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of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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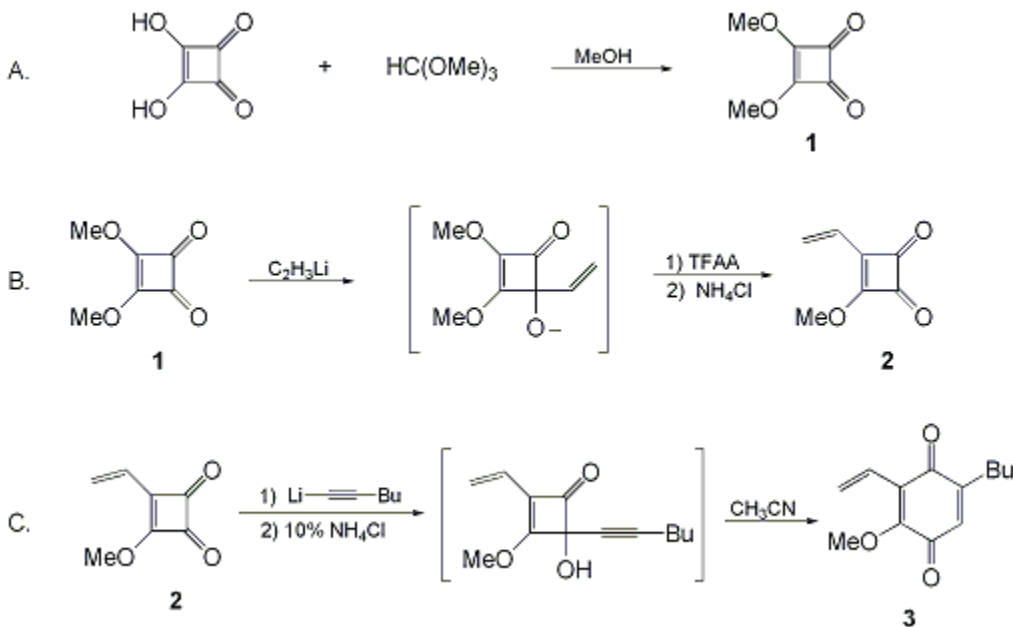
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

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DIMETHYL SQUARATE AND ITS CONVERSION TO 3-ETHENYL-4-METHOXYCYCLOBUTENE-1,2-DIONE AND 2-BUTYL-6-ETHENYL-5-METHOXY-1,4-BENZOQUINONE

[3-Cyclobutene-1,2-dione, 3-ethenyl-4-methoxy- and 2,5-cyclohexadiene-1,4-dione, 5-butyl-3-ethenyl-2-methoxy- from 3-cyclobutene-1,2-dione, 3,4-dimethoxy-]



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Checked by Shino Manabe and Kenji Koga.

1. Procedure

A. Dimethyl squarate (1) An oven-dried, 500-mL, round-bottomed flask equipped with a magnetic stirring bar and an 18-cm reflux condenser topped with a U-shaped drying tube/ (Note 1) is charged with 20.52 g (180.0 mmol) of squaric acid (Note 2), 180 mL of methanol (Note 3), and 38.78 g (365.4 mmol) of trimethyl orthoformate (Note 4) and (Note 5). The mixture is heated at reflux (Note 6) with stirring for 4 hr (Note 7). At this time 50 mL of the solvent is slowly removed by distillation (Note 8) over the next 2 hr (Note 9). The resulting solution is heated at reflux for an additional 18 hr. The reaction solution is then concentrated under reduced pressure to remove the volatile components (Note 10). The resulting pale yellow solid is dissolved in 40 mL of methylene chloride (Note 11), and the mixture is purified by flash chromatography on a 40-mm column containing 60 g of silica gel 60 (Note 12) using 600 mL of methylene chloride as the eluant. Removal of the solvent at reduced pressure with the use of a rotary evaporator (Note 13) provides a white solid that is redissolved in 40 mL of methylene chloride. This solution is diluted with 150 mL of anhydrous ether (Note 14). The solvent is removed under reduced pressure (Note 10) to afford 22.75 g (89% yield) of dimethyl squarate as a white solid (Note 15) that is stored under nitrogen, mp 55–56°C (lit.² mp 55–57°C) (Note 16), (Note 17), and (Note 18).

B. 3-Ethenyl-4-methoxycyclobutene-1,2-dione (2). A 2-L, flame-dried, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and nitrogen bubbler is charged with 10.0 g (70.4 mmol) of dimethyl squarate, 1, and 1 L of dry tetrahydrofuran (THF) (Note 19). The stirred solution is cooled in a dry ice-acetone bath at –78°C, and 39.0 mL (91.7 mmol) of vinyl lithium (2.35 M) (Note 20)

and (Note 21) is added via syringe in four portions to the dimethyl squarate solution. After the addition is complete, the yellow solution is stirred for 2 hr (Note 22), whereupon 14.8 mL (105 mmol) of trifluoroacetic anhydride (Note 23) is added dropwise via syringe. The resulting yellow solution is stirred for 30 min and quenched by pouring the cold solution into a 3-L separatory funnel containing 500 mL of aqueous ammonium chloride (10%) (NH₄Cl) and 500 mL of ethyl acetate. The separatory funnel is shaken vigorously and allowed to warm to room temperature. The aqueous layer is removed and washed twice with 200 mL of ethyl acetate. The combined organic layers are washed with 400 mL of brine and dried over solid anhydrous magnesium sulfate. The solution is filtered and concentrated under reduced pressure on a rotary evaporator (Note 24). The resulting oil is dissolved in 30 mL of ethyl acetate and purified by flash chromatography (9.5 × 45.0-cm column) through silica gel (400 g, 32–63 microns) using hexanes/ethyl acetate (7/3) (Note 25) to yield 6.55 g (67%) of the title compound **2** as yellow crystals (Note 26), (Note 27), and (Note 28) (mp 59–61°C).

C. *2-Butyl-6-ethenyl-5-methoxy-1,4-benzoquinone* (**3**). A 100-mL, flame-dried, round-bottomed flask equipped with a magnetic stirring bar, rubber septum and nitrogen bubbler is charged with 1.84 g (22.44 mmol) of 1-hexyne (Note 29) and 50 mL of dry THF. The stirred solution is cooled in a dry ice-acetone bath at –78°C and 20.4 mL (22.44 mmol) of 1.1 M butyllithium (BuLi) (Note 30) is added via syringe. The resulting solution is stirred for 20 min. This solution is transferred via cannula to a solution of 2.58 g (18.70 mmol) of 2-ethenyl-3-methoxycyclobutendione in 350 mL of dry THF in a dry ice-acetone bath. The resulting solution is stirred for 60 min and then quenched with 100 mL of aqueous 10% NH₄Cl. The aqueous layer is separated and extracted with ethyl acetate (2 × 50 mL), and the combined organic layers are washed with brine (150 mL), dried (MgSO₄), and concentrated under reduced pressure. The crude cyclobutenone is dissolved in 350 mL of freshly distilled acetonitrile (CH₃CN) (Note 31) and refluxed for 1.5 hr (Note 32). The CH₃CN is then removed under reduced pressure. The resulting red oil is purified by flash chromatography (SiO₂, 110 g) eluting with ethyl acetate:hexanes (1:10) to yield 2.01 g (49% from cyclobutendione **2**) of **3** as a red oil (Note 33).

2. Notes

1. The drying tube contains Drierite as the drying agent.
2. Squaric acid can be obtained from the Aldrich Chemical Company, Inc.
3. Methanol (99.9%, 0.02% H₂O) was used as received from Fisher Scientific Company.
4. Trimethyl orthoformate (98%) was used as received from the Aldrich Chemical Company, Inc. It is important to use the 98% solution rather than the available 99.8% solution in order to avoid unwanted excess of this reagent (Note 5).
5. The use of more trimethyl orthoformate than specified results in the eventual formation of 2,3,4,4-tetramethoxy-2-cyclobuten-1-one as a side product.
6. The temperature of the refluxing solution is approximately 56°C.
7. The initial heterogeneous mixture become homogeneous after approximately 2.5 hr under reflux conditions.
8. The purpose of this operation is to remove the by-product, methyl formate (bp 34°C), by short path distillation.
9. The temperature of the solution after distillation is approximately 63°C.
10. All volatile components are removed under reduced pressure using a rotary evaporator; the crude product is subsequently placed under an oil pump for 2 hr.
11. Methylene chloride (99.9%) was used as received from Fisher Scientific Company.
12. The silica gel (230–400 mesh) was purchased from East Merck Science.
13. The precipitate is very hard and difficult to remove from the flask. By redissolving in methylene chloride/diethyl ether the product is obtained as a fluffy white solid.
14. Anhydrous ether (99.9%, 0.002% H₂O) was used as received from Fisher Scientific Company.
15. The product shows no contaminant at the baseline by TLC analysis and has the following spectral properties: ¹H NMR (300 MHz, CDCl₃) δ: 4.37 (s); ¹³C NMR (75 MHz, CDCl₃) δ: 61.0, 184.5, 189.2.
16. For the first preparation of dimethyl squarate see Cohen.²
17. For a recent review on the synthetic utility of squaric acid and related cyclobutenones see Moore.³
18. The synthesis of dimethyl squarate as outlined here is a general method that can be employed for the synthesis of a variety of other alkyl squarates.⁴
19. Tetrahydrofuran was distilled under nitrogen from benzophenone ketyl.

20. **Vinyllithium** was purchased from Organometallics Inc. as a 2.35 M solution in **tetrahydrofuran** and used as such. Best results are obtained when a new bottle is used, and yields are very dependent upon the quality of the reagent.
21. **Vinyllithium** can also be generated in situ by the dropwise addition of 90 mL of a 1.02 N solution of **methyllithium** in ether (91.48 mmol) to a solution of 4.5 mL (24.63 mmol) of **tetravinyltin** (Aldrich Chemical Company, Inc.) in **tetrahydrofuran** (60 mL) at 0°C. The solution is stirred at 0°C for 30 min and used directly. The checkers obtained a 93% yield of product using **vinyllithium** thus prepared.
22. A 1-mL aliquot is taken from the reaction flask and 2 drops of **trifluoroacetic anhydride** (Note 23) is added. The solution is then checked against **dimethyl squarate** by TLC (7/3 hex/EtOAc). If **dimethyl squarate**, **1**, is present an additional 5 mL (11.75 mmol) of **vinyllithium** is added. The solution is allowed to stir for 20 min and the above procedure is repeated until there is no evidence of **dimethyl squarate**.
23. **Trifluoroacetic anhydride** was purchased from the Aldrich Chemical Company, Inc., and used as such.
24. The water bath should not exceed 35°C because of possible decomposition.
25. The vinylcyclobutenedione **2** will elute from the column as the second yellow band.
26. Prolonged exposure to air will result in decomposition of the vinylcyclobutenedione.
27. If a solid is not initially formed the oil will solidify upon standing under vacuum.
28. Spectral properties are as follows: IR (CHCl₃) cm⁻¹: 2690, 1790, 1770, 1750, 1620, 1590, 1580, 1460, 1410, 1370, 1350, 1050; ¹H NMR (300 MHz, CDCl₃) δ: 4.48 (s, 3 H), 5.87 (dd, 1 H, J = 10.5, 1.9), 6.50 (dd, 1 H, J = 17.6, 1.8), 6.65 (dd, 1 H, J = 17.6, 10.5); ¹³C NMR (500 MHz, CDCl₃) δ: 61.4, 122.1, 128.9, 173.4, 192.6, 192.8, 194.6; MS (EI), m/e (rel intensity) 138 (12), 110 (30), 95 (75), 82 (22), 67 (39), 58 (14), 53 (100). Exact mass calcd for C₇H₆O₃: 138.0317, found 138.0335.
29. **1-Hexyne** (97% purity) was purchased from Lancaster Chemical Company, Inc., and used as such.
30. **Butyllithium** was purchased from Aldrich Chemical Company, Inc., as a 1.6 M solution in **hexane** and titrated with **diphenylacetic acid** to indicate a concentration of 1.1 M at the time of use.
31. **Acetonitrile** was distilled under **nitrogen** from **calcium hydride**.
32. The progress of the reaction can be monitored by TLC (**ethyl acetate**:**hexanes** = 1:5).
33. The spectral properties are as follows: IR (CCl₄) cm⁻¹: 2959, 2783, 1655, 1448, 1321, 1215, 1143, 999, 935, 885; ¹H NMR (300 MHz, CDCl₃) δ: 0.93 (t, 3 H, J = 7.0), 1.43 (m, 4 H), 2.42 (t, 2 H, J = 6.7), 4.08 (s, 3 H), 5.63 (dd, 1 H, J = 12.0, 2.4), 6.26 (dd, 1 H, J = 17.7, 2.1), 6.41 (s, 1 H), 6.70 (dd, 1 H, J = 17.7, 12.0); ¹³C NMR (300 MHz, CDCl₃) δ: 13.7, 22.3, 28.7, 29.9, 60.8, 124.7, 125.1, 125.4, 130.6, 149.5, 154.4, 183.8, 187.2; MS (EI) m/e (rel int) 220 (19), 177 (44), 160 (65), 135 (45), 91 (43), 79 (43), 67 (54), 53 (100); exact mass calcd for C₁₃H₁₆O₃: 220.1099, found 220.1108.

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

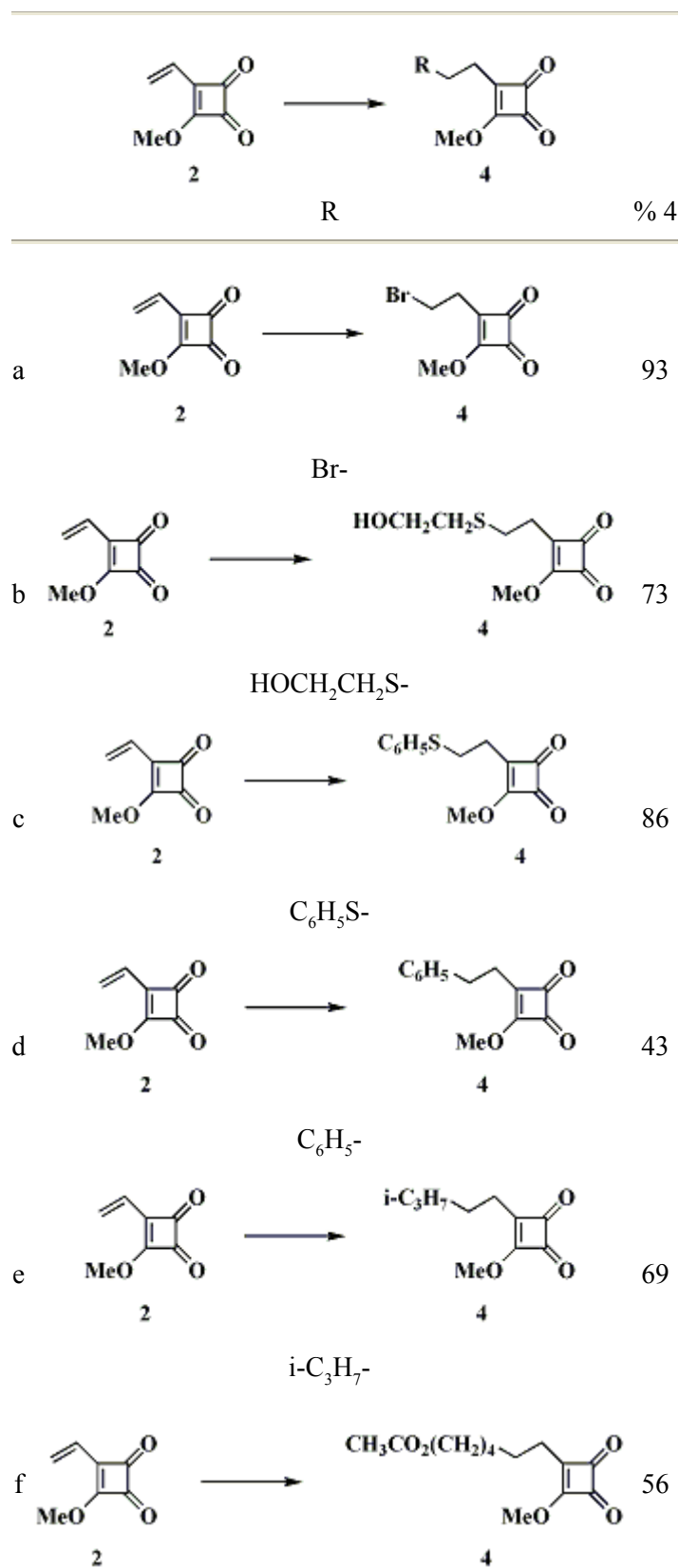
Dimethyl squarate has recently been used for the versatile and regiospecific synthetic routes to highly substituted benzo- and naphthoquinones and related aromatic compounds.³

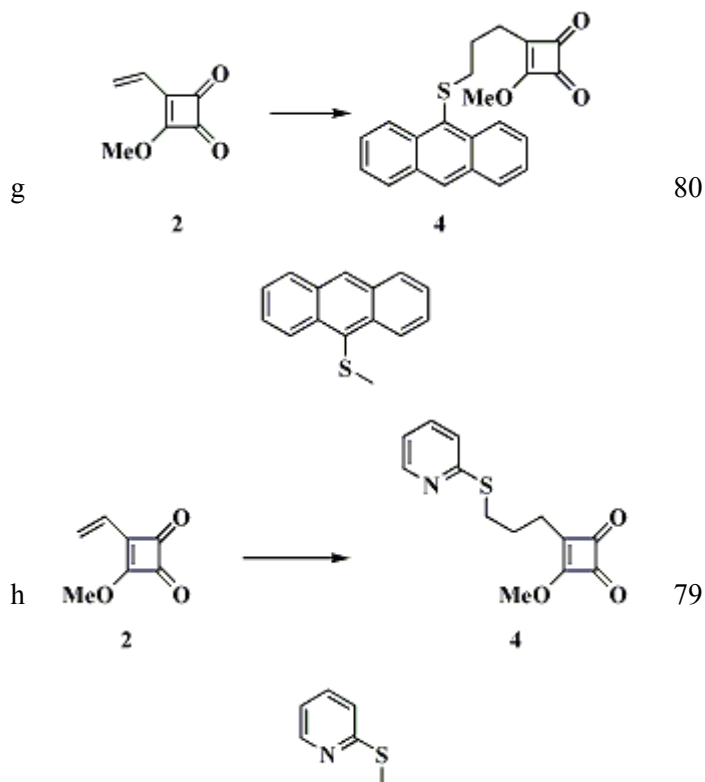
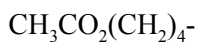
Two other syntheses of **dimethyl squarate** have been reported.² One such method involves the formation of the disilver salt of **squaric acid** followed by treatment with **methyl iodide**. This process, unfortunately, is laborious as well as costly. The other synthesis involves the reaction of **squaric acid** with **diazomethane**. This reaction not only gives a lower yield, but is inherently unsuited for large scale preparations. The synthesis presented here provides a convenient and inexpensive route to the preparation of **dimethyl squarate**, and is also suitable for large scale synthesis.⁴ One should take precautions when synthesizing or using dialkyl squarates, particularly **dimethyl squarate**, since they are known to cause severe contact dermatitis.⁵ Thus, all procedures should be carried out in the hood and protective clothing and gloves should be worn.

This procedure describes a synthetic route to vinylcyclobutenediones that are important intermediates in the synthesis of other cyclobutenediones (Table) and quinones.^{6,7} For example

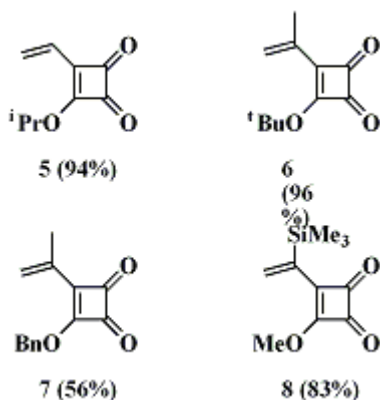
vinylcyclobutenedione **2** readily undergoes 1,6-addition of nucleophiles such as thiols and organocuprates to form more highly substituted products as shown in the generalized scheme below.

TABLE
SYNTHESIS OF CYCLOBUTENEDIONES





The vinylcyclobutenediones **5-8** are representative of other analogs that have been prepared by the general method outlined here.⁸



References and Notes

1. Department of Chemistry, University of California, Irvine, CA 92717.
2. Cohen, S.; Cohen, S. G. *J. Am. Chem. Soc.* **1966**, *88*, 1533.
3. Moore, H. W.; Yerxa, B. R. *Adv. Strain Org. Chem.* **1995**, *4*, 81-162.
4. Liu, H.; Tomooka, C. S.; Moore, H. W. *Synthetic Comm.* **1997**, *27*, 2177.
5. Avalos, J.; Moore, H. W.; Reed, M. W.; Rodriguez, E. *Journal of Contact Dermatitis* **1989**, *21*, 341.
6. Xu, S.; Yerxa, B. R.; Sullivan, R. W.; Moore H. W. *Tetrahedron Lett.* **1991**, *32*, 1129.
7. For a review on the synthetic utility of cyclobutenone ring expansions Moore, H. W.; Yerxa, B. R. *ChemTracts* **1992**, *5*, 273.

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

Dimethyl squarate:

Cyclobutenedione, dimethoxy- (8);
3-Cyclobutene-1,2-dione, 3,4-dimethoxy- (9); (5222-73-1)

3-Ethenyl-4-methoxycyclobutene-1,2-dione:

3-Cyclobutene-1,2-dione, 3-ethenyl-4-methoxy- (12); (124022-02-2)

2-Butyl-6-ethenyl-5-methoxy-1,4-benzoquinone:

2,5-Cyclohexadiene-1,4-dione, 5-butyl-3-ethenyl-2-methoxy- (12); (134863-12-0)

Squaric acid:

Cyclobutenedione, dihydroxy- (8);
3-Cyclobutene-1,2-dione, 3,4-dihydroxy- (9); (2892-51-5)

Trimethyl orthoformate:

Orthoformic acid, trimethyl ester (8);
Methane, trimethoxy- (9); (149-73-5)

Vinyl lithium:

Lithium, vinyl- (8);
Lithium, ethenyl- (9); (917-57-7)

Trifluoroacetic anhydride:

Acetic acid, trifluoro-, anhydride (8,9); (407-25-0)

1-Hexyne (8,9); (693-02-7)

Butyllithium:

Lithium, butyl- (8,9); (109-72-8)