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Communications

Oxidative Rearrangement of 4-Hydroxy-2-cyclobutenone. A New Route to Highly Substituted Furanones from Squaric Acid

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Summary: 4-Hydroxy-2-cyclobutenones, which were obtained by the reaction of diethyl squarate with an organolithium, reacted with lead tetraacetate (to generate an oxy radical) affording 5-acetoxy-2(5*H*)-furanones and 5-alkylidene-2(5*H*)-furanones. This type of rearrangement was realized in a simple four-membered cyclic α-ketol but not in the corresponding five-membered ring.

The ring enlargement of small ring compounds is one efficient strategy for the synthesis of highly functionalized ring systems.[1] For this purpose, squaric acid (**1**) is a fascinating C_4-synthon; a wide variety of 3,4-disubstituted cyclobutenediones and 4-hydroxycyclobutenones are readily accessible from acid **1**,[2] and further transformation of the modified cyclobutenone rings by thermolysis, photolysis, and catalysis is aided by the relief of ring strain.[3] Along this line, a major focus has been the conversion of **1** to highly functionalized phenols and quinones. We have recently developed a new method for C−C bond formation on a cyclobutenedione ring using unsaturated organosilanes,[2d,e] and the 4-hydroxycyclobutenone derivative with a 4-acylmethyl substituent was fruitfully applied to a stereoselective synthesis of γ-acylmethylenetetronates by thermal rearrangement.[4] Although a γ-ylidene-2(5*H*)-furanone structure, which is found in many biologically active natural products,[5] was constructed from **1**, the ring transformation concerned still relied on sequential electrocyclic ring-opening and reclosure.[3,4] Therefore, we envisaged another effective route and found a more versatile method for synthesis of highly substituted furanones by means of the novel oxidative rearrangement of 4-hydroxycyclobutenones. This rearrangement involved oxy-radical-triggered ring-opening and subsequent intramolecular radical addition to the carbonyl oxygen.

The chemistry of cycloalkoxy radicals has been studied extensively,[6] and these studies revealed that the cycloalkoxy radical generated from an appropriate precursor undergoes β-scission to give a ring-opened carbon radical intermediate with a carbonyl terminus, which leads to a variety of products *via* pathways including recyclization, elimination, and addition.[7] Strained cyclobutoxy radicals inevitably undergo these types of reactions.[8] Accordingly, 4-hydroxycyclobutenones, which

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(1) (a) De Meijere, A., Ed. *Small Ring Compounds in Organic Synthesis*; Topics in Current Chemistry; Springer-Verlag: Berlin, 1990; Part 4, Vol. 155 and preceding series. (b) Hesse, M. *Ring Enlargement in Organic Chemistry*; VCH: Weinheim, 1991.

(2) (a) Reed, M. W.; Pollart, D. J.; Perri, S. T.; Foland, L. D.; Moore, H. W. *J. Org. Chem.* **1988**, *53*, 2477. (b) Liebeskind, L. S.; Fengel, R. W.; Wirtz, R.; Shawe, T. T. *Ibid.* **1988**, *53*, 2482. (c) Liebeskind, L. S.; Yu, M. S.; Yu, R. H.; Wang, J.; Hagen, K. S. *J. Am. Chem. Soc.* **1993**, *115*, 9048 and references cited therein. (d) Ohno, M.; Yamamoto, Y.; Shirasaki, Y.; Eguchi, S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 263. (e) Yamamoto, Y.; Nunokawa, K.; Ohno, M.; Eguchi, S. *Synlett* **1993**, 781.

(3) (a) Edwards, J. P.; Krysan, D. J.; Liebeskind, L. S. *J. Org. Chem.* **1993**, *58*, 3942 and references cited therein. (b) Moore, H. W.; Yerxa, B. R. *Chemtracts: Org. Chem.* **1992**, *5*, 273.

(4) Ohno, M.; Yamamoto, Y.; Eguchi, S. *Tetrahedron Lett.* **1993**, *34*, 4807.

(5) (a) Pattenden, G. *Fortsch. Chem. Org. Naturst.* **1978**, *35*, 133. (b) Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625. (c) Yamamoto, M. *Yuki Gosei Kagaku Kyokaishi* **1981**, *39*, 25.

(6) Burn, P.; Waegell, B. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum Press: New York, 1983; Vol. 3, Chapter 6.

(7) (a) O'Dell, D. E.; Loper, J. T.; Macdonald, T. L. *J. Org. Chem.* **1988**, *53*, 5225. (b) Kobayashi, K.; Suzuki, M.; Suginome, H. *Ibid.* **1992**, *57*, 519. (c) Schreiber, S. L.; Hulin, B.; Liew, W.-F. *Tetrahedron* **1986**, *42*, 2945. (d) Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091.

(8) (a) Suginome, H.; Kobayashi, K.; Itoh, M.; Furusaki, A. *Chem. Lett.* **1985**, 727. (b) Kobayashi, K.; Itoh, M.; Suginome, H. *Tetrahedron Lett.* **1987**, *28*, 3369. (c) Dowd, P.; Zhang, W. *J. Org. Chem.* **1992**, *57*, 7163. (d) Snider, B. B.; Vo, N. H.; Foxman, B. M. *J. Org. Chem.* **1993**, *58*, 7228.

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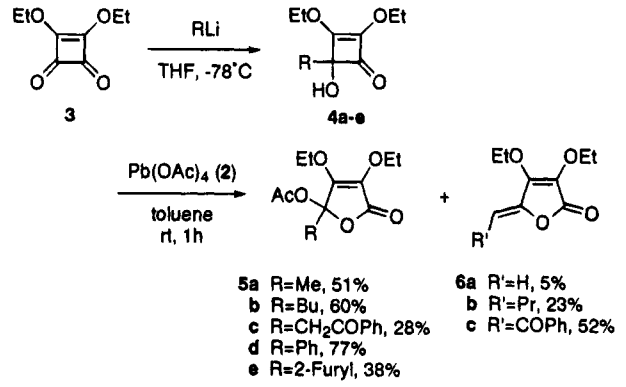
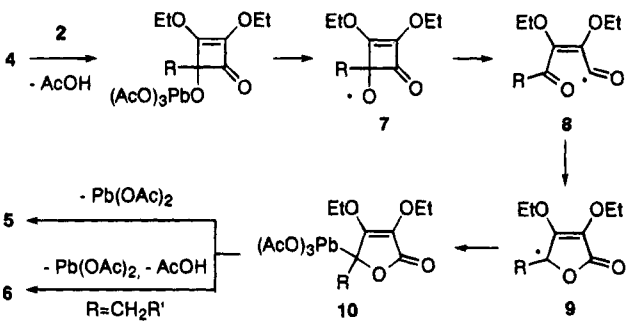
Scheme 1



Scheme 2

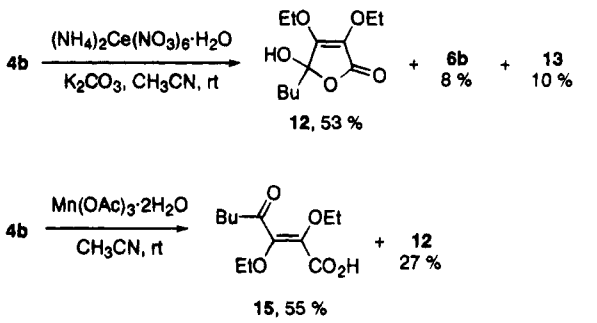


are derived from **1**, are believed to be susceptible to ring expansion *via* the oxy-radical.

In this case the oxy-radical was generated by the action of lead tetraacetate (**2**)[9] on alcohols **4a**–**e** obtained from diethyl ester **3** and the appropriate organolithium reagents. Alcohol **4a**, a typical example, was treated with **2** (2 equiv) in dry toluene at ambient temperature. The reaction was completed within 1 h. Standard workup and separation by preparative TLC gave the rearranged products, 5-acetoxy-2(5*H*)-furanone **5a** (51%) and 5-methylene-2(5*H*)-furanone **6a** (5%) (Scheme 1). The structural assignment of major product **5a** was based on the spectral data. The IR spectrum indicated, instead of the hydroxy group of **4a**, two new carbonyl absorptions at 1782 and 1769 cm^{-1} corresponding to the acetoxy and furanone moieties. The ^{13}C NMR spectrum indicated the furanone structure by the presence of one quarternary carbon (δ 99.1 ppm) and two pairs of olefinic and carbonyl carbons (δ 121.4, 156.4, 166.8, and 168.4 ppm). In the mass spectrum the required M^+ (*m/z* 244, 85%) was observed together with the parent peak (*m/z* 202). Minor product **6a** was characterized by a carbonyl absorption at 1779 cm^{-1}, methylene signals in both the ^1H NMR (δ 4.95 ppm; s, 2 H) and the ^{13}C NMR spectra (δ 92.1 ppm), and the M^+ (*m/z* 184, 55%). In the same manner, **5b** and **6b** (total yield 83%) and **5c** and **6c** (total yield 80%) were obtained from **4b** and **4c**, respectively.[10] However, only 5-acetoxy-2(5*H*)-furanones **5d** and **5e** were produced from **4d** and **4e**, which have no α-hydrogens to eliminate (Scheme 1).

Scheme 2 illustrates a possible mechanism for the formation of furanones **5** and **6** from **4**. Initially formed

Scheme 3



alkoxy radical **7** generated from alcohol **4** and **2** undergoes β-scission to produce acyl radical intermediate **8**. Recyclization (**8** → **9**) proceeds through addition of the radical to the carbonyl oxygen.[11] Resulting lead(IV) intermediate **10** collapses finally *via* the reductive elimination of lead(II) acetate to give acetoxyfuranone **5** or alternatively *via* concomitant elimination of acetic acid to give 5-ylidenefuranone **6**.[12] A related *endo*-cyclization of 4-oxo-2-butenyl radical has been reported in the photorearrangement of benzocyclobutenol to phthalide.[8b]

Although **2** was found to be effective for this rearrangement, other oxidants were also tested (Scheme 3). Oxidative rearrangement of **4b** with CAN [$(NH_4)_2Ce(NO_3)_6{\cdot}H_2O$ (**11**) (2 equiv)/K_2CO_3/CH_3CN, rt, 1 h] afforded 5-hydroxyfuranone **12** together with **6b** and 3-ethoxy-4-butyl-3-cyclobutene-1,2-dione (**13**). The structure of **12** was proved by acetylation to **5b**. Also Mn(III) oxidation of **4b** [$Mn(OAc)_3{\cdot}2H_2O$ (**14**) (2 equiv)/CH_3CN, rt, 1.5 h] afforded **12** together with **15**. However, anhydrous ferric chloride did not promote the rearrangement of **4b** but instead catalyzed the formation of **13**.

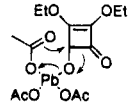
The versatility of this method was demonstrated in the stereoselective synthesis of (*Z*)-isomer **19** of multicolanate (Scheme 4). Multicolanic acid[13] has a 4-acylmethylenetetronic acid skeleton, and its (*E*)-stereochemistry was established by Pattenden in a synthesis of a 1:3 mixture of methyl (*E*)- and (*Z*)-*O*-methylmulticolanate by the Wittig condensation of acid anhydride.[14] In our hands, starting mono ester **16**, which was obtained from **3** by means of the known procedure,[2a] was allowed to react with the lithium enolate of benzyl acetate to give alcohol

(9) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; Benjamin Inc.: Menlo Park, 1972; p 359.

(10) (*Z*)-Isomers were formed selectively: **6b** contained less than 3% of the (*E*)-isomer and **6c** contained no (*E*)-isomer. The stereochemistry was deduced from the ^1H NMR in **6b** by the relative chemical shift of the olefinic protons [(*Z*) δ 5.35, (*E*) δ 5.59; see ref 13] and in **6c** by analogy with (*Z*)-5-phenacylidene-4-methoxy-2(5*H*)-furanone (see ref 4).

(11) The process **7** → **8** → **9** seems to be energetically favored; the recent calculation reported for a benzoanalog indicated that the 2-oxobenzocyclobutoxy radical is 27 kcal less stable than the 2-formyl benzoyl radical, which is, in turn, 26 kcal less stable than the 3-phthalidyl radical (Mendenhall, G. D.; Protasiewicz, J. D.; Brown, C. E.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc.* **1994**, *116*, 1718).

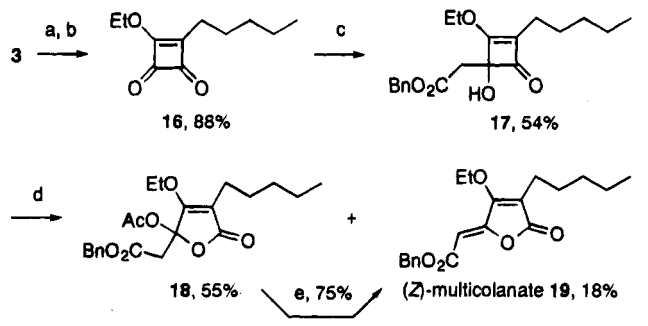
(12) Oxy radical **7** might add to a carbonyl group to give a 5-oxabicyclo[2.1.0]pent-2-enyloxy radical intermediate, which undergoes ring opening to afford **9** by means of the process demonstrated in the Dowd's ring-expansion reaction. However, this mechanism seems to be energetically less favored (see ref 7d). Alternatively, a reviewer suggested the concerted mechanism depicted in the following figure.



(13) Gudgeon, J. A.; Holker, J. S. E.; Simpson, T. J. *J. Chem. Soc., Chem. Commun.* **1974**, 636.

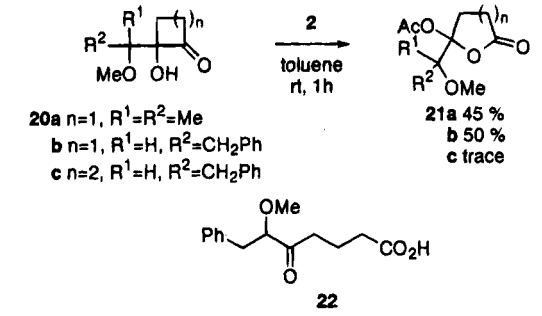
(14) (a) Begley, M. J.; Gedge, D. R.; Pattenden, G. *Ibid.* **1978**, 60. (b) Gedge, D. R.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 89.

Scheme 4[a]



[a] Key: (a) $CH_3(CH_2)_4MgBr$, THF, −78 °C; (b) Cat. HCl, CH_2Cl_2, rt; (c) CH_2=COLi(OBn), THF, −78 °C; (d) $Pb(OAc)_4$, toluene, rt; (e) DBU, THF, rt.

Scheme 5



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17. The oxidation of **17** with **2** afforded **19**[15] together with acetoxytetronate **18**, which was converted to **19** in good yield with DBU in THF.

In order to gain general insight into this oxidative rearrangement, simple α-hydroxycycloalkanones[16] were subjected to lead tetraacetate oxidation. On the one hand, oxidation of α-hydroxycyclobutanones **20a,b** gave expected γ-acetoxy γ-lactones **21a,b** in moderate yields by means of a 5-*endo-trig* cyclization of the 4-oxobutanoyl radical. The success of this reaction implies that unsaturation is not required for the ring closure. On the other hand, the oxidation of related α-hydroxycyclopentanone **20c** resulted in the formation of open chain product **22** in 49% yield together with a trace of cyclized product **21c**; 6-*endo-trig* cyclization of the acyl radical intermediate is disfavored[17] (Scheme 5). Thus, the present oxidative rearrangement is realized in four-membered ring α-ketols.

Supplementary Material Available: Details of experimental procedures (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.

(15) Spectral data for **19**: IR (neat) 1790, 1725, 1713, 1672, 1638 cm^{-1}; ^1H NMR δ 0.89 (3 H, t, J = 6.4 Hz), 1.2−1.6 (6 H, m), 1.42 (3 H, t, J = 7 Hz), 2.45 (2 H, t, J = 8 Hz), 4.40 (2 H, q, J = 7 Hz), 5.24 (2 H, s), 7.3−7.5 (5 H, m); ^{13}C NMR δ 13.9, 15.2, 22.4, 23.6, 29.8, 31.6, 66.6, 68.0, 95.1, 107.4, 128.6, 128.9, 136.1, 153.5, 161.2, 163.8, 169.6; MS *m/z* (rel intensity) 344 (M^+, 2), 238 (100), 210 (26), 181 (32). These data were similar to those reported for the methyl ester (see ref 13).

(16) Shimada, J.; Hashimoto, K.; Kim, B. H.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 1759.

(17) For examples of lead tetraacetate promoted ring-opening of α-ketol, see: (a) Hurd, C. D.; Saunders, W. H., Jr. *Ibid.* **1952**, *74*, 5324. (b) Anderson, R. J.; Henrick, C. A. *Ibid.* **1975**, *97*, 4327.