Reactions of Dichlorocyclobutenones with Nucleophiles: A Synthesis of Some New Cyclobutenones and an Unusual Ring Expansion to a Butenolide

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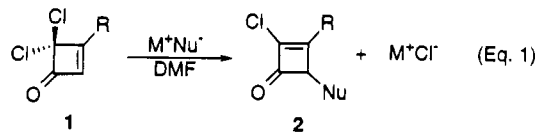
Cyclobutenones serve as useful intermediates in a variety of synthetic transformations. Thermolysis or photolysis of these compounds produces vinylketene intermediates which have been exploited in the synthesis of unsaturated esters,[2] eight-membered carbocycles,[3] phenols,[4,5] and quinones,[5] the latter of which proceeds by a fascinating cascade of electrocyclic reactions. Dichlorocyclobutenones are readily prepared by the cycloaddition of dichloroketene with alkynes[2] and are useful precursors to cyclobutenones through reduction with zinc in acetic acid containing pyridine[6] or TMEDA.[7] However, the chloro substituents have not been used extensively for further functionalization of this ring system.[8] Roberts has shown that 4,4-dichloro-3-phenyl-2-cyclobutenone (**1a**) reacts with metal-halide salts in refluxing acetone to give the products from allylic displacement of chloride.[9] We now report that compound **1a** reacts with a variety of nucleophiles in DMF under mild conditions to afford cyclobutenones **2a–g** (eq 1) and that product **2a**, resulting from displacement of chloride in **1a** with acetate, undergoes an unusual ring expansion to butenolide **9** upon treatment with sodium bicarbonate in methanol at room temperature or simply by refluxing in methanol.



1 **2**

1a R = Ph

Cyclobutenone **1a** reacts with several types of nucleophiles including acetate, iodide, bromide, chloride, thiocyanate, malonate, and azide to afford cyclobutenones **2a–g** (Table 1). Reaction of **1a** with potassium acetate in DMF at room temperature for 2 h leads to the allylic displacement product **2a** as a crystalline solid in 85% yield. The mild conditions under which the chloride of **2a** is displaced with acetate is surprising since acetate is a relatively weak nucleophile.

Table 1. Reactions of 1a with Nucleophiles

M⁺Nu⁻	reaction temp, °C	reaction time, h	cyclobutenone, **2**		
				Nu	% yield, **2**
KOAc	20	2	**a**	OAc	85
KI	50	3	**b**	I	73
LiBr	50	16	**c**	Br	17
KCl	35	18	**d**	Cl	58
KSCN	20	18	**e**	SCN	64
$NaCH(CO_2Et)_2$	0	5 min	**f**	$CH(CO_2Et)_2$	45
NaN_3	−10	5 min	**g**	N_3	62

The proton on the carbon bearing the nucleophilic substituent in **2a** displays a chemical shift in the ^1H NMR spectrum at δ 6.65 which is comparable to that of the vinylic proton in the starting material. To distinquish between structure **2a** and the less likely product resulting from direct displacement of chloride at the C-4 position (via the allylic cation),[8] an X-ray crystal structure was obtained for **2a**.[10] The presumed structure was verified and the cyclobutenone ring was shown to be planar.

When KI or LiBr is used, the reaction is complicated by the formation of **2d** due to competetive, internal rearrangement of chloride. Rearrangement of **1a** to **2d** can be readily effected by reaction with KCl in DMF and the structure of **2d** verified by NMR (^1H and ^{13}C) and mass spectrometry. The problem of product contamination by **2d** is minimized in the case of the iodide **2b** by using an excess of KI at 50 °C (3.5% of **2d**). In the case of the bromide **2c**, the isolated product contains only 17.4% of **2c** and the remainder is **2d** as judged by ^1H NMR and mass spectrometry. Reaction of **1a** with excess KBr at 50 °C rather than room temperature still gives **2d** as the major product since Br^- is a less effective nucleophile than I^- for the displacement of Cl in **2d**.[11] The malonate and azide reactions are nearly instantaneous and have to be conducted at lower temperatures and quenched rapidly (5 min) to avoid extensive decomposition. Reaction with stronger nucleophiles such as cyanide or methoxide gives extensive decomposition of starting material.

Compound **2d** is a possible intermediate in the conversion of **1a** to **2a**, since internal rearrangement of chloride is a known process.[9] However, reaction of **2d** with potassium acetate in DMF at room temperature gives little conversion to **2a**. Even the iodide **2b**, under the same reaction conditions, requires 24 h to completely convert to **2a**.

In an effort to determine the generality of this reaction, alternate, starting cyclobutenones were prepared. Treatment of the alkyl-substituted cyclobutenone, **1b** (R =

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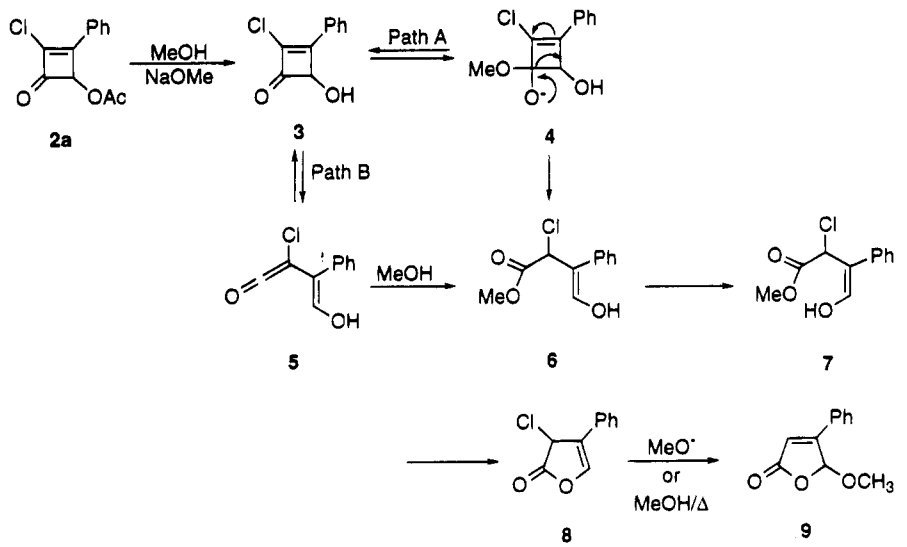
(10) (a) A crystal of **2a** measuring 0.13 mm × 0.13 mm × 0.50 mm was used for X-ray measurements. Crystal data: $C_{12}H_9ClO_3$; orthorhombic, $P2_12_12_1$; a = 6.727(2) Å, b = 11.200(1) Å, and c = 29.851(5) Å, $\alpha = \beta = \gamma = 90°$, V = 2249.0(9) Å^3, Z = 8, d_x = 1.398 g/cm^3. A total of 1963 independent reflections were measured of which 1691 were observed $|F|/\sigma \geq 3$. Final agreement factors were R = 0.041 and wR = 0.040 for 289 variables. (b) The authors have deposited atomic coordinates for structure **2a** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 IEZ, UK.

(11) No effect is observed in changing the cation from Li^+ to K^+ or Na^+.

0022-3263/94/1959-6868$04.50/0

Scheme 1



nBu), with potassium acetate in DMF produces a deep-blue solution which decomposes with time or upon quenching. This may be attributable to deprotonation of the α-hydrogens on the C-3 alkyl chain by KOAc. In fact, it has been shown by Dreiding that these hydrogens are acidic as evidenced by deuterium exchange when **1b** is treated with ^{1}D-acetic acid and pyridine. This is presumably due to stabilization of the anion which is vinylogously delocalized by the carbonyl of the four-membered ring.[6] However, the situation may be even more complicated since in other cases (**1c**, R = $SiMe_3$, and **1d**, R = $(CH_3)C{=}CH_2$), the displacement reaction with acetate fails and extensive decomposition of starting material is observed even though acetate-induced anion formation on the C-3 side chain position is not possible for these compounds. It has been shown by Moore[4c] that chlorocyanocyclobutenones are in equilibrium with vinyl ketenes at ambient temperature, which also may account for the failure of these compounds to undergo clean displacement reactions.

When acetate **2a** is treated with sodium methoxide in methanol at room temperature in an attempt to prepare hydroxycyclobutenone **3**, an unusual ring expansion results and the butenolide **9** is isolated as the major product in 40% yield after chromatography (Scheme 1).[12] The hydroxycyclobutenone **3** can be produced as the major product in 51% yield with mild methanolysis conditions ($NaHCO_3$/MeOH), but is converted predominantly to **9** upon further treatment at room temperature with $NaHCO_3$/MeOH. While the mechanism for the conversion of **3** to **9** has not been established, one possibility for this transformation is shown in Scheme 1 with two reasonable modes for ring opening.[13,14]

Compound **9** also forms cleanly and is isolated in 75% yield after **2a** is simply refluxed in methanol for 8 h. In this case, it is possible that **3**, produced by methanolysis of **2a**, undergoes an electrocyclic ring opening to a vinylketene **5** which is trapped by methanol to give the enol **7**, which then cyclizes to **8** and subsequently reacts with methanol with elimination of HCl to give **9**.

The reaction even proceeds to some extent at room temperature, simply by treatment of **2a** or **3** with methanol. After 10 days at room temperature, a 48% conversion of **3** to **9** was observed as judged by ^{1}H NMR. Apparently, bicarbonate or heat is needed in order to drive the reaction by removing the HCl produced.

In summary, it has been shown that dichlorocyclobutenone **1a** undergoes clean displacement reactions with O, S, N, and C-nucleophiles to form new cyclobutenones, which should be of interest in the synthesis of novel compounds derived from electrocyclic ring opening. A new rearrangement of chlorohydroxycyclobutenone **3** has also been discovered, leading to a functionalized butenolide.

Experimental Section

DMF and methanol were obtained commercially as high purity, anhydrous (>99.9%) solvents and used without further purification. Proton and carbon NMR spectra were recorded on a Bruker AM 360 spectrometer at 360 and 90.6 MHz respectively in $CDCl_3$, CD_2Cl_2, or acetone-d_6 solution. IR spectra were recorded on a Digilab FTS-45 Fourier transform spectrometer. Mass spectra were obtained by FAB ionization on a Fisons VG Quattro triple stage quadrapole spectrometer or by thermospray on a Hewlett-Packard 5985 single-stage spectrometer. Melting points were obtained on an Electrothermal capillary machine and are uncorrected. Elemental analyses were performed in the Bristol-Myers Squibb Pharmaceutical Research Institute Analytical Research and Development Department. Cyclobutenones **1a–d** were prepared according to literature procedures.[2]

General Procedure for the Preparation of Cyclobutenones (2a–g). To a solution of 10 mmol of cyclobutenone **1a** in 10 mL of DMF was added 20 mmol of M^+Nu^-. The reaction mixture was stirred at −10 to 50 °C, (see Table 1) until complete as judged by TLC (silica gel, λ 254, 10% EtOAc/hexanes, 2–18 h). The mixture was poured into ether (50 mL) and washed with 2 × 50 mL of water and the organic phase dried over anhydrous $MgSO_4$. Concentration of the ether under vacuum afforded the products which were purified by recrystallization or chromatography over silica gel.

2-Chloro-4-acetoxy-3-phenyl-2-cyclobutenone(2a). Compound **2a** was recrystallized from n-hexane in 85% yield. **2a**: off-white solid; mp 116–117 °C; IR (KBr) 1798, 1786, 1752, 1739, 1602, 1246 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.87 (m, 2H), 7.55 (m, 3H), 6.65 (s, 1H), 2.1 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 181.5 170.1, 167.7, 133.3 129.8, 129.7, 129.4, 128.0, 81.3, 20.8; MS, FAB, *m/z*

(12) Roberts has reported **9** as a byproduct in the acid-catalyzed thermolysis of 3-phenylcyclobutenedione in methanol at 115 °C. Mallory, F. B.; Roberts, J. D. *J. Am. Chem. Soc.* **1961**, *83*, 393.

(13) (a) Studies have shown that thermal ring openings proceed by outward rotation of the electron-donating substituent. See Baldwin, J. E.; McDaniel, M. C. *J. Am. Chem. Soc.* **1968**, *90*, 6118. For steric reasons the enol in **7** must be *trans* in order for cyclization to occur. This can be accomplished by equilibration through the aldehyde. (b) For a related rearrangement see Ohno, M.; Yamamoto, Y.; Eguchi, S. *Tetrahedron Lett.* **1993**, *34*, 4807.

(14) It has been shown that chlorocyanocyclobutenones are in equilibrium with vinylketenes at room temperature; see ref 4c.

(relative intensity) 237 [MH^+ (43) with Cl isotope at 239], 194 (12), 177 (28), 165 (20), 154 (100). Anal. Calcd for $C_{12}H_9O_3Cl$: C, 60.90; H, 3.83. Found: C, 60.75; H, 3.79.

2-Chloro-4-iodo-3-phenyl-2-cyclobutenone (2b). Compound **2b** was recrystallized from 2-propanol in 73% yield. **2b**: yellow needles, mp 88.5–90 °C (lit.[9] 91–92 °C); IR (KBr) 1793, 1772, 1597 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.95 (m, 2H), 7.59 (m, 3H), 5.76 and 5.64 (two singlets, ratio 96.5 to 3.5); ^{13}C ($CDCl_3$) δ 179.4, 166.4, 133.7, 130.7, 130.3, 129.6, 128.1, 28.8; MS, FAB, *m/e* (relative intensity) 304 [MH^+ (14) with Cl isotope at 306], 179 (7), 177 (21), 151 (33), 149 (100), 127 (7), 114 (22). Compound **2d** was present in the isolated product at a level of 3.5% as determined by ^1H NMR.

2-Chloro-4-bromo-3-phenyl-2-cyclobutenone (2c). After workup, the crude material was obtained as a crystalline solid from hexane. ^1H NMR showed the presence of **2c** at a level of 17.4% and the remainder was **2d**.

2,4-Dichloro-3-phenyl-2-cyclobutenone (2d). Compound **2d** was recrystallized from hexane in 58% yield. **2d**: yellow needles; mp 77–78 °C (lit.[9] 78–80 °C); IR (KBr) 1781, 1597 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.96 (m, 2H), 7.58 (m, 3H), 5.64 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 178.5, 166.4, 133.6, 130.0, 129.4, 127.7, 126.4, 65.7; MS thermospray (CH_3CN–H_2O–NH_4OAc), *m/z* (relative intensity), 213 [MH^+ (100) with Cl isotope at 215], 195 (11), 161 (10), 149 (13), 142 (39), 136 (24), 122 (67). Anal. Calcd for $C_{10}H_6Cl_2O$; C, 56.37; H, 2.89. Found: C, 56.35; H, 2.91.

2-Chloro-4-thiocyano-3-phenyl-2-cyclobutenone (2e). Compound **2e** was obtained by recrystallization from $CHCl_3$ at <40 °C in 64% yield. Attempts to recrystallize at a temperature above 40 °C led to decomposition. **2e**: off-white crystalline solid; mp 145 °C dec; IR (KBr) 1764, 1564 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.95 (m, 2H), 7.61 (m, 3H), 5.05 (s, 1H); ^{13}C NMR (CD_2Cl_2) δ 177.5, 164.9, 134.4, 130.4, 130.0, 127.7, 126.5, 107.5, 59.7; MS FAB *m/e* (relative intensity), 235 [MH^+ (17) with Cl isotope at 237], 210 (13), 208 (36), 182 (34), 180 (80), 172 (24), 151 (43), 149 (100), 145 (22), 114 (55). Anal. Calcd for $C_{11}H_6NSClO$: C, 56.06; H, 2.57. Found: C, 55.93; H, 2.58.

2-Chloro-4-(dicarbethoxymethyl)-3-phenyl-2-cyclobutenone (2f). Compound **2f** was purified by column chromatography over silica gel using 20% EtOAc in hexanes as eluant and afforded a clear oil which solidified upon standing. Recrystallization from 2-propanol afforded **2f** in 45% yield. **2f**: white needles; mp 60–60.5 °C; IR (KBr) 1786, 1769, 1745, 1731, 1599 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.83 (m, 2H), 7.49 (m, 3H), 4.59 (d, 1H, J = 5.2 Hz), 4.18 (q, 2H, J = 7.1 Hz), 4.06 (q, 2H, J = 7.1 Hz), 3.87 (d, J = 5.2 Hz, 1H), 1.21 (t, 3H, J = 7.1 Hz), 1.11 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) 182.8, 167.0, 166.3, 132.5, 129.4, 129.1, 122.9, 62.0, 57.3, 50.5, 13.9, 13.8; MS FAB *m/e* (relative intensity) 337 [MH^+ (100) with Cl isotope at 339], 293 (8) 291 (19), 265 (11), 263 (25), 247 (10), 245 (19), 235 (37), 217 (50), 207 (34). Anal. Calcd for $C_{17}H_{17}ClO_5$: C, 60.63; H, 5.09. Found: C, 60.56; H, 4.98.

2-Chloro-4-azido-3-phenyl-2-cyclobutenone (2g). Compound **2g** was obtained by crystallization from 95% EtOH at −20 °C in 62% yield. **2g**: yellow crystalline solid; mp 52–54 °C; IR (KBr), 2107, 1785, 1770, 1599 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.90 (m, 2H), 7.55 (m, 3H), 5.20 (s, 1H); ^{13}C NMR ($CDCl_3$) 181.5, 166.6, 133.6, 129.7, 129.5, 128.2, 128.0, 72.4; MS FAB *m/e* (relative intensity) 220 [MH^+ (12) with Cl isotope at 222], 191 (6.4), 165 (10), 163 (29), 156 (100), 138 (37), 136 (93), 129 (65), 128 (36), 101 (69).

4-Methoxy-3-phenyl-2-butenoic Acid Lactone (9). To a slurry containing 236 mg (1 mmol) of **2a** in 10 mL of MeOH was added 2.16 mL (0.95 mmol) of a 25 wt% solution of NaOMe in MeOH. The mixture was stirred at room temperature for 18 h and poured into a mixture of 75 mL of ether and 75 mL of dilute HCl. The organic phase was washed with water and dried over anhydrous $MgSO_4$. Concentration *in vacuo* at room temperature afforded a yellow-brown oil which was purified by chromatography over silica gel using 6% CH_2Cl_2 in CH_3CN as eluant to afford **9** as a pale-yellow oil in 40% yield. **9**: IR (KBr) 1748, 1630.7 cm^{-1}; ^1H NMR (DMSO-d_6); δ 7.76 (m, 2H), 7.51 (m, 3H), 6.89 (s, 1H), 6.58 (s, 1H), 3.48 (s, 3H); ^{13}C ($CDCl_3$) δ 170.4, 161.0, 131.8, 129.2, 129.0, 127.6, 115.8, 103.0, 55.6; MS FAB *m/e* (relative intensity) 191 (MH^+, 56), 159 (60), 115 (36), 103 (100). Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.07; H, 5.26.

2-Chloro-3-phenyl-4-hydroxy-2-cyclobutenone (3) and 4-methoxy-3-phenyl-2-butenoic Acid Lactone (9). To a solution of 236 mg (1 mmol) of **2a** in 10 mL of anhydrous methanol was added 89.5 mg (1.06 mmol) of $NaHCO_3$ and the mixture stirred for 28 h, at which time a pinkish-orange solution remained. TLC (silica, 6% CH_3CN in CH_2Cl_2) indicated the presence of two major zones. The solution was added to a mixture of 75 mL of EtOAc and 75 mL of dilute HCl. The organic phase was washed with water (75 mL) and concentrated to give a yellow residue which was chromatographed over silica gel using 6% CH_3CN in CH_2Cl_2 as eluant. Alcohol **3** was recovered as an off-white crystalline solid in 51% yield. An analytical sample was obtained by recrystallization from ether–hexane. **3**: mp 111.5–112 °C; IR (KBr) 3375, 1754, 1596, 1270, 963, 720; ^1H NMR (acetone-d_6) δ 8.03 (m, 2H), 7.64 (m, 3H), 5.70 (d, J = 7.9 Hz, 1H), 5.61 (d, J = 7.9, Hz, 1H). Upon standing in acetone-d_6 for 3 days, the doublets were not visible and a singlet was present at δ 5.69 (1H). ^{13}C NMR (acetone-d_6) δ 187.6, 172.1, 133.2, 130.0, 129.7, 129.5, 83.2; MS *m/e* (relative intensity) FAB 195 [MH^+ (43.6) with Cl isotope at 197], 177 (37.5), 159 (17.8) 151 (8.8), 149 (22.7), 147 (5.6). Anal. Calcd for $C_{10}H_7O_2Cl$: C, 61.72; H, 3.63; Cl, 18.22. Found: C, 61.93; H, 3.57; Cl, 17.91.

The lactone **9** was obtained as a pale yellow oil in 21% yield with identical spectral properties as described in the preceding example.

4-Methoxy-3-phenyl-2-butenoic Acid Lactone by Thermolysis 2a in Methanol (9). A solution of 118 mg (0.5 mmol) of **2a** in 10 mL of MeOH is heated at reflux for 8 h. The methanol is removed by concentration *in vacuo* and the residue is crystallized from ether–hexane to afford **9** in 74.9% yield. **9**: mp 49.5–50.5 °C (lit. 52 °C). Spectral properties of this compound were identical to those for compound **9** prepared in the preceding example.

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