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β-Keto Acetals. II. Synthesis of 3-Methyl- and 3-Phenyl-furans

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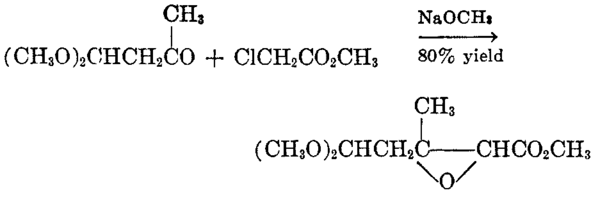
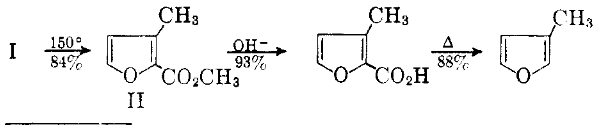
A new and convenient synthesis of the hitherto rare 3-methyl- and 3-phenyl-furan and their corresponding 2-furoic esters has been found. β-Ketobutyracetal (4,4-dimethoxy-2-butanone) has been converted to 3-methylfuran in four short steps *via* the Darzens glycidic ester condensation in 55% over-all yield.

In Part I methods have been described for the conversion of β-keto acetals to various heterocyclic nitrogen compounds.[1] The fact that 3-alkyl- and 3-aryl-furans also can be prepared rather easily from the readily accessible β-keto acetals is of considerable interest. Until now, furans, unsubstituted in either of the *alpha*-positions, were rare and difficult to attain in contrast to 2-substituted furans. Just 20 years ago, investigators[2] in the field of furan chemistry decried the "paucity of simple *beta*-substituted furans, which are uncommonly difficult of synthesis"; this situation has changed but little since then.

As an example, the simplest of these compounds, 3-methylfuran, until now has been synthesized only by a long series of steps (six or more) from citric acid[3] or malic acid.[4] The only other source has been from degradation of the naturally occurring "Elsholtzia" ketone.[5] The method of furan synthesis from β-keto acetals reported here constitutes a novel and relatively simple synthesis of 3-methylfuran, 3-methyl-2-furoic acid, and analogs thereof. The preferred route involves rearrangement of the glycidic ester (I) to the furoic ester (II), as shown below; in this way, the over-all yield of 3-methylfuran from β-ketobutyracetal (four steps) is 55%.



I



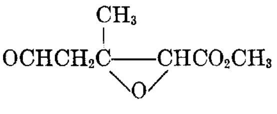
II

In a similar manner, β,β-dimethoxypropiophenone undergoes the Darzens condensation in 85% yield, the glycidic ester from which is converted to methyl 3-phenyl-2-furoate in 58% yield. The latter reaction does not occur with the facility of the corresponding methyl compound, *i.e.*, by moderate heat alone; a trace of acid as catalyst was necessary and a temperature of 250°. The somewhat low yield was due to formation of some resinous material under conditions which are rather drastic for a furan.

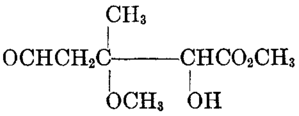
This experience tended to confirm a suspicion that the reaction of the glycidic ester from β-ketobutyracetal was actually catalyzed by free hydrogen chloride resulting from the presence of a chloro compound as impurity. The reaction product always contained free hydrochloric acid. The phenyl glycidic ester was shown to contain little or no impurity of this type; hence acid had to be added.

The glycidic ester (I) was readily hydrolyzed to the glycidic acid, which, when heated, produced small amounts of 3-methylfuran and 3-methyl-2-furoic acid. Obviously, it is preferable to run the furan rearrangement on the ester.

Since it was found that the glycidic ester-acetal from β-ketobutyracetal could be converted directly to a furan, or after hydrolysis by alkali to the free acid-acetal, the question remained whether the acid hydrolysis product, the ester-aldehyde (III), could also be cyclized to the furan. Although acid hydrolysis apparently produced compound IV rather than III, heating with a trace of acid converted it to methyl 3-methyl-2-furoate; however, the yield was very poor.



III



IV

Ketovinyl ethers are often formed as by-products in the synthesis of the β-keto acetals, and may even predominate;[6] also, the two ketones are often difficult to separate. Although these ethers can be converted entirely to the acetal by treatment with an alcoholic sodium alkoxide, the advantage of

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(1) Burness, *J. Org. Chem.*, **21**, 97 (1956).

(2) Gilman, Burtner, and Wright, *J. Am. Chem. Soc.*, **54**, 1696 (1932).

(3) Rinkes, *Rec. trav. chim.*, **50**, 1127 (1931); *Chem. Abstr.*, **26**, 1279 (1932); Reichstein and Zschokke, *Helv. Chim. Acta*, **14**, 1270 (1931).

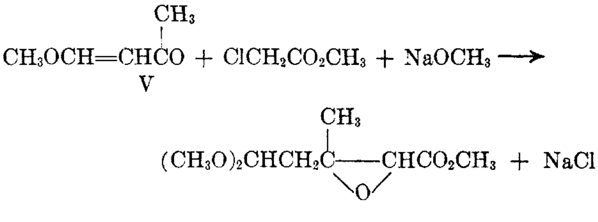
(4) Gilman and Burtner, *J. Am. Chem. Soc.*, **55**, 2903 (1933).

(5) Asahina, *Acta Phytochim. Japan*, **2**, 1 (1924); *Chem. Abstr.*, **19**, 1139 (1925).

(6) Royals and Brannock, *J. Am. Chem. Soc.*, **75**, 2050 (1953).

being able to use the mixture in a given reaction is considerable. Such is the case in the furan synthesis.

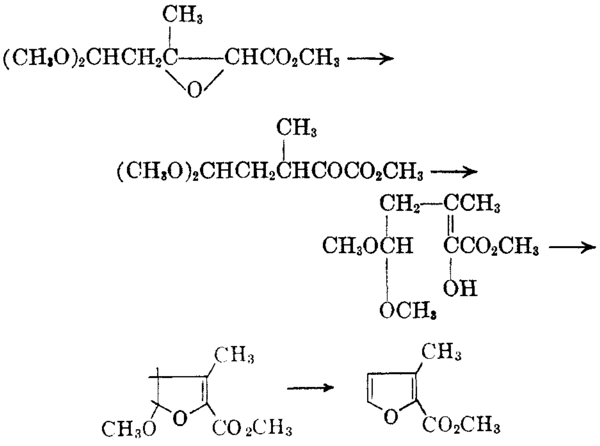
The initial reaction (Darzens) with 4-methoxy-3-buten-2-one (V) proceeds equally as well (80% yield) as with the corresponding β-ketobutyracetal, and, in fact, the properties and analysis of the glycidic ester show it to be identical with that from the keto acetal. Apparently, the methanol derived from sodium methoxide in the reaction adds to the double bond.



Thus, it is obvious that in the Darzens reaction the vinyl ether-acetal mixtures can be used as starting materials without separation.

Surprisingly enough, the Darzens reaction failed with the corresponding ester, 4-acetoxy-3-buten-2-one. No reaction occurred, and the methyl chloroacetate was recovered. Likewise, no reaction occurred with sodium formylacetone and methyl chloroacetate, although there is some precedent for such a reaction. The sodium derivative of acetone itself is reported to undergo a successful Darzens reaction with ethyl chloroacetate.[7]

The cyclization of these glycidic esters or acids to the furans can readily be explained if one assumes an intermediate rearrangement of the epoxy group to an α-keto group. This is a reasonable assumption, for ethyl β,β-diphenylglycidate is isomerized to ethyl β,β-diphenyl-α-ketopropionate on distillation.[8,9] The probable route is as follows:



EXPERIMENTAL

A. 3-METHYLFURAN

1. Methyl 5,5-dimethoxy-3-methyl-2,3-epoxypentanoate. (a). From 4,4-dimethoxy-2-butanone. A 2-liter, 3-necked flask was equipped with a centrifugal stirrer with airtight seal, a thermometer inserted through a gas outlet tube connected to a drying tube, and a solid addition tube containing a gas inlet. The apparatus was dried with a free flame; and 800 ml. of ether, 132 g. (1.0 mole) of dry 4,4-dimethoxy-2-butanone, and 174 g. (1.6 mole) of freshly dried and distilled, neutral methyl chloroacetate were added. A flask containing 86 g. of sodium methoxide (Mathieson sodium methylate) was attached to the addition tube by means of a Gooch rubber tube. This charging of reagents was done preferably under dry nitrogen, and a very slow stream of dry nitrogen was passed through the apparatus during the reaction.

The solution was cooled in an ice-salt bath to −10°, and the sodium methoxide was added gradually at a rate which allowed the temperature to be maintained below −5° (about two hours were required). The mixture was stirred for two hours longer, and allowed to warm to room temperature overnight. The mixture then was cooled again to 0° and made slightly acid by the addition of a solution of 10 ml. of acetic acid in 150 ml. of water. The ether was decanted and the residual slurry was extracted thoroughly with ether. The ether solution was washed with saturated brine containing sodium bicarbonate until the washes were no longer acidic, then with brine alone, and finally was dried over magnesium sulfate.

Distillation through a short Vigreux column yielded 190–200 g. of product, b.p. 113–122° (8 mm.). Redistillation through a 10-in. column packed with $^3/_{16}$-in. helices gave 164 g. of glycidic ester, b.p. 93° (0.7 mm.), -89° (1.0 mm.); n_D^{25} 1.4405–1.4419. Yield 80%.

Anal. Calc'd for $C_9H_{16}O_5$: C, 53.0; H, 7.9. Found: C, 52.5; H, 7.7.

The low value for carbon can be accounted for by the presence of a chlorine-containing impurity; a Beilstein test was positive.

(*b*) *From 4-methoxy-3-buten-2-one.* From 25 g. of 4-methoxy-3-buten-2-one,[10] 43.5 g. of methyl chloroacetate, and 21.6 g. of sodium methoxide, using the above procedure, there was obtained 40.4 g. (80% yield) of methyl 5,5-dimethoxy-3-methyl-2,3-epoxypentanoate. A representative sample boiled at 66.5–69.5° (0.25 mm.); n_D^{25} 1.4394.

Anal. Calc'd for $C_9H_{16}O_5$: C, 53.0; H, 7.9. Found: C, 53.4; H, 8.0.

(*c*) *Attempted from 4-acetoxy-3-buten-2-one.*[11] Two attempts to carry out this reaction using this enol ester met with failure. Over two-thirds of the methyl chloroacetate was recovered and only insignificant amounts of material boiling in the range of the glycidic ester were obtained.

2. Methyl 3-methyl-2-furoate. Methyl 5,5-dimethoxy-3-methyl-2,3-epoxypentanoate (47.6 g.) was placed in a 100-ml. flask under a 5-in. column and heated. When the liquid temperature reached about 160°, methanol began to distill. When the theoretical amount (13 g.) had distilled, the column was replaced by a simple head, and 27.4 g. (84%) of methyl 3-methyl-2-furoate was collected at 72–76° (8 mm.). The ester solidified in the receiver (m.p. 34.5–36.5°) as an essentially pure compound. A sample was recrystallized from alcohol; m.p. 36.5–37°.

Anal. Calc'd for $C_7H_8O_3$: C, 59.9; H, 5.7; M.W., 140. Found: C, 59.6; H, 5.7; M.W., 141.

3. 3-Methyl-2-furoic acid. The ester (26 g.) was boiled under reflux with 60 ml. of 20% sodium hydroxide solution for two hours. The solution was cooled, acidified with 35 ml. of concentrated hydrochloric acid, etc., to give 21.8 g. (93%) of 3-methyl-2-furoic acid,[4] m.p. 132–132.5°.

4. 3-Methylfuran. A mixture of 430 g. of 3-methyl-2-furoic

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(7) Rutowski and Dajew, *Ber.*, **64**, 693 (1931).

(8) Troell, *Ber.*, **61**, 2498 (1928).

(9) Kohler, Richtmyer, and Hester, *J. Am. Chem. Soc.*, **53**, 211 (1931).

(10) Franke, Kraft, Tietjen, and Weber, *Ber.*, **86**, 793 (1953).

(11) This compound was prepared in 57% yield from sodium formyl acetone and acetyl chloride in ether; b.p. 92–98° (18 mm.); n_D^{25} 1.4624. *Anal.* Calc'd for $C_6H_8O_3$: C, 56.3; H, 6.3. Found: C, 56.6; H, 6.5.

acid, 860 g. of quinoline, and 80 g. of copper powder was heated in a 3-liter flask surmounted by a 12-in. Vigreux column. The vapors of 3-methylfuran were condensed by a water-cooled condenser leading to a receiver immersed in an ice-salt bath. A Dry Ice trap completed the setup. Carbon dioxide was evolved at a moderate rate, and when the reaction was nearly complete, the heat was increased until the temperature at the head began to rise rapidly above 65°.

The receiver contained 250 g. of slightly wet product, and the Dry Ice trap an additional 20 g. for a total crude yield of 270 g. (96.5%). This was dried over magnesium sulfate, followed by Drierite, and redistilled to give 246 g. (88%) of colorless 3-methylfuran;[5] b.p. 65.5°, n^{25}_{D} 1.4315. The product turned light yellow on standing, even overnight. It may be stabilized with hydroquinone or similar material.[12]

B. 4-METHYL-3,6-ENDOXO-1,2,3,6-TETRAHYDROPHTHALIC ANHYDRIDE

A concentrated solution of 0.5 g. of maleic anhydride and 0.4 g. of 3-methylfuran in ether yielded, after three days at 25°, 0.74 g. (89%) of this Diels-Alder product; m.p. 78–79°. Recrystallization from ethyl acetate failed to raise the melting point, although Rinkes[3] gives a value of 82° for this adduct.

C. OTHER REACTIONS OF METHYL 5,5-DIMETHOXY-3-METHYL-2,3-EPOXYPENTANOATE

1. Alkaline hydrolysis. To 100 ml. of methanol containing 5.0 g. (0.217 mole) of sodium was added 41.5 g. (0.20 mole) of the glycidic ester, followed by 3.6 g. (0.20 mole) of water. The solution was warmed at 40° for two hours and allowed to stand 16 hours. It was concentrated to one-half volume, and after the addition of 100 ml. of water, it was extracted with ether. The resulting aqueous solution was cooled and a concentrated solution of 33 g. of tartaric acid was added gradually. The liberated acid was extracted with ether, and the ether solutions were dried over magnesium sulfate and evaporated. The residual yellow oil, after heating at 40° (2–5 mm.), weighed 25.5 g. (68%); n^{29}_{D}1 .4557. Infrared analysis indicated it to be largely the desired glycidic acid. Heating at elevated temperatures produced mostly tars, accompanied by small amounts of 3-methylfuran and 3-methyl-2-furoic acid.

A by-product crystallized from the oily glycidic acid on long standing. The crystals were purified by recrystallization from heptane containing a little absolute ethanol to give colorless needles; m.p. 83°. Insufficient material was available for complete identification, but analysis indicated the likelihood of a methoxyvinyl glycidic acid, *i.e.*, 5-methoxy-3-methyl-2,3-epoxy-4-pentenoic acid.

Anal. Calc'd for $C_7H_{10}O_4$: C, 53.2; H, 6.4. Found: C, 53.3; H, 6.2.

2. Acid hydrolysis. A solution of 5 g. of the glycidic ester in 25 ml. of methanol containing 5 ml. of 1.2 *N* hydrochloric acid was heated at reflux for three hours and allowed to stand five days at 25°. The mixture was worked up with ether; the ether solutions were washed with dilute carbonate and dried. Distillation yielded a considerable forerun containing some methyl 3-methylfuroate, and a chief fraction (0.75 g.) distilling at 130–133° (22 mm.); n^{25}_{D} 1.4520. The latter gave positive tests for free —CHO with both Tollen's reagent and Fehling's solution. Analysis indicated cleavage of the epoxy group in addition to the acetal to give, perhaps, methyl γ-formyl-α-hydroxy-β-methoxyisovalerate (IV).

Anal. Calc'd for $C_8H_{14}O_5$: C, 50.6; H, 7.2. Found C, 50.4, 50.8, 50.7; H, 7.2, 7.2, 7.1.

When the latter product was heated in the presence of a trace of *p*-toluenesulfonic acid, the index rose to n^{25}_{D} 1.47 and a distillate was collected consisting of methyl 3-methyl-2-furoate, m.p. 36–37°. The identity was confirmed by a mixture melting point.

D. METHYL 3-PHENYL-2-FUROATE

1. Methyl 5,5-dimethoxy-3-phenyl-2,3-epoxypentanoate. The same procedure as described above for the corresponding 3-methyl compound was used. From 48.5 g. of β,β-dimethoxypropiophenone,[13] 43.4 g. of methyl chloroacetate, and 21.6 g. of sodium methoxide there was obtained 56.8 g. (85.4%) of a nearly colorless, viscous oil; b.p. 119–123° (0.5 mm.); n^{25}_{D} 1.5020.

Anal. Calc'd for $C_{14}H_{18}O_5$: C, 63.2; H, 6.8. Found: C, 63.2; H, 6.7.

2. Methyl 3-phenyl-2-furoate. Methyl 5,5-dimethoxy-3-phenyl-2,3-epoxypentanoate (5 g.) was heated with *ca.* 0.05 part of *p*-toluenesulfonic acid at 250° until methanol ceased to distill. The residual oil was distilled at reduced pressure to give 2.2 g. (58% yield) of crude methyl 3-phenylfuroate, b.p. 147–172° (10 mm.), which solidified on cooling. Recrystallization from heptane produced 1.6 g. of the pure colorless compound; m.p. 63.5–64.5°.

Anal. Calc'd for $C_{12}H_{10}O_3$: C, 71.2; H, 5.0. Found: C, 70.8; H, 4.7.

Acknowledgment. We are indebted to D. Ketchum, of the Kodak Research Laboratories, for the microanalytical data furnished by his group.

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[12] Cass, U. S. Patent 2,489,265; *Chem. Abstr.*, 44, 1543 (1950).

[13] The β-ketovinyl ether derived from acetophenone[6] is converted to β,β-dimethoxypropiophenone by treatment with methanolic sodium methoxide; b.p. 90.5–93.5° (0.2 mm.); n^{25}_{D} 1.5164. *Anal.* Calc'd for $C_{11}H_{14}O_3$: C, 68.1; H, 7.3. Found: C, 67.8; H, 7.1.