Ketene dimethyl thioacetal monoxide (6) can thus be prepared in moderate yield by a convenient two-step reaction sequence representing a significant improvement over the previously reported method both in terms of preparation time and cost of reagents.

Experimental Section

Proton NMR spectra were recorded on a Hitachi Perkin-Elmer R-24B instrument with tetramethylsilane as internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 621 grating instrument and mass spectra were obtained from a Hitachi Perkin-Elmer RMU-6E double-focusing instrument. Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, IN.

Tetrahydrofuran (THF) was dried and purified by distillation from sodium–potassium alloy prior to use. Diisopropylamine was distilled from calcium oxide and stored over 3-Å molecular sieves. Standardization of *n*-butyllithium and methylmagnesium chloride was performed by reaction with excess standard acid and back titration with standard base to a phenolphthalein end point.

Ketene Dimethyl Thioacetal (5). A solution of 90.0 mL (2.8 M, 252 mmol) of methylmagnesium chloride in THF under N_2 was diluted with THF to make a 1 M solution. Then a solution made by diluting 28.55 g (375 mmol) of carbon disulfide with an equal volume of THF was added to the mechanically stirred[7] Grignard reagent at a rate sufficient to increase the temperature of the reaction mixture to 40–45 °C and maintain this temperature range during the remainder of the carbon disulfide addition. After addition was complete the reaction mixture was stirred for 2 h, maintaining the temperature between 40–45 °C, and then cooled to −78 °C with a dry ice–acetone bath. Then a 0 °C solution of lithium diisopropylamide[8] was added dropwise, during 30 min, to the cold reaction mixture. The resulting solution was stirred at −78 °C for 2 h and then 63.6 g (504 mmol) of dimethyl sulfate was added during 1 h while the same low temperature was maintained. The resulting mixture was allowed to warm to room temperature and stirred at this temperature for 2 h. Then 300 mL of ether was added and after being stirred briefly the solution was allowed to stand during which time inorganic salts precipitated. The supernatant solution was decanted from the salts into 500 mL of 1% aqueous $NaHCO_3$ solution and the salts were washed with ether. The combined ether washings were added to the $NaHCO_3$ solution, the resulting mixture was shaken, and the layers were separated. The aqueous layer was extracted with two 150-mL portions of ether which were then added to the organic layer. The resulting organic solution was washed with two 100-mL portions of water, dried ($MgSO_4$), and distilled of solvent on a rotary evaporator to give 28.8 g (95%) of the crude product which was distilled under reduced pressure to give 18.2 g (60%) of a yellow liquid: bp 76–78 °C (26 mm); ^1H NMR ($CDCl_3$) δ 2.28 (6 H, s), 5.08 (2 H, s); IR (neat) 1580, 1560, 1445, 1430, 1327, 1108, 983, 802–865 cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 120 (79.5, M^+), 105 (18.8), 73 (100.0), 61 (40.6), 58 (49.7), 45 (53.0).

Anal. Calcd for $C_4H_8S_2$: C, 39.96; H, 6.71. Found: C, 40.11; H, 6.76.

Ketene Dimethyl Thioacetal Monoxide (6). To a solution of 6.8 g (50 mmol) of **5** in 100 mL of CH_2Cl_2 under an atmosphere of N_2 and maintained at −5 °C with a ice–salt bath was added 10.2 g (50 mmol) of 85% *m*-chloroperbenzoic acid in portions at such a rate that the temperature did not exceed 0 °C. The resulting solution was allowed to stir for 15 min at −5 °C and then for 1 h at room temperature after which time the reaction mixture was poured into 200 mL of 5% aqueous $NaHCO_3$ solution. The aqueous layer was extracted with two 50-mL portions of CH_2CL_2 which were combined with the organic layer. The resulting solution was dried ($MgSO_4$) and distilled of solvent on a rotary evaporator to give 5.8 g (85%) of **6** sufficiently pure (NMR analysis) for most purposes. Further purification by distillation under reduced pressure gave 4.8 g (71%) of a yellow liquid: bp 145–150 °C (27 mm); ^1H NMR ($CDCl_3$) δ 2.38 (3 H, s), 2.64 (3 H, s), 5.51 (1 H, d, J = 2 Hz), 6.01 (1 H, d, J = 2 Hz); IR (neat) 3490, 1593, 1429, 1330, 1070, 970, 893 cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 136 (5.9, M^+), 126 (0.8), 120 (1.6), 108 (3.2), 90 (8.4), 73 (100.0), 58 (15.1).

(7) Mechanical stirring is necessary because when the intermediate dianion is formed the reaction mixture is too viscous to permit the use of magnetic stirring.

(8) The LDA was made by adding 158 mL (1.6 M, 252 mmol) of *n*-butyl lithium in hexane to a solution of 25.5 g (252 mmol) of diisopropylamine in THF under N_2 and cooled in a salt–ice bath at such a rate that the temperature of the reaction mixture did not rise above 0 °C. The resulting solution was allowed to react for 0.5 h and then added to the ketene acetal reaction mixture.

Acknowledgment. We express our appreciation to the Robert A. Welch Foundation (Grant B-746 to N.R.B.) and to the North Texas State University Faculty Research Fund for support of this research.

Registry No. 2, 594-03-6; **3**, 2168-84-5; **5**, 51102-74-0; **6**, 51534-42-0; methyl chloride, 74-87-3; carbon disulfide, 75-15-0; dimethyl sulfate, 77-78-1.

Enone Mesylates. Precursors to β-Substituted Cyclohexenones

Conrad J. Kowalski* and Kevin W. Fields

Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556

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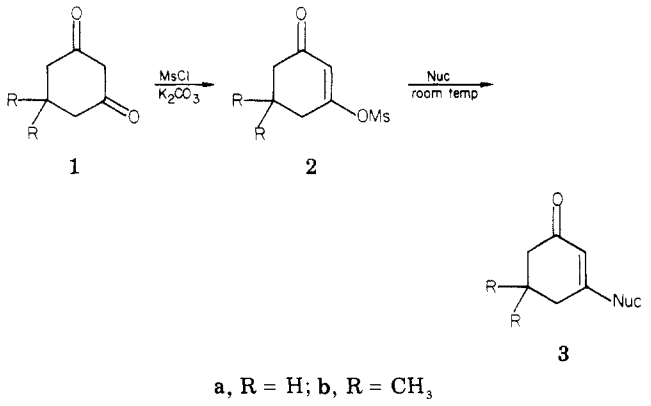
β-Substituted cyclohexenones are valuable synthetic intermediates which are frequently employed in various schemes. Piers uses the conjugate addition of a suitable cyclopropylcuprate to 3-iodo-2-cyclohexenone in his approach to β-himachalene.[1] Wender generates spiro compounds by adding an organobiscuprate to β-chlorocyclohexenones.[2] Okamura's approach to the vitamin D system employs 3-iodo-2-methylcyclohexenone,[3] while Stork's widely used entry into 4-alkylcyclohexenones starts from β-alkoxycyclohexenones.[4] β-Aminocyclohexenones are important intermediates in Mariano's amino-Claisen rearrangement,[5] and the thioalkyl-substituted enones are starting materials for Bryson in forming functionalized 3-alkylcyclohexenones.[6] These represent but a few of the many uses to which such compounds have been put.

As a result of their importance, β-substituted cyclohexenones have been prepared by numerous methods.[1-6] Significant improvements have recently been made by Piers[7] and Heathcock[8] in approaches to the haloenones from 1,3-diones, their usual precursors. Both the orthoester approach[9] and "Organic Syntheses" procedure[10] allow formation of 3-alkoxycyclohexenones from the 1,3-diones. Other procedures are used to prepare amino-[5] and mercapto-substituted[6] enones. Despite these advances and others, however, there is no simple, general route which

(1) Piers, E.; Ruediger, E. H. *J. Chem. Soc., Chem. Commun.* **1979**, 166.
(2) Wender, P. A.; Eck, S. L. *Tetrahedron Lett.* **1977**, 1245.
(3) Hammond, M. L.; Mouriño, A.; Okamura, W. H. *J. Am. Chem. Soc.* **1978**, *100*, 4907.
(4) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775.
(5) Mariano, P. S.; Dunaway-Mariano, D.; Huesmann, P. L. *J. Org. Chem.* **1979**, *44*, 124.
(6) Bryson, T. A.; Dardis, R. E.; Gammil, R. B. *Tetrahedron Lett.* **1978**, 743.
(7) Piers, E.; Nagakura, I. *Synth. Commun.* **1975**, 193.
(8) Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 636.
(9) Meek, E. G.; Turnbull, J. H.; Wilson, W. *J. Chem. Soc.* **1953**, 811.
(10) Gannon, W. F.; House, H. O. "Organic Syntheses"; Wiley; New York, 1973; Collect. Vol. 5, p 539.

0022-3263/81/1946-0197$01.00/0

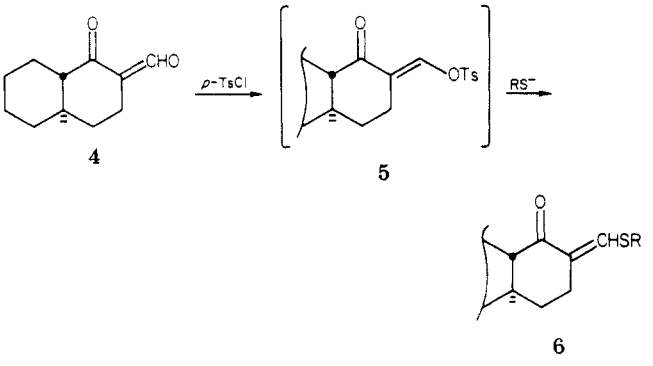
Scheme I



a, R = H; b, R = CH_3

leads to all of the above compound types from a cyclohexane-1,3-dione precursor. We sought such a method, and, moreover, one which would proceed under mild conditions, at room temperature, and in high yield.

Our solution to this problem centers about the use of 3-(mesyloxy)-2-cyclohexenones (enone mesylates) as illustrated in Scheme I. We have found only one such compound, **2b**, in the literature,[11] prepared in 55% yield from dimedone, **1b**, and utilized only once since in a study unrelated to our objectives.[12] While little is known of the chemistry of such compounds, an earlier report by Ireland[13] describes in situ formation of tosylate **5** from hydroxymethylene ketone **4**, followed by mercaptide addition to



produce **6**. Although the yield for this procedure was only 60%, it provided a strong precedent for our planned transformation.

After a variety of attempts, mild conditions were found for reproducibly preparing both enone mesylates **2a** and **2b** in high yield. Stirring diketone **1a** or **1b** at room temperature in methylene chloride with excess potassium carbonate afforded after 2 h crude mesylate **2a** or **2b** in 92% yield. These compounds gave excellent IR and NMR spectra and could be stored without appreciable decomposition in methylene chloride solution at 0 °C for several days. On attempted purification or on standing as neat liquids for several hours at room temperature, however, these compounds consistently decomposed. Thus the mesylates were generally prepared fresh just prior to use and were employed without further purification; yields from subsequent reactions suggest a mesylate purity of at least 90–95%. Unfortunately, attempts to extend this procedure to acyclic 1,3-diketones (e.g., acetoacetone) were unsuccessful, generally returning starting diketone. This aspect was not extensively pursued.

Reactions of mesylates **2a** and **2b** with a variety of nucleophiles to afford β-substituted enones are summarized in Table I. All reactions were effected in a matter of hours or minutes at room temperature simply by stirring the mesylate with the appropriate soluble nucleophile. In the case of the halides, the readily available benzyltriethylammonium salts[14] (soluble in methylene chloride) were used, along with 1 equiv or less of boron trifluoride etherate to speed the reaction. Under these conditions, mesylate **2a** afforded halides **7a–9a** in less than 1 h, while the dimedone mesylate **2b** required 4 to 8 h for product formation. The longer times required in these latter cases presumably reflect the presence of an axial methyl group 1,3 to the site of nucleophilic attack on the enone. Halides obtained from this procedure after aqueous workup were simply filtered (not chromatographed) through silica gel to remove the remaining ammonium salt. In every case, the product so obtained (in 86–91% yield) was identical with that from subsequent Kugelröhr distillation. Especially noteworthy among the halide results are the formation times and yields for iodides **9a** and **9b**, to be contrasted with those of the literature procedure[7] which requires from 1 day (~60% yield) to 4 days (~80% yield).

Formation of vinylogous ester **10** was trivially accomplished by merely adding mesylate **2a** to a stirred solution of sodium ethoxide in ethanol. Although the procedure requires two steps from diketone **1a**, the preparation of **10** via this route is extremely easy and high yielding, and in contrast to the acid-catalyzed literature procedures,[9,10] employs basic conditions during both steps. Similarly, vinylogous amides **11a** and **11b** are obtained simply by mixing the appropriate mesylate with aqueous dimethylamine and stirring. Benzyl mercaptan reacts only sluggishly with mesylate **2a**, but the mercaptide sodium salt adds quite well, affording enone **12**.

When mesylate **2a** was added to excess lithium dimethylcuprate, the bis adduct **13** readily formed. Several attempts to induce monoaddition, by using 1 equiv of cuprate, inverse addition, and various temperatures, all produced mixtures containing starting **2a**, **13**, and 3-methylcyclohexenone. Thus, it appears that loss of the mesylate group from the monoadduct, and subsequent addition to the 3-methylenone, must compete with initial addition to **2a**.

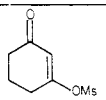
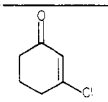
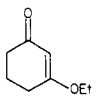
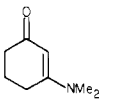
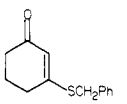
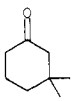
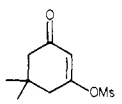
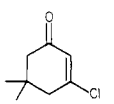
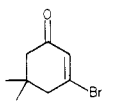
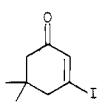
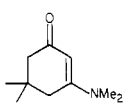
In summary, we have developed an extremely simple approach to β-substituted cyclohexenones from the 1,3-diketones via enone mesylates. Both mesylate formation and transformation to product occur in high yield at room temperature after short periods of time. The products formed are quite easily purified, and a variety of different β-substituted cyclohexenones can be obtained from a single mesylate.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian A-60A spectrometer and are reported in δ values (parts per million) relative to tetramethylsilane. Infrared spectra were recorded on a Perkin-Elmer Infracord spectrometer, as neat films for liquids or as ~10% solutions for solids in the solvent indicated. Dry ether was distilled from lithium aluminum hydride just before use; boron trifluoride etherate was distilled once and stored protected from air and light. Methanesulfonyl

(11) Esayan, G. T.; Galoyan, G. A.; Baboyan, A. A.; Postoyan, N. R. *Dokl. Akad. Nauk. Arm. SSSR* **1964**, *38*, 301; *Chem. Abstr.* **1964**, *61*, 13207.
(12) DeMayo, P.; Wasson, J. S. *Chem. Commun.* **1967**, 970.
(13) Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1962**, *27*, 1615.
(14) Both the chloro- and (bromobenzyl)triethylammonium salts are available from Aldrich Chemical. The iodo salt may be prepared by the following method: Finkelstein, M.; Petersen, R. C.; Ross, S. D. *J. Am. Chem. Soc.* **1959**, *81*, 2361.

Table I

mesylate	reagent[a]	solvent	time	product	% yield[b]
 2a	$BzNEt_3Cl$	CH_2Cl_2	45 min	 7a	83 (86)
	$BzNEt_3Br$	CH_2Cl_2	45 min	 8a	77 (87)
	$BzNEt_3I$	CH_2Cl_2	30 min	 9a	85 (91)
	NaOEt	EtOH	1 h	 10	91
	Me_2NH	H_2O/CH_2Cl_2	30 min	 11a	93
	$NaSCH_2Ph$	Et_2O/CH_2Cl_2	6 h	 12	89[c]
	Me_2CuLi	Et_2O		 13	72[d]
 2b	$BzNEt_3Cl$	CH_2Cl_2	4 h	 7b	85 (89)
	$BzNEt_3Br$	CH_2Cl_2	5 h	 8b	78 (87)
	$BzNEt_3I$	CH_2Cl_2	8 h	 9b	89 (90)
	Me_2NH	H_2O/CH_2Cl_2	8 h	 11b	80

[a] Boron trifluoride etherate used as catalyst for all halide additions. [b] Distilled product unless otherwise noted. Values in parentheses represent halide yields after silica gel filtration to remove salts. [c] Chromatographed material. [d] Crude product.

chloride (Aldrich Chemical Company) and methylene chloride were used without purification. Elemental analysis was performed by Midwest Microlab, Ltd., Indianapolis, IN.

3-(Mesyloxy)-2-cyclohexen-1-one (2a). To a stirred, room temperature solution of 436 mg (3.89 mmol) of 1,3-cyclohexanedione in 20 mL of methylene chloride was added 0.30 mL (3.89 mmol) of methanesulfonyl chloride and then 1.6 g (11.58 mmol) of anhydrous potassium carbonate. After being stirred for 2 h, the reaction mixture was diluted with 80 mL of methylene chloride and washed consecutively with 20 mL of water and 20 mL of saturated brine. The solution was dried over anhydrous magnesium sulfate, filtered, and rotary evaporated to afford 667 mg (92%) of mesylate **2a** as a yellow oil: IR (film) 1680, 1630 cm^{-1}; NMR ($CDCl_3$) δ 6.10 (t, 1 H, J = 1 Hz), 3.30 (s, 3 H, SCH_3), 2.8–1.8 (m, 6 H). This material decomposed on standing neat at room temperature for several hours, and thus no analysis was obtained; it could be stored as a methylene chloride solution at 5 °C for several days, however, with no evidence of decomposition. In general, freshly prepared mesylate was used for subsequent reactions.

3-(Mesyloxy)-5,5-dimethyl-2-cyclohexen-1-one (2b).[11] By the same procedure used to prepare **2a** above, 520 mg (3.7 mmol)

of dimedone, **1b**, was converted into 940 mg (92%) of crude mesylate **2b** as a yellow oil: IR (film) 1680, 1635 cm^{-1}; NMR ($CDCl_3$) δ 6.10 (t, 1 H, J = 1 Hz), 3.30 (s, 3 H, SCH_3), 2.55 (d, 2 H, J = 1 Hz), 2.30 (s, 2 H), 1.16 (s, 6 H).

3-Chloro-2-cyclohexen-1-one (7a).[7,8] To a stirred, room temperature solution of 586 mg (3.08 mmol) of mesylate **2a** in 15 mL of methylene chloride was added 1.4 g (6.16 mmol) of benzyltriethylammonium chloride. After addition of 0.095 mL (0.77 mmol) of boron trifluoride etherate in a single portion, the solution was stirred for 45 min and then diluted with 80 mL of methylene chloride. This solution was washed with 20 mL of water and 20 mL of saturated brine and dried with anhydrous magnesium sulfate. After removal of the drying agent and evaporation, the resulting oil was filtered through a column of 3.5 g of silica gel, using 30% ether in hexanes. Upon removal of the solvent, there remained 343 mg (86%) of crude product, which, after Kugelröhr distillation, afforded 333 mg (83%) of chloride **7a** as a pale yellow oil: IR (film) 1680, 1610 cm^{-1}; NMR ($CDCl_3$) δ 6.28 (t, 1 H, J = 1 Hz), 1.8–2.9 (m, 6 H).

Compounds **8a** and **9a** and **7b–9b** were prepared on a 1.17- to 3.13-mmol scale by using the following general procedure. To a stirred 0.2 M solution of mesylate in methylene chloride was added 2.5 equiv of the appropriate benzyltriethylammonium halide at room temperature. After addition of 1 equiv of boron trifluoride etherate in a single portion, the solution was stirred for the time indicated in Table I and then diluted with 80 mL of methylene chloride. This solution was washed with 20 mL of water and 20 mL of saturated brine and dried with anhydrous magnesium sulfate. After removal of the drying agent and evaporation of solvent, the resulting oil was filtered through about ten times its weight of silica gel, using 10–20% ether in hexanes. Removal of the solvent afforded a crude product which was further purified by Kugelröhr distillation. In every instance, the distilled product exhibited satisfactory spectral properties which were essentially unchanged from those of filtered material prior to distillation.

3-Chloro-5,5-dimethyl-2-cyclohexen-1-one (7b).[7] By the above procedure, 255 mg (1.17 mmol) of mesylate **2b** was converted into 165 mg (89%) of chloride **7b** as a pale yellow oil: IR (film) 1680, 1610 cm^{-1}; NMR ($CDCl_3$) δ 6.29 (t, 1 H, J = 1 Hz), 2.63 (d, 2 H, J = 1 Hz), 2.30 (s, 2 H), 1.15 (s, 6 H).

3-Bromo-2-cyclohexen-1-one (8a).[7] By the above procedure, 280 mg (1.47 mmol) of mesylate **2a** was converted into 224 mg (87%) of bromide **8a** as a pale yellow oil: IR (film) 1690, 1610 cm^{-1}; NMR ($CDCl_3$) δ 6.55 (t, 1 H, J = 2 Hz), 1.8–3.0 (m, 6 H).

3-Bromo-5,5-dimethyl-2-cyclohexen-1-one (8b).[7] By the above procedure, 590 mg (2.71 mmol) of mesylate **2b** was converted into 476 mg (87%) of bromide **8b** as a pale yellow oil: bp 95 °C (10 mm); IR (film) 1700, 1620 cm^{-1}; NMR ($CDCl_3$) δ 6.50 (t, 1 H, J = 1 Hz), 2.75 (d, 2 H, J = 1 Hz), 2.30 (s, 2 H), 1.15 (s, 6 H).

3-Iodo-2-cyclohexen-1-one (9a).[7] By the above procedure, 300 mg (1.58 mmol) of mesylate **2a** was converted into 320 mg (91%) of iodide **9a** as a pale yellow oil: IR (film) 1670, 1590 cm^{-1}; NMR ($CDCl_3$) δ 6.87 (t, 1 H, J = 1 Hz), 1.7–3.1 (m, 6 H).

3-Iodo-5,5-dimethyl-2-cyclohexen-1-one (9b).[7] By the above procedure, 682 mg (3.13 mmol) of mesylate **2b** was converted into 702 mg (90%) of iodide **9b** as a red oil: bp 110 °C (10 mm); IR (film) 1785, 1600 cm^{-1}; NMR ($CDCl_3$) δ 6.85 (t, 1 H, J = Hz), 2.85 (d, 2 H, J = 2 Hz), 2.39 (s, 2 H), 1.15 (s, 6 H).

3-Ethoxy-2-cyclohexen-1-one (10).[9,10] To a stirred, warm solution of 1.3 g (56.6 mmol) of metallic sodium dissolved in 50 mL of absolute ethanol was added 2.15 g (11.3 mmol) of mesylate **2a** in 30 mL of absolute ethanol. After being stirred for 1 h, the mixture was diluted with 375 mL of methylene chloride and washed with 100 mL of saturated aqueous ammonium chloride, 75 mL of water, and 75 mL of saturated brine. The solution was dried over anhydrous magnesium sulfate, filtered, and rotary evaporated. Short-path distillation of the residue afforded 1.443 g (91%) of vinylogous ester **10** as a clear oil: bp 96–99 °C (3 mm); IR 1640, 1603 cm^{-1}; NMR ($CDCl_3$) δ 5.40 (s, 1 H), 4.00 (q, 2 H, J = 6 Hz), 2.65–1.65 (m, 6 H), 1.4 (t, 3 H, J = 6 Hz).

3-(Dimethylamino)-2-cyclohexen-1-one (11a).[15] To a stirred, room temperature solution of 375 mg (1.97 mmol) of mesylate **2a** in 15 mL of methylene chloride was added 1.78 g (5 equiv) of 25% aqueous dimethylamine followed by 1.37 g (5 equiv) of anhydrous potassium carbonate. After being stirred for 30 min, the two-phase mixture was diluted with 150 mL of methylene chloride and washed consecutively with 40 mL of saturated aqueous sodium bicarbonate and 40 mL of saturated brine and dried with anhydrous magnesium sulfate. After removal of drying agent and evaporation, the residue was purified by Kugelröhr distillation to afford 255 mg (93%) of vinylogous amide **11a** as a yellow solid: mp 44–47 °C; IR (melted film) 3400, 1610, 1560 cm^{-1}; NMR ($CDCl_3$) δ 5.20 (s, 1 H), 3.04 (s, 6 H), 1.75–2.6 (m, 6 H).

3-(Dimethylamino)-5,5-dimethyl-2-cyclohexen-1-one (11b).[16] To a stirred, room temperature solution of 475 mg (2.18 mmol) of mesylate **2b** in 13 mL of methylene chloride was added 1.05 g (2.7 equiv) of 25% aqueous dimethylamine followed by 809 mg (2.7 equiv) of anhydrous potassium carbonate. After being stirred for 8 h, the two-phase mixture was diluted with 150 mL of methylene chloride and washed consecutively with 50 mL of saturated aqueous sodium bicarbonate and 50 mL of saturated brine and dried with anhydrous magnesium sulfate. Removal of drying agent and evaporation afforded 353 mg (97%) of yellow crystals. Recrystallization from hexanes afforded 291 mg (80%) of vinylogous amide **11b** as pale yellow-white crystals: mp 95–96 °C; IR (CCl_4) 1630, 1570 cm^{-1}; NMR ($CDCl_3$) δ 5.20 (s, 1 H), 3.03 (s, 6 H), 2.30 (s, 2 H), 2.17 (s, 2 H), 1.10 (s, 6 H).

3-(Benzylthio)-2-cyclohexen-1-one (12). To a stirred, room temperature mixture of 416 mg (8.7 mmol) of 50% sodium hydride in oil in 20 mL of dried ether under a nitrogen atmosphere was added 1.06 mL (9.0 mmole) of benzyl mercaptan. Ten minutes later, 660 mg (3.47 mmol) of mesylate **2a** in 4 mL of methylene chloride was added. After 6 h, the reaction mixture was diluted with 180 mL of methylene chloride and washed consecutively with 45 mL of saturated aqueous ammonium chloride, 45 mL of water, and 45 mL of water, and 45 mL of saturated brine. The solution was dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue was chromatographed on 17 of silica gel with 40% ether in hexanes to afford 676 mg (89%) of sulfide **12** as a pale yellow solid. The analytical sample was provided by recrystallization from methanol which provided white platelets: mp 77–78 °C; IR (CCl_4) 1660, 1580 cm^{-1}; NMR (CCl_4) δ 7.36 (s, 5 H), 5.85 (s, 1 H), 4.02 (s, 2 H), 1.70–2.70 (m, 6 H). Anal. Calcd for $C_{13}H_{14}OS$: C 71.52; H 6.46; S 14.69. Found: C 71.31; H 6.67; S 14.52.

3,3-Dimethylcyclohexanone (13).[17] To a stirred, −78 °C mixture of 2.03 g (5 equiv) of cuprous iodide in 60 mL of dry ether under a nitrogen atmosphere was added dropwise 15.24 mL (10 equiv) of 1.4 M methyllithium in ether. This solution was stirred at −30 °C for 30 min and then recooled to −78 °C; 405 mg (2.13 mmol) of mesylate **2a** in 20 mL of dry ether was added over 7 min. The mixture was allowed to warm slowly to room temperature, after which it was diluted with 100 mL of 10% aqueous hydrochloric acid. Sufficient 2.5 M aqueous ammonium hydroxide was added to make the aqueous layer just basic, and the mixture was then extracted with 400 mL of ether. The ether extract was washed consecutively with 75 mL of water and 75 mL of saturated brine and dried with anhydrous magnesium sulfate. Evaporation of solvent afforded 193 mg (72%) of ketone **13** as a pale yellow oil: IR 1715 cm^{-1}; NMR ($CDCl_3$) δ 2.5–1.4 (m, 8 H), 1.0 (s, 6 H). Distillation of this product did not alter the spectra.

Attempted Preparation of 3-Methyl-2-cyclohexenone (14).[17] To a stirred, −78 °C mixture of 823 mg (4.32 mmol) of cuprous iodide in 30 mL of dried ether under a nitrogen atmosphere was added dropwise 5.7 mL (8 mmol) of 1.4 M methyllithium in ether. The solution was stirred at −30 °C for 30 min, then recooled to −78 °C, and added to a −40 °C solution of 764 mg (4 mmol) of mesylate **2a** in 60 mL of dried ether over 10 min. This mixture was stirred for 1 h at −15 °C and then diluted with 200 mL of ether and 80 mL of cold 10% aqueous hydrochloric acid. The aqueous layer was removed, and the ether layer was washed consecutively with 50 mL of water and 50 mL of saturated brine. Drying over anhydrous magnesium sulfate, filtering, and evaporation of the solvent afforded 327 mg of a crude mixture

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of **2a**, **14**, and **13**, in a ratio of 35:60:5 as determined by NMR. Attempts to convert more of mesylate **2a** into product by use of additional dimethylcuprate under similar conditions afforded less **14** and more of the dimethyl ketone **13**.

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Registry No. **1a**, 504-02-9; **1b**, 126-81-8; **2a**, 75700-18-4; **2b**, 18922-00-4; **7a**, 5682-75-7; **7b**, 17530-69-7; **8a**, 56671-81-9; **8b**, 13271-49-3; **9a**, 56671-82-0; **9b**, 56671-85-3; **10**, 5323-87-5; **11a**, 6135-22-4; **11b**, 31039-88-0; **12**, 75700-19-5; **13**, 2979-19-3; **14**, 1193-18-6; dimethylamine, 124-40-3; benzyl mercaptan, 100-53-8.

A Facile Synthesis of Ochratoxin A

George A. Kraus

Department of Chemistry, Iowa State University, Ames, Iowa 50011

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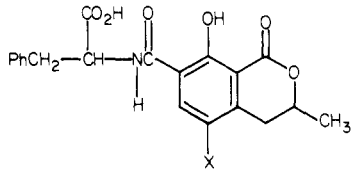
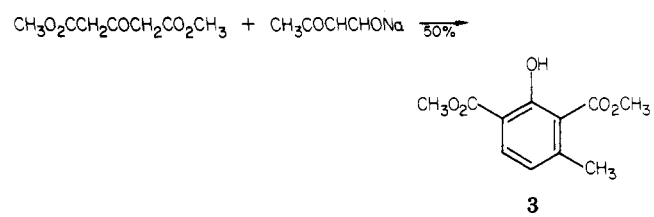
Ochratoxin A (1) was isolated by Steyn and co-workers[1] from some strains of *Aspergillus ochraceus*. Interest in this toxic metabolite and related compounds such as ochratoxin B (2) is prompted by the health hazard they pose because of their occurrence in agricultural products.



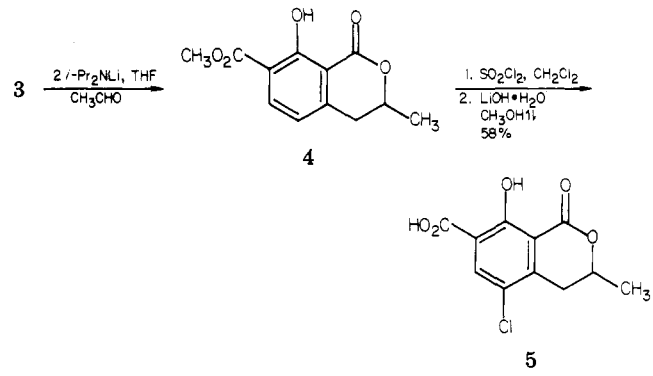
1, X = Cl
2, X = H

In addition, the availability of more highly oxygenated analogues for structure–activity studies is currently limited. Although two syntheses of 1 have been previously reported,[2] both are lengthy routes which proceed in low overall yield. In conjunction with another project, diester **3** was prepared in one step from dimethyl 3-oxopentanedicarboxylate and the sodium salt of (hydroxymethylene)acetone.[3] The transformation of **3** into the known acid **5** which has been converted into ochratoxin A in one step is the subject of this note. The reaction sequence is shown in Scheme I.



3

Scheme I



Diester **3** was deprotonated with 2 equiv of lithium diisopropylamide in tetrahydrofuran (THF)–hexamethylphosphorictriamide at −78 °C. After the addition of freshly distilled acetaldehyde and aqueous acid workup, lactone **4** could be isolated in 69% yield. Chlorination of **4** with sulfuryl chloride in methylene chloride[4] afforded a chloro lactone which was immediately suspended in methanol and saponified with lithium hydroxide. The melting point of the resulting acid **5** was in close agreement with the literature[2] melting point. Since the overall yield from commercially available starting material is 20%, this route is by far the most efficient preparation of ochratoxin intermediates and should be amenable to considerable variation.

Experimental Section

General. THF was distilled from lithium aluminum hydride. Melting points were determined on a Fisher-Johns melting-point apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined on Hitachi Perkin-Elmer R20 B. The ^{13}C NMR spectrum was determined on a JEOLCO FX-90Q.

Methyl 3,4-Dihydro-8-hydroxy-3-methyl-1*H*-2-benzopyran-1-one-7-carboxylate (4). To a solution of 14.9 mmol of lithium diisopropylamide prepared from 2.4 M *n*-butyllithium (6.2 mL, 14.9 mmol) and diisopropylamine (2.24 mL, 16 mmol) in 10 mL of THF at −78 °C was added diester **3** (1.54 g, 6.9 mmol) in 3 mL of THF over 3 min. After the deep red solution was stirred for 10 min, neat acetaldehyde (1.2 mL, 21.5 mmol) was added and the solution was stirred for 5 min at −78 °C and 15 min at 0 °C. The reaction was quenched at 0 °C with acetic acid (1.99 g) and diluted with ether and water. The aqueous layer was extracted twice with ether. The combined organic layers were dried over sodium sulfate, concentrated in vacuo, and chromatographed on silica gel to afford 1.13 g of yellow solid. The solid had a melting point of 108–110 °C; NMR ($CDCl_3$) δ 1.53 (d, 3 H, J = 6 Hz), 2.6–3.2 (m, 2 H), 3.93 (s, 3 H), 4.4–4.8 (m, 1 H), 6.72 (d, 1 H, J = 9 Hz), 8.03 (d, 1 H, J = 9 Hz).

5-Chloro-3,4-dihydro-8-hydroxy-3-methyl-1*H*-2-benzopyran-1-one-7-carboxylic Acid (5). To a solution of 4 (0.361 g, 1.53 mmol) in 3 mL of methylene chloride at ambient temperature was added sulfuryl chloride (0.50 mL, 5.18 mmol). The solution was stirred under a nitrogen atmosphere for 20 h, concentrated in vacuo, and suspended in 5 mL of methanol. Lithium hydroxide monohydrate (0.700 g, 16.6 mmol) was added to the suspension and the suspension was heated to reflux under a nitrogen atmosphere for 20 h. After the solution had cooled, most of the methanol was removed in vacuo. The semisolid was dissolved in water and extracted once with ether and the aqueous layer was then acidified to pH 2 with 3 N HCl. The solution was extracted twice over sodium sulfate, concentrated in vacuo, and recrystallized from acetone–methanol to afford 0.189 g of a white solid with a melting point of 246 °C: NMR (Me_2SO-d_6) δ 1.5 (d, 3 H, J = 6 Hz), 2.6–3.2 (m, 2 H), 4.3–4.8 (m, 1 H), 8.0 (s, 1 H);

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