ChemComm

Unprecedented and novel hetero [6+3] cycloadditions of fulvene: a facile synthesis of the 11-oxasteroid framework

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Received (in Cambridge, UK) 24th August 1999, Accepted 9th September 1999

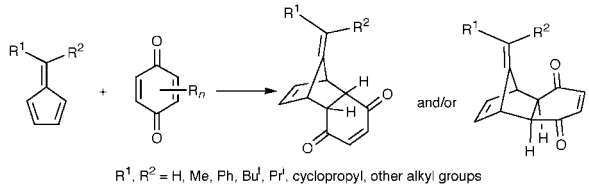
In contrast to the Diels–Alder reaction of fulvenes and benzoquinone, 6-dimethylaminofulvene reacts with benzoquinones to give the hetero [6+3] cycloaddition adduct, constituting an efficient and novel route to cyclopenta[*c*]-chromenes including 11-oxasteroids.

Fulvene and its derivatives have received a great deal of attention over the years.[1] Cycloadditions of fulvenes (*e.g.* [4+3],[2] [2+2],[3] [4+2],[4] [2+4],[5] [6+4],[6] [6+2][7]) provide general and powerful approaches to various polycyclic systems and natural products. We recently reported a new type of reaction: the [6+3] cycloaddition of fulvenes[8] for the facile synthesis of indane derivatives.[9] In conjunction with our continuing efforts in fulvene chemistry,[10] we have developed a novel hetero [6+3] cycloaddition of 6-dimethylaminofulvene[11] to benzoquinone that provides a series of cyclopenta[*c*]chromene derivatives. The latter constitute the basic skelton of biologically active 11-oxasteroids.

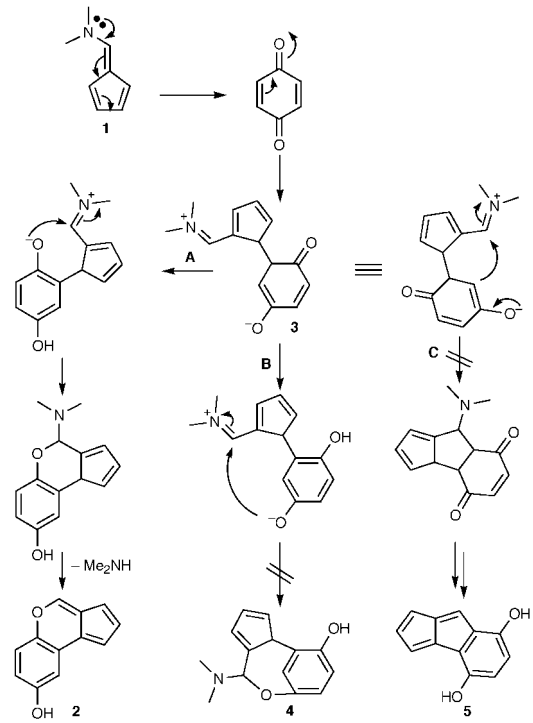
Fulvenes usually react with benzoquinones to give the [4+2] cycloaddition adducts (Scheme 1).[12] In contrast, we have found that reaction of the 6-dimethylaminofulvene **1** and benzoquinone results in the formation of the oxatricyclic product **2** (Scheme 2).[13] Syntheses of the cyclopenta[*c*]pyrans and cyclopenta[*c*]chromene have received a lot of attention.[14] To the best of our knowledge, this is the first example of the synthesis of the 3-oxa-bicyclo[4.3.0]nonane system *via* the [6+3] approach. Reaction of 6-dimethylaminofulvene and benzoquinone in benzene at 25 °C for 20 min provided the cyclopenta[*c*]chromene **2** in 65% yield as the only isolable adduct (entry 1, Table 1). The structure of **2** was assigned based on IR, ^{1}H and ^{13}C NMR, COSY, DEPT, HMQC, HMBC, MS and HRMS analyses.† This striking difference in the chemoselectivity of fulvene **1** *vs*. regular fulvenes may be attributed to an increase in the electron density of the 6-dimethylaminofulvene π-system. The formation of **2** may be rationalized *via* the following stepwise mechanism, shown in Scheme 2. Initial addition of **1** to benzoquinone generates the zwitterionic intermediate **3**, and tautomerization followed by loss of dimethylamine (path **A**) gives the hetero [6+3] product **2**. On the other hand, the direct cyclization of the hydroquinone intermediate (path **B**) is prohibited since it would lead to a highly strained and unstable product **4**. The reason why the pentalene product **5** does not form is not clear. This may be due to the HSAB principle, namely that *O*-alkylation (hard base) of the iminium salt (hard acid) is favored over the *C*-alkylation (soft base).

A series of homologous benzoquinones were also reacted with **1** to give the corresponding cyclic products **6**–**14** (entries 2–10, Table 1). Reaction of **1** with 1,4-naphthoquinone affords the adduct **13** (Table 1, entry 9), which constitutes the basic skeleton of the 11-oxasteroids. The synthesis and physiological activity of heterosteroids have received a lot of attention over the years.[15] In light of the physiological significance of the 11-oxoadrenocortical hormones, heterosteroids in which the methylene group at position 11 is replaced by a heteroatom are of special interest (Scheme 3).[16] For example, 11-oxaprogesterone **15** shows little progestational activity, but had significantly enhenced ovulation inhibitory activity. In addition, 11-oxaestradiol **16** shows extremely low estrogenic (uterotropic) activity but possesses antifertility activity.[17] The ratio of antifertility activity to estrogenic activity is *ca.* 10 times larger than estradiol. Many other 11-oxasteroids with antiandrogenic, corticoid and antiinflammatory activities have been reported.[18] However, the syntheses of oxasteroids reported so far are based on tedious transformation of available steroids (10–22 steps),[19] a serious bottleneck for the biological testing of 11-oxasteroids. Hydrogenation of **13** for 1 and 6 h affords **17** and **18**, respectively. As illustrated by the entries of Table 1, the combination of [6+3] cycloaddition followed by hydrogenation allows a rapid and efficient entry into the terahydropyran ring systems as well.

In summary, the hetero [6+3] cycloaddition provides a remarkably efficient route to the 3-oxabicyclo[4.3.0]nonane system. This method also establishes the experimental framework for a conceptually new approach to 11-oxasteroids. Further investigation of the scope of this hetero [6+3] cycloaddition as well as the application of this methodology to



Scheme 1



Scheme 2

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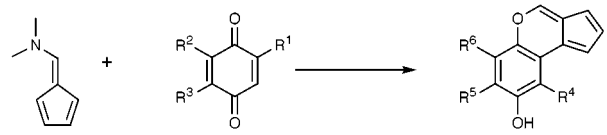
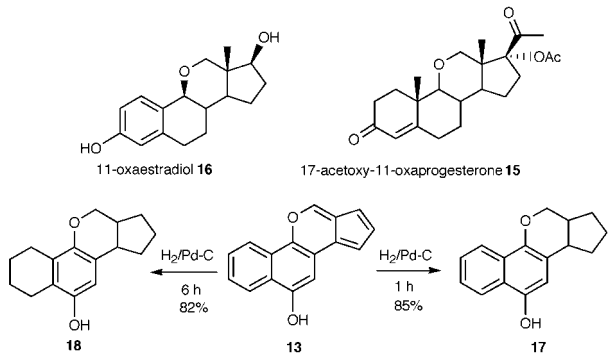
Table 1 Hetero [6+3] cycladdition of benzoquinones to fulvene



Entry	Benzoquinone R¹	R²	R³	Product	R⁴	R⁵	R⁶	Yield (%)[a]
1	H	H	H	**2**	H	H	H	65[b]
2	Me	H	H	**6a**	H	H	Me	82
				6b	H	Me	H	(2.1 : 1)
3	Me	H	Me	**7**	Me	H	Me	77
4	Me	Me	H	**8**	Me	Me	H	77
5	Cl	H	H	**9a**	H	Cl	H	86
				9b	H	H	Cl	(2.2 : 1 : 3.8)
				9c	Cl	H	H	
6	Cl	H	Cl	**10**	Cl	H	Cl	85
7	Cl	Cl	H	**11**	Cl	Cl	H	80
8	Br	H	Br	**12**	Br	H	Br	79
9	H	–CH=CHCH=CH–		**13**	H	–CH=CHCH=CH–		75
10	H	–CH=CHC(OH)=CH–		**14**	H	–CH=C(OH)CH=CH–		82

[a] Isolated yield based on starting fulvene. [b] Some of the products decomposed during the purification or after few hours at ambient temperature. However, protection of the alcohol as a benzoate (Et_3N, cat. DMAP, BzCl) in one pot before work up gave the stable benzoate of **2** in better yield (75%).



Scheme 3

the synthesis of various oxasteroids for biological studies are currently underway in our laboratories.

This research was supported by the National Science Council (NSC 88-2113-M-194-013) and National Chung Cheng University. The authors also thanks to Dr Sepehr Sarshar for valuable discussions.

Notes and references

† All new compounds gave satisfactory spectral and analytical data. Typical experimental procedure: To a solution of 6-dimethylaminofulvene **1** (ref. 20) (242.2 mg, 2 mmol) in dry benzene (3 ml) was added a solution of benzoquinone (259.2 mg, 2.4 mmol) in dry benzene (3 ml). The suspension was vigorously stirred for 20 min at 25 °C. The solution was concentrated *in vacuo* and the residue was purified by flash column chromatography with 8% EtOAc–hexane (R_f = 0.30 in 10% EtOAc–hexane) to give **2** as a yellow solid (239.2 mg, 65% yield). ν_{max}(neat)/cm^{-1} 3300–3000, 2930, 1627, 1470, 1359, 1194, 1092, 816, 738; δ_H(DMSO-d_6, 400 MHz) 6.77–6.78 (dd, *J* 4.5, 0.8, 1 H), 6.85–6.88 (m, 2 H), 7.00–7.02 (dd, *J* 4.6, 2.5, 1 H), 7.32–7.33 (d, *J* 2.8, 1 H), 7.50-7.52 (d, *J* 9, 1 H), 8.64 (s, 1 H); δ_C(DMSO-d_6, 100 MHz) 106.85 (CH), 110.81 (CH), 113.11 (CH), 115.43 (CH), 119.22 (CH), 121.25 (C), 123.29 (C), 123.64 (C), 131.96 (CH), 141.37 (C), 147.54 (CH), 154.91 (C); *m/z* 184 (M^+, 100), 155 (13), 128 (17), 127 (14), 92 (17), 77 (10), 63 (15), 51 (21) [calc. for $C_{12}H_8O_2$ (M^+): 184.0524; found 184.0521].

1 For a recent review on fulvene chemistry, see: M. Neuenschwander, in *The Chemistry of Double-Bonded Functional Groups*, ed. S. Patai, Wiley, Chichester, 1989, vol. 2, p. 1131.
2 D. I. Rawson, B. K. Carpenter and H. R. Hoffmann, *J. Am. Chem. Soc.*, 1979, **101**, 1786; R. Noyori, Y. Hayakawa, H. Takaya, S. Murai, R. Kobayashi and N. Sonoda, *J. Am. Chem. Soc.*, 1978, **100**, 1759.
3 K. Imafuku and K. Arai, *Synthesis*, 1989, 501; L. A. Paquette, J. A. Colapret and D. R. Andrews, *J. Org. Chem.*, 1985, **50**, 201.
4 M. Harre, P. Raddatz, R. Walenta and E. Winterfeldt, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 480; R. Gleiter and O. Borzyk, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1001.
5 Y. Himeda, H. Yamataka, I. Ueda and M. Hatanaka, *J. Org. Chem.*, 1997, **62**, 6529; V. Nair, A. G. Nair, K. V. Radhakrishnan, M. V. Nadakumar and N. P. Rath, *Synlett*, 1997, 767.
6 Y. N. Gupta, M. J. Doa and K. N. Houk, *J. Am. Chem. Soc.*, 1982, **104**, 7336; Z.-I. Yoshida, M. Shibata, E. Ogino and T. Sugimoto, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 60.
7 M. Suda and K. Hafner, *Tetrahedron Lett.*, 1977, 2453; T. C. Wu and K. N. Houk, *J. Am. Chem. Soc.*, 1985, **107**, 5308.
8 B.-C. Hong, S.-S. Sun and Y.-C. Tsai, *J. Org. Chem.*, 1997, **62**, 7717.
9 For a recent review in the synthesis of indan systems, see: B.-C. Hong and S. Sarshar, *Org. Prep. Proced. Int.*, 1999, **31**, 1.
10 For previous papers in this series, see: B.-C. Hong, Z.-Y, Chen and E. S. Kumar, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1135; B.-C. Hong and J.-H. Hong, *Tetrahedron Lett.*, 1997, **38**, 255; B.-C. Hong and S.-S. Sun, *Chem. Commun.*, 1996, 937.
11 For the other types of reactions of 6-aminofulvene, see: D. Mukherjee, L. C. Dunn and K. N. Houk, *J. Am. Chem. Soc.*, 1979, **101**, 251; T. Ishizu, M. Mori and K. Kanematsu, *J. Org. Chem.*, 1981, **46**, 526.
12 A. G. Griesbeck, K. Peters, E.-M. Peters and H. G. Schnering, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 803; G. Mehta, S. H. K. Reddy and S. Padma, *Tetrahedron*, 1991, **47**, 7821.
13 This skeleton is present in many natural products, see: F. A. Davis and B.-C. Chen, *J. Org. Chem.*, 1993, **58**, 1751; A. Arnoldi, A. Bassoli, G. Borgonovo and L. Merlini, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2447.
14 These skeletons occur widely in many natural products, see: K. Shimano, Y. Ge, K. Sakaguchi and S. Isoe, *Tetrahedron Lett.*, 1996, **37**, 2253; J.-L. Brayer, J.-P. Alazard and C. Thal, *Chem. Commun.*, 1983, 257; K. C. Joshi, P. Singh, S. Taneja, P. J. Cox, R. A. Howie and R. H. Thomson, *Tetrahedron*, 1983, **38**, 2703.
15 R. C. Rastogi, M. N. R. Chowdhury and C. R. Engel, *Steroids*, 1973, **21**, 147.
16 H. Suginome, S. Yamada and J. B. Wang, *J. Org. Chem.*, 1990, **55**, 2170; K. Hildebrandt, T. Debaerdemaeker and W. Friedrichsen, *Tetrahedron Lett.*, 1988, **29**, 2045.
17 C. R. Engel, I. H. Ibrahim, D. Mukherjee, R. Szöghy and V. S. Salvi, *Heterocycles*, 1989, **28**, 905.
18 S. Takegawa, N. Koizumi, M. Mieda and K. Shibata, *Chem. Pharm. Bull.*, 1996, **44**, 746; A. Planas, N. Sala and J.-J. Bonet, *Helv. Chim. Acta*, 1989, **72**, 725; H. Suginome and J. B. Wang, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 193.
19 C. R. Engel, S. Salvi and M. N. R. Chowdhury, *Steroids*, 1975, **25**, 781.
20 For the preparation of 6-dimethylaminofulvene, see: K. Hafner, K. H. Vopel, G. Ploss and C. Konig, *Liebigs. Ann. Chem.*, 1963, **661**, 52.

Communication 9/06877E