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Synthesis of Acetylenic Acetals, Ketals and Orthoesters

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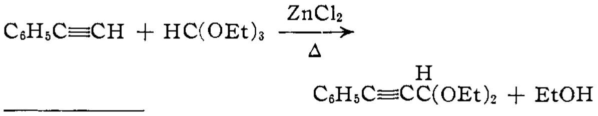
Synthesis of acetylenic acetals or ketals by the zinc halide-catalyzed reaction of a monosubstituted acetylene with an orthoester is described. The method appears to be general and gives yields ranging from 15 to 80%, depending upon the reactant combination employed. Acetylene itself undergoes this catalytic reaction with triethyl orthoformate to give the expected acetal in 48% yield, along with smaller amounts of malonaldehyde bis-(diethyl acetal). An extension to the synthesis of an acetylenic orthoester by the analogous interaction of tetraethyl orthocarbonate with phenylacetylene has also been made.

Acetylenic acetals in which the ethynyl group is attached to the acetal group have been known for a long time and have found various applications as organic intermediates. The synthesis of this class of compounds generally has involved dehydrohalogenation procedures for forming the ethynyl group.[1] Acetylenic acetals also have been prepared by the reaction of an acetylenic Grignard reagent or a sodium acetylide with an orthoformate.[2] There appears to be only a single example of an acetylenic orthoester,[3] namely, $C_6H_5C{\equiv}C{-}C(OC_2H_5)_3$. This compound was made by adding tetraethyl orthocarbonate to an equivalent amount of the phenylacetylenic Grignard reagent. Acetylenic ketals have not been reported previously in the literature.

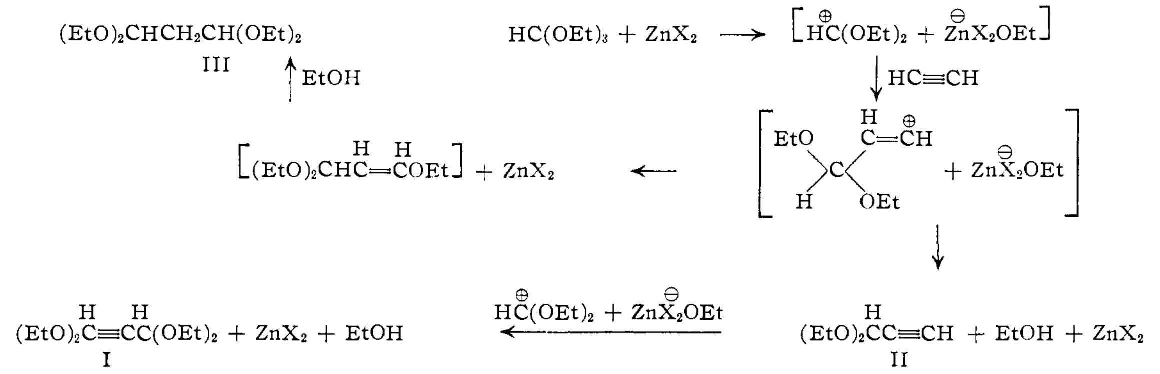
This paper describes the synthesis of these classes of compounds by a one-step catalytic process from readily available starting materials. The method is illustrated below for the synthesis of phenylpropiolaldehyde diethylacetal.



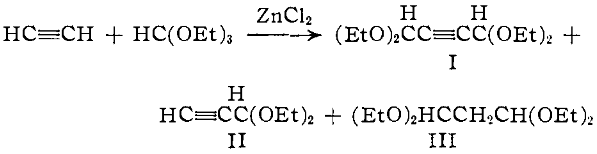
$$C_6H_5C{\equiv}CH + HC(OEt)_3 \xrightarrow[\Delta]{ZnCl_2} C_6H_5C{\equiv}C\overset{H}{C}(OEt)_2 + EtOH$$

Molar equivalents of the acetylene and orthoester are heated in the presence of the catalyst at atmospheric pressure, removing the alcohol as it forms. The alcohol begins distilling out of the reaction mixture at a flask temperature of about 135°, and the last of the alcohol is removed as the flask temperature reaches 200°.

The reactions in general are complete for one-half mole size runs in 0.4–3.0 hr. and the yields have ranged from 15 to 80%. With low-boiling acetylenes, such as 1-hexyne, the reaction must be carried out in a rocker bomb under autogenous pressure. The most effective catalysts found in this study are zinc chloride, zinc iodide, zinc nitrate and cadmium iodide.



Acetylene itself reacts under pressure with triethyl orthoformate to give mainly acetylenedicarboxaldehyde bis-(diethyl acetal) (I) in yields up to 48%, along with very small amounts of propiolaldehyde diethyl acetal (II). Malonaldehyde bis-(diethyl acetal) (III) has been obtained as a by-product in amounts ranging up to 28%.



$$HC{\equiv}CH + HC(OEt)_3 \xrightarrow{ZnCl_2} \underset{I}{(EtO)_2\overset{H}{C}C{\equiv}C\overset{H}{C}(OEt)_2} + \underset{II}{HC{\equiv}C\overset{H}{C}(OEt)_2} + \underset{III}{(EtO)_2HCCH_2CH(OEt)_2}$$

An ionic mechanism to account for the formation of these products is proposed as shown above.

The method appears to be a general one, and extensions to a variety of orthoesters and monosubstituted acetylenes have been made. For example, the reaction of phenylacetylene with triethyl orthoacetate or trimethyl orthovalerate has led to the formation of acetylenic ketals, representatives of a new class of compounds.

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[1] W. E. Bachmann, *Org. Syntheses*, **25**, 92 (1945); G. W. Hearne, H. L. Yale and M. C. Hoff, U. S. Patent 2,508,257 (1950).

[2] J. Chauvelier and M. Eugene, *Bull. soc. chim. France*, [5] **17**, 272 (1950); F. A. Raphael, "Acetylenic Compounds in Organic Syntheses," Butterworths Scientific Publications, London, England, 1955, pp. 68–75; A. Wohl and E. Bernreuther, *Ann.*, **481**, 1 (1930); M. J. Grard, *Compt. rend.*, **189**, 541 (1929); **189**, 925 (1929); A. Wohl and K. Jaschinowski, *Ber.*, **54**, 472 (1921); K. Henkel and F. Weygand, *ibid.*, **76**, 812 (1943); N. A. Preobrazhenskii, *C. A.*, **40**, 6488 (1946); E. Charon and E. Dugoujon, *Compt. rend.*, **137**, 126 (1903); J. P. Wibaut, *C. A.*, **45**, 5167 (1951); C. Moureu and R. Delange, *Compt. rend.*, **133**, 106 (1901); M. J. Grard, *Ann. chim.*, **13**, 336 (1930); C. Moureu and R. Delange, *Compt. rend.*, **138**, 1341 (1904).

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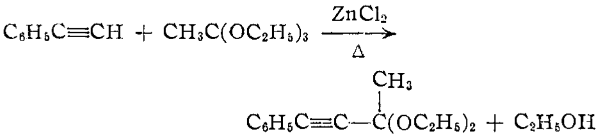
Table I

Catalytic Synthesis of Ethynyl Acetals, Ketals and Orthoesters from Monosubstituted Acetylenes

Acetylene	Orthoester	Reaction conditions	Product[a]	Yield, %	Carbon % Calcd. Found	Hydrogen % Calcd. Found	B.p. °C.	Mm.	$n^{25}D$
n-$C_4H_9C{\equiv}CH$	$HC(OC_2H_5)_3$	190°/3 hr. in closed bomb; $ZnI_2/ZnCl_2$ catalyst; 0.7 mole scale	$n\text{-}C_4H_9C{\equiv}C\overset{H}{C}(OC_2H_5)_2$	32.0	71.7 71.8	10.9 10.8	90	10	1.4327
$C_6H_5C{\equiv}CH$	$CH_3C(OC_2H_5)_3$	Ethyl alcohol removed in 3.7 hr.; $ZnCl_2$ catalyst; 0.4 mole scale	$C_6H_5C{\equiv}CCCH_3(OC_2H_5)_2$[b]	34.0	77.0 76.8	8.3 8.3	92	3	1.5115
$C_6H_5C{\equiv}CH$	n $C_4H_9C(OCH_3)_3$	Methanol removed in 3.0 hr.; $ZnI_2/ZnCl_2$ catalyst; 0.15 mole scale	$C_6H_5C{\equiv}CC_4H_9(OCH_3)_2$[c]	40.0			121–124	5	1.5339
$C_6H_{11}CH_2C{\equiv}CH$[d]	$HC(OC_2H_5)_3$	Ethyl alcohol removed in 1.8 hr.; $ZnI_2/ZnCl_2$ catalyst; 0.18 mole scale	$C_6H_{11}CH_2C{\equiv}C\overset{H}{C}(OEt)_2$[d]	54.0	75.1 75.1	10.7 10.8	98–100	3	1.4623
$C_6H_5C{\equiv}CH$	$C(OC_2H_5)_4$	Ethyl alcohol removed in 1.8 hr.; $ZnCl_2$ catalyst; 0.2 mole scale	$C_6H_5C{\equiv}CC(OC_2H_5)_3$	14.2	72.6 71.9	8.1 8.3	126	5	1.5004

[a] Infrared spectra, obtained for all products, were consistent with the structures as written. Absorption for internal —C≡C— at 4.45 or 4.50 μ, and for ether –C–O– in the 9μ region was noted. [b] This ketal was converted into the 2,4-dinitrophenylhydrazone of the corresponding ketone, m.p. 195–198°. *Anal.* Calcd. for $C_{16}H_{12}N_4O_4$: C, 59.3; H, 3.7; N, 17.3. Found: C, 59.3; H, 3.9; N, 17.0. [c] This ketal was converted into the 2,4-dinitrophenylhydrazone of the corresponding ketone, m.p. 130–131°. *Anal.* Calcd. for $C_{19}H_{18}N_4O_4$: C, 62.4; H, 4.9; N, 15.3. Found: C, 62.1; H, 5.0; N, 15.1. [d] C_6H_{11} = cyclohexyl.



$$C_6H_5C{\equiv}CH + CH_3C(OC_2H_5)_3 \xrightarrow[\Delta]{ZnCl_2} C_6H_5C{\equiv}C{-}\overset{CH_3}{\overset{|}{C}}(OC_2H_5)_2 + C_2H_5OH$$

Tetraethyl orthocarbonate reacted similarly to the orthoesters, leading to an acetylenic orthoester as the product

$$C_6H_5C{\equiv}CH + C(OEt)_4 \xrightarrow[\Delta]{ZnCl_2} C_6H_5C{\equiv}CC(OEt)_3 + EtOH$$

Experimental

Materials.—Commercial-grade acetylene was purified according to a previously described procedure.[4] The substituted acetylenes, orthoesters and tetraethyl orthocarbonate were obtained from commercial sources and were purified by distillation.

Analytical Data.—The infrared spectra were determined on a Perkin–Elmer 21 double-beam spectrometer. Melting points are uncorrected, and yields are based on the amount of orthoester consumed.

Synthesis of Phenylpropiolaldehyde Diethyl Acetal.—A mixture of triethyl orthoformate (74 g.), phenylacetylene (51 g.) and zinc iodide (3 g.) was heated in a flask attached to a 14-inch still equipped with variable take-off. When the still-flask temperature reached 135°, ethyl alcohol started refluxing. During about one hour a total of 26.4 g. of distillate, b.p. 65–88° (mostly 78°), was removed as the temperature of the reaction mixture gradually rose to 200°. The reaction mixture was then cooled to room temperature and filtered. The flask and a small amount of precipitate on the filter paper were washed with 5 ml. of ether. The filtrate and ether washing were combined and distilled. The acetal fraction distilling at 99–100° (2 mm.) weighed 80.3 g. (79%, $n^{25}D$ 1.5152). The boiling point, refractive index and infrared spectrum of phenylpropiolaldehyde diethyl acetal prepared by this method were identical with those of an authentic sample prepared by the Grignard method.[5] The infrared spectrum showed absorption at 4.5 μ for –C≡C— and broad, strong absorption in the 9 μ region for ether —C—O—.

Extensions of the Ethynylation Reaction to Other Acetylenes and Orthoesters.—Several combinations of acetylenes and orthoesters gave acetylenic acetals or ketals by heating in the presence of zinc halides as catalysts. Likewise, triethyl orthophenylpropiolate was prepared from phenylacetylene and tetraethyl orthocarbonate. These results, along with the analytical data, are summarized in Table I.

Synthesis of Acetylenedicarboxaldehyde Bis-(diethyl Acetal) (I).—A 500-ml. stainless steel rocker bomb was swept out with oxygen-free nitrogen and was then charged with 156 g. of triethyl orthoformate and 4 g. of zinc chloride. The bomb was closed, pressure tested with nitrogen, cooled in a mixture of solid carbon dioxide–methanol, and evacuated to 5 mm. pressure. The bomb was installed behind a heavy barricade, and all operations were controlled from the outside. With a bomb temperature of 27°, acetylene was introduced to a bomb gauge reading of about 15 atmospheres, and the reaction mixture heated to 170° during a period of 2 hours. During this period the pressure reached a maximum of about 32 atmospheres and then dropped steadily to 17 atmospheres. The pressure was maintained at 12–17 atmospheres by periodic repressuring with acetylene for 7 hours while maintaining the temperature at 170°. The bomb was then cooled to room temperature, pressure released, and contents removed. The reaction mixture was filtered to remove a small amount of a solid cuprene-like product and the filtrate distilled. After recovering 72.3 g. of triethyl orthoformate (b.p. 50–55° (24 mm.), $n^{25}D$ 1.3911), there were obtained 9 g. of an intermediate cut (b.p. 40–86° (2 mm.)) and 18 g. of I (b.p. 91–94°) (1 mm.), $n^{25}D$ 1.4306, m.p. 17–18.5°. This represents a 31% yield; in cases where several runs were combined prior to work-up, yields of the bisacetal were as high as 48%.

Additional Characterization of I.—In addition to agreement of refractive index and melting point with reported values,[6] the infrared spectrum was consistent with the bisacetal structure. Absorption at 3.35 and 3.45 μ and broad, strong absorption in the 9 μ region indicate saturated CH and ether –C–O–, respectively. There was no absorption for the symmetrically located —C≡C—, as expected. *Anal.* Calcd. for $C_{12}H_{22}O_4$: C, 62.6; H, 9.6; OEt, 78.3. Found: C, 62.9; H, 9.8; OEt, 78.2. An ethyl alcohol solution of I was hydrogenated to completion over palladium-on-carbon catalyst. A portion of the solution was treated with 2,4-dinitrophenylhydrazine reagent. The resulting bis-2,4-dinitrophenylhydrazone of succinaldehyde melted at 260–262°.[7]

Isolation and Identification of Malonaldehyde Bis-(diethyl Acetal) (III).[8]—From a composite (95 g.) of the lower boiling fractions of similar runs, there was obtained

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[4] J. C. Sauer, This Journal, **79**, 5314 (1957).

[5] C. Moureu, *Compt. rend.*, **133**, 106 (1901).

[6] C. Moureu, *Ann. chim.*, [8] **7**, 550 (1906); K. Henkel and F. Weygand, *Ber.*, **76**, 812 (1943).

[7] A. C. Cope and W. R. Schmitz, This Journal, **72**, 3056 (1950), report m.p. 262–264°.

[8] This portion of the work was carried out by Dr. J. C. Collins, to whom acknowledgment is made.

TABLE II

CATALYST EVALUATION

$$C_6H_5C\equiv CH + HC(OEt)_3 \xrightarrow[\Delta]{\text{cat.}} C_6H_5C\equiv C\overset{H}{C}(OEt)_2 + EtOH$$

Catalyst, g.	Time, hr.	Ethyl alcohol, g.	Yield of acetal, %
None	2.0	None	None
2, ZnI$_2$	0.4	15.5	71
2, ZnCl$_2$[b] (coml.)	1.7	17.0	64.0
1.5, ZnCl$_2$ (coml.)	3.5	12.4	53.5
10, ZnCl$_2$[a,b]	3.2	..	28.3
2, ZnBr$_2$	3.0	28.9	11.8
2, Zn(NO$_3$)$_2$	0.4	15.5	71
2, ZnSO$_4$	5.7	8.0	29.4
2, Zn(OAc)$_2$·2H$_2$O	3.5	8.8	37.1
2, (C$_{17}$H$_{35}$COO)$_2$Zn	5.5	29.5	6.3
2, Zn formate	5.0	8.7	31
2, Zn molybdite	4.7	10.0	7.4
2, CdI$_2$	3.0	16.0	72.3
2, CdI$_2$	1.5	7.4	45.5
2, CdCl$_2$	9.0	5.0	22.5
2, HgBr$_2$	7.0	10.5	20.6
2, HgI$_2$	2.5	3.5	Not isolated
2, MgCl$_2$	3.0	14	8.1

[a] Freshly fused. [b] Slightly larger charge of reactants used in this run.

55 g. of malonaldehyde bis-(diethyl acetal), b.p. 108° (20 mm.), $n^{25}D$ 1.4099. *Anal.* Calcd. for $C_{11}H_{24}O_4$: C, 60.0; H, 11.0; OEt, 81.8. Found: C, 61.5; H, 11.1; OEt, 81.1. The infrared spectrum of III was identical to that of a commercial sample of malonaldehyde bis-(diethyl acetal) (b.p. 115° (25 mm.), $n^{25}D$ 1.4088). The infrared spectrum showed absorption at 3.35 and 3.45 μ for saturated CH, as well as broad, strong absorption in the 9 μ region for ether –C–O–.

Identification of Propiolaldehyde Diethyl Acetal (II).—Since the boiling point of II is so close to that of recovered triethyl orthoformate, II was isolated only as its 2,4-dinitrophenylhydrazone derivative. The amount of II present was undetermined but small. The infrared spectra of the dinitrophenylhydrazone of II and of the same derivative prepared from an authentic sample of propiolaldehyde were identical. Bands in the spectra were obtained at 4.75 μ for $-C\equiv C-$; 3.25 μ for aromatic CH; 6.15, 6.25 and 6.45 μ for aromatic $>C=C<$; 6.6 and 7.5 μ for $-NO_2$; and 3.05 μ for $HC\equiv$ and –NH–.

Acetylene reacted very slowly with higher orthoesters. Very low yields of products believed to be acetylenic ketals were obtained, and these materials were not fully characterized.

Study of Catalysts.—For catalyst evaluation, the reaction between phenylacetylene and triethyl orthoformate was employed. Unless otherwise specified, one-third molar amounts of the two reactants were charged into a still-flask, the candidate catalyst added, and the reaction mixture heated while removing ethyl alcohol. Generally, the distillation of ethyl alcohol started at an initial flask temperature of 130–140°. Near the end of the reaction, the flask temperature frequently reached 200° or slightly higher. Of the catalysts evaluated, zinc iodide, zinc chloride, zinc nitrate and cadmium iodide were most effective. A variety of other zinc salts, as well as certain cadmium, mercury or magnesium halides, were less effective. These results are summarized more fully in Table II.

WILMINGTON, DEL.

[CONTRIBUTION FROM THE CHEMISTRY DIVISION, LAKESIDE LABORATORIES, INC.]

Hypotensive Agents. I. Acetylenic Diamines

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The introduction of a triple bond into a number of active blood pressure lowering agents has yielded compounds which were effective hypotensors in the dog, being superior to the saturated parent compounds in regard to potency, duration of action and ease of absorption from the gastro-intestinal tract. Four series of derivatives were prepared: (1) bis-*t*-amino-alkynes, (2) N-(ω-*t*-aminoalkynyl)-1,2,3,4-tetrahydroisoquinolines, (3) α-(4-*t*-amino-2-butynyl)-N-methylpyrrolidines, (4) β-(4-*t*-amino-2-butynyl)-N-methylpiperidines. Only the bis-quaternary ammonium salts displayed hypotensive properties. A general method of synthesis was developed for the aminoalkylation of acetylene and N,N-disubstituted propargylamines which afforded the desired compounds in high yields and did not necessitate the use of pressure equipment. This process also represents a facile synthetic route for the preparation of "mixed" acetylenic, olefinic and alkylenic diamines, as well as "mixed" diaminoketones (Mannich bases) and diaminoalcohols.

Acetylene derivatives have found limited usefulness as therapeutic agents. Some of the more outstanding applications have been in the fields of steroids and non-barbiturate sedatives. Estrone which is poorly absorbed from the gastro-intestinal tract can be converted to a potent, orally highly effective preparation, 17-ethynylestradiol[1]; 17α-ethynyl-19-nortestosterone is an orally active progestational hormone and ovulation inhibitor.[1] In these instances the acetylenic group imparts apparently greater stability to the compound in the gastro-intestinal tract.

The introduction of a triple bond into a variety of tertiary alcohols[2–5] has yielded several clinically effective non-barbiturate sedatives.[6–8] The presence of an acetylenic moiety greatly enhanced the sedative properties of the saturated parent compounds.[9]

While this work was in progress, Marszak[10] and his co-workers reported that the acetylenic function increased the parasympathomimetic activity in a series of aliphatic aminoethers.

We became interested in exploring the effect of a triple bond in a variety of hypotensively active bis-ammonium alkanes for several reasons: (1) The "methonium" hypotensive drugs are notorious for

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(1) F. Hartley, *J. Pharm. and Pharmacol.*, **9**, 10 (1957).

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(3) G. Franke, *Med. Klin.*, **49**, 891 (1954).

(4) K. E. Hamlin, U. S. Patent 2,779,799 (1957).

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