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Communication to the Editor

Observation of Bromomethyl Ethers during the Bromomethylation of Aromatic Compounds

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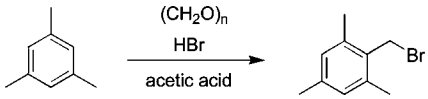
Abstract:

A literature method claiming to avoid the generation of highly toxic intermediates during bromomethylation of aromatic compounds was investigated. Gas chromatography revealed that such toxic intermediates may be present in the reaction mass in significant concentration. Indeed, these intermediates can be the major components under certain reaction scenarios. It is thus inaccurate to consider this chemistry free of hazardous intermediates. These potential hazards should be considered in any laboratory or scale-up implementation of this chemistry.

Introduction

The reaction of aromatic substrates with paraformaldehyde and anhydrous HBr in acetic acid has been reported to be an efficient and convenient method for the synthesis of bromomethyl aromatic derivatives.[1] For example, 1-bromomethyl-2,4,6-trimethylbenzene may be prepared in high yield from mesitylene as shown in eq 1.

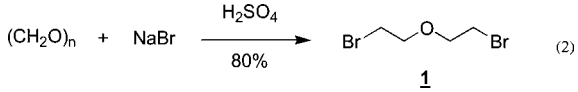


(1)

As stated in the original report,[1] a key feature of this method is that highly toxic bromomethyl ether byproducts are not formed during the course of the reaction. This is important since convenient procedures for preparation of the corresponding chloromethyl aromatics[2] are generally plagued with formation of bis(chloromethyl)ether (BCME), a well-documented carcinogen and acutely hazardous material.[3] This formation of BCME raises serious concerns regarding the safe operation of chloromethylation chemistry both in the laboratory and, especially, in larger scale industrial manufacture.

While the toxicity of the corresponding bis(bromomethyl)ether (BBME) has not been characterized as extensively as BCME, it is expected to have similar hazards. Like BCME, BBME should be an effective alkylation agent and thus have significant mutagenic potential. In addition, BBME may readily hydrolyze to hydrogen bromide and formaldehyde, which have their own corrosivity and toxicity hazards. Prudence thus dictates that chemistry involving BBME be approached with the same precautions as that for BCME, a stance adopted by previous workers in this field.[1,2] As a result, a bromomethylation route to halomethyl aromatics which avoided the generation of BBME and other hazardous intermediates appeared quite attractive.

That BBME would not be formed in the bromomethylation reaction mass is somewhat surprising considering that very similar conditions have been reported for the actual synthesis of BBME (eq 2).[4]



1 (2)

Of course, in this latter case the reaction medium is more strongly acidic than in the bromomethylation reaction and offers few reactive alternatives for the halomethyl ether species. It is conceivable that BBME would be generated and persist in significant amounts in the reaction medium of eq 2, while under the bromomethylation conditions of eq 1 it would either not be formed or else react as quickly as formed and not be observable by GC/MS. However, as we considered the use of this bromomethylation process in our laboratories, we thought it prudent to revisit the issue of halomethyl ether intermediates and confirm that they are indeed not generated in the bromomethylation reaction mass. Because BBME was not available commercially and its direct synthesis would involve significant hazards, direct detection of BBME by GC/MS was investigated.

An initial study was conducted in which paraformaldehyde and HBr in acetic acid were heated at 60 °C, sampled, and analyzed by GC/MS.[5] This experiment, which modeled the literature reaction conditions[1] except for omitting the

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(2) (a) Warshawsky, A.; Deshe, A.; Gutman, R. *Br. Polym. J.* **1984**, *16*, 234 and references therein. (b) Dauben, W. G. et al, Eds. *Org. React.* **1972**, *19*, 422.

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(5) To 10.0 g (333 mmol) of paraformaldehyde in 75 mL of acetic acid was added all at once 90 g of HBr solution (30% in acetic acid, 333 mmol HBr). The mixture was heated at 60 °C for 1 h and then analyzed with the use of a Hewlett-Packard 5890 gas chromatograph equipped with a 60-m DB-1 capillary column and mass spectral detector. Molecular weights were confirmed using both electron ionization and chemical ionization mass spectral analysis. The product samples were also analyzed on a similar Hewlett-Packard GC with identical configuration/programming using a flame ionization detector.

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Table 1. **GC peak retention times, identities and area percents for model bromomethylation reaction mass using both mass spectrometry (MS) and flame ionization (FID) detection**

retention time (min)			area %[a]	
MS	FID	peak ID	MS	FID
11.8	13.3	AcO−CH_2−Br	15.5	24.3
13.9	15.5	AcO−CH_2−OAc	3.4	4.6
14.5	16.1	Br−CH_2OCH_2−Br (*1*)	24.7	35.3
16.6	18.2	AcO−CH_2OCH_2−Br	15.5	15.0
17.8	19.4	AcO−CH_2OCH_2−OAc	7.7	3.5
19.3	21.0	Br−$(CH_2O)_2CH_2$−Br	14.0	6.8
20.2	21.9	AcO−$(CH_2O)_2CH_2$−Br	11.1	6.7
21.0	22.7	AcO−$(CH_2O)_2CH_2$−OAc	4.3	1.9
22.8	24.6	Br−$(CH_2O)_3CH_2$−Br	2.0	0.9
23.3	25.1	AcO−$(CH_2O)_3CH_2$−Br	1.4	0.5
23.9	25.6	AcO−$(CH_2O)_3CH_2$−OAc	0.6	0.3

[a] Acetic acid solvent peak not included.

Table 2. **GC peak retention times, identities and FID area percents for ether intermediates during the bromomethylation of mesitylene and mesitol**

retention time (min)	peak ID	mesitylene study (area %)[a]		mesitol study (area %)[a]	
		0 min	30 min	0 min	30 min
13.1	AcO−CH_2−Br	0.11	0.12	0.05	0.11
15.3	AcO−CH_2−OAc	0.05	0.11	0.05	0.14
15.9	Br−CH_2OCH_2−Br (*1*)	0.05	0.04	0.04	0.02
18.2	AcO−CH_2OCH_2−Br	*b*	*b*	0.11	0.03
19.3	AcO−CH_2OCH_2−OAc	0.05	0.04	0.05	0.02
20.9	Br−$(CH_2O)_2CH_2$−Br	0.09	0.00	0.02	0
21.8	AcO−$(CH_2O)_2CH_2$−Br	0.12	0.00	0.02	0
22.6	AcO−$(CH_2O)_2CH_2$−OAc	0.04	0.00	0	0
24.5	Br−$(CH_2O)_3CH_2$−Br	0.04	0.06	0	0
25.0	AcO−$(CH_2O)_3CH_2$−Br	0.05	0.07	0	0
25.6	AcO−$(CH_2O)_3CH_2$−OAc	0.01	0	0	0

[a] Acetic acid solvent peak not included. [b] Obscured by mesitylene peak.

aromatic substrate, was designed to maximize the concentration and persistence of BBME while simplifying the analysis. The peaks observed in the resulting GC chromatogram are listed in Table 1 along with their identity as revealed by mass spectroscopy. The analysis nicely shows that the paraformaldehyde is broken down into a series of oligomeric methyl ethers having the formula X−$(CH_2O)_n$−CH_2−Y where n = 0, 1, 2, 3, ... and X and Y are independently −Br or −O(C═O)CH_3 (acetyl). It clearly demonstrates that BBME is indeed produced under the reaction conditions; in fact **BBME is the major nonsolvent component in the GC/MS of the reaction mass**. Furthermore, a variety of other mono- and bis-bromomethyl ethers are produced which are likely to be just as toxic as BBME itself.

Unfortunately, this GC/MS analysis did not allow quantitation of the BBME or other bromomethyl ether intermediates since authentic samples of the compounds were not available for use as analytical standards. However, further evidence that significant levels of BBME were indeed present was provided by the observation of similar relative peak areas when the analysis was repeated using identical GC conditions but with FID detection instead of MS detection (see Table 1). Two such dissimilar GC detection methods affording quantitatively comparable results supports the conclusion that the relative area percents do correspond at least roughly to the relative molar ratios of the compounds in the reaction mass.

With an analytical method for detection of BBME in the reaction mass in hand, it was now possible to study whether BBME was also formed when an aromatic substrate was present in the bromomethylation reaction mass. Bromomethylation experiments were run employing either mesitylene or 2,4,6-trimethylphenol (mesitol) as the aromatic substrate under conditions similar to the control study and representative of the original literature report.[6] Samples were drawn over time and analyzed by GC/FID for BBME and the other intermediates observed in the initial control study. The results of these analyses are summarized in Table 2.

In each case, low but finite levels of BBME and other bromomethyl ethers were observed in the reaction mass during the early stages of the reaction. The concentrations were quite low and did not persist over an extended reaction time, but even after 30 min BBME was present in the reaction mass at ppm levels. Even higher levels of BBME could be present when the bromomethylation is carried out using less reactive aromatic substrates having more sterically hindered or less-activated aromatic rings.

Thus, the earlier report[1] that hazardous intermediates are not generated in the bromomethylation of aromatic compounds under these conditions is potentially misleading. It is true that, at least with highly reactive aromatics such as mesitylene and mesitol, bromomethyl ether intermediates do not persist through extended reaction periods or aqueous workup and are not detected in reaction products. Indeed, this method remains a highly efficient route to halomethylated aromatics which may be preferable to alternative routes involving chloromethyl ethers or high in situ concentrations of bromomethyl ethers.

However, these highly toxic materials are formed in the reaction mass during the early stages of the reaction. Further, the levels of these intermediates can be very high if the reaction is conducted in such a way that paraformaldehyde and HBr are combined in the absence or molar deficit of an aromatic compound, and likely also when relatively unreactive aromatic substrates are used. *Extreme caution should be exercised if the use of this bromomethylation method is contemplated to ensure that exposure to BBME is avoided.*

(6) For example, to 10.8 g (90 mmol) of 1,3,5-trimethylbenzene and 3.0 g (100 mmol) of paraformaldehyde in 50 mL of acetic acid was added all at once 27.1 g of HBr solution (30% in acetic acid, 100 mmol HBr). The mixture was heated to 50 °C and sampled initially and after 30 min. The samples were analyzed using the same GC/FID method as in the control study.[5] Note that these conditions involve a 11% molar excess paraformaldehyde/HBr relative to aromatic. This is higher than the 1:1 ratio in the General Procedure of ref 1, but well below the 100% and 230% molar excesses of subsequent procedures reported therein.

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