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Unprecedented sequential oxidative dimerization and cycloaddition of 1,3-diketones to fulvenes. A facile synthesis of the cyclopenta[*b*]chromenes

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Abstract—A one-pot Ag_2CO_3 mediated oxidative dimerization of 1,3-diketone followed by cycloaddition to fulvenes is described. This methodology has been applied to the synthesis of 7-oxatricyclo[6.4.0.$0^{2,6}$]dodecanes and/or 8-oxatricyclo[7.4.0.$0^{3,7}$]tridecanes. © 2001 Elsevier Science Ltd. All rights reserved.

Various oxidative addition reactions of 1,3-dicarbonylalkyl radicals to alkenes have been described over the years including those mediated by salts of Mn^{III}, Cu^{II}, Ag^{I}, V^{V}, Fe^{III}, Ce^{IV} etc.[1] The reaction of 1,3-dicarbonyl dipoles with alkenes in the presence of such salts is known to afford dihydrofurans. In fact, the silver-mediated oxidative cyclization of cyclohexane-1,3-dione to 2,3-dihydrofuran was applied to the synthesis of demethoxyaflatoxin B_2.[2] To date, however, no reports of an addition of 1,3-dicarbonyl compounds to fulvenes have appeared. In conjunction with our continuing efforts in fulvene chemistry,[3] we have developed a novel one-pot two-step, oxidative dimerization and cycloaddition of cyclohexane-1,3-dione to fulvenes that provides a series of cyclopenta[*b*]chromenes. Initially, we studied the addition of cyclohexane-1,3-dione to 6,6-dimethylfulvene. Heating a CH_3CN solution of 6,6-dimethyl fulvene, cyclohexane-1,3-dione and Ag_2CO_3 to reflux for 5 h provided 46% of 1-oxacyclopenta[*a*]indene **1** along with 14% of an interesting cyclopenta[*b*]chromene **2**. The structure of **2** was unambiguously assigned based on ^1H, ^{13}C NMR, COSY, DEPT, HMQC, MS, elemental and single crystal X-ray analysis (Fig. 1).[4]

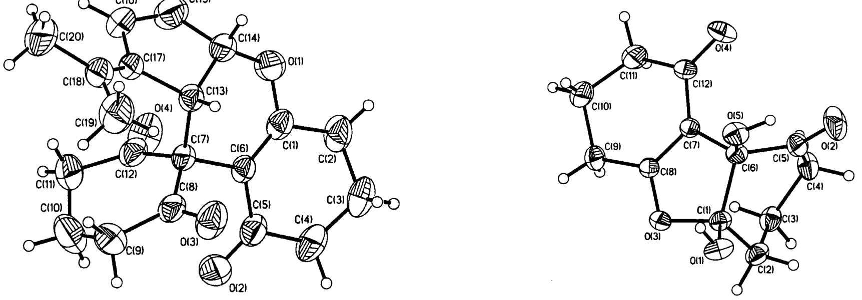

Figure 1. ORTEP plots for X-ray crystal structures of **2** and **6**.

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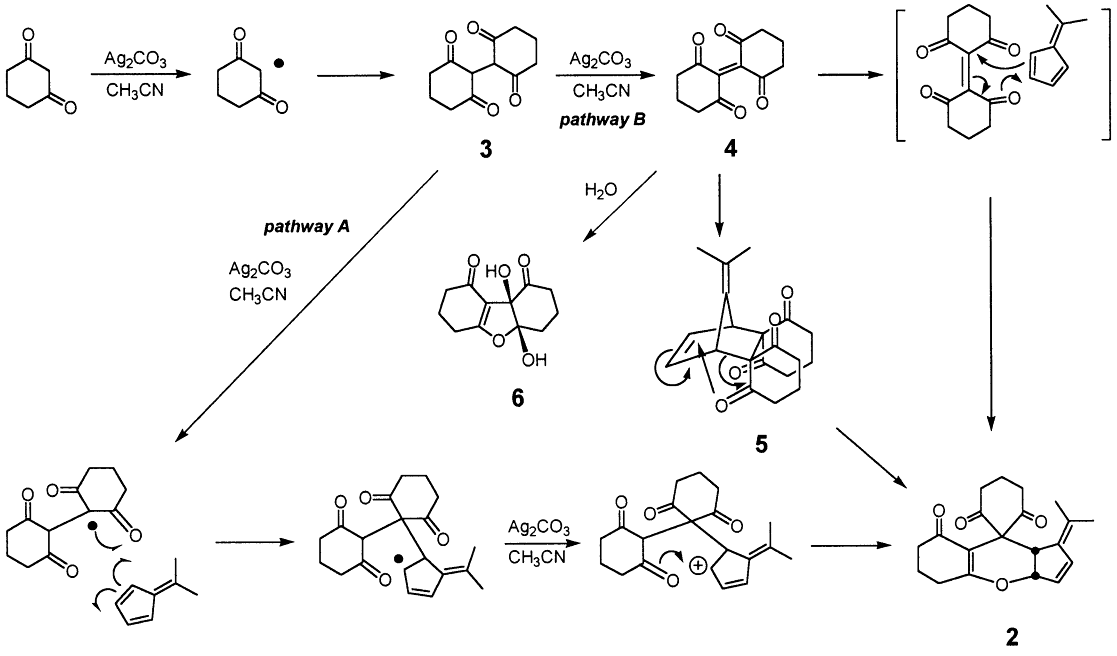

Scheme 1.

The yield of pyran **2** increased dramatically when the fulvene solution was added after prolonged reaction of cyclohexa-1,3-dione and Ag_2CO_3. This result implies that the dimerization of cyclohexadione probably occurs prior to addition to fulvene. A plausible mechanism for the formation of **2** is shown in Scheme 1. Initial dimerization of cyclohexane-1,3-dione[5] gives tetraone **3**.[6] This is then followed by two possible pathways. A radical mechanism, (pathway A), in which the resulting 1,3-diketoalkyl radical attacks at the endocyclic double bond of fulvene to generate an allyl radical,[7,8] followed by oxidation to provide an allyl cation, and cyclization to afford the pyran product **2**.

Alternatively in pathway B, tetraone **3** may oxidize to **4** which can undergo a hetero-Diels–Alder reaction with fulvene to give **2**.[9] On the other hand, the Diels–Alder reaction of **4** with fulvene gives intermediate **5**, which may undergo facial [3,3] sigmatropic rearrangement to afford **2**.[10] Isolation of diol **6**[11,12] from the reaction mixture lends further support to pathway B.[13] Table 1 describes a variety of reactants and reaction conditions (entries 2–10).[14] Similar results were observed for other fulvenes with the exception of 6,6-diphenylfulvene, which gave regioisomers **11** and **12**. This is most likely due to the steric hindrance of **11** (Table 1, entry 4). On the other hand, the reaction of acetylacetone and fulvenes gave the furan adducts exclusively (Table 1, entries 6–7, condition A). In this case, addition of fulvenes after prolonged reaction of acetylacetone and Ag_2CO_3 (condition B) resulted in recovery of the starting fulvenes. No reaction took place when 3,4-diacetylhex-3-ene-2,5-dione (acetoacetone dimer)[15] and fulvene were heated to reflux in CH_3CN for 3 days.[16] Furthermore, it is noteworthy that the oxidative alkylation of 1,3-diketone dimers with fulvene is specific since the pyran product did not form with other simple alkenes (entries 8–10, Table 1). In summary, a novel one-pot oxidative dimerization[17] and cycloaddition of 1,3-diketone to fulvenes has been reported. This constitutes a new methodology for the synthesis of polycyclic pyrans.[18] We are actively pursuing the application of this methodology to the synthesis of natural products.

Acknowledgements

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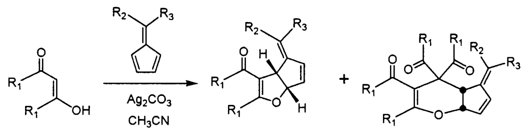
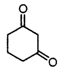
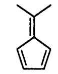
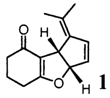
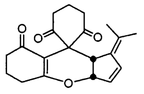
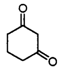
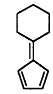
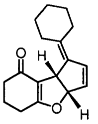
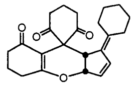
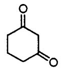
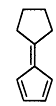
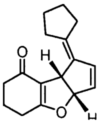
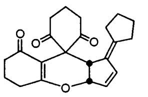
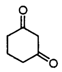
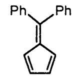
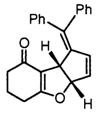
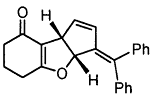
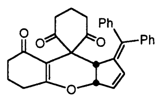
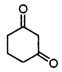
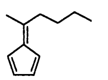
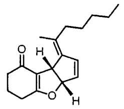
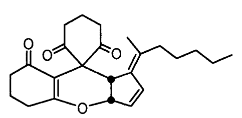
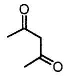
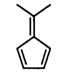
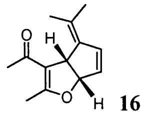
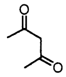
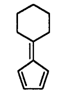
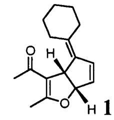
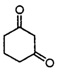
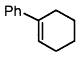
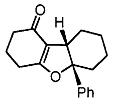
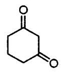
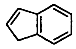
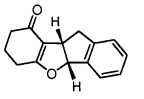
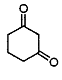
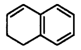
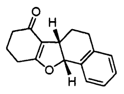
Table 1. Oxidative alkylation of 1,3-diketones to fulvenes



entry	ketones	fulvenes	product		condition	yields[a]
1			 **1**  **2**	77:23 4:96	A B	60 92
2			 **7**  **8**	78:22 5:95	A B	68 93
3			 **9**  **10**	100:0 0:100	A B	85 85
4			 **11**  **12**  **13**	57:43:0 0:0:100	A B	65 90
5			 **14**  **15**	75:25 4:96	A B	63 92
6			 **16**		A B	55 ~0[b]
7			 **17**		A B	60 ~0[b]
8			 **18**		A B	86 ~0[b]
9			 **19**		A B	95 ~0[b]
10			 **20**		A B	93 ~0[b]

[a] Isolated yield based on starting alkenes. [b] No reaction; starting alkenes were recovered. Condition A: ketone, alkene and Ag_2CO_3 were heated to reflux for 5 h in CH_3CN. Condition B: ketone and Ag_2CO_3 was heated to reflux for 12 h in CH_3CN, followed by addition of alkene.

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B.-C.; Sun, S.-S. *Chem. Commun.* **1996**, 937. (f) Hong, B.-C.; Sun, S.-S.; Tsai, Y.-C. *J. Org. Chem.* **1997**, *62*, 7717.

4. Crystallographic data for **2**: $C_{20}H_{22}O_4$, $M = 326.38$, monoclinic, space group $P2_1/c$, $T = 293$ K, $a = 7.900(1)$, $b = 20.287(4)$, $c = 10.702(1)$ Å, $\beta = 100.99(1)°$, $V = 1683.7(4)$ Å^3, $Z = 4$, $D = 1.288$ g/cm^3, λ(Mo-K$_\alpha$) = 0.71073 Å, 2971 reflections collected, 242 parameters refined on F^2, $R = 0.0512$ [2119 data with $F^2 > 2\sigma(F^2)$], $wR_2[F^2] = 0.0567$.
5. Saegusa et al. have reported that β-ketoesters and β-diketones react with silver oxide in DMSO to form dimers. A radical intermediate was implicated in the dimerization reaction, see: Ito, Y.; Fujii, S.; Konoike, T.; Saegusa, T. *Synth. Commun.* **1976**, *6*, 429.
6. For the preparation of bicyclohexyl-2,6,2′-6′-tetraone (**3**) via electrolysis, see: Johnston, K. M.; Stride, J. D. *J. Chem. Soc., Chem. Commun.* **1966**, 325.
7. Examples of radical additions to fulvene are rare. For reductive coupling of 6-dimethylaminofulvenes furnishing 6,6′-bifulvenyl, see: Kawase, T.; Nisato, N.; Oda, M. *J. Chem. Soc., Chem. Commun.* **1989**, 1145. For coupling of 6,6-dimethylfulvenyl radical, see: You, S.; Neuenschwander, M.; Huber, H. *Helv. Chim. Acta* **1993**, *76*, 2111.
8. During the addition of muonium atom to fulvene, radicals are formed exclusively by addition to the 1 and 2 positions, see: Rhodes, C. J.; Roduner, E.; Reid, I.; Azuma, T. *J. Chem. Soc., Chem. Commun.* **1991**, 208.
9. To the best of our knowledge, the hetero-Diels–Alder reaction of fulvene has never been reported. However, the hetero-Diels–Alder reaction of 3,4-diacetylhex-3-ene-2,5-dione to alkenes has been reported, see: Celli, A. M.; Scotton, M.; Sega, A. *Tetrahedron* **1992**, *48*, 5883–5900.
10. For the first example of a tandem Diels–Alder, [3,3] sigmatropic rearrangement reaction of fulvene, see: Wu, H.-J.; Chern, J.-H. *Tetrahedron* **1997**, *53*, 17653.
11. For an example of transformation of an analog of **4** to an analog of **6**, see: Schank, K.; Frocken, M. *Chem. Ber.* **1992**, *125*, 675–677.
12. Crystallographic data for **6**: $C_{12}H_{14}O_5$, $M = 238.23$, monoclinic, space group $P2_1/c$, $T = 293$ K, $a = 6.707(1)$, $b = 10.355(1)$, $c = 8.795(1)$ Å, $\beta = 109.23(1)°$, $V = 576.7(1)$ Å^3, $Z = 2$, $D = 1.372$ g/cm^3, λ(Mo-K$_\alpha$) = 0.71073 Å, 1178 reflections collected, 173 parameters refined on F^2, $R = 0.0388$ [1113 data with $F^2 > 2\sigma(F^2)$], $wR_2[F^2] = 0.1060$.
13. Reaction of **4** with fulvene in CH_3CN also gave **2** in similar yield.
14. **Typical experimental procedure**: (**method A**): A solution of *cyclohexane-1,3-dione* (112 mg, 1 mmol), 6,6-dimethylfulvene (107 mg, 1 mmol) and Ag_2CO_3 (551 mg, 2 mmol) in CH_3CN (10 mL) was heated to reflux for 5 h. The solution was filtered through Celite 545 and concentrated in vacuo to give a dark-red oil. The crude product was purified by flash column chromatography (silica gel) with 20% EtOAc–hexane to give **1** (105 mg, 42%; $R_f = 0.85$, 50% EtOAc–hexane) and **2** (40 mg, 18%; $R_f = 0.57$, 50% EtOAc–hexane) as colorless solids. Spectroscopic data for **1**: IR (neat): 2947, 1741, 1666, 1626, 1406, 1187 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.61 (d, $J = 5.44$ Hz, 1H), 5.75–5.79 (m, 2H), 4.20 (d, $J = 7.64$ Hz, 1H), 2.35–2.38 (m, 2H), 2.23–2.29 (m, 2H), 2.06 (s, 3H), 1.90–1.96 (m, 2H), 1.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.5 (C), 177.6 (C), 137.5 (C), 137.0 (C), 129.6 (C), 129.0 (CH), 116.4 (C), 93.3 (CH), 46.2 (CH), 38.1 (CH_2), 25.1 (CH_2), 23.5 (CH_3), 22.2 (CH_3), 21.9 (CH_2); MS (*m*/*z*, relative intensity): 216 (M$^+$, 23), 99 (17), 91 (100), 88 (39); exact mass calculated for $C_{14}H_{16}O_2$ (M$^+$): 216.1151; found 216.1150. Spectroscopic data for **2**: IR (neat): 2957, 1700, 1631, 1396, 1227, 1102 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.34 (dd, $J = 3.36$, 2.6 Hz, 1H), 5.89 (d, $J = 5.28$ Hz, 1H), 5.28 (d, $J = 6.52$ Hz, 1H), 3.64 (d, $J = 6.72$ Hz, 1H), 3.00–3.06 (m, 1H), 1.88–2.60 (m, 12H), 1.75 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 213.2 (C), 208.8 (C), 196.5 (C), 174.3 (C), 136.2 (C), 136.0 (CH), 131.8 (C), 128.0 (C), 115.4 (C), 81.9 (CH), 62.1 (C), 49.5 (CH), 42.6 (CH_2), 41.4 (CH_2), 36.6 (CH_2), 29.5 (CH_2), 23.3 (CH_3), 21.5 (CH_3), 21.0 (CH_2), 18.6 (CH_2); MS (*m*/*z*, relative intensity): 327 (M$^+$+1, 22), 326 (M$^+$, 100), 311 (15), 267 (18), 253 (17), 205 (32), 106 (51); exact mass calculated for $C_{20}H_{22}O_4$ (M$^+$): 326.1519; found 326.1518. (**Method B**): A solution of *cyclohexane-1,3-dione* (225 mg,2 mmol) and Ag_2CO_3 (2.20 g, 8 mmol) in CH_3CN (20 mL) was heated to reflux for 12 h. A solution of 6,6-dimethylfulvene (107 mg, 1 mmol) in CH_3CN (5 mL) was added to the reaction mixture and the resulting solution was heated for 2 h. The solution was filtered through Celite 545 and concentrated in vacuo to give the dark-red oil. The crude product was purified by flash column chromatography (silica gel) with 30% EtOAc–hexane to give **2** as a colorless solid (209 mg, 87% yield).
15. For preparation, see: Adembri, G.; Celli, A. M.; Sega, A. *J. Heterocycl. Chem.* **1997**, *34*, 541.
16. Microwave heating (Prolabo Synthewave 402, Power 30%, 60°C for 6 h) had no effect either.
17. To the best of our knowledge, a simple one-step oxidative dimerization of 2,2-dihydro-1,3-dikeone has not been reported.
18. Polycyclic pyrans are abundant in nature. For example, the 2-oxatricyclo[7.4.0.0^{3,7}]tridecane system is present in pseudobtuceol I, see: Rashid, M. A.; Armstrong, J. A.; Gray, A. I.; Waterman, P. G. *Phytochemistry* **1992**, *31*, 3583.