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of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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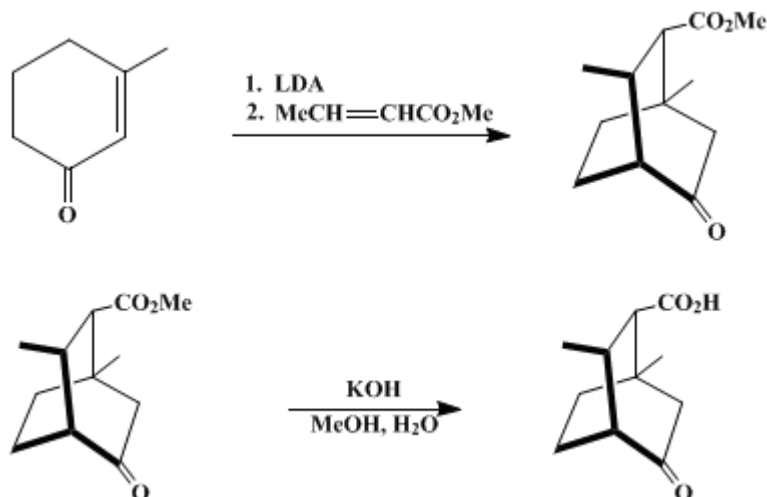
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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APROTIC DOUBLE MICHAEL ADDITION: 1,3-DIMETHYL-5-OXOBICYCLO[2.2.2]OCTANE-2-CARBOXYLIC ACID

[Bicyclo[2.2.2]octane-2-carboxylic acid, 1,3-dimethyl-5-oxo-]



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Checked by Michael P. Trova, Mary A. Kinsella, and Leo A. Paquette.

1. Procedure

A. *Methyl 1,3-dimethyl-5-oxobicyclo[2.2.2]octane-2-carboxylate*.² An oven-dried, 250-mL, round-bottomed flask equipped with a stirring bar and a rubber septum is charged with 100 mL of dry tetrahydrofuran and 5.56 g (55 mmol) of anhydrous diisopropylamine. The flask is flushed with argon via a needle inlet–outlet and cooled to -78°C with a dry ice–isopropyl alcohol bath (Note 1), (Note 2), (Note 3). To the stirred solution is added dropwise with a syringe 30 mL (54 mmol) of a 1.8 M solution of butyllithium in hexane (Note 4) to form lithium diisopropylamide, followed after 30 min by a solution of 5.50 g (50 mmol) of 3-methyl-2-cyclohexen-1-one (Note 5) in 60 mL of dry tetrahydrofuran via a flex-needle over a 15-min period. Stirring and cooling is continued for an additional 30 min. To the resulting yellow solution of the lithium dienolate, 10.0 g (0.1 mol) of methyl (*E*)-crotonate (Note 6) is added with a syringe within 2 min. The cooling bath is removed and the reaction mixture is allowed to warm to room temperature (Note 7). Stirring is continued at room temperature for 2 hr. The reaction mixture is quenched by adding 1 N hydrochloric acid until the mixture turns acidic. Extraction with three 80-mL portions of dichloromethane followed by evaporation of the solvent yields a light-yellow oil that is taken up in 100 mL of diethyl ether. This solution is filtered through 100 g of silica gel to remove polymers and water. Elution with diethyl ether and evaporation of the solvent gives a yellow oil that is distilled in a Kugelrohr distillation apparatus (Note 8) under reduced pressure. After a small forerun (ca. 0.5 g of unreacted 3-methyl-2-cyclohexen-1-one) at 50°C , 0.05 mm, the main fraction is collected at 110 – 120°C (oven temperature), 0.05 mm to give 8.25–9.43 g (78–90%) of a colorless oil, which solidifies on standing in the freezer. One recrystallization from cold pentane (approximately 10 mL of pentane per 8 g of ester mixture) gives 6.0 g of product as white crystals, mp 37°C (Note 9), of approximately 97% isomeric purity (Note 10).

B. *1,3-Dimethyl-5-oxobicyclo[2.2.2]octane-2-carboxylic acid*. A mixture of 11.2 g (53.4 mmol) of the foregoing crude ester in 40 mL of methanol and 8.0 g (143 mmol) of potassium hydroxide in 16 mL of water is refluxed under argon until the ester is no longer present when monitored by TLC (Note 7). This takes about 1 day. Methanol is removed with a rotary evaporator, and the remaining dark solution is extracted with ether (2×50 mL), acidified to pH 1 with dilute sulfuric acid, and extracted with dichloromethane (4×50 mL). The organic layer is filtered through 100 g of silica gel and eluted with

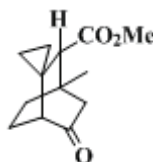
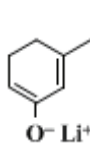
ether to remove most of the dark impurities. Concentration under reduced pressure gives 10.0 g of acid mixture. Distillation in a Kugelrohr apparatus at 180°C, 0.03 mm and one recrystallization from ether-pentane gives 7.0 g (67%) of pure bicyclic acid (isomeric purity >98%) as white crystals, mp 130–131°C (Note 11).

2. Notes

- All glassware, syringes, and flex needles were baked in an oven at 120°C overnight and assembled while hot.
- Tetrahydrofuran was purified by passing it through activated (12 hr at 450°C) neutral aluminum oxide purchased from ICN and distilling it fresh from lithium aluminum hydride.
- Diisopropylamine was distilled from calcium hydride prior to use.
- Butyllithium in hexane was purchased from Metallgesellschaft AG, Frankfurt, Germany and standardized by titration with diphenylacetic acid.³
- 3-Methyl-2-cyclohexen-1-one was purchased from Aldrich-Europe, but is easily prepared from ethyl acetoacetate and paraformaldehyde.⁴
- Methyl crotonate may polymerize to some extent under these conditions. An excess is used in order to insure complete formation of the product. Unreacted methyl crotonate is easily removed by distillation.
- The reaction was monitored by TLC (silica gel 60PF254, Merck, Darmstadt, Germany; 1 : 1 diethyl ether : pentane as the mobile phase, 2,4-dinitrophenyl-hydrazine as revealing reagent) and by GLC (N₂, 3% SE30 rubber on Volaspher A2, Merck, Darmstadt, Germany, 140°C isotherm). The Michael reaction is very slow at -78°C, and the optimum temperature depends on the acceptor (Table I).

TABLE I
EXAMPLES OF CARBOCYCLIC ESTERS PREPARED BY
THE APROTIC DOUBLE MICHAEL ADDITION

Dienolate	Acceptor	Product	Yield (%)	Ref.
			98	6
			90	7
			64	10
			75	11
			61	5



8. A Büchi rotary evaporator was used.

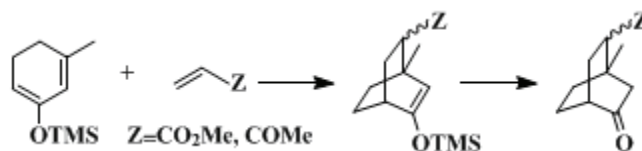
9. The spectra are as follows: IR (neat) cm^{-1} : 1730 (ester, ketone); EI-GCMS (70 eV): $m/e = 210$ (M^+ , 5%), 110 (100), 95 (30); ^1H NMR (250 MHz, CDCl_3 , TMS) δ : 0.94 (s, Me, 3 H), 1.10 (d, 3 H, $J = 7$), 1.30–2.35 (m, 8 H), 2.75 (dd, 1 H, $J = 3$ and 19), 3.67 (s, OMe).

10. The oily product contains approximately 8% of the *exo* isomer (estimated by ^1H NMR on the basis of the ester methyl at 3.70 ppm (major) and at 3.67 ppm (minor)).

11. An additional 1.2 g (9.5%) of pure acid may be recovered from the mother liquor. The spectra are as follows: ^{13}C NMR (62.88 MHz, CDCl_3) δ : 17.3 (t), 17.4 (q), 23.7 (q), 31.8 (d), 33.9 (t), 35.7 (s), 44.9 (t), 47.9 (d), 50.9 (q), 54.5 (d), 174.8 (s), 214.1 (s); ^1H NMR (250 MHz, CDCl_3) δ : 1.05 (s, 3 H), 1.15 (d, 3 H, $J = 6.8$), 1.35–2.15 (m, 8 H), 2.32 (m, 1 H), 2.81 (dd, 1 H, $J = 19, 3$), 11.2 (broad s, 1 H); EI-MS (70eV): $m/z = 196$ (M^+ , 40%), 178 (5), 110 (100), 95 (45); IR (CH_2Cl_2) cm^{-1} : 3480 (m), 2920 (s), 1725 (s), 1705 (s).

3. Discussion

The aprotic double Michael addition was discovered by R. A. Lee⁶ and used^{7,8,9,10,11} to synthesize functionalized bicyclo[2.2.2]octanes, which may serve as starting materials in natural products syntheses (Table I). These bicyclo[2.2.2]octanes can also be obtained by a Diels–Alder cycloaddition of 2-trimethylsiloxy-substituted cyclohexadienes and dienophiles:¹²



But there are many cases known where the (4 + 2) cycloaddition fails even with siloxy-activated dienes; for example, methyl (*E*)-crotonate does not react with diene **1** at normal pressure and elevated temperature (110°C), whereas the aprotic double Michael addition does give the desired bicyclo[2.2.2]octane in high yield. This reaction¹³ gives mainly (92%) bicyclic esters with the *endo* configuration.

References and Notes

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

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

potassium hydroxide (1310-58-3)

Diphenylacetic acid (117-34-0)

Ethyl acetoacetate (141-97-9)

2,4-dinitrophenyl-hydrazine (119-26-6)

Pentane (109-66-0)

dichloromethane (75-09-2)

aluminum oxide (1344-28-1)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

argon (7440-37-1)

calcium hydride (7789-78-8)

methyl crotonate,
methyl (E)-crotonate (623-43-8)

3-methyl-2-cyclohexen-1-one

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

1,3-Dimethyl-5-oxobicyclo[2.2.2]octane-2-carboxylic acid,

Bicyclo[2.2.2]octane-2-carboxylic acid, 1,3-dimethyl-5-oxo- (121829-82-1)

bicyclo[2.2.2]octane (280-33-1)

Methyl 1,3-dimethyl-5-oxobicyclo[2.2.2]octane-2-carboxylate (121917-73-5)

paraformaldehyde (30525-89-4)