and the cooling bath was removed. After the mixture was stirred for 18 h at 25 °C, water (5 mL) was added, and the resulting mixture was extracted with pentane/ether (9/1, 50 mL). The organic phase was washed with brine (5 mL) and 10% aqueous $NaHCO_3$ (2 mL) and dried ($MgSO_4$). Concentration gave a crude product (140 mg), which was purified by HPLC to give 93 mg (65%) of *exo*-**6**: ^1H NMR ($CDCl_3$, 300 MHz) δ 9.58 (d, 1 H, J = 2.1 Hz, C*H*O), 2.75–1.7 (m, 14 H), 0.90 (d, 3 H, J = 6.89 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 214.30 (C-6), 203.80 (C-11), 61.45 (C-5), 50.24 (C-2), 41.67, 37.99, 35.23, 31.76, 29.85, 25.43, 23.07, 16.07 (CH_3); M/S 194 (M^+); IR (NaCl, $CDCl_3$) 2970 (s), 2880, 2260, 1720 (s), 1700 (s), 1460, 890 (s), 705 cm^{-1}.

2-(1-Hydroxyethyl)-6,10-dimethylspiro[4.5]decan-6-ol (*exo*-14). To **6** (66 mg, 0.34 mmol) in anhydrous ether (5 mL) was added 1.55 M MeLi (1.1 mL, 1.7 mmol) in ether. The reaction mixture was stirred overnight at 25 °C and was then quenched with brine (0.8 mL). The ether layer was separated, and the water phase was extracted with ether (2 × 8 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to give 56 mg (73%) of **14** as a mixture of four diastereomers.

***dl*-Hinesol (1).** Compound **14** (56 mg) was transformed into *dl*-hinesol by utilizing the procedure described by Marshall and Brady.[10] Isolation by HPLC gave 7 mg of pure *dl*-hinesol (**1**). The ^1H NMR (lit.[10]), ^{13}C NMR, and capillary GLC data were identical with those of a sample of *dl*-hinesol provided by Professor Ibuka:[11f] ^{13}C NMR (100 MHz, $CDCl_3$)[20] δ 140.1 (s, C-6), 121.63 (d, C-7), 71.95 (s, C-11), 51.38 (d, C-2), 48.78 (s, C-5), 36.67 (d, C-10), 35.57 (t), 33.22 (t), 28.39 (q), 27.93 (2 C, t and q), 27.65 (t), 24.16 (t), 19.86 (q, C-12), 16.15 (q, C-13).

Acknowledgment. We thank Dr. Joseph Kowalewski (Division of Physical Chemistry, University of Stockholm) for running the ^{13}C NMR spectrum of our synthetic hinesol (**1**). We also thank Professor Toshiro Ibuka (Kyoto University) and Professor Pierre Deslongchamps (University of Sherbrooke) for samples of *dl*-hinesol (*1*) and *dl*-agaspirol (**2**), respectively. This work was financially supported by the Swedish Natural Science Research Council, the University of Notre Dame, and the U.S. National Science Foundation.

(20) Our ^{13}C NMR spectrum is identical with that of the authentic sample, but it differs somewhat from the ^{13}C NMR spectrum reported by Deslongchamps et al.[11e] The largest differences in these authors' data compared to our data reported above are the following chemical shift values: 31.78 vs 48.78 (C-5), 32.82 vs 36.67 (C-10), and 23.98 vs 19.86 (C-12). However, these authors' data were obtained with CCl_4 instead of $CDCl_3$ as the solvent. For several related spiro[4.5]decane derivatives, the quaternary, spirofused carbon atom (C-5) has a chemical shift in the range of 43.5–54.6 ppm. See: (a) Wenkert, E.; Buckwalter, B. L.; Craveiro, A. A.; Sanchez, E. L.; Sathe, S. S. *J. Am. Chem. Soc.* **1978**, *100*, 1267. (b) Suzuki, M.; Kowata, N.; Kurosawa, E. *Tetrahedron* **1980**, *36*, 1551. (c) Oppolzer, W.; Gorrichon, L.; Bird, T. G. C. *Helv. Chim. Acta* **1981**, *64*, 186. See also ref 3.

Improved Preparation of γ-Ketocyclobutanones

Janet A. Kaydos, Jeffrey H. Byers, and Thomas A. Spencer*

Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755

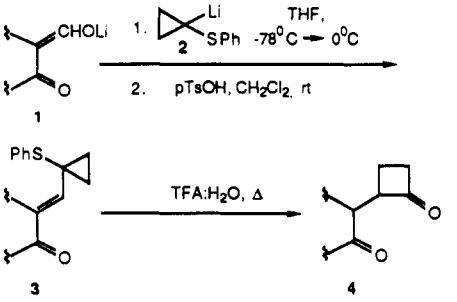
Received March 9, 1989

We have previously described[1] the preparation of γ-ketocyclobutanones by reaction of the lithium salts of 2-hydroxymethylene ketones **1** with lithiocyclopropyl phenyl sulfide (**2**) to afford β-(1-phenylthio)cyclopropyl enones **3**, followed by treatment with refluxing aqueous trifluoroacetic acid to effect rearrangement and hydrolysis to form the diones **4**. While this synthesis of enones **3** worked reasonably well on a small scale, difficulties were encountered, for reasons still not apparent, when the reactions of **1** with **2** were conducted on the larger scales necessary to prepare adequate quantities of γ-ketocyclobutanones (**4**) for exploration of their chemistry. Accordingly, a modification of the procedure for preparing **3** was sought that would work well on multigram quantities.

Table I. Synthesis of γ-Ketocyclobutanones from 2-Pyrrolidinomethylene Ketones

reactant	product (% yield)[a]	product (% yield)[a]
5	**6** (76)	**11** (75)[b]
7	**9** (69)	**12** (67)[c]
8	**10** (65)	**13** (85)

[a] Yield refers to directly crystallized or chromatographically purified material that was homogeneous by TLC. [b] A 3:2 mixture of unidentified diastereomers. [c] A 5:4 mixture of unidentified diastereomers.

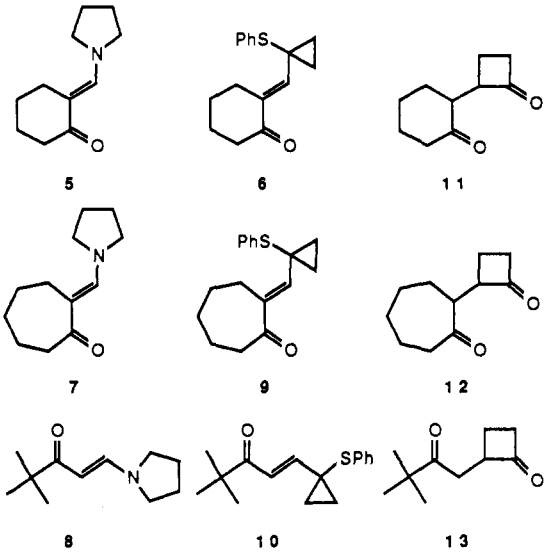


2-Pyrrolidinomethylene ketones seemed promising as an alternate to **1** as reactant, because such enamino ketones are very readily prepared from α-hydroxymethylene ketones[2-4] and are known usually to undergo predominantly 1,4-addition with nucleophiles[2,3,5] (as opposed to 2-(alkylthio)methylene,[6] 2-(silyloxy)methylene,[7] or 2-alkoxymethylene ketones,[2,8] all of which give significant and usually predominant amounts of products of 1,2-addition). Accordingly, 2-(pyrrolidinomethylene)cyclohexanone (**5**)[9] was prepared by standard procedures[2,10] and treated with **2**. The result was encouraging because 58% of (phenylthio)cyclopropyl enone **6** was obtained directly, β elimination of pyrrolidine from the initial 1,4 adduct having occurred spontaneously. In the reaction of **1** with **2** a separate acid-catalyzed β elimination of water from the initial adduct was required. An improvement in yield was readily achieved once the avidity of **5** for water was appreciated. The tendency of such enamino ketones to absorb and cling tenaciously to water has been documented,[11] and we were unable to prepare neat samples of **5** that did

(1) Byers, J. H.; Spencer, T. A. *Tetrahedron Lett.* **1985**, *26*, 717–720.

(2) Ireland, R. E.; Schiess, P. W. *J. Org. Chem.* **1963**, *28*, 2–16.
(3) Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277–294.
(4) Cromwell, N. H. *Chem. Rev.* **1946**, *38*, 83–137.
(5) Jutz, C. *Chem. Ber.* **1958**, *91*, 1867–1880. Abdulla, R. F.; Fuhr, K. H. *J. Org. Chem.* **1978**, *43*, 4248–4250. Cuvigny, T.; Normant, H. *Bull. Soc. Chim. Fr.* **1961**, 2423–2433. Pasteur, A.; Riviere, H.; Tchoubar, B. *Bull. Soc. Chim. Fr.* **1965**, 2328–2332.
(6) Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1962**, *27*, 1620–1627. Sowerby, R. L.; Coates, R. M. *J. Am. Chem. Soc.* **1972**, *94*, 4758–4759. Garst, M. E.; Spencer, T. A. *J. Am. Chem. Soc.* **1973**, *95*, 250–252. DeGroot, A.; Jansen, B. J. M. *Synthesis* **1978**, 52–53.
(7) Tius, M. A.; Ali, S. *J. Org. Chem.* **1982**, *47*, 3163–3166.
(8) Dreiding, A. S.; Nickel, S. N. *J. Am. Chem. Soc.* **1954**, *76*, 3956–3968. Church, R.; Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1962**, *27*, 1118–1125. Ramage, R.; Sattar, A. *Tetrahedron Lett.* **1971**, 649–652.
(9) Gandini, A.; Schenone, P.; Bignardi, G. *Monatsh. Chem.* **1967**, *98*, 1518–1531.
(10) Ainsworth, C. *Org. Synth.* **1963**, *Coll. Vol. IV*, 536–539.
(11) Dabrowski, J.; Kamienska, K. *Rocz. Chem. Ann. Soc. Chim. Polonorum* **1964**, *38*, 1121–1127. See also: Taft, R. W.; Gal, J. F.; Geribaldi, S.; Maria, P. C. *J. Am. Chem. Soc.* **1986**, *108*, 861–863, for discussion of the notable hydrogen bonding properties of these compounds.

0022-3263/89/1954-4698$01.50/0



5 6 11

7 9 12

8 10 13

not shown an O–H stretching band in the IR. The simple expedient of removing water from **5** by azeotropic distillation with benzene directly before reaction with **2** led to formation of 76% of **6**. An analogous procedure was applied to 2-(pyrrolidinomethylene)cycloheptanone (**7**)[12] and 2-(pyrrolidinomethylene)pinacolone (**8**), and all three (phenylthio)cyclopropyl enones (**6**, **9**, and **10**) were converted to the corresponding γ-ketocyclobutanones (**11**, **12**, and **13**) in the yields specified in Table I. Diones **11** and **12** were obtained, as would be expected, as mixtures of diastereomers, as evidenced by their ^{13}C NMR spectra. These mixtures resisted separation by TLC or flash chromatography.

Experimental Section

Melting points are uncorrected. The boiling points reported for bulb-to-bulb distillations refer to the oven temperature of the apparatus employed. Head temperatures are given for short-path distillations. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} plates from EM Reagents, and visualization was accomplished with 254-nm UV light, iodine, or ceric sulfate–ammonium molybdate–sulfuric acid spray. Flash chromatography was performed in the manner of Still[13] with EM Reagents silica gel 60 (230–400 mesh). MPLC refers to medium-pressure liquid chromatography as described by Meyers.[14]

Reactions requiring anhydrous conditions were performed in glassware that had been flame dried or heated in an oven overnight at 155 °C and then allowed to cool in a desiccator containing anhydrous $CaSO_4$ prior to assembly. The terms "under N_2" and "under Ar" refer to maintenance of a positive pressure of Airco nitrogen or argon gas over the reaction mixture. Alkyllithium reagents were standardized prior to use by titration against either 2,5-dimethoxybenzyl alcohol or diphenylacetic acid. Brine refers to a saturated aqueous solution of NaCl.

Solvents were purified as follows: tetrahydrofuran (THF) was distilled from sodium or potassium with benzophenone indicator; methanol, benzene, toluene, *m*-xylene, and dimethyl sulfoxide (DMSO) were dried by distillation from calcium hydride; hexamethylphosphoramide (HMPA) was distilled from barium oxide; methylene chloride (CH_2Cl_2) was dried by distillation from phosphorus pentoxide; reagent grade hexane was distilled prior to use. Anhydrous ether refers to the commercially available solvent, while dry ether refers to that obtained by distillation from lithium aluminum hydride (LAH). All other solvents were used as received.

(*E*)-2-[(1-(Phenylthio)cyclopropyl)methylene]cyclohexanone (6). 2-(Hydroxymethylene)cyclohexanone was prepared in 82% yield by the procedure of Ainsworth[10] and converted to 2-(pyrrolidinomethylene)cyclohexanone (**5**)[9] in 76% yield by the procedure of Ireland and Schiess.[2] To a solution of 2.87 mL (20.0 mmol) of cyclopropyl phenyl sulfide in 100 mL of dry THF at 0 °C under Ar was added 15.3 mL (20.0 mmol) of 1.31 M *n*-butyllithium in hexane, and the resulting mixture was stirred for 1.5 h. A solution of 3.58 g (20.0 mmol) of **5** in 30 mL of benzene was distilled under Ar until 20 mL of benzene was displaced. The remaining benzene solution of **5** was added via syringe to the THF solution of 1-lithio-1-(phenylthio)cyclopropane to form a mixture which was stirred for 1 h at 0 °C and then for 1 h at room temperature. The reaction was quenched with 125 mL of water, and the separated aqueous layer was saturated with NaCl and extracted with hexane (5 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to afford 5.47 g of orange oil, which was purified by flash chromatography (CH_2Cl_2) to give 3.94 g (76%) of **6** as a yellow solid. Recrystallization from methanol afforded 2.77 g (54%) of pale yellow **6**: mp 68–69 °C. Repeated recrystallization from methanol:water gave a colorless analytical sample of **6**: mp 69–70 °C (lit.[15] mp 69.5–70 °C); IR (KBr) 3060, 3030, 2940, 2865, 1690, 1615, 1480, 1390, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05–1.45 (4 H, m), 1.45–2.05 (4 H, m), 2.15–2.75 (4 H, m), 6.65 (1 H, br s), 7.08–7.58 (5 H, m); MS *m/e* 258 (M^+). Anal. Calcd for $C_{16}H_{18}OS$: C, 74.30; H, 7.02; S, 12.41. Found: C, 74.34; H, 7.06; S, 12.42.

(*E*)-2-[(1-(Phenylthio)cyclopropyl)methylene]cycloheptanone (9). 2-(Hydroxymethylene)cycloheptanone[16] was prepared in 88% yield by the procedure of Ainsworth[10] and converted to 2-(pyrrolidinomethylene)cycloheptanone[12] (**7**) in 82% yield by the procedure of Ireland and Schiess.[2] To a solution of 10.2 g (68.0 mmol) of cyclopropyl phenyl sulfide in 250 mL of dry THF at 0 °C under Ar was added 62.0 mL of 1.14 M (70.7 mmol) *n*-butyllithium, and the resulting mixture was stirred for 1 h. A solution of 13.0 g (67.0 mmol) of **7** in 30 mL of benzene was distilled under Ar until most of the benzene was displaced. The remaining benzene solution of **7** was added via syringe to the THF solution of 1-lithio-1-(phenylthio)cyclopropane to form a mixture which was stirred for 18 h while being allowed to warm to room temperature. The reaction was quenched with 500 mL of brine and was then extracted with 500 mL of hexane and 500 mL of ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 21.7 g of orange oil, which was purified by flash chromatography (gradient, hexane to $CHCl_3$) to give 13.3 g (69%) of **9** as a golden oil. Bulb-to-buld distillation afforded an analytical sample of **9**: bp 110–130 °C (0.005 mmHg); IR (film) 3060, 3010, 2930, 2860, 1690, 1620, 1595, 1485, 1445, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80–1.90 (10 H, m), 2.10–2.90 (4 H, m), 6.70 (1 H, br s), 6.95–7.55 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 17.6, 19.0, 23.5, 25.1, 27.1, 28.6, 30.8, 43.0, 125.4, 128.5, 130.1, 135.4, 138.2, 142.9, 203.9. Anal. Calcd for $C_{17}H_{20}OS$: C, 74.96; H, 7.40; S, 11.77. Found: C, 75.03; H, 7.44; S, 11.69.

1-(Pyrrolidinomethylene)-3,3-dimethyl-2-butanone (8). 1-(Hydroxymethylene)-3,3-dimethyl-2-butanone[17] was prepared in 90% yield by the procedure of Ainsworth.[10] According to the prcoedure of Ireland Schiess,[2] a solution of 34.1 g (266 mmol) of 1-(hydroxymethylene)-3,3-dimethyl-2-butanone and 22.2 mL (266 mmol) of pyrrolidine in 125 mL of benzene was heated at reflux for 14 h under a Dean–Stark trap. Evaporation afforded a gold solid residue, which was recrystallized from hexane to give 38.6 g (80%) of **8** as white needles: mp 78.5–79.5 °C; IR (KBr) 3430 (H_2O), 2945, 2860, 1640, 1550, 1475, 1450, 1275, 900, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (9 H, s), 1.60–2.18 (4 H, m), 3.01–3.56 (4 H, m), 5.16 (1 H, d, J = 12 Hz), 7.79 (1 H, d, J = 12 Hz); ^{13}C NMR ($CDCl_3$) δ 25.0, 27.5, 41.6, 90.9, 91.0, 148.5, 203.1. Anal. Calcd for $C_{11}H_9NO$: C, 72.88; H, 10.56; N, 7.73. Found: C, 73.00; H, 10.60; N, 7.71.

(12) Minardi, G.; Schenone, P.; Bignardi, G. *Ann. Chim. (Rome)* **1968**, *58*, 1320–1335.
(13) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.
(14) Meyers, A. I.; Slade, J.; Smith, R. K.; Mihelich, E. D.; Hersendon, F. M.; Liang, C. D. *J. Org. Chem.* **1979**, *44*, 2247–2249.
(15) Supplementary material to: Trost, B. M.; Jungheim, L. N. *J. Am. Chem. Soc.* **1980**, *102*, 7910–7925.
(16) Treibs, W.; Neubert, H. *J. Justus Liebigs Ann. Chem.* **1955**, *595*, 219–223.
(17) Bargagna, A.; Cafaggi, S.; Schenone, P. *J. Heterocycl. Chem.* **1980**, *17*, 507–511.

(*E*)-1-[(1-(Phenylthio)cyclopropyl)methylene]-3,3-dimethyl-2-butanone (10). To a solution of 3.97 mL (27.6 mmol) of cyclopropyl phenyl sulfide in 10 mL of dry THF at 0 °C under Ar was added 20.0 mL (28.0 mmol) of 1.4 M *n*-butyllithium, and the resulting mixture was stirred for 2.5 h. A solution of 5.00 g (27.6 mmol) of **8** in 30 mL of benzene was distilled under N_2 until 15 mL of solvent was displaced. The remaining benzene solution of **8** was added via syringe to the THF solution of 1-lithio-1-(phenylthio)cyclopropane. The resulting mixture was stirred for 18 h at room temperature. The reaction was quenched with 125 mL of water, and the separated aqueous layer was saturated with NaCl and then extracted with hexane (5 × 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated to give 8.27 g of gold solid, which was recrystallized from methanol to afford 3.90 g (54%) of **10** as very pale orange crystals: mp 66–67 °C. An additional 0.81 g was obtained by flash chromatography (hexane, $CHCl_3$) for a total yield of 4.71 g (65%) of **10**. Four recrystallizations from methanol:water with hot filtration provided a colorless analytical sample of **10**: mp 65–66 °C; IR (KBr) 3020, 2990, 1690, 1620, 1588, 1480, 1443, 1420 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (9 H, s), 1.33–1.54 (4 H, m), 6.47 (1 H, d, J = 14 Hz), 6.85 (1 H, d, J = 14 Hz), 7.23 (5 H, br s); ^{13}C NMR ($CDCl_3$) δ 20.4, 26.0, 26.9, 42.9, 124.2, 125.3, 127.0, 128.7, 136.2, 150.0, 203.9. Anal. Calcd for $C_{16}H_{20}OS$: C, 73.80; H, 7.74; S, 12.31. Found: C, 73.76; H, 7.78; S, 12.26.

2-(2-Oxo-1-cyclobutyl)cyclohexanone (11). A solution of 1.56 g (6.03 mmol) of **6** in 50 mL of 1:1 trifluoroacetic acid:water was heated at reflux for 18 h. The mixture was then cooled to room temperature and combined with 400 mL of ether. The separated organic layer was treated with 2 L of 10% NaOH, washed with brine (2 × 50 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated to afford an orange oil, which was purified by flash chromatography (gradient, hexane to 1:1 hexane:ether) to give 0.75 g (75%) of **11** as an orange oil. Further purification by bulb-to-bulb distillation gave 0.73 g (73%) of clear, colorless **11** as a 3:2 mixture of diastereomers which were inseparable by TLC: bp 109–117 °C (0.37 mmHg). MPLC (1:1 hexane:ether) of a different batch of **11** obtained in 90% yield afforded an analytical sample of **11**: IR (film) 2940, 2875, 1780, 1715, 1450, 1130, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80–2.60 (10 H, m), 2.60–3.80 (4 H, m); ^{13}C NMR ($CDCl_3$) δ 13.9, 14.5, 24.0, 24.5, 27.0, 27.1, 30.8, 31.4, 41.0, 41.2, 43.8, 43.9, 50.7, 50.8, 59.0, 59.3, 209.6, 209.9, 210.3, 210.5. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.14; H, 8.50.

2-(2-Oxo-1-cyclobutyl)cycloheptanone (12). A solution of 0.81 g (2.8 mmol) of **9** in 75 mL of 3:1 trifluoroacetic acid:water was heated at reflux for 18 h. The mixture was cooled to room temperature and combined with 250 mL of ether. The separated organic layer was washed with water (2 × 75 mL) treated with 500 mL of 10% NaOH, washed with brine (2 × 50 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated to afford 0.62 g of brown oil, which was subjected to flash chromatography (gradient, hexane to 1:1 hexane:ether) to give 0.34 g (67%) of gold oily **12**. Further purification by bulb-to-bulb distillation yielded 0.21 g (42%) of clear colorless **12** as a 5:4 mixture of diastereomers which were inseparable by TLC: bp 100–110 °C (0.05 mmHg); IR (film) 2930, 2860, 1780, 1705, 1460, 1200, 1080, 940 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90–2.30 (10 H, m), 2.30–2.71 (2 H, m), 2.79–3.26 (3 H, m), 3.30–4.00 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 14.6, 15.7, 23.4, 23.7, 28.9, 28.9, 29.1, 29.3, 29.3, 29.4, 43.1, 43.2, 44.4, 44.4, 51.0, 52.6, 61.2, 61.5, 210.4, 211.1, 213.1, 213.2. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.34; H, 8.95.

1-(2-Oxo-1-cyclobutyl)-3,3-dimethyl-2-butanone (13). A solution of 3.01 g (11.6 mmol) of **10** in 150 mL of 1:1 trifluoroacetic acid:water was heated at reflux for 18 h. The mixture was then cooled to room temperature, and 300 mL of ether was added. The organic layer was separated, washed successively with 100 mL of water, 400 mL of 10% NaOH, 100 mL of water, and 50 mL of brine, dried over $MgSO_4$, filtered, and evaporated to give 1.75 g of yellow oil, which was subjected to flash chromatography (hexane, 25% ether in hexane) to afford 1.65 g (85%) of yellow oily **13**. Further purification by bulb-to-bulb distillation yielded 1.44 g (74%) of **13** as a pale yellow oil: bp 90–110 °C (0.45 mmHg). MPLC (1:1 hexane:ether) afforded an analytical sample of **13**: IR (film) 2970, 2920, 2880, 1787, 1710, 1485, 1400, 1370, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (9 H, s), 1.24–2.60 (2 H, m), 2.60–3.34 (4 H, m), 3.34–3.94 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 16.4, 25.7, 35.8, 43.2, 44.4, 54.4, 210.0, 212.3. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.41; H, 9.59. Found: C, 71.45; H, 9.62.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

Oxidation of 3- or 4-Substituted *N,N*-Dimethylanilines with Molecular Oxygen in the Presence of either $FeCl_3$ or [Fe(salen)]OAc

Satoru Murata, Masahiro Miura,* and Masakatsu Nomura

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565, Japan

Received March 31, 1989

Iron-catalyzed oxidation of amines is of considerable interest because of the relevance to enzymatic degradation of N-containing compounds in biological systems.[1-3] We have recently reported that *N,N*-dimethylaniline (**1a**) is oxidized by molecular oxygen in the presence of various iron complexes and salts, the product composition being remarkably influenced by the identity of the iron species employed:[4] The reaction of **1a** using $FeCl_3$ is considered to proceed via initial one-electron oxidation and subsequent dimerization to give 4,4′-methylenebis(*N,N*-dimethylaniline) (**5a**) along with *N*-methylaniline (**2a**), whereas with [Fe(salen)]OAc (salen = *N,N*′-ethylenebis(salicylidenaminato)] *N*-methylformanilide (**3a**) is obtained as the predominant product together with **2a** in a free-radical chain process.

We report herein the results for the oxidation of a series of 3- (**1b,c**) and 4-substituted *N,N*-dimethylanilines (**1d–f**) in the presence of either $FeCl_3$ or [Fe(salen)]OAc; the position of the substituents also appeared to be an important factor determining the course of the reaction.

When **1a** (1.0 M) in acetonitrile was treated with $FeCl_3$ (3 mM) under oxygen (1 atm) at 60 °C for 20 h, a mixture of **2a** and **5a** was favored (eq 1 and Table I). Similar results were also obtained in the reactions of 3-substituted *N,N*-dimethylanilines **1b** and **1c**. The order of reactivity for **1a–c** was found to be **1b** (3-Me) > **1a** (H) > **1c** (3-Cl)

(1) (a) Hanzlik, R. P.; Tullman, R. H. *J. Am. Chem. Soc.* **1982**, *104*, 2048. (b) Macdonald, T. L.; Zirvi, K.; Burka, L. T.; Peyman, P.; Guengerich, F. P. *Ibid.* **1982**, *104*, 2050. (c) Miwa, G. T.; Walsh, J. S.; Kedderis, G. L.; Hollenberg, P. F. *J. Biol. Chem.* **1983**, *258*, 14445. (d) Heimbrook, D. C.; Murray, R. I.; Egeberg, K. D.; Sligar, S. G.; Nee, M. W.; Bruice, T. C. *J. Am. Chem. Soc.* **1984**, *106*, 1514. (e) Kedderis, G.; Hollenberg, P. F. *J. Biol. Chem.* **1984**, *259*, 3663. (f) Murugesan, N.; Hecht, S. M. *J. Am. Chem. Soc.* **1985**, *107*, 493. (g) Burka, L. T.; Guengerich, F. P.; Willard, R. J.; Macdonald, T. L. *Ibid.* **1985**, *107*, 2549.

(2) (a) Galliani, G.; Rindone, B. *J. Chem. Soc., Perkin Trans. 1* **1978**, 456. (b) Ball, S.; Bruice, T. C. *J. Am. Chem. Soc.* **1980**, *102*, 6498. (c) Shannon, P.; Bruice, T. C. *Ibid.* **1981**, *103*, 4580. (d) Miyata, N.; Kiuchi H.; Hirobe, M. *Chem. Pharm. Bull.* **1981**, *29*, 1489. (e) Takata, T.; Ando, W. *Tetrahedron Lett.* **1983**, *24*, 3631. (f) Lindsay Smith, J. R.; Mortimer, D. N. *J. Chem. Soc., Chem. Commun.* **1985**, 64. (g) Dicken, C. M.; Lu, F.-L.; Nee, M. W.; Bruice, T. C. *J. Am. Chem. Soc.* **1985**, *107*, 5776. (g) Castro, C. E.; Jamin, M.; Yokoyama, W.; Wade R. *Ibid.* **1986**, *108*, 4179. (i) Lindsay Smith, J. R.; Mortimer, D. N. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1743. (j) Fujimori, K.; Fujiwara, S.; Takata, T.; Oae, S. *Tetrahedron Lett.* **1986**, *27*, 581. (k) Fujimori, K.; Takata, T.; Fujiwara, S.; Kikuchi, O.; Oae, S. *Ibid.* **1988**, *29*, 1617. (l) Pautet, F.; Barret, R.; Daudon, M. *Pharmazie* **1986**, *41*, 286. (m) Sawyer, D. T.; Spencer, L.; Sugimoto, H. *Isr. J. Chem.* **1987**, *28*, 3.

(3) (a) Santa, T.; Miyata, N.; Hirobe, M. *Chem. Pharm. Bull.* **1984**, *32*, 1252. (b) Karasevich, E. I.; Khenkin, A. M.; Shilov, A. E. *J. Chem. Soc., Chem. Commun.* **1987**, 731.

(4) Murata, S.; Miura, M.; Nomura, M. *J. Chem. Soc., Chem. Commun.* **1989**, 116.

0022-3263/89/1954-4700$01.50/0