Synthesis of 2-Acetylbicyclo[2.2.1]hept-2-ene[1a]

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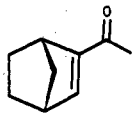
In regard to the synthesis of various bicyclic alkaloids and terpenes,[2] the preparation of 2-acetylnorbornene (1) was undertaken as a model system. Only one synthesis



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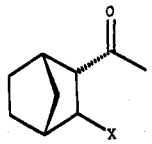
of this simple compound has been reported,[3] and that involves a Diels–Alder cycloaddition of cyclopentadiene with 4-(benzyloxy)-3-buten-2-one followed by hydrogenation and dehydration. This provides the target molecule in 48% overall yield. Unfortunately, extension of this direct synthesis to less reactive nitrogen-containing dienes such as substituted pyrroles in place of cyclopentadiene is not possible. Another straightforward preparation would be the cycloaddition of cyclopentadiene and 3-butyn-2-one[4] and selective reduction of the nonconjugated double bond, but this also would be difficult to extend to nitrogen systems because of low cycloaddition reactivity of the dienophile.

The first dienophile which was tried here was 4-chloro-3-buten-2-one.[5] Reaction with cyclopentadiene gives the expected adduct in good yield which undergoes hydrogenation smoothly to give the chloro ketone 2 (X = Cl).



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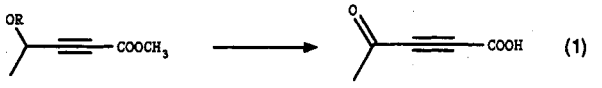
Unfortunately, suitable conditions for elimination of hydrogen chloride were not found. Reaction with sodium hydride, triethylamine, and *N,N*-dimethylaniline gave only small amounts of enone 1. Sodium methoxide gives the product of apparent elimination and addition (2, X = OCH_3). Because of low yields, this approach was abandoned.

Maleic anhydride was the next dienophile to be considered. This material adds to cyclopentadiene so well that this reaction is a standard undergraduate experiment.[6] The plan was then to open the anhydride ring with a methyl anion to give the keto acid; however, all attempts to accomplish this with either methylmagnesium iodide or methyllithium gave the lactone 3[7] (Scheme I). Fortunately, the cuprate reagent from the reaction of methyllithium with cuprous iodide[8] successfully opens the anhydride adduct to give the keto acid 4 in 65% yield. Reduction of the alkene double bond[9] gives saturated acid 5, and a modified Hunsdiecker reaction[10] gives the pure bromo compound 6 as a mixture of diastereomers in 75% yield. This material reacts with base to give the desired enone 1 identical with material described earlier.[3] *N,N*-Diethylaniline in hot benzene does not give satisfactory results for the loss of HBr, but 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[11] in refluxing toluene, warm DMSO, or hot chloroform (best results) yields acetylnorbornene in 65% isolated yield. This product is contaminated with the "dimer" when the reaction time is too long or as in the preparation starting with 4-chloro-3-buten-2-one.

Since maleic anhydride proved to be too unreactive for extension to nitrogen-containing dienes, a third, more reactive, dienophile was prepared—namely, esters of 4-oxo-2-pentynoic acid.[12] 3-Butyn-2-ol was protected as a tetrahydropyranyl (THP) or ethoxyethyl (EE) ether in 80–90% yields, and the alkyne anion was generated with butyllithium. This reacts with methyl chloroformate to give the ester 7 in 85% yield (eq 1). Attempts to use benzyl



(1)

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R = THP, EE

chloroformate gave results which are difficult to reproduce—presumably because the benzyl chloroformate hydrolyzes so easily and the resulting HCl and benzyl alcohol quench the acetylene anion. Benzyl cyanoformate[13] at first gave good results (85% yield of acylation product) but even this was not reproducible. In addition,

(1) (a) This work was presented in part at the 22nd Middle Atlantic Regional Meeting of the American Chemical Society, Millersville, PA, May 24–26, 1988 (Abstract ORGN 262); taken in part from the MS thesis of L. C., 1991. (b) Summer undergraduate research participant from Cambridge University, 1986. (c) Visiting faculty member from Westminster College, 1986. (d) Summer undergraduate research participant from Allegheny College, 1988.

(2) (a) For example, see: Jung, M. E.; Kaas, S. M. *Tetrahedron Lett.* **1989**, 641. (b) The primary target for which acetylnorbornene is a model is anatoxin-a: Devlin, J. P.; Edwards, O. E.; Gorham, P. R.; Hunter, N. R.; Pike, R. K.; Stavric, B. *Can. J. Chem.* **1977**, *55*, 1367.

(3) Gottschalk, F.-J.; Weyerstahl, P. *Chem. Ber.* **1980**, *113*, 555.

(4) Jones, E. R. H.,; Mansfield, G. H.; Whiting, M. C. *J. Chem. Soc.* **1956**, 4073. Hirao, K.-i.; Yamashita, A.; Ando, A.; Hamada, T.; Yonemitsu, O. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2913.

(5) This compound is available from the aluminum chloride catalyzed acetylation of acetylene with acetyl chloride (Benson, W. R.; Pohland, A. E. *J. Org. Chem.* **1964**, *29*, 385). β-Bromo methyl vinyl ketone readily undergoes Diels–Alder cycloaddition with cyclopentadiene: Bloch, R.; Marty, R. A.; de Mayo, P. *Bull. Soc. Chem. Fr.* **1972**, 2031.

(6) For example, see Fieser, L. F.; Williamson, K. L. *Organic Experiments*, 5th ed.; D. C. Heath & Co.: 1983; p 185.

(7) This type of reaction was studied later in great detail by Canonne. Hindered Grignard reagents do give the desired keto acids. For example, see: Canonne, P.; Kassou, M.; Akssira, M. *Tetrahedron Lett.* **1986**, 2001.

(8) Posner, G. H. *Org. React.* **1975**, *22*, 253.

(9) Attempts to do an oxidative decarboxylation with lead tetraacetate (LTA) on this hydrogenation product destroyed the compound and did not leave any identifiable products. Nevertheless, the addition of cupric acetate to the LTA reaction gave a mixture of at least four compounds having the correct molecular weight but these acetoxy ketones were not pursued further. See: McMurry, J. E.; Blaszczak, L. C. *J. Org. Chem.* **1974**, *39*, 2217.

(10) Meyers, A. I.; Fleming, M. P. *J. Org. Chem.* **1979**, *44*, 3405. Wiberg, K. B.; Dailey, W. P.; Walker, F. H.; Waddell, S. T.; Crocker, L. S.; Newton, M. *J. Am. Chem. Soc.* **1985**, *107*, 7247.

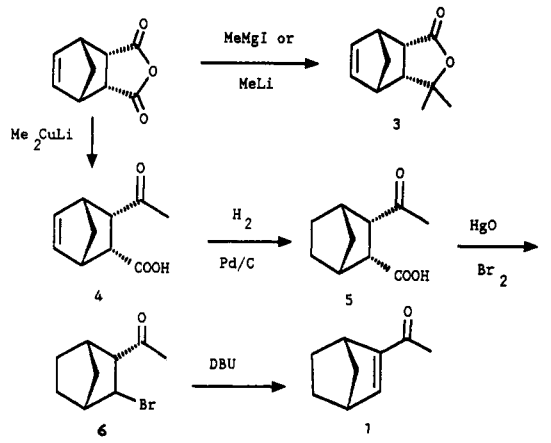
(11) Amidine bases are particularly effective for E2 eliminations: Oediger, H.; Moller, F.; Eiter, K. *Synthesis* **1972**, 591.

(12) For recent papers describing the preparation and some chemistry of acetylenic ketones, see: Yerino, L. V.; Osborn, M. E.; Mariano, P. S. *Tetrahedron* **1982**, *38*, 1579. Obrecht, D. *Helv. Chim. Acta* **1989**, *72*, 447.

(13) Childs, M. E.; Weber, W. P. *J. Org. Chem.* **1976**, *41*, 3486.

0022-3263/93/1958-3188$04.00/0

Scheme I. Synthesis of 2-Acetylnorbornene



the benzyl ester corresponding to 7 is not stable to distillation so the remainder of the synthesis was carried out with the methyl ester. Deprotection of the THP ether with aqueous acid is slow. Fortunately, the EE ether is deprotected readily with pyridinium *p*-toluenesulfonate (PPTS),[14] and the resulting alcohol is oxidized with Jones reagent to give methyl 4-oxo-2-pentynoate in 50% yield from the EE ether (eq 1). This dienophile undergoes cycloaddition with cyclopentadiene to give the expected adduct in quantitative yield. Hydrogenation of this material over palladium reduces the alkene double bonds in 92% yield, and cleavage of the methyl ester with sodium iodide and trimethylsilyl chloride (TMSCl) in acetonitrile[15] (via TMSI) gives a 68% yield of the keto acid **5**. Application of the Hunsdiecker reaction and elimination of HBr as before gives acetylnorbornene (**1**).

While the overall yield for this synthesis is in the 30% range from the dienophile (33% from maleic anhydride and 13% from 3-butyn-2-ol), incorporation of unreactive dienes, particularly nitrogen-containing ones, should be possible[16] and allow the preparation of a wide variety of analogous compounds of greater synthetic interest.[2b] This and the chemistry of acetylnorbornene and the identity of the dimer are under investigation and will be reported soon.

Experimental Section

General. NMR spectra were run in $CDCl_3$ on 60- or 90-MHz instruments using TMS (δ_H 0.0) and $CDCl_3$ (δ_C 77.0) as internal reference peaks. Melting points are uncorrected. Anhydrous THF and ether were distilled from potassium and sodium/benzophenone, respectively.

3-Acetylbicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (4). CuI (5.71 g, 30.0 mmol) was flame dried under a flow of N_2. Anhydrous ether (40 mL) was added, and the slurry was cooled to −78 °C. Methyllithium in ether (1.5 M, 40 mL, 60 mmol) was added via syringe, and this was stirred for 10 min and then allowed to warm to −10 °C for 10 min more.

Bicyclo[2.2.1]hept-2-ene-5,6-dicarboxylic anhydride[6] (1.64 g, 10.0 mmol) was added all at once, the reaction mixture was allowed to stir for 45 min and then allowed to warm to just above 0 °C, and 50 mL of saturated NH_4Cl was added dropwise. This mixture was filtered, and dilute HCl was added to the filtrate until acidic. This mixture was filtered through Celite, and the aqueous layer was extracted with ether. The combined ether layers were extracted twice with aqueous $NaHCO_3$. These combined bicarbonate layers were acidified with 6 M HCl, and the mixture was extracted with several portions of CH_2Cl_2. After drying ($MgSO_4$) and concentration, 1.17 g (65%) of the desired keto acid was obtained as a white solid: mp 119–121 °C;[17] ^1H NMR ($CDCl_3$) δ 1.45 (s, 2H), 2.28 (s, 3H), 2.5–3.6 (m, 4H), 6.34 (m, 2H), 11.90 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.48, 45.34, 46.48, 46.69, 55.47, 135.82, 137.60, 179.32, 208.36; MS *m/e* (rel int) 180 (P, 0.6), 162 (9), 115 (55), 91 (53), 66 (100), 65 (50), 43 (92), 39 (72); IR (KBr) 3500–2300, 1730–1660, 1430 cm^{-1}. Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71, Found: C, 66.25; H, 6.54.

2-Acetyl-3-bromobicyclo[2.2.1]heptane (6). A solution of the keto acid **4** (3.6 g, 20 mmol) in 50 mL of methanol was shaken with 100 mg of 10% palladium on carbon in a Parr hydrogenator with 30 psi of H_2 for 24 h. The catalyst was filtered off, and the filtrate was concentrated to give 3.64 g (100% yield) of the pure dihydro keto acid **5**: mp 100–105 °C; ^1H NMR ($CDCl_3$) δ 1.35 (m, 6H), 2.22 (s, 3H), 2.4–3.4 (m, 4H), 10.72 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.54, 26.02, 29.36, 32.42, 40.03, 41.12, 47.18, 56.72, 179.53, 268.25.

A solution of the keto acid **5** (2.50 g, 13.7 mmol) was dissolved in 80 mL of dry CH_2Cl_2 and stirred with 4.38 g (20.2 mmol) of red HgO and 1.8 g of anhydrous $MgSO_4$. The light and heat of a 100-W incandescent light bulb were directed into the flask using aluminum foil so that reflux resulted. A solution of Br_2 (3.23 g, 20.2 mmol) in 20 mL of CH_2Cl_2 was then added over 10 min. The reaction mixture was refluxed for 3 h, cooled to rt, and quenched with 25 mL of saturated $NaHCO_3$. This mixture was stirred vigorously for 15 min and filtered through Celite. The organic layer was washed with aqueous $NaHCO_3$, water, and saturated aqueous NaCl and was dried ($MgSO_4$) and concentrated to give 2.02 g (68%) of the sensitive bromo ketone **6** which was a mixture of several stereoisomers: ^1H NMR ($CDCl_3$) δ 1.1–1.8 (m, 6H), 2.14, 2.22, 2.47 (three s, total of 3H), 2.4–3.0 (m, 3H), 4.3–4.8 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 199.80, 206.82, 206.51 (C=O peaks); IR (NaCl) 3000, 2900, 1725, 1370 cm^{-1}.

2-Acetylbicyclo[2.2.1]hept-2-ene (1). The base DBU (4.77 g, 31.0 mmol) was added to a solution of 1.59 g (7.30 mmol) of the bromo ketone **6** in 50 mL of $CHCl_3$. The dark brown reaction mixture was refluxed under nitrogen for 15 min, cooled, and poured into 100 g of ice and 10 mL of 6 M HCl. The aqueous layer was extracted twice with CH_2Cl_2, and the organic layers were combined, washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated to give 10 g of dark brown liquid. This material was chromatographed on alumina (60 cm × 4 cm) using Et_2O as the eluent to give purified product which was then distilled to yield 0.74 g (75%) of very pure acetylnorbornene as a colorless liquid: bp 120 °C (2 mm); ^1H NMR δ 1.0–1.8 (m, 6H), 2.22 (s, 3H), 3.04 (m, 1H), 3.32 (m, 1H), 6.88 (d, J = 3 Hz, 1H); ^{13}C NMR δ 24.38, 25.83, 25.79, 40.58, 43.83, 47.73, 146.98, 150.39, 195.24; MS (rel int) 136(P,14), 108(46), 93(70), 65(38), 43(100); IR (NaCl) 1665 (C=O), 1585 (C=C) cm^{-1}.

Methyl 4-Hydroxy-2-pentynoate (7, R = H). 3-Butyn-2-ol (4.92 g, 70.0 mmol) and ethyl vinyl ether (5.59 g, 77.6 mmol) were dissolved in 150 mL of CH_2Cl_2, and 1.75 g of PPTS was added. The reaction mixture was stirred under N_2 and was monitored by GC. The reaction was complete after 1 h whereupon it was diluted with ether and washed with saturated aqueous NaCl. After drying and concentration below 30 °C, a light yellow liquid was obtained which was 89% pure. The desired product showed as two peaks on GC analysis (presumably, two pairs of diastereomers). Distillation gave 9.2 g (93%) of colorless liquid: bp

(14) Miyashita, N.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* 1977, *42*, 3772.

(15) Olah, G. A.; Hussain, A.; Singh, B. P.; Mehrotra, A. K. *J. Org. Chem.* **1983**, *48*, 3667.

(16) Initial attempts to combine this dienophile with substituted pyrroles gave a reaction, but the adducts are apparently unstable since they could not be satisfactorily characterized. This chemistry will be explored further.

(17) This melting point *may* correspond to the diexo keto acid which reportedly has a melting point of 122 °C: Mousseron, M.; Jacquier, R.; Soulier, J. *Comp. Rend.* **1958**, *247*, 665. These authors report that the compound having the acid group endo and an exo acetyl group melts at 101 °C. Russian workers give a melting point of 108–110 °C which apparently corresponds to the material with an exo acid group and an endo acetyl group: *Zh. Org. Khim.* **1979**, *15*, 50 (Engl. Trans. p 43). While the workup used in the present study included both base and acid, it is unlikely that extensive epimerization, especially of the carboxylate group, could have occurred under these conditions. Authentic material with both acetyl and carboxylate groups in the endo positions is apparently not known but may well melt in the same range as the bis exo material. This issue will be explored further.

120–125 °C; IR (NaCl) 3300, 2950, 2830, 2750, 1080 cm^{-1}; MS *m/e* (rel int) 141 (P-1, 1), 127 (25), 97 (32), 75 (47), 73 (78), 53 (85), 45 (100).

This protected hydroxy alkyne (4.90 g, 35.0 mmol) was dissolved in 200 mL of dry THF at −78 °C. Butyllithium (36 mmol of 1.6 M solution in hexane) was added via syringe. After 15 min of stirring, methyl chloroformate (2.78 mL, 36.0 mmol) was added via syringe. This reaction mixture was stirred for 15 min, allowed to warm to rt, diluted with 300 mL of ether, washed several times with water and then saturated aqueous NaCl, dried over $MgSO_4$, and concentrated to give 6.5 g of dark yellow liquid which was 79% pure (two peaks on GC). This was chromatographed on silica gel (60 × 2.5 cm) using ether/pentane (1:2) for elution. A 78% yield (5.4 g) of 95% pure (by GC) ester **7** (R = EE) was obtained.

A solution of 1.30 g (6.50 mmol) of this ester (**7**, R = EE) in 100 mL of absolute ethanol was stirred with 0.16 g (0.65 mmol) of PPTS, and the reaction mixture was refluxed for 36 h, cooled, diluted with 250 mL of ether, washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated to give a crude product which was filtered as a CH_2Cl_2 solution through a sintered glass funnel half full with silica gel to remove colored impurities. After concentration, 0.72 g (82%) of the desired alcohol was obtained: ^1H NMR ($CDCl_3$) δ 1.50 (d, *J* = 7 Hz, 3H), 3.30 (s, 1H), 3.78 (s, 3H), 4.64 (q, *J* = 7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 23.24, 52.82, 57.86, 75.38, 89.33, 154.87; IR (NaCl) 3400, 2980, 2220, 1710, 1240 cm^{-1}.

Methyl 4-Oxo-2-pentynoate. The alcohol from above (**7**, R = H, 4.5 g, 35.1 mmol) was dissolved in 100 mL of acetone and placed in a water bath. Ice-cold Jones reagent (the stock reagent was made from 67 g of CrO_3, 58 mL of concentrated H_2SO_4, and 160 mL of water) was added dropwise so that a clear orange color was evident (about a 50% excess was used). The reaction mixture was stirred for 1 h and filtered. The filtrate was diluted with 300 mL of CH_2Cl_2, washed several times with water, aqueous $NaHCO_3$, and then saturated aqueous NaCl, dried, and concentrated to give 3.9 g of product as a yellow liquid. This material was chromatographed on silica gel (60 × 2.5 cm) using CH_2Cl_2/hexane (3:1) for elution. Concentration of the material from the column gave 3.3 g (75%) of pure ketone: ^1H NMR ($CDCl_3$) δ 2.4 (s, 3 H), 3.8 (s, 3 H).

3-Acetylbicyclo[2.2.1]heptane-2-carboxylic Acid (5). Methyl 4-oxo-2-pentynoate (9.46 g, 75.1 mmol) was dissolved in 200 mL of dry CH_2Cl_2, 5.0 g (75.8 mmol) of freshly cracked cyclopentadiene was added, and the reaction mixture was stirred for 18 h. This was concentrated to give a dark yellow oil which was chromatographed on silica gel (60 × 4 cm) using 2:1 CH_2Cl_2/hexane as the eluent. Dicyclopentadiene came off with the solvent front, and then the desired product eluted which amounted to 14.2 g (100%) after concentration.

This keto ester (11.0 g, 37.7 mmol) was dissolved in 100 mL of methanol, and 0.1 g of 10% palladium on carbon was added. This was hydrogenated in a Parr hydrogenator for 18 h under an initial H_2 pressure of 30 psi. This dropped to 25 psi within 10 min (probably corresponding to the reduction of the more accessible carbon–carbon double bond) while the second equivalent of H_2 was absorbed very slowly. Removal of the catalyst by filtration and concentration of the filtrate gave 9.0 g (81%) of the desired product which was three peaks by GC (one was 83% of the mixture of presumed diastereomers): MS (major peak) *m/e* (rel int) 196 (P, 3), 181 (1), 164 (16), 87 (62), 43 (100).

This reduced compound (1.00 g, 3.38 mmol) was dissolved in 40 mL of dry acetonitrile and stirred with 1.95 g (13.0 mmol) of sodium iodide. Trimethylchlorosilane (1.40 mL, 11.0 mmol) was added via syringe, and the reaction mixture was refluxed for 14 h. This was cooled, poured onto ice, and extracted several times with ether. The combined organic extracts were washed with aqueous Na_2SO_3 and then extracted with dilute NaOH. The basic extracts were then acidified with HCl, and this was extracted several times with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated to give the keto acid **5** (0.63 g, 68%) which was identical by MS to the material obtained from the maleic anhydride route.

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Supplementary Material Available: ^1H and/or ^{13}C NMR spectra for all compounds (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.