COMMUNICATION

Unprecedented oxidative addition of α-halo acyl halides to 6,6-dialkoxyfulvene

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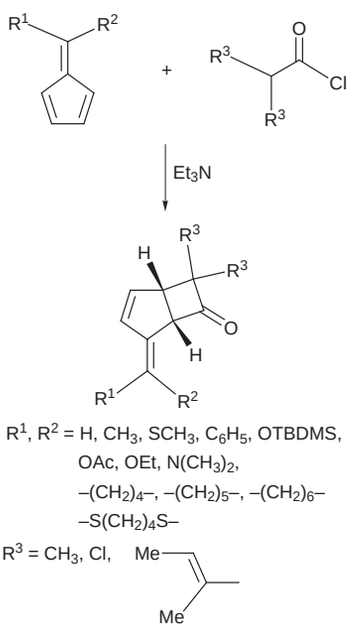
In contrast to the [2 + 2] cycloaddition of fulvenes and ketenes, fulveneketene acetal, 2-cyclopentadienylidene-1,3-dioxolane, reacts with α-halo acyl halides to give various C-1 substituted fulvenes that constitute an important class of intermediates for organic synthesis.

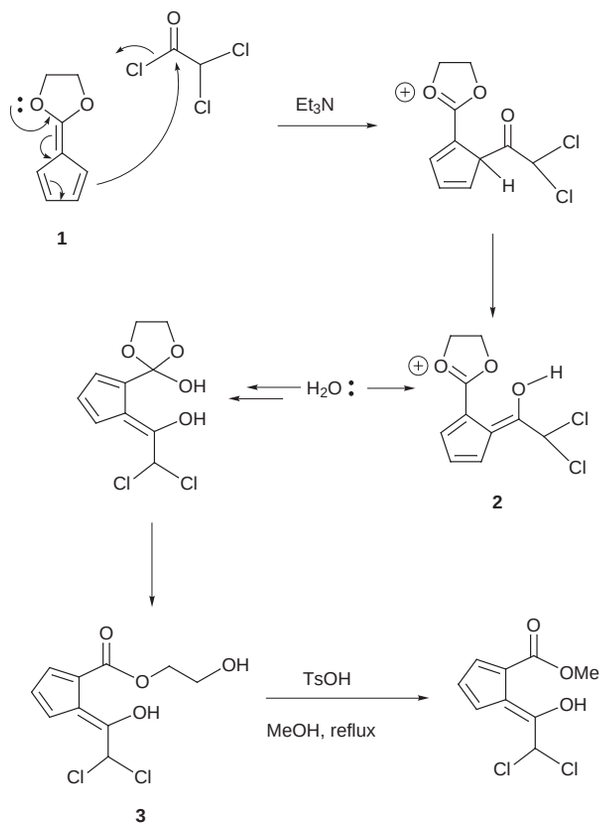
Fulvenes and their derivatives have received a great deal of attention over the years.[1] The [2 + 2] cycloaddition of α-chloroketenes to fulvenes is a general and powerful approach to the synthesis of various polycyclic systems (Scheme 1).[2,3] Amongst



Scheme 1

others, the [2 + 2] reaction adduct has been applied to the synthesis of ophiobolin, filifolone, chrysanthemic acid and thienamycin analogs, *etc.* In conjunction with our continuing interest in the chemistry of fulvenes,[4] we have developed a novel oxidative addition of α-haloacetyl chloride to fulveneketene acetal that provides a series of C-1 substituted fulvene derivatives.[5] Herein we describe the first example of the oxidative addition of α-chloroacetyl chloride to fulveneketene acetal.

Fulvene usually reacts with ketene to give [2 + 2] cycloaddition products. In contrast, we have found that generation of dichloroketene in the presence of fulvene **1** and triethylamine results in the formation of the fulvene **3** (Scheme 2).[6] Although the benzoylation of cyclopentadienide has been reported to afford a mixture of 1-benzoyl-6-hydroxy-6-phenylfulvenes in medium yield,[7] a practical synthesis of 1-carboxy-6-hydroxyfulvene has never been realized. In our hands, addition of a benzene solution of 2,2-dichloroacetyl chloride to a mixture of 6,6-dialkoxyfulvene **1** and Et_3N in benzene at 25 °C for 1 h provided the fulvene **3** in 90% yield as the only detectable

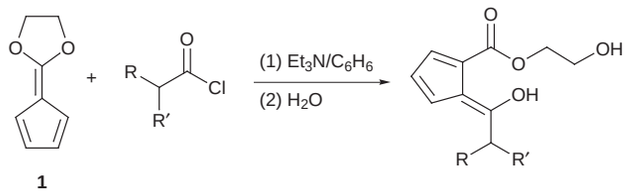


Scheme 2

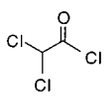
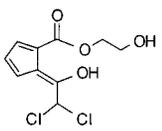
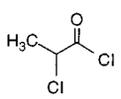
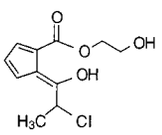
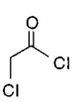
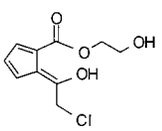
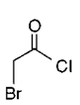
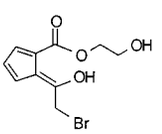
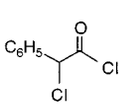
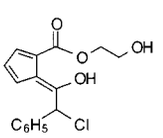
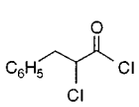
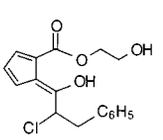
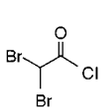
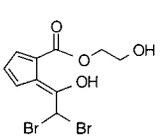
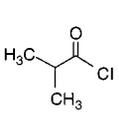
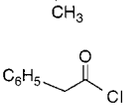
adduct (entry 1, Table 1). The structure of **3** was assigned based on ^1H, ^{13}C NMR, COSY, DEPT, HMQC, HMBC, INEPT-INADEQUATE, MS and elemental analysis.† This striking difference in the chemoselectivity of fulvene **1** *versus* regular fulvenes may be attributed to an increase in the electron density of the 6,6-dialkoxyfulvene π-system. The formation of **3** may be rationalized *via* the following stepwise mechanism: initial addition of the acyl chloride to C-1 of the fulvene affords the reactive acylated intermediate **2**. Subsequent addition of H_2O during work-up and isomerization gives **3** (Scheme 2). Ester exchange in compound **3** (TsOH, refluxing MeOH) provided the corresponding fulvene methyl ester.

Reaction of a series of homologous acyl chlorides with **1** gave the corresponding adducts **4**–**9** (entries 2–7, Table 1). Unfortunately, **1** did not react with acid chlorides that lack an α-substituted electron-withdrawing group (entries 8–9, Table 1).‡ This may be due to the lower electrophilicity of the acyl group, which would in turn disfavor the first addition step. Hydrogenation of **4** to the keto ester **10** followed by transesterification provided the known volatile methyl ester **11**, an intermediate in the synthesis of the carbocyclic analogs of captopril (Scheme 3).[8] Thus, as illustrated by the entries of Table 1, this new sequential addition reaction allows an efficient

Table 1 Oxidative addition of α-halo acyl halides to fulvene



1

Entry	Acyl halides	Product		Yields (%)[a]
1			**3**	90
2			**4**	89
3			**5**	80
4			**6**	72
5			**7**	74
6			**8**	72
7			**9**	86
8		NR		~0[b]
9		NR		~0[b]

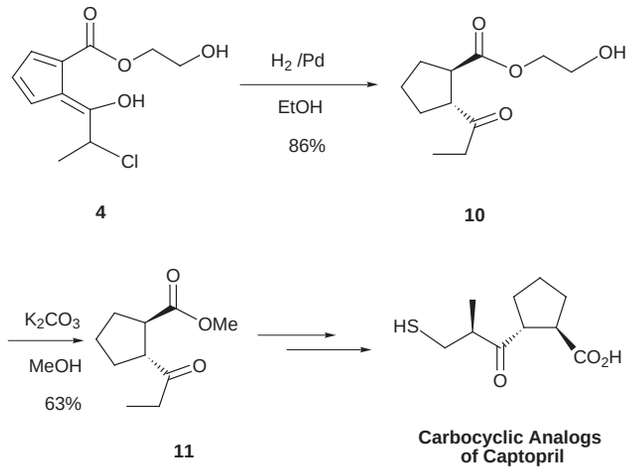
[a] Isolated yield based on starting fulvene. [b] No reaction at ambient temperature after 72 h. Only a small amount of products (less than 5%) was found under reflux conditions after 72 h.

entry into C-1 substituted fulvene derivatives. This method establishes the experimental framework for a conceptually new approach to such systems.

Experimental

General procedure for the oxidative addition

To a mixture of fulveneketene acetal **1** (272 mg, 2 mmol) and Et_3N (2 mL, 14.3 mmol) in dry benzene (15 mL) was added dichloroacetyl chloride (0.2 mL, 2.1 mmol). The suspension was vigorously stirred for 1 h at 25 °C. The solution was concentrated *in vacuo* and the residue was purified by flash column chromatography with 20% EtOAc–hexane (R_f 0.53 in 50% EtOAc–hexane) to give **3** as a yellow solid (443 mg, 90% yield); ^{1}H NMR (d_6-acetone, 400 MHz): δ_H 3.85–3.95 (m, 2 H), 4.40–4.50 (m, 2 H), 6.49 (dd, J = 5, 3 Hz, 1 H), 7.42 (dd, J = 5, 1.6 Hz, 1 H), 7.62 (s, 1 H), 7.68 (dd, J = 3, 1.6 Hz, 1 H), 16.09 (br s, 1 H); ^{13}C NMR (d_6-acetone, 125 MHz): δ_C 61.12 (CH_2), 67.83 (CH), 69.47 (CH_2), 118.13 (C), 121.40 (C), 125.96 (CH), 131.09 (CH), 143.93 (CH), 165.75 (C), 170.80 (C); MS (*m*/*z*, relative intensity): 268 (M^+ + 4, 3%), 266 (M^+ + 2, 12), 264 (M^+, 17), 204 (39), 202 (60), 181 (30), 163 (22), 139 (70), 119 (100); exact mass calc. for $C_{10}H_{10}O_4Cl_2$ (M^+): 263.9957; found 263.9941. Anal. Calc. for $C_{10}H_{10}O_4Cl_2$: C, 45.31; H, 3.80; O, 24.14, found C, 45.49; H, 3.78; O, 24.28%.



4 **10** **11**

Scheme 3

Acknowledgements

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Notes and references

† All new compounds gave satisfactory spectral and analytical data.
‡ Dimethylketene, generated *in situ* from isobutyl chloride and Et_3N, reacted with 6,6-dimethylfulvene, 6,6-diphenylfulvene, 6-ethoxyfulvene and 6,6-dimercaptofulvene to give the [2 + 2] adducts, see refs. 2 and 3.

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