Tetrahedron Letters,Vol.29,No.39,pp 4997-5000,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

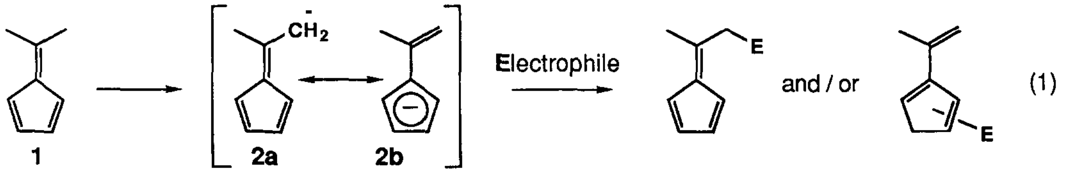
Functionalization of 6,6-Dimethylfulvene: A Fulvene Analogue of the Aldol Condensation.

Jan-Erik Nyström*, Styrbjörn E. Byström, Taina Ristola,[1] and John Ekström[1]
Department of Organic Chemistry, Royal Institute of Technology, S-100 44 Stockholm,
Sweden

Summary. 6,6-Dimethylfulvene **1** was regioselectively functionalized at the 7-position by reacting the fulvene anion **2** with aldehydes at low temperature. The adducts **3** were trapped at low temperature and isolated as fulvenols **4** or as the corresponding trimethylsilyl ethers **5** in good yields (57-82%). The kinetically favored exocyclic addition of aldehydes was explained by invoking a frontier orbital controlled process which is supported by a Hückel calculation.

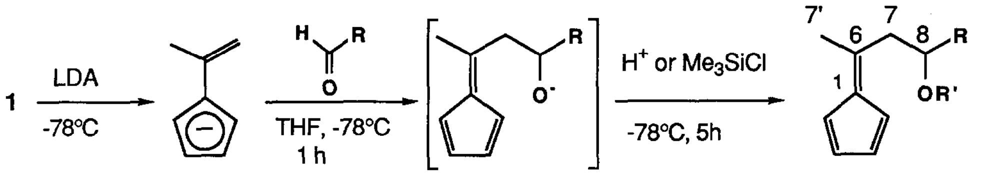
The dipolar character of the exocyclic double bond in fulvenes[2] give them reactivities similar to carbonyl compounds. This is reflected by the addition of strong nucleophiles (RLi, $LiAlH_4$) to the 6-position, and after workup monosubstituted cyclopentadienes can be isolated.[3] Furthermore, a proton α to the exocyclic double bond is fairly acidic, pK_a=22.7 (DMSO),[4] i. e. comparable to a proton α to the carbonyl group in an aldehyde or a ketone. Fulvenes are also prone to undergo cycloadditions, in which they can act either as diene or dienophile.

Fulvenes in general are prepared by a Knoevenagel type condensation between a cyclopentadienyl anion and a ketone or an aldehyde.[5] It occured to us that a new entry to functionalized fulvenes may be achieved by (1) α-deprotonation and (2) addition of a suitable electrophile at the exocyclic position. A complication, however, can arise by the ambident nature of the anion **2**, and an electrophile may add to the cyclopentadienyl ring instead (eq 1). Upon surveying the literature, we learned that this approach for fulvene synthesis has been little studied. It has been reported that proton[6] and trimethylsilyl chloride[7] give vinylcyclopentadienes upon reaction with the fulvene anion **2**. Furthermore, p-



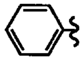
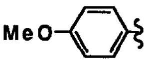
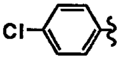
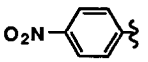
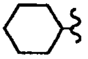
methoxybenzaldehyde[8] and acetone[9] gave condensation products 7 (*vide infra*) upon reaction with dimethylfulvene **1** in the presence of a base. In this communication, we report a selective addition of aldehydes to the exocyclic position of deprotonated 6,6-dimethylfulvene, the fulvene we chose as a prototypical compound.

Deprotonation of **1** was achieved with LDA in THF at -78°C. The anion **2** was then allowed to react with the aldehyde at -78°C, and conversion to the adducts **3** was complete within 1 h (**3e**, 2h). The fulvenols **4a-e** can be isolated in good crude yields by quenching with NH_4Cl (aq) at low temperature; however, they suffered from partial decomposition upon attempted purification by silicagel chromatography. Trapping the adducts **3** from aromatic aldehydes as trimethylsilylethers gave the more stable and synthetically more useful derivatives **5a-d** (eq 2). In the case of cyclohexanecarboxaldehyde (last entry) the trapping with trimethylsilyl choride failed. Instead the corresponding fulvenol **4e** could be isolated in good yield. Our results are summerized in the table.



2 **3** **4a-e (R'=H)** **5a-d (R'=Me3Si)** (2)

Table 1.

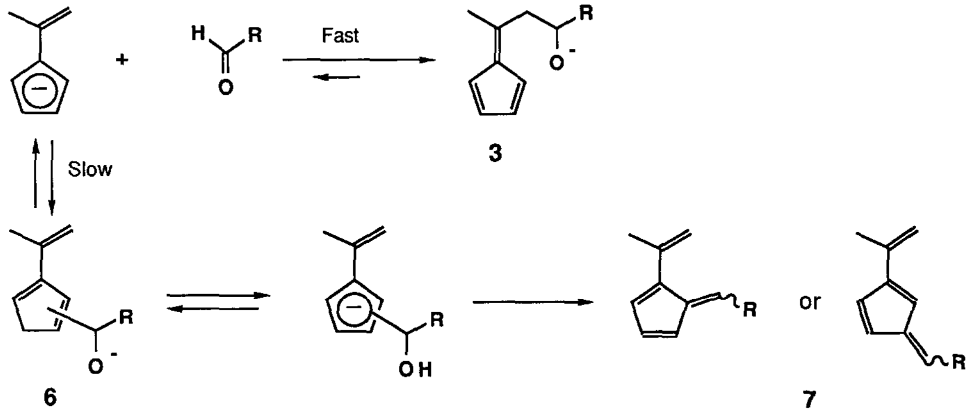
Aldehyde	**Product** [a,b]	**R**	**Yield (%)** [c]
Bensaldehyde	**5a**		76
Anisaldehyde	**5b**		76
p-Chloro-bensaldehyde	**5c**		82
p-Nitro-bensaldehyde	**5d**		57
Cyclohexane-carboxaldehyde	**4e** [d]		60

(a) For experimental procedure ,see text. (b) All new compounds gave satisfactory spectral data, NMR data of **5a** is given in the text. (c) Yields refer to pure compounds isolated by column chromatography (silica).
(d) The reaction time was 2h.

Typical experimental procedure. Preparation of 5a: Dimethylfulvene[5] (127 mg, 1.2 mmol) was added dropwise to a THF (4 mL) solution of LDA (from 1.3 mmol diisopropylamine and 1.2 mmol n-butyllithium in hexane) at -78°C under a nitrogen atmosphere. The yellow color of **1** disappeared in a few minutes resulting in a colorless solution of **2**, to which benzaldehyde (106 mg, 1.0 mmol) was added and a yellow color appeared immediatly. After stirring at -78°C for 0.5 h, trimethylsilyl choride (252 μL, 2 mmol) was added. The reaction mixture was stirred for further 5 h at -78°C, whereupon aqueous $NaHCO_3$ (sat., 2 mL) was added. The resulting mixture was extracted with ether (3x15 mL) and the combined organic phase was washed with aqueous $NaHCO_3$ (sat., 4 mL), aqueous NH_4Cl (sat., 4mL) and dried ($MgSO_4$). Concentration gave a crude product which was purified by flash chromatography on silica (hexanes:ethyl acetate 95:5) to give 224 mg (76%) of **5a** as a yellow oil. ^{1}HNMR($CDCl_3$, 400.1 MHz) 7.4-7.2 (5H, Ph), 6.50 (4H, br s, H2-H5), 4.89 (1H, dd, J=8.3 and 4.7 Hz, H8), 2.92 (1H, dd, J=13 and 8.3 Hz, one of H7), 2.82 (1H, dd, J=13 and 4.7 Hz, one of H7), 2.20 (3H, s, H7'), -0.02 (9H, s, Me_3Si); ^{13}CNMR($CDCl_3$, 100.6 MHz) 149.72(s), 144.78(s), 144.23(s), 130.76 and 130.65(two d, C3 and C4), 128.18(d), 127.23(d), 125.57(d), 120.89 and 120.48(two d, C2 and C5), 75.70(d, C8), 47.99(t, C7), 22.60(q, C7'), -0.21(q, Me_3Si).

If the initial reaction mixture is not quenched at low temperature the adduct **3** slowly and completely rearranges to condensation products between the cyclopentadienyl ring and the aldehyde, resulting in an isomeric mixture of isopropenyl substituted fulvenes **7**. This observation can be explained (scheme 1) by kinetically favored formation of adduct **3** which is in slow equilibrium with adduct **6** which in turn, after a proton shift irreversibly eliminates hydroxide to form the isolated fulvenes **7**. For the aromatic aldehydes the rearrangement is accompanied by drastic color change from an initial yellow to a deep purple reaction mixture.

Scheme 1.

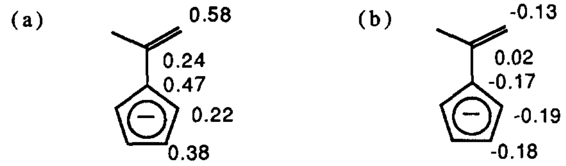


The regiochemical outcome for addition of electrophiles to a fulvene anion can be explained by HOMO-LUMO considerations. A simple Hückel calculation[10] on the anion **2** shows that the negative charge is highly concentrated to the cyclopentadienyl ring. This is confirmed by the ^{13}C NMR spectrum of **2** which shows a fully developed acyclic carbon-carbon double bond in the isopropenyl group.[11] On the other hand, the distribution of the HOMO over the π system shows a large coefficient on carbon 7, scheme 2. Thus, a charge controlled reaction between **2** and an electrophile would favor addition to the ring (compare the regiochemistry for adding the hard electrophiles H^+ and Me_3SiCl), but a frontier orbital controlled reaction would favor at carbon 7 which appears to be the kinetically favored process for a softer electrophile like an aldehyde.[12]

Scheme 2: Hückel calculation

a: coefficients for HOMO

b: charge distribution



To summarize, we have shown that aldehydes add to the exocyclic position on deprotonated dimethylfulvene at low temperature giving kinetic adducts which can be trapped at low temperature and isolated in synthetically useful yields. The regiochemical outcome from addition of electrophiles to fulvene anions depends on the nature of the electrophile and this work suggests that exocyclic additon is favored if the frontier orbitals are governing (soft electrophiles) the addition whereas a charged controlled reaction (hard electrophiles) will be favored at the cyclopentadienyl ring. Our ongoing work is concerned with studying reactions of fulvene anions with other types of electrophiles.

Acknowledgements. This work was supported by the Swedish Natural Science Foundation. Mr Tobias Rein is also acknowledged for valuable comments.

References and footnotes

1. Undergraduate research collaborator.
2. For reviews, see: (a) Yates, P. *Adv. Alicyclic Chem.* **1968**, *2*,59. (b) Neuenschwander, M. *Pure Appl. Chem.* **1986**, *58*, 55.
3. See for example: (a) Sternbach, D. D.; Hughes, J. W.; Burdi, D. F. *J. Org. Chem.* **1984**, *49*, 201. and (b) Antczak, K.; Kingston, J. F.; Fallis, A. G. *Tetrahedron Lett.* **1984**, *25*, 2077.
4. Knight, D. B.; Harrelson, J. H. *J. Chem. Soc., Chem. Commun.* **1987**, 116
5. Stone, K. J.;Little, R. L. *J. Org. Chem.* **1984**, *49*, 1849.
6. (a.) Hoffmann, H. M. R.; Koch, O. *J. Org. Chem.* **1986**, *51*, 2939 (b) Knight, D. B.; Hartless, R. L.; Jarvis, D. A. *ibid.* **1972**, *37*, 688.
7. Koshutin, V. I.; Koshutina, L. L.; Markov, V. I. *J. Gen. Chem. USSR* **1981**, *51*, 1430
8. Ziegler, K.; Crössman, F. *Liebigs Ann. Chem.* **1934**, *511*, 89.
9. Shanima, H.; Gianetti, J. P.; Henry, R. B.; Melbardis, A. *Tetrahedron* **1963**, *19*, 1409.
10. Hückel Molecular Orbital, program for Macintosh, © Farrel, J.J. and Addon, H.H., Franklin and Marshall College, PA 17604, USA.
11. ^{13}C NMR(100.6 MHz, THF-d_8) of **2**: 142.88 (s, C1 or C6), 121.14 (s, C1 or C6), 104.66 (d), 102.47 (d), 98.70 (t, C7), 22.98 (q, C8). The ^1H NMR spectrum has published elsewere: Macomber, D. W.; Hart, W. P.; Rausch, M. D. *J. Amer. Chem. Soc.* **1982**, *104*, 884.
12. In addition, we have found that methyl iodide, allyl chloride, and n-alkyl tosylates all gave sole ring addition products upon reaction with **2**.

(Received in UK 8 August 1988)