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[6+3] Cycloaddition of fulvenes with 3-oxidopyrylium betaine: a novel methodology for the synthesis of fused cyclooctanoid natural products

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Dedicated with respect to Dr. Vijay Nair, our mentor, for his inspiration, constant encouragement and scholarly criticism

Abstract—Fulvenes undergo an easy [6+3] cycloaddition with 3-oxidopyrylium betaines leading to 5–8 fused oxabridged cyclooctanoids.

The synthesis of cyclooctanoids is of great importance in organic chemistry due to their wide occurrence in many biologically active natural products and synthetic compounds.[1] The interesting biological activities combined with the synthetic challenges have served to make them target molecules in a number of synthetic studies.[2] Some of the interesting cyclooctanoids are shown in Figure 1. Designing efficient, short routes for the stereoselective construction of cyclooctanoids is an interesting challenge in synthetic organic chemistry. Among the various strategies for the synthesis of eight-membered rings,[3] higher-order cycloadditions that directly form eight-membered rings[4] are attractive because of their ability to produce complex molecules with extensive functionality in a single step, with good control over the creation of new stereocentres (Scheme 1).

As part of our programme on the synthesis of cyclooctanoids, we undertook an investigation of the higher-order dipolar cycloaddition of 3-oxidopyrylium betaines with pentafulvenes. 3-Oxidopyrylium betaines[5] have been well utilized in the synthesis of cycloheptanoids.[5,6] Pentafulvenes, on the other hand can act as a 2π, 4π or 6π components in cycloaddition reactions[2,7–11] and have served as excellent synthons for the synthesis of triquinanes, pyrindines, etc. Investigations from our own laboratory have unraveled interesting reactivity profile of fulvenes in cycloaddition reactions.[8] Though fulvenes have been known to act as 6π partners in cycloadditions,[9] to the best of our knowledge, there is no report on the [6+3] cycloaddition of 3-oxidopyrylium betaines with pentafulvenes. Barluenga et al. have reported a [6+3] cycloaddition of Fischer carbene complexes[7l] with fulvenes. Recent reports from Hong et al. have shown that fulvenes can undergo [6+3] cycloaddition with azomethine ylides leading to the formation of [2]pyrindines,[10] and other molecules of biological importance.

Our studies were initiated with the reaction of 3-oxidopyrylium betaine, generated from the corresponding pyranulose acetate,[11] with 6,6-diphenylfulvene.[12] The reaction proceeded smoothly affording the [6+3] adduct in 70% yield (Scheme 1).

The product was characterized on the basis of spectroscopic data. The IR spectrum showed characteristic absorptions at 1691 cm^{-1}, indicating the presence of an α,β-unsaturated carbonyl, and at 1077 cm^{-1}

Keywords: Fulvenes; Oxidopyrylium betaines; [6+3] Cycloaddition; Cyclooctanoids.

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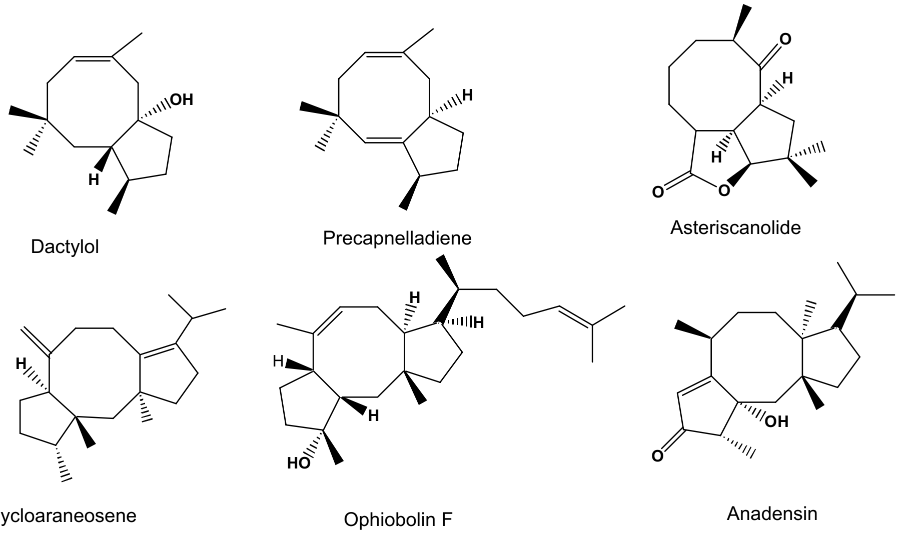
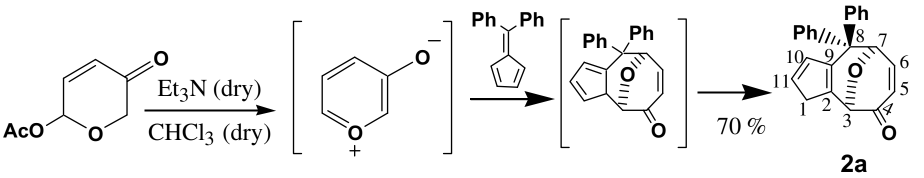


Figure 1. Examples of biologically active cyclooctanoids.



Scheme 1. [6+3] Cycloaddition of diphenylfulvene with oxidopyrylium betaine.

indicative of the ether linkage. In the ^{1}H NMR spectrum, the two protons at C-1 appeared as a singlet at δ 3.06 ppm. Two bridgehead protons resonated as a singlet and doublet at δ 4.88 and δ 5.36 ppm, respectively. The protons at C-5 and C-6 appeared as a doublet and double doublet at δ 5.76 and δ 5.99 ppm, respectively. ^{13}C NMR spectroscopy showed a characteristic signal for a carbonyl group at δ 194.5 ppm. The bridgehead carbons appeared at δ 74.9 and δ 52.7 ppm, respectively. Unambiguous evidence for the structure and stereochemistry of the product was obtained by single crystal X-ray analysis[13] (Fig. 2). The product is formed by a [6+3] cycloaddition followed by a 1,5-hydrogen shift leading to the product **2a**.

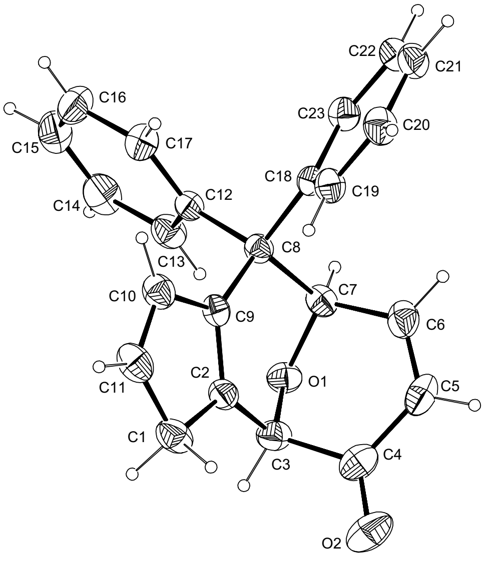


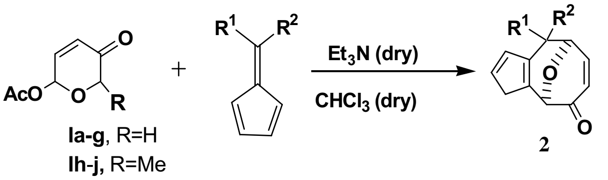
Figure 2. ORTEP plot of the X-ray crystal structure of **2a**.

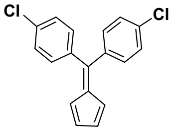
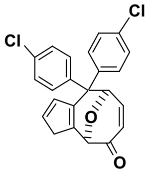
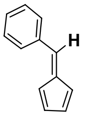
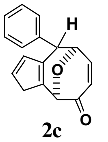
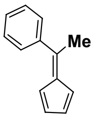
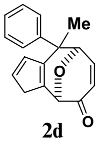
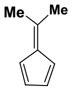
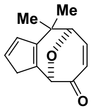
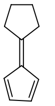
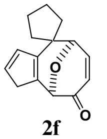
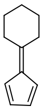
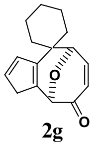
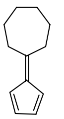
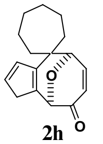
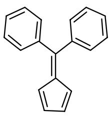
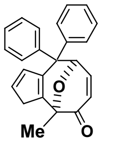
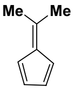
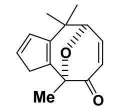
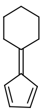
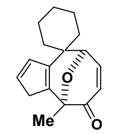
Similar reactivity was observed with other fulvenes leading to 5–8 fused cyclooctanoid products in good to excellent yields.[14] 3-Methyl-3-oxidopyrylium betaine also reacted in this way and the results are summarized in Table 1.

Eight-membered rings are the main structural features of a number of natural products such as dactylol, asteriscanolide, cycloaraneosene, ophiobolin F, etc. (Fig. 1). The presence of an α,β-unsaturated ketone, an oxa bridge and the cyclopentadiene functionality makes these adducts amenable to a number of synthetic transformations. It is presumed that by using appropriately functionalized fulvenes and oxidopyrylium betaines, the present methodology may be useful in the synthesis of cyclooctanoid natural products.

In conclusion, we have exemplified a novel reactivity pattern of pentafulvenes with 3-oxidopyrylium betaines. It offers a useful methodology for the synthesis of 5–8 fused cyclooctanoids. The issues of stereocontrol and the application of this methodology for the synthesis of various fused cyclooctanoids are under study and will be reported in due course.

Table 1. [6+3] Cycloaddition of fulvenes with 3-oxidopyrylium betaines[a]



Entry	Pyranulose acetate	Fulvene	Product	Yield (%)
1	**1a**		 **2b**	57
2	**1b**		 **2c**	65
3	**1c**		 **2d**	67
4	**1d**		 **2e**	83
5	**1e**		 **2f**	70
6	**1f**		 **2g**	60
7	**1g**		 **2h**	58
8	**1h**		 **2i**	62
9	**1i**		 **2j**	79
10	**1j**		 **2k**	59

[a] Reaction conditions: Fulvene (1.0 equiv), pyranulose acetate (1.2 equiv), Et_3N (1.2 equiv), $CHCl_3$, 50 °C, 6 h.

Acknowledgements

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13. Crystal data for **2a**: CCDC 257223 $C_{23}H_{18}O_2$ $M = 326.37$, crystal dimensions $0.31 \times 0.26 \times 0.22$ mm, monoclinic, space group $P2_1/n$, $a = 9.1496(16)$, $b = 12.372(2)$, $c = 15.310(3)$ Å, $\beta = 105.748(3)°$, $V = 1667.9(5)$ Å^3, $Z = 4$; $\rho_{\text{calcd}} = 1.300$ g cm^{-3}, $\mu(\text{Mo-K}_\alpha) = 0.082$ mm^{-1}, $2\theta_{\max} = 50.00°$, 8180 reflections collected, 2934 unique, 2230 observed ($I > 2\sigma(I)$) reflections, 226 refined parameters, R value 0.0551, $wR2 = 0.1075$ (all data $R = 0.0798$, $wR2 = 0.1165$), $S = 1.091$, maximum and minimum residual electron densities +0.135 and −0.117 e Å^{-3}. X-ray data intensity were collected on a Bruker SMART APEX CCD diffractometer with omega and phi scan mode, $\lambda_{\text{Mo-K}\alpha} = 0.71073$ Å at $T = 293(2)$ K. All the data were corrected for Lorentzian, polarization and absorption effects using Bruker's SAINT and SADABS programs. SHELX-97 (G. M. Sheldrick, SHELX-97 program for crystal structure solution and refinement, University of Göttingen, Germany, 1997) was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were located in the difference Fourier map and refined using the full matrix least squares method isotropically. Crystallographic data (excluding structure factors) for the compound CCDC 257223 reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 257223. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223 336 033; or deposit@ccdc.cam.ac.uk.
14. *Details of a typical experiment*: Diphenyl fulvene (100 mg, 0.43 mmol), pyranulose acetate (81 mg, 0.52 mmol) and dry triethylamine (52 mg, 0.52 mmol) were taken in anhydrous chloroform and stirred at 50 °C in a Schlenk tube for 6 h under nitrogen. The solvent was removed under reduced pressure and the residue was subjected to chromatography on silica gel (60–120 mesh) using 5% ethyl acetate–hexane mixture as eluent to afford the product as a pale yellow crystalline solid (98 mg, 70%). The product **2a** was recrystallized from dichloromethane–hexane mixture. Mp 173–175 °C.
Spectral data for **2a**. IR(KBr) $\nu_{\max}$: 3062, 2928, 1691, 1598, 1443, 1376, 1247, 1160, 1077, 1036, 943 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 3.06 (s, 2H), 4.88 (s, 1H), 5.36 (d, 1H, $J = 4.2$ Hz) 5.76 (d, 1H, $J = 10.5$ Hz), 5.99 (dd, 1H, $J_1 = 4.3$, $J_2 = 10.4$ Hz), 6.44 (d, 1H, $J = 5.3$ Hz), 6.56 (d, 1H, $J = 5.3$ Hz), 7.0–7.5 (m, 10H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 194.5, 148.5, 145.8, 142.3, 141.4, 132.9, 132.3, 129.0, 128.6, 128.4, 128.3, 127.3, 126.4, 123.2, 97.1, 96.3, 74.9, 52.7, 40.7. HRMS(EI): m/z Calcd for $C_{23}H_{18}O_2$: 326.1307. Found: (M+) 326.1323. Anal. Calcd for $C_{23}H_{18}O_2$ C, 84.64; H, 5.56%. Found : C, 84.37; H, 5.41%.