Tri-*n*-butylphosphine-Catalyzed Addition and Ring-Cleavage Reactions of Cyclobutenones

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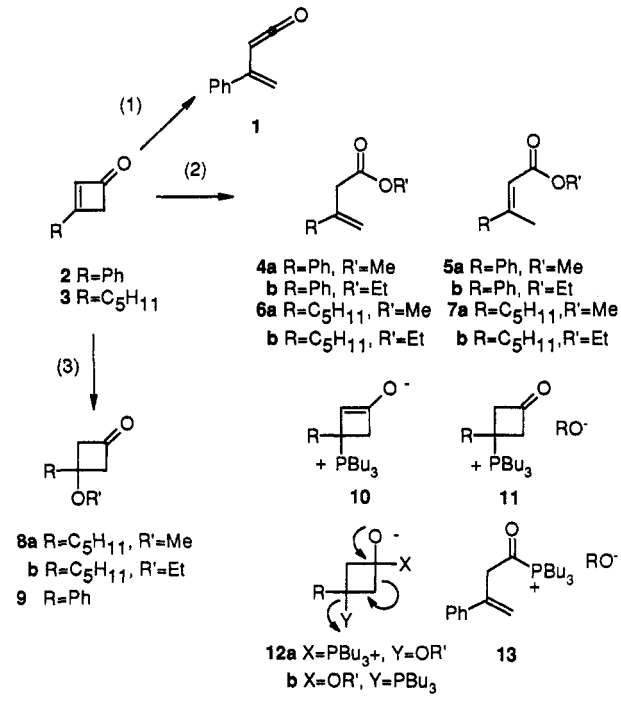
Cyclobutenones undergo ring-opening reactions upon heating or upon treatment with anionic species. The thermal reactions involve electrocyclic cleavage[1] to vinyl ketenes (eq 1, Scheme I), while the anionic reactions appear to occur by 1,2- or 1,4-addition followed by a similar rearrangement.[2] We have observed that tributylphosphine, a weakly basic nucleophilic catalyst,[3] can also induce ring-opening reactions of cyclobutenones in alcoholic solution (eq 2, Scheme I). In some cases these reactions proceed at room temperature. Thus, 3-phenylcyclobutenone[4] (**2**) and tributylphosphine (4 mol %) in methanol or ethanol (ca. 1 M) gave the β,γ-unsaturated esters, **4a**[5] and **4b**[6] respectively, contaminated by ca. 1% methyl (*E,Z*)-3-phenyl-2-butenoates **5a** or ethyl (*E,Z*)-3-phenyl-2-butenoates **5b**,[7] respectively. Methanolic solutions of **2** alone or with added triethylamine were unreactive at room temperature. In contrast, the analogous ring opening of **3**[8] was slower than that of **2**. When a methanolic solution of **3** was treated with tributylphosphine (23 °C, 2 h), methoxy adduct **8a**[9] was the only product (eq 3, Scheme I). Similar conditions in ethanol gave **8b**. At increased concentrations of the phosphine and with longer reaction times, the ring-opened esters **6a** and **6b** were also observed along with small amounts of **7**[10] (^{1}H NMR assay).

The presence of the phosphine also effected facile proton exchange. From a mixture of **2**, PBu_3, and CH_3OD, **4a** was isolated with 85% deuterium incorporation at both the α-carbon center and the terminal vinyl center. Furthermore, deuteriated **2** was recovered from a similar experiment (0 °C, 2 h) with ca. 80% deuterium incorporation at both the olefinic and the methylene carbons in the four-membered ring. Catalytic sodium methoxide in methanol at 60 °C converted **4a** to a 96:4 mixture of **5a**/**4a**; thus, phosphine catalysis led to the formation of the less-stable ester. In similar experiments with **3**, cyclobutanone **8a** was extensively deuteriated at the α centers when CH_3OD was used as the solvent (80 and 65% deuterium incorporation for the two chemically distinct protons in **8a**).

Scheme I



4-(Dimethylamino)pyridine (DMAP) also catalyzed the conversions described above, but less efficiently than did the phosphine. Heating at 45–50 °C in the presence of DMAP (1 M, 1 equiv) was required for the ring cleavage of **2** and **3**. In the presence of DMAP, 44% ring cleavage occurred after 24 h to give a 2:1 mixture of **4a**/**5a** whereas, in the absence of DMAP, 17% of the mass was converted to the ring-opened esters **4a** and **5a** at this temperature. Electrocyclic ring cleavage of **2** and **3** to the corresponding vinyl ketenes is known to occur at ca. 70 °C.[11] Thus, the uncatalyzed methanolysis may involve the ketene mechanism (eq 1). Michael addition of methanol to **3** was also catalyzed by DMAP, but the reaction was ca. 3×10^2 slower than in the PBu_3-catalyzed reaction under similar conditions. This result indicated that the mode of catalysis was more likely to be nucleophilic[12] instead of basic.

Tributylphosphine could function herein as a nucleophilic catalyst in at least two ways. Michael addition of tributylphosphine to electron-poor olefins has precedent in the literature.[13] Thus, the simplest rationale for the phosphine-catalyzed deuteriation of **2** is via Michael addition of the phosphine to give enolate **10** which could be converted to symmetrical cyclobutanone **11** upon protonation. S_N1 displacement of phosphorus from the 3 position by the alcohol is a possible route to **8**, while

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(9) The respective ^{1}H NMR chemical shifts of this compound were very similar to those reported for 3-methoxy-3-methylcyclobutanone. Kirmse, W.; Rode, K. *Chem. Ber.* **1987**, *120*, 839.

(10) For the ^{1}H NMR spectra of these esters see (a) Carpita, A.; De Magistris, E.; Rossi, R. *Gazz. Chim. Ital.* **1989**, *119*, 99. (b) Guittet, E.; Bibang Bi Ekogha, C.; Julia, S. A. *Bull. Soc. Chim. Fr.* **1985**, 325. (c) Kuwahara, Y.; Sakuma, L. *Aric. Biol. Chem.* **1982**, *46*, 1855.

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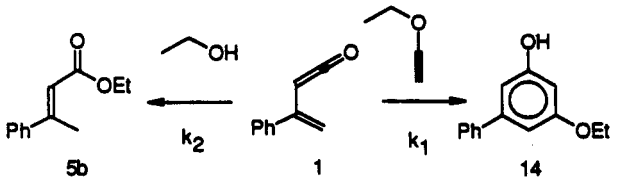
Scheme II



reversible 1,2-addition of the proximal alkoxide to the carbonyl carbon of the four-membered ring ketone **11** opens a Grob fragmentation[14] pathway to **4** and **6** via intermediate **12b**. The kinetics of these synchronous fragmentations depend on the lability of both of the bonds to be broken.[15] Hence, the reluctance of **3** to cleave under conditions that caused the cleavage of **2** supports such a fragmentation mechanism since benzylic stabilization should make **12b** more labile when the substituent is phenyl. Another way PBu_3 could function as a nucleophilic catalyst is via 1,2 addition of the phosphine to ketones **8** and **9** followed by a similar Grob fragmentation to the one proposed above with the subsequent loss of alkoxide from the 3 position of **12a** to give acylphosphonium intermediate **13**. Structure **13** could have been a source of vinyl ketene **1** upon loss of the α-proton.[16] However, this pathway is unlikely according to the following evidence. In a competition study of ethyl ethynyl ether and ethanol for vinyl ketene **1** under conditions of thermal cleavage of cyclobutenone **2** (85 °C), ethanol trapped the ketene intermediate **1** *ca.* 2× faster (k_1/k_2 = 0.49 ± 0.03) than did the alkynyl ether[17] as determined by ^{1}H NMR integration of the downfield signals corresponding to **14** and **5b** in Scheme II. However, under conditions of the phosphine-catalyzed ring opening of **2**, in the presence of the alkynyl ether the same competition experiment gave **5b**, but not **14**. Furthermore, the vinyl ketene **1** or the acylphosphonium species **13** should have been susceptible to nucleophilic addition by hindered secondary amines; however, the presence of diisopropylamine or 2,2,6,6-tetramethylpiperidine did not result in the formation of amides under conditions of the phosphine catalyzed ring opening of **2**. Thus, the pathway via **12a** or **12b** with rapid collapse of ion pair **13** are most likely for the phosphine-induced ring cleavage reaction of cyclobutenones.

Experimental Section

Methyl 3-Phenyl-3-butenoate (4a): Cyclobutenone **2** (68 mg, 0.47 mmol) dissolved in MeOH (500 μL) was treated with PBu_3 (5.4 mg, 5 mol%) via syringe under N_2. The reaction was stirred at 23 °C for 24 h. The solvent was removed and the residue purified via preparative layer silica gel chromatography (PF254, 10 × 10 cm, 1:10 EtOAc/hexane eluent) to give **4a** (71 mg, 85%). The spectral data matched that of the title compound.

3-Pentylcyclobutenone (3). Cyclobutenone **3** was obtained in 60% distilled yield from 1-heptyne by the method of Danheiser.[1] Analytical TLC on silica gel: 1:9 EtOAc/hexane, R_f = 0.30. Distillation of the product gave a clear, colorless liquid: bp 47–49 °C, 0.08 mm, short path; IR (CCl_4, cm^{-1}) 1771, (C=O), 2958 (C—H; 1586 (C=C); 200-MHz NMR ($CDCl_3$, ppm) δ 5.90 (1 H, s), 3.15 (2 H, s), 2.56 (2 H, t, J = 7.7 Hz), 1.7–1.6 (2 H, m), 1.4–1.22 (6 H, m), 0.91 (3 H, m).

3-Methoxy-3-pentylcyclobutanone (8a).[18] Cyclobutenone **3** (98 mg, 0.71 mmol) dissolved in MeOH (500 μL) was treated with PBu_3 (10 mg) via syringe. The reaction was stirred at 23 °C for 2 h. The entire reaction mixture was diluted with hexane/ether 1:1 (500 μL). The organic phase was washed 3× with regular Clorox bleach (250 μL) and saturated NaCl solution. Using silica gel column chromatography (1:20 EtOAc/hexane), **8a** (98.2 mg, 82%) was isolated. Analytical TLC on silica gel; 1:9 EtOAc/hexane, R_f = 0.32. No parent ion for $C_{10}H_{18}O_2$: M − pentyl = 99.0449, error = 3 ppm; base peak = 128 amu; IR (CCl_4, cm^{-1}) 2932 (C—H); 1790 (C=O); 270-MHz NMR ($CDCl_3$, ppm) δ 3.24 (3 H, s), 3.10, 2.85 (4 H, AA′BB′, J_{ab} = 17.8, $J_{aa'}$ = 5.7, $J_{bb'}$ = 5.0, $J_{ab'}$ = 1.4 Hz), 1.9–1.6 (2 H, m), 1.3–1.1 (6 H, m), 0.91 (3 H, m); ^{13}C NMR (125-MHz, $CDCl_3$, ppm) δ 205.5, 72.0, 56.0, 51.3, 34.4, 31.8, 23.5, 22.5, 13.9.

3-Ethoxy-3-pentylcyclobutanone (8b).[18] Cyclobutenone **3** (43 mg, 0.31 mmol) dissolved in EtOH (200 μL) was treated with 8 mg of PBu_3. The reaction stirred at 23 °C for 26 h. Workup and purification were performed as with **8a** to obtain **8b** (40.1 mg, 70%). Open chain esters **7b** (9:1 trans/cis 20%) were also isolated from the column. Analytical TLC on silica gel: 1:9 EtOAc/hexane, R_f = 0.33. Molecular ion calcd for $C_{11}H_{20}O_2$: 184.14630, found m/e = 184.1463, error = 0 ppm; M − pentyl = 113.0600, error = 2 ppm; IR (CCl_4, cm^{-1}) 1791 (C=O), 2930 (C—H), 1076 (C—O); 270-MHz NMR ($CDCl_3$, ppm) δ 3.37 (2 H, q, J = 7.0 Hz), 3.10, 2.86 (4 H, AA′BB′, J_{ab} = 18.0, $J_{aa'}$ = 6.1, $J_{bb'}$ = 5.9, $J_{ab'}$ = 1.8 Hz), 1.8–1.7 (2 H, m), 1.4–1.2 (6 H, m), 1.21 (3 H, t, J = 7.0 Hz), 0.89 (3 H, m); ^{13}C NMR (125-MHz, $CDCl_3$, ppm) δ 206.1, 71.5, 59.2, 56.5, 35.2, 31.8, 23.7, 22.6, 15.6, 14.0.

Methyl 3-Methyleneoctanoate (6a). Cyclobutenone **3** (48 mg, 0.35 mmol) dissolved in MeOH (1 mL) in a one-piece flask/condenser microapparatus was treated with 12 mg of PBu_3. The reaction stirred under N_2 at 50 °C for 24 h. The crude reaction mixture contained esters **6a** and **7a** (trans and cis) in a ratio 79:16:6. Workup was performed as with **8a**. After removal of solvent, the residue was purified by preparative layer chromatography over silica gel (PF254, 10 × 10 cm, 1:20 EtOAc/hexane) and the ester **6a** was isolated (38 mg, 65%). Analytical TLC on silica gel: 3:25 EtOAc/hexane, R_f = 0.51. Analytical GLPC (Alltech RSL-ISO capillary column, 30 m × 0.25 mm): flow 0.9 mL/min helium. Molecular ion calcd for $C_{10}H_{18}O_2$: 170.13064, found m/e = 170.1304, error = 1 ppm; M − 15 = 155.1072, error = 10 ppm; IR (CCl_4, cm^{-1}) 1743.5 (C=O), 3080.1 (=C—H), 2931.6 (C—H); 200-MHz NMR ($CDCl_3$, ppm) δ 4.92 (1 H, s), 4.89 (1 H, s), 3.69 (3 H, s), 3.05 (2 H, s), 2.09 (2 H, t, J = 7.0 Hz), 1.4–1.3 (6 H, m), 0.89 (3 H, m).

3-Ethoxy-5-phenylphenol (14). Synthesized by the method of Danheiser.[11] Thus 3-phenylcyclobutenone **2** (45.7 mg, 0.32 mmol) was taken up with 100 mg of freshly distilled ethyl ethynyl ether (Farchan. 50 wt% hexane), diluted with 500 μL of C_6H_6 and sealed in a glass tube. The tube was heated to 85 °C for 19 h. After removal of solvent (aspirator), the residue was purified by preparative layer silica gel (30 × 3 cm), 1:9 EtOAc/hexane eluent. Analytical TLC on silica gel: 3:7 EtOAc/hexane, R_f = 0.46. Distillation of the product at 85–90 °C, 0.01 mm, in a sublimation chamber and condensed on a cold finger at 0 °C gave a clear liquid (40%). Molecular ion calcd for $C_{14}H_{14}O_2$: 214.09933, found m/e = 214.0994, error = 0 ppm; IR (CCl_4, cm^{-1}) 3609 (O—H), 2982 (C—H), 1577 (=C—H); 200-MHz NMR ($CDCl_3$, ppm) δ 7.57–7.54 (2 H, m), 7.45–7.26 (3 H, m), 6.71 (1 H, dd, J = 2.2, 1.5 Hz), 6.65 (1 H, dd, J = 2.2, 1.5 Hz), 6.40 (1 H, t, J = 2.2 Hz), 4.9 (1 H, bs), 4.06 (2 H, q, J = 7.0 Hz), 1.43 (3 H, t, J = 7.0 Hz).

Competition/Trapping Study of 1-(1-Phenylethenyl)ketene. A solution of 137 μmol of ethanol, 32 μmol of **2**, 36 μmol of ethyl ethynyl ether, and 250 μL of C_6D_6 was placed in an NMR tube (medium walled, precision, Wilmad) and sealed under partial vacuum. The contents of the tube were heated at

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(18) The coupling constants were corroborated by comparison to simulated spectra generated by *Racoon*-2. Shatz, P. F.; Reich, H. J. University of Wisconsin—Madison.

85 °C for 14 h. NMR analysis showed a 13:87 ratio of products **14** and **5b**.

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Supplementary Material Available: Copies of selected NMR spectra (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.