Oxidation and Bromodehydroxymethylation of Benzylic Alcohols Using $NaBrO_3/NaHSO_3$ Reagent

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The oxidation of benzylic alcohols to benzaldehydes is an important organic reaction and a number of methods have been developed for this purpose.[1,2] Whilst numerous reagents have been developed to effect this process, bromate anion has been used for oxidizing alcohols to aldehydes or ketones,[3-6] esters[5,7] and carboxylic acids.[6,7] Bromate anion was also known to oxidize sulfides to sulfoxides,[8] hydroquinones or polyaromatics to quinones,[8,9] thiols to disulfides,[6,10] iodobenzenes to iodoxybenzenes.[11] In addition, there are some other examples such as cleavage of carbohydrate benzyl ethers and benzylidene acetals,[12] preparation of bromohydrin derivatives,[13] oxidative deprotection of tetrahydropyranyl ethers, ethylene acetals,[14] aromatic bromination,[15] and bromination of alkylbenzenes.[16] Meanwhile, Ishii and co-workers examined an appropriate method for generating HOBr equivalents from $NaBrO_3$ combined with various reducing agents ($NaHSO_3$, Na_2SO_3, $Na_2S_2O_3$, Na_2HPO_3, $FeSO_4$, and $H_2C_2O_4$ etc.) and found that $NaHSO_3$ was the best reducing agent.[13] They also showed that $NaBrO_3/NaHSO_3$ reagent was an efficient oxidizing agent of primary alcohols to dimeric esters,[7] diols to hydroxyketones and/or diketones,[17] and ethers to esters[12] in aqueous medium. Ho emphasized that bromate ion without any mediate was not capable of oxidizing benzylic alcohols.[4]

Recently, we described that Oxone® and bromide ions have been used for the oxidation of benzylic alcohols to benzaldehydes[18] and the bromodecarbonylation of benzaldehydes with an electron-donating substituent at *para* position to bromoarenes.[19] In this paper, we report the oxidation of benzylic alcohols to benzaldehydes and the bromodehydroxymethylation of benzylic alcohols with an electron-donating substituent at *para* position to bromoarenes using a mixture of equimolar amounts of $NaBrO_3$ and $NaHSO_3$.

Optimization of the reaction conditions revealed that simple stirring a solution of benzylic alcohol (1 equivalent), $NaBrO_3$ (2 equivalents) and $NaHSO_3$ (2 equivalents) in a 1 : 1 mixture of CH_3CN/H_2O effected the formation of benzaldehyde and benzoic acid in 77% and 21% isolated yields within 1.5 h, respectively.[7] When one equivalent of $NaBrO_3$ and $NaHSO_3$ were employed, benzaldehyde (44%) and undesirable benzoic acid (11%) were obtained again. Further studies showed that this oxidation method could be applied to a wide range of benzylic alcohols as shown in Table 1.

The presence of electron-withdrawing groups in the aromatic ring has lowered the oxidation rates. Thus, *p*-nitrobenzyl alcohol was oxidized to aldehyde in 48% yield and to acid in 32% yield over 5 h. However, an electron-rich aromatic having unshared electron-pair at *para* position, *p*-methoxybenzyl alcohol, not only was the ring brominated in the 2-position but the 4-hydroxymethyl group was eliminated and replaced by bromine, 4-bromoanisole (67%) and 2,4-dibromoanisole (12%) being products isolated.[20] Similarly *p*-acetamidobenzyl alcohol afforded 4-bromoacetanilide (53%) and 2,4-dibromoacetanilide (4%). On the other hand, *m*-methoxybenzyl alcohol gave exclusively ring brominated product, 4-bromo-3-methoxybenzyl alcohol (76%)[21] and a small amount of 4-bromo-3-methoxybenzaldehyde (3%).[22] No 3-methoxybenzaldehyde and bromodehydroxymethylation product were observed. The oxidation of 1-phenylethanol afforded acetophenone in 99% yield, and 1-phenyl-1,2-ethanediol was oxidized to 2-hydroxyacetophenone in 87% yield.[17]

A plausible mechanism of the bromodehydroxymethylation is shown in Scheme 1. The oxidation of benzylic alcohols by the hypobromous acid affords benzaldehydes, which presumably proceed *ipso*-bromination and followed by nucleophilic attack of hydroxide ion or water on the aldehyde and subsequent elimination of formic acid to give bromoarenes.[19,23]

In conclusion, we have shown in the present study that facile bromodehydroxymethylation of benzylic alcohols bearing *para*-electron donating substituents having unshared electron-pair can be carried out using a mixture of $NaBrO_3$ and $NaHSO_3$. However, other simple benzylic alcohols were oxidized to form benzaldehydes and benzoic acids.

Experimental Section

Melting points were determined in open capillaries with an Electrothermal melting point apparatus and are uncorrected. Progresses of reactions were followed by TLC using silica gel with fluorescent indicator coated on aluminium sheets. Infrared spectra were recorded on a Nicolet Magna 550 FTIR spectrometer and ^1H NMR spectra were measured

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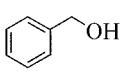
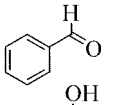
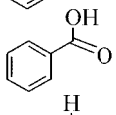
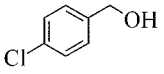
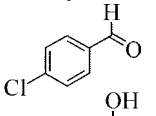
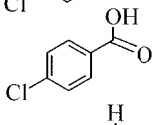
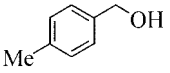
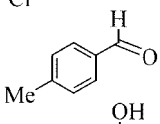
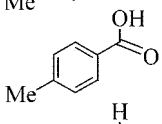
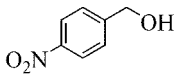
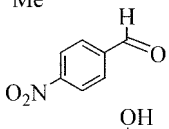
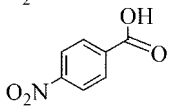
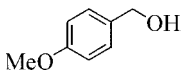
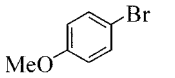
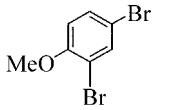
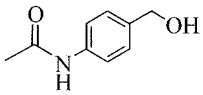
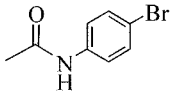
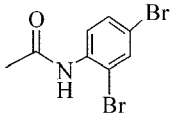
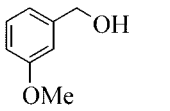
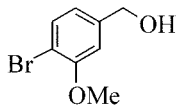
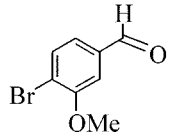
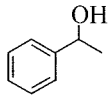
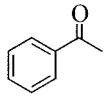
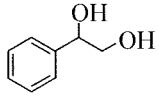
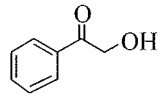
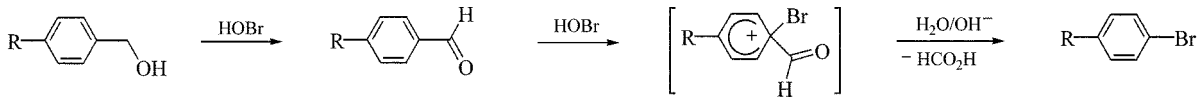
Table 1. Oxidation and Bromodehydroxymethylation of Benzylic Alcohols Using $NaBrO_3$ and $NaHSO_3$

Entry	Substrate	Product	No.	Time (h)	% Yield[a]	mp (Lit.)[b]
1			**1**	1.5	77	liquid (bp 178)
					21	119-121 (122)
2			**2**	3	84	44-46 (47.5)
					15	231-236 (243)
3			**3**	2	85	liquid (bp 204-205)
					14	174-177 (182)
4			**4**	5[c]	48	103-104 (106)
					32	237-242 (242)
5			**5a**	1.5	67	liquid (bp 215)
			**5b**		12	59-61 (61-63)
6			**6a**	0.5	53	166-168 (168)
			**6b**		4	142-143 (144)
7			**7a**	1.5	76	47-49 (bp 110-118/ 2 10^{-3} Torr)[d]
			**7b**		3	71-73 (74)[e]
8			**8**	1	99	liquid (bp 202)
9			**9**	4	87	79-81 (90)

[a]Yields are based on isolated products. [b]CRC Handbook of Chemistry and Physics. [c]18% of alcohol was recovered. [d]Reference 21. [e]Reference 22.



Scheme 1

on a Varian Gemini 300 spectrometer in $CDCl_3$ using TMS as an internal standard. Mass spectra were obtained on a ThermoQuest Polaris Q mass spectrometer operating at 70 eV.

General Procedure for the Reaction of Benzylic Alcohols with $NaBrO_3$ and $NaHSO_3$. To a stirred solutions of alcohols (5 mmol) in aqueous CH_3CN (30 mL, 1 : 1 by volume) was added $NaBrO_3$ (1.51 g, 10 mmol) and $NaHSO_3$ (1.04 g, 10 mmol). Reactions were continuously monitored by thin-layer chromatography and stirred at r.t. for the time indicated in Table 1. The reaction mixture was quenched with aqueous sodium thiosulfate, and extracted with ether (3 × 30 mL). The combined organic layers were washed with aqueous Na_2CO_3, water, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was chromatographed on a silica gel column and eluted with hexane-EtOAc 10 : 1 to give aldehydes or aryl bromides (Table 1). The combined aqueous layer was acidified with a 10% HCl solution to pH 2 and extracted with EtOAc (2 × 50 mL). The organic layers were washed with water, dried and evaporated to afford acid products.

The spectral data of products are as follows:

1: IR (neat) cm^{-1}: 1701, 1600, 1460, 1312, 1204, 827, 749; ^1H NMR δ 7.45-7.67 (m, 3H), 7.87-7.90 (m, 2H), 10.02 (s, 1H); MS m/z (rel intensity) 106 (M^+, 34), 105 (74), 77 (100), 51 (22).

2: IR (KBr) cm^{-1}: 1697, 1576, 1479, 1386, 1204, 1013, 811, 539, 477; ^1H NMR δ 7.53 (d, J = 8.5 Hz, 2H), 7.83 (d, J = 8.5 Hz, 2H), 9.99 (s, 1H); MS m/z (rel intensity) 142 (M^+, 17), 141 (58), 140 (M^+, 46), 139 (100), 113 (7), 111 (19), 77 (6), 75 (13).

3: IR (neat) cm^{-1}: 1701, 1607, 1386, 1308, 1207, 1169, 847, 808; ^1H NMR δ 2.43 (s, 3H), 7.33 (d, J = 7.9 Hz, 2H), 7.78 (d, J = 7.9 Hz, 2H), 9.97 (s, 1H); MS m/z (rel intensity) 120 (M^+, 40), 119 (100), 91 (72), 65 (28).

4: IR (KBr) cm^{-1}: 1712, 1607, 1538, 1344, 1293, 1196, 854, 819, 738; ^1H NMR δ 8.08 (d, J = 8.5 Hz, 2H), 8.41 (d, J = 8.5 Hz, 2H), 10.17 (s, 1H); MS m/z (rel intensity) 151 (M^+, 44), 150 (100), 77 (13), 51 (16).

5a: IR (neat) cm^{-1}: 1577, 1487, 1289, 1239, 1172, 1033, 823; ^1H NMR δ 3.77 (s, 3H), 6.78 (d, J = 8.9 Hz, 2H), 7.37 (d, J = 8.9 Hz, 2H); MS m/z (rel intensity) 188 (M^+, 98), 186 (M^+, 100), 173 (31), 171 (30), 145 (23), 143 (26), 77 (31), 63 (47).

5b: IR (KBr) cm^{-1}: 1576, 1475, 1378, 1263, 1052, 807, 679, 617; ^1H NMR δ 3.87 (s, 3H), 6.77 (d, J = 8.8 Hz, 1H), 7.37 (dd, J = 8.8, 2.3 Hz, 1H), 7.66 (d, J = 2.3 Hz, 1H); MS m/z (rel intensity) 268 (M^+, 35), 266 (M^+, 75), 264 (M^+, 42), 253 (9), 251 (18), 249 (20), 225 (16), 223 (35), 221 (16), 172 (15), 170 (14), 63 (100).

6a: IR (KBr) cm^{-1}: 3293, 1677, 1603, 1526, 1483, 1394, 1305, 1254, 1013, 823, 737, 504; ^1H NMR δ 2.04 (s, 3H), 7.47 (d, J = 8.9 Hz, 2H), 7.56 (d, J = 8.9 Hz, 2H), 10.07 (s, 1H); MS m/z (rel intensity) 215 (M^+, 43), 213 (M^+, 43), 173 (96), 171 (100), 92 (96), 65 (41).

6b: IR (KBr) cm^{-1}: 3289, 1658, 1572, 1522, 1460, 1367, 1293, 1040, 831, 602, 547; ^1H NMR δ 2.24 (s, 3H), 7.42 (dd, J = 8.9, 2.1 Hz, 1H), 7.57 (s, 1H), 7.68 (d, J = 2.1 Hz, 1H), 8.26 (d, J = 8.9 Hz, 1H); MS m/z (rel intensity) 295 (M^+, 12), 293 (M^+, 20), 291 (M^+, 10), 253 (47), 251 (100), 249 (54), 214 (70), 212 (75), 172 (31), 170 (37), 91 (36), 90 (69), 63 (44).

7a: IR (KBr) cm^{-1}: 3417, 1596, 1572, 1471, 1293, 1266, 1234, 1188, 1161, 1130, 1052, 1009, 854, 803; ^1H NMR δ 2.62 (s, 1H), 3.78 (s, 3H), 4.66 (s, 2H), 6.69 (dd, J = 8.6, 3.1 Hz, 1H), 7.03 (d, J = 3.1 Hz, 1H), 7.38 (d, J = 8.6 Hz, 1H); MS m/z (rel intensity) 218 (M^+, 89), 216 (M^+, 100), 137 (57), 109 (72), 94 (20).

7b: IR (KBr) cm^{-1}: 1673, 1592, 1467, 1285, 928, 819, 648, 601; ^1H NMR δ 3.85 (s, 3H), 7.05 (m, 1H), 7.41 (m, 1H), 7.52 (m, 1H), 10.32 (s, 1H); MS m/z (rel intensity) 216 (M^+, 100), 214 (M^+, 99), 215 (95), 213 (89).

8: IR (neat) cm^{-1}: 1681, 1596, 1448, 1359, 1262, 951, 765, 687; ^1H NMR δ 2.60 (s, 3H), 7.43-7.59 (m, 3H), 7.94-7.98 (m, 2H); MS m/z (rel intensity) 120 (M^+, 16), 105 (100), 77 (23), 51 (9).

9: IR (KBr) cm^{-1}: 3421, 1689, 1600, 1456, 1409, 1301, 1231, 1106, 970, 761, 683; ^1H NMR δ 3.51 (t, J = 4.6 Hz, 1H), 4.89 (d, J = 4.6 Hz, 2H), 7.49-7.67 (m, 3H), 7.92-7.95 (m, 2H); MS m/z (rel intensity) 136 (M^+, 1), 105 (77), 77 (100), 51 (17).

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