Preparation and Photochemistry of Cyclohexene-1-carbonitriles

John J. McCullough* and Carl Manning

Department of Chemistry, McMaster University, Hamilton, Ontario, Canada L8S 4M1

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Irradiation of cyclohexene-1-carbonitriles with the full arc of a Hanovia 450-W lamp gives bicyclo[3.1.0]hexane-1-carbonitriles. Specifically, cyclohexene-1-carbonitrile gives bicyclo[3.1.0]hexane-1-carbonitrile and bicyclo[3.1.0]-hexane-6-carbonitrile. Similar irradiation of 3,3,5,5-tetramethylcyclohexene-1-carbonitrile gives rise to 2,2,4,4-tetramethylbicyclo[3.1.0]hexane-6-carbonitrile and 3,3,6,6-tetramethylbicyclo[3.1.0]hexane-1-carbonitrile. The structures were assigned on the basis of synthesis and NMR spectroscopy. The nitriles for irradiation were synthesized from the appropriate ketones. Cyclohexene-1-carbonitrile was prepared by dehydration of the cyanohydrin of cyclohexanone. 3,3,5,5-Tetramethylcyclohexene-1-carbonitrile was prepared from 3,3,5,5-tetramethylcyclohexanone by conversion to the corresponding vinyl chloride followed by treatment with cuprous cyanide. In the photolysis, significant amounts of unsaturated nitriles are sometimes formed, but they have not been characterized since they are photolabile and their yields are variable.

In this paper, we report the synthesis of two cyclohexene-1-carbonitriles, their photochemistry, and the identification of the photolysis products. The study is restricted at present to two substrates, 1 and 2.
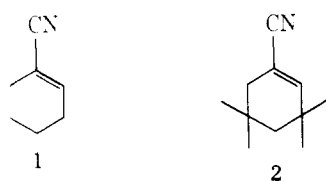
Results

Synthesis of Cyanocyclohexenes, 1 and 2. Nitrile 1 was prepared from cyclohexanone cyanohydrin as described in the literature.[1]

The tetramethyl derivative 2 could not be obtained in such a straightforward manner from ketone 4, since the equilibrium constant for cyanohydrin formation is unfavorable.[2a] The compound was obtained as depicted in Chart I, using isophorone as a starting point.[2b]

Photolysis of Cyanocyclohexenes, 1 and 2. The solvent for these irradiations was hexane, which had been treated with fuming sulfuric acid to remove absorbing impurities. This was necessary because of the low intensity, short wavelength absorption of the acrylonitrile derivatives. For example, acrylonitrile has an absorption maximum (EtOH) at 215.5 nm, log ϵ 1.69.[3]

Irradiation of a $\sim10^{-2}$ M solution of cyanocyclohexene 1 with the full arc (quartz) of the Hanovia 450-W medium pressure mercury lamp gave rise to two products. The reaction progress was monitored by VPC analysis. The irradiation was continued for 24 h. The products were separated by preparative VPC.

The NMR spectra were not particularly informative, but

they showed no resonances in the vinyl region (δ 5–7). The structures were proved by unambiguous synthesis after the tentative structures 6 and 7 had been assigned.

Compound 6 was prepared by reaction of cyclopentene with cyanocarbene,[4,5] which gave an oil identical with one of the photoproducts according to VPC, NMR, and infrared spectral comparison. Both the synthesis and photolysis gave mixtures of the epimers of 6.
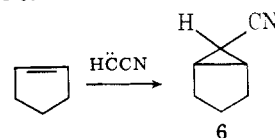
The second product (7) of the rearrangement of 1-cyanocyclohexene was synthesized from 1-cyanocyclopentene by treatment with dimethyloxosulfonium methylide, as described by Corey and Chaykovsky.[6]
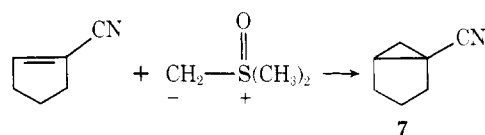
Compound 7 synthesized this way was identical in all respects with one of the above photoproducts. However, the synthesis was not without some difficulties. The cyanocyclopentene was obtained pure only after treatment with *tert*-butoxide. A chlorine-containing impurity is apparently formed when the cyanohydrin of cyclopentanone is dehydrated with phosphorus oxychloride–pyridine. However, the material shown to be present by VPC was not identified, but its mass spectrum showed a parent ion at m/e 129, with the isotope distribution of a single chlorine atom. In the synthesis of 7, a poor yield (15%) of the required compound was obtained. The product was not contaminated with other volatile compounds, and the balance of material was water soluble. The water-soluble substance was not investigated.

Photolysis of 3,3,5,5-Tetramethylcyclohexene-1-carbonitrile. This nitrile was irradiated with the Hanovia 450-W mercury lamp as described above. After 24 h, two components were observed (ratio 4:1, by VPC). The products were isolated as described in the Experimental Section.

The minor product was identified from its 220-MHz NMR spectrum, which indicated the structure 2,2,4,4-tetramethylbicyclo[3.1.0]hexane-6-carbonitrile (8).
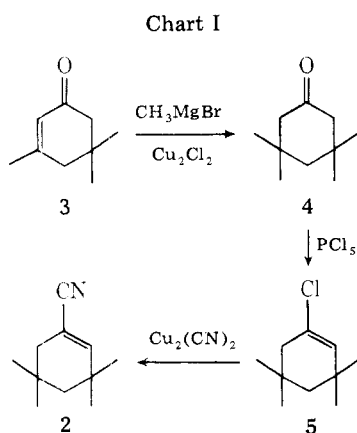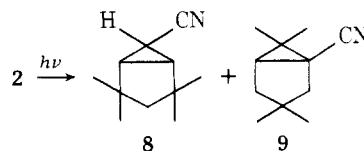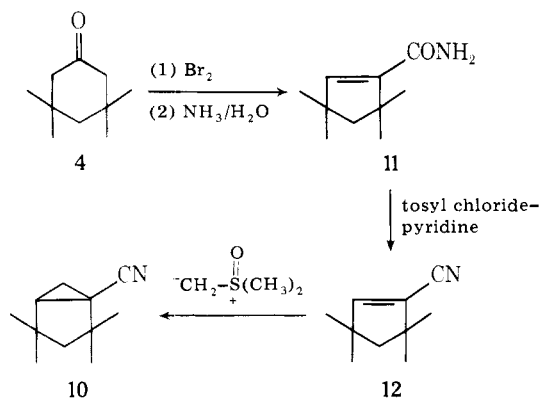
Chart I

Chart II

The NMR spectrum of **8** is simple owing to the symmetry of the molecule. Resonances appeared at δ 0.86 and 1.28 (each 1 H, d, *J* = 14.0 Hz, ring CH₂), 1.01 [1 H, t, *J* = 3.5 Hz, C(CN)H, partially obscured by a Me signal], 1.02 and 1.21 (each 6 H, s, Me), and 1.77 (2 H, t, bridgehead CH).

Interpretation of the NMR spectrum of **9** was not so straightforward. The gross features of the spectrum were consistent with structure **9**. The spectrum, 220 MHz, showed resonances at δ 0.98, 1.06, 1.17, and 1.31 (all 3 H, s, Me). A doublet of doublets (*J* = 4.0 and 8.0 Hz) at δ 1.94, is assigned to the bridgehead, cyclopropyl methine proton. The methylene group vicinal to the nitrile function showed an AB quartet (centered at δ 1.75 and 1.5, respectively, with *J* = 12.0 Hz). The lower field doublet showed a further, long-range splitting of 2.0 Hz. One resonance showed complex splitting (δ 1.64) and is assigned to one methylene group proton, vicinal to the bridgehead methine. The second proton of this methylene group is obscured by the methyl group signals.

Although the spectra of **9** support this structure, it was not possible from the spectra alone to rule out the alternative structure, 2,2,4,4-tetramethylbicyclo[3.1.0]hexane-1-carbonitrile (**10**).

Thus, to verify the structural assignment, a sample of **10** was synthesized as shown in Chart II, and the spectra were compared with those of the photoproduct.

The ketone **4** was converted to the known[7] amide **11**, which was dehydrated to afford the nitrile **12**. The latter on treatment with dimethyloxosulfonium methylide gave **10**.

The VPC behavior and NMR spectrum of **10** were different from those of the photoproduct **9**. In the 220-MHz NMR spectrum, the resonance furthest downfield (δ 1.88) was a doublet of doublets (*J* = 6.0 and 4.0 Hz), and is assigned to the bridgehead methine proton of the cyclopropyl ring. The spectrum showed four 3-proton resonances at δ 0.98, 1.10, 1.27, and 1.40. Resonances attributed to the AB system associated with the methylene group flanked by the two *gem*-dimethyl groups were also observed, interspersed with the methyl group resonances. Thus, the spectrum is similar to that of the major photoproduct from the photolysis of nitrile **9**, but the spectra are not identical. Also, the retention times of the two compounds (photoproduct and synthetic) are different on VPC. Thus, we can confidently assign structure **9** to the photolysis product.

Discussion

Even though the light output is low in the region of their absorption, the cyclohexene-1-carbonitriles **1** and **2** rearrange to bicyclo[3.1.0]hexanecarbonitriles on irradiation with a medium-pressure mercury lamp. The reaction formally resembles the "type A" rearrangement of enones,[8] in that a vinyl group is converted to a cyclopropyl moiety. (We note that rearrangements have been observed in the photochemistry of dinitriles.[9])

A rationale involving free-radical intermediates can be proposed.
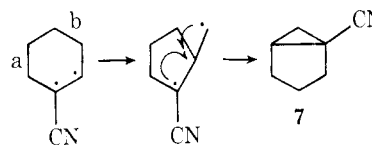
Note that either bond "a" or "b" above could have migrated to the neighboring free-radical center. Either possibility would give the same product in the case of **1**. However, in the case of the tetramethyl nitrile **2**, migration of bond "b" will give a different product, i.e., **9**, from migration of bond "a", i.e., **10**. This question was resolved by a synthesis of the product of migration of bond "a". This product proved to be different from the major photoproduct from **2** and the structure assigned to the major photoproduct therefore seems secure. The second type of product formed in the irradiation is the secondary nitriles, **6** and **8**.
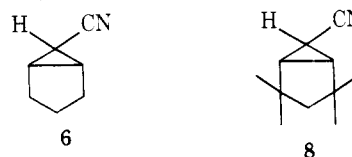
To form these products from the cyclohexenecarbonitrile starting materials, a hydrogen shift must take place. The latter
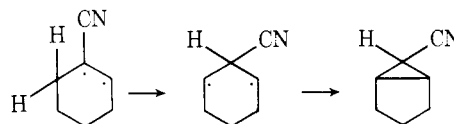
type of products, although formed in both reactions, was quite unexpected.

Experimental Section

Photolysis of Cyclohexene-1-carbonitrile (1): Cyclohexene-1-carbonitrile (100 mg, 0.93 mmol) in hexane (400 mL) was thoroughly purged with argon and irradiated for 24 h under argon. After 14 h irradiation, the lamp well was scrubbed clean as a thick deposit tended to coat the walls. After removal of the solvent, VPC analysis (80 °C, helium at 60 mL/min) of the residual yellow oil showed the presence of two components, retention times 4.5 and 6.5 min, in the approximate ratio 1:1. These products were separated by preparative VPC and found to be bicyclo[3.1.0]hexane-1-carbonitrile and *exo*- and

endo-bicyclo[3.1.0]hexane-6-carbonitrile **7** and **6**, as described in the text.

Synthesis of Bicyclo[3.1.0]hexane-6-carbonitrile (6). Diazoacetonitrile was prepared by a modification of the method of Harper and Sleep.[11] Methyleneaminoacetonitrile[12] (18.7 g, 0.275 mol) was stirred with 135 mL of 2 N HCl overnight. The mixture was cooled to −5 °C with acetone–dry ice and 100 mL of methylene chloride was added. To the cooled and stirred mixture was added dropwise an ice-cold solution of sodium nitrite (22.8 g in 70 mL of H_2O); 5% sulfuric acid (25 mL) was then added slowly, the temperature being kept below 0 °C at all times. The mixture was allowed to warm to room temperature and the organic layer was separated. The aqueous layer was extracted with 50 mL of methylene chloride and the combined organic extracts were washed thoroughly with 10% sodium bicarbonate solution. After drying over sodium sulfate, the solution was concentrated to approximately 10 mL by carefully removing the methylene chloride via a 35 × 2.5 cm column of glass helices at aspirator pressure. No external heating was used as the yellow diazoacetonitrile tended to co-distil if the temperature rose to above approximately 25 °C. Purified hexane (50 mL) was added and this mixture was slowly dripped into cyclopentene (6 mL) and copper powder (150 mg) under dry nitrogen. Immediate evolution of nitrogen was observed which subsided after 1 h of stirring. A further 150 mg of copper powder was added and the mixture was refluxed for 1 h, after which time the mixture was filtered and poured into 100 mL of 2 N HCl. The organic layer was separated, washed with 10% sodium bicarbonate, and dried over sodium sulfate. Removal of the solvent yielded 1 g of yellow oil, which on VPC showed the presence of two major products at retention times of 5 and 7 min (80 °C, helium at 60 mL/min) in the approximate ratio 3:2. A small amount of fumaronitrile was also present, which was brominated (1 drop of Br_2), prior to distillation. Fractional distillation yielded 150 mg of a colorless, low-boiling fraction [bp ~35 °C (20 mm)] the NMR and mass spectra of which showed it to be chloroacetonitrile, presumably formed via attack of cyanocarbene on residual methylene chloride.[13] The residue from the distillation was subjected to preparative VPC (90 °C helium at 60 mL/min), the two major peaks, epimers of **6**, were collected together and distilled.

Anal. Calcd for C_7H_9N: C, 78.50; H, 8.41; N, 13.08. Found: C, 78.35; H, 8.39; N, 12.95%.

Synthesis of Bicyclo[3.1.0]hexane-1-carbonitrile (7). A suspension of dimethyloxosulfonium methylide in dimethyl sulfoxide was prepared from sodium hydride (0.504 g, 0.021 mL), trimethyloxosulfonium iodide (4.62 g, 0.021 mol) and Me_2SO (25 mL) by the method of Cory.[6] Cyclopentene-1-carbonitrile (1.86 g, 0.02 mmol) in dimethyl sulfoxide (5 mL) was added dropwise with stirring. The mixture was stirred at room temperature for 2 h and then at 50 °C for 1 h. It was then poured into water (80 mL) and extracted with two 25-mL portions of ether. The ether layer was dried, the ether removed, and the residue distilled to yield 0.35 g (16%) of bicyclo[3.1.0]hexane-1-carbonitrile, bp ~75 °C (12 mm).

Anal. Calcd for C_7H_9N: C, 78.50; H, 8.41; N, 13.08. Found: C, 78.42; H, 8.28; N, 13.22.

Synthesis of 1-Chloro-3,3,5,5-tetramethylcyclohex-1-ene (5). 3,3,5,5-Tetramethylcyclohexanone[14] (12.3 g, 0.08 mol) in methylene chloride (30 mL) was added dropwise to a slurry of phosphorus pentachloride (18.5 g, 0.09 mol) and methylene chloride (60 mL). The mixture was refluxed overnight, cooled, poured onto ice, and extracted with ether. The ethereal extracts were washed with 10% sodium bicarbonate and dried over sodium sulfate. After removal of the ether, the residue was distilled, yielding 7.7 g of 1-chloro-3,3,5,5-tetramethylcyclohexene [bp 75 °C (10 mm)]; yield, 56%.

Anal. Calcd for $C_{10}H_{17}Cl$: C, 69.58; H, 9.86; Cl, 20.56. Found: C, 69.54; H, 9.92; Cl, 20.43.

Synthesis of 3,3,5,5-Tetramethylcyclohexene-1-carbonitrile (2). 1-Chloro-3,3,5,5-tetramethylcyclohexene (7.7 g, 0.045 mol) was added to a stirred suspension of cuprous cyanide (7.7 g) in *N*-methyl-2-pyrolidinone (50 mL) and the mixture refluxed for 2 h. The mixture was cooled, poured into 100 mL of 5% sodium cyanide solution, and extracted with two 50-mL portions of benzene. The organic extract was washed with 100 mL of 10% sodium cyanide and 100 mL of water and then dried over sodium sulfate. After removal of the benzene, the residue was distilled to yield 4.5 g (62%) of 3,3,5,5-tetramethylcyclohexene-1-carbonitrile [bp 45–47 °C (0.2 mm)].

Anal. Calcd for $C_{11}H_{17}N$: C, 80.98; H, 10.43; N, 8.59. Found: C, 80.63; H, 10.37; N, 8.29.

Photolysis of 3,3,5,5-Tetramethylcyclohexene-1-carbonitrile. 3,3,5,5-Tetramethylcyclohexene-1-carbonitrile (1.5 g, 9.2 mmol) in hexane (3 L) was thoroughly purged with argon and irradiated for 24 h under argon. The hexane was removed under aspirator pressure. VPC analysis (100 °C, helium at 60 mL/min) of the residue showed

the presence of two major components in the approximate ratio 4:1, with retention times 6 and 7 min. The major product was isolated by column chromatography on silica gel (55 × 2.5 cm column) using benzene/hexane (1:1) as eluent for the first 800 mL followed by pure benzene; 100-mL fractions were collected and fractions 10, 11, and 12 contained the major product of the photolysis. Distillation of these fractions yielded 3,3,6,6-tetramethylbicyclo[3.1.0]hexane-1-carbonitrile (**9**; 450 mg, 30%), bp 60–62 °C (0.1 mm).

Anal. Calcd for $C_{11}H_{17}N$: C, 80.98; H, 10.43; N, 8.59. Found: C, 80.81; H, 10.53; N, 8.48.

The minor component was isolated by preparative VPC (100 °C, helium at 90 mL/min). Its identification as 2,2,4,4-tetramethylbicyclo[3.1.0]hexane-6-carbonitrile (**8**) is described in the text.

Low Conversion Photolysis of 3,3,5,5-Tetramethylcyclohexene-1-carbonitrile. The nitrile (100 mg, 0.6 mmol) in hexane (400 mL) was irradiated for 5 h under argon. Removal of the hexane left a yellow oil, the VPC of which (100 °C, 60 mL/min) showed the presence of three components, two of which coincided with the products formed upon prolonged photolysis. Isolation of the new product was effected by preparative VPC (100 °, 90 mL/Min) and its spectral properties were found to be consistent with the structure 2,2,4,4-tetramethylcyclopentyl-1-acetonitrile. The major product was isolated under the same VPC conditions and its NMR spectrum showed it to be mainly the bicyclic carbonitrile previously characterized. There were, however, two new resonances in the NMR spectrum, a triplet at δ 5.06 ppm (*J* = 1 Hz) and a doublet at δ 2.56 ppm (*J* = 1 Hz). It appeared that a compound similar to the new product, which was not separable from the major product by VPC, was present.

Synthesis of 3,3,5,5-Tetramethylcyclopentene-1-carbonitrile (12). 3,3,5,5-Tetramethylcyclopentene-1-carboxamide[7] (4 g, 0.024 mmol) was dissolved in pyridine (5 mL), and tosyl chloride (5 g, 0.026 mmol) was added in small portions. The mixture was stirred for 3 h. Ether (25 mL) was added, the solution was washed with water, and the organic layer was dried over sodium sulfate. After removal of the ether, distillation yielded 2.7 g (60%) of 2,2,4,4-tetramethylcyclopentene-1-carbonitrile, bp 70–72 °C (13 mm).

Anal. Calcd for $C_{10}H_{15}N$: C, 80.54; H, 10.07; N, 9.40. Found: C, 80.34; H, 9.99; N, 9.28.

Synthesis of 2,2,4,4-Tetramethylbicyclo[3.1.0]hexane-1-carbonitrile (10). A suspension of dimethyloxosulfonium methylide in dimethyl sulfoxide was prepared, according to the method of Corey,[6] from sodium hydride (0.013 g, 0.01 mol), trimethyloxosulfonium iodide (1.1 g, 0.005 mol), and Me_2SO (15 mL). 2,2,4,4-Tetramethylcyclopentene-1-carbonitrile (0.7 g, 0.005 mol) in Me_2SO (5 mL) was added slowly with stirring. The mixture was heated to 90 °C and stirred for 3 days, additional portions of dimethyloxosulfonium methylide being added every 24 h. After this time, the mixture was poured into 25 mL of cold water and extracted with two 25-mL portions of ether. The ether extracts were dried and evaporated and distillation of the residue yielded 0.5 g (66%) of 2,2,4,4-tetramethylbicyclo[3.1.0]hexane-1-carbonitrile, bp 90–92 °C (10 mm).

Anal. Calcd for $C_{11}H_{17}N$: C, 80.98; H, 10.43; N, 8.59. Found: C, 81.45; H, 10.16; N, 8.33.

Synthesis of Cyclopentene-1-carbonitrile. Cyclopentanone cyanohydrin (27.8 g, 0.25 mol), from cyclopentanone (21 g, 0.25 mol), was dehydrated with phosphorus oxychloride following the literature procedure.[1] Distillation yielded 10.4 g of colorless liquid, bp 60 °C (9 mm), which was dissolved in 50 mL of dry *tert*-butyl alcohol. Potassium *tert*-butoxide (3.5 g, 0.05 mol) was added and the mixture was refluxed for 1 h after which time it was poured into 100 mL of ice–water. The aqueous mixture was extracted with two 50-mL portions of Et_2O, the organic layer was dried (Na_2SO_4), the ether removed, and the residual oil distilled to yield 8.1 g of cyclopentene-1-carbonitrile, bp 67–70 °C (15 mm).

Anal. Calcd for C_6H_7N: C, 77.18; H, 7.59; N, 14.99. Found: C, 77.42; H, 7.55; N, 15.05%.

Registry No.—**1**, 1855-63-6; **2**, 63261-34-7; **4**, 14376-79-5; **5**, 66323-36-2; *endo*-**6**, 63261-36-9; *exo*-**6**, 63261-35-8; **7**, 31357-72-9; **8**, 63261-38-1; **9**, 63261-37-0; **10**, 66323-37-3; **11**, 66323-38-4; **12**, 66323-39-5; dimethyloxosulfonium methylide, 5367-24-8; cyclopentene-1-carbonitrile, 3047-38-9; diazoacetonitrile, 13138-21-1; cyclopentene, 142-29-0.

References and Notes

(1) O. H. Wheeler and I. Lerner, *J. Am. Chem. Soc.*, **78**, 63 (1956).
(2) (a) O. H. Wheeler and J. Z. Zabricky, *Can. J. Chem.*, **36**, 656 (1958). (b)

An alternative approach could utilize diethylaluminum cyanide to obtain the cyanohydrin. See "The Use of Aluminum Alkyls in Organic Synthesis", The Ethyl Corporation, Baton Route, La., 1969–1972 Supplement, p 108.

(3) M. T. Rogers, *J. Am. Chem. Soc.*, **69**, 2544 (1947).

(4) M. J. S. Dewar and R. Petit, *J. Chem. Soc.*, 2026 (1956).

(5) Our procedure was modeled on that of Warkentin for a carbethoxycarbene addition: J. Warkentin, E. Singleton, and J. F. Edgar, *Can. J. Chem.*, **43**, 3456 (1965).

(6) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).

(7) C. Sandris and G. Ourisson, *Bull. Soc. Chim. Fr.*, 958 (1956).

(8) H. E. Zimmerman, R. G. Lewis, J. J. McCullough, A. Padwa, S. W. Staley,

and M. Semmelhack, *J. Am. Chem. Soc.*, **88**, 1965 (1966).

(9) R. C. Cookson, V. N. Gagte, J. Hudec, and N. A. Mirza, *Tetrahedron Lett.*, 3955 (1965); M. Sharma, *J. Am. Chem. Soc.*, **97**, 1153 (1975).

(10) B. B. Corson and V. U. Ipatieff, "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 151.

(11) S. H. Harper and K. C. Sleep, *J. Sci. Food Agric.*, **6**, 116 (1955).

(12) R. Adams and W. D. Langley, "Organic Syntheses", Collect. Vol. I, Wiley, New York, N.Y., 1932, p 355.

(13) If methylene chloride is used as solvent in this reaction, the major product is chloroacetonitrile, which was characterized by its NMR and mass spectra.

(14) S. Kharasch and P. O. Taurney, *J. Am. Chem. Soc.*, **63**, 2308 (1941).

Coordinative Role of Alkali Cations in Organic Synthesis. 3.[1] Selective Methylations of 5-Hydroxy-2-hydroxymethyl-γ-pyrone

Narinder S. Poonia* and Brij Pal Yadav

Department of Chemistry, University of Indore, Indore 452001, India

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Methylation of 5-hydroxy-2-hydroxymethyl-γ-pyrone (kojic acid, 1) has been investigated using dimethyl sulfate and caustic alkalis to obtain 5-methoxy (2), 2-methoxymethyl (3), and 5-methoxy-2-methoxymethyl (4) methyl ethers free of each other. The phenolic OH of 1 is methylated through salification, whereas the alcoholic one is methylated due to its coordination with the alkali cations (M^+); the former can be selectively methylated using a stoichiometric amount of an alkali of a low charge density M^+(KOH), the latter by employing excess alkali of a high charge density M^+(LiOH), and both with the alkali of a medium charge density M^+(NaOH). When KOH is the alkali and excess methylating reagents are used, a large amount of the substrate is lost as K^+-2 complexes in the aqueous phase. Opening of the γ-pyrone ring is attributed to the coordination of its carbonyl with H^+ (in acidic medium) or M^+ (in alkaline medium); in alkaline medium, 1 and 3 do not undergo ring opening due to the creation of an electron-supplying phenoxide.

Methylation of kojic acid (1) with dimethyl sulfate (DMS) in aqueous caustic alkalis (MOH) leads[2–4] to all three possible ethers 2, 3, and 4. However, selective preparation of 3 and 4 in high yields was never achieved and it is not convenient to separate them. Coordination of neutral organic nucleophiles with alkali cations (M^+) is becoming known,[5–11] so we attribute their low yields to the formation of water-soluble complexes with M^+; we indeed isolated a number of alkali sulfate complexes of 2 from the aqueous phase of reaction mixtures involving use of excess DMS and KOH.[12] This paper reports the results of a detailed systematic study leading to procedures by which each of the three ethers can be obtained free of the other in 60 to 75% yields.

The reactants of a reaction mixture are written in the order

1, DMS, MOH such that the reaction mixture 142 denotes 1–DMS–MOH (1:4:2). Experimental conditions of a reaction are also described by notations; 132 (KOH), 10 aq, DMS (↓), 25 °C reads that 1–DMS–KOH (1:3:2) was the reaction mixture in 10 mL of water where DMS was added to the 1–KOH system maintained at 25 °C.

Results and Discussion

The results of selected experiments are shown in Table I and synthetic routes in Scheme I. Employing 111 reactions, only phenolic OH was methylated to obtain 2 (Scheme I, reaction a). Methylation, however, was hampered and M^{+-}OkH (metal kojate) instead of 2 was mainly recovered for LiOH and

Scheme I. Routes of Methylation Reactions of Kojic Acid