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Cycloaddition of cyclohexa-2,4-dienones with electron deficient 2π partners: a novel and stereoselective route to functionalised bicyclo[2.2.2]octenones

Vishwakarma Singh,*[a] Shantanu Pal[a] and Shaikh M. Mobin[b]

[a] *Department of Chemistry, Indian Institute of Technology, Bombay, Mumbai 400 076, India. E-mail: vks@ether.chem.iitb.ac.in*

[b] *National Single Crystal X-ray Diffraction Facility, Indian Institute of Technology, Bombay, Mumbai 400 076, India*

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A novel route to functionalised bicyclo[2.2.2]octenones *via* π^{4s} + π^{2s} cycloaddition of cyclohexa-2,4-dienones with electron deficient 2π partners, and crystal structure of 1,7-dimethyl-5-hydroxy-5-chloromethyl-2-carboethoxy bicyclo[2.2.2]oct-7-ene-6-one, is reported.

Functionalised bicyclo[2.2.2]octenones of type **1** and congeners have proved to be versatile precursors in organic synthesis since these systems undergo a variety of reactions in both ground and excited states.[1–3] In general, such bicyclic systems are prepared in several steps *via* Diels–Alder reaction of a cyclic 1,3-diene and a ketene equivalent followed by manipulation of the resulting adduct.[4] Recently, some other methods involving double Michael addition,[5a,c] Michael addition followed by reductive amination[5b] and homoallyl–homoallyl radical rearrangement,[6] have also been developed. However, these methods have several limitations with regard to introduction of functional groups and substituents on the bicyclo[2.2.2]octane frame and often give a mixture of regioisomers. In view of the above, and our interest in the chemistry of cyclohexa-2,4-dienones,[7] we examined cycloaddition between cyclohexa-2,4-dienones of type **3** and **4** (Fig. 1) with electron deficient dienophiles in order to develop a versatile and general route to highly functionalised and substituted bicyclo[2.2.2]octenones of type **2**, and wish to report our exploratory results herein.

Thus, the chlorohydroxy dimer **5a**, readily prepared from 3,5-dimethylsalicyl alcohol following an analogous procedure,[8] was heated with ethyl acrylate in a sealed tube at ~ 140 °C for 8 h. Chromatography of the product mixture furnished a crystalline adduct in excellent yield (96%). The spectral features of adduct clearly suggested its gross structure. However, it was difficult to distinguish between the two regioisomers **6a** and **7a**, on the basis of spectral data alone. Hence, a single crystal X-ray structure of adduct was determined which clearly established the structure of adduct as **6a** (Fig. 2). Similar pyrolysis of the dimers **5b**,**c** in the presence of ethyl acrylate gave the adducts **6b**,**c** (Scheme 1) whose structures were deduced on the basis of their spectral data, COSY analysis and comparison with the spectral features of **6a**.†

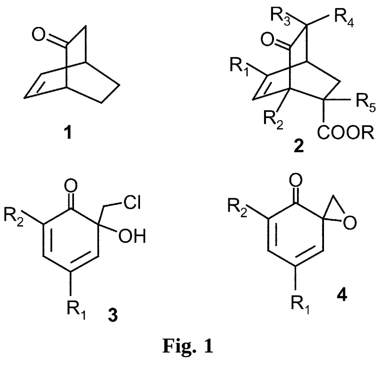


Fig. 1

In order to test the generality and scope of this cycloaddition, reaction of the dimers **5a**–**c** with methyl methacrylate was also examined. Thus, pyrolysis of **5a**–**c** with methyl methacrylate furnished *endo* adducts **8a**–**c** in major amounts along with the minor amounts of *exo* isomers **9a**–**c** respectively, in excellent yields (Scheme 2). However, pyrolysis of **5a** in the presence of acrolein and acrylonitrile did not give any adduct. The structures of all adducts were clearly revealed from their spectral data and comparison with the spectral features of the adduct **6a**–**c**.

The efficiency and ease of aforementioned cycloadditions is remarkable especially since electron deficient systems such as cyclohexa-2,4-dienones and *o*-benzoquinone ketals generally react with electron rich π partners in inverse demand fashion.[7,9,10] Further, the regioselectivity observed in the above

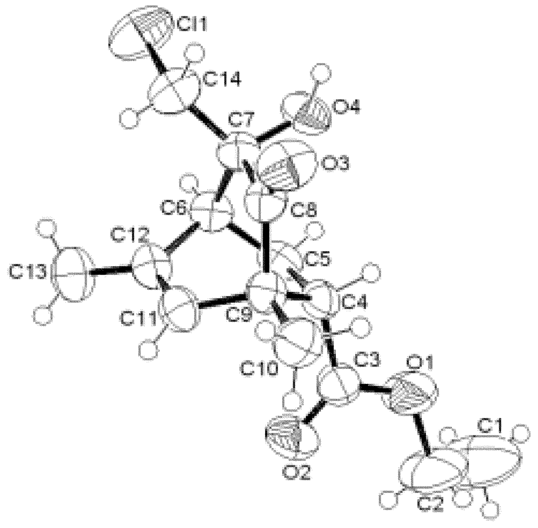
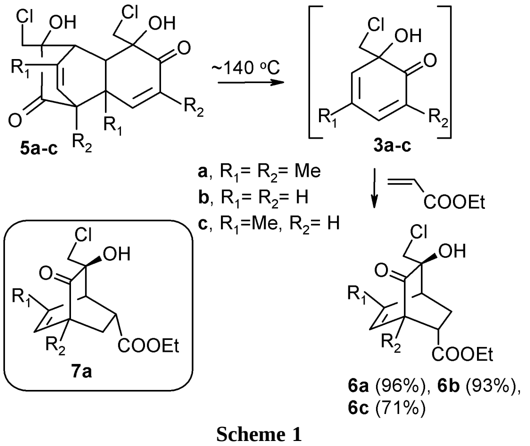


Fig. 2 ORTEP diagram of compound **6a**.



Scheme 1

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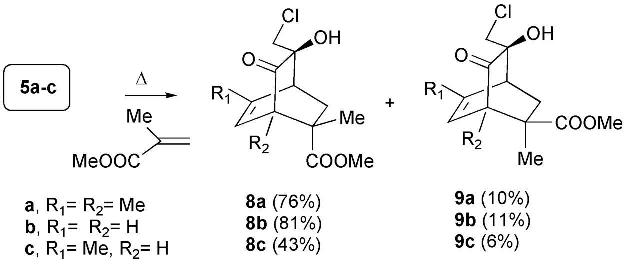
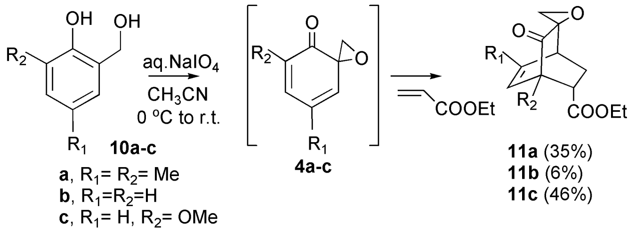


Scheme 2

cycloaddition seems to be unusual since the carbon bearing polar electron withdrawing group in the dienophile is bonded to C_2 of cyclohexa-2,4-dienones. It may be mentioned that similar regioselectivity is also observed during cycloaddition of cyclohexa-2,4-dienones even with electron rich dienophiles such as vinyl ethers wherein the carbon having polar electron donating group forms bond with C_2 carbon of cyclohexa-2,4-dienone.[9-11]

At this juncture, it was intriguing to examine whether the spiroepoxycyclohexa-2,4-dienones of type **4** can be intercepted with ethyl acrylate to give the corresponding adducts especially since spiroepoxycyclohexadienones have a fleeting existence and readily dimerise. Thus, a solution of 3,5-dimethylsalicyl alcohol **10a** in aqueous acetonitrile containing ethyl acrylate was oxidized with $NaIO_4$. It was indeed surprising to obtain the adduct **11a** in reasonably good yield (35%), in a regio- and stereoselective fashion. While, similar treatment of salicyl alcohol in the presence of ethyl acrylate gave the adduct **11b** in poor yield (6%), oxidation of *o*-vanilyl alcohol **10c** having an electron donating group, gave the adduct **11c** in good yield (46%) (Scheme 3). The structures of **11a–c** were deduced from their spectral data and comparison with spectral features of other adducts.



Scheme 3

In summary, we have described a novel, versatile and stereoselective route to functionalised bicyclo[2.2.2]octenones which are not easily available otherwise. The method is flexible, readily adaptable and permits introduction of various substituents on the bicyclo[2.2.2]octane framework.

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Notes and references

† All the compounds gave satisfactory spectral and analytical data. Selected data for **6a**: ν_{max}/cm^{-1}: 1719, 3387. δ_H (400 MHz, $CDCl_3$): 5.45(brs, 1H), 4.10 (m, 2H, OCH_2-CH_3), 3.70(part of AB system, J_{AB}12, 1H, -OCH_2-Cl), 3.45(part of an AB system, J_{AB}12, 1H, -OCH_2-Cl), 3.07 (br m, 1H), 2.77–2.73 (m, 2H), 2.50 (m, 1H), 1.98 (d, J 1.5, 3H, CH_3), 1.69(ddd, J_1 13, J_2 6, J_3 2.8, 1H), 1.25 (t partly overlapped with s, J 7.12, 3H, CH_3), 1.23 (s, 3H, CH_3). δ_C (100 MHz, $CDCl_3$): 207.89, 173.19, 144.91, 123.55, 73.19, 60.73, 50.33, 49.91, 45.19, 44.20, 26.23, 20.78, 15.32,14.17 (14 Carbons). Analysis: Found C, 59.07; H, 6.76% Calc. C, 58.63; H, 6.6% for $C_{14}H_{19}O_4Cl$.

Crystal data: $C_{14}H_{19}Cl_1O_4$, M = 286.74, orthorhombic, *Pbca*, $Z = 8$, $\lambda = 0.70930$ Å, $a = 10.3270(12)$, $b = 14.2240(14)$, $c = 20.1930(15)$ Å, $U = 2966.2(5)$ Å^3, $T = 293(2)$ K, $Dc = 1.284$ Mg m^{-3}, $\mu = 0.265$ mm^{-1}, $F(000) = 1216$, size = 0.40 × 0.40 × 0.35 mm , Reflections collected/unique = 2046/2046 [R(int) = 0.0000] , Final R indices [$I > 2\text{sigma}(I)$] : $R_1 = 0.0474$, $wR_2 = 0.1195$, R indices (all data) : $R_1 = 0.0619$, $wR_2 = 0.1219$. CCDC 188197. See http://www.rsc.org/suppdata/cc/b2/b205475m/ for crystallographic files in .cif or other electronic format.

Selected data for **8b**: ν_{max}/cm^{-1} 1719, 3445. δ_H (300 MHz, $CDCl_3$): 6.44 (superimposed dd with structure, J 7.2, 1H), 6.21 (superimposed dd with structure, J 7.2, 1H), 3.65 (s, 3H, OCH_3), 3.61(part of an AB system, J_{AB} 12, 1H, -CH_2Cl), 3.50 (part of an AB system, J_{AB} 12 Hz, 1H, -CH_2Cl), 3.41 (dd, J_1 6, J_2 1.2, 1H), 3.13 (m, 1H), 2.74 (s, 1H), 2.28 (d of AB system, J_{AB} 12.8, $J_2$3.3, 1H), 2.06 (d of an AB system, J_{AB} 12.8, J_2 2.4, 1H), 1.26 (s, 3H, CH_3). δ_C (75 MHz): 208.39, 176.21, 135.82, 129.20, 73.63, 55.83, 52.49, 51.08, 47.81, 39.50, 30.34, 25.32 (12 Carbons). Analysis: Found C, 55.89; H, 5.67% Calc. C, 55.70; H, 5.80% for $C_{12}H_{15}O_4Cl$.

Selected data for **11c**: mp. 67–69 °C. ν_{max}/cm^{-1}: 1741. δ_H (300 MHz, $CDCl_3$): 6.52(superimposed dd, J 7.8, 1H), 6.27(d, J 7.8, 1H), 4.14(m, 2H, OC$H_2$$CH_3$), 3.58(s, 3H, OC$H_3$), 3.24 (dd, J_1 9.9, J_2 5.7, 1H), 3.15(part of an AB system, J_{AB} 6.3, 1H, OCH_2), 2.81(part of an AB system, J_{AB} 6.3, 1H, -OCH_2-), 2.56 (m, 1H), 2.44 (superimposed dd, J 12.5, 1H), 1.90(d, J 12.5, 1H), 1.27 (t, J 7, 3H, CH_3). δ_C (75 MHz, $CDCl_3$): 201.23, 171.80, 132.01, 129.64, 85.80, 60.83, 57.11, 53.97, 52.87, 42.70, 37.83, 28.82, 14.31. Mass (*m*/*z*): 152 ($M^+ - 100$, it undergoes retro Diels–Alder reaction).

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