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[6+3] Cycloaddition of Fulveneketene Acetal[1]

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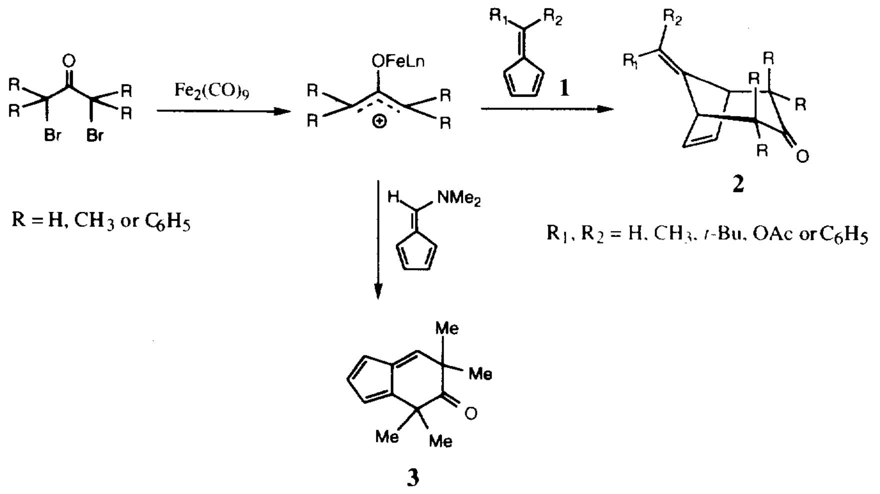
Summary: A novel [6+3] cycloaddition of 2-oxyallyl cation and fulveneketene acetal is described which provides a conceptually novel methodology for the synthesis of indan ring systems.

Traditionally, the Diels-Alder reaction has served as an elegant tool for the construction of 6-membered rings. However, much effort has also focused on the search for alternative cycloaddition strategies in order to complement the [4+2] approach. This was in fact highlighted by recent advances in transition metal mediated [2+2+2] and [3+3] cycloadditions.[2,3]

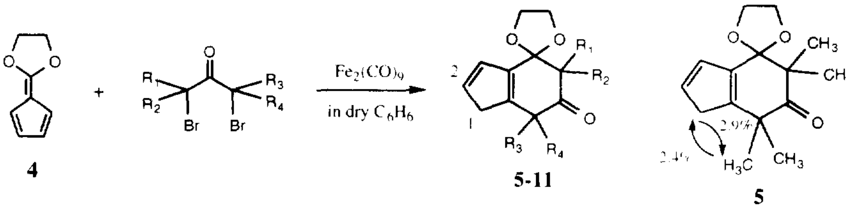
In the first example of a [6+3] cycloaddition, Trost *et al.* demonstrated that 2-[(trimethylsilyl)methyl]allyl carboxylates react with tropones to yield exclusively the [6+3] nine-membered carbocycles.[4] This methodology was successfully applied to the synthesis of bicyclo[4.3.1]alkenones.[5] Heterobicyclo[4.3.1]alkenones have also been prepared *via* metal mediated [6+3] cycloaddition of azirines to coordinated cycloheptatriene.[6] As part of our efforts focused on the synthesis of complex natural products, we have developed a homologue of the [6+3] cycloaddition which takes advantage of the 6π electronic character of fulvene. Herein we report the first example of a [6+3] cycloaddition of fulveneketene acetal which provides rapid access to highly substituted indan ring systems.

Scheme 1



The reaction of 6-mono and 6,6-dialkyl fulvenes **1** with 2-oxyallyl cations has been reported (Scheme **1**).[7] In fact, this cycloaddition leads exclusively to the [4+3] adducts **2** in good yield.[8] However, when 2-oxyallyl-Fe(II) cation (R = Me) is reacted with 6-(dimethylamino)fulvene, one recovers only a novel fulvene adduct **3** in relatively low yield (17%). This striking difference in chemoselectivity may be attributed to an increase in the electron density of the 6-(dimethylamino)fulvene π system. The formation of **3** may be rationalized *via* a stepwise mechanism: initial addition to the C-1 of the fulvene by the electrophilic cation followed by cyclization and elimination to give **3**. We suspected that the yield in this two-step cycloaddition could be enhanced by further increasing the electron density on the fulvene. To this end, we prepared and reacted 2-cyclopentadienyliden-1,3-dioxolane (**4**) with a host of 2-oxyallyl-Fe(II) cations (Scheme **2**).[9]

Scheme 2



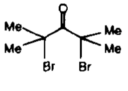
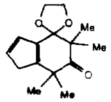
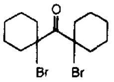
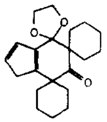
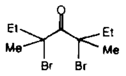
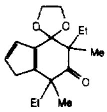
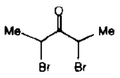
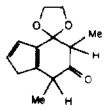
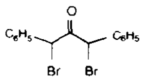
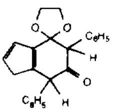
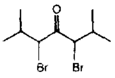
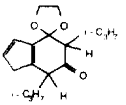
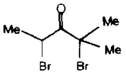
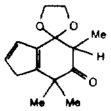
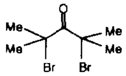
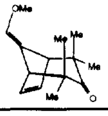
R_1, R_2, R_3, R_4 = H or CH_3 or C_2H_5 or *i*-C_3H_7 or C_6H_5

A solution of fulveneketene acetal **4**, 2,4-dibromo-2,4-dimethylpentan-3-one, and $Fe_2(CO)_9$ in dry benzene was stirred at 25 °C for 2 h. Following purification by flash chromatography, the [6+3] cycloadduct **5** was isolated as a colorless oil in 86% yield. Adduct **5** arises from the addition of the 2-oxyallyl cation across C-1 and C-6 of the fulvene ring. The structure of **5** was assigned based on ^{1}H, ^{13}C NMR, COSY, DEPT, HETCOR and mass spectral data.[10] As illustrated by the entries of Table 1, this new cycloaddition allows an efficient synthesis of indandiones. The reaction is relatively insensitive to the steric bulk of the cation substituents (Table 1, entries 1-3). Yields range from 50 to 86%, and in most cases a single compound was produced. The results of nOe studies carried out on indan **5** were consistent with the structure depicted in Scheme 2. Irradiation of the C-1 protons gave rise to a 2.9% enhancement of the neighboring methyl protons, while irradiation of the methyl protons caused a 2.4% enhancement of the C-1 signal. Products **7-10** were isolated as single stereoisomers. However, the exact stereochemistry of these compounds has not yet been established.[11] As suspected, decreasing the electron density of the fulvene disfavors the [6+3] pathway. This was demonstrated by the reaction of 6-methoxyfulvene with 2-oxyallyl cation which yielded the [4+3] adduct exclusively (Table 1, entry 8).[12]

Typical procedure for the [6+3] cycloaddition: To a mixture of fulveneketene acetal **4** (370 mg, 2.7 mmol) and $Fe_2(CO)_9$ (1.49 g, 4.1 mmol) in dry benzene (80 mL) was added 2,4-dibromo-2,4-dimethylpentan-3-one (1.12 g, 4.1 mmol). The suspension was vigorously stirred for 2 h at 25 °C and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography with 3% EtOAc-hexane (R_f = 0.68 in 10% EtOAc-hexane) to give indan **5** as a colorless oil (580 mg, 86% yield). IR (neat): 2969, 2936, 2869, 1712, 1476, 1381, 1329, 1273, 1212, 1150, 1118, 1103, 1047, 984, 952 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.12 (s, 6 H), 1.27 (s, 6 H), 3.03 (br.s, 2 H), 3.96-4.08 (m, 4 H), 6.33 (d, J = 5.4 Hz, 1 H), 6.46 (d, J = 5.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.22 (two CH_3), 27.90 (two CH_3), 39.65 (CH_2), 44.95

(C), 53.77 (C), 66.13 (two CH_2), 108.65 (C), 129.98 (CH), 131.42 (CH), 139.23 (C), 147.21 (C), 216.61 (C); MS (m/z, relative intensity): 248 (M^+, 38), 233 (7); 178 (100), 163 (65), 149 (57), 119 (29), 107 (49), 105 (29), 91 (68); exact mass calculated for $C_{15}H_{20}O_3$ (M^+): 248.1412; found 248.1421.

TABLE 1. CYCLOADDITION OF FULVENE 4 AND DIBROMOKETONES

Entry	Dibromoketone	Product		Yield (%)[(a)]
1			5	86
2			6	66
3			7	70
4			8	66
5			9	79[(b)]
6			10	50[(b)]
7			11	60[(b)]
8[(c)]			12	56[(d)]

(a) Isolated yield.

(b) After a few hours at ambient temperature, these products isomerized to an unseparable mixture of compounds having the same MS as the original samples. The ^1H NMR of these mixtures contained several double bond patterns.

(c) Dibromoketone was reacted with 6-methoxyfulvene.

(d) No [6+3] product was observed.

In summary, the transition metal mediated cycloaddition of 2-oxyallyl cations to electron rich fulveneketene acetal **4** provides an efficient route to the indan skeleton. This method establishes the experimental framework for a conceptually new approach to indan systems. Further investigation of the scope of this [6+3] cycloaddition as well as the application of this methodology to the synthesis of natural products containing the indan skeleton is currently underway in our laboratory.

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References and Notes:

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[1] Dedicated to Professor E. J. Corey, an inspiring teacher and scholar to whom we are very grateful.

[2] For examples of [2+2+2] cycloadditions see: (a) Vollhardt, K. P. C. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 539-556. (b) Brown, S.; Clarkson, S.; Grigg, R.; Sridharan, V. *Tetrahedron Lett.* **1993**, *34*, 157-160. (c) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1987**, *109*, 4753-4755. (d) Hoberg, H.; Oster, B. W. *Synthesis*, **1982**, 324-325. (e) Grigg, R.; Scott, R.; Stevenson, P. *J. Chem. Soc., Perkin Trans I*, **1988**, 1357-1364.

[3] For examples of [3+3] cycloadditions see: (a) Mori, M.; Sugiyama, T.; Nojima, M.; Kusabayashi, S.; McCullough, K. J. *J. Org. Chem.* **1992**, *57*, 2285-2294. (b) Bambal, R. B.; Kemmitt, R. D. W. *J. Organomet. Chem.* **1989**, *362*, C18-C20. (c) Pearson, W. H.; Fang, W.; Kampf, J. W. *J. Org. Chem.* **1994**, *59*, 2682-2684. (d) Bonini, B. F.; Maccagnani, G.; Mazzanti, G.; Zwanenburg, B. *J. Chem. Soc., Chem. Commum.* **1985**, 237-238. (e) Tominaga, Y.; Ueda, H.; Ogata, K.; Kohra, S. *J. Heterocycl. Chem.* **1992**, *29*, 209-214.

[4] Trost, B. M.; Seoane, P. R. *J. Am. Chem. Soc.* **1987**, *109*, 615-617.

[5] Prior to the work in reference 4, several cycloadditions of diphenylnitrileimine or nitrile oxides with tropone were reported. However, these reactions were low yielding and the [6+3] adducts were minor products. See: (a) Bonadeo, M.; De Micheli, C.; Gandolfi, R. *J. Chem. Soc., Perkin Trans. I*, **1977**, 939; (b) Houk, K. N.; Watts, C. R. *Tetrahedron Lett.* **1970**, 4025; (c) De Micheli, C.; Gandolfi, R.; Grünanger, P.; *Tetrahedron*, **1974**, *30*, 3765.

[6] Chaffee, K.; Morcos, H.; Sheridan, J. B. *Tetrahedron Lett.* **1995**, *36*, 1577-1580.

[7] (a) Kashman, Y.; Rudi, A. *Tetrahedron*, **1974**, *30*, 109-115. (b) Ishizu, T.; Mori, M.; Kanematsu, K. *J. Org. Chem.* **1981**, *46*, 526-531.

[8] For a recent review on [4+3] cycloadditions, see: Hosomi, A.; Tominaga, Y. in *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: London, **1991**, Vol 5, 593-615.

[9] For the preparation of 2-cyclopentadienyliden-1,3-dioxolane, see Olsson, T.; Wennerström, O. *Acta Chemica Scandinavica B*, **1978**, *32*, 293-296.

[10] All new compounds were characterized by full spectroscopic (^{1}H, ^{13}C NMR, IR, MS, and HRMS) data. Yields refer to spectroscopically and chromatographically homogeneous (>95%) materials.

[11] NOe experiments carried out on these products have been inconclusive. Work is in progress to produce a crystalline derivative which will be suitable for single crystal x-ray analysis.

[12] For the preparation of 6-methoxyfulvene, see: (a) Paulson, P. L.; Sandler, M. A.; Watts, E. *J. Chem. Soc. (C)*, **1980**, 860-863. (b) Bönzli, P.; Otter, A.; Neuenschwander, M.; Huber, H.; Kellerhals, H. P. *Helv. Chim. Acta.* **1986**, 69, 1052-1064.

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