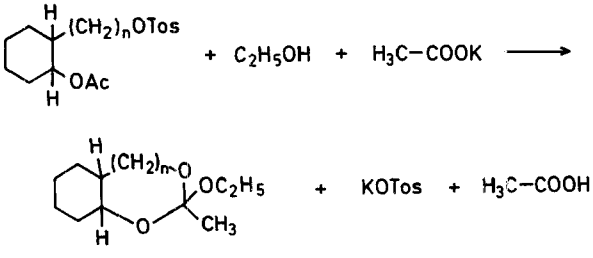
2-Methoxy-2-trichloromethyl-1,3-dioxolane[104]:
A solution of 2-dichloromethylene-1,3-dioxolane (8.5 g; 0.055 mol) in dichloromethane (25 ml) is cooled to −60°, and chlorine (3.9 g, 0.055 mol) is slowly conducted into the stirred solution by means of a stream of dry nitrogen. Then a mixture of methanol (1.92 g, 0.60 mol) and triethylamine (6.06 g, 0.060 mol) in petroleum ether (10 ml) is added dropwise to the stirred reaction mixture at 60°. The triethylaminium chloride is filtered off, and the filtrate is washed with aqueous sodium carbonate and with water, and dried over anhydrous sodium sulfate. The solvent is evaporated and the residue is recrystallized from petroleum ether to give 2-methoxy-2-trichloromethyl-1,3-dioxolane; yield: 8.3 g, 84%; m.p. 77–78°.

4.1.4. 2-Alkoxy-1,3-dioxolanes and 2-Alkoxy-1,3-dioxanes from Acyloxy Arenesulfonates and Acyloxy Halides

If an acyloxy group is properly located and oriented relative to a neighboring leaving group such as tosylate or bromide, solvolytic replacement of the leaving group in buffered alcohol solutions leads to cyclic ortho esters via dioxolenium or dioxenium ion intermediates.



For example, solvolysis of *trans*-2-acetoxycyclohexyl tosylate or *cis*- or *trans*-2-acetoxycyclohexylmethyl tosylates in absolute ethanol containing slightly more than 1 equivalent of potassium acetate affords bicyclic 2-ethoxy-1,3-dioxolanes and -dioxanes.



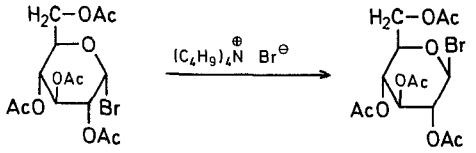
n = 0, ref. 97
n = 1, ref. 105, 106

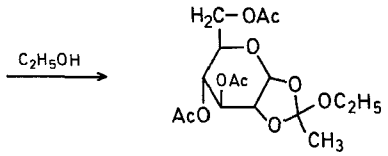
Reactions of this type are of limited utility, since the cyclic ortho esters are usually more conveniently prepared by transesterification of diols with trialkyl

[103] S. M. McElvain, M. J. Curry, *J. Amer. Chem. Soc.* **70**, 3781 (1948).
[104] H. Gross, J. Freiberg, B. Costisella, *Chem. Ber.* **101**, 1250 (1968).
[105] O. J. Kovacs, G. Schneider, K. Lang, *Proc. Chem. Soc.* **1963**, 374.
[106] G. Schneider, O. J. Kovacs, *Chem. Commun.* **1965**, 202.

orthocarboxylates. However, they are quite useful for the preparation of 1,2-*O*-ortho esters of sugars from acylglycosyl halides. Since the sugar ortho esters serve as starting materials in syntheses of disaccharides and oligosaccharides, this reaction is quite useful in synthetic carbohydrate chemistry.

Facile formation of dioxolenium ions from acylglycosyl halides occurs only if the acyloxy group and halogen are oriented *trans* to each other. Frequently the stable anomer of an acyglycosyl halide is that in which the halogen on C-1 and the acyloxy group on C-2 are *cis* on the pyranose ring. Ortho ester formation from such *cis*-acylglycosyl halides is greatly facilitated by the presence of bromide ion in the reaction mixture. Bromide ion presumably catalyzes the epimerization of the *cis*-acylglycosyl halide to the reactive *trans* anomer. The best yields of sugar ortho esters are obtained by buffering the reaction mixtures with non-nucleophilic bases such as 2,6-dimethylpyridine or 2,4,6-trimethylpyridine. The conversion of tetra-*O*-acetyl-α-D-glucopyranosyl bromide to the cyclic 1,2-*O*-orthoacetate illustrates this type of synthesis:





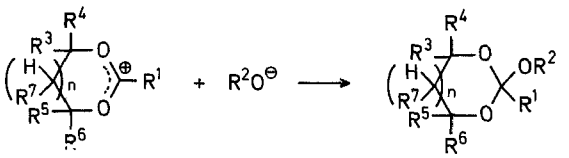
3,4,6-Tri-*O*-acetyl-1,2-*O*-(1-ethoxyethylidine)-α-D-glucopyranose[107]:

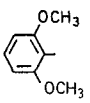
Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (4.1 g, 0.01 mol) is dissolved in a mixture of 2,4,6-trimethylpyridine (10 ml) and dry ethanol (0.6 ml, 0.01 mol). Tetra-*n*-butylaminium bromide (1.0 g, 0.003 mol) is added, and the mixture is heated at 50°, with occasional shaking, until a homogeneous solution is obtained. After 12 hours at 50° the nearly solid reaction mixture is dissolved in the minimum amount of chloroform and washed first with just enough hydrochloric acid to neutralize the trimethylpyridine, then with aqueous sodium bicarbonate, and finally with water. The chloroform layer is dried by filtration through chloroform-wetted filter paper, and the chloroform is evaporated at reduced pressure. After recrystallization of the semisolid residue from hot ethanol containing a drop of 2,4,6-trimethylpyridine and water added just to turbidity, the crystals are collected on a filter, washed with water, and dried *in vacuo*. This gives the *exo*-diastereomer of the 1,2-*O*-(ethyl orthoacetate); yield: 85%; m.p. 95–96°.

4.1.5. 2-Alkoxy-1,3-dioxolanes and 2-Alkoxy-1,3-dioxanes from Dioxolenium and Dioxenium Salts

1,3-Dioxolenium and 1,3-dioxenium salts react with alkoxides to form 2-alkoxy-1,3-dioxolanes and 2-alkoxy-1,3-dioxanes, respectively. These salts, particularly the tetrafluoroborates and hexachloroantimonates, are reasonably stable substances which can, in many instances, be prepared in excellent yields. Table 5 summarizes reported syntheses of ortho esters by reaction of alkoxides with these carbonium salts.

Table 5. 2-Alkoxy-1,3-dioxolanes and 2-Alkoxy-1,3-dioxanes from Dioxolenium and Dioxenium Salts[a]



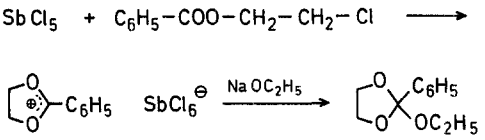
R¹	R²	R³	R⁴	R⁵	R⁶	R⁷	n	Ref
CH_3	C_2H_5	H	H	H	H	–	0	92
	C_2H_5	H	H	H	H	–	0	92
	CH_3	H	H	H	H	–	0	108
CH_3	CH_3	H	*cis*-$(CH_2)_4$–		H	–	0	109
	C_2H_5	CH_3	H_3C CH_3 | | –C=C–		CH_3	–	0	110
CH_3	C_2H_5	H	H	H	*cis*-$(CH_2)_4$–		1	99
	CH_3	H	H	H	–$(CH_2)_4$– (*cis* and *trans*)		1	111

[a] Reactions in which the carbonium salts were prepared from a 2-alkoxy-1,3-dioxolane or 2-alkoxy-2,3-dioxane are not reported here.

In addition to their facile formation from 2-alkoxy-1,3-dioxolanes or 2-alkoxy-1,3-dioxanes and proton or Lewis acids, the dioxolenium and dioxenium salts

[107] R. U. Lemieux, A. R. Morgan, *Can. J. Chem.* **43**, 2199 (1965).
[108] F. M. Beringer, S. A. Galton, *J. Org. Chem.* **32**, 2630 (1967).
[109] C. B. Anderson, E. C. Friedrich, S. Winstein, *Tetrahedron Lett.* **1963**, 2037.
[110] C. F. Wilcox, D. F. Nealy, *J. Org. Chem.* **28**, 3446 (1963).
[111] G. Schneider, L. K. Lang, *Chem. Commun.* **1967**, 13.

can be prepared from haloalkylcarboxylates and antimony pentachloride[92], boron trifluoride[92] or silver tetrafluoroborate[108,112]; from alkoxyalkyl carboxylates and trialkyloxonium tetrafluoroborates[92]; from 1,3-dioxolanes and trityl tetrafluoroborate[113]; from diols, carboxylic anhydrides and perchloric acid[114]; from 2-hydroxyethyl carboxylates and fluorosulfonic acid[115]; and from diesters of *vic*-diols and boron trifluoride[112]. The preparation of 2-phenyl-2-ethoxy-1,3-dioxolane from 2-chloroethyl benzoate illustrates this type of synthesis.

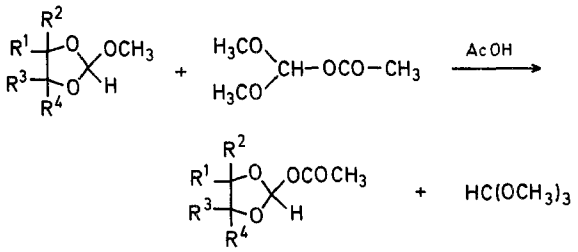


2-Ethoxy-2-phenyl-1,3-dioxolane[92]:
2-Chloroethyl benzoate (68 g, 0.37 mol) is dissolved in dichloromethane (50 ml), and to the stirred, cold (ice-salt bath) solution is added dropwise antimony pentachloride (99 g, 0.33 mol). After the reaction has subsided, the reaction mixture is allowed to come to room temperature. 2-Phenyl-1,3-dioxolenium hexachloroantimonate crystallizes from the clear, yellow solution after 1–2 hours. After standing overnight, the reaction mixture is diluted with dichloromethane (50 ml), the crystalline mass is pulverized and collected by suction filtration, and washed on the filter with dichloromethane (50 ml). The yield of 2-phenyl-1,3-dioxolenium hexachloroantimonate is about 129 g (81%), m.p. 210°.

The dioxolenium salt (96.8 g, 0.2 mol) is added, with careful exclusion of atmospheric moisture, to a cold (ice-salt bath) solution of sodium (10 g) in absolute ethanol (250 ml). After allowing the mixture to stand for a short period, alcohol is distilled off and the residue is extracted with ether. The filtered extract is distilled to give 2-ethoxy-2-phenyl-1,3-dioxolane; yield: 11.5 g, 30%; b.p. 121–126°/12 torr.

4.2. 2-Acetoxy-1,3-dioxolanes and 2-Acetoxy-1,3-benzodioxole

2-Acetoxy-1,3-dioxolanes and 2-acetoxy-1,3-benzodioxole can be prepared by a procedure[116] similar to that described in section 1.4.3 for the preparation of dialkoxymethyl acetates. Several 2-acetoxy-1,3-dioxolanes were prepared in 75–83% yields by reaction of the 2-methoxy-1,3-dioxolanes with dimethoxymethyl acetate:



$R^1 = R^2 = R^3 = H, R^4 = H, CH_3, CH_2Cl;$

$R^1 = R^3 = H, R^2 = R^4 = CH_3;$

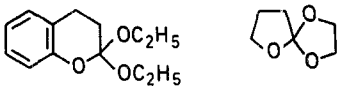
$R^1 = R^2 = R^3 = R^4 = CH_3$

The equilibrium is displaced to the right by distilling off the most volatile component of the reaction mixture, trimethyl orthoformate.

2-Acetoxy-1,3-dioxolanes[116]:
An equimolar mixture of the 2-methoxy-1,3-dioxolane and dimethoxymethyl acetate, and twice the molar amount of acetic acid, is refluxed for about 10 hours at a pressure of 15–20 torr. The mixture is then fractionally distilled with an efficient column, taking care that the pot temperature does not exceed 60°. Thus prepared are: *2-acetoxy-1,3-dioxolane*; b.p. 42–43°/0.4 torr; *2-acetoxy-4-methyl-1,3-dioxolane*, b.p. 44–45°/0.6 torr; *2-acetoxy-4-chloromethyl-1,3-dioxolane*, b.p. 74–75°/0.5 torr; *2-acetoxy-4,5-dimethyl-1,3-dioxolane*, b.p. 46–48°/0.5 torr; and *2-acetoxy-4,4,5,5-tetramethyl-1,3-dioxolane*, b.p. 50–51°/0.4 torr.

4.3. Lactone Acetals

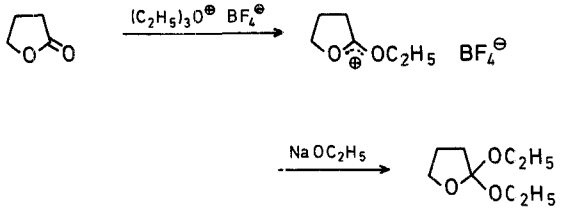
A number of heterocyclic ortho esters may be regarded as acetals of γ- or δ-lactones. These include monocyclic compounds such as 2,2-dialkoxytetrahydrofurans (**3**), bicyclic substances such as 2,2-diethoxychroman (**6**), and spirocyclic ortho esters such as 1,4,5-trioxaspiro[4.4]nonane (**7**).



6 **7**

4.3.1. Lactone Acetals from O-Alkyllactonium salts

γ- And δ-lactones are alkylated on carbonyl oxygen by trialkyloxonium tetrafluoroborates. The resulting *O*-alkyllactonium salts are converted to lactone acetals by treatment with alkoxides. The synthesis of 2,2-diethoxytetrahydrofuran from γ-butyrolactone is typical[117].



2,2-Diethoxytetrahydrofuran:
Triethyloxonium tetrafluoroborate is added to an equimolar amount of dry γ-butyrolactone. The salt dissolves, and the solution soon becomes colored and separates into two layers. After three days the layers are separated. The lower layer solidifies to a crystalline mass when cooled. Suction filtration of the cold, crude product (with exclusion of atmospheric moisture) gives the extremely hygroscopic *O*-ethyllactonium tetrafluoroborate; yield: 87%.

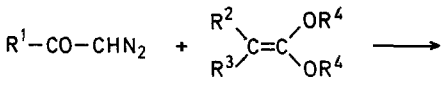
[112] H. Meerwein, V. Hederich, K. Wunderlich, *Arch. Pharm.* **291**, 541 (1958).
[113] H. Meerwein, V. Hederich, H. Moschel, K. Wunderlich, *Liebigs Ann. Chem.* **635**, 1 (1960).
[114] G. N. Dorofeenko, L. V. Mezherilskaya, *Zh. Obshch. Khim.* **38**, 1192 (1968).
[115] D. A. Tomalia, *U.S. Patent* 3480649 (1969); *C. A.* **72**, 31808 (1970).
[116] J. W. Scheeren, A. P. M. van der Veek, W. Stevens, *Rec. Trav. Chim. Pays-Bas* **88**, 195 (1969).
[117] H. Meerwein, P. Borner, O. Fuchs, H. J. Sasse, H. Schrodt, J. Spille, *Chem. Ber.* **89**, 2060 (1956).

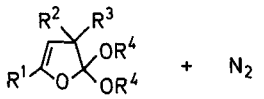
A solution of the lactonium salt (101 g, 0.5 mol) in dichloromethane (70 ml) is cooled in an ice bath, and a solution of sodium (13.8 g, 0.6 mol) in absolute ethanol (250 ml) is added dropwise, with stirring. The mixture is stirred for one hour after the addition is complete, and then mixed with 3–4 times its volume of dilute aqueous sodium carbonate and extracted with ether. The ether layer is separated and dried over anhydrous potassium carbonate. The ether is distilled off and the residue fractionally distilled to give 2,2-diethoxytetrahydrofuran: yield: ~68%, 85%; b.p. 60–61.5°/10 torr.

Other lactone acetals prepared from *O*-alkyllactonium salts include 2,2-dimethoxytetrahydrofuran[117], 2,2-diethoxy-2,5*H*-dihydro-3,4-benzofuran[117], 2,2-diethoxychroman (**6**)[118], and 2,2-dimethoxy- and 2,2-diethoxybenzo-2*H*-pyrans[118].

4.3.2. Lactone Acetals from Ketene Acetals

Diazomethyl ketones react with ketene acetals to form 2,2-dialkoxy-2,3-dihydrofurans[119].





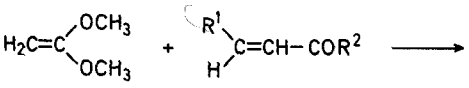
R^1 = CH_3, C_2H_5,  , O_2N-  , H_3CO-  ;

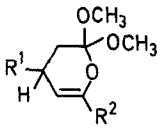
R^2 and R^3 = H or CH_3;

R^4 = CH_3, C_2H_5

Yields of substituted dialkoxydihydrofurans are fair to good. The products can be hydrogenated to 5-substituted-2,2-dialkoxytetrahydrofurans.

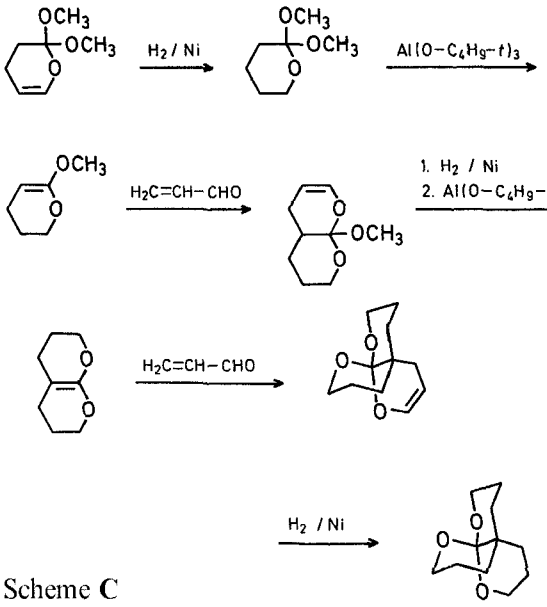
2,2-Dimethoxy-2,3-dihydropyran derivatives are obtained from [4+2] cycloaddition reactions of ketene dimethyl acetal with α,β-unsaturated carbonyl compounds[120].





R^1 = R^2 = H; R^1 = C_6H_5, R^2 = H, CH_3

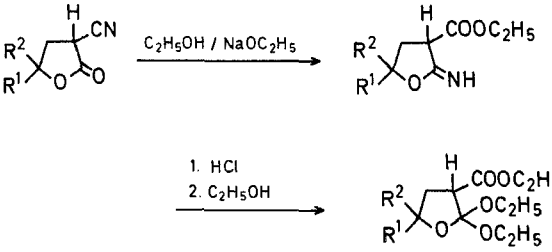
The dihydropyran derivatives can be hydrogenated to the corresponding 2,2-dimethoxytetrahydropyrans[121]. 2,2-Dimethoxy-2,3-dihydropyran is the starting material for an interesting series of bicyclic and tricyclic ortho esters (Scheme **C**).



Scheme **C**

4.3.3. Lactone Acetals from 2-Iminofurans and 2-Iminopyrans

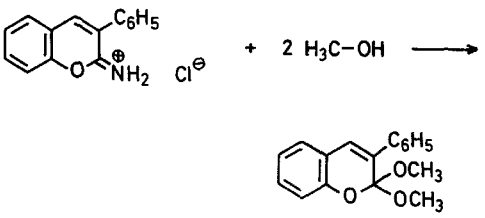
2-Iminofurans and 2-iminopyrans are cyclic imidic esters, and alcoholysis of their conjugate acids yields lactone acetals. 2-Amino-3-ethoxycarbonyl-4,5-dihydrofurans are obtained by ethanolysis of α-cyano-γ-lactones; ethanolysis of their hydrochlorides gives the corresponding 2,2-diethoxy-3-ethoxycarbonyltetrahydrofurans[122].



R^1 = R^2 = H

R^1 = H, CH_3; R^2 = H

3-Phenylcoumarin dimethyl acetal was obtained from 3-phenylcoumarinimide (which is prepared from salicylaldehyde and phenylacetonitrile)[123,124].



[118] H. Meerwein in Houben-Weyl, "*Methoden der Organischen Chemie*" (E. Müller, Ed.), Vol. VI, Part 3, G. Thieme, Stuttgart, 1965, p. 361.

[119] R. Scarpati, M. Cioffi, G. Scherillo, R. A. Nicolaus, *Gazz. Chim. Ital.* **96**, 1164 (1966).

[120] S. M. McElvain, E. R. Degginger, J. D. Behun, *J. Amer. Chem. Soc.* **76**, 5736 (1954).

[121] S. M. McElvain, G. R. McKay, *J. Amer. Chem. Soc.* **77**, 5601 (1955).

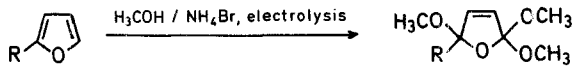
[122] F. Korte, K. Trautner, *Chem. Ber.* **95**, 281 (1962).

[123] R. Kuhn, D. Wieser, *Angew. Chem.* **69**, 371 (1957).

[124] R. Kuhn, D. Wieser, *Liebigs Ann. Chem.* **600**, 144 (1960).

4.3.4. 2,2-Dimethoxy-2,5-dihydrofurans by Electrochemical Methoxylation of Furans

Electrolysis of furan and 2-substituted furans in methanolic ammonium bromide under the proper conditions affords 2,2,5-trimethoxy-2,5-dihydrofuran derivatives[125].

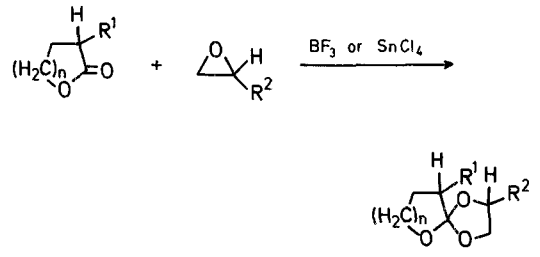


R = H, $-CH(OCH_3)_2$, $-COOCH_3$

2-Bromofurans are probably intermediates under these reaction conditions, and the same products are obtained by electrolyzing them in methanolic sulfuric acid solutions[126].

4.3.5. Spirocyclic Lactone Acetals from Lactones and Epoxides

Epoxides add to the carbonyl groups of γ- and δ-lactones in the presence of Lewis acids to form spirocyclic lactone acetals[127].



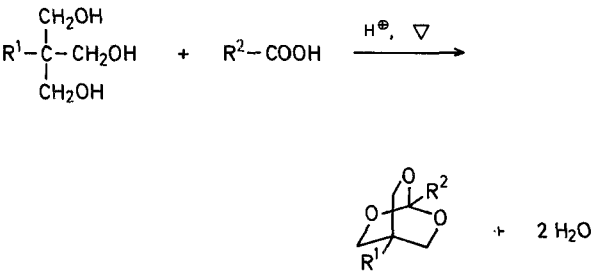
n = 1, R^1 = H, R^2 = H, CH_3, CH_2Cl, $CH_2OC_6H_5$;
n = 1, R^1 = Cl, R^2 = CH_2Cl;
n = 2, R^1 = H, R^2 = CH_2Cl.

Coumarin and phthalide are converted to the benzo-substituted spirocyclic lactone acetals under the same reaction conditions.

2-Chloromethyl-1,4,6-trioxaspiro[4.4]nonane:
A mixture of γ-butyrolactone (43 g, 0.5 mol), epichlorohydrin (55 g, 0.6 mol), and carbon tetrachloride (150 ml) is added dropwise to a stirred solution of tin(IV) chloride (10 g) in carbon tetrachloride (100 ml). The temperature of the reaction mixture is kept between 28–32° by occasional cooling. At the beginning of the reaction a white precipitate forms, which soon disappears. The reddish reaction mixture is extracted with aqueous 10% sodium hydroxide solution (250 ml). The organic phase is washed twice with water, dried over anhydrous potassium carbonate, and fractionally distilled to give 2-chloromethyl-1,4,6-trioxaspiro-[4.4]nonane; yield: ~61 g, 68%; b.p. 100–104°/13 torr. A 64% yield was obtained using boron trifluoride etherate as the catalyst.

4.4. 2,6,7-Trioxabicyclo[2.2.2]octanes

Most ortho esters are so thermodynamically unstable relative to their hydrolysis products that they cannot be prepared directly from carboxylic acids and alcohols. 2,6,7-Trioxabicyclo[2.2.2]octanes (**4**) are exceptions to this generalization: several of them have been prepared by direct orthoesterification of 2-substituted-2-hydroxymethyl-1,3-propanediols.



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Apparently the contribution of the entropy term to the free energy change accompanying this reaction (in which there are more product than reactant molecules) is sufficient to shift the equilibrium much further toward the ortho ester than is normally the case. The reaction is further aided by the facts that the triols used are not susceptible to dehydration, and that the equilibrium can be shifted toward products by azeotropic removal of the water. This reaction is most rapid with acids having electronegative acyl substituents, but is successful with other carboxylic acids also.

4-Methyl-1-trichloromethyl-2,6,7-trioxabicyclo[2.2.2]octane[128]: Trichloroacetic acid (81.7 g, 0.5 mol), 2-hydroxymethyl-2-methyl-1,3-propanediol (60 g, 0.5 mol), *p*-toluenesulfonic acid (6 g), and xylene (400 ml) are refluxed, using a Dean-Stark trap to remove water formed during the reaction. Water (~16 ml, 90%) is collected over a period of 12 to 15 hours. When the reaction mixture is chilled, crude product (about 33 g) precipitates and is filtered off. Both the precipitate and filtrate are washed with sodium carbonate solution. Evaporation of the xylene from the filtrate yields additional product. Recrystallization of the crude product from benzene gives the ortho ester; yield: 51 g, 41%; m.p. 218–221° (sealed capillary).

Other 1-R^2-4-R^1-2,6,7-trioxabicyclo[2.2.2]octanes (**4**) which have been prepared by direct ortho esterification of the triols include: **4**, $R^1 = CH_3$, $R^2 = CH_3$[129], CF_3[128,129], CCl_3[128], $CHCl_2$[128], CH_3CCl_2[128], 3,5-$(NO_2)_2C_6H_3$[128], $C(CH_3)_3$[131]; $R^1 = C_2H_5$, $R^2 = H$[129], CH_3[129], CH_2Cl[129], $C(CH_3)_3$[129], *n*-C_5H_{11}[129], *n*-C_6H_{13}[129]; and $R^1 = C_3H_7$, $R^2 = C_2H_5$[129].

Trioxabicyclooctanes are also obtained by transesterification of trialkyl orthocarboxylates with 2-hydroxymethyl-1,3-propanediols. The first reported member of this class of ortho esters (**4**, $R^2 = H$, $R^1 = CH_3$) was thus prepared[132]. Other tri-

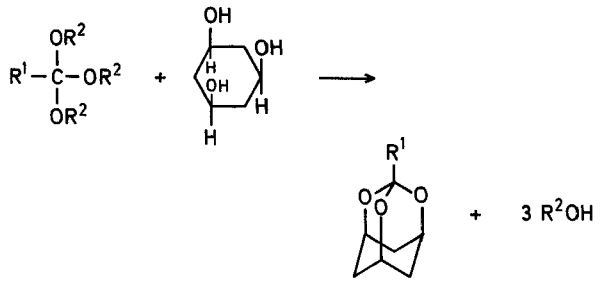
[125] S. Hillers, G. P. Sokolov, A. Y. Karmilchik, *C. A.* **62**, 6449 (1965).
[126] G. P. Sokolov, S. Hillers, *Khim. Geterosikl. Soedin.* **1965**, 163.
[127] K. Bodenbenner, *Liebigs Ann. Chem.* **623**, 183 (1959).
[128] R. A. Barnes, G. Doyle, J. A. Hoffman, *J. Org. Chem.* **27**, 90 (1962).
[129] Celanese Corp. of America, *Netherlands Appl.* 6412635 (1965); *C. A.* **63**, 16370 (1965).
[130] R. L. Talbot, *J. Org. Chem.* **32**, 834 (1967).
[131] S.-C. Lu, *M. A. Thesis*, University of California, Santa Barbara 1967.
[132] W. von E. Doering, L. K. Levy, *J. Amer. Chem. Soc.* **77**, 509 (1955).

oxabicyclooctane derivatives prepared by transesterification include: **4**, $R^1=CH_3$, $R^2=CH_3$[131], C_2H_5[131], C_6H_5[131]; and $R^1=C_2H_5$, $R^2=H$, CH_3[133].

Perfluoro-1,4-dimethyl-2,6,7-trioxabicyclo[2.2.2]octane was synthesized by direct fluorination of **4**, $R^2=CF_3$, $R^1=CH_3$[130].

4.5. 2,4,10-Trioxaadamantanes

Reactions of acyclic ortho esters with all-*cis*-1,3,5-cyclohexanetriol yield a group of ortho esters having interesting chemical and stereochemical properties.



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These compounds, which have the rigid tricyclic ring system of adamantane, were christened trioxaadamantanes by Stetter[134]. They are named systematically as derivatives of 2,4,10-trioxatricyclo-[3.3.1.$1^{3,7}$]decane (**5**, $R^1=H$), and are conveniently synthesized by heating the cyclohexanetriol with the appropriate trimethyl or triethyl orthocarboxylate in methanolic hydrogen chloride solution.

3-Substituted-2,4,10-trioxaadamantanes[134]:
Anhydrous, finely powdered all-*cis*-1,3,5-cyclohexanetriol [prepared by Raney-nickel catalyzed hydrogenation of phloroglucinol[135] (see ref. 136 for a superior catalyst)] (0.1 mol, 13.2 g) and the methyl or ethyl orthocarboxylate (0.2 mol) are dissolved in absolute methanol (50 ml) containing hydrogen chloride (0.5 g, or a little boron trifluoride). The reaction mixture is agitated frequently at room temperature until the triol dissolves. After a day anhydrous potassium carbonate is added to neutralize the catalyst, and the solution is evaporated to dryness in vacuo. The residue is extracted with ether, leaving behind the salts and any unreacted triol. Evaporation of the ether leaves the tricyclic ortho ester, usually in yields exceeding 70% of theory.

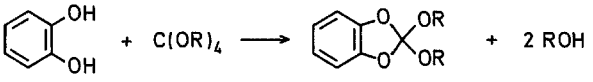
Ortho esters prepared in this way include **5**, $R^1=H$[134], CH_3[134], CH_2Cl[134], CH_2Br[134], C_2H_5[134], C_6H_5[134], $C_2H_5OCO(CH_2)_2$[137], $C_2H_5OCOCH_2$[138], and $HC\equiv C(CH_2)_n$ (n=3,4)[139].

Formation of 3-substituted-2,4,10-trioxaadamantanes provides a useful means of protecting carboxyl functions during multistep syntheses. The tricyclic ortho ester function is inert to Grignard reagents, alkali, metal hydrides, diazomethane, acid chlorides, and hydrogen in the presence of palladium, and is less reactive toward acid hydrolysis than most ortho esters. For synthetic sequences involving chemical transformations of the orthoacyl substituents of these tricyclic ortho esters, see references 134, 137–139.

4.6. Heterocyclic Orthocarbonates

4.6.1. 1,3-Benzodioxole Derivatives

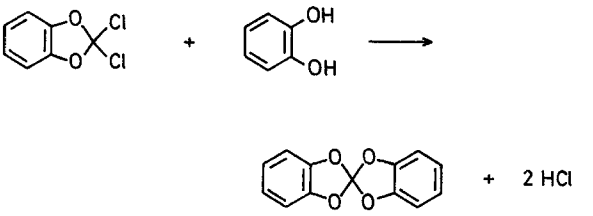
2,2-Dialkoxy-1,3-benzodioxoles are formed in excellent yields by heating equimolar amounts of pyrocatechol and a tetraalkyl orthocarbonate together[140,141].



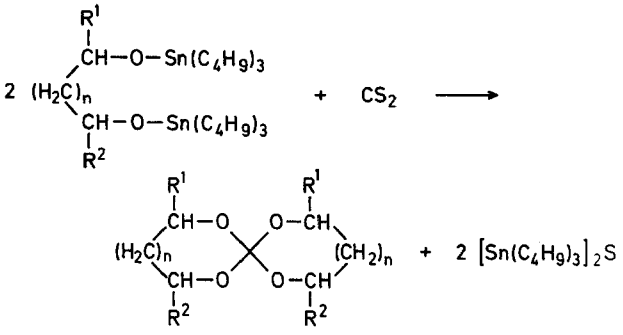
They are also obtained by reaction of 2,2-dichlorobenzodioxole (prepared from pyrocatechol carbonate[80], 2-ethoxy-1,3-benzodioxole[80], or 1,3-benzodioxole[142] and phosphorus pentachloride) with alcoholic sodium alkoxides[140] or with alcohols in the presence of tertiary amines[140]. 2,2-Diphenoxy-1,3-benzodioxole[80] and its 5-*n*-propyl derivative[142] are the products of reactions of phenol with the 2,2-dichloro-1,3-benzodioxoles.

4.6.2. Spirocyclic Orthocarbonates

2,2-Dichloro-1,3-benzodioxole and pyrocatechol react to form the spirocyclic orthocarbonate 2,2′-spirobis[1,3-benzodioxole][80].



Spirocyclic orthocarbonates are formed in moderate yields by the reaction of bis[tributyltin] alkylene glycolates with carbon disulfide[143], and in good yields from carbon disulfide and cyclic dibutyltin dialkoxides[83].



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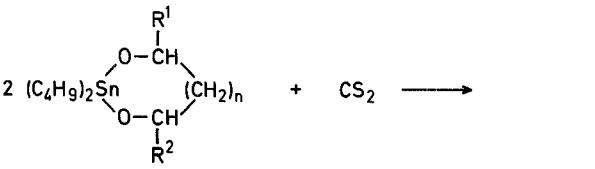

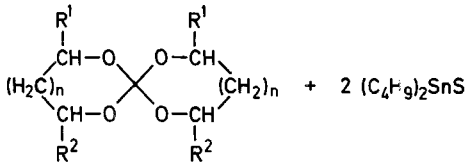

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$R^1 = R^2 = H$, $n = 0, 1, 2$;

$R^1 = H, R^2 = CH_3$, $n = 0$;

$R^1 = R^2 = CH_3$, $n = 0$.

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