Facile synthesis of azulenols: [6 + 4] cycloadditions of fulveneketene acetal

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In contrast to the Diels–Alder reaction of fulvenes and pyrones, fulveneketene acetal reacts with α-pyrene to give the [6 + 4] cycloaddition adduct, an efficient and novel route to the azulenols.

The [6 + 4] cycloaddition1 of dienes to fulvenes has proved to be an efficient synthesis of the azulenes.2 However, the [6 + 4] cycloaddition of heterofulvenes using a fulveneketene acetal moiety as a 6 π component has never been realized. During the course of our studies on the chemistry of fulvenes, a novel example of the dichotomous periselectivity of fulvene was discovered. This type of high-order cycloaddition constitutes an efficient synthesis of azulenols. In general, the Diels–Alder reactions of electron deficient dienes such as α-pyrene 1 with alkylfulvenes 2 favour addition across one of the endocyclic double bonds of 2 to yield the [4 + 2] adduct 3, Scheme 1.3 In contrast, electron rich dienes react with 2 to afford the [6 + 4] cycloadducts 4.4 Additionally, the transition state for the [6 + 4] cycloaddition is favoured over the [4 + 2] when electron rich fulvenes and electron deficient dienes are employed. For example, 6-dimethylaminofulvene 5 with 3,4-dichlorothiophene dioxide 6 at ambient temperature to give azulene 7 in 60% yield.5 This striking difference in periselectivity between 5 and alkylfulvenes 2 may be attributed to an increase in the electron density of the 6-dimethylaminofulvene π system. Moreover, 5 adds to α-pyrones in a [6 + 4] manner to give azulenes in relatively low yields.6 According to FMO theory, electron donating substituents with large coefficients at the C-6 position of fulvene sufficiently elevate the energy of its next highest occupied molecular orbital (NHOMO) and promote [6 + 4] cycloadditions to electron deficient 4 π systems.7 We suspected that the yield in this high order cycloaddition could be enhanced by further increasing the electron density on the C-6 position of fulvene. To this end, we prepared and reacted 2-cyclopentadienyldiene-1,3-dioxolane 8 with α-pyrene 1, Scheme 2.8 A benzene solution of fulveneketene acetal 8 and α-pyrene 1 was heated at reflux for 72 h in the dark. The [6 + 4] cycloadduct 9 was isolated as a purple oil in 54% yield after purification by flash chromatography. The purple colour of 9 is characteristic of azulenic compounds. Adduct 9 arises from the addition of α-pyrene across C-1 and C-6 of the fulvene ring followed by cheletropic extrusion of CO₂. The structure of 9 was established based on 1H, 13C NMR, COSY and DEPT experiments and mass spectral data. Our assignment was unequivocally confirmed when 9 was transformed quantitatively into the previously known 4-ethoxazulene 10 (KOH, EtOH, reflux, 8–10 h).9 This method provides direct access to stable analogues of 4-hydroxyazulenes.10 In fact, no decomposition of adduct 9 was observed after 4 months at 25 °C in the dark. The tetter on azulenol 9 may be easily functionalized or elongated to provide various useful azulene analogues.‡ Scheme 3 depicts another application of this methodology to the synthesis of azulene 11. When a benzene solution of fulveneketene acetal 8 and α-pyrene 12 was heated at reflux for 4 d in the dark, the [6 + 4] cycloadduct 11 was isolated as a dark-green solid in 40% yield. A solution of 11 in EtOAc or acetone turns deep blue (red shift).

Thus, the [6 + 4] cycloaddition of α-pyrene to electron rich fulveneketene acetal 8 provides an efficient route to the synthesis of azulenols. This method establishes the experimental framework for a conceptually new approach to such systems.

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Footnotes
† All new compounds gave satisfactory spectral and analytical data. Selected spectral data for azulenol: 1H NMR (CDCl₃, 200 MHz): δ 8.30 (d, J 9.0 Hz, 1 H), 7.67 (t, J 3.8 Hz, 1 H), 7.47–7.63 (m, 2 H), 7.31 (qd, J 3.7, 1.7 Hz, 1 H), 7.02 (d, J 9.6 Hz, 1 H), 6.92 (d, J 11.4 Hz, 1 H), 4.43 (s, J 4.5 Hz, 2 H), 4.03–4.20 (m, 2 H) and 2.18 (t, J 6.4 Hz, 1 H); 13C NMR (CDCl₃, 50 MHz): δ 161.90 (C), 139.30 (C), 137.59 (CH), 135.84 (CH), 132.93 (CH), 127.64 (C), 118.91 (two CH), 114.03 (CH), 108.51 (CH), 70.57 (CH₂) and 61.52 (CH₂). For 10: 1H NMR (CDCl₃, 200 MHz): δ 8.28 (d, J 9.4 Hz, 1 H), 7.44–7.70 (m, 3 H), 7.28 (dd, J 3.7, 1.9 Hz, 1 H), 6.84–7.04 (m, 2 H), 4.39 (q, J 6.9 Hz, 2 H) and 1.58 (t, J 6.8 Hz, 3 H); 13C NMR (CDCl₃, 50 MHz): δ 162.44 (C), 139.14 (C), 137.53 (CH), 135.87 (CH), 132.44 (CH), 127.5 (C), 118.61 (CH), 114.42 (CH), 114.28 (CH), 108.27 (CH), 64.75 (CH₂), 14.99 (CH₃). For 11: 1H NMR ([D₆]acetone, 200 MHz): δ 10.78 (br s, 1 H), 8.37 (d, J 7.8 Hz, 1 H), 7.83 (s, 1 H), 7.42–7.67 (m, 5 H), 7.26 (t, J 7.5 Hz, 1 H), 4.57 (t, J 4.9 Hz, 2 H), 4.20–4.33 (m, 1 H), 4.04–4.18 (m, 2 H) and 3.20 (s, 3 H); 13C NMR ([D₆]acetone, 50 MHz): δ 156.55 (C), 140.11 (C), 137.18 (C), 135.22 (C), 133.11 (C), 130.35 (CH), 130.24 (CH), 128.04 (C), 127.91 (CH), 126.78 (C), 124.96 (C), 121.21 (CH), 119.97 (CH), 114.87 (CH), 112.04 (CH), 98.06 (CH), 71.67 (CH₂), 61.68 (CH₃) and 19.05 (CH₃).
‡ Azulene derivatives have been widely used in pharmaceuticals, cosmetics, photosensitizers, liquid crystals and electric conductors.
§ Purchased from Aldrich Chemical Co.

References
7 See ref. 1, p. 627.
10 4-Hydroxyzulene is a tautomer of a cyclopentadienotropone and its instability is not due to an equilibrium favouring cyclopentadionotropone, but rather to oxidation. Ester or alkoxy substituents at the 4-position enhance the stability of the system. See: N. Anderson, J. Am. Chem. Soc., 1951, 73, 232; A. Shani, Israel J. of Chem., 1975, 13, 53.

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