Notes

Synthesis of 3- and 4-(Carboethoxy)-2,4,6-cycloheptatrien-1-one

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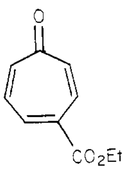
A study of substituent effects in [6 + 4] cycloadditions has required cycloheptatrienones (tropones) with functional groups in the 3- and 4-positions.[1] These rare compounds could also become intermediates for the synthesis of colchicine, stipatitic acid, or hydroazulenes.[2] In this note we describe an efficient synthesis of two novel tropones, 4-(carboethoxy)-2,4,6-cycloheptatrien-1-one (**1**) and 3-(carboethoxy)-2,4,6-cycloheptatrien-1-one (**2**). The tropones are easily oxidized to yield 2-tropolones and undergo rearrangement catalyzed by acid or base to give benzenoid compounds. Our preparation addresses these potential side reactions.



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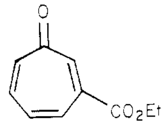

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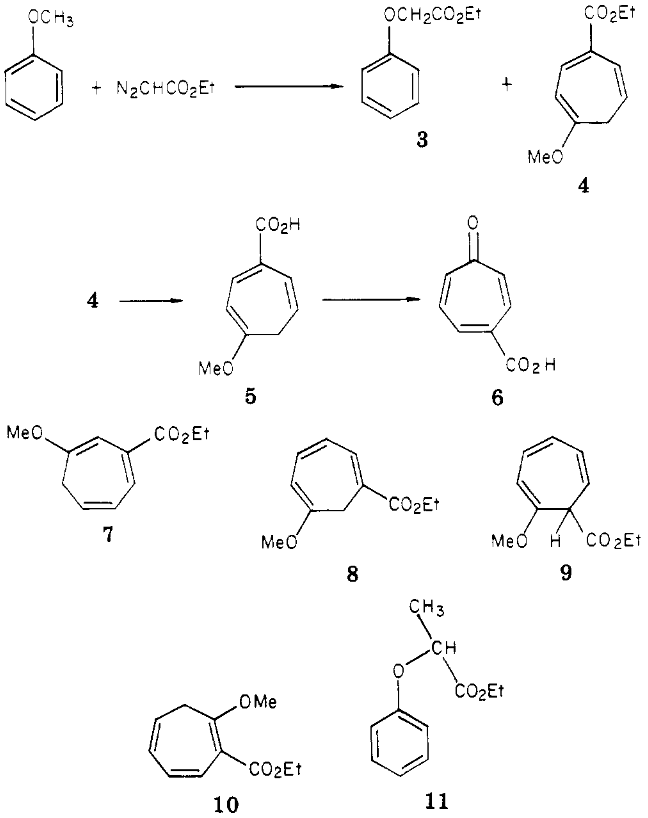
We anticipated that carbenoid-mediated ring expansion of an aromatic[3] followed by mild oxidation would provide **1** or **2**. Johnson[4] reported that thermolysis of ethyl diazoacetate in anisole yielded **3** and **4**. Saponification of this mixture, separation of **5** by crystallization, and bromine oxidation of **5** provided Johnson[4] with cycloheptatrienone acid **6**. The reaction has been examined by others[5-7] and the structure of **5** secured by NMR spectroscopy.[5] The product composition appeared to be independent of diazo decomposition mode[8] with the possible exception of a recently reported method using a rhodium catalyst.[9,10]

We have repeated the Buchner reaction[3] examined by Johnson[4] and noted the formation of several trienes. Completion of the sequence provided **6** in 6% yield, an amount considerably lower than the triene mixture suggested. Separation of this mixture by HPLC provided seven components to which were assigned structures **3**, **4**, and **7**–**11** (Scheme I). Compounds **3** (8% yield based on ethyl diazoacetate) and **11** (<0.5% yield) are benzenoid with the assignments based upon NMR and mass spectral (MS) data. The remaining compounds each exhibited mass spectral parent ions of m/e 194, suggesting that they were isomers of **4**. Detailed analysis of the NMR spectra has permitted a definitive structure assignment in each case.

Scheme I



Acid **5** corresponding to the major component **4** of our mixture (15% yield) has been identified by Hanessian,[5] using NMR spectroscopy. The NMR spectra of **4** and **5** are nearly identical. Thus, acid **5** arises from the major triene ester in the reaction, as previously implied.[3-6]

Trienes **7** and **8** accounted for 9% of the diazo compound.[7] Triene **7** (8% yield) exhibited an olefin singlet at 5.90 ppm, a low-field doublet at 7.41 ppm, and a two-proton doublet at 2.53 ppm. These resonances were assigned to an olefin between two groups, to the β proton of the α,β-unsaturated ester, and to a methylene group adjacent to a methoxy group, respectively. The methylene group appeared at the same chemical shift in **4** and **7**. A two-proton singlet at 2.90 ppm in compound **8** (1% yield) permitted the assignment of two substituents flanking the allylic protons; the remainder of the NMR spectral data is consistent with this structure.

The structures of the minor trienes **9** and **10** were determined as follows. The spectrum of **9** (2% yield) had overlapping olefin signals and an additional one-proton

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[1] Garst, M. E.; Roberts, V. A.; Prussin, C., manuscript submitted.

[2] For a review on cycloheptatrienone synthesis and difficulties encountered therein, see Pietra, F. *Chem. Rev.* **1973**, *73*, 294–306.

[3] For reviews of aryl carbenoid reactions, see Dave, V.; Warnoff, E. W. *Org. React.* **1970**, *18*, 217. Wulfman, D. S.; Linstrumelle, G.; Cooper, C. F. In "The Chemistry of Diazonium and Diazo Groups"; Patai, S., Ed.; Wiley-Interscience: New York, 1978; Vol. 2, p 821 ff. Kirmse, W. "Carbene Chemistry"; Acdemic Press: New York, 1971; pp 381–407.

[4] Johnson, A. W.; Langermann, A.; Murray, J. *J. Chem. Soc.* **1953**, 2136. Johns, R. B.; Johnson, A. W.; Murray, J. *Ibid.* **1954**, 198: Bartels-Keith, J. R.; Johnson, A. W.; Langemann, A. *Ibid.* **1952**, 4461.

[5] Hanessian, S.; Schütze, G. *J. Org. Chem.* **1969**, *34*, 3196.

[6] De Graff, G. B. R.; van De Kolk, G. *Recl. Trav. Chim. Pays-Bas* **1978**, *77*, 224. De Graff, G. B. R.; van Dijck-Rothuis, J. H.; van De Kolk, G. *Recl. Trav. Chim. Pays-Bas* **1955**, *74*, 143.

[7] Brember, A. R.; Gorman, A. A.; Sheridan, J. B. *Tetrahedron Lett.* **1973**, 475.

[8] Ledon, H.; Linstrumelle, G.; Julia, S. *Bull. Soc. Chim. Fr.* **1973**, 2065.

[9] Anciaux, A. J.; Demonceau, A.; Hubert, A. J.; Noels, A. F.; Petinoit, N.; Teyssié, P. *J. Chem. Soc., Chem. Commun.* **1980**, 765.

[10] Rhodium catalysis of this reaction afforded a 73% yield of ethyl 4-methoxy-2,4,6-cycloheptatriene-1-carboxylate and **9** in a 4.5:1 ratio.

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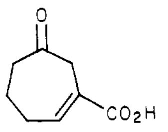
doublet at 3.26 ppm. The chemical shift and intensity of this bisallylic proton resonance requires a geminal ester group, while the multiplicity of this signal necessitates the adjacent methoxyl functionality. Triene **10** (<0.5%) showed four adjacent olefinic protons and a two-proton doublet at 2.67 ppm. This doublet must have one neighboring substituent. The low-field peak at 7.07 ppm is consistent with a proton vicinal to, yet not conjugated with, the carboethoxy group.

The synthesis of **1** and **2** was completed by oxidation of the appropriate triene. Although any of several oxidants can be used, *N*-bromosuccinimide smoothly converts **4** into **1** and **7** into **2** in 88% and 90% yield, respectively.[11] The spectra of **1** and **2** do not permit a priori structure assignment. The spectral data for **1** and **2** are similar; the constitution of **1** and **2** is defined by the triene precursor. These cycloheptatrienes are sensitive to acid, base, and oxygen, yielding several unidentified aromatics. They are stable in solution in degassed solvents. Further, **1** and **2** are surprisingly polar and appear to be inseparable under usual GC or HPLC conditions.

To eliminate the triene isomer separation, we examined other routes to **1** and **2**.[12] For example, oxidation of **12**,[13] readily prepared from cyclopentanone, would yield **2**. Treatment of **12** with quinones, manganese dioxide, nickel dioxide, selenium dioxide, halogenation–dehydrohalogenation, palladium–carbon, sulfur, or selenium did not yield **2**.[14] Recently Büchi and Pak[15] reported similar observations.



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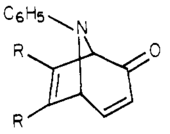

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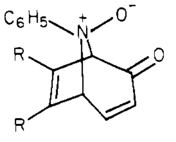

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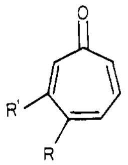

15

An alternative route to **1** utilized cycloaddition–fragmentation chemistry developed by Katritzky.[16] We prepared four cycloadducts (**13**) of 1-phenyl-3-oxidopyridinium betaine and acetylenes with electron-withdrawing substituents in moderate recrystallized yield. Chelotropic removal of "phenyl-N" should provide the cycloheptatriene **15**. Katritzky[17] had demonstrated Hoffmann elimination sequences provide tropolones. We anticipated that nitrogen-oxidation would afford an *N*-oxide **14**, the pyrolysis of which would give nitrosobenzene and **15**.[18] Oxidation of **13** proceeded capriciously with peracids or hydrogen peroxide. Pyrolysis of **14** on a 0.1-mmol scale did yield trace amounts of **15**. The pyrolysis was not amenable to scale-up. We subsequently determined that **1** was unstable to the reaction conditions.

We have developed a two-step preparation of **1** and **2** in gram amounts. We have shown that (carboethoxy)carbene shows little site selectivity in reactions with anisole. Any other diazo compound should provide analogous products, permitting the synthesis of several tropones by this approach.

Experimental Section

General Procedures. Infrared spectra were recorded as thin films on a Beckman IR 18-AX spectrophotometer; bands yielding structural information are reported in reciprocal centimeters (cm^{-1}), using polystyrene calibration. Nuclear magnetic resonance spectra were recorded on a Varian EM 390 spectrometer at 35 °C in deuteriochloroform and peak positions are reported in parts per million (ppm) from tetramethylsilane (Me$_4$Si) internal standard, using multiplet (m), quartet (q), triplet (t), doublet (d), or singlet (s). Decoupling experiments were completed on a Varian HR-220 instrument. Proton-decoupled ^{13}C NMR spectra were recorded in CDCl$_3$ on a Varian CFT-20 spectrometer. These peak positions are reported in ppm, using Me$_4$Si as an internal standard. Mass spectra were obtained from an LKB 9000 or on a Finnigan 4021 instrument at 70 eV. The percentage of the base peak is given in parentheses.

A Varian 3700 gas chromatograph with FID detector outfitted with a 6 ft × $^1/_4$ in. glass column containing 3% SE 30 or 3% DEXIL on 100/120 Gas Chrom Q was used for GC analysis.

Column chromatography was executed at medium pressure (50–100 psi) on E. Merck silica gel 60, particle size 0.040–0.063 mm. Preparative HPLC was completed on a Waters analytical instrument using a 4 ft × $^3/_8$ in. column packed with Li Chrosorb SI 100 of 5-μm particle size (EM reagents) or on a Waters "Prep-500" instrument.

Triene Mixture 3, 4, 7–11. The method of Johnson[4] was followed. Ethyl diazoacetate (30 g, 0.26 mol) was added dropwise over a period of 4 h to 140 mL of refluxing anisole. After the mixture was refluxed an additional 2.5 h, the anisole was removed at reduced pressure. Distillation at 0.05 mm afforded three fractions. Fraction 1 (bp 65–85 °C) weighed 5.06 g and contained compounds **3**, **4**, and **7–11**. Fraction 2 (bp 85–90 °C), 8.70 g, contained predominately compound **4** with some **3**, **7**, **8**, and **9**. Further purification of fractions 1 and 2 by HPLC (ethyl acetate–hexane) afforded analytical samples. Fraction 3 (90–110 °C), 1.14 g, consisted of pure **4**. Yields and spectral data are as follows.

Ethyl Phenoxyacetate (3): 8% yield; IR (film) 2980, 2940, 1760, 1735, 1600, 1495, 1255, 1200, 755, 690 cm^{-1}; NMR δ 1.28 (t, 3 H, $J = 7$ Hz), 4.25 (q, 2 H, $J = 7$ Hz), 4.60 (s, 2 H), 6.82–7.40 (m, 5 H); mass spectrum, *m/e* 180 (44), 107 (94), 94 (13), 79 (29), 77 (100), 51 (27).

Ethyl 4-Methoxy-1,3,6-cycloheptatriene-1-carboxylate (4): 15% yield; IR 3020, 2990, 1715, 1612, 1535, 730, 665 cm^{-1}; NMR δ 1.34 (t, 3 H, $J = 7$ Hz), 2.55 (d, 2 H, $J = 7$ Hz), 3.68 (s, 3 H), 4.27 (q, 2 H, $J = 7$ Hz), 5.37 (dt, 1 H, $J = 7, 10$ Hz), 5.53 (d, 1 H, $J = 7$ Hz), 6.73 (d, 1 H, $J = 10$ Hz), 7.64 (d, 1 H, $J = 7$ Hz); mass spectrum, *m/e* 194 (22), 166 (10), 165 (14), 149 (73), 121 (100), 91 (71), 78 (28), 77 (39).

Ethyl 3-Methoxy-2,5,7-cycloheptatriene-1-carboxylate (7): 8% yield; IR 3030, 2985, 1715, 1620, 1535, 1265, 1245, 730 cm^{-1}; NMR δ 1.33 (t, 3 H, $J = 7$ Hz), 2.53 (d, 2 H, $J = 7$ Hz), 3.67 (s, 3 H), 4.28 (q, 2 H, $J = 7$ Hz), 5.67 (dt, 1 H, $J = 7, 9$ Hz), 5.90 (s, 1 H), 6.27 (dd, 1 H, $J = 6, 9$ Hz), 7.41 (d, 1 H, $J = 6$ Hz); mass spectrum, *m/e* 194 (41), 166 (12), 165 (24), 149 (74), 122 (11), 121 (100), 91 (86), 78 (28), 77 (48).

Ethyl 6-Methoxy-1,3,5-cycloheptatriene-1-carboxylate (8): 1% yield; IR 2990, 1715, 1700, 1615, 1520, 1280, 733, 683 cm^{-1}; NMR δ 1.30 (t, 3 H, $J = 7$ Hz), 2.90 (s, 2 H), 3.65 (s, 3 H), 4.25 (q, 2 H, $J = 7$ Hz), 5.48 (d, 1 H, $J = 7$ Hz), 6.33 (dd, 1 H, $J = 6, 11$ Hz), 6.77 (dd, 1 H, $J = 7, 11$ Hz), 7.29 (d, 1 H, $J = 6$ Hz); mass spectrum, *m/e* 194 (13), 165 (100), 121 (20), 91 (43), 78 (14), 77 (19).

Ethyl 2-Methoxy-2,4,6-cycloheptatriene-1-carboxylate (9): 2% yield; IR 2990, 1735, 1620, 1530, 1220 cm^{-1}; NMR δ 1.22, (t,

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(11) Oxidation of ethyl 4-methoxy-2,4,6-cycloheptatriene-1-carboxylate with NBS or bromine afforded a complex mixture containing little **1**.

(12) We have also attempted reduction of 2-chlorocycloheptatrienones with several reagents. This process has been quite capricious, giving substantial amounts of overreduction.

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(14) We are grateful to V. Paul for completing some of these experiments.

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3 H, J = 7 Hz), 3.26 (d, 1 H, J = 8 Hz), 3.60 (s, 3 H), 417 (q, 2 H, J = 7 Hz), 5.55 (m, 2 H), 6.3 (m, 3 H); mass spectrum, *m/e* 194 (11), 121 (100), 91 (28), 78 (15), 77 (15).

Ethyl 2-Methoxy-1,4,6-cycloheptatriene-1-carboxylate (10): trace; IR 2990, 1717, 1640, 1270 cm^{-1}; NMR δ 1.31 (t, 3 H, J = 7 Hz), 2.67 (d, 2 H, J = 7 Hz), 3.70 (s, 3 H), 4.23 (q, 2 H, J = 7 Hz), 5.37 (dt, 1 H, J = 7, 9 Hz), 6.00 (dd, 1 H, J = 2, 7 Hz), 6.19 (dd, 1 H, J = 7, 9 Hz), 7.07 (d, 1 H, J = 2 Hz); mass spectrum, *m/e* 194 (19), 165 (77), 149 (19), 148 (23), 121 (100), 120 (32), 91 (33), 78 (23), 77 (34).

Ethyl 2-Phenoxypropanoate (11): trace; IR 2970, 2940, 1760, 1730, 1605, 1595, 1500, 1290, 1250, 755, 690 cm^{-1}; NMR δ 1.30 (t, 3 H, J = 7 Hz), 1.60 (d, 2 H, J = 7 Hz), 4.30 (q, 2 H, J = 7 Hz), 4.73 (q, 1 H, J = 7 Hz), 6.70–7.40 (m, 5 H); mass spectrum, *m/e* 194 (20), 121 (100), 94 (24), 93 (11), 77 (39).

4-(Carboethoxy)-2,4,6-cycloheptatrienone (1). *N*-Bromosuccinimide (0.85 g, 0.0048 mol) and benzoyl peroxide (ca. 5 mg) were added to a solution of 0.70 g (0.0036 mol) of triene 4 in 25 mL of CCl_4. Nitrogen was slowly bubbled through this refluxing solution for 1 h. After the solution was cooled under nitrogen, the mixture was treated with solid sodium bicarbonate. This heterogeneous mixture was stirred for 15 min and the solid removed by filtration. Evaporation of the solvent left a brown oil which was immediately filtered through silica gel (hexanes–ethyl acetate, 1:1).[19] Removal of solvent yielded 0.57 g (88%) of 2 as brownish crystals: UV (EtOH) 233 nm (ϵ 17 000), 305 (ϵ 4200), 315 (ϵ 4200); IR 2990, 1720, 1640, 1595, 1270, 1220 cm^{-1}; NMR δ 1.40 (t, 3 H, J = 7 Hz), 4.40 (q, 2 H, J = 7 Hz), 6.95–7.35 (m, 3 H), 7.70–8.05 (m, 2 H); ^{13}C NMR δ 13.9, 62.1, 134.2, 134.6, 135.5, 137.6, 140.9, 145.1, 165.4, 187.3; mass spectrum, *m/e* 178, 150, 149, 133, 122, 105 (100).

3-(Carboethoxy)-2,4,6-cycloheptatrienone (2). By use of the method described for 1 above, 3-(carboethoxy)tropone (2) was obtained from 7 in 90% yield:[19] UV (EtOH) 216 nm (ϵ 9900), 228 (sh, ϵ 9600), 310 (ϵ 2500), and 325 (sh, ϵ 2300); IR (film) 2990, 1720, 1640, 1250 cm^{-1}; NMR δ 1.40 (t, 3 H, J = 7 Hz), 4.40 (q, 2 H, J = 7 Hz), 6.95–8.00 (m, 5 H); ^{13}C NMR δ 14.1, 62.6, 133.5, 133.8, 136.9, 137.0, 142.4, 143.6, 166.8, 187.4; mass spectrum, *m/e* 178, 150, 149, 133, 105 (100).

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Registry No. 1, 80865-79-8; 2, 80865-80-1; 3, 2555-49-9; 4, 60058-37-9; 7, 41585-58-4; 8, 41585-61-9; 9, 80865-81-2; 10, 80865-82-3; 11, 42412-84-0; 12, 17606-97-2.

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(19) These compounds were stable for days in dilute benzene solution under N_2 at 0 °C. They could not be distilled by use of a Kugelrohr apparatus without complete decomposition. Storage as neat compounds led to complete decomposition within 48 h. In all instances, these products appeared to be polymeric.

Thermodynamic and Kinetic Aspects of Tropinone Oxide

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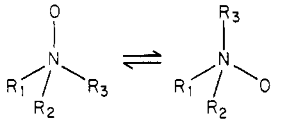
To the best of our knowledge no reaction leading to the racemization (or epimerization) of a tetracoordinated N atom of an amine oxide is known. Such a process could possibly provide an insight into the nature of the nonbonded interactions of the oxygen atom and enable the evaluation of various thermodynamic parameters. Previously we have evaluated such parameters in the 1-methylpiperidine 1-oxide system using the average chemical shift method.[1]

Table I. Diastereomeric Distribution of Tropinone Oxide

reaction method	% composition	
	1 (δ 3.42)	2 (δ 3.65)
A	90	10
B	60	40
C	40	60

We have ascertained that oxidation of amines to amine oxides is a kinetically controlled reaction.[1] Various attempts to induce equilibration of amine oxides (eq 1) have failed. Such attempts were based on bond breaking and making reactions involving the N–O linkage. In fact, our discovery of the reactivity of amine oxides toward organometallic carbonyl complexes,[2] which turned out to be a widely accepted method for the mild oxidation (disengagement) of such comlexes, evolved from such futile attempts.



(1)

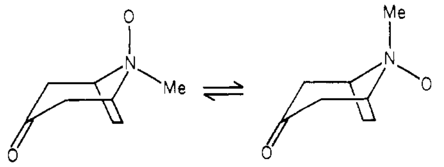
Consequently, we have turned to a different approach which involves the reversible N–R rather than N–O bond cleavage, which indeed turned out to be a successful one. This approach has two basic requirements: (a) activation of the N–R (R = alkyl) bond toward a reversible bond breaking and making process; (b) The availability of an appropriate molecular system which will enable the experimental detection of the equilibrating species.

It turned out that tropinone-1-oxide is an ideal system for such a study.

Tropinone 1-oxide was prepared by the foollowing three methods at 25 °C: (a) oxidation of tropinone with H_2O_2(aq) in acetone; (b) cycloaddition of *N*-methylhydroxylamine to 2,6-cycloheptadienone; (c) oxidation of tropinone with *m*-chloroperbenzoic acid in CH_2Cl_2.

In each case the final reaction mixture was examined by NMR. Invariably two N–Me signals at δ 3.42 and 3.65 were observed. Their relative intensities were dependent on the method of preparation (Table I).

Next, it was necessary to correlate the NMR signals of the N–Me group with the configurations of the diastereomeric tropinone oxides. For this purpose we have separated and purified the two components and converted them to the picrates. Kashman et al.,[3] using method B, obtained the two isomeric tropinone oxides 1 and 2 (eq 2).



(2)

1 2

They were characterized on the basis of the infra red spectrum of 1 (picrate) which lacks the C=O stretching band. It was argued that only 1 may interact to give 3[3,4] (eq 3).

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