Addition of a Twisted Diacylketene Aminal to Dimethyl Acetylenedicarboxylate. A New Spirocyclic System

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Two products have been isolated from the reaction of the ketene aminal **8** with dimethyl acetylenedicarboxylate (DMAD) in boiling xylene. A 1:1 adduct with the spiro structure **9** was obtained in 75 % yield, formed by addition of the $^{-}O-C=C-C^{+}$ unit to DMAD. Another product (**11**) formed in low yield was found to be a 1:2 adduct of *N,N'*-dimethylethylenediamine and DMAD. The structures of the products were determined by use of 2D NMR and NOE techniques; that of **9** was also confirmed by partial hydrolysis to a 4-pyrone derivative, and that of **11** by independent synthesis.

In other works[1–3] we have studied the addition of 2-thioacylketene aminals derived from 5,5-dimethylcyclohexane-1,3-dione (dimedone) (**1** and **3**, Scheme 1) to dimethyl acetylenedicarboxylate (DMAD). Owing to steric effects, **1** and **3** are strongly twisted about the double bond[4,5] and are best described as betaines (**1a**, **3a**). Consequently they are 1,4-dipoles with a thiolate sulfur as the negative and an amidinium carbon as the positive pole, and they add to DMAD with formation of the spiro compounds **2** and **5a** and **5b**. The compounds are probably formed with the unobserved compounds **4** as intermediate. The structures of **5a** and **5b** have been confirmed by X-ray crystallography.[3]

It was considered of interest to explore the same reaction with the much less nucleophilic oxygen analogue of **3**, viz. **6** (Scheme 2). While the reaction of **1** and **3** with DMAD was complete within a few hours at room temperature, no reaction occurred when a 1:2 mixture of **6** and DMAD in dichloromethane was refluxed for seven days. However, when the reaction was performed in boiling xylene, all DMAD was consumed within 48 h. Work-up of the reaction mixture by flash chromatography[6] gave 35 % unchanged **6** together with two crystalline products in yields of 75 % and < 5 % (based on consumed **6**). The major products has the empirical formula $C_{19}H_{26}N_2O_6$, i.e. it is a 1:1 adduct of **6** and DMAD, whereas the minor one, $C_{16}H_{24}N_2O_8$, is formally derived from *N,N'*-dimethylethylenediamine and DMAD in the ratio 1:2.

The ^1H NMR spectrum of the major product (Fig. 1 and Scheme 3) is in agreement with that expected for the spiro structure **7** formed in a [2+4] cycloaddition of the $^{-}O-C=C-C^{+}$ dipole in **6** to DMAD. The *C*-methyl groups give one singlet as do the *N*-methyl groups, the dimedone methylene groups give one singlet each, and the imidazolidine methylenes give an AA'BB' spectrum, indicating two equivalent CH_2 groups with non-equivalent protons. The ^{13}C NMR spectrum (Fig. 1 and Scheme 3) is also in agreement with the spiro structure **7** with the imidazolidine ring perpendicular to and bisected by the dimedone ring plane. The chemical shift for the spiro carbon atom, 77.36 ppm, corresponds well with those found for **2** and **5**.[2,3] A complete assignment of the ^1H and ^{13}C chemical shifts (Scheme 3) was made by use of the 2D NMR technique and with the aid of the DEPT pulse sequence.[7] The one-bond couplings were established by HETCOR experiments,[8–10] and the long-range $^1H-^{13}C$ couplings shown in Fig. 2 were found through a COLOC experiment.[11] The correlation peaks show the connectivities outlined in Fig. 1 together with the one-bond couplings in the methyl and methylene groups. The absence of correlations between the quaternary carbon resonance at 31.8 ppm and the proton resonances at 2.28 and 2.54 ppm may be due to unfavourable values of the coupling constants in the COLOC experiment optimized for a 7 Hz coupling. C-2, C-3 and C-10 were assigned based on the shifts for the structurally analogous C-8a, C-4a and C-5.

The IR spectrum of **7** shows strong bands at 1735 and 1680 cm^{-1}, corresponding to ester and keto carbonyl stretching modes, and at 1653 and 1614 cm^{-1}, corresponding to C=C bond stretching modes.

Brief reflux of **7** in aqueous, methanolic HCl led to a complicated product mixture, from which only the 4-pyrone **8a** could be isolated in low yield (ca. 4 %) by chromatography. This reaction is analogous to the hydrolysis of the aminal function in the spiro compounds **2** and **5**, which leads to thiopyrones.[2,3] The structure of **8a**

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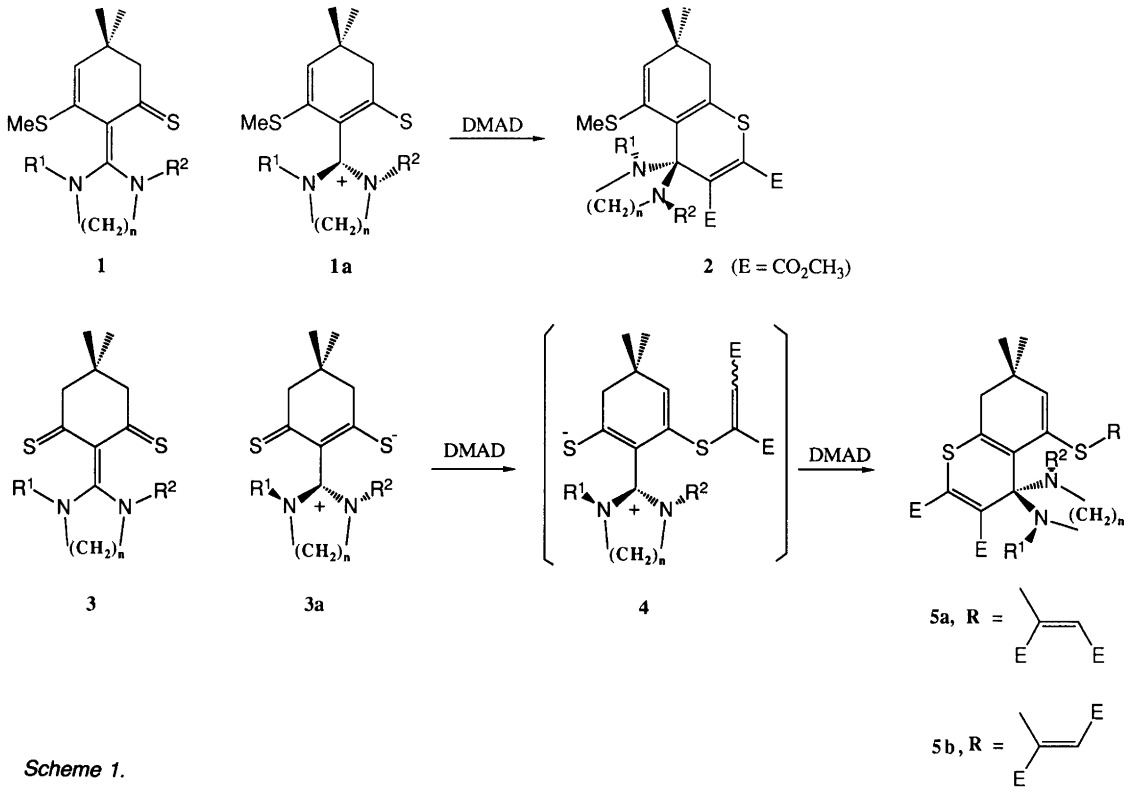
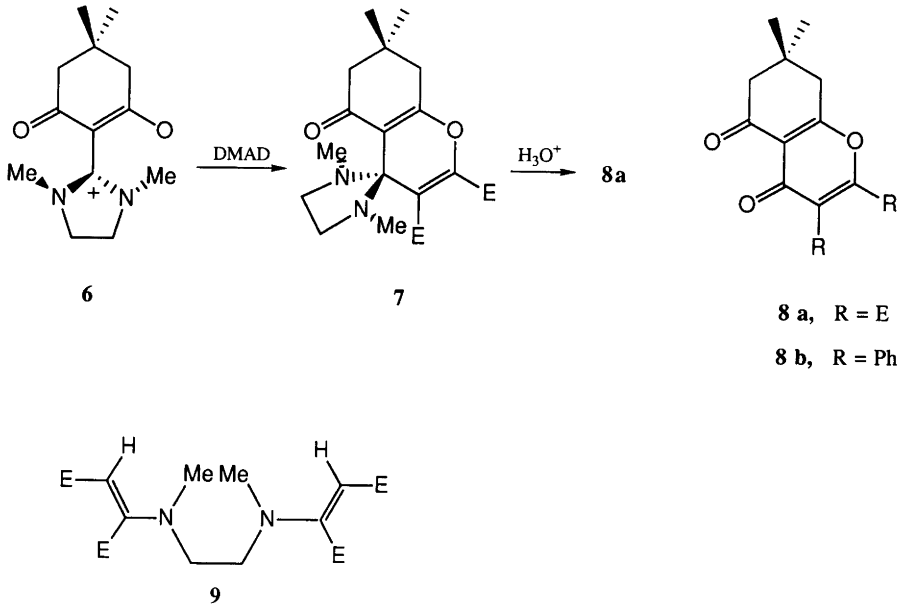


1 1a 2 (E = CO_2CH_3)

3 3a 4

Scheme 1.



6 7 **8a**

8 a, R = E

8 b, R = Ph

9

Scheme 2.

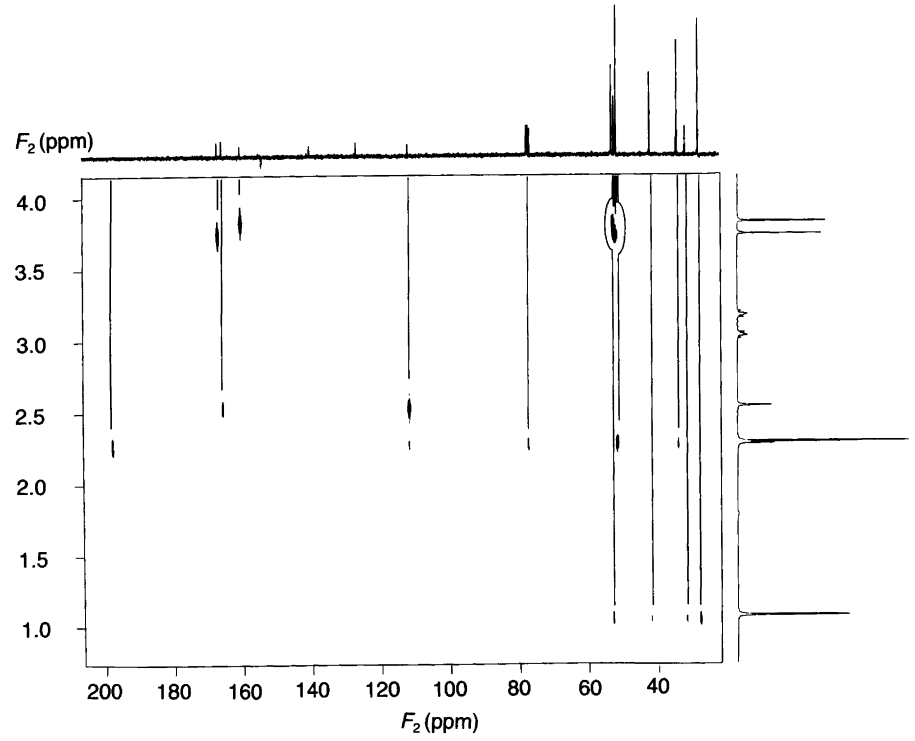


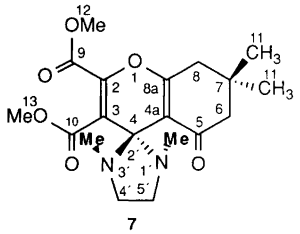
Fig. 1. ^1H (F_1) and ^{13}C (F_2) 2D spectrum of **7** in $CDCl_3$ solution, based on COLOC experiments. The connectivities are shown both for one-bond and long-range couplings.

follows from its ^1H and ^{13}C NMR spectra (see the Experimental section) and from its IR spectrum, which shows carbonyl bands at 1740 and 1700 cm^{-1} and 4-pyrone bands at 1645 and 1576 cm^{-1}.

The formation of **7** is probably a stepwise process with the addition of the enolate oxygen to DMAD as the first step. A somewhat analogous reaction is found in the addition of a dimethylselenio betaine derived from dimedone to 2,3-diphenylcyclopropenone.[12] The dimedone betaine gives both O and C addition, and in both cases dimethyl selenide is eliminated in subsequent steps with formation of bicyclic systems. The main product of O-addition is the 4-pyrone **8b**, and the IR bands reported at 1726, 1698, 1613 and 1550 cm^{-1} are in reasonable agreement with those found for **8a**.

The spectral data found for the minor product formed in the reaction of **6** with DMAD (see the Experimental section) support the structure **9**, which was confirmed by the

Atom	^{13}C	^1H
2	140.12	
3	126.64	
4	77.36	
4a	111.83	
5	197.50	
6	52.91	2.28
7	31.82	
8	41.98	2.54
8a	165.72	
9	167.01	
9-OMe	52.25	3.73
10	160.36	
10-OMe	52.87	3.82
11	28.00	1.07
4',5'	51.60	ca. 3.0, ca. 3.2
NCH_3	34.17	2.29



7

Scheme 3.

formation of the same compound in 84 % yield on the reaction of DMAD with *N,N'*-dimethylethylenediamine in boiling toluene. The configurations at the double bonds are the same and were confirmed as being *E* by an NOE difference experiment. The *N*-methyl resonance at 2.84 ppm was saturated, and a difference spectrum obtained with a reference irradiation (see the Experimental section) showed an NOE enhancement of the vinylic proton resonance at 4.61 ppm of 8 %. This was expected, since the most stable configuration of push–pull ethylenes have the donor and the acceptor group in a *trans* relationship.[13] The mechanism for the formation of **9** is not clear, but it is unlikely that **7** is hydrolysed during the reaction, since water is carefully excluded in the starting system. Small amounts of **9** have also been isolated in chromatography of the reaction mixture from **3** and DMAD, and it appears to be formed in a formal elimination of *N,N'*-dimethylethylenediamine from a 1:2 adduct of **3** and DMAD, involving addition of two more molecules of DMAD.[14] It is possible that a similar reaction sequence is responsible for the formation of **9** in the present case, although no other products from this sequence have been isolated.

Experimental

The preparation of **6** has been reported previously.[15] A solution of **6** (0.96 g) and DMAD (1.16 g) in dry xylene (50 ml) was refluxed under argon until, after 48 h, all DMAD had been consumed (TLC). Flash chromatography[6] on silica (Merck 60) with hexane and increasing concentration of ethyl acetate eluted unchanged **6** (0.34 g), **7** (0.74 g), and **9** (0.045 g). *2,3-Bis(methoxycarbonyl)-1',3',7,7-tetramethyl-5-oxo-5,6,7,8-tetrahydro-*4H*-benzo-*

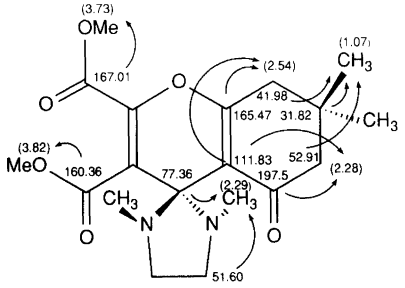


Fig. 2. Long-range $^{1}H-^{13}C$ couplings in **7** observed with a modified COLOC experiment.

[b]*pyran-4-spiro-2'-imidazolidine* (**7**) was obtained as light orange prisms, m.p. 112–113 °C after recrystallization from toluene–petroleum ether. MS [CI-NH_3, *m/z* (% rel. intensity)]: 379 (M^++1, 100), UV [λ_{max} nm (ε)]: 312 (1800), 265 (5500), 215 (15700).

A solution of **7** (0.15 g) in methanol (20 ml), conc. HCl (0.1 ml) and water (4 ml) was refluxed for 10 min and then rapidly cooled, quenched with sodium acetate (4 g), concentrated to 12 % of the original volume and extracted with dichloromethane. Flash chromatography of the extract as above gave *2,3-bis(methoxycarbonyl)-7,7-dimethyl-4,5-dioxo-5,6,7,8-tetrahydro-*4H-*benzo*[b]*pyran* (**8a**, 0.005 g) as a reddish, semisolid mass. ^{1}H NMR (300 MHz, $CDCl_3$): 1.16 (s, 6 H), 2.45 (s, 2 H), 2.84 (s, 2 H), 3.92 (s, 3 H), 3.96 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): 28.1 (2 CH_3), 31.9 (C), 42.3 (CH_2), 52.1 (CH_3OCO), 53.3 (CH_3OCO), 54.0 (CH_2), 119.4 (C), 122.8 (C), 130.9 (C), 147.5 (C), 159.0 (CH_3OCO), 162.4 (CH_3OCO), 176.0 (CO), 192.2 (CO). MS (CI-NH_3): 326 (M^+ + 18, 100), 309 (M^+ + 1, 100). UV: 251 (shoulder, 5500), 212 (13300).

N,N'-*Dimethyl*-N,N'-*bis-[1,2-bis(methoxycarbonyl)vinyl]-ethylenediamine* (**9**). A solution of DMAD (3.55 g) in dry toluene (50 ml) was added dropwise with stirring under nitrogen to a solution of *N,N'*-dimethylethylenediamine (1.10 g) in dry toluene (50 ml). The following day, 3.11 g of **11** had separated, colourless crystals, m.p. 181–183 °C after recrystallization from toluene–heptane. Concentration of the mother liquor gave a further 0.8 g of less pure product. The pure product had the same spectral properties (IR, NMR) as that isolated in the original reaction. ^{1}H NMR (300 MHz, $CDCl_3$): 2.84 (s, 6 H), 3.30 (s, 4 H), 3.64 (s, 6 H), 3.94 (s, 6 H), 4.61 (s, 2 H). ^{13}C NMR (300 MHz, $CDCl_3$): 38.4 (CH_3–N), 50.9 (CH_2), 51.0, 53.2 (CH_3OCO), 85.7 (=CH), 154.2 (C=CH), 165.8, 167.8 (CH_3OCO). MS (70 eV): 372 (M^+, 1), 341 (2), 313 (4), 281 (3), 228 (6), 199 (10), 186 (100), 140 (14), 82 (100), 59 (22), 45 (100). MS (CI-NH_3): 373 (M^+ + 1, 100), 317 (17), 266 (22), 231 (57), 199 (48), 160 (57). UV: 287 (33800), 238 (5700). IR (KBr): 3000, 2945, 1736, 1690, 1572 (broad, strong), 1475, 1451, 1433, 1438, 1418, 1370 cm^{-1}.

^{1}H and ^{13}C NMR spectra. These were recorded with a Varian Model XL-300 NMR spectrometer. For the 2D NMR experiments **7** (25 mg) was dissolved in $CDCl_3$ (0.7 ml), and the experiments were run at 24 °C. The HETCOR experiments were optimized for $^{1}J_{CH} = 140$ Hz and decoupled in the F_1 dimension. In one experiment the spectral range in the F_2 dimension was 14451 Hz on 2048 complex data points and 1114 Hz in F_1 to cover the entire spectra. In order to differentiate between the carbon resonances at 52.87 and 52.91 ppm, one experiment was performed with a reduced spectral width of 3748 Hz in F_2, covering the high-field part of the ^{13}C resonances, sampled on 2048 complex data points, and with F_1 as above.

The modified COLOC experiment was optimized for $^{1}J_{CH} = 140$ Hz and $^{n}J_{CH} = 7$ Hz ($n = 2$–4) with magnetization-transfer delay calculated according to: $\Delta_1 = 0.5\ {}^{n}J_{CH}^{-1}$ and $\Delta_2 = [0.667 \times \Delta_1/2] - [0.5\ {}^{1}J_{CH}^{-1}]$. Full spectral ranges of 14451 Hz and 1114 Hz in the F_2 and F_1 dimensions, respectively, were used, and 128 repetitions of 64 × 2K complex data points were collected. An acquisition time of 70.9 ms and a relaxation delay of 2 s resulted in a total experiment time of 4 h and 50 min. A mild pseudo-echo-shaped weighting function was used in both dimensions before transformation into a 128 × 2K data matrix.

The NOE difference experiment was performed through irradiation at the *N*-methyl resonance and 200 Hz upfield for the reference spectrum. Irradiation was applied for 20 s before the read pulse and acquisition.

UV spectra were recorded with a Cary Model 2290 spectrophotometer, IR spectra with a Perkin Elmer Model 298 spectrophotometer, and mass spectra with Finnigan 4021 and Jeol SX-102 mass spectrometers.

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