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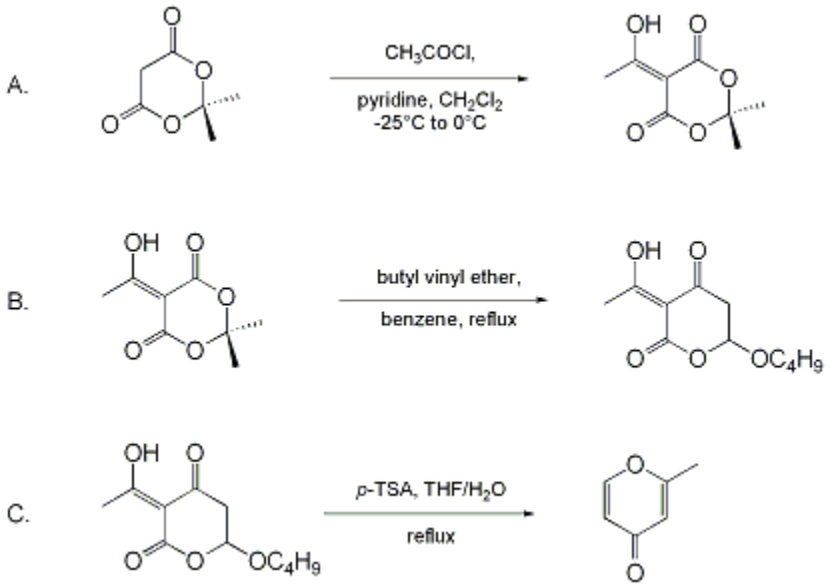
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.077.0114

Organic Syntheses, Coll. Vol. 10, p.355 (2004); Vol. 77, p.114 (2000).

THE SYNTHESIS OF 2-ALKYL-4-PYRONES FROM MELDRUM'S ACID



Submitted by Michael T. Crimmins, David G. Washburn, and Frank J. Zawacki[1] .
Checked by Michelle Pacholec and Steven Wolff.

1. Procedure

A. 5-(1-Hydroxyethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione . A flame-dried, 500-mL, three-necked, round-bottomed flask is equipped with a stir bar, nitrogen inlet adapter, and a pressure-equalizing addition funnel fitted with a rubber septum. The flask is charged with 22.0 g of Meldrum's acid dissolved in 153 mL of methylene chloride , and 24.8 mL of pyridine (Note 1), and the mixture is cooled to −25°C (Note 2). A mixture of 18.3 mL of methylene chloride and 13.1 mL of acetyl chloride is slowly added to the reaction mixture via the addition funnel over 1 hr (Note 3). After the addition of the acetyl chloride is complete, the reaction is slowly warmed over 3 hr to 0°C. Methanol (30 mL) is added to quench the reaction and stirring is continued for 15 min. The reaction mixture is transferred to a 2000-mL separatory funnel, diluted with 100 mL of methylene chloride and washed with saturated aqueous ammonium chloride (3 × 140 mL) and 140 mL of water. The aqueous layers are combined and extracted with methylene chloride (3 × 100 mL). The combined organic layers are dried over 200 g of sodium sulfate for 3 hr (Note 4). The solution is filtered into a 1000-mL, round-bottomed flask and the methylene chloride is removed under reduced pressure. The residual orange solid can be purified by breaking up the solid into a fine powder with a mortar and pestle and placing it under vacuum overnight to remove any remaining pyridine to yield 26.0 g of acylated Meldrum's acid suitable for use in the next step (Note 5).

B. and C. 2-Methyl-4H-pyran-4-one . A 1000-mL, round-bottomed flask equipped with a stir bar and a reflux condenser is charged with the crude acylated Meldrum's acid, 80 mL of butyl vinyl ether and 287 mL of toluene (or benzene) (Note 6). The reaction mixture is heated to 80°C for 7 hr (Note 7). The volatile components are removed under reduced pressure to yield 31.81 g of product (Note 8). To the residue are added 765 mL of tetrahydofuran , 191 mL of water and 2.7 g of p-toluenesulfonic acid . The mixture is heated to reflux for 18 hr, then the reaction is quenched with 10 g of solid sodium bicarbonate and allowed to stir for 15 min at 25°C (Note 9). The mixture is filtered to remove the sodium bicarbonate and the volatile components are removed under reduced pressure. The residue is dissolved in 500 mL of methylene chloride , placed in a separatory funnel and washed with 200 mL of water and 200 mL of brine solution. The aqueous layers are collected and extracted with methylene

chloride (2 × 200 mL). The organic layers are combined, dried over 20 g of sodium sulfate for 1 hr, filtered into a 1000-mL, round-bottomed flask, and concentrated under reduced pressure. The resulting red oil is purified by chromatography using a 6-cm diameter glass column packed with 400 g of silica gel (Note 10) with 2.5% methanol/methylene chloride as the eluant yielding 5.25-5.81 g (38.6-42.7%) of 2-methyl-4H-pyran-4-one (Note 11).

2. Notes

1. Meldrum's acid was purchased from Aldrich Chemical Company, Inc. Pyridine was distilled from calcium hydride . Methylene chloride was dried over alumina . The checkers found that recrystallization of Meldrum's acid from benzene was necessary in order to obtain reproducible yields of the acylated product.
2. A temperature of −25°C was reached through the use of a 29% calcium chloride - dry ice slurry.
3. Acetyl chloride was purchased from Aldrich Chemical Company, Inc. , and was freshly distilled prior to use.
4. Alternatively, the addition of 5 g of magnesium sulfate ensures a dry product within 1 hr.
5. The product has an R_f of 0.22 in 5% methanol/methylene chloride (silica gel) and displays the following spectral data: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.71 (s, 6 H), 2.64 (s, 3 H) ; ^{13}C (75 MHz, $CDCl_3$) δ: 37.5, 42.4, 45.1, 106.2, 118.6, 174.8, 184.2, 207.5 . Checkers found this material to contain approximately 5% of Meldrum's acid. The acidic proton was not observed in the ^{1}H NMR spectrum.
6. Butyl vinyl ether was purchased from Aldrich Chemical Company, Inc. , and was distilled from sodium under reduced pressure. Toluene was distilled from calcium hydride.
7. Reaction times vary depending on scale. For optimum results the consumption of the acylated Meldrum's acid is monitored by TLC.
8. The product has an R_f of 0.60 in 5% methanol/methylene chloride (silica gel) and can be purified with difficulty by column chromatography. The product had the following spectral characteristics: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.81 (t, 3 H, J = 7), 1.22 (dt, 2 H, J = 7, 7), 1.47 (m, 2 H), 2.53 (s, 3 H), 2.60 (dd, 1 H, J = 17, 3), 2.92 (dd, 1 H, J = 17, 1.5), 3.52 (m, 1 H), 3.83 (m, 1 H), 5.29 (dd,1 H, J = 3, 1.5) ^{13}C (75 MHz, $CDCl_3$) δ: 27.5, 33.2, 40.3, 45.5, 52.7, 83.5, 101.1, 118.0, 176.8, 208.1, 214.0.
9. Solid sodium bicarbonate was added to reach a slightly basic (pH = 7.5-8) solution.
10. Silica gel was purchased from VWR Scientific .
11. The product is a red oil. The product has an R_f of 0.38 in 5% methanol/methylene chloride (silica gel) and shows the following spectral characteristics: IR (neat) cm^{-1}: 3007, 1665, 1615, 1410, 1385, 1340, 1250, 1215, 1170, 1055, 1005, 925, 890, 855, 820 ; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.27 (d, 3 H, J = 0.75), 6.15 (d, 1 H, J = 1.75), 6.27 (dd, 1 H, J = 6, 6), 7.68 (d, 1 H, J = 6) ; ^{13}C (75 MHz, $CDCl_3$) δ: 18.7, 114.5, 115.5, 154.7, 165.6, 178.3 .

Waste Disposal Information

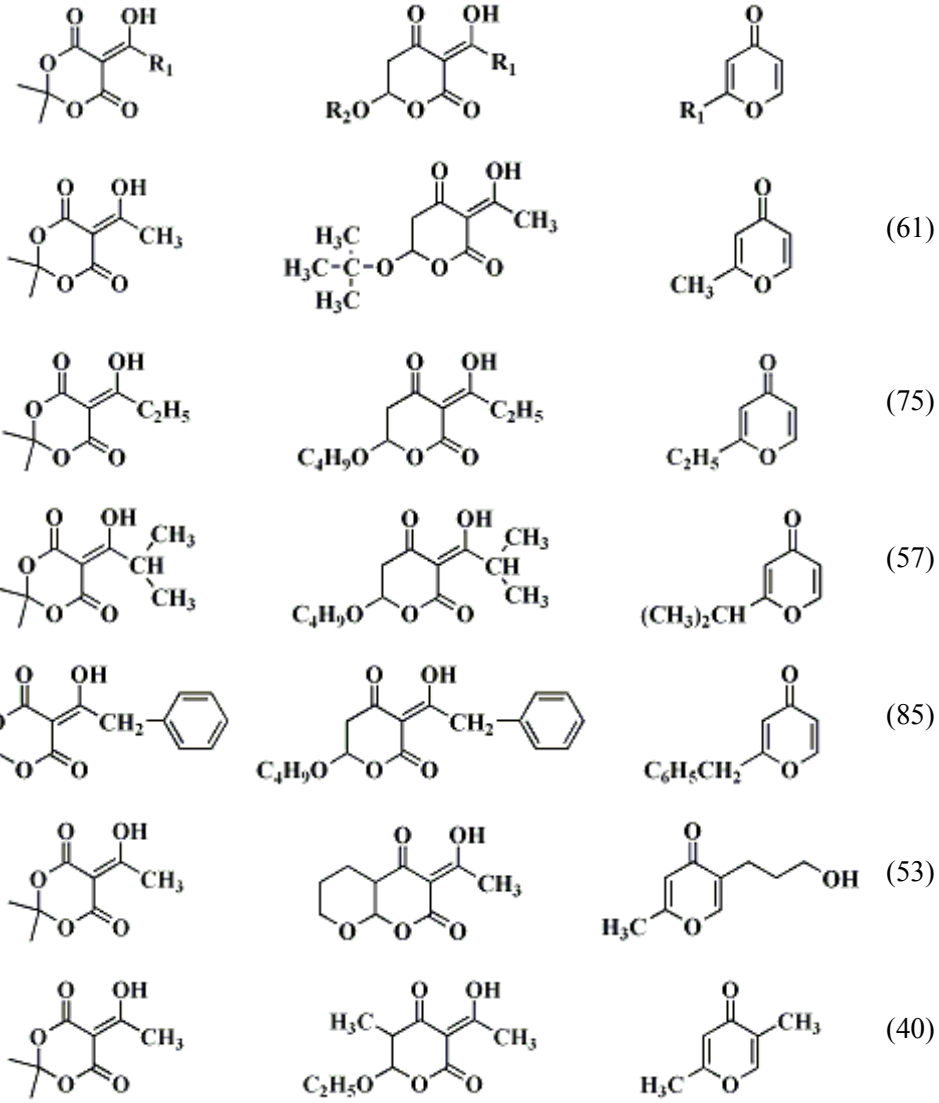
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The procedure described here offers a general route to a variety of unsymmetrically substituted γ-pyrones from Meldrum's acid.[2] Substitution at the 2-position depends on the acid chloride chosen, while substitution at the 5-position is derived from the vinyl ether. A variety of substituted γ-pyrones have been synthesized by utilization of this method as illustrated in the Table. The intermediate pyrandione is believed to arise through the addition of the vinyl ether to an acyl ketene that results from the thermal loss of acetone from the acylated Meldrum's acid.[3] Treatment of the pyrandione with acid catalyzes decarboxylation and the loss of butanol to form the γ-pyrone.

TABLE

Acylated Meldrum's Acid	Pyrandione	Pyrone	(Yield)



(61)

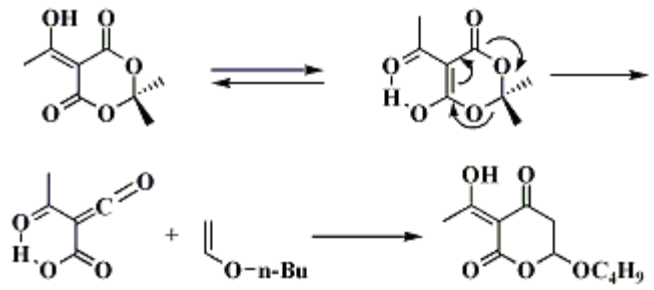
(75)

(57)

(85)

(53)

(40)



Substituted γ-pyrones are versatile synthetic precursors. There is strong precedent for the metalation[4] and bromination[5] of the γ-position, which allows γ-pyrones to be used in alkylation and aldol reactions and makes them attractive intermediates in the synthesis of polyacetate and spiroketal containing natural products.[6] They can also be used as cycloaddition substrates in the construction of complex polycyclic systems as West has demonstrated.[7] Furthermore, γ-pyrones have been used by Wender in an oxidopyrilium-alkene cycloaddition, a key reaction in his synthesis of phorbol.[8]

Past methods used to synthesize γ-pyrones consist of the acylation of methoxy-butyne [9] or 4-methoxy-3-buten-2-one [10] followed by acid-catalyzed hydrolysis and cyclization. Addition of ketenes to siloxydienes followed by acid-catalyzed elimination has also been employed.[11] The present method is

superior to these procedures because of the greater diversity of substituted γ-pyrones that can be constructed, and because of the fact that the previous methods demand the use of strong base and low temperatures that make them less suited for scale up.

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Meldrum's acid:
Malonic acid, cyclic isopropylidene ester (8);
1,3-Dioxane-4,6-dione, 2,2-dimethyl- (9); (2033-24-1)

Pyridine (8,9); (110-86-1)

Acetyl chloride (8,9); (75-36-5)

Acetylated Meldrum's acid: 1,3-Dioxane-4,6-dione, 5-(1-hydroxyethylidene)-2,2-dimethyl- (11); (85920-63-4)

Butyl vinyl ether:
Butane, 1-(ethenyloxy)- (9); (111-34-2)

3-Acetyl-6-butoxy-2H-pyran-2,4(3H)-dione:
2H-Pyran-2,4(3H)-dione, 6-butoxydihydro-3-(1-hydroxyethylidene)- (13); (182616-30-4)

p-Toluenesulfonic acid monohydrate (8);
Benzenesulfonic acid, 4-methyl-, monohydrate (9); (6192-52-5)

2-Methyl-4-pyrone:
4H-Pyran-4-one, 2-methyl- (8,9); (5848-33-9)

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