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-pyrone to give the [6 + 4] cycloaddition adduct, an efficient and novel route to the azulenols.

The [6 + 4] cycloaddition[1] 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-pyrone **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-cyclopentadienylidene-1,3-dioxolane **8** with α-pyrone **1**, Scheme 2.[8]

A benzene solution of fulveneketene acetal **8** and α-pyrone **1** was heated at reflux for 72 h in the dark. The [6 + 4] cycloadduct
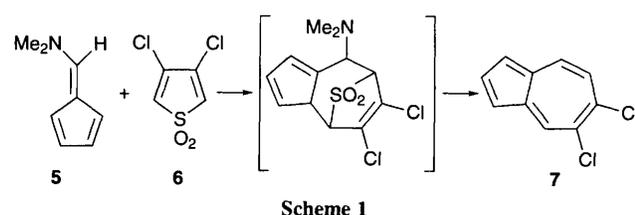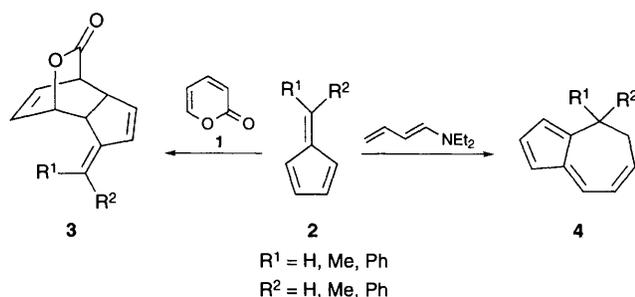
9 was isolated as a purple oil in 54% yield after purification by flash chromatography. The purple colour of **9** is characteristic of azulenic compounds. Adduct **9** arises from the addition of α-pyrone across C-1 and C-6 of the fulvene ring followed by cheleotropic extrusion of CO_2. The structure of **9** was established based on ^{1}H, ^{13}C NMR, COSY and DEPT experiments and mass spectral data.† Our assignment was unequivocally confirmed when **9** was transformed quantitatively into the previously known 4-ethoxyazulene **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 tether 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-pyrone **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-pyrone 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.

Scheme 2

R¹ = H, Me, Ph
R² = H, Me, Ph
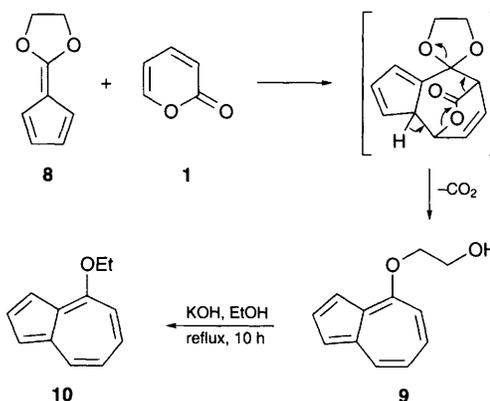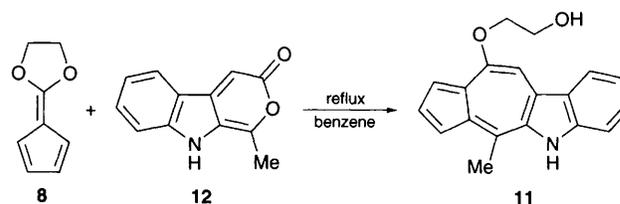
Scheme 1

Scheme 3

Footnotes

† All new compounds gave satisfactory spectral and analytical data. *Selected spectral data* for azulenol **9**: ^{1}H NMR (CDCl$_3$, 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 (dd, *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 (t, *J* 4.5 Hz, 2 H), 4.03–4.20 (m, 2 H) and 2.18 (t, *J* 6.4 Hz, 1 H); ^{13}C NMR (CDCl$_3$, 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 (CH$_2$) and 61.52 (CH$_2$). For **10**: ^{1}H NMR (CDCl$_3$, 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); ^{13}C NMR (CDCl$_3$, 50 MHz): δ 162.44 (C), 139.14 (C), 137.53 (CH), 135.87 (CH), 132.44 (CH), 127.75 (C), 118.61 (CH), 118.42 (CH), 114.28 (CH), 108.27 (CH), 64.75 (CH$_2$), 14.99 (CH$_3$). For **11**: ^{1}H NMR ([^{2}H$_6$]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); ^{13}C NMR ([^{2}H$_6$]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 (CH$_2$), 61.68 (CH$_2$) and 19.05 (CH$_3$).

‡ Azulene derivatives have been widely used in pharmaceuticals, cosmetics, photosensitizers, liquid crystals and electric conductors.

§ Purchased from Aldrich Chemical Co.

References

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10 4-Hydroxyazulene is a tautomer of a cyclopentadienotropone and its instability is not due to an equilibrium favouring cyclopentadienotropone, 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.