Cycloaddition of 6-hydroxy-2,6-dimethylcyclohexa-2,4-dienone: A stereoselective entry into functionalized bicyclo[2.2.2]octanes and a novel 1,2-migration of methyl group

Vishwakarma Singh*, Girish Chandra & Shaikh M Mobin

*Department of Chemistry, a National Single X-ray Diffraction Facility, Indian Institute of Technology Bombay, Mumbai 400 076, India
E-mail: vks@chem.iitb.ac.in

Received 30 July 2008; accepted (revised) 30 September 2008

Cycloaddition of 6-hydroxy-2,6-dimethylcyclohexa-2,4-dienones with ethyl vinyl ether, butyl vinyl ether, vinyl acetate and vinyl phenyl sulphone leading to a stereoselective entry into bicyclo[2.2.2]octanes having quaternary methyl group is reported. A novel thermal 1,2-methyl migration has also been described.

Keywords: Cycloaddition, cyclohexa-2,4-dienone, Diels-Alder reaction, bicyclo[2.2.2]octane, 1,2-migration

There has been an upsurge of interest in the synthesis and chemistry of functionalized bicyclo[2.2.2]-octanes. This is presumably due to their versatile role as a building block in organic synthesis since these systems undergo various types of regio- and stereoselective transformations by virtue of the rigid framework and the interactions among functional groups. Moreover, the discovery of bridged bicyclo[2.2.2]octane framework in several recently isolated natural products such as rezishanone B, C (1,2) that exhibit interesting biological activity has further contributed to the interest in such systems (Figure 1) (Ref. 4).

In continuation with the interest in the chemistry of cyclohexa-2,4-dienes, developing a stereoselective route to bridged bicyclic compounds was considered. These were of the type 3 having a carbocyclic framework with some functionality and substituents present in compounds 1 and 2. It was contemplated that the cycloaddition of 2,6-dimethyl-6-hydroxy-cyclohexa-2,4-dienone 4 with dienophiles such as vinyl ethers and vinyl acetate would provide a stereoselective route to functionalized bicyclo[2.2.2]-octanes of type 3 endowed with a quaternary centre having a hydroxyl and a methyl group, a methyl group at the bridge head, and an alkoxy function at a much desired position with correct stereochemical orientation by virtue of regio- and stereocontrols. The presence of the double bond in the ethano bridge was advantageous since it would provide opportunity for further manipulation (Scheme I).

In view of the above, the cycloaddition of in situ generated cyclohexadienone 4 with various dienophiles such as vinyl ethers, vinyl acetate and...
Results and Discussion

The, dimer 5, readily prepared from 2,6-dimethylphenol6, and ethyl vinyl ether were heated in o-dichlorobenzene at ~130°C for 20 hr. Chromatography of the product gave a mixture of two compounds (1H and 13C NMR spectra) that were inseparable by column chromatography on silica gel. Fractional crystallization of the mixture however, provided a pure crystalline compound to which the structure 6 was assigned. Further, chromatography of the mother liquor gave the expected adduct 7 as a thick liquid (Scheme II).

The structure of the adduct 6 was deduced from the following spectral features and their comparison with those of other adducts. Thus, the 1H NMR (300 MHz) spectrum of 6 exhibited signals at δ 6.23 (d, J = 7 Hz, 1H) and 6.04 (dd, J = −7 Hz, 1H) indicating the presence of two olefinic protons. It further exhibited signals at δ 3.94-3.89 (dt, J1 = 8.4 Hz, J2 = 2.9 Hz, 2H), 2.58-2.48 (dd, J1 = 13.5 Hz, J2 = 8.4 Hz, 1H), 1.20 (br s, 1H) and 1.16-1.11 (m, 1H). In addition, signals were observed at δ 1.25 (s, 3H), 1.19 (s, merged with a triplet, 3H) and 1.17 (t, J = 7.3 Hz, 3H) for the methyl groups. It may be mentioned that in bicyclo[2.2.2]octenones having a β,γ-ene moiety, the γ-proton generally appears downfield as compared to the β-proton (because of homoconjugation) as a superimposed dd as a result of coupling with the adjacent bridgehead proton and the other olefinic proton. So, the presence of a downfield olefinic signal at δ 6.23 as a doublet was surprising. Similarly, the presence of upfield signal due to β-proton as a superimposed dd also appeared to be highly unusual. Such a pattern would not be expected in the normal cycloadduct. The NMR patterns strongly suggested that some rearrangement had occurred during the cycloaddition.

The doublet for the γ-olefinic proton indicated that there must be a substituent at the bridgehead carbon adjacent to the γ-olefinic carbon. Similarly, the superimposed dd for the β-olefinic proton indicated that there is a proton on the bridgehead carbon adjacent to it. The above observation was supported by COSY experiment. Thus, the signal at δ 6.04 (assigned to the proton at the β-carbon of the β,γ-ene moiety) showed correlation with the signal at δ 6.23 (assigned to the proton at the γ-carbon of the β,γ-ene moiety) as well as one bridgehead hydrogen (δ 3.62-3.57) (Figure 2). The signal at δ 6.23 coupled strongly with the resonance at δ 6.04 and weakly coupled with bridgehead hydrogen (δ 3.62-3.57, W-coupling).

The signals at δ 1.16-1.09 and 2.58-2.48 mutually coupled with each other as well as with the proton attached to the carbon bearing OEt group. The signal at δ 3.94-3.89 (due to HCOEt) correlated with the signal at δ 6.04 (due to HCOEt) correlated with the signal at δ 3.62-3.57 (due to the bridgehead proton). These and other spectral features suggested structure 6. In order to thoroughly establish its structure, a single crystal X-ray (Figure 3) diffraction pattern was obtained which confirmed the formulation 6.

The pyrolysis of the dimer 5 with vinyl acetate also gave three adducts 8, 9 and 10 (Scheme III). The compound 10 was formed as a result of structural reorganization during the cycloaddition. Also, pyrolysis of dimer 5 in the presence of n-butyl vinyl ether provided an inseparable mixture of normal adduct 11 and the rearranged adduct 12 in a 2:1 ratio as suggested by 1H NMR spectrum.
The above cycloaddition was also explored with vinylphenyl sulphone. Thus, the dimer 5 was heated in the presence of vinylphenyl sulphone which gave a single adduct 13. In this case, however, the cycloadduct formed from the rearranged cyclohexa-2,4-dienone was not observed (Scheme IV).

The formation of adducts 6, 10 and 12 in the aforementioned cycloaddition appeared to be highly unusual and suggested that a rearrangement had occurred. A plausible mechanism for their formation is presented in the Scheme V. It appears that retro Diels-Alder reaction of the dimer 5 initially gives the cyclohexadienone 4 which upon interception with dienophiles leads to the formation of the expected adducts 7, 8, 9, 11 and 13. Perhaps, the cyclohexadienone 4 undergoes a rearrangement leading to the cyclohexadienone 14 via proton transfer and methyl migration which is then intercepted by dienophiles to give the unusual adducts such as 6, 10 and 12 (Scheme V).

**Scheme III**

**Scheme IV**

**Scheme V**
Such rearrangements are known to occur in α-hydroxyketones. However, it is rarely observed in cyclohexa-2,4-dienes. In general, such a migration in α-hydroxyketones is usually catalyzed by acids and or bases. Initially, it was thought that the presence of acidic impurities in solvent or basic impurities in dienophiles, the formation of cycloaddition was carried out in the presence of acid/base free solvent/dienophiles, the formation of the unusual adduct was once again observed. So, it appears that the rearrangement occurs via intramolecular proton transfer under thermal conditions (Scheme V).

Experimental Section

IR spectra were recorded on Perkin-Elmer 681 and Nicolet Impact 400 FT-IR instruments. 1H and 13C NMR were recorded on Varian VXR 300 and Mercury Varian 400 NMR instruments. The samples were dissolved in CDCl₃ as solvent and tetramethyl silane as internal standard. The standard abbreviations s, d, t, m, dd and td refer to singlet, doublet, triplet, multiplet, doublet of doublet and triplet of doublet, respectively. Coupling constants are reported in Hertz. The high-resolution mass spectra were recorded on a Q-Tof micro instrument (YA-105). Melting point were determined on a Veego apparatus of Buchi type and are uncorrected. All the organic extracts were dried over anhydrous Na₂SO₄. Reactions were monitored by thin layer chromatography and the spots were visualized with iodine vapour. Column chromatography was performed using SRL silica gel (60-120 or 100-200 mesh). The column was eluted with petroleum ether (60-80°C) and ethyl acetate. The fractions eluted out were concentrated under reduced pressure. The solvents used for all reactions were purified and dried by using standard procedures.

3,4-Dimethyl-7-endo-ethoxy-3-exo-hydroxy-bicyclo[2.2.2]oct-5-en-2-one, 6 and 1,3-dimethyl-7-endo-ethoxy-3-exo-hydroxy-bicyclo[2.2.2]oct-5-en-2-one, 7

Dimer 5 (0.5 g, 1.812 mmol) in o-dichlorobenzene (5 mL) was taken in a RB flask fitted with a reflux condenser. Inert atmosphere was created by evacuative displacement of air by nitrogen and freshly distilled ethyl vinyl ether (5 mL) was added. The reaction-mixture was heated at 130°C for 20 hr with stirring under cold water circulation around reflux condenser. The reaction mixture was brought to RT and charged as such on silica gel (60-120 mesh, 65 g, column size 35 × 2.5 cm). Elution with petroleum ether first gave the solvent o-dichlorobenzene. Continued elution with petroleum ether-ethyl acetate (95:5) gave the mixture of adducts. Fractional crystallization gave 6 (0.265 g, 33%). Chromatography of the mother liquor provided the desired compound 7 as a thick liquid (0.080 g, 11%).

Data for compound 6: 3,4-Dimethyl-7-endo-ethoxy-3-exo-hydroxy-bicyclo[2.2.2]oct-5-en-2-one

M.p. 105-06°C. IR (KBr): 3471, 1727 cm⁻¹; 1H NMR (300 MHz, CDCl₃): δ 6.23 (d, J = 7 Hz, 1H), 6.04 (superimposed dd, J = 7Hz, 1H), 3.94-3.89 (dt, J₁ = 8.4 Hz, J₂ = 2.9 Hz, 1H), 3.62-3.34 (set of complex multiplets, 3H), 2.58-2.48 (dd, J₁ =13.5 Hz, J₂ = 8.4 Hz, 1H), 2.20 (br s, 1H), 1.25 (s, 3H), 1.19 (s merged with a triplet, 3H), 1.17 (t, J = 7.3 Hz, 3H), 1.16-1.11 (m, 1H); 13C NMR (75 MHz, CDCl₃): δ 213.37, 141.74, 124.28, 76.26, 73.51, 53.03, 43.47, 37.54, 22.93, 17.73, 15.40; HRMS (ESI): m/z Found 233.1164 (M⁺+ Na). Calcd for C₁₂H₁₄O₃Na: 233.1154 (M⁺+ Na).

Crystal data of 6: C₁₂H₁₄O₃, Mol. wt. 210.11, space group, monoclinic, P21/c, a = 6.2115(3), b = 15.598 (2), c = 12.0910(8)Å, α = 90.08, β = 98.833(5), γ = 90.0°, U =1157.57(18)Å³, Z =4, Dc = 1.333 mg/m³, T =293(2)K, F(000) = 496, size = 0.30×0.3×0.25 mm, Reflections/collected/unique 2129/2029 [R(int) = 0.0159], final R indices (T>2sigma(I)) = R₁ = 0.0397, wR₂ =0.0932, R indices (all data) R₁ = 0.08535, wR₂=0.1078.

Data for compound 7: 1,3-Dimethyl-7-endo-ethoxy-3-exo-hydroxy-bicyclo[2.2.2]oct-5-en-2-one

IR (neat): 3500, 1730 cm⁻¹; 1H NMR (400 MHz, CDCl₃): δ 6.50 (superimposed dd, J = 7.3 Hz, 1H), 5.7 (d, J = 8.0 Hz, 1H), 3.64-3.48 (m, 3H), 3.44-3.34 (m, 1H), 2.92 (br s, 1H), 2.84-2.80 (m, 1H), 2.76-2.66 (m, 1H), 1.32 (s, 3H), 1.28 (s, 3H), 1.15 (t, J = 6.9 Hz, 3H); HRMS (ESI): m/z Found 233.1157 (M⁺+Na). Calcd for C₁₂H₁₄O₃Na: 233.1154 (M⁺+ Na).

7-endo-Acetoxy-1,3-dimethyl-3-exo-hydroxy-bicyclo[2.2.2]oct-5-en-2-one, 8, 7-exo-acetoxy-1,3-dimethyl-3-exo-hydroxy-bicyclo[2.2.2]oct-5-en-2-one, 9

A mixture of the dimer 5 (1.0 g, 3.623 mmol) and vinyl acetate (6 mL) in o-dichlorobenzene (3 mL) was heated in a sealed tube at 140°C for 14 hr. The reaction mixture was then brought to ambient
temperature and charged as such on silica gel (100-200 mesh, 80 g, column size 35 × 4 cm). Elution with petroleum ether gave the solvent o-dichlorobenzene. Continued elution with petroleum ether-ethyl acetate (92:8) gave the adduct 10 (0.068 g, 5%) as a colorless solid. Further elution with petroleum ether-ethyl acetate (9:1) gave the compound 8 as a colorless solid (0.452 g, 33%) and compound 9 also as a colorless solid (0.376 g, 27%).

Data for compound 8: Acetoxy-1,3-dimethyl-3-exo-hydroxy-bicyclo[2.2.2]oct-5-en-2-one

m.p. 88-89°C. IR (KBr): 3439, 1731 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 6.55 (superimposed dd, J = 8, Hz, 1H), 5.82-5.74 (m, 1H), 5.02-4.94 (m, 1H), 2.96-2.82 (m, 2H), 2.20 (bs, 1H), 2.03 (s, 3H), 1.3 (s, 3H), 1.25 (s, 3H), 1.35-1.20 (m, 1H); 13C NMR (75 MHz, CDCl₃); δ 211.45, 170.52, 136.30, 130.57, 73.33, 71.34, 53.53, 41.83, 31.16, 28.12, 21.07, 13.91; HRMS (ESI): m/z found 247.0945 (M⁺ + Na). Calcd for C₁₃H₁₆O₄Na: 247.0946 (M⁺ + Na).

Data for compound 9: 8-endo-Acetoxy-1,3-dimethyl-3-exo-hydroxy-bicyclo[2.2.2]oct-5-en-2-one

m.p. 85-86°C. IR (KBr): 3572, 1732 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 6.53 (superimposed dd, J = 6.6 Hz, 1H), 5.7 (dd, J₁ = 8.4Hz, J₂ = 1.8 Hz, 1H), 4.8 (dd, J₁ = 8.7 Hz, J₂ = 4.3 Hz, 1H), 2.94-2.84 (m, 1H), 2.5 (bs, 1H), 2.17-2.06 (m, 2H), 2.03 (s, 3H), 1.33 (s, 3H), 1.22 (s, 3H); 13C NMR (75 MHz, CDCl₃); δ 211.40, 170.79, 138.68, 130.99, 76.01, 72.29, 52.58, 42.97, 29.30, 26.50, 21.10, 14.29; HRMS (ESI): m/z found 247.0937 (M⁺ + Na). Calcd for C₁₃H₁₆O₄Na: 247.0946 (M⁺ + Na).

Data for compound 10: 8-endo-Acetoxy-1,3-dimethyl-3-exo-hydroxy-bicyclo[2.2.2]oct-5-en-2-one

m.p. 105-106°C. IR (KBr): 3572, 1732 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 6.25 (d, J = 7.6 Hz, 1H), 6.06 (m, 1H), 5.22-5.16 (m, 1H), 3.53-3.48 (m, 1H), 2.68 (dd, J₁ = 14.2 Hz, J₂ = 8.7 Hz, 1H), 2.03 (s, 1H), 2.01 (s, 3H), 1.27 (s, 3H), 1.22 (s, 3H), 1.13 (dd, J₁ = 13.8 Hz, J₂ = 3.2 Hz, 1H); 13C NMR (75 MHz, CDCl₃); δ 210.68, 170.32, 142.37, 124.30, 72.96, 70.51, 52.68, 43.49, 37.08, 22.95, 21.20, 17.68; HRMS (ESI): m/z found 247.0949 (M⁺ + Na). Calcd for C₁₃H₁₆O₄Na: 247.0946 (M⁺ + Na).

7-n-Butoxy-1,3-dimethyl-3-exo-hydroxy-bicyclo-[2.2.2]oct-5-en-2-one (11, 12)

Dimer 5 (0.5 g, 1.812 mmol) and o-dichlorobenzene (6 mL) was taken in RB flask. Inert atmosphere was created by evacuative displacement of air by nitrogen and n-butyl vinyl ether (4 mL, excess) was added. The reaction-mixture was heated at 120°C for 8 hr with stirring. The reaction-mixture was brought to RT and charged as such on silica gel (60-120 mesh, 60 g, column size 35 × 2.5 cm). Elution with petroleum ether first gave the solvent o-dichlorobenzene. Continued elution with petroleum ether-ethyl acetate (95:5) gave a inseparable mixture of adducts 11 and 12 (0.472 g, 55%) as a thick colorless liquid.

IR (neat): 3468, 1727 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, mixture of two isomers): δ 6.52 (m, 6.24-6.20 (m, 1H), 6.06-6.0 (m, 5.90-5.74 (m, 1H), 3.92-3.86 (m, 3.60-3.54 (m, 1H), 3.52-3.42 (m, 2H), 3.36-3.58 (m, 2H), 2.88-2.82 (m, 1H), 2.66 (dd, J₁ = 10.99, J₂ = 8.24 , J₃ = 2.75 Hz, 1H), 2.51 (dd, J₁ = 13.74, J₂ = 8.24, 1H), 2.20-2.0 (bs, 1H), 1.54-1.46 (m, 1.38-1.28 (m, 2H), 1.32 (s, 1.24 (s, 3H), 1.27 (s), 1.19 (s, 3H), 0.89 (t, J = 7.33 Hz, 3H); 13C NMR (100 MHz, CDCl₃, mixture of two isomers): δ 213.28, 141.67, 135.42, 130.83, 124.17, 78.86, 76.10, 73.25, 71.44, 69.56, 68.49, 55.29, 53.00, 43.44, 42.02, 37.43, 31.83, 31.76, 30.43, 25.97, 22.68, 19.28, 17.67, 14.01, 13.82; HRMS (ESI): m/z found 261.1456 (M⁺ + Na). Calcd for C₁₃H₂₂O₃Na: 261.1467 (M⁺ + Na).

7-Benzencesulfonyl-1,3-dimethyl-3-exo-hydroxy-bicyclo[2.2.2]octan-5-en-2-one, 13

A mixture of dimer 5 (0.23 g, 0.616 mmol) and phenyl vinyl sulphone (0.142 g) in o-dichlorobenzene (3 mL) was heated in a sealed tube at 140°C for 22 hr. The reaction-mixture was brought to ambient temperature and charged as such on silica gel (60-120 mesh, 50 g, column size 30 × 2.5 cm). Elution with petroleum ether first gave the solvent o-dichlorobenzene. Continued elution with petroleum ether-ethyl acetate (78:22) gave the adduct 13 (0.240 g, 56%) as a colorless solid.

m.p. 139-40°C. IR (KBr): 3463 and 1735 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.87-7.82 (m, 2H), 7.68-7.61 (m, 1H), 7.59-7.52 (m, 2H), 6.46 (dd, J₁ = 8.06, J₂ = 6.96 Hz, 1H), 5.89 (d, J = 6.96 Hz, 1H), 3.51 (dd, J₁ = 9.89, J₂ = 7.33 Hz, 1H), 2.90-2.84 (m, 1H), 2.50 (s, 1H), 2.27 (superimposed ddd, J₁ = 9.53, J₂ = 2.93 Hz, 1H), 1.67 (ddd, J₁ = 9.53, J₂ = 6.96, J₃ = 2.56 Hz, 1H), 1.58 (s, 3H), 1.27 (s, 3H); 13C NMR (75 MHz, CDCl₃); δ 209.25, 139.80, 135.43, 133.73, 130.93, 129.27 (for two carbons), 128.41 (for two carbons), 71.35, 62.61, 50.37, 41.95, 26.97, 25.91, 16.19; HRMS (ESI): m/z found 329.0811(M⁺ + Na). Calcd for C₁₆H₁₈O₄Na: 329.0824 (M⁺ + Na).
Conclusion
A stereoselective entry into highly functionalized bicyclo[2.2.2]octanes 6-13 having quaternary centres and a novel 1,2-methyl migration has been described. It may be mentioned that such types of bicyclo[2.2.2]octanes are not readily accessible otherwise. The results reported herein would pave the way for further studies in the synthesis of natural products containing the bicyclo[2.2.2]octane framework.

Acknowledgement
The authors thank CSIR New Delhi for continuing financial support. One of the authors (GC) thanks CSIR New Delhi for a fellowship. The authors also thank SAIF, IIT Bombay for spectral facilities.

References