Unexpected Products from the Reactions of 1-(Bromodifluoromethyl)-2-bromocyclohexanes with Potassium Hydroxide

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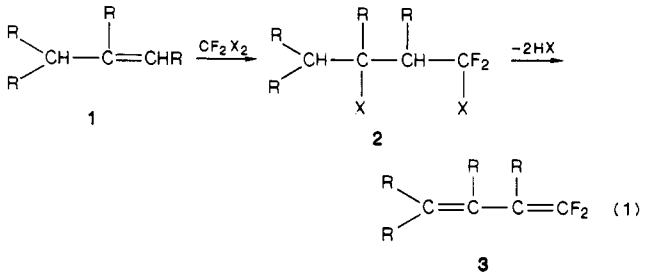
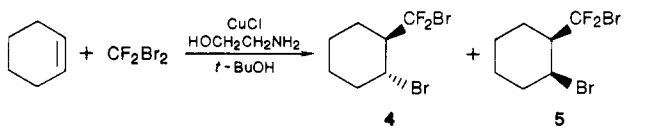
As part of our interest in the synthetic utility of difluorodiiodomethane,[1] we sought a general route into 1,1-difluoro 1,3-dienes **3** based on addition to alkenes followed by double dehydrohalogenation (eq 1, X = I). As a preliminary study we investigated the reactions of some of the analogous dibromides (eq 1, X = Br).



(1)

In their pioneering work on similar dibromide systems, Tarrant and Lovelace found that potassium hydroxide "was not suitable for conversion of the 1,3-dibromides into butadienes since high-boiling products always were obtained in considerable quantities".[2] We report herein the identities of some similar unexpected products and evidence that supports a mechanistic rationale for their formation.

Dibromides **4** and **5** were prepared by adding CF_2Br_2 to cyclohexene (eq 2). We found that the CuCl-catalyzed process reported by Burton and Kehoe[3] is better suited for large-scale preparations than the traditional benzoyl peroxide initiated[2] addition. The reactions gave satisfactory yield and could be carried out in conventional glassware rather than a sealed autoclave.



(2)

When a mixture of dibromides **4** and **5** was heated in the presence of excess aqueous potassium hydroxide at 150–170 °C for 5 h, none of the double dehydrohalogenated product **8** was observed. The exclusive organic product was 1-cyclohexene-1-carboxylic acid (**11**). When the reaction was carried out in a distillation apparatus to allow continous removal of products as they were formed, the distillate contained water along with intermediate products **7**, **8**, and **10** in 39%, 9%, and 17% yields, respectively. The pot residue was composed of **11** and some unreacted **4**. None of the cis isomer **5** remained.

These observations are consistent with the mechanistic pathways shown in Scheme I. The favored conformers of the dibromides **4** and **5** presumably have the bulkier CF_2Br group in the equatorial position. The most acidic hydrogen is that on the ring carbon that bears the CF_2Br group. The observed greater reactivity of **5** relative to **4** suggests that an anti elimination is favored. The cis isomer **5** can undergo rapid elimination to **7**; however, the diequatorial conformation shown for **4** has the ring bromine gauche to the acidic hydrogen. There is no conformation of **4** that allows the hydrogen on the tertiary carbon to be anti to the ring bromine.[4]

Even so, eliminations of this type need not be regiospecific. Both **4** and **5** can eliminate HBr to give **6**, a compound with an exocyclic double bond.[5]

Once formed, compound **6** can further react to give **9** by an S_N2' or addition–elimination process. Subsequent loss of HF from the α,α-difluoro alcohol **9** to give the acyl fluoride **10** is facile under the reaction conditions and is consistent with the observed instability of primary perfluro alcohols.[7] Product **11** presumably results from nucleophilic acyl substitution on **10** by hydroxide.[8]

We have considered the possibility that **9** could have resulted from nucleophilic substitution of bromide on **7** by hydroxide. Although nucleophilic substitutions on fluoroalkyl substrates are generally not observed,[9] the allylic bromide of **7** may be sufficiently activated to offset the normally reduced reactivity. When **7** was refluxed in the presence of less than a stoicheometric amount of KOH for 1 h, **11** was observed along with a small amount of unreacted **7**. It is noteworthy that none of the diene **8** could be detected by ^1H or ^{13}C NMR spectroscopy.

Another possible pathway for the formation of **11** could involve the intermediacy of **8**, which is subsequently attacked by hydroxide at the exocyclic carbon to give **9**. As a test of this possibility, a sample of **8** was subjected to the original reaction conditions. As expected, the major product formed was the acid **11** along with smaller amounts of unidentified (probably dimeric) materials.

Finally, product **11** could also have been formed from **10** via the ketene **12**. We tend to reject this pathway since the hydroxide-catalyzed hydrolysis of **10** would probably be faster,[10] and, although vinyl ketenes have been prepared by vinylogous elimination of HCl from α,β-unsaturated acyl chlorides,[11] we know of no precedent for an analogous HF elimination.

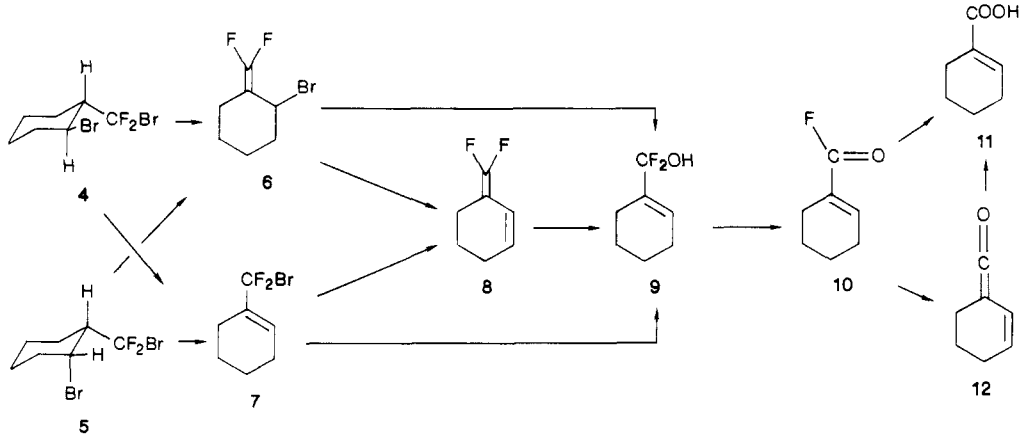
Summary

Dibromides **4** and **5** react with potassium hydroxide to give the unsaturated acid **11** as the final product. The cis isomer **4** reacts faster than the trans isomer **5**, which implies anti elimination. The acid **11** is formed via intermediate products **7** and **10**. At least part of the product is formed via a pathway involving the intermediacy of the *gem*-difluoro diene **8**, however, nucleophic substitution on

(1) Elsheimer, S.; Dolbier, W. R., Jr.; Murla, M.; Seppelt, K.; Paprott, G. *J. Org. Chem.* **1984**, *49*, 205.
(2) Tarrant, P.; Lovelace, A. M. *J. Am. Chem. Soc.* **1954**, *76*, 3466.
(3) Burton, D. J.; Kehoe, L. J. *Tetrahedron Lett.* **1966**, 5163.
(4) Of course one can envisage an anti elimination from the diaxial conformation of **4** to give 3-(bromodifluoromethyl)cyclohexene. Since none of this product was observed, we reasoned that either the population of diaxial **4** is so low that 2,3-elimination does not compete or, more likely, any 3-(bromodifluoromethyl)cyclohexene formed was rapidly converted to **7** or **8** under the reaction conditions.
(5) An analogous reaction of 1,3-dibromo-1,1-difluoropropane with aqueous KOH, for example, has been reported to yield a 5:2 mixture of the two regioisomers 3-bromo-3,3-difluoropropene and 1,1-difluoro-3-bromopropene.[6]
(6) Seyferth, D.; Simon, R. M.; Sepelak, D. J.; Klein, H. A. *J. Am. Chem. Soc.* **1983**, *105*, 4634.
(7) Banks, R. E. *Fluorocarbons and their Derivatives*; McDonald & Co.: London, 1970; p 165.
(8) Swain, C. G.; Scott, C. B. *J. Am. Chem. Soc.* **1953**, *75*, 246.
(9) Chambers, R. D. *Fluorine in Organic Chemistry*; Wiley: New York, 1973; Chapter 5.
(10) The hydroxide-catalyzed hydrolysis of benzoyl fluoride, for example, is actually faster than that of benzoyl chloride (k_F/k_{Cl} = 1.4).[8]
(11) (a) Hickmott, P. W.; Miles, G. J.; Sheppard, G., Urbani, R.; Yoxall, C. T. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1514. (b) Holder, R. W.; Freiman, H. S.; Stefanchik, M. F. *J. Org. Chem.* **1976**, *41*, 3303.

0022-3263/88/1953-6151$01.50/0

Scheme I



7 by hydroxide cannot be rigorously excluded as a possible competing pathway.

Experimental Section

General Methods. All NMR spectra were obtained in $CDCl_3$ solutions at ambient temperature on a Varian Gemini 200 spectrometer. Chemical shifts (δ) are reported in parts per million downfield of internal tetramethylsilane. Infrared spectra were obtained from neat liquids or solutions as capillary films between KBr plates on a Perkin-Elmer 1420 ratio recording infrared spectrophotometer. All reagents and solvents were commercial samples used without purification. Potassium hydroxide pellets were ground to powder before use. Elemental analyses were performed by Robertson Laboratory, Inc., Madison, NJ.

Preparation of 4 and 5. The procedure was patterned after that reported by Burton and Kehoe for the addition of polyfluorinated alkanes to olefins.[3] Into a 500-mL round-bottom flask were placed 120 mL of *tert*-butyl alcohol, 4.07 g of 2-aminoethanol (66.6 mmol), 10.72 g of cyclohexene (130 mmol), 49.35 g of dibromodifluoromethane (235 mmol), and 0.17 g of cuprous chloride (1.7 mmol). The mixture was magnetically stirred and refluxed for 47 h,[12] and then cooled to room temperature and treated with 200 mL of deionized water and 100 mL of diethyl ether. The ether layer was separated, washed five times with 25-mL portions of water, dried over anhydrous calcium chloride, and rotary evaporated to give 8.52 g (22% yield) of dibromides **4** and **5**. The ratio of **4** to **5** was found to be 2.3 to 1 by ^1H NMR integration. Anal. Calcd for $C_7H_{10}Br_2F_2$: C, 28.80; H, 3.54; Br, 54.74; F, 13.01. Found: C, 29.10; H, 3.47; Br, 54.51; F, 12.84. **4**: ^1H NMR δ 4.20 (td, J = 9 Hz, J = 4 Hz, 1 H, CHBr), 1.1–2.5 (unresolved mults, 9 H); ^{13}C NMR δ 126.4 (dd, J_{FC} = 314 Hz, J'_{FC} = 308 Hz, CF_2Br), 55.6 (t, J_{FC} = 36.5 Hz, C(1)), 49.4 (d, J_{FC} = 2.8 Hz, C(2)), 37.3 (s, C(3)), 27.3 (t, J_{FC} = 3.3 Hz, C(6)), 25.6, 23.4; IR 2930 (br), 2855, 1445, 1365 (w), 1325 (w), 1305, 1256, 1240, 1190, 1159, 1138, 1104, 1092, 1056 (w), 1037 (w), 1017, 980 (vw), 930 (br), 899 (w), 879 (w), 861 (w), 848 (w), 821 (w), 800 (w), 750 (w), 693, 620 cm^{-1}. **5**: ^1H NMR δ 4.76 (br s, 1 H, CHBr), 1.0–2.6 (unresolved mults); ^{13}C NMR δ 124.7 (dd, J_{FC} = 313 Hz, J'_{FC} = 309 Hz, CF_2Br), 55.3 (dd, J_{FC} = 21.6 Hz, J'_{FC} = 19.0 Hz, C(1)), 50.2 (t, J_{FC} = 3.1 Hz, C(2)), 35.6, 25.1, 21.6, 20.4. IR: Although no infrared spectrum was taken of pure **5**, the infrared spectrum for a mixture **4** and **5** showed all the same absorptions as the spectrum of pure **4**. In addition absorptions were also observed in the mixture at 1070, 787, 764, 660, and 635 cm^{-1}.

Reaction of 4 and 5 with KOH in a Closed Vessel. Into a 10-mL screw-top tube were weighed 0.35 g of a 2.3 to 1 mixture of **4** and **5** (1.2 mmol), 0.58 g of KOH (85% pure, 8.8 mmol), and 1.73 g of deionized water. The mixture was magnetically stirred and heated at 150–170 °C for 5 h. The reaction mixture was acidified with 3 M HCl and extracted with three 2-mL portions of chloroform. The combined extracts were dried over anhydrous calcium sulfate and rotary evaporated to give 0.14 g of **11** (93% yield[13]). ^1H NMR and IR spectra agreed with those previously reported.[14] ^{13}C NMR: δ 173.7 (CO_2H), 143.0 (C(2)), 130.2 (C(1)), 26.1, 23.9, 22.1, 21.5.

Continuous Distillation of Products from the Reaction of 4 and 5 with KOH. Into a 50-mL round-bottomed flask were placed 6.10 g of a 2.3 to 1 mixture of **4** and **5** (20.9 mmol) and 3.87 g of KOH (69.1 mmol). The flask was equipped with a magnetic stir bar and a small distillation head. The heterogeneous reaction mixture was heated over an oil bath up to a maximum bath temperature of 200 °C. Distillate was collected over a head temperature range of 88–105 °C. The organic products codistilled over with the water which was formed in the reaction. The two-phase liquid distillate was separated, and the organic layer was washed several times with water and then dried over anhydrous $CaCl_2$ to give 2.42 g of product mixture. Yields were determined by ^1H NMR integration to be 39% **7**, 17% **10**, and 9% **8**. Pure samples of these products were isolated by preparative gas chromatography (10% SP-2100 on Supelcoport 80/100 6 ft × $^1/_8$ in., 80 °C, He flow = 15 mL/min). The residue from the reaction (7.55 g) was treated with water to dissolve the inorganics and then extracted with methylene chloride. The organic solution was washed several times with water, dried over $CaCl_2$, and rotary evaporated. The ^1H NMR and IR spectra indicated the presence of unreacted **4** and the enoic acid **11**. **7**: ^1H NMR δ 6.28 (br s, 1 H, vinyl), 2.37–2.05 (mult, 4 H, on C(3) and C(4)), 1.74–1.50 (mult, 4 H, on C(4) and C(5)); ^{13}C NMR δ 135.6 (t, J = 19.9 Hz, C(1)), 128.5 (t, J = 7.5 Hz, C(2)), 120.5 (t, J = 305 Hz, CF_2Br), 24.6, 23.3, 21.8, 21.5; IR 3050 (vw), 2930, 2855, 1799 (w), 1680, 1660, 1445, 1432, 1422 (w), 1370 (w), 1345 (w), 1304 (vw), 1274, 1232, 1210 (shoulder), 1178 (w), 1120, 1070, 1056, 1017, 950, 920, 905 (w), 879, 850, 815, 803 (shoulder), 793, 733, 701, 613 (w) cm^{-1}. Anal. Calcd for $C_7H_9BrF_2$: C, 39.84; H, 4.30; Br, 37.86, F, 18.00. Found: C, 39.98; H, 4.24; Br, 38.02; F, 17.96. **10**: ^1H NMR δ 7.24 (fine mult, 1 H, vinyl), 2.32 (fine mult, 4 H), 1.35–1.57 (mult, 4 H); ^{13}C NMR δ 158.4 (d, J_{CF} = 347 Hz, COF), 148.1 (s, C(2)), 126.7 (d, J_{CF} = 52.4 Hz, C(1)), 26.4, 24.2, 21.8, 21.1; IR 2930, 2855, 1793 (vs), 1680, 1638, 1446, 1432, 1417, 1372 (w), 1340 (w), 1303 (w), 1270, 1257 (w), 1212, 1195 (shoulder), 1185 (shoulder), 1160 (vw), 1148 (w), 1112 (vw), 1090 (vw), 1062 (w), 1050 (w), 1039 (vw), 1019 (w), 1000, 945, 915, 880 (w), 865 (vw), 846, 815 (vw), 799 (w), 780 (vw), 760 (w), 732, 716, 671, 648 (w) cm^{-1}. **8**: ^1H NMR δ 6.12 (d, J = 10.7 Hz, 1 H, vinyl), 5.81 (mult, 1 H, vinyl), 2.28 (mult, 2 H), 2.12 (mult, 2 H), 1.68 (quintet, 2 H, J = 6 Hz); ^{13}C NMR δ 152.4 (dd, J_{FC} = 292 Hz, J'_{FC} = 288 Hz, CF_2), 129.2 (dd, J_{FC} = 11.1 Hz, $J_{FC'}$ = 4.7 Hz, =CH), 119.5 (d, J_{FC} = 2.2 Hz, =CH), 88.3 (dd, J_{FC} = 23.0 Hz, J'_{FC} = 15.4 Hz, $=CR_2$), 25.1, 21.5, 21.1; IR ($CDCl_3$) 3035 (w), 2930, 2860 (w), 2830 (w), 1796, 1721 (s), 1615, 1440 (w), 1430 (w), 1400 (w), 1345 (w), 1332 (w), 1290, 1254 (w), 1235, 1229,

(12) The low-boiling CF_2Br_2 can easily be lost out the top of a water-cooled reflux condenser. A dry ice/2-propanol condenser or refrigerated condenser is recommended.

(13) Loss due to handling of this small-scale reaction makes the isolated yield appear deceptively low. Conversion of **4** and **5** to **11** was essentially quantitative. No other products or unreacted starting material were detected.

(14) Dieter, R. K.; Lin, Y. J.; Dieter, J. W. *J. Org. Chem.* **1984**, *49*, 3183.

1185 (w), 1155 (w), 1140 (w), 1073, 1033, 967 (w), 861 (w), 849 (w) cm^{-1}.

Reaction of 7 with KOH. Into a 5-mL round-bottomed flask were weighed 0.41 g of **7** (1.9 mmol) and 0.10 g of KOH (1.8 mmol). The flask was equipped with magnetic stirrer and a reflux condenser, and the mixture was heated over a 180 °C oil bath for 1 h. The mixture was cooled to room temperature, and then 1 mL of $CDCl_3$ was used to wash down the inside of the reflux condenser into the reaction vessel. The reaction mixture was washed three times with 2-mL portions of water and then dried over anhydrous calcium sulfate. ^1H NMR analysis showed a 3.7:1 ratio of **11** to unreacted **7**.

Reaction of 8 with KOH. Into a 5-mL screw-top tube were weighed 0.15 g of **8** (1.2 mmol), 0.18 g of KOH (3.2 mmol), and 0.07 g of deionized water. The mixture was magnetically stirred and heated over an oil bath at 184–210 °C for 3.5 h. The mixture was cooled to 0 °C, taken up in 0.75 g of $CDCl_3$, washed with three 2-mL portions of 3 M HCl and two 3-mL portions of water, and then dried over anhydrous $CaSO_4$. The resulting solution was analyzed by ^1H and ^{13}C NMR and found to contain predominantly **11** along with a small amount of some unidentified high molecular weight side products.

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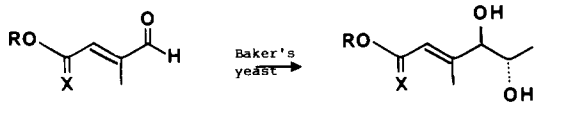
Registry No. **4**, 117711-58-7; **5**, 117711-59-8; **7**, 117711-60-1; **8**, 117711-61-2; **10**, 117711-62-3; **11**, 636-82-8; CF_2Br_2, 75-61-6; cyclohexene, 110-83-8.

Communications

Conversion of 4-Oxy-Substituted Crotonaldehyde into 1-Protected (2*R*)-1,2,4-Butanetriol: A New Synthetic Capacity of Bakers' Yeast

Summary: The bakers' yeast mediated conversion of 4-oxy-substituted crotonaldehydes **3** and **4** into 1-protected (2*R*)-1,2,4-butanetriols **7a** and **8a**, in ca. 25% yield, is reported.

Sir: The ability of bakers' yeast to reduce the carbonyl group and to saturate the double bond of α,β-unsaturated aldehydes is well known.[1] When an aromatic substituent is present in the γ-position of the substrate (e.g., in cinnamaldehyde), the above transformations compete with the decarboxylative incorporation of pyruvate. The resulting (3*R*)-$C_6H_5CH{=}CHCH(OH)COCH_3$ is subsequently reduced to the 2*S*,3*R* diol $C_6H_5CH{=}CHCH(OH)CH(OH)CH_3$.[2] Crotonaldehyde and tiglic aldehyde do not undergo the latter acyloin-type condensation. However, current studies[3] indicate that, under suitable experimental conditions, γ-oxy-substituted tiglic aldehydes like **1** and **2** afford the corresponding diols **5** and **6**, the ultimate products of the acyloin-type condensation, in 35% and 10% yield, respectively.



1 R= Et; X= O
2 R= COC_6H_5; X= H_2
5 R= Et; X= O
6 R= COC_6H_5; X= H_2

We now report a new synthetic capacity of bakers' yeast toward α,β-unsaturated aldehydes that emerges when 4-(benzoyloxy)- and 4-(benzyloxy)crotonaldehyde (**3** and **4**) are incubated with bakers' yeast under the conditions in which **1** and **2** are converted to **5** and **6**. In a typical experiment, a mixture of aldehyde **3** (8 g) and D-glucose (100 g) in tap water (1.5 L) at pH 5–5.2 and 35 °C is stirred as commercial bakers' yeast (200 g) is added in portions during 3 h. After that time, extractive workup (AcOEt) affords in 60–70% yield a mixture, separated by column chromatography, composed of unreacted aldehyde **3** (15%), a mixture of alcohols **9** and **10** in variable ratios (60%), and diol **7a** (25%). The last product, an oil showing a moderate negative rotation, was characterized as the diacetate (**7b**), $[\alpha]^D_{20}$ +17° (*c* 1, MeOH). Acidic hydrolysis of **7a** and acetylation afforded the triacetate **7c**, $[\alpha]^D_{20}$ +10.3° (*c* 1, MeOH). ^1H NMR spectra of **7c** in the presence of tris[3-(trifluoromethyl)hydroxymethylene]-[(+)-camphorato]europium(III) and comparison with racemic material, showed the presence of a single enantiomer (95%). This was assigned the 2*R* absolute configuration depicted in **7c** because the triacetyl derivative of (2*S*)-1,2,4-butanetriol, prepared by hydrolysis of the 2-THP derivative,[4] obtained in turn from (*S*)-malic acid, showed $[\alpha]^D_{20}$ −10.8° (*c* 1, MeOH). Similar results were obtained by using (4-(benzyloxy)crotonaldehyde (**4**) as substrate: together with the expected reduction products, diol **8a** was obtained in ca. 25% yield. Acetylation of the latter afforded the diacetate **8b**, $[\alpha]^D_{20}$ +14° (*c* 1, MeOH), which after hydrogenolysis (H_2/Pd–C/AcOEt) gave **8c**, which was then acetylated to **7c**, $[\alpha]^D_{20}$ +9.85° (C 1, MeOH). As above, ^1H NMR studies indicated predominance of the 2*R* enantiomer (90–95%). Alcohol **9** is apparently not converted into the diol **7a** under the above conditions.

The formation of diols **7a** and **8a** from **3** and **4** is expected to be the consequence of two chemical changes involving water addition across the double bond of **3** and **4**, followed by reduction of the intermediate 3-hydroxy aldehydes. The steric course of the water addition is identical with that observed recently[5] in the microbiological conversion of the 4-nitrogen-substituted α,β-unsaturated crotonobetaine $Me_3N^+CH_2CH{=}CHCOO^-$ and in the enoyl-CoA hydratase (EC 4.2.1.17)-catalyzed conversion of crotonoyl-CoA to (3*R*)-3-hydroxybutyryl-CoA.[6]

In order to determine the steric course of the water addition, we prepared [2,3-$^2H_2$]-4-(benzoyloxy)croton-

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