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A Facile Process for the Preparation of 2-Bromoethyl Methyl Ether

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Abstract:

A convenient and large-scale synthesis of 2-bromoethyl methyl ether is described.

Introduction

Alkyl bromides are useful electrophilic reagents for the alkylation of organic compounds. The alkyl bromides are synthesized on large-scale by a variety of brominating reagents,[1] of which hydrobromic acid[2] is by far the most popular. For ongoing antisense development projects,[3] an alkyl bromide, 2-bromoethyl methyl ether was required on a large scale. The 2-bromoethyl methyl ether has been utilized as an alkylating agent for the synthesis of 2′-modified nucleosides[3c] as building blocks for therapeutic oligonucleotides, serotonin receptor agonists,[4] antitumor agents,[5] insecticides,[6] photoinitiators,[7] and for compounds containing organic metal complexes that are used in nuclear magnetic resonance studies.[8]

The synthesis of 2-bromoethyl methyl ether is reported in two patents. The first protocol describes the bromination of 2-methoxyethanol with phosphorus tribromide in presence of pyridine.[6] Because of the toxic and hazardous nature of phosphorus tribromide, we decided not to utilize this protocol for scale up. The second procedure utilized a high-temperature (140 °C) and high-pressure (50 kg/cm^2) reaction of ethylene, oxygen, and methanol with cupric bromide.[9] In order to scale up the later protocol, we will need specialized equipment and stringent safety measures. The lack of a scaleable protocol for the synthesis of 2-bromoethyl methyl ether triggered the current investigation.

Results and Discussion

We elected to use 2-methoxyethanol (**1**) as the starting material due to its commercial availability and low-cost. The bromination **1** was carried out under a variety of reaction conditions. The results are summarized in Table 1. The efficiency of the reaction was judged by the formation of 2-bromoethyl methyl ether (**2**) detected by gas chromatography (GC). Our initial bromination attempts were based on the use of conventional reagents. The use of hydrobromic acid under acidic conditions (entries 1 and 2) furnished the desired product **2** (<10% by GC) contaminated with several byproducts. An improvement in the product formation was observed (18% or 14% by GC) with a combination of sodium bromide, sulphuric acid, and tetrabutylammonium bromide (TBAB) (entry 3), thionyl chloride and TBAB under reflux (entry 4), chlorotrimethylsilane, sodium bromide or lithium bromide in refluxing acetonitrile (entry 5). The combination of lithium bromide with thionyl chloride in DMF or acetonitrile furnished a complex mixture of products (entries 6 and 7). Next, refluxing **1** in toluene with TBAB in the presence of phosphorous pentoxide exhibited significant improvement in product formation (74% by GC; entry 8). However, separation of **2** from toluene via distillation proved to be very difficult due to the closeness of their boiling points. Therefore, the latter reaction was repeated with dichloromethane as a low-boiling solvent, assuming that the separation will be easier. Unfortunately, the use of dichloromethane as a solvent led to the formation of multiple products (entry 9). Interestingly, the reaction of the more reactive 2-methoxyethyl tosylate with TBAB in refluxing toluene for 3−4 h showed a complete conversion of the starting material to the desired product by GC (entry 10). Our attempts to isolate the product from the reaction mixture by distillation resulted in an inseparable mixture of toluene and 2-bromoethyl methyl ether. We also tried reacting 2-methoxyethyl mesylate with TBAB in acetone under reflux without much success (entry 11).

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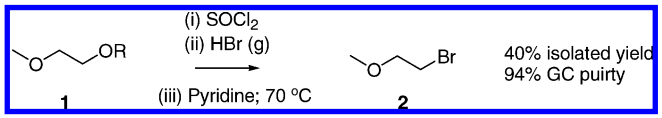
Table 1. **Experimental conditions for various brominations**

entry	R in **1**	reaction conditions	**2** in crude mixture (% by GC)
1	H	HBr/H_2SO_4	complex mixture of products
2	H	HBr/AcOH (37%)	complex mixture of products
3	H	$NaBr/H_2SO_4$/TBAB/ACN	18
4	H	$SOCl_2$/TBAB/Reflux	14
5	H	TMS-Cl/NaBr/ACN	14
6	H	$SOCl_2$/LiBr/DMF/reflux	complex mixture of products
7	H	$SOCl_2$/LiBr/CH_3CN/reflux	complex mixture of products
8	H	P_2O_5/toluene/TBAB/reflux	74
9	H	P_2O_5/DCM/TBAB/reflux	complex mixture of products
10	Ts	Toluene/TBAB/reflux	99
11	Ms	acetone/TBAB/reflux	no reaction
12	H	$SOCl_2$/pyridine/HBr (g)	80

Scheme 1



The reactivity of 2-methoxyethyl tosylate prompted us to consider a route in which alcohol **1** is transformed into a reactive intermediate, which is then brominated in situ to furnish the desired product **2**. A literature search revealed that the treatment of alcohols with thionyl chloride, followed by halogen exchange (Cl → Br) with gaseous HBr, resulted in the formation of bromosulfite, which upon heating in the presence of a base furnished the brominated products.[10] We implemented this protocol for the synthesis of compound **2**. Thus, the reaction of alcohol **1** with 1.05 equiv of thionyl chloride furnished the chlorosulfite, which underwent halogen exchange with HBr (1.05 equiv) to provide bromosulfite as the reactive intermediate. Heating of the bromosulfite in the presence of triethylamine furnished the expected product in low yield (10% isolated). Switching over to pyridine as the base for the final reaction with bromosulfite gave the product **2** in a significantly improved yield (Scheme 1; 80% crude by GC; entry 12). The reaction mixture was diluted with dichloromethane and the organic layer washed with saturated sodium bicarbonate and brine. The organic layer was dried over sodium sulfate, and the solution was concentrated by distillation to remove excess of dichloromethane at 45−50 °C. The residual oil was then subjected to fractional distillation under vacuum (50−60 mm) using a 3-foot-tall Vigreux column. The GC analysis of all fractions and pooling of appropriate fractions (>93 area % by GC) furnished 40% isolated yield of the 2-bromoethyl methyl ether. The forgoing protocol was repeated on small scale (3 × 100 grams) to check the reproducibility of the reaction. The optimized bromination protocol (see Experimental Section) had been transferred successfully to the pilot plant on kilogram scale. The isolated yield of 40% (distilled product) was maintained on kilogram scale with the final product purity between 93 and 95% by GC. One possible reason for the lower isolated yield could be attributed to the loss of product during vacuum distillation. It is important to note that the overall product purity could be further improved at the cost of lower yield by pooling only high-purity fractions after distillation.

In summary, we have developed a convenient, one-pot procedure for the large-scale synthesis of 2-bromoethyl methyl ether from 2-methoxyethanol. Multikilogram quantities of 2-bromoethyl methyl ether have been synthesized and used as an alkylating agent for the preparation of 2′-modified nucleosides required for the assembly of antisense oligonucleotides.

Experimental Section

A 20-L, three-necked, round-bottomed flask equipped with a condenser, thermometer, and addition funnel was charged with thionyl chloride (5.1 kg, 42.86 mol) under nitrogen atmosphere. To the stirred solution was gradually added 2-methoxyethanol (**1**, 3.1 kg, 40.78 mol) over a period of 1 h while maintaining the internal temperature at 35−40 °C. After complete addition, the stirring was continued for 0.5 h at the same temperature until there was no visible (gas bubbler) elimination of HCl gas from the reaction mixture. The HCl gas was passed through a sodium hydroxide scrubber to prevent its discharge in the air. The reaction mixture was cooled to 10 °C after evolution of HCl gas had ceased. Anhydrous gaseous HBr (3.47 kg, 42.9 mol) was bubbled into the reaction mixture over a period of 2−3 h, while maintaining the internal reaction temperature at 0−5 °C. After completion of the bubbling of HBr (gas), anhydrous pyridine (310 g, 3.9 mol) was added dropwise while maintaining the same temperature over 0.5−1.0 h. The resulting reaction mixture was stirred and gradually heated to 70 °C and held at this temperature until completion. Progress of the reaction was monitored by quenching an aliquot of the reaction mixture with sodium bicarbonate solution followed by washing with water and analyzing the organic layer by GC. The reaction was found to be complete in 5−6 h by GC analysis (80% area of the desired product). The reaction mass was diluted with dichloromethane and washed with saturated sodium bicarbonate, water, and brine solution until the washings were of neutral pH. The dichloromethane layer was dried over sodium sulfate and carefully concentrated by atmospheric distillation at 45−50 °C. The crude product (contains ∼10−15% dichloromethane) was distilled under vacuum (50−60 mm) using a tall Vigreux column (3 feet), and six fractions were collected. The fractions collected at the vapor temperature of 107−109 °C were found to be 94% pure by GC. These fractions were pooled to furnish 2.4 kg of 2-bromoethyl methyl ether (**2**) as a pale-yellow liquid. The integrity of the final product was further confirmed by GC/MS analysis.

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