J. Org. Chem. **1998,** *63,* 9555−9556

Haller−Bauer-Type Cleavage of Cyclobutabenzofuranones

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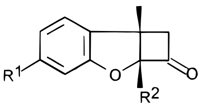
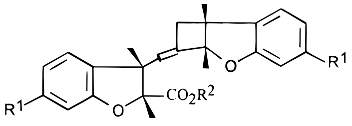
Received June 9, 1998

The base-induced Haller−Bauer-type cleavage of nonenolizable ketones has found useful application in synthesis.[1] Although this cleavage has been widely investigated in the case of open-chain and common-ring ketones, extension of this protocol to cyclobutanones has not been explored. However, cyclobutanones have been known to undergo cleavage by nucleophilic bases when the α-carbon is suitably substituted by an anion-stabilizing group.[2] We have, in recent years, been concerned with transformations of a class of cyclobutanones, the cyclobutabenzofuranones, under various conditions to furnish useful synthetic intermediates.[3] In an extension of such studies, it was felt appropriate to investigate the base-induced Haller−Bauer-type cleavage of these cyclobutanones to lead to functionalized dihydrobenzofurans, since the presence of the α-furanyl oxygen atom might induce a selective cleavage. We report here the results obtained with the cyclobutabenzofuranones **1**−**3**.



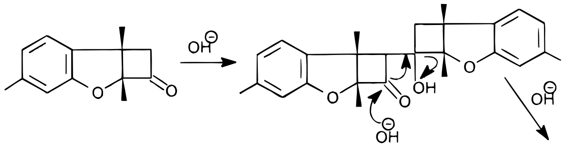
1; R1=R2=Me
2; R1=H, R2=Me
3; R1=Me, R2=H



4; R1=Me, R2=H
5; R1=R2=Me
6; R1=R2=H
7; R1=H, R2=Me

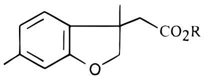
Refluxing a mixture of cyclobutabenzofuranone **1**[4] and aqueous sodium hydroxide solution (15−20%) in benzene for several hours, a condition frequently employed in Haller−Bauer reactions,[1] resulted in only recovery of **1**. We then decided to try a homogeneous reaction medium using a solvent that can also provide a somewhat elevated reaction temperature. A homogeneous mixture of cyclobutabenzofuranone **1** and aqueous sodium hydroxide solution (15%) in 2-methoxyethanol was refluxed for 10 h. The neutral fraction left no residue. The aqueous alkaline fraction on acidification furnished an acid that was esterified with diazomethane. The crystalline methyl ester, obtained in 80% overall yield, was characterized as **5** from detailed spectral studies. High-resolution mass spectrometry revealed a molecular weight of 418.2145 corresponding to a molecular formula of $C_{27}H_{30}O_4$. ^{1}H NMR spectrum displayed four three-proton singlets at δ 1.24, 1.35, 1.45, and 1.46 for the aliphatic methyl groups, two singlets at δ 2.28 and 2.30 for the aromatic methyl groups, and a three-proton singlet at δ 3.65 for the methoxycarbonyl group. The cyclobutane methylene and the olefinic protons appeared as an ABX system at δ 2.01 (q), 2.29 (q), and 5.54 (t). The ^{13}C spectrum in combination with a DEPT experiment showed the presence of 27 carbon atoms and a single methylene group. The above data fit the assigned structure **5**, which may be visualized to arise from an initial self-condensation of the cyclobutabenzofuranone **1** to the ketol **10** followed by a hydroxide anion induced cleavage (Scheme 1). It would seem that dehydration follows a nucleophilic attack on the free cyclobutanone carbonyl group in the intermediate **10**, and the observed selectivity of bond cleavage may be explained in terms of the mode of dehydration. The cyclobutabenzofuranone **2**,[3] also under similar reaction conditions, afforded the acid **6** in very good yield (90%) and was characterized as the methyl ester **7**.

Scheme 1



1 **10** **4**

In sharp contrast to **1** and **2**, the cyclobutabenzofuranone **3**[3] when subjected to the above reaction conditions furnished the acid **8** in 80% yield, additionally characterized as the methyl ester **9**. The structure was identified from analytical and spectral data, particularly ^{1}H NMR, which showed both the furanyl methylene and the methylene α to the ester function as AB quartets. It is of interest to note the selectivity of bond cleavage in **3** in contrast to the previous cases. It would appear that the absence of the angular methyl group adjacent to the ketone in **3** facilitates direct attack by base on the carbonyl group leading to Haller−Bauer-type cleavage. Two other conditions, viz. potassium *tert*-butoxide in dimethyl sulfoxide−water and aqueous sodium hydroxide in tetrahydrofuran, frequently employed in Haller−Bauer-type reactions[1] were also tried with the benzofuranones **1**−**3**. In all cases, the same product profile was observed in comparable yields.



8; R=H
9; R=Me

Experimental Section

All the compounds described and having asymmetric centers are racemates. Melting points are uncorrected. All reactions were performed under N_2. Preparative-layer chromatography was done with silica gel $60HF_{254}$ plates. Organic extracts were

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(1) (a) Mehta, G.; Reddy, D. S. *Synlett.* **1996**, *3*, 229. (b) Mehta, G.; Reddy, K. S.; Kunwar, A. C. *Tetrahedron Lett.* **1996**, *37,* 2289. (c) Mehta, G.; Praveen, M. *J. Org. Chem.* **1995**, *60*, 279 and references therein. (d) Hamlin, K. E.; Weston, A. W. *Org. React.* **1957**, *9*, 1. (e) Gassman, P. G.; Lumb, J. T.; Zalan, F. V. *J. Am. Chem. Soc.* **1967**, *89*, 946. (f) Paquette, L. A.; Maynard, G. D. *J. Org. Chem.* **1989**, *54*, 5054 and earlier related papers.

(2) For a review see: Bellus, D.; Ernst, B. *Angew Chem. Int. Ed. Engl.* **1988**, *27*, 797.

(3) (a) Mittra, A.; Biswas, S.; Venkateswaran, R. V. *J. Org. Chem.* **1993**, *58*, 7913. (b) idem, *J. Indian Inst. Sci.* **1994**, *74*, 199.

(4) Biswas, S.; Ghosh, A.; Venkateswaran, R. V. *J. Org. Chem.* **1990**, *55*, 3498.

10.1021/jo9810922 CCC: $15.00

dried using anhydrous sodium sulfate. IR spectra were determined for $CHCl_3$ solutions. ^1H NMR spectra were recorded at 60 MHz for CCl_4 solutions and at 200 or 300 MHz for $CDCl_3$ solutions. ^{13}C NMR spectra were recorded at 75 MHz. Petroleum ether refers to the fraction of boiling point 60−80 °C.

General Procedure for the Reaction of Cyclobutabenzofuranones with Aqueous Alkali. A mixture of cyclobutabenzofuranone **1** (250 mg), aqueous sodium hydroxide (15%, 4 mL), and 2-methoxyethanol (10 mL) was refluxed for 10 h. It was then cooled and extracted once with ether. The ethereal layer left no residue. The aqueous portion was acidified with cold dilute HCl (6 N) and extracted with ether. The ethereal extracts were washed with water, dried,and concentrated to afford an acid as a foamlike solid (230 mg). This showed the following spectral feature: ^1H NMR (CCl_4) δ 1.16 (s, 3H), 1.23 (s, 3H), 1.49 (s, 6H), 1.69−2.0 (m, 2H), 2.23 (s, 3H), 2.30 (s, 3H), 5.63 (m, 1H), 6.29−6.79 (m, 6H).

This acid was esterified with diazomethane and purified by preparative-layer chromatography. Elution with 5% ethyl acetate in petroleum ether afforded the ester **5** (200 mg, 80%) as a crystalline solid, crystallized from ether−petroleum ether: mp 150−52 °C; IR 1755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (s, 3H), 1.35 (s, 3H), 1.45 (s, 3H), 1.46 (s, 3H), 2.01 (q, A of ABX, $J_{AB} = 16.8$ Hz, $J_{AX} = 2.6$ Hz, 1H), 2.29 (q, B of ABX, $J_{BA} = 16.8$ Hz, $J_{BX} = 2.6$ Hz, 1H), 2.28 (s, 3H), 2.30 (s, 3H), 3.65 (s, 3H), 5.54 (t, X of ABX, $J_{AX} = J_{BX} = 2.6$ Hz, 1H), 6.55 (s, 1H), 6.63 (d, 2H), 6.66 (s, 1H), 6.77 (d, 1H), 6.87 (d, 1H); ^{13}C NMR ($CDCl_3$) δ 18.08, 19.78, 20.83, 20.95, 21.90, 22.0, 42.53, 49.04, 51.82, 52.27, 94.53, 95.31, 110.93, 111.39, 121.64, 122.37, 123.62, 124.45, 128.07, 129.73, 133.15, 138.48, 139.34, 145.79, 157.81, 160.22, 172.09; HRMS found 418.2145 for $C_{27}H_{30}O_4$.

The cyclobutabenzofuranone **2** (100 mg) on treatment as above afforded the acid **6** (90 mg, 90%) as a crystalline solid, crystallized from ethyl acetate−petroleum ether: mp 218−19 °C; ^1H NMR ($CDCl_3$−DMSO-d_6) δ 1.23 (s, 3H), 1.43 (s, 3H), 1.50 (s, 6H), 1.72 (q, A of ABX, $J_{AB} = 16$ Hz, $J_{AX} = 2$ Hz, 1H), 2.36 (q, B of ABX, $J_{BA} = 16$ Hz, $J_{BX} = 2$ Hz, 1H), 5.71 (t, X of ABX $J_{AX} = J_{BX} = 2$ Hz, 1H), 6.66−7.33 (m, 8H). Anal. Calcd for $C_{24}H_{24}O_4$: C, 76.57; H, 6.43. Found: C, 76.40; H, 6.38.

The corresponding methyl ester **7** was obtained as a crystalline solid and was crystallized from ether−petroleum ether: mp 130−32 °C; IR 1755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (s, 3H), 1.36 (s, 3H), 1.46 (s, 3H), 1.49 (s, 3H), 1.96 (q, A of ABX, $J_{AB} = 16$ Hz, $J_{AX} = 3$ Hz, 1H), 2.32 (q, B of ABX, $J_{BA} = 16$ Hz, $J_{BX} = 3$ Hz, 1H), 3.64 (s, 3H), 5.60 (t, X of ABX, $J_{AX} = J_{BX} = 3$ Hz, 1H), 6.72−7.28 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 17.64, 19.30, 20.23, 20.55, 42.0, 48.89, 51.57, 51.93, 93.76, 94.82, 109.87, 110.36, 120.60, 121.29, 123.67, 124.44, 127.66, 127.98, 128.75, 132.27, 135.61, 145.56, 157.23, 159.52, 171.58. Anal. Calcd for $C_{25}H_{26}O_4$: C, 76.90; H, 6.71. Found: C, 76.62; H, 6.46.

Similar treatment of the cyclobutabenzofuranone **3** (250 mg) furnished the acid **8** (220 mg, 80%) as a crystalline solid, crystallized from ether−petroleum ether: mp 104−5 °C; ^1H NMR ($CDCl_3$) δ 1.44 (s, 3H), 2.30 (s, 3H), 2.75 (AB_q, $J_{AB} = J_{BA} = 15$ Hz, 2H), 4.40 (AB_q, $J_{AB} = J_{BA} = 9$ Hz, 2H), 6.64 (s, 1H), 6.75 (d, $J = 9$ Hz, 1H), 7.13 (d, $J = 9$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.49, 25.03, 43.39, 44.09, 82.47, 110.68, 121.48, 122.28, 131.16, 138.98, 159.27, 176.96. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.63; H, 6.39.

The corresponding methyl ester **9** was purified by preparative-layer chromatography using 2% ethyl acetate in petroleum ether and was obtained as an oil: bp (oven temperature) 110−12 °C (0.2 mmHg); IR 1755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 3H), 2.30 (s, 3H), 2.65 (AB_q, $J_{AB} = J_{BA} = 15$ Hz, 2H), 4.44 (AB_q, $J_{AB} = J_{BA} = 9$ Hz, 2H), 6.63 (s, 1H), 6.69 (d, $J = 9$ Hz, 1H), 6.97 (d, $J = 9$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.49, 25.08, 43.57, 44.23, 51.57, 82.62, 110.61, 121.38, 122.29, 130.90, 138.85, 159.35, 171.68. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.10; H, 7.44.

The above reaction was also carried out using potassium *tert*-butoxide in dimethyl sulfoxide−water and aqueous sodium hydroxide in tetrahydrofuran. In both cases, the cyclobutanones **1**−**3** furnished the acids **4**, **6**, and **8**, respectively, in comparable yields.

Acknowledgment. We sincerely thank Dr. E. W. Colvin, Chemistry Department, Glasgow University, Glasgow, U.K. for some of the high-resolution ^1H NMR and mass spectra and fruitful discussions. Financial support from the Department of Science and Technology, Government of India, is gratefully acknowledged.

Supporting Information Available: NMR spectra of **5**, **7**, and **8** (4 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.

JO9810922