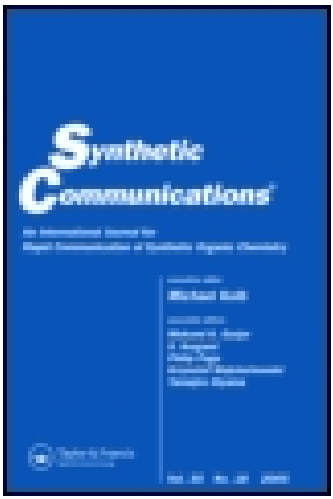

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A New Simple and Industrial Process for Bromination of Alcohols

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A NEW SIMPLE AND INDUSTRIAL PROCESS FOR BROMINATION OF ALCOHOLS

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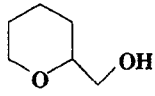
Abstract : Alcohols treated with thionyl chloride, followed by chlorine/bromine exchange using gaseous hydrobromic acid and thermal decomposition in the presence of a tertiary amine give the corresponding brominated compounds. The process is regio / stereo selective.

Transformation of an alcohol function to a bromide function is well known and widely used on the laboratory scale. The most widely used reagents are phosphorus tribromide [1], thionyl bromide [2], or brominated Villsmeier salt[3], which is generaly prepared in situ starting from dimethylformamide, triphenylphosphine and bromine. On the industrial scale, the only economical and safe method is the use of hydrobromic acid.

In the course of our investigations, we needed to carry out to the bromination of three different alcohols, namely 2-hydroxymethyltetrahydropyran 1, 2-pentanol 2 and D-methyl lactate 3.



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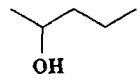

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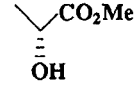

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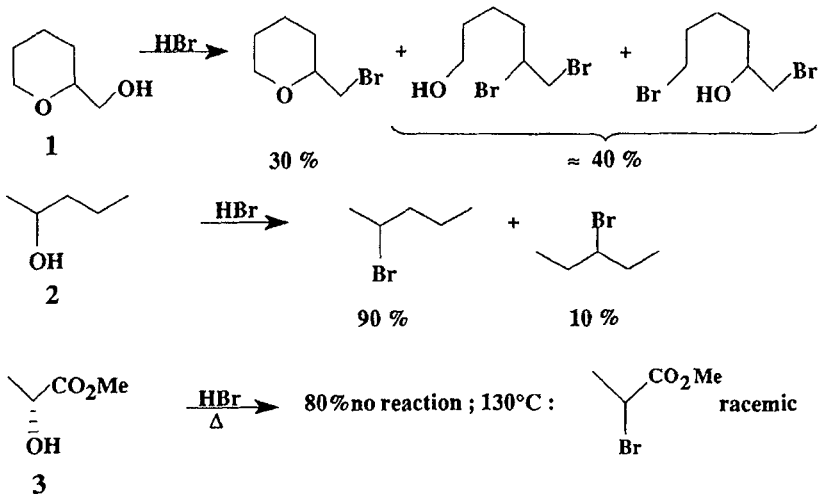
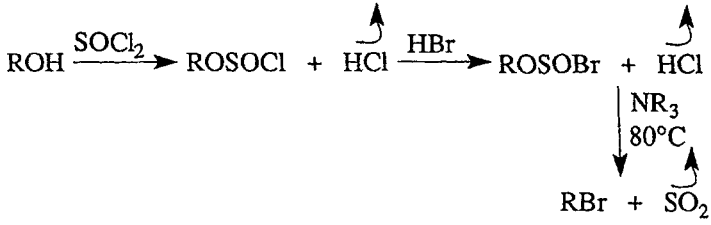


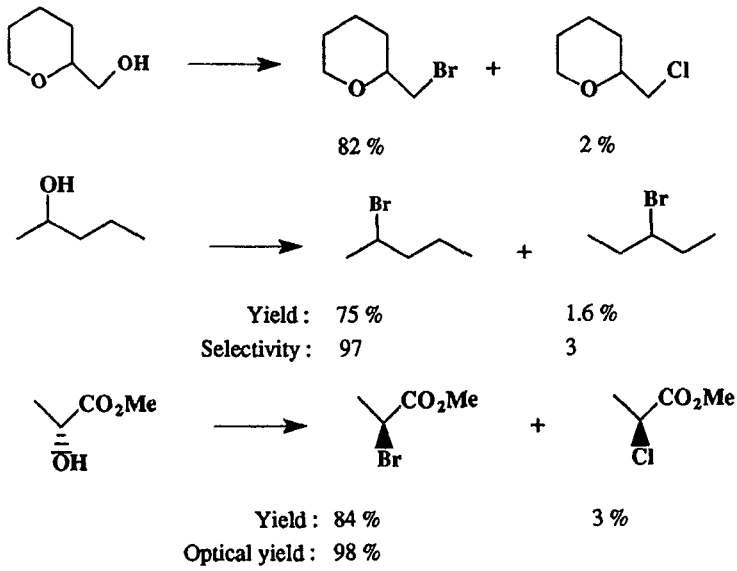
Scheme 1 : Bromination using HBr gas

Each case represents a different challenge, for which the standard HBr method is ineffective (Scheme 1). In the first case, the reaction should ideally be carried out without opening of the sensitive tetrahydropyran ring ; in the second case, a mixture of 2-bromopentane and 3-bromopentane is obtained, when only the 2-brompentane isomer is desired ; and in the third case, the methyl 2 bromopropionate must be obtained in reasonable yield with conservation of optical activity.

We wish to report here a general method which has been used with success for the synthesis of those three brominated compounds[4]. The process involves the use of thionyl chloride (Scheme 2) to form in situ the chlorosulfite followed by chlorine/bromine exchange with HBr gas. The resulting bromosulfite is then heated in presence of catalytic pyridine or triethylamine to give the brominated compound via an SN_2 type process. The results we obtained for the bromination of the three representative alcohols are given in Scheme 3.



Scheme 2 : general principle of reaction.



Scheme 3 : results obtained with the $SOCl_2/HBr/NR_3$ system.

In all cases yields are around 80% and no more than 2 to 3% of the corresponding chlorinated product is observed ; this side product is easily removed by distillation. This "one-pot" method is very powerful because of its regio and stereoselectivity. The reaction can be carried out in bulk and is very economic. Furthermore, the reaction conditions are mild and thus applicable to a wide range of substrates.

EXPERIMENTAL

2-Bromomethyltetrahydropyran

The reaction mixture is analysed using a VARIAN 3400 gas chromatograph equipped with a flame ionisation detector and using a 15 m x 0.53 mm L.D. fused quartz semicapillary column bonded with a DB-17 stationary phase. Titrations are performed using hexadecane ($C_{16}H_{34}$) as internal standard.

17,4 g (0,15 mole) of 2-hydroxymethyltetrahydropyran are added to 20,2 g (0,165 mole) of thionyl chloride over a period of 1.5 hour while keeping the reaction mixture at 20-25°C. The reaction mixture is maintained at 25°C while stirring for half an hour ; the emission of HCl stops after 20 minutes. 13.35 g (0.165 mole) of HBr gas were then added to the mixture over a period of 1.5 hour, while maintaining temperature between 25 and 30°C. 1.5 g (0.015 mole) of triethylamine is then quickly added to the reaction mixture which is then heated to 70°C for 5 hours. CPG titration indicates a conversion of 100% of the alcohol, 86% yield of the brominated compound and 3% of the corresponding chloro compound. The reaction mixture is then diluted with dichloromethane, and washed until neutrality with a concentrated hydrogen carbonate solution, dried over Na_2SO_4 and evaporated to dryness. 25.9 g of a brown oil is then obtained which is distilled (75-79°C under 17 mmHg). 21.5 g of a colorless liquid is obtained. Titration of the product indicates 94% purity (75.3% yield).

2-Bromopentane

The reaction mixture is analysed on a VARIAN 3400 gaz chromatograph equiped with a flame ionization detector, an autosampler and using a 30 m x 0.53 mm L.D. fused quartz semicapillary columm with a DB1 stationary phase. Titrations were performed using external standards.
15g (0,16 moles) of thionyl chloride is introduced into a 100 ml reaction vessel. 9.27g (0,105 mole) of 2-pentanol and 10.2g (0,126 mole) gaseous bromhydric acid are introduced simultaneously into the reactor at 25°C in one hour. $SOCl_2$ is added using an automatic syringe, and HBr is bubbled into the reaction mixture while stirring. The reaction mixture is then stirred for one hour at 25°C. 0.1 g triethylamine is added to the mixture ; which is then heated to 80°C. for three hours. Titration of the crude reaction mixture gives the following results : conversion 100%, 2-bromopentane 75%, 3-bromopentane 1,6%. The reaction mixture is diluted with 100 ml of dichloromethane, neutralised with aqueous $NaHCO_3$, and then washed three times with 100 ml water, dried on Na_2SO_4 and then distilled to obtain the mixture of the 2- and 3- bromopentane.

S (-) Methyl 2-bromopropionate

The reaction mixture was analysed using two chromatographic methods, one for chemical titration and one for enantiomeric determination.

Chemical determination was performed using a VARIAN 3700 gas chromatograph equipped with an autosampler and a flame ionisation detector using a 15 m x 0.53 mm L.D. fused quartz

semicapillary column, with a bonded DB.1 stationary phase. Titrations were performed using 1,2-dichlorobenzene as internal standard.

Enantiomeric purity : the product is analysed using a VARIAN 6000 gas chromatograph equipped with a flame ionisation detector using a capillary Ni-R-CAM column[5].

10,8 g R (-) Methyl lactate (0.104 mole, ee = 92.8%) is added to 18,75 g thionyl chloride (0,157 mole) over one hour at 25°C while stirring. The reaction mixture is then kept at 25°C for one more half hour while stirring and 82,2 mg of pyridine is then added. 12,74 g of gaseous HBr is then added over a period of 55 minutes. The temperature rises to 35°C. The reaction mixture is then stirred at 30°C for half an hour and then heated at 80°C for two hours and cooled back to room temperature. Titration shows a conversion of 99% to methyl lactate, a yield of 84% of bromopropionate and 3% of chloropropionate. The reaction mixture is diluted with 20 ml dichloromethane, and washed until neutrality with water. The organic layer is then dried with Na_2SO and dichloromethane is evaporated. 11,42 g of a yellow oil is obtained with à 97% GC purity in bromopropionate. Chiral gas chromatography indicates ee is 91,4% (optical yield 98,5%).

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