Improved Procedure for Functionalized 3,3-Dimethoxycyclobutenes: Useful Intermediates in Organic Synthesis

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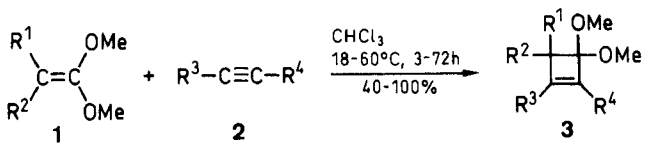
The [2+2] cycloaddition of the 1,1-dimethoxyalkenes **1** and the electron-poor alkynes **2** in dry chloroform affords the functionalized 3,3-dimethoxycyclobutenes **3** in good to excellent yields (40–100%). The latter by electrocyclic ring opening give the dienes **4**, starting materials to multifunctional compounds such as the esters **5** and the cyclohexenes **6**.

Four-membered carbocycles represent excellent tools in organic synthesis.[1] In particular, the 3,3-dialkoxycyclobutenes can be considered as synthetic precursors to naturally occurring products and biologically active compounds.[2] However, 3,3-dialkoxycyclobutenes, other than the halogen derivatives prepared by nucleophilic substitution of polyhalogenated cyclobutenes,[3] had been obtained only occasionally[4] before our work on the mechanism of the reaction between some 1,1-dimethoxyalkenes and acetylenic esters.[5] During this mechanistic work, we observed that in the first stage of the reaction 1,4-dipolar intermediates are formed which successively cyclize into the functionalized 3,3-dimethoxycyclobutenes. However when hydrogen is present on the acetylenic partner, the latter partly traps the intermediate and the cyclobutene is formed only in low yield. In all other cases the yield of cyclobutene is moderate.[5] Therefore, it was desirable to find the best reaction conditions to obtain functionalized 3,3-dimethoxycyclobutenes selectively and with higher yields and to evaluate the range of applicability of the synthetic method.

We now report that when the reaction of the alkenes **1** and the electron-poor alkynes **2** (Scheme 1) is carried out in dry chloroform using a molar ratio of **1**:**2** = 2:1 at the reaction temperatures and for the times reported in Table 1, the cyclobutenes **3** are obtained in high yields and selectively; the trapping products under these conditions are not formed. As shown in Table 1, the reaction has wide applicability. However, in contrast to the alkenes **1a–d** which are mono- and unsubstituted at C-2, the disubstituted alkene **1f** reacts only with the butynone **2d** to give **3m** with the lowest yields of the series, while, with the least reactive alkyne **2c** and the most sterically hindered ones **2a** and **2b**, the reaction is too slow and alkene polymerization occurs to a large extent.[6] The lower reactivity of **1f**, also observed in other cycloadditions,[7,8] is due partly to a more symmetrical π-electron distribution and partly to more steric hindrance.[9] It is noteworthy that when the 2-phenyl substituted alkene **1e** is allowed to react with the alkyne **2a**, the diene **4c** is the sole product even if the reaction is carried out at $-10\,^{\circ}C$.[10] On the basis of the behaviour reported below of the cyclobutenes **3a,d**, it is evident that the cyclobutene **3l** undergoes a very rapid electrocyclic ring opening to the diene **4c**, as the latter has a greater resonance stabilization. All attempts to use electron-poor alkynes less reactive than **2** such as methyl 2-butynoate or methyl phenylpropiolate failed even in the presence of a Lewis acid, such as zinc chloride, which bonds to the carbonyl oxygen and lowers the LUMO energy of the electron-poor alkynes.[11] Under the influence of the catalyst, only polymerization of the alkene **1** occurs.

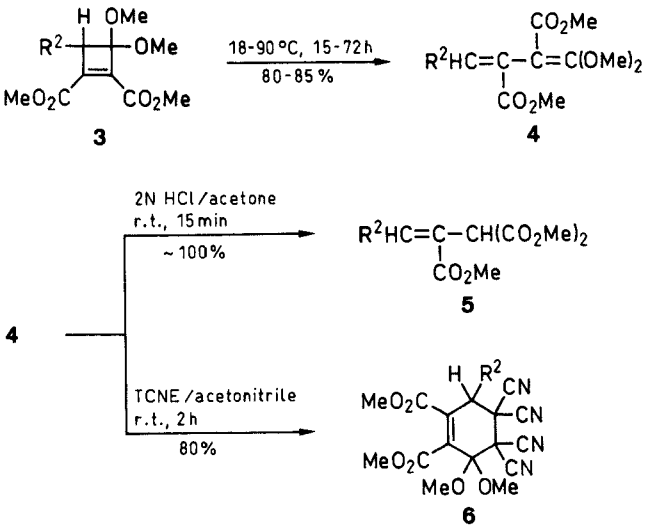
Compounds **3**, except **3l**, are stable under the reaction conditions but at higher temperatures undergo easy electrocyclic ring opening to functionalized 1,1-dimethoxyalka-1,3-dienes **4**, starting materials for multifunctional



1	R^1	R^2	2	R^3	R^4
a	H	H	a	CO_2Me	CO_2Me
b	H	Me	b	COPh	COPh
c	H	Et	c	H	CO_2Me
d	H	CH_2CO_2Et	d	H	COMe
e	H	Ph			
f	Me	Me			

3	R^1	R^2	R^3	R^4	3	R^1	R^2	R^3	R^4
a	H	H	CO_2Me	CO_2Me	h	H	Et	CO_2Me	CO_2Me
b	H	H	COPh	COPh	i	H	Et	H	CO_2Me
c	H	H	H	CO_2Me	j	H	Et	H	COMe
d	H	Me	CO_2Me	CO_2Me	k	H	CH_2CO_2Et	CO_2Me	CO_2Me
e	H	Me	COPh	COPh	l	H	Ph	CO_2Me	CO_2Me
f	H	Me	H	CO_2Me	m	Me	Me	H	COMe
g	H	Me	H	COMe					

Scheme 1



3	R^2	4-5	R^2	6	R^2
a	H	a	H	a	Me
d	Me	b	Me	b	Ph
l	Ph	c	Ph		

Scheme 2

Table 1. 3,3-Dimethoxycyclobutenes **3** Prepared[a]

Product[b]	Temp. (°C)/ Time (h)	Yield[c] (%)	IR ($CHCl_3$) ν (cm^{-1})	H^1 NMR ($CDCl_3$/TMS) δ, J (Hz)
3a[d]	18/3	100		
3b	18/4	98	1650, 1620	3.17 (s, 2H, CH_2), 3.42 (s, 6H, 2 OMe), 7.20–7.80 (m, 10 H_{arom})
3c[d]	18/72	40		
3d[d]	18/3	100		
3e	18/4	100	1652, 1619	1.37 (d, J = 7.1, 3H, Me), 3.41 and 3.46 (2s, 6H, 2 OMe), 3.56 (q, J = 7.1, 1H, CH), 7.20–7.80 (m, 10 H_{arom})
3f[d]	50/10	65		
3g	18/8	65	1677, 1597	1.17 (d, J = 7.1, 3H, Me), 2.27 (s, 3H, COMe), 3.02 (dq, J = 7.1, 1.3, 1H, CH) 3.35 and 3.46 (2s, 6H, 2 OMe), 7.05 (d, J = 1.3, 1H, CH)
3h	18/3	100	1719, 1651	0.99 (t, J = 7.5, 3H, Me), 1.56–1.73 (m, 2H, CH_2), 3.02 (m, 1H, CH), 3.34 and 3.47 (2s, 6H, 2 OMe), 3.80 and 3.81 (2s, 6H, 2 CO_2Me)
3i	50/10	65	1719, 1608	0.97 (t, J = 7.5, 3H, Me), 1.39–1.71 (m, 2H, CH_2), 2.80 (dt, J = 7.5, 1.6, 1H, CH) 3.35 and 3.48 (2s, 6H, 2 OMe) 3.75 (s, 3H, CO_2Me), 7.18 (d, J = 1.6, 1H, CH)
3j	18/8	67	1677, 1597	0.99 (t, J = 7.5, 3H, Me), 1.37–1.76 (m, 2H, CH_2), 2.26 (s, 3H, COMe), 2.82 (dt, J = 7.6, 1.6, 1H, CH), 3.33 and 3.46 (2s, 6H, 2 OMe), 7.11 (d, J = 1.6, 1H, CH)
3k	18/6	85	1728, 1659	1.24 (t, J = 7.0, 3H, Me), 2.64 (m, AB part of ABX system, J = 16.9, 5.4, 8.3, 2H, CH_2), 3.38 and 3.43 (2s, 6H, 2 OMe), 3.55 (dd, X part of ABX system, J = 5.4, 8.3, 1H, CH), 3.79 and 3.80 (2s, 6H, 2 CO_2Me), 4.13 (q, J = 7.0, 2H, CO_2CH_2)
3m	60/24	40	1675, 1600	1.21 (s, 6H, 2 Me), 2.20 (s, 3H, COMe), 3.32 (s, 6H, 2 OMe), 6.92 (s, 1H, CH)

[a] Satisfactory microanalysis obtained: C ± 0.31; H ± 0.15%.
[b] All the new cyclobutenes **3** are oils except **3b** (mp 75–76°C from hexane).
[c] Yield of isolated pure product.
[d] These compounds are reported as oils in ref. 5.

Table 2. Physical, Analytical and Spectral Data of Compounds **4, 5** and **6**[a]

Product	mp (°C) or bp (°C)/Torr	IR ($CHCl_3$) ν (cm^{-1})	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)	^{13}C NMR ($CDCl_3$) δ
4a	134–135/1.5	1719, 1594	3.67, 3.71, 3.75 and 3.96 (4s, 12H, 4 OMe), 5.62 and 6.36 (2s, 2H, CH_2)	51.2, 52.0, 56.3 and 60.1 (4q, 4 OMe), 90.0 (s, C-2), 128.2 (t, C-4), 134.9 (s, C-3), 166.7, 167.6 and 168.6 (3s, C-1 and 2 CO_2)
4b	137–139/1.5	1715, 1592	2.10 (d, 3H, J = 7.0, Me), 3.66, 3.70, 3.71 and 3.90 (4s, 12H, 4 OMe), 6.10 (q, 1H, J = 7.0, CH)	15.8 (q, Me), 51.2, 51.3, 56.5 and 59.4 (4q, 4 OMe), 92.7 (s, C-2), 127.0 (s, C-3), 141.7 (d, C-4), 167.2, 167.7 and 168.1 (3s, C-1 and 2 CO_2)
4c	180–182/1.5	1713, 1586	3.61, 3.67, 3.78 and 3.91 (4s, 12H, 4 OMe), 6.79 (s, 1H, CH), 7.25–7.40 (m, 5 H_{arom})	50.9, 51.1, 57.0 and 58.8 (4q, 4 OMe), 92.3 (s, C-2), 127.4 (s, C-3), 127.6 and 128.0 (2d, CH_{arom}), 135.7 (s, C_{arom}), 137.1 (d, C-4), 166.5, 168.4 and 168.9 (3s, C-1 and 2 CO_2)
5a	oil	1737, 1640	3.78 and 3.83 (2s, 9H, 3 OMe), 4.65 (s, 1H, CH), 5.90 and 6.52 (2s, 2H, CH_2)	52.3 and 52.8 (2q, 3 OMe), 53.0 (d, C-2), 129.1 (t, C-4), 132.9 (s, C-3), 165.7 and 167.6 (2s, 3 CO_2)
5b	oil	1738, 1650	2.12 (d, 3H, J = 7.0, Me), 3.76 and 3.77 (2s, 9H, 3 OMe), 4.46 (s, 1H, 2-H), 6.34 (q, 1H, J = 7.0, 4-H)	15.2 (q, Me), 50.8 and 51.8 (2q, 3 OMe), 54.7 (d, C-2), 125.1 (s, C-3), 142.2 (d, C-4), 165.5 and 167.6 (2s, 3 CO_2)
5c	91–92[b]	1738, 1620	3.63 and 3.79 (2s, 9H, 3 OMe), 4.54 (s, 1H, 2-H), 7.03 (s, 1H, 4-H), 7.25–7.35 (m, 5 H_{arom})	51.7 and 52.8 (2q, 3 OMe), 56.3 (d, C-2), 125.5 (s, C-3), 127.9 and 128.5 (2d, CH_{arom}), 134.9 (s, C_{arom}), 140.8 (d, C-4), 167.3 and 167.7 (2s, 3 CO_2)
6a	131–133[b]	2255, 1742 1650	1.63 (d, 3H, J = 6.8, Me), 3.71 (s, OMe), and 3.72 (q, J = 6.8, CH) together 4H, 3.77, 3.78 and 3.86 (3s, 9H, 3 OMe)	15.9 (q, Me), 37.8 (d, C-6), 52.1, 53.4, 53.5 and 55.8 (4q, 4 OMe), 98.1 (s, C-3), 107.7, 107.9, 109.4 and 110.9 (4s, 4 CN, C-4 and C-5), 134.2 and 137.7 (2s, C-1 and C-2), 163.4 and 164.8 (2s, 2 CO_2)
6b	127–128[b]	2258, 1748, 1658	3.52, 3.75, 3.79 and 3.89 (4s, 12H, 4 OMe), 4.85 (s, 1H, CH), 7.25–7.55 (m, 5 H_{arom})	48.7 (d, C-6), 52.1, 53.2, 53.4 and 55.7 (4q, 4 OMe), 98.1 (s, C-3), 107.7, 108.1, 109.2 and 110.8 (4s, 4 CN, C-4 and C-5), 128.9, 129.7 and 130.6 (3d, CH_{arom}), 131.2 (s, C_{arom}), 136.1 and 136.6 (2s, C-1 and C-2), 163.6 (s, 2 CO_2)

[a] Satisfactory microanalysis obtained: C ± 0.35; H ± 0.14; N ± 0.23%.
[b] Recrystallization solvent: hexane.

compounds such as the unsaturated esters **5** and the cyclohexenes **6** (Scheme 2). The esters **5** are formed almost quantitatively by mild acidic hydrolysis of the dienes **4** whereas the cyclohexenes **6** are obtained in high yields by [4+2] cycloaddition of the dienes **4** with tetracyanoethene (TCNE).

In conclusion, the method described here provides a convenient access to the 3,3-dimethoxycyclobutenes **3** which have to be considered key intermediates in organic synthesis.

Mps and bps are uncorrected. IR spectra were obtained on a Perkin-Elmer 1760X-FT spectrophotometer. The NMR spectra of the pure products were recorded with a Varian XL-200 spectrometer. Microanalyses were obtained using a Carlo Erba EA 1108-Elemental Analyzer. $CHCl_3$ used in the reactions was passed through alumina (Merck). Dry MeCN was purchased from Aldrich Chemical Co. The monitoring of the reaction mixtures of **1** and **2** was performed with a Varian EM-360 spectrometer using dry $CHCl_3$ as solvent. When **2b** was used as the alkyne, the reaction was monitored by TLC, performed on silica gel plates (Merck). Silica gel [0.05–0.20 mm (Merck)] and light petroleum (bp 40–70 °C) were used for column chromatography.

The alkenes **1a**,[12] **1b**,[13] **1c**,[14] **1d**,[7] **1e**[15] and **1f**[16] and the alkyne **2b**[17] were prepared as previously reported. The alkynes **2a**, **2c** and **2d** were purchased from Aldrich Chemical Co.

3,3-Dimethoxycyclobutenes 3; General procedure:
To solutions of the alkenes **1a–d,f** (10 mmol; 5 mmol for **1d** to allow a better purification of **3k**) in dry $CHCl_3$ (5 mL) was added the alkyne **2** (5 mmol) and the resulting mixtures were kept at 18–60 °C (Table 1) under strictly anhydrous conditions. The solutions were monitored for the disappearance of the alkyne **2** by ^1H NMR or TLC. When the reaction was complete, the solvent and the unchanged alkene **1** were removed at reduced pressure and the residue chromatographed on silica gel (30 g). Elution with light petroleum/Et_2O (9:1) (7:3 for **3k**) afforded pure cyclobutenes **3a–k,m** (Table 1).

Dimethyl 1,1-Dimethoxyalka-1,3-diene-2,3-dicarboxylates 4a,b:
The cyclobutenes **3a,d** (5 mmol) were heated at 90 °C under strictly anhydrous conditions without solvent. After 15 h the dienes **4a** and **4b** (Table 2) were obtained by distillation as pale-yellow oils; yields 0.98 and 1.04 g, respectively, 85%.

Dimethyl 1,1-Dimethoxy-4-phenylbuta-1,3-diene-2,3-dicarboxylate (4c):
To a solution of the alkene **1e** (2.46 g, 15 mmol) in dry $CHCl_3$ (10 mL) the alkyne **2a** (1.42 g, 10 mmol) was added and the resulting mixture was kept at 18 °C under strictly anhydr. conditions. The solution was monitored for the disappearance of the alkyne **2a** by ^1H NMR. After 72 h the ^1H NMR spectrum showed the diene **4c** as the sole product. Removal of the solvent in vacuo and distillation of the residue afforded the diene **4c** (Table 2) as a yellow oil; yield 2.6 g, 85%.

Methyl 2,3-Dimethoxycarbonylalk-3-enoates 5:
To a solution of the diene **4** (1 mmol) in acetone (5 mL) was added 2 M HCl (0.2 mL) and the mixture was kept at r.t. After 15 min, the solvent was removed under reduced pressure, the residue was treated with $CHCl_3$ (5 mL) and washed with water (2 × 3 mL). The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo. Filtration of the residue through a short column of silica gel (10 g), using light petroleum/Et_2O (1:1) as eluent, gave the esters **5** (Table 2) with almost quantitative yields.

Dimethyl 4,4,5,5-Tetracyano-3,3-dimethoxy-6-methylcyclohex-1-ene-1,2-dicarboxylate (6a) and Dimethyl 4,4,5,5-Tetracyano-3,3-dimethoxy-6-phenylcyclohex-1-ene-1,2-dicarboxylate (6b):
To solutions of the dienes **4b,c** (1 mmol) in dry MeCN (5 mL) tetracyanoethene (1 mmol) was added and the resulting mixtures were kept at r.t. under strictly anhydrous conditions for 2 h. After removal of the solvent, filtration of the mixtures through a short column of silica gel (10 g), using light petroleum/Et_2O (1:1) as eluent, gave the cyclohexenes **6a** and **6b** (Table 2); yields 0.30 and 0.35 g, respectively, 80%.

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