Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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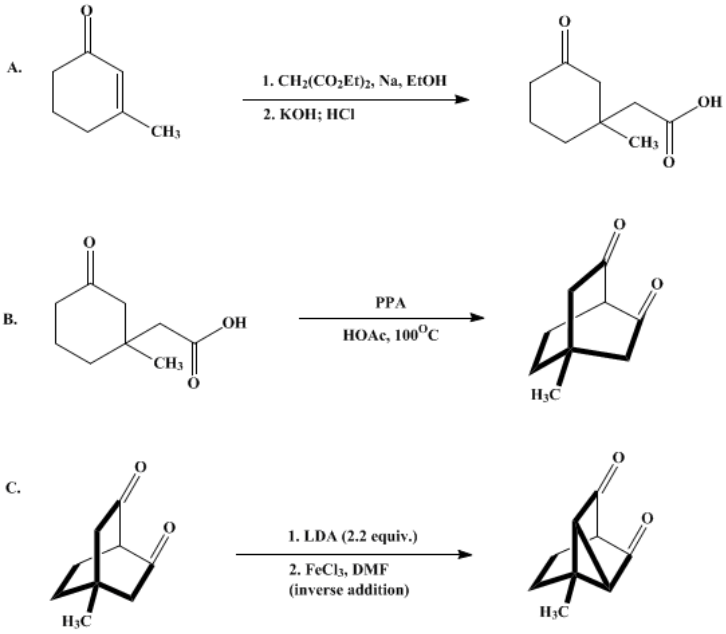
INTRAMOLECULAR OXIDATIVE COUPLING OF A BISENOLATE: 4-METHYLTRICYCLO[2.2.2.0^{3,5}]OCTANE-2,6-DIONE

[Tricyclo[3.2.1.0^{2,7}]octane-6,8-dione, 2-methyl-]



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Checked by L. A. Stolz and Robert K. Boeckman, Jr..

1. Procedure

A. *3-Methylcyclohexanone-3-acetic acid.* A 2-L, three-necked Morton flask fitted with a low-temperature thermometer, a 250-mL addition funnel, an exit tube attached to a calcium chloride drying tube, and a Teflon-coated magnetic stirring bar is charged with 1.1 L of anhydrous ethanol. The stirred solution is cooled to 0°C and 23 g (1 mol) of sodium cut into small pieces is added through the exit tube. During the addition, the temperature of the reaction mixture increases; therefore, cooling is applied (Note 1). After all of the sodium has completely reacted, 160.2 g (1 mol) of neat diethyl malonate is slowly added through the addition funnel while the temperature is maintained at 0°C (Note 2). At this point, 110.2 g (1 mol) of 3-methyl-2-cyclohexen-1-one (Note 3) is gradually introduced through the addition funnel at 0°C. A white precipitate eventually appears. After 9 days of stirring, the brown reaction mixture is poured onto ice, brought to neutrality with concentrated hydrochloric acid while being vigorously stirred, and extracted with one 600-mL portion and four 300-mL portions of ether (Note 4). The combined organic layers are washed with three 250-mL portions of saturated brine and dried over anhydrous magnesium sulfate. After evaporation under reduced pressure to remove the solvent, the residual oil is distilled through a 20-cm Vigreux column under reduced pressure. The first fraction (bp <60°C at 0.15 mm) consists of a mixture of unreacted starting materials. The second fraction (bp 145–165°C at 1.5 mm), a mixture of diesters (Note 5), is a colorless oil: 202–205 g (74–76%).

In a 2-L, one-necked, round-bottomed flask fitted with a magnetic stirring bar is placed 99 g (0.366 mol) of the diesters. A 1.0-*M* solution of potassium hydroxide (750 mL, 0.75 mol) is added to the flask with stirring. The mixture is stirred overnight and subsequently heated to reflux for 1 hr. After the mixture is cooled, it is acidified with 100 mL of concentrated hydrochloric acid and gently boiled for 20 min. Following return to room temperature, the mixture is transferred to a 2-L separatory funnel and extracted with dichloromethane (6 × 100 mL). The combined organic layers are washed with saturated brine (100 mL) and dried over sodium sulfate. The solvent is removed in a rotary evaporator and the residue is distilled in a Kugelrohr apparatus (140–160°C and 0.3–0.5 mm) to provide 49.3 g (79%) of the keto acid (Note 6).

B. *4-Methylbicyclo[2.2.2]octane-2,6-dione.* A 2-L, three-necked, Morton flask fitted with a mechanical stirrer, a thermometer, and a reflux condenser is charged with 245.0 g of polyphosphoric acid (PPA, (Note 7)), 26.8 g (158 mmol) of the keto acid, and 427 mL of glacial acetic acid. The vigorously stirred mixture is heated at 100°C for 7 hr. After being cooled, the reaction mixture is diluted with 500 mL of saturated brine and extracted with four 200-mL portions of benzene (Note 8). The combined organic layers are washed with saturated sodium bicarbonate (4 × 100 mL) and brine (1 × 100 mL) solutions, and dried over anhydrous magnesium sulfate. After removal of the solvents on a rotary evaporator, the viscous residue is distilled under reduced pressure in a Kugelrohr apparatus, affording 11.0–13.3 g (46–55%) of cyclized diketone as a colorless liquid, bp 100°C at 0.1 mm, which may solidify on standing at room temperature (Note 9).

C. *4-Methyltricyclo[2.2.2.0^{3,5}]octane-3,5-dione.* A 500-mL, one-necked, round-bottomed flask fitted with a Teflon-coated magnetic stirring bar and a rubber septum is charged under nitrogen with a solution of 30.8 mL (220 mmol) of dry diisopropylamine in 170 mL of anhydrous tetrahydrofuran. The solution is cooled to 0°C (acetone–dry ice bath), and 137.5 mL (220 mmol) of a 1.6 *M* solution of butyllithium in hexanes is introduced over a 35-min period. The resulting colorless solution is stirred for 15 min at 0°C and then cooled to −78°C.

The diketone (15.20 g, 100 mmol) is dissolved in 27 mL of dry tetrahydrofuran in a 50-mL, round-bottomed flask and added dropwise through a 16-gauge cannula (nitrogen pressure) during 35 min to the lithium diisopropylamide solution. This mixture is stirred for 30 min at −78°C and is added in turn to 280.4 mL (300 mmol) of a 1.07 *M* solution of anhydrous ferric chloride (Note 10) in dry dimethylformamide, diluted with 39 mL of dry dimethylformamide and contained in a 1-L, three-necked, round-bottomed flask equipped with an efficient mechanical stirrer and cooled to −78°C (Note 11). This addition is accomplished as rapidly as possible through an 8-gauge cannula (nitrogen pressure). After the reaction mixture is stirred for 2 hr at −78°C, it is quenched by the dropwise addition of 24 mL of dry methanol and allowed to reach room temperature. Saturated brine (300 mL) is added and the entire mixture is filtered through Celite. The aqueous phase is extracted with four 250-mL portions of ether. The combined organic layers are washed with saturated brine (3 × 150 mL) and dried over anhydrous magnesium sulfate. After solvent evaporation under reduced pressure, the residue is chromatographed (100 g of TLC-grade silica gel; eluant is 15% ethyl acetate in petroleum ether). There is isolated 6.4–6.5 g (43%, (Note 12)) of the cyclized diketone as a colorless oil (Note 13) and 1.11 g (7.3%) of starting material.

2. Notes

1. Cooling should be applied to moderate the reaction while maintaining a vigorous evolution of gas or the reaction time is prolonged unduly.

2. Cooling below 0°C will induce precipitation of the sodium diethyl malonate.

3. 3-Methyl-2-cyclohexen-1-one can be purchased from the Aldrich Chemical Company, Inc. or prepared according to a known procedure.[2] Checkers obtained material from Aldrich Chemical Company, Inc. and Lancaster Synthesis, Inc.

4. The checkers employed 600 mL of ether in the first extraction to ensure separation of the phases.

5. According to the literature,[3] these esters consist of the product of Michael addition to 3-methylcyclohexenone and of an isomer arising from rearrangement of this primary adduct.

6. The keto acid exhibits the following spectral properties: IR (neat) cm^{-1}: 3500–2500, 1730, 1705; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.07 (s, 3 H), 1.61–1.77 (m, 2 H), 1.77–1.97 (m, 3 H), 2.14–2.44 (m, 5 H), 8.4–10 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.8, 25.3, 35.7, 38.0, 40.7, 45.4, 53.0, 176.9, 179.7.

7. Polyphosphoric acid can be prepared by the addition of 200 g of phosphorus pentoxide (P_2O_5) to 100 mL of an 85% solution of phosphoric acid and heating to 170°C with vigorous stirring until all of the P_2O_5 is dissolved (ca. 6 hr).

8. Continuous extraction of the aqueous phase with toluene can also be applied for 3 days in order to yield 80% of the diketone after Kugelrohr distillation.

9. The pure diketone is a colorless solid, mp 75–76°C; IR (neat) cm^{-1}: 1735, 1710; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.17 (s, 3 H), 1.67–1.73 (m, 2 H), 2.07–2.13 (m, 2 H), 2.22 (ABq, 4 H, J_{AB} = 8.0, $\Delta\nu_{AB}$ = 35.05), 3.16 (t, 1 H, J = 2.9); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.7, 25.7, 31.0, 33.9, 50.4, 63.4, 206.6.

10. The 1.07 *M* anhydrous ferric chloride solution in dimethylformamide is prepared as follows: 178.43 g (1.1 mmol) of anhydrous solid ferric chloride is refluxed over 360 mL of thionyl chloride for 4 days at atmospheric pressure. After the solution is cooled, thionyl chloride is removed by distillation at 20 mm and trapped in a 1-L, round-bottomed flask cooled to −78°C. The sold residue is stirred for 1 hr at room temperature under reduced pressure (ca. 20 mm) and heated at 40°C for 1 hr under high vacuum (ca. 1 mm). Drying without heating is then continued overnight under high vacuum. The flask is filled with argon and cooled to 0°C. Approximately 600 mL of freshly distilled dimethylformamide is then slowly added (exothermic reaction). The entire dissolution of solid ferric chloride is achieved in an ultrasound bath during 24 hr. After decantation, the dark brown solution is transferred under argon to a 1-L volumetric flask and the required level is adjusted with freshly distilled dimethylformamide.

11. The checkers found that vigorous mechanical stirring was required because of the viscosity of the dimethylformamide solution at −78°C; otherwise, diminished yields were observed.

12. The yields obtained range from 40 to 54% depending principally on the rate of the inverse addition and the scale of the reaction.

13. The tricyclic diketone, a colorless oil which slowly solidifies, exhibits mp 34.5–35.0°C; IR (neat) cm^{-1}: 1760, 1710; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.26 (s, 3 H), 2.00–2.06 (m, 2 H), 2.27–2.30 (m, 2 H), 2.46–2.68 (m, 1 H), 2.68 (d, 2 H, J = 1.3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.3, 26.6, 30.9, 47.1, 48.9, 52.6, 203.5.

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3. Discussion

The initial Michael addition step is a modified and improved version of a procedure originally developed by Farmer and Ross.[3] The second step involving acid-catalyzed dehydration of the cyclohexanone-3-acetic acid is adapted from earlier work developed for the desmethyl series.[4]

The intermolecular dimerization of ketone enolates to give 1,4-diketones has been accomplished earlier with cupric[5] [6,7] and ferric salts.[8] These transition-metal salts have also been used to achieve intramolecular carbon–carbon bond formation.[7,9,10] However, Step C represents the only reported example[11] of cyclopropane construction via technology of this type.

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References and Notes

1. Department of Chemistry, The Ohio State University, Columbus, OH 43210.
2. ApSimon, J. W.; Badripersaud, S.; Nguyen, T. T. T.; Pike, R. *Can. J. Chem.* **1978**, *56*, 1646.
3. Farmer, E. H.; Ross, J. *J. Chem. Soc.* **1925**, *127*, 2358.
4. Gerlach, H.; Müller, W. *Angew. Chem., Intn. Ed. Engl.* **1972**, *11*, 1020; see also Oplinger, J. A.; Paquette, L. A. *Tetrahedron Lett.* **1987**, *28*, 5441.
5. Ito, Y.; Konoike, T.; Saegusa, T. *J. Am. Chem. Soc.* **1975**, *97*, 2912;
6. Kobayashi, Y.; Taguchi, T.; Tokuno, E. *Tetrahedron Lett.* **1977**, 3741.
7. Ito, Y.; Konoike, T.; Harada, T.; Saegusa, T. *J. Am. Chem. Soc.* **1977**, *99*, 1487.
8. Frazier, R. H., Jr.; Harlow, R. L. *J. Org. Chem.* **1980**, *45*, 5408.
9. Paquette, L. A.; Snow, R. A.; Muthard, J. L.; Cynkowski, T. *J. Am. Chem. Soc.* **1978**, *100*, 1600.
10. Kobayashi, Y.; Tagushi, T.; Morikawa, T. *Tetrahedron Lett.* **1978**, 3555.
11. Poupart, M.-A.; Paquette, L. A. *Tetrahedron Lett.* **1988**, *29*, 269.
12. Unpublished results courtesy of Deeter, J. B. (Eli Lilly Company).

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

petroleum ether

brine

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

thionyl chloride (7719-09-7)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

sodium (13966-32-0)

phosphoric acid (7664-38-2)

ferric chloride (7705-08-0)

diethyl malonate (105-53-3)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

dimethylformamide (68-12-2)

argon (7440-37-1)

3-methyl-2-cyclohexen-1-one,
3-methylcyclohexenone

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

phosphorus pentoxide (1314-56-3)

4-Methyltricyclo[2.2.2.$0^{3,5}$]octane-2,6-dione,

Tricyclo[3.2.1.$0^{2,7}$]octane-6,8-dione, 2-methyl- (119986-99-1)

sodium diethyl malonate

3-Methylcyclohexanone-3-acetic acid (119986-97-9)

4-Methylbicyclo[2.2.2]octane-2,6-dione (119986-98-0)