Simple and efficient synthesis of 3-oxo-2,6,6-trimethylcyclohex-1-ene-1-carboxylic acid, a key synthon for (.+-.)-strigol

ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · DECEMBER 1983

Impact Factor: 4.72 · DOI: 10.1021/jo00173a062

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excess of 10% Pd/C in EtOAc;[11] $(PPh_3)_3RhCl$ in benzene[12]) were unsuccessful.

2-Norbornanone ethylene dithioketal was obtained in 90% yield from 2-norbornanone following the procedure used for preparation of 1: ^{13}C NMR ($CDCl_3$) δ 72.2 (s, 1 C), 51.8 (d, 1 C), 49.4 (t, 1 C), 39.8 (t, 1 C), 39.7 (m, 2 C), 36.8 (d, 1 C), 28.3 (t, 1 C), 26.6 (t, 1 C); ^1H NMR ($CDCl_3$) δ 3.4–3.0 (m, 4 H), 2.4–2.1 (m, 3 H), 2.0–1.1 (m, 7 H); IR (film) 2960 (s), 2872 (m), 1452 (m), 1307 (w), 1275 (w), 970 (w) cm^{-1}; MS, *m/z* (relative intensity) 186 (M^+, 43), 158 (100), 125 (19), 93 (18), 67 (31), 66 (26). Anal. Calcd for $C_9H_{14}S_2$: C, 58.06; H, 7.53; S, 34.41. Found: C, 58.22; H, 7.74; S, 34.69.

Treatment of 2-norbornanone ethylene dithioketal with bromine under the same conditions as those used for 1 yielded ~100% of a 8:1 mixture of two products. The products were separated by column chromatography on silica gel with methylene chloride–pentane (1:4) as the eluent. The major product was isolated in 75% yield (2.0 g) as a bright yellow oil and was shown to be 3-bromo-2-norbornanone ethylene dithioketal (≥98% pure by GC, DEGS 170 °C): ^{13}C NMR ($CDCl_3$) δ 78.8 (s), 69.2 (d), 53.1 (d), 49.2 (d), 40.1 (m), 39.5 (m), 38.0 (t), 28.3 (t), 26.9 (t); ^1H NMR ($CDCl_3$) δ 4.33 (d, J = 2.4 Hz, 1 H), 3.4–3.0 (m, 4 H), 2.6–2.4 (m, 2 H), 2.2–1.2 (m, 6 H); IR (film) 2965 (s), 2920 (s), 2875 (m), 1475 (w), 1450 (m), 1420 (w), 1308 (w), 1210 (w), 780 (w), 660 (w) cm^{-1}; MS, *m/z* (relative intensity) 266 (M^+, 6), 264 (M^+, 6), 238 (7), 236 (6), 187 (9), 186 (11), 185 (100), 157 (20), 156 (13), 131 (12), 105 (9), 81 (16). Anal. Calcd for $C_9H_{13}S_2Br$: C 40.75; H, 4.91; S, 24.15; Br, 30.19. Found: C, 41.03; H, 4.87; S, 24.07; Br, 29.91. The minor product (isolated as white crystals in ~10% yield after recrystallization from pentane) exhibited the following characteristics: mp 37–39 °C; ^{13}C NMR ($CDCl_3$) δ 213.7 (s), 71.9 (s), 48.6 (d), 48.4 (d), 39.4 (m), 39.0 (m), 37.4 (t), 27.0 (t), 25.5 (t); ^1H NMR ($CDCl_3$) δ 3.7–3.2 (m, 4 H), 2.8 (br s, 2 H), 2.3–1.5 (m, 6 H); IR (KBr) 2960 (s), 2870 (m), 1742 (s), 1450 (m), 1282 (m), 1180 (m), 1078 (m), 755 (m) cm^{-1}; MS, *m/z* (relative intensity) 200 (M^+, 6), 172 (11), 144 (22), 131 (100), 71 (39). Anal. Calcd for $C_9H_{12}S_2O$: C, 54.05; H, 6.05; S, 32.01. Found: C, 54.25; H, 6.27; S, 31.80.

Acknowledgment. This work was supported by a grant from the Research Council of the Republic of Croatia (SIZ II).

Registry No. 1, 50511-34-7; 2, 87450-45-1; Br_2, 7726-95-6; 4-homoadamantanone, 24669-56-5; 1,2-ethanedithiol, 540-63-6; 2-norbornanone ethylene dithioketal, 172-69-0; 3-bromo-2-norbornanone ethylene dithioketal, 87450-46-2; 2,3-norbornanedione monoethylene dithioketal, 87450-47-3; 2-norbornanone, 497-38-1.

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Simple and Efficient Synthesis of 3-Oxo-2,6,6-trimethylcyclohex-1-ene-1-carboxylic Acid, a Key Synthon for (±)-Strigol

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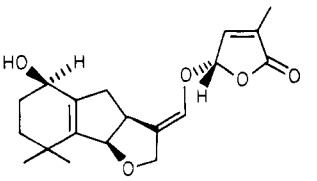
Received April 21, 1983

Methyl 3-oxo-2,6,6-trimethylcyclohex-1-ene-1-carboxylate (**1b**) is an important A-ring intermediate for the synthesis of (±)-strigol (**3**), a well-known potent witchweed seed germination stimulant. due to the possible role of **3** as a control agent in witchweed-infested fields, much effort has recently been devoted to improve the preparation of **1a** and/or **1b**.

1a, R = H
b, R = Me

2a, R = H
b, R = Me



3

Sih et al.[1] in their total synthesis of **3**, described two sequences for their preparations. One of them startes from α-cyclocitral, requires three steps, and produces **1a** in 36% overall yield. The second one, from β-cyclocitral, gives **1b** after five steps in 40% overall yield but requires chromatographic purification. Later, Pepperman[2] carried out a careful analysis of the first sequence showing lower yields than those reported, but by introduction of a two-step oxidation procedure the final yield was significantly increased. Recently, Brooks et al.[3] reported a five-step synthesis of **1b** from α-ionone with a 48% overall yield. We describe herein a simple, efficient one-step preparation of **1a** from a mixture of α- and β-cyclocitrals.

Treatment of the mixture of α- and β-cyclocitrals[4] by a modification of the procedure for the oxidation of allylic methylenes previously described[5] produced a ca. 9:1 mixture of two carboxylic acids. In a first run they were chromatographically separated as methyl esters and spectroscopically characterized as **1b**, the major product, and **2b**. Subsequent experiments showed that from the crude reaction product pure crystalline **1a** could be obtained and Jones oxidation of the mother liquors furnished and additional amount of **1a**, increasing the total yield to better than 70%.

Experimental Section

Melting points were determined on an Ernst Leitz hot-stage microscope and are uncorrected. IR spectra were measured with a Beckman Acculab 8 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded at 80.13 and 20.15 MHz, respectively, on a Bruker WP 80 SY spectrometer in $CDCl_3$ solutions. GC analyses were conducted by using a Perkin-Elmer 820 gas chromatograph equipped with a 0.3 × 300 cm 15% Carbowax 20M column. Silica gel GF_{254} (type 60) was utilized for TLC, and spots were visualized by staining with anisaldehyde–sulfuric acid.[6]

Methyl 3-Oxo-2,6,6-trimethylcyclohex-1-ene-1-carboxylate (1b) and Methyl 3-Hydroxy-2,6,6-trimethylcyclohex-1-ene-1-carboxylate (2b). The crude product obtained from the NBS oxidation as described below (500 mg) was dissolved in Et_2O (20 mL) and treated with an excess of diazomethane. Chromatography of the resulting product over silica gel (50 g) with hexane and increasing amounts of EtOAc resulted in the isolation of **1b** (405 mg) and **2b** (46 mg) as colorless oils. **1b**: IR (film) 1727, 1678, 1620, 1240, 1053, 1020 cm^{-1}; ^1H NMR δ 1.24 (s, 6 H, C-6, 2 × Me), 1.72 (s, 3 H, C-2, Me), 1.90 (m, 2 H, H-5), 2.55 (m, 2 H, H-4), 3.83 (s, 3 H, OMe); ^{13}C NMR δ 12.8 (q, C-2, Me), 26.6 (q,

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C-6, 2 × Me), 33.8 (t, C-4), 33.8 (s, C-6), 37.2 (t, C-5), 51.4 (q, OMe), 130.6 (s, C-2), 154.4 (s, C-1), 168.2 (s, COOMe), 198.1 (s, CO). **2b**: ^{1}H NMR δ 1.08 and 1.11 (s, 6 H, C-6, 2 × Me), 1.15-1.90 (m, 5 H, H-4, H-5, OH), 1.76 (s, 3 H, C-2, Me), 3.76 (s, 3 H, OMe), 3.98 (t, 1 H, H-3).

3-Oxo-2,6,6-trimethylcyclohex-1-ene-1-carboxylic Acid (1a). To a stirred solution of a mixture of α- and β-cyclocitrals (5.5 g, 0.036 mol) containing 55% of the β-isomer[4] (GC) in purified dioxane[7] with 10% of H_2O (500 mL) were added finely divided $CaCO_3$ (14.6 g, 0.146 mol) and freshly crystallized NBS (15 g, 0.086 mol). The mixture was efficiently stirred while being irradiated with visible light from a 1000-W halogen lamp and heated gently just to start boiling. When the initial color faded away, an additional amount of NBS (17 g, 0.098 mol) in dioxane (270 mL) was added dropwise (approximately in 1 h). After the addition was complete, the reaction mixture remained colorless and a white solid stuck to the walls of the reaction flask. The solution was decanted and the solvent removed in vacuo. The residue was taken up with an aqueous saturated solution of $NaHCO_3$ (150 mL) and Et_2O (50 mL), cooled, and filtered, and the filtrate was extracted with Et_2O (3 × 100 mL). The aqueous layer was then cooled (0 °C), brought to pH 3 by addition of cold (0 °C) aqueous 50% HCl, and extracted with Et_2O (5 × 100 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. The residue (3.01 g) was recrystallized from benzene to give pure **1a** (2.33 g): mp 187.5-188 °C (lit.[1] mp 187-189 °C). From the mother liquors, after treatment with Jones reagent[8] in cooled (0 °C) acetone, followed by crystallization from benzene, an additional amount (276 mg) of **1a** (mp 187-189 °C) was obtained; total amount of **1a**: 2.6 g, 72% yield.

Acknowledgment. This work was carried out with the financial support from CONICET (Consejo Nacional de Investigaciones Científicas y Técnicas) and UNR (Universidad Nacional de Rosario). We thank FRISCHE SAICA (Argentina) for a generous gift of citral and Dr. R. Chazarreta, PASA (Petroquímica Argentina S.A.) for the GC analyses. R.A.S. thanks CONICET for a fellowship.

Registry No. **1a**, 51823-74-6; **1b**, 28120-76-5; (±)-**2b**, 60078-94-6; (±)-**3**, 51820-11-2; (±)-α-cyclocitral, 59462-59-8; β-cyclocitral, 432-25-7.

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α-Methyl Functionalization of Electron-Poor Heterocycles:[1a] 2,9-Bis(chloromethyl)-1,10-phenanthroline. Synthesis of a [3.3]Cyclophane Containing the 1,10-Phenanthrolino Moiety

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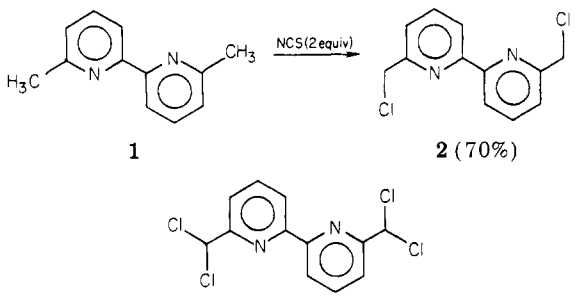
Received May 5, 1983

Introduction

It has been shown that electron-deficient heteroaromatics with 2,6-oxo substituents do not readily form transition-metal complexes.[2] In order to circumvent the major causes of the poor ligandophilicity, e.g., the inherent imidate moiety and diminished N electron density, inclusion of an α-methylene unit between the bridge oxygen atoms and heterocyclic ring has been deemed necessary. Numerous macrocycles containing the pyridino and dipyridino subunits have been reported;[3] however, only a few examples of macrocycles containing the related phenanthrolino moiety are known.[4] Further, no phenanthrolino macrocycles have yet been reported that contain α-methylene units. It was evident that reactions, which were applicable to the α-functionalization of 2,6-dimethylpyridine and 6,6′-dimethyl-2,2′-bipyridine (**1**),[1] could *not* be readily applied to 2,9-dimethyl-1,10-phenanthroline. We now describe the α-functionalization of 2,9-dimethyl-1,10-phenanthroline along with its incorporation into a [3.3]cyclophane.

Results and Discussion

A. α-Methyl Functionalization. Treatment of **1** with 2 equiv of *N*-chlorosuccinimide (NCS) under appropriate free-radical conditions gives primarily the desired *sym*-chloromethyl derivative **2**;[1] in contrast, however, **4** experiences enhanced reactivity under identical conditions. Thus, treatment of **4** with 2 equiv of NCS and benzoyl peroxide initiator gave the hexachloro derivative **5** and a complex mixture of chloro derivatives. Attempts to obtain the desired *sym*-chloromethyl **8** in one step, as the major product and in pure form by NCS chlorination have been unsuccessful. The trichloromethyl intermediate **5** was prepared (100%) when 6 equiv of NCS was utilized.[5] A one-pot hydrolysis of **5** in concentrated sulfuric acid and subsequent esterification afforded **6** in quantitative overall yield.[6] Reduction of **6** with $LiAlH_4$ resulted in low yields of the biscarbinol **7**, whereas with $NaBH_4$, **6** was quantitatively transformed to **7**.[7]



The chloromethyl derivative **8** was obtained (72%) by the use of PCl_3;[8,9] when $SOCl_2$ was used for this conversion,

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