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Direct Conversion of *tert*-β-Bromo Alcohols to Ketones with Zinc Sulfide and DMSO

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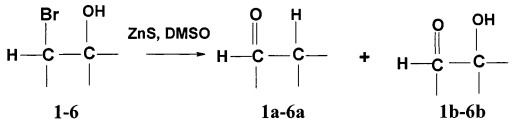
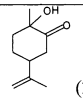
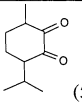
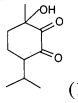
Abstract: *tert*-β-Bromo alcohols, derived from simple monoterpene hydrocarbons, react with zinc sulfide in dimethyl sulfoxide to afford saturated ketones as the major and hydroxy ketones as the minor products. The reaction involves initial nucleophilic attack by DMSO on the carbon attached to the halogen, which is assisted by electrophilic zinc sulfide. Subsequent Kornblum type oxidation yields the α-hydroxy ketone. On the other hand, abstraction of proton β to the hydroxyl group followed by an attack of the neighboring hydroxyl moiety on the sulfur of the dimethylsulfoxonium intermediate and its subsequent collapse yields an enol, which tautomerizes to a saturated ketone. The latter pathway is predominantly followed.

Cohalogenation is an important method of functionalization of olefins, since the resultant halohydrins and related derivatives enable subsequently regio- and stereospecific introduction of heteroatomic groups.[1] The transformation of halohydrins to carbonyl compounds is effected by bases and/or acids[2] as well as transition metal salts.[3] Mention may be made of the stereospecific synthesis of *trans*-β-terpineol[4] and preparation of *cis*-3-carene oxide[5] from the corresponding monoterpenic hydrocarbons. Direct conversion of bromohydrins to ketones by irradiation in benzene or toluene is known,[6] but the reaction does not proceed when the alcohol is tertiary. More recently, a free radical-mediated method for the conversion of bromohydrins to ketones has been reported,[7] wherein the abstraction of proton α to the hydroxyl is followed by the elimination of β-halogen atom and then tautomerization of the resultant enol. Understandably, *tert*-β-bromo alcohols do not undergo this reaction due to the absence of an α-proton. In both these methods, the hydroxyl group is converted to a ketone or aldehyde with the elimination of hydrogen bromide. We got interested in the direct conversion of the bromo group in (1*S*,2*S*,4*R*)-2-bromo-1-hydroxy-*p*-menthane,[4] and other similar *tert*-β-bromo alcohols derived from monoterpenes by Kornblum type of oxidation.

TABLE 1. Reaction of Bromohydrins with Zinc Sulfide and DMSO at 70 °C



1-6 1a-6a 1b-6b

Entry No.	Bromohydrin	Reaction time (h)	Product a (% Yield)	Product b (% Yield)
1		6	 (41)	 (39)
2		5	 (66)	 (13)
3		10	 (60)	 (22)
4		30	 (50)	 (31)
5		10	 (62)	———
6		12	 (50)	 (15)

Kornblum oxidation[8] is facile mainly with activated halides.[9−11] Simple aliphatic primary bromides and iodides are first converted to more reactive tosylates and then oxidized to the corresponding aldehydes in fairly good yields.[12] Thus Kornblum oxidation, for its general applicability to halides, obviously needs electrophilic catalysis as in the case of silver-salt assisted DMSO oxidation of halides[13] as well as Swern oxidation of alcohols to carbonyl compounds.[14] Earlier, we had observed that zinc polarized the C−X bond in S_N1-active

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TABLE 2. Physical and Spectral Data of Products

product	bp (°C/mm)	specific rotation[a] $[\alpha]^{20}_D$ (c = $CHCl_3$)	^{1}H NMR[b] δ ppm(J=Hz)	IR[c] γ cm^{-1}	MS (m/z)[d]
1a	160−161	0 (2.0)	1.13(d, 3H, J = 6 Hz), 1.56−2.06 (m, 6H), 2.20−2.36 (m, 3H)	2935, 1712 (s)	112 (18), 97 (4), 84 (12), 68 (95), 55 (65), 41 (100)
1b	152−154	0 (2.0)	1.43 (s, 3H), 1.53−2.66 (m, 8H), 3.16 (s, 1H)	3398 (br), 2935, 1705 (s)	128 (2), 113 (5), 112 (25), 97 (60), 84 (35), 79 (40), 68 (40), 55 (50), 41 (100)
2a	73−75/1.5	−4° (1.0)	0.86 (d, 6H, J = 6 Hz), 1.20 (d, 3H, J = 6 Hz), 1.20−2.16 (m, 6H), 2.20−2.46 (m, 3H)	2872, 1712	154 (12), 139 (2), 125 (5), 111 (60), 97 (15), 83 (12), 69 (18), 55 (100), 41 (55)
2b	74−75/8	−25° (2.0)	0.86 (d, 6H,J = 6 Hz), 1.36 (s, 3H), 1.39−2.50 (m, 8H), 3.26 (s, 1H)	3448 (br), 2960, 1710	170 (2), 154 (10), 152 (2), 139 (5), 126 (4), 111 (10), 97 (15), 82 (50), 69 (60), 55 (60), 43 (100)
3a	85−87/3	−18° (2.0)	1.36 (d, 1H, J = 6 Hz), 1.83 (s, 3H), 1.90−2.86 (m, 8H), 4.89 (s, 2H)	2972, 1715	152 (9), 137 (6), 109 (15), 95 (52), 67 (100), 55 (35), 41 (80)
3b	71−72/8	+55.33° (1.5)	1.40 (s, 1H), 1.83 (s, 3H), 1.90−2.83 (m, 7H), 3.20 (s, 1H), 4.89 (s, 2H)	3450 (br), 2975, 1725	168 (2), 152 (3), 140 (4), 125 (18), 111 (7), 97 (9), 82 (30), 71 (90), 67 (55), 55 (35), 43 (100)
4a	76−77/2	−140° (2.0)	0.93 (s, 6H), 1.03 (d, 3H, J = 3 Hz), 1.13−1.20 (m, 4H), 2.13−2.50 (m, 3H)	3004, 1711 (s)	152 (15), 137 (9), 109 (24), 82 (32), 81 (75), 67 (100), 41 (90)
4b	124−126	−5° (2.0)	0.93 (s, 6H), 1.36 (s, 3H), 1.16−1.23 (m, 4H), 2.16−2.20 (m, 2H), 2.50 (s, 1H)	3451 (br), 2950, 1710 (s)	168 (2), 150 (4), 135 (18), 119 (75), 107 (20), 91 (90), 79 (50), 55 (70), 43 (100)
5a	160−162	+82° (0.5)	1.03 (s, 6H), 1.20 (d, 3H, J = 4.5 Hz), 1.26−2.26 (m, 8H), 3.03 (s, 1H)	3449 (br), 2972, 1702 (s)	170 (2), 155 (3), 152 (3), 137 (3), 112 (52), 97 (50), 84 (22), 70 (40), 59 (100), 43 (80)
6a	79−80/1	+10.43° (2.3)	0.96 (d, 6H, J = 4.5 Hz), 1.46 (d, J = 4.5 Hz, 3H), 1.56−2.56 (m, 7H)	2962 (s), 1711 (s)	168 (2), 153 (3), 139 (15), 125 (15), 111 (7), 97 (23), 83 (12), 69 (90), 55 (80), 41 (100)
6b	65−66 (mp)	−25° (2.0)	0.96 (d, 6H, J = 4.5 Hz), 1.50 (s, 3H), 1.50−2.67 (m, 6H), 3.01 (s, 1H)	3437 (br), 2961, 1709 (s)	184 (2), 168 (8), 150 (8), 126 (54), 108 (30), 91 (15), 69 (40), 55 (50), 41 (100)

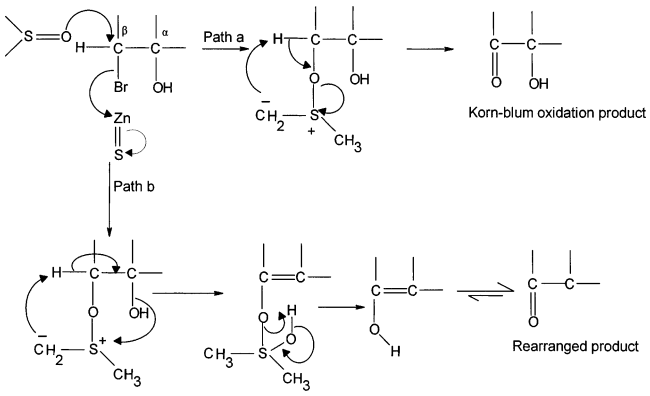
[a] Perkin-Elmer- 243 Polarimeter. [b] Varian EM 390, 90 MHz ($CDCl_3$; TMS as internal standard). [c] Perkin-Elmer-FTIR, Spectrum 2000. [d] Shimadzu QP 5000 GC-MS, 70 eV.

halides without actually forming a carbenium ion and facilitated substitution with a number of nucleophiles at a tertiary center.[15]

Now, we chose to study the effect of various electrophilic zinc salts on the oxidation of bromohydrins in DMSO. In the reactions where zinc carbonate or zinc oxide was employed, exclusive formation of epoxides was observed, apparently due to the basic nature of these salts. On the other hand, when zinc sulfide was used, the halohydrins reacted smoothly with DMSO, giving mainly the carbonyl compounds in good yields. The results are tabulated in Table 1 (entries 1−6). While at lower temperatures (40−60 °C) the reaction was very slow, at higher temperatures (80−120 °C) dehydrohalogenation and dehydration became competitive. At an optimum temperature of 70 °C, hydroxy ketones (1b-6b), the expected Kornblum products, were minor, whereas the saturated ketones (**1a**−**6a**) were major (50−60% yield). The probable mechanism of formation of these ketonic products is given in Scheme 1.

Nucleophilic attack of DMSO on the β-carbon atom of bromohydrin and concomitant abstraction of bromine by zinc sulfide led to a dimethylsulfoxonium intermediate. One of the methyl protons in the latter was, apparently, abstracted by $Zn(Br)S^-$ species to afford the ylide and ZnBrSH. Subsequent loss of dimethyl sulfide afforded a hydroxy ketone, the Kornblum oxidation product (path a). Alternatively, the intermediate could undergo rearrangement (path b), wherein the hydroxyl group on α-carbon atom migrated to sulfur with the formation of a double bond between the carbon atoms involved.

SCHEME 1



Subsequent breakdown of the rearranged intermediate afforded, besides DMSO, an enol that readily tautomerized to a saturated ketone. Path b was preferred because of the participation of the neighboring hydroxyl group in the reaction, as substantiated by the following experiments. The methyl ether of **2** did not yield either of the oxidation products in the reaction; but on prolonged heating, underwent dehydrohalogenation to give allyl methyl ether. On the other hand, cyclohexyl bromide, a secondary halide, required prolonged heating (48 h), at a higher temperature (100 °C) to afford cyclohexanone, the Kornblum product, in only moderate yield (30%).

In conclusion, a direct conversion of *tert*-β-bromo alcohols to saturated ketones is being reported for the first time. It involves activation of the substrate by zinc sulfide and its reaction with DMSO, leading to the formation of a sulfoxonium ylide with concomitant loss of HBr. An interesting rearrangement of this ylide, involving the shift of neighboring hydroxyl group, is

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envisaged to explain the formation of the ketone as the major product.

Experimental Section

Preparation of Bromohydrins. Bromohydrins (**1**−**6**) were prepared by reacting the corresponding olefins (20 mmol) viz., 1-methylcyclohexene (entry no. 1), dihydrolimonene (entry no. 2), (+)-limonene (entry no. 3), Δ^3-carene (entry no. 4), α-terpineol (entry no. 5), and piperitone (entry no. 6) with *N*-bromosuccinimide (20 mmol) in aq acetone at 10 °C. The reaction was monitored for the disappearance of olefin on GC (HP-1 fused silica column, 30m × 0.53 mm × 0.88 μm film thickness, temp program 60°/8°/220° C, 5 min). After completion of the reaction, acetone was removed under vacuum, and residue was diluted with water followed by extraction into CH_2Cl_2 (15 mL × 3). The organic layer was washed with water (30 mL × 2), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude products were chromatographed over SiO_2 (100−200 mesh) using 2% EtOAc in hexane as eluant. The pure fractions were combined and subjected to distillation under reduced pressure or crystallization from 1:1 mixture of Et_2O and petroleum ether (40−60 °C). The yield, boiling point/melting point, optical rotation, IR, ^{1}H NMR, and MS (*m*/*z*) of bromohydrins are given below.

2-Bromo-1-hydroxy-1-methylcyclohexane (entry no. 1): yield 94%, bp 58−60 °C/0.6 Torr, $[\alpha]^{20}_D = +6°$ (*c* = 2, $CHCl_3$), IR (γ cm^{-1}) = 3418 (br), 2939, 2864, ^{1}H NMR: δ = 1.49 (s, 3H), 1.53−2.50 (m, 8H), 2.93 (s, 1H), 4.30 (dd, *J* = 3 Hz, 1H), MS (*m*/*z*): 194 (1), 192 (1), 179 (2), 177 (2), 161 (1), 151 (2), 149 (3), 113 (15), 97 (4), 95 (22), 81 (2), 71 (65), 58 (18), 43 (100).

2-Bromo-1-hydroxy-*p*-menthane (entry no. 2): yield 94%, bp 92−94/0.8 Torr, $[\alpha]^{20}_D = +62°$ (neat), IR (γ cm^{-1}) = 3419 (br), 2957, 2873, ^{1}H NMR: δ = 0.80 (d, *J* = 3 Hz, 6 H), 1.26 (s, 3H), 1.50−1.80 (m, 6H), 1.96−2.13 (m, 3H), 4.13 (br, 1H), MS (*m*/*z*): 236 (0.5), 234 (0.5), 221 (1), 219 (1), 203 (1), 201 (1), 176 (43), 174 (20), 155 (4), 138 (14), 121 (4), 95 (6), 71 (100), 67 (30), 55 (20), 43 (70).

2-Bromo-1-hydroxy-*p*-menth-8-ene (entry no. 3): yield 91%, bp 88 °C/ 0.4 Torr, $[\alpha]^{20}_D = +59°$ (neat), IR (γ cm^{-1}) = 3428 (br), 3082, 2938, ^{1}H NMR: δ = 1.16 (s, 3H), 1.46−1.66 and 1.83−2.43 (m, 8H), 1.76 (s, 3H), 4.16 (br, 1H), 4.80 (s, 2H), MS (*m*/*z*): 234 (0.2), 232 (0.2), 216 (1), 214 (1), 152 (8), 135 (16), 93 (27), 91 (20), 67 (43), 43 (100).

Δ^3-Carene bromohydrin (entry no. 4): yield 84%, mp 49−51 °C (decomp), $[\alpha]^{20}_D = -55°$ (*c* = 2, $CHCl_3$), IR (γ cm^{-1}) = 3446 (br), 2938, 2867, ^{1}H NMR: δ = 0.60−0.70 (m, 2H), 0.89 (d, *J* = 3 Hz, 6H), 1.16 (s, 3H), 1.90−2.23 (m, 4H), 2.30 (s, 1H), 3.80 (t, 1H, *J* = 9 Hz), MS (*m*/*z*): 234 (0.5), 232 (0.5), 219 (1), 217 (1), 192 (1), 174 (1), 153 (3), 151 (1), 138 (5), 135 (15), 119 (4), 109 (5), 93 (20), 71 (15), 67 (20), 55 (10), 43 (100).

2-Bromo-1,8-dihydroxy-*p*-menthane (entry no. 5): yield 92% mp 111−113 °C, $[\alpha]^{20}_D = -57°$ (*c* = 2, $CHCl_3$), IR (γ cm^{-1}) = 3458 (br), 2940, 2867, ^{1}H NMR: δ = 0.90 (s, 6H), 1.13 (s, 3H), 1.30−2.0 (m, 7H), 2.96 (s, 1H), 3.63 (s, 1H), 4.06 (br, 1H), MS (*m*/*z*): 252 (0.5), 250 (0.5), 234 (1), 232 (1), 219 (3), 217 (3), 176 (2), 174 (2), 153 (3), 138 (5), 111 (5), 108 (10), 95 (70), 71 (40), 59 (90), 43 (100).

2-Bromo-1-hydroxy-*p*-menth-3-one (entry no. 6): yield 80%, mp 92−94 °C, $[\alpha]^{20}_D = +15.15°$ (*c* = 2, $CHCl_3$), IR (γ cm^{-1}) = 3425 (br), 2965, 2873, 1719, ^{1}H NMR: δ = 1.09 (d, 6 H, *J* = 4.5 Hz,), 1.20 (s, 3H), 2.10−2.50 (m. 6H) 2.70 (s, 1H), 4.83 (s, 1H), MS (*m*/*z*): 250 (0.5), 248 (0.5), 235 (2), 233 (2), 217 (2), 215 (2), 204 (2), 190 (4), 188 (3), 169 (10), 160 (3), 152 (2), 109 (28), 87 (70), 69 (75), 55 (50), 43 (100).

General Procedure: Reaction of Bromohydrins with ZnS and DMSO. In a flask, bromohydrin (10 mmol) was taken in 15 mL of dry DMSO. To this was added dry ZnS (10 mmol), and the mixture was stirred at 70 °C. Reaction was monitored by injection of a worked-up aliquot on GC. At the end, the reaction mixture was poured into water (150 mL) and extracted into CH_2Cl_2 (10 mL × 3). The organic layer was dried over anhydrous Na_2SO_4, and solvent was evaporated. The residue was chromatographed over SiO_2 using a mixture of EtoAc−hexane (1:9) as eluant to obtain pure fractions of ketone (**1a**−**6a**) and hydroxy ketone (**1b**−**6b**). The yields of the products are presented in Table 1, and their physical and spectral spectral data in Table 2.

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