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An Oxidation of Benzyl Methyl Ethers with NBS that Selectively Affords Either Aromatic Aldehydes or Aromatic Methyl Esters

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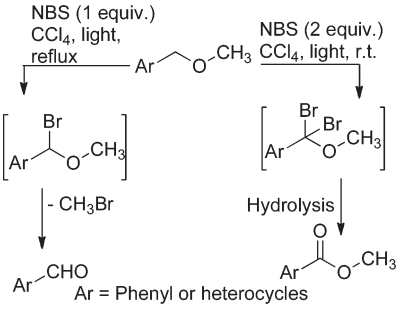

Either mono- or dibromination of benzyl methyl ethers can be achieved by controlling the amount of NBS and the temperature. Elimination of methyl bromide from the monobrominated intermediates produces aromatic aldehydes, whereas hydrolysis of the dibrominated intermediates affords aromatic methyl esters in good yields.

Chemical reactions that result in oxidation of benzyl ether methylene carbons are important chemical transformations because they often convert chemically stable functional groups into reactive groups, including aldehydes[1] and esters,[2] that are widely used in organic synthesis.

Most studies on benzyl ether oxidation with NBS have focused on cleavage to the corresponding aldehyde via formation of *N*-benzylsuccinimide derivatives followed by acid hydrolysis. Although the first aldehyde formation from benzyl methyl ether was reported by Markees in 1958,[3] it has not been widely applied due to its moderate yields and harsh reaction conditions.[4,5] Recently, a more efficient method has been reported by Pradhan et al. utilizing an oxoammonium salt.[6] On the other hand, the oxidation of benzyl ethers to yield esters was reported using either strong oxidizing agents such as Cr(VI)-periodic acid,[7] 4-methoxy-TEMPO-catalyzed sodium hypochlorite oxidation,[8] or heavy metals such as uranium hexafluoride.[9] More recently, Strazzolini and Runcio reported a facile method for the oxidation of benzyl ethers to esters by concentrated nitric acid in dichloromethane.[10] Such conditions are incompatible with a wide range of functional groups, and/or the reagents are expensive.

This paper describes a method to selectively convert benzyl methyl ethers to either aromatic aldehydes or aromatic methyl esters by reaction with either 1 or 2 equivalents of NBS in carbon tetrachloride. The conversion of benzyl methyl ethers to the corresponding methyl esters by NBS has not been previously reported.

Initially, NBS oxidative cleavage of 2,6-dichlorobenzyl methyl ether **1b** in refluxing CCl_4 was studied utilizing excess NBS. The reaction mixture was illuminated by a normal 60-W light bulb (Table 1, entry 5). The purification method was optimized by extraction with dilute NaOH to remove the unreacted NBS and the reaction byproducts (succinimide and HBr). As reported, the corresponding aldehyde **2b** was obtained in low yield. Interestingly, the major product was the corresponding methyl ester, which may be formed through reaction of the dibromobenzyl intermediate **8** with NaOH (Scheme 1). Next, the conditions for each oxidation type were examined. To determine whether higher temperatures are essential for bromide elimination and methyl ether cleavage to produce the aldehyde, the reaction was conducted at room temperature (entry 3). Interestingly, the only isolable product was the methyl ester **3b**, in excellent yield, with no detectable aldehyde.

The initial step in the proposed mechanism is formation of a monobromo intermediate **4** (Scheme 1) that can either break down, at higher temperature, into an aldehyde, or undergo an immediate second free-radical bromination. The relatively unstable dibromomethoxyl intermediate **8** may react with 0.1 M NaOH to afford the corresponding ester (Scheme 1). The reported[3] moderate yields of aldehydes may be due to the use of excess NBS, leading to formation of dibromomethoxymethyl intermediates. These intermediates may decompose at high reaction temperature. Unlike the

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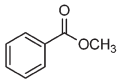
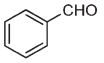
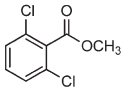
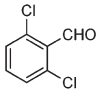
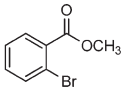
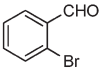
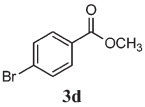
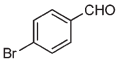
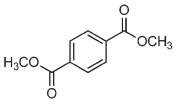
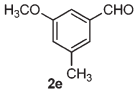
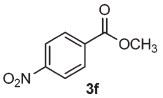
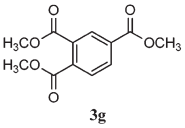
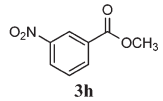
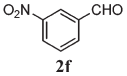
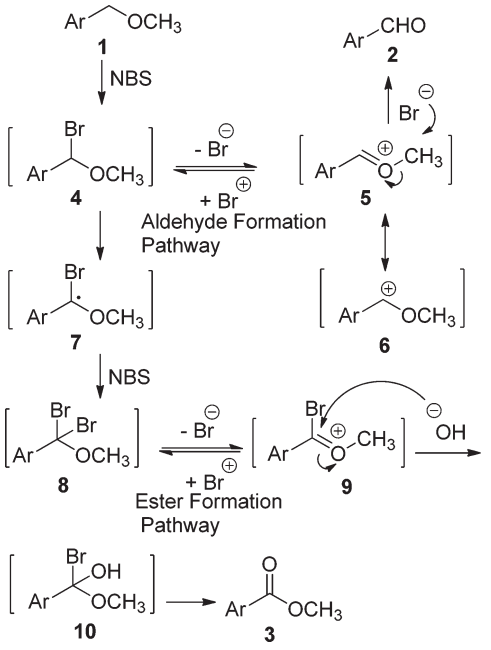
TABLE 1. Benzyl Methyl Ether Oxidation Reactions

entry	sm	conditions			product	yield (%)
		NBS (eq)	time (h)	temp.		
1	**1a**	2	16	r.t.	 **3a**	82
2	**1a**	1	1	Reflux	 **2a**	65
3	**1b**	2	16	r.t.	 **3b**	92
4	**1b**	1	1	Reflux	 **2b**	77
5	**1b**	3	2	Reflux	3b : 2b (3:2)	75
6	**1c**	2	16	r.t	 **3c**	81
7	**1c**	1	1	Reflux	 **2c**	60
8	**1d**	2	12	r.t	 **3d**	91
9	**1d**	1	1	Reflux	 **2d**	63
10	**1e**	1	12	r.t.		20
11	**1e**	2	12	r.t.		38
12	**1e**	2	2	Reflux	 **3e**	35
13	**1e**	3	12	r.t.		58
14	**1e**	4[a]	12	r.t.		73
15	**1e**	4	16	r.t.		89
16	**1f**	1	0.5	Reflux	 **2e**	45
17	**1f**	2	12	r.t.		63
18	**1g**	1	0.5	Reflux	 **3f**	45
19	**1g**	2	2	r.t.		91
20	**1h**	1	0.5	Reflux	 **3g**	30
21	**1h**	2	2	r.t.		81
22	**1i**	2	2	r.t.	 **3h**	85
23	**1i**	1	1	Reflux	 **2f**	65

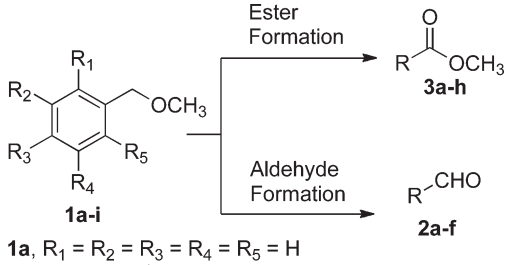
[a]Added portionwise.

reported *N*-benzylsuccinimide intermediates[3] obtained by conducting the reaction at high temperature, dibromomethoxymethyl intermediates are hypothesized to be formed under very mild conditions.

SCHEME 1. Postulated Reaction Pathways



SCHEME 2. Benzyl Methyl Ether Oxidation Reactions



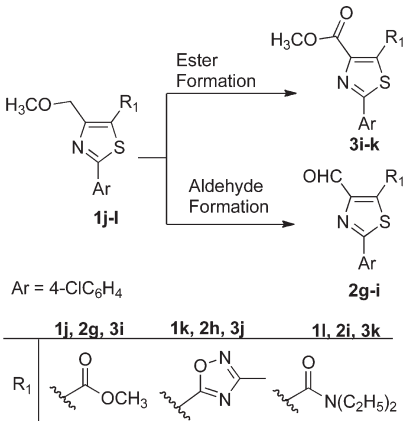
1a, $R_1 = R_2 = R_3 = R_4 = R_5 = H$
1b, $R_1 = R_5 = Cl$, $R_2 = R_3 = R_4 = H$
1c, $R_1 = R_2 = R_3 = R_4 = H$, $R_5 = Br$
1d, $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = Br$
1e, $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = CH_2OCH_3$
1f, $R_1 = R_3 = R_5 = H$, $R_2 = OCH_3$, $R_4 = CH_3$
1g, $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = NO_2$
1h, $R_1 = R_4 = R_5 = H$, $R_2 = R_3 = C(O)OCH_3$
1i, $R_1 = R_3 = R_4 = R_5 = H$, $R_2 = NO_2$

With respect to the proposed reaction mechanism, the optimal NBS stoichiometry is informative. In the case of aldehyde formation, using 1.0 equivalent of NBS afforded a slightly better yield than reported.[3] In the case of ester formation, 2.0 equivalents of NBS are necessary for optimal yield. Using more than the optimal NBS equivalent(s) resulted in lower yields.

With the optimal conditions identified, the full scope of the methodology was investigated. A range of benzyl methyl ethers were subjected to both reaction conditions (Scheme 2). Unsubstituted phenyl as well as ortho-, para-, and meta-substituted derivatives were utilized (Table 1, entries 1, 2, and 6−23). The same trends were observed. The modified reported conditions (1 equivalent of NBS/reflux) afforded aldehydes in moderate yields (Table 1, entries 2, 4, 7, and 9), while our new method (2 equivalents of NBS/room temperature) afforded esters in high yields (Table 1, entries 1, 3, 6, and 8).

In the case of electron-deficient aromatic rings, the oxidative ester formation proceeded smoothly in a shorter

SCHEME 3. Thiazolyl Methyl Ether Oxidation Reactions



time (entries 18−21). In contrast, an electron-rich system afforded only the aldehyde (entries 16 and 17).

Based on these findings, the details of the reaction mechanism outlined in Scheme 1 may be considered. There are two possible pathways following the first bromination step. First, the aldehyde-formation pathway includes elimination of bromide anion to form the resonance-stabilized benzylic carbocation intermediate **5** ↔ **6**. The liberated bromide anion may then attack the intermediate **5** ↔ **6** leading to cleavage of the C−O bond to yield the corresponding aldehyde. The other possibility for the monobromo derivative **4**, when the reaction is performed at room temperature, is to undergo a second free-radical bromination to form a dibromobenzyl intermediate **8** that decomposes in the presence of hydroxide to afford the esters (Scheme 1).

This mechanism is supported by the fact that certain electron-withdrawing groups (e.g., *p*-NO_2) on the aromatic ring completely disfavor aldehyde formation, presumably by increasing the energy of the cationic intermediate **5** ↔ **6** (Scheme 1). On the other hand, a *m*-NO_2 group, which would have less of an effect on the energy of the proposed carbocation intermediate **5** ↔ **6**, afforded either aldehyde or ester products as determined by the reaction conditions (Table 1, entries 22 and 23). Moreover, it was expected that selective aldehyde and/or ester formation could be performed by controlling the reaction conditions involving bis(methoxymethyl)benzene (**1e**, Scheme 4). It was expected that compounds **16**, **17**, **18**, and **3e** might be obtained by treatment of **1e** with 1, 2, 3, and 4 equivalents of NBS, respectively, and controlling the temperature. Instead, the only isolable product was the diester **3e** under all reaction conditions (Table 1, entries 10−15). The only observed difference was the yield. In the first case (Table 1, entry 10), instead of all of the starting material reacting with NBS (1 equivalent) to form 1 equivalent of monobromo intermediate **11** that could decompose to afford the aldehyde **16** (1 equivalent), approximately 20% of the starting material reacted to form the tetrabromo intermediate **13** that decomposed into the diester **3e** (0.2 equivalents), and 75% of the starting material was recovered. Similarly, approximately 40% of the starting material reacted when 2 equivalents NBS was used (Table 1, entry 11), and 60% was reacted when 3 equivalents of NBS were used with 40% of starting material being recovered (Table 1, entry 13). It was assumed that the aldehyde **17** could be obtained by enhancing the cleavage step of the

SCHEME 4. Conversion of 1e to 3e

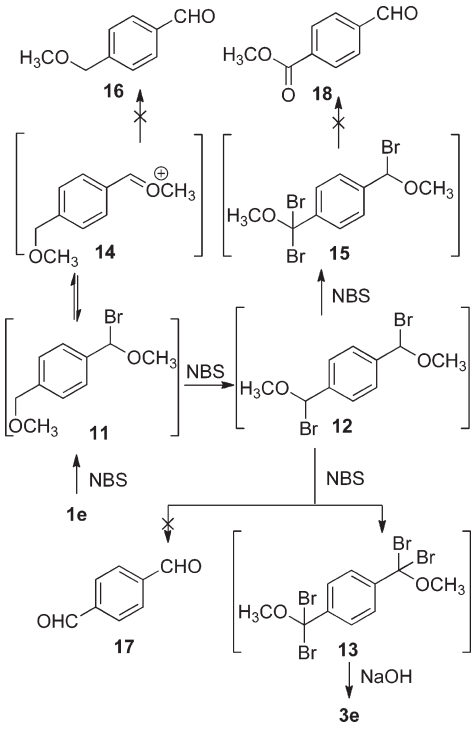


TABLE 2. Thiazolyl Methyl Ether Oxidation Reactions

		reaction conditions				
entry	starting material	NBS (equiv)	time (h)	temp (°C)	product	yield (%)
1	**1j**	1	1	reflux	**2g**	74
2	**1j**	2	24	rt	**3i**	79
3	**1k**	1	1	reflux	**2h**	55
4	**1k**	2	24	rt	**3j**	71
5	**1l**	1	1	reflux	**2i**	57
6	**1l**	2	24	rt	**3k**	65

bis(monobromo) intermediate **12** (Scheme 4), and therefore, the reaction was conducting using 2 equivalents of NBS at reflux (Table 1, entry 12). Instead, such reaction conditions also furnished the diester **3e** in a lower yield (Table 1, entry 12) in comparison with running the reaction at room temperature (Table 1, entry 11). Next, when 4 equivalents of NBS were added to the reaction mixture in portions, at a rate of 1 equivalent every 3 h, the diester **3e** was obtained in an excellent yield (Table 1, entry 15). Evidently, once bromination starts, all of the brominated intermediates **11**, **12**, and **15** are rapidly brominated until the tetrabrominated intermediate **13** is formed and all of the available NBS is consumed.

Encouraged by the mild conditions and high yields of this reaction, the same reaction conditions were investigated on more complicated structures utilizing several phenylthiazoles (Scheme 3). The corresponding aldehydes and esters were obtained selectively in good yields (Table 2, entries 1−6).

In conclusion, a method was developed to generate aldehydes and esters in good yields under mild conditions using an inexpensive and commercially available reagent. Regulating the NBS/ether ratio and temperature controlled formation of aldehydes vs methyl esters. The advantages of this

newly developed methodology include no restrictions on humidity conditions required and no heavy metal used.

Experimental Section

General Procedure for Preparation of Esters. The methyl ether (1 mmol) and NBS (356 mg, 2 mmol) were added to CCl_4 (10 mL). The reaction mixture was stirred at room temperature for 3−24 h and illuminated by a 60-W light bulb. The light source was placed 10 cm away from the flask. The solvent was removed under reduced pressure. An aq NaOH solution (0.1 M, 3 mL) was added to the residue, the mixture was stirred for 15−30 s at room temperature, and then EtOAc (10 mL) was added. The organic layer was separated, dried over anhydrous $MgSO_4$, and removed under reduced pressure. The crude products were 92−98% pure. For further purification, the obtained oil/solid was subjected to chromatography. The reaction worked properly with crystallized NBS, not with the crude form.

General Procedure for Preparation of Aldehydes. The methyl ether (1 mmol) and NBS (178 mg, 1 mmol) were added to CCl_4 (15 mL). The reaction mixture was heated at reflux for 1 h and was illuminated by a 60-W light bulb. The light source was placed 10 cm away from the flask. The solvent was removed under reduced pressure. The obtained mass was partitioned between EtOAc (10 mL) and NaOH (0.1 M NaOH, 5 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, and removed under reduced pressure. The obtained oil/solid could then be purified by making a sodium bisulfite addition compound or by chromatography. The reaction worked properly with crystallized NBS, not with the crude form.

Physical and spectral data of compounds **3i** and **2g** as representative examples for synthesized esters and aldehydes are shown below.

Dimethyl 2-(4-Chlorophenyl)thiazole-4,5-dicarboxylate (3i): yellow solid (79%); mp 72−73 °C; ^{1}H NMR ($CDCl_3$) δ 7.90 (d, J = 8.4 Hz, 2 H), 7.43 (d, J = 8.4 Hz, 2 H), 4.00 (s, 3 H), 3.94 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.8, 160.3, 151.6, 137.7, 130.4, 129.3, 128.1, 53.1, 53.0; MS (m/z, rel intensity) 336 (MNa^+, 36.7), 334 (MNa^+, 100); HRMS (ESI) m/z MNa^+ 333.9921, calcd for $C_{13}H_{10}ClNO_4SNa$ 333.9917.

Methyl 2-(4-Chlorophenyl)-4-formylthiazole-5-carboxylate (2g): white solid (74%); mp 139−140 °C; ^{1}H NMR ($CDCl_3$) δ 10.61 (s, 1 H), 7.96 (d, J = 8.7 Hz, 2 H), 7.45 (d, J = 8.7 Hz, 2 H), 3.99 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 184.8, 169.8, 160.4, 155.7, 138.1, 135.3, 130.1, 129.3, 128.4, 53.3; MS (m/z, rel intensity) 284 (MH^+, 36.7), 282 (MH^+, 100); HRMS (ESI) m/z MH^+ 281.9987, calcd for $C_{12}H_9ClNO_3S$ 281.9992.

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Supporting Information Available: Preparation of methyl ethers, characterization data, and copies of NMR spectra for all new and known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.