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REACTIONS OF KETENES WITH ETHOXYALKYNES

SYNTHESIS OF 2,2,4-TRIALKYLCYCLOBUTANE-1,3-DIONES

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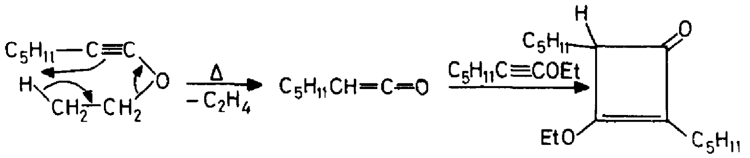
Abstract—Treatment of dimethyl ketene with ethoxyacetylene **1a**, 1-ethoxyoct-1-yne **1b**, and 1-ethoxytetradec-1-yne **1c** afforded the 3-ethoxycyclobutenones **2a–c**. Hydrolysis of **2a–c** with dilute hydrochloric acid gave the cyclobutane-1,3-diones **3a–c**. The ^{1}H NMR spectra of these compounds indicate that in $CDCl_3$ solution 2,2-dimethylcyclobutane-1,3-dione **3a** exists as the diketone, whereas the 2,2,4-trialkylcyclobutane-1,3-diones **3b** and **3c** exist as the monoenols.

The first reported example of a cycloaddition reaction between a ketene and an alkoxyalkyne was carried out by Ficini who observed that 1 - ethoxyhept - 1 - yne underwent a self-condensation reaction at 120°.[1] The product of this reaction was shown to be a 3-ethoxycyclobutenone formed by cycloaddition of one molecule of the alkynylether with one molecule of a monoalkyl ketene (Eqn 1).[2] Rosebeek and Arens subsequently prepared a series of 3 - alkoxy - 2 - alkylcyclobutenones by reacting alkoxyalkynes with ketene,[3] and Johns and Kriegler prepared 3 - ethoxy - 2 - methylcyclobutenone by this method (eqn 2).[4] Other workers, notably Martin[5] and Wasserman,[6] have prepared 4,4 - dialkyl - 3 - ethoxycyclobutenones by reacting dialkylketenes with ethoxyacetylene (eqn 3).

1.



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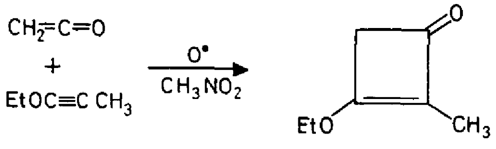

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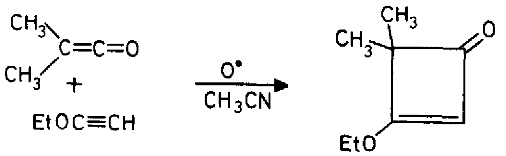

In this paper we report the preparation of 3 - ethoxy - 2,2,4 - trialkylcyclobutenones from dimethyl ketene and ethoxyalkynes, and their subsequent hydrolysis to give trisubstituted cyclobutane - 1,3 - diones.

Dimethyl ketene and ethoxyacetylene were prepared by standard procedures.[7,8] 1 - Ethoxyoct - 1 - yne was prepared by alkylation of sodium ethoxyacetylide with hexyl iodide. 1 - Ethoxytetradec - 1 - yne could not be prepared in high yield by direct alkylation due to the lower solubility, higher melting point and lower reactivity of dodecyl bromide. No reaction occurred when the reaction was carried out in a mixture of ammonia and ether. The highest yield (11%) was obtained when a mixture of ammonia and dimethyl formamide was used. However 1 - ethoxytetradec - 1 - yne was prepared in higher yield by reacting lithium ethoxyacetylide with tridodecylborane in tetrahydrofuran solution followed by treatment with iodine (Fig. 1).[9]

Dimethyl ketene reacted smoothly at 0° with ethoxyacetylene **1a**, 1 - ethoxyoct - 1 - yne **1b**, and 1 - ethoxytetradec - 1 - yne **1c**, forming the ethoxycyclobutenones **2a–c**. Hydrolysis of the ethoxycyclobutenones **2a–c** with dilute hydrochloric acid gave the cyclobutane - 1,3 - diones **3a–c**. Hydrolysis became more difficult as the length of the alkyl chain increased. Thus, whereas **2a** was hydrolysed by 5% aqueous hydrochloric

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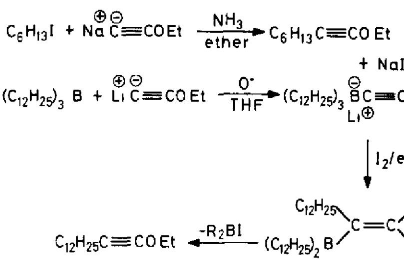


Fig. 1.

acid, **2b** required 10% aqueous acid, and in the case of **2c** it was necessary to add ethanol as co-solvent. These observations probably reflect the differing solubilities of the ethoxycyclobutenones and the differing acidities of the resulting cyclobutanediones. The yields and melting/boiling points of these products are shown in Table 1.

The ^1H NMR spectra (Table 2) indicate that although 2,2 - dimethylcyclobutane - 1,3 - dione **3a** exists as the diketone in $CDCl_3$ solution, the 2,2,4 - trialkylcyclobutane - 1,3 - diones **3b** and **3c** like the 2,4-dialkylcyclobutanediones,[10] exist as the corresponding monoenols.

The mass spectra of the cyclobutanediones (Table 3) show many expected fragments, but show principally a fragmentation pathway involving retro-cycloaddition to give *m/e* 70 ($Me_2C{=}C{=}O^+$, Fig. 2) as a major fragment, followed by loss of CO to give *m/e* 42.

Another possible route to substituted cyclobutane - 1,3 - diones involves direct alkylation of 2,2 - dimethylcyclobutane - 1,3 - dione **3a**. Several reactions were attempted using hexyl iodide and sodium, lithium and thallium enolates of **3a**. However only the lithium enolate gave detectable quantities of the C-alkylated product **3b**.

EXPERIMENTAL

IR and UV spectra were recorded on a Perkin–Elmer Infracord 257 and a Pye Unicam SP800 spectrophotometer. NMR spectra were obtained using a Varian HA100 instrument (TMS as internal reference) and mass spectra using an A.E.I. MS9 double-focussing instrument (electron beam energy 70 eV; source temperature 250°). Thin-layer chromatograms were run on Silica Gel GF_{254} in benzene-methanol–acetic acid (10:2:1). Tetrahydrofuran was distilled from lithium aluminium hydride and stored under nitrogen.

Table 2. ^1H NMR data* (τ values, in $CDCl_3$)

Compound	H-2	CH_3	OH	OEt	R
2a	5.29s	8.80s	—	5.84q(7) 8.59t(7)	—
3a	6.15s	8.77s	—	—	—
2b	—	8.84s	—	5.73q(7) 8.61t(7)	7.99 br.t(7) *ca.* 8.7 *m* 9.15 br.t(7)
3b	—	8.78s	−2.22s	—	8.05 br.t(7) *ca.* 8.8 m 9.15 br.t(7)
3c	—	8.79s 8.80s	−0.58s	—	8.06 br.t.(7) *ca.* 8.8 m 9.14 br.t.(6)

*All assignments supported by appropriate integration. Coupling constants (Hz) in brackets.

Table 3. Mass spectral data

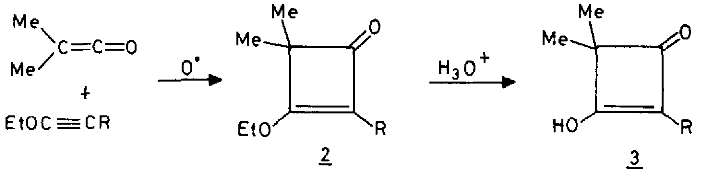
m/e	**3a**	**3b**	**3c**	**4***
280			2(M$^+$)	
196		2(M$^+$)		
154			2	
140		3		8(M$^+$)
127		15		
126		2		
112	2(M$^+$)			
71		13	7	4
70	100	100	100	100
69		3	5	4
67		3	4	
57		26	4	
56		3	2	
55		10	6	
44		24		
43	4	21	7	
42	100	18	7	67
41	48	17	9	27

*Compound **4** is 2,2,4,4 - tetramethylcyclobutane - 1,3 - dione.

2-*Bromoisobutyryl bromide*

Prepared by the standard procedure from isobutyric acid, red phosphorus and bromine.[7] The distilled product was decolourised with a high-boiling olefin (e.g. oct - 1 - ene) and redistilled. B.p. 63–7°/23 mm (lit.[7] 91–98°/100 mm). Yield 73%, ν_{max}(film) 1805, 1765, 670 cm^{-1}.

Table 1. Synthesis of trialkyl cyclobutane-1,3-diones



1a, R = H
1b, R = C_6H_{13}
1c, R = $C_{12}H_{25}$

Product	% Yield	m.pt	b.pt.
2a	58	——	58–60°/2 mm
2b	68	——	75–76°/0·015 mm
2c	not isolated	——	——
3a	62	131–3°	——
3b	81	65·5–67°	——
3c	33‡	73·5–74·5°	——

‡ Overall yield from ethoxyacetylene

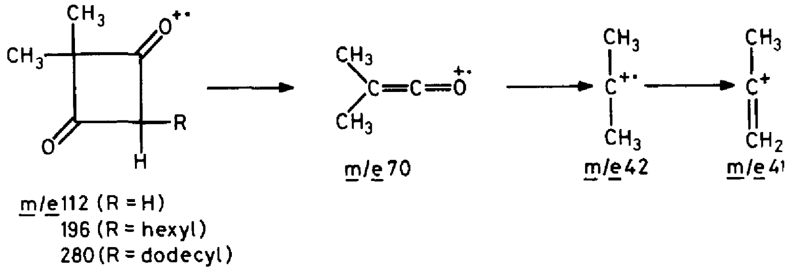


Fig. 2.

Dimethyl ketene

Zinc granules (14 g, washed with ether and dried at 100°) and dry ethyl acetate (100 ml) were placed in a flask attached to a receiver cooled by liquid nitrogen. The apparatus was flushed with nitrogen and the pressure reduced to 250 mm. The mixture was stirred, heated until boiling commenced (approx. 40°) and 2 - bromo - isobutyryl bromide (37 g) added dropwise over 30 min. Vigorous boiling ensued and distillation continued until the distillate was no longer yellow. The vacuum was released by admitting nitrogen and the receiver allowed to warm to room temperature giving a yellow solution of dimethyl ketene (70 ml).

Over a period of 2 days the solution became colourless and evaporation gave a fluffy white solid (5.6 g). Recrystallisation from petroleum ether (b.p. 60–80°) gave 2,2,4,4 - tetramethylcyclobutane - 1,3 - dione as white prisms (4.8 g), m.p. 108–111° (lit.[11] 115–6°). ν_{max} (Nujol) 1750, 1725 cm^{-1}. τ ($CDCl_3$) 8.73 (s).

Ethoxyacetylene

Prepared by the standard procedure from chloroacetal and sodium amide in liquid ammonia.[8] The product was dried over calcium chloride and redistilled under nitrogen from lithium aluminium hydride. B.p. 50–2° (lit.[8] 51°). Yield 76%. ν_{max} (film) 3300, 2140 cm^{-1}.

1 - *Ethoxyoct* - 1 - *yne*

A suspension of sodium amide in liquid ammonia was prepared from sodium (1.0 g) and liquid ammonia (20 ml), and ethoxyacetylene (3.0 g) added. After 20 min hexyl iodide (10 g) was added with stirring over 5 min. Ether (5 ml) was added and the stirring continued for 3 hr after which GLC indicated that no more product was being formed. Ammonium chloride (0.8 g) was added and the ammonia left to evaporate overnight. Water (10 ml) was then added and the organic layer separated. The aqueous layer was extracted with ether (15 ml) and the combined organic extracts washed with water (3 ml), dried ($MgSO_4$), and evaporated, to leave a yellow-brown oil (5 g). Distillation through a 1 m spinning-band column using a compound of higher boiling point (3 ml, ethyl 2-hexylacetoacetate) as chaser, gave 3 fractions: (i) 57–8°/8.5 mm (2.14 g, mostly hexyl iodide); (ii) 58–74°/8.5 mm (1.16 g, pure hexyl iodide); (iii) 80–1°/9.5 mm (1.92 g, 1 - ethoxyoct - 1 - yne) (lit. 43°/0.5 mm). ν_{max} (film) 2285 cm^{-1} τ ($CDCl_3$) 6.05 (q, 2H, 7 Hz), 7.93 (broad triplet, 2H, 7 Hz), 8.71 (t, 3H, 7 Hz), *ca.* 8.7 (broad multiplet, 8H), 9.13 (broad triplet, 3H, 6 Hz).

1-*Ethoxytetradec* - 1 - *yne*

(a) A suspension of sodium amide in liquid ammonia was prepared from sodium (0.12 g) and liquid ammonia (20 ml), and ethoxyacetylene (0.35 g) added with stirring. After 20 min a solution of dodecyl bromide (1.25 g) in dry DMF (10 ml) was added. After a further 2.5 h GLC showed only a small decrease in the concentration of dodecyl bromide but the IR spectrum contained two acetylene peaks at 2170 and 2280 cm^{-1} (ethoxyacetylene and alkylated ethoxyacetylene respectively), the latter being slightly more intense. The ammonia was allowed to evaporate leaving a black mixture which was poured into water (30 ml). Toluene (30 ml) was added and the brown organic layer separated. This was washed with water (2 × 15 ml) to remove DMF, dried ($MgSO_4$) and evaporated to leave a dark oil (0.8 g) which rapidly set to a solid. The acetylene was purified by elution through a dry alumina column (Spence type H) with benzene. Three fractions (20 ml) were collected: (i) yellow oil (0.25 g). ν_{max} (film) 2280 cm^{-1}. τ ($CDCl_3$) 6.06 (q, 2H, 7 Hz; OCH_2CH_3), 7.93 (broad triplet, 2H, 6 Hz; $RCH_2C{\equiv}C$), *ca.* 8.7 (multiplet, 44 H), 9.16 (broad triplet, 8 H). GLC and NMR indicated that this fraction was approx. 50% pure; (ii) yellow oil (0.04 g) containing a trace of white solid. ν_{max} 2280 cm^{-1}; (iii) yellow oil containing considerable quantities of white solid (0.03 g); no C≡C stretch in IR spectrum. The solid was low melting and could be dodecylamine (lit. m.p. 28°).

(b) A solution of tridodecylborane was prepared from dodec - 1 - ene (2.53 g, distilled from lithium aluminium hydride) and a solution of diborane in THF (4.05 ml of 1.36 M solution). The mixture was left at 30° for 4 hr to complete the formation of the trialkylborane.

A suspension of lithium ethoxyacetylide was prepared by dropwise addition of a solution of *n*-butyl lithium in hexane (2.44 ml of 2.05 M solution) to a solution of ethoxyacetylene (0.35 g) in THF (5 ml) at 0° with stirring. Completion of the reaction was indicated by formation of a suspension after 15 min, and replacement of the band at 2140 cm^{-1} due to the ethoxyacetylene by a band at 2045 cm^{-1} in the IR spectrum due to the salt.

The solution of tridodecylborane was then added at 0° to the suspension of lithium ethoxyacetylide and left stirring at 0° for 3 h. The suspension dissolved and the IR spectrum showed a new C≡C band at 2165 cm^{-1} due to the lithium trialkylethoxyethynyl borate. The solution was cooled to −50° and a solution of iodine (1.60 g) in ether (10 ml) added dropwise over 30 min. The mixture was allowed to warm to −30° and after a further 1.5 hr the IR spectrum of the solution showed a strong band at 2280 cm^{-1}. The mixture was quenched by pouring into water (20 ml) containing saturated sodium thiosulphate solution (1 ml). The separated organic layer was dried ($MgSO_4$) and evaporated to leave an orange oil (3.55 g). The product was purified by elution through a dry alumina column (Spence type H, 100 g) using petroleum ether (b.p. 40–60°). The first 20 ml was discarded since the IR spectrum showed no C≡C stretch. The following 60 ml was collected and evaporated to give a colourless oil (0.67 g). ν_{max} (film) 2280 cm^{-1}.

3 - *Ethoxy* - 4,4 - *dimethylcyclobuten* - 1 - *one* **2a**

A solution of dimethylketene in ethylacetate was prepared from zinc (31 g) and 2-bromoisobutyryl bromide (81.5 g). Ethoxyacetylene (12.3 g) was added with stirring at 0°, the mixture left at 0° for a further 4 hr, and allowed to warm to room temperature overnight. Evaporation left a dark-brown oil (23.9 g). 2,2,4,4 - Tetramethylcyclobutane - 1,3 - dione (300 mg) was precipitated with petroleum ether (b.p. 40–60°) and filtered. The filtrate was evaporated and the residue distilled through a 10 cm Vigreux column to give 3 - ethoxy - 2,2 - dimethyl cyclobuten - 1 - one (14.3 g). B.p. 58–60°/2 mm. ν_{max} (film) 1760, 1580 cm^{-1}; λ_{max} (EtOH) 231 nm (4.042); τ ($CDCl_3$) 5.29 (s, 1H), 5.84 (q, 2H, 7Hz), 8.59 (t, 3H, 7 Hz), 8.80 (s, 6H).

2,2 - *Dimethylcyclobutane* - 1,3 - *dione* **3a**

5% Hydrochloric acid (5 ml) was added to 3 - ethoxy - 4,4 - dimethylcyclobuten - 1 - one (500 mg) and the mixture stirred at room temperature overnight. The resulting suspension was extracted with chloroform (2 × 30 ml) and the product extracted from the chloroform solution with 10% sodium carbonate solution (30 ml) which was acidified with dilute hydrochloric acid and the liberated cyclobutane - 1,3 - dione extracted back into chloroform (2 × 30 ml). The combined chloroform layers were dried ($MgSO_4$) and evaporated to leave a white solid (280 mg) which was recrystallised from benzene-petroleum ether (b.p. 60–80°) to give 2,2 - dimethylcyclobutane - 1,3 - dione as white needles (250 mg), m.p. 131–3° (lit.[5] 131–2°). R_f 0.28. ν_{max} (KBr) 3500–2100, 2000–1780, 1705 cm^{-1}. λ_{max} (EtOH) 205 (sh, 3.595) 233 (4.215) nm; τ ($CDCl_3$) 6.15 (s, 2H), 8.77 (s, 6H).

3 - *Ethoxy* - 4,4 - *dimethyl* - 2 - *hexylcyclobuten* - 1 - *one* **2b**

A solution of dimethylketene in ethyl acetate was prepared from zinc (3 g) and 2-bromoisobutyryl bromide **8a**. The solution was allowed to warm to 0° and 1 - ethoxyoct - 1 - yne (2.5 g) added with stirring. The mixture was left at 0° for 5 hr and then allowed to warm to room temperature overnight. Evaporation left a yellow oil (4.1 g) which was distilled through a Claisen head using Nujol as a chaser to give 3 - ethoxy - 4,4 - dimethyl - 2 - hexylcyclobuten-1 - one (2.47 g), b.pt. 73–6°/0.015 mm. R_f 0.89. (Found: C, 74.9; H, 11.0; Calc. C, 74.9; H, 10.76%); ν_{max} (film) 1755, 1625 cm^{-1}. λ_{max} (EtOH) 242 (5.082) nm, τ ($CDCl_3$) 5.73 (q, 2H, 7 Hz), 7.99 (broad triplet, 2H, 7 Hz), 8.61 (t, 3H, 7 Hz), *ca.* 8.7 (m, 8H), 8.84 (s, 6H), 9.15 (broad triplet, 3H, 7 Hz).

2,2 - *Dimethyl* - 4 - *hexylcyclobutane* - 1,3 - *dione* **3b**

10% Hydrochloric acid (10 ml) was added to 3 - ethoxy - 4,4 - dimethyl - 2 - hexylcyclobuten - 1 - one (1.55 g) and the mixture left stirring overnight. A large quantity of solid precipitated and was filtered and dissolved in 10% sodium carbonate solution (15 ml). This solution was extracted with ether (15 ml) to remove non acidic materials and acidified with dilute hydrochloric acid. The product was extracted into ether (20 ml), dried ($MgSO_4$) and evaporated to give a white solid (886 mg) which was recrystallised from aqueous ethanol to give 2,2 - dimethyl - 4 - hexylcyclobutane - 1,3 - dione, m.p. 65.5–7°. R_f 0.63. ν_{max} (KBr) 3000–2100, 2000–1750, 1730 cm^{-1}. τ ($CDCl_3$) – 2.22 (s, 1H), 8.05 (broad triplet, 2H, 7 Hz), 8.78 (s, 6H), *ca.* 8.8 (m, 8H), 9.15 (broad triplet, 3H, 7 Hz).

3 - *Ethoxy* - 4,4 - *dimethyl* - 2 - *dodecylcyclobuten* - 1 - *one* **2c**

A solution of dimethylketene in ethyl acetate was prepared from zinc (0.88 g) and 2-bromoisobutyryl bromide (2.31 g). After allowing the solution to warm to 0° 1 - ethoxytetradec - 1 - yne (670 mg) was added with stirring. The mixture was left at 0° for a further 5 hr and then allow to warm to room temperature overnight. Evaporation of the solution gave a yellow oil (782 mg) which was not purified further. ν_{max} (film) 1755, 1625 cm^{-1}.

2,2 - *Dimethyl* - 4 - *dodecylcyclobutane* - 1,3 - *dione* **3c**

Crude 3 - ethoxy - 4,4 - dimethyl - 2 - dodecylcyclobuten - 1 - one (782 mg) was dissolved in ethanol (10 ml) and 18% hydrochloric acid (5 ml) added. The mixture was left overnight, and the ethanol evaporated, whereupon a solid precipitated. The mixture was basified with M sodium hydroxide solution (15 ml) and extracted with ether (25 ml). (A full separating funnel was used to avoid the formation of an emulsion). The organic layer was separated and extracted with 0.1 M sodium hydroxide solution (25 ml). The combined aqueous extracts were acidified with dilute hydrochloric acid and extracted with ether (2 × 50 ml). The ethereal solution was dried ($MgSO_4$) which was recrystallised from petroleum ether (b.p. 40–60°) to give 2,2 - dimethyl - 4 - dodecylcyclobutane - 1,3 - dione, m.p. 73.5–74.5°. R_f 0.78. ν_{max}(KBr) 2100–1850, 1775, 1600 cm^{-1}; τ ($CDCl_3$) – 0.58 (broad singlet, 1H), *ca.* 8.06 (broad triplet, 2H, 7 Hz), 8.79 (s, 3H), 8.80 (s, 3H), *ca.* 8.8 (broad multiplet, 20H), 9.14 (broad triplet, 3H, 6 Hz).

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