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Synthesis and Reactivity of Captodative Cyanoketenes

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Abstract : An expedient synthesis and the reactivity of donor substituted cyanoketenes **7** (captodative substitution) are described. 3-Cyano β-lactams are formed from **7** and imines.

INTRODUCTION

Cyanoketenes have found extensive use in [2+2] cycloaddition reactions thereby providing an easy entry to substituted cyclobutanones[1-3]. Hexynyl and chlorocyanoketenes are known to react even with unreactive ketenophiles, e.g., tri- and tetrasubstituted olefins[3,4].
Likewise, ketenes carrying donor heteroatoms (OR, SR, NR_2) have become versatile building blocks because they react with a large array of olefins, dienes, imines and even with azo compounds[5-7].
In contrast, ketenes bearing simultaneously an electronwithdrawing and -accepting group are little known and their reactivity remains unexplored despite their interesting functionality. One isolated example describes the photolysis of diazomalonic monothiolester which leads to an alkylthio carboethoxyketene[8]. A recent report describes the preparation of trimethyl-silyloxycyanoketene via a retro Diels-Alder fragmentation of the corresponding 9,10 dimethoxyanthracene adduct[9].
We report here the synthesis of new cyanoketenes bearing ether, thioether or amino substituents. This approach uses the known fragmentation reactions of cyclic azido ketones[10,11]. The three methods of formation of cyanoketenes **2** are described in Fig. 1[12-14].

Our experience shows that squaric acid derivatives **4** are more suitable precursors of captodative ketenes **7** than chloroquinones **1** and chlorofuranones **3**. The corresponding azides were not isolated since they decompose already at room temperature. It is the purpose of this publication to describe the trapping of **7** by various imines whereas unactivated olefins failed to react[15].

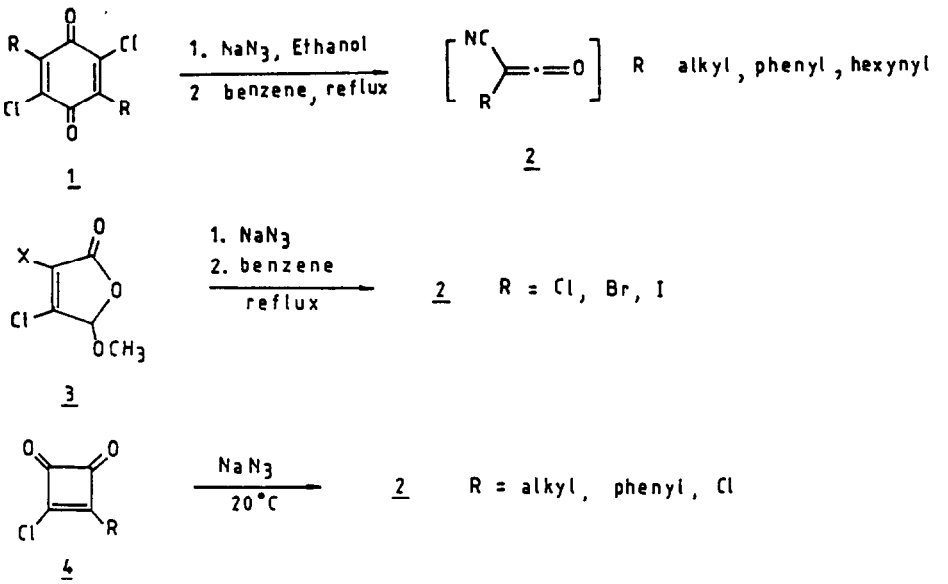

Figure 1. Cyanoketene Formation from Cyclic Azides.

RESULTS AND DISCUSSION

The requisite cyclobutenediones **6** are obtained from squaric acid dichloride **5** and the appropriate nucleophiles (Fig. 2). In order to avoid the formation of disubstituted products, the choice of experimental conditions is crucial. Ethanethiol led invariably to a small amount of disubstituted product. Squaric acid chloride monodimethylamide **6a** has already been described in the literature[16], and the neopentyloxy compound **6b** was prepared in low yield along with the disubstituted product[17]. By proper modification of reaction conditions, **6b** can be obtained as a single reaction product. Simple alcohols (methanol, ethanol) afford invariably disubstitution products.

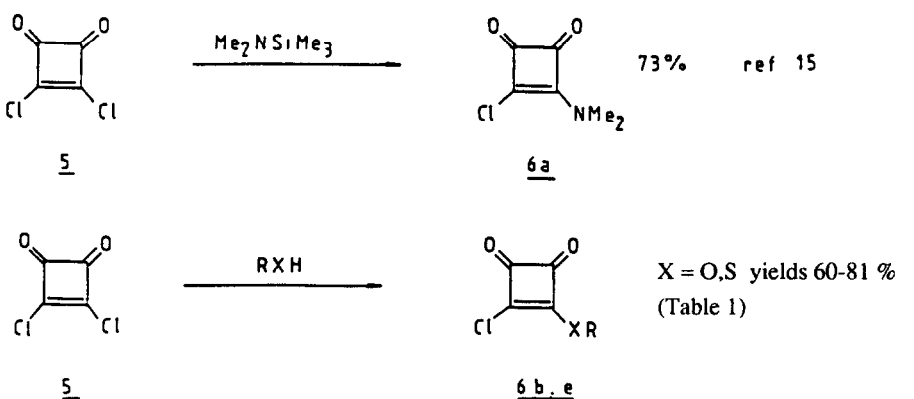

Figure 2. Synthesis of Squaric Acid Derivatives **6**

Reagent RXH	Conditions	Yield of 6
b) $(CH_3)_3CCH_2OH$	Et_2O/15'/reflux	81 %
c) $CH_2 = C(CH_3)CH_2CH_2OH$	Et_2O/30'/reflux	61 %
d) $CH_2 = CHCH_2CH_2OH$	Et_2O/15'/reflux	70 %
e) SEt	Toluene/-30°/NEt_3	60 %

Table 1. Yields of Squaric Acid Derivatives **6**

6a-e react with sodium azide either in acetonitrile or in benzene/crown ether [15,5] under nitrogen and carbon monoxide evolution at temperatures not yet optimized between 0 and 50°C. The arising cyanoketenes **7** are trapped by various aldimines and imidates **8** to give the new cyano β-lactams 9 (Fig. 3). The results are listed in Table 2.

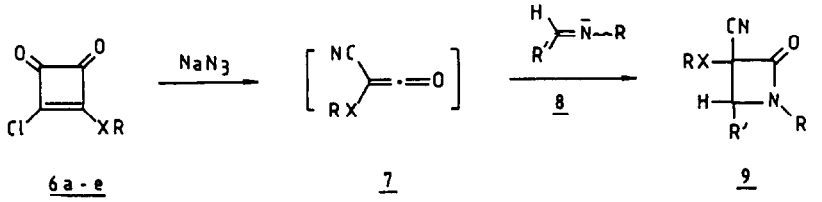

Figure 3 Cyanoketene Cycloaddition

Entry	RX- in **6** and **9**	Imine **8**		Yield of **9**	Ratio of Isomers
		R	R'		
a	Me_2N	Ph	Ph	89 %	85/15
b	Me_3CCH_2O	Ph	Ph	50 %	44/56
c	CH_2=C(Me)CH_2CH_2O	Ph	Ph	65 %	100
d	$CH_2 = CHCH_2CH_2O$	Ph	Ph	55 %	40/60
e	CH_3CH_2S	Ph	Ph	22 %	100
f	Me_2N	Ph	OEt	42 %	100
g	Me_3CCH_2O	Ph	OEt	30 %	100
h	$CH_2 = CHCH_2CH_2O$	Ph	OEt	42 %	100

Table 2. β-Lactams **9** from Imines, Imidates and Ketenes

A single stereoisomer is obtained in the majority of cases (entries c, e-h). Only the neopentyloxy and 3-butenoxyketene (entries b and d) show no selectivity Inasmuch as the stereochemistry of **9** cannot be established purely by spectroscopical means, X-ray studies will be performed and published separately.

To conclude, the formation of new captodative ketenes as reactive intermediates from the readily available azidocyclobutenediones with donor substituents constitutes a quite general method of obtention of these compounds. Such ketenes show a high propensity to undergo cycloadditions with imines to give 2-azetidinones containing a useful substitution pattern. These and similar reactions as well as intramolecular cycloadditions will be exploited in further work[15].

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 257 spectrometer. NMR spectra (^1H and ^{13}C) were measured using a Varian XL-200 apparatus at 200 and 50 MHz, respectively. Mass spectra were determined using a Varian Mat 44S spectrometer. Microanalyses were performed at the University of Wien (Austria).

Preparation of 3-chlorocyclobutenediones 6b-e

3-Chloro-4-neopentyloxycyclobutenedione 6b

A solution of 13.2 g (0.15 mole) of neopentyl alcohol in dry ether is added over 10 mn to a stirred solution of 15.1 g (0.1 mole) of 3,4-dichlorocyclobutenedione **5** in 100 ml of dry ether. The resulting mixture is refluxed during 15 min. The ether and excess alcohol are evaporated under reduced pressure. The residue is purified by vacuum distillation (110°/0.04 mm Hg) to give 16.4 g, 81 %, of **6b** as oil; ^1H NMR ($CDCl_3$) δ = 4.45 (2H,s), 1.0 (9H,s); ^{13}C NMR ($CDCl_3$) δ = 25.62, 32.09, 84.50, 188.95, 191.40, 194.06, 196.59; MS (m/e) = 203, 132, 71, 57; IR (film) = 1602, 1763, 1811 cm^{-1}.

3-Chloro-4-(3-methyl-3-butenoxy)cyclobutenedione 6c

The solution of 10.3 g (0.12 mole) of 3-methyl-3-butenol and 15.1 g (0.1 mole) of **5** in 100 ml of ether is refluxed for 30 min. The volatiles are removed and the residue is chromatographed on silicagel (ethyl acetate/petroleum ether : 1/4) to give 12.2 g, 61 %, of **6c** as oil; ^1H NMR ($CDCl_3$) δ = 1.80 (3H,s), 2.58 (2H,t), 4.8-5 (4H,m); ^{13}C NMR δ = 22.13, 37.42, 73.65, 114.10, 139.50, 166.22, 188.83, 191.87, 196.69; MS (m/e) = 200 (M^+), 172, 159, 69; IR (film) = 1605, 1740, 1810 cm^{-1}.

3-Chloro-4-(3-butenoxy)cyclobutenedione 6d

Prepared as described for **6c**, Bp 84°/0.08 mm Hg (Kugelrohr) to give 70 % of **6d** as oil; ^1H NMR ($CDCl_3$) δ = 2.60 (2H,q), 4.82 (2H,t), 4.9-6.2 (3H,m); ^{13}C NMR δ = 33.54, 74.33, 118.77, 131.46, 165.27, 188.39, 191.31, 196.12; MS (m/e) = 186 (M^+), 158, 130, 55; IR (film) = 1643, 1763, 1810 cm^{-1}.

3-Chloro-4-ethylthiocyclobutenedione 6e

A solution of 10.1 g (0.1 mole) of triethylamine in toluene (30 ml) is added dropwise to a cooled solution (-30°C) of 15.1 g (0.1 mole) of **5** and 6.2 g (0.1 mole) of ethanethiol. The solution is alowed to warm up to 20°, the precipitated hydrochloride and then the solvent are removed. Kugelrohr distillation (60°/0.04 mm Hg) gives 10.6 g, 60 %, of **6e**; ^1H NMR ($CDCl_3$) δ = 1.46 (3H,t), 3.45 (2H,q); ^{13}C NMR = 16.36, 25.87, 175.29, 187.07, 191.81, 197.12; MS (m/e) = 176 (M^+), 148, 120, IR (film) = 1620, 1757, 1783 cm^{-1}

Cycloaddition of Captodative Ketenes to Benzalaniline : General procedure

A solution of 2.5 mmoles of 3-chlorocyclobutenedione **6** in 3 ml of dry benzene is added dropwise to a suspension of 0.19 g (3 mmoles) of sodium azide and 0.45 g (2.5 mmoles) of benzalaniline **8a** in 10 ml of dry benzene. A few drops of [15,5] crown ether are added and the solution is stirred at 60°C for 3 hrs. The mixture is then treated with 5 ml of water and extracted with benzene. The organic layer is dried over sodium sulfate and the solvent is removed in vacuo. β-lactams **9a-e** are recrystallised from ethanol.

3-Dimethylamino-3-cyano-1,4-diphenyl-2-azetidinone 9a

Is obtained from 0.4 g of **6a** and benzalanine **8a** in 89 % yield. M.P. 165°; ^1H NMR ($CDCl_3$) δ = 2.10 (6H,s), 5.20 (1H,s), 7.13-7.61 (10H,m); ^{13}C NMR δ = 41.22, 65.73, 74.47, 113.86, 117.77, 125.28, 128.65, 129.16, 129.46, 129.95, 130.88, 136.63, 157.28; Anal Calc for $C_{18}H_{18}N_3O$: C 74.20, H 5.33, N 14.4; Found : C

74.25, H 5.92, N 14.51; MS (m/e) = 291 (M^+), 181, 172, 110, 82; IR (CH_2Cl_2) = 1760 (C=O), 2241 cm^{-1} (CN).

3-Neopentyloxy-3-cyano-1,4-diphenyl-2-azetidinone 9b

0.5 g of 3-chlorocyclobutenedione **6b** and **8a** give **9b** in 50 % yield. M.P. 162°; ^1H NMR ($CDCl_3$) δ = 1.00 (9H,s), 3.60 (2H,dd), 5.07 (1H,s), 7.25 (10H,m); ^{13}C NMR δ = 26.03, 31.61, 66.52, 79.05, 86.41, 112.21, 117.74, 125.33, 126.72, 129.23, 129.33, 129.93, 131.58, 157.09; Anal. Calc. for $C_{21}H_{22}N_2O_2$: C 75.42, H 6.63, N 8.37, O 9.57; Found : C 75.45, H 6.67, N 8.41, O 9.68; MS (m/e) = 334 (M^+), 215, 181; IR (CH_2Cl_2) = 1774 (CO), 2232 cm^{-1} (CN).

3-(3-Methyl-3-butene-1-oxy)-3-cyano-1,4-diphenyl-2-azetidinone 9c

From 0.5 g of **6c** and 0.45 g of **8a**, **9c** is obtained in 65 % yield; M.P. 117°; ^1H NMR ($CDCl_3$) δ= 1.77 (3H,s), 2.42 (2H,t), 4.1 (1H,m), 4.81 (2H,d), 5.15 (1H,s), 7.14-7.47 (10H,m); ^{13}C NMR δ = 22.60, 37.26, 66.73, 67.98, 86.24, 112.14, 112.53, 117.79, 125.42, 126.77, 129.28, 129.36, 130.01, 131.49, 136.03, 141.09, 156.96; Anal. Calc. for $C_{21}H_{20}N_2O_2$: C 75.88, H 6.06, N 8.43, 0 9.63; Found : C 75 15, H 6.05, N 8.35; MS (m/e) = 332 (M^+), 213, 181, 119, 91, 77, 69; IR (CH_2Cl_2) = 1776 cm^{-1} (CO)

3-(3-Butene-1-oxy)-3-cyano-1,4-diphenyl-2-azetidinone 9d

From 0.47 g of **6d** and 0.45 g of **8a**, **9d** is obtained in 55 % yield; M P. 112°; ^1H NMR ($CDCl_3$) δ = 2.47 (2H,qt), 4.03 (2H,dm), 5.03-5.22 (2H,m), 5.15 (1H,s), 5.70-5.96 (1H,m), 7.05-7.52 (10H,m); ^{13}C NMR δ = 33.51, 66.60, 68.77, 86.21, 112.08, 117.51, 117.72, 126.70, 128.73, 129.19, 129.92, 131.42, 133.38, 156.80; MS (m/e) = 318 (M^+), 199, 181, 119; IR (CH_2Cl_2) = 1780 cm^{-1} (CO).

3-Ethylthio-3-cyano-1,4-diphenyl-2-azetidinone 9e

Is obtained from 0.44 g of **6e** and 0.45 g of **8a** after chromatography on silicagel (hexane/ethylacetate 85/15) in 22 % yield. M.P. 113.5°; ^1H NMR ($CDCl_3$) δ = 1.41 (3H,t), 3.08 (2H,q), 5.3 (1H,s), 7.19-7.54 (10H,m); ^{13}C NMR δ = 14.54, 26.18, 66.60, 75.36, 112.83, 117.56, 125.37, 126.79, 129.35, 129.50, 130.29, 131.97, 135.43, 156.81; IR (CH_2Cl_2) = 1775 (CO), 2150 cm^{-1} (CN)

Cycloadditions to O-ethyl-N-phenylformimidate 8b are performed in the same manner as with 8a.

3-Cyano-3-dimethylamino-4-ethoxy-1-phenyl-2-azetidinone 9f

Obtained from 0.4 g of **6a** and 0.4 g of **8b** in 42 % yield after chromatography on silicagel (dichloromethane). M.P. 95°C, ^1H NMR ($CDCl_3$) δ = 1 38 (3H,t), 2 53 (6H,s), 3.34 (2H,q), 5 15 (1H,s), 7 1-7.5 (5H,m); ^{13}C NMR δ = 14.75, 41.27, 64 90, 78.24, 87.16, 110.51, 117.74, 125.83, 129.36, 136.05, 155.70; Anal. Calc. for $C_{14}H_{17}N_3O_2$: C 64.85, H 6.61, N 16 20; Found · C 64.65, H 6.53, N 16 14; MS (m/e) = 259 (M^+), 149, 140, 104, 82; IR (CH_2Cl_2) = 1790 (CO), 2310 cm^{-1} (CN).

3-Cyano-3-neopentyloxy-4-ethoxy-1-phenyl-2-azetidinone 9g

Is obtained from 0.5 g of **6b** and 0.4 g of **8b** in 30 % yield after chromatography on silicagel (hexane/ethylacetate . 85/15). M.P. 119°; ^1H NMR ($CDCl_3$) δ = 0 96 (9H,s), 1.42 (3H,t), 3.68 (2H,dd), 3.93 (2H,q), 5.26 (1H,s), 7.22-7.49 (5H,m); ^{13}C NMR δ = 14 78, 26.13, 31.71, 65.44, 79 15, 86.32, 88.29, 112.30, 117.83, 126.06, 128.45, 135.87, 156.00; Anal Calc for $C_{17}H_{22}N_2O_3$: C 67.53, H 7 33, N 9.26; Found : C 67.31, H 7.24, N 9.13; MS (m/e) = 302 (M^+), 183, 149, 119; IR (CH_2Cl_2) = 1780 (CO), 2300 cm^{-1} (CN).

3-(3-Butene-1-oxy)3-cyano-4-ethoxy-1-phenyl-2-azetidinone 9h

From 0.47 g of **6d** and 0.4 g of **8b**, **9h** is obtained after chromatography on silicagel (petroleum ether/ethylacetate : 80/20) in 42 % yield, ^1H NMR ($CDCl_3$) δ = 1.4 (3H,t), 2 42 (2H,qt), 3 92 (2H,q), 4.82-4.18 (2H,dm), 5.03-5.20 (2H,m), 5.25 (1H,s), 5.68-5 92 (1H,m), 7.13-7.5 (5H,m); ^{13}C NMR = 14.87, 33.48, 65.49,

68.68, 85.96, 88.11, 112.01, 117.47, 117.65, 125.92, 129.24, 133.34, 135.52, 155.95; MS (m/e) = 286 (M^+), 257, 167, 149, 139; IR (film) = 1780 cm^{-1} (CO).

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