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Short Communication

Magnesium Bromide as a Mild and Efficient Selective Deblocking Agent for Isopropylidene and Trityl Protecting Groups

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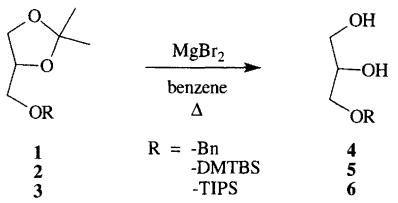
This report describes the highly selective and efficient deprotection of isopropylidene and trityl groups in various glycerol derivatives possessing the more stable TBDMS, TIPS and benzyl protecting groups, which were unaffected. This was effected by magnesium bromide under non-aqueous conditions in refluxing benzene. The performance of the cleaving agent was very dependent upon the reaction medium as well as the reaction temperature. The presence of a chelating solvent such as diethyl ether was observed dramatically to reduce the cleaving power of magnesium bromide. Magnesium bromide has not been extensively employed as a deblocking agent. It has previously been used selectively to deprotect THP ethers of primary and secondary alcohols,[1] 1-ethoxyethyl ethers[2] and acetal esters,[3] and in conjunction with acetic anhydride to cleave cyclic ethers.[4] Magnesium bromide in a diethyl ether–benzene solution has also been used for the highly selective cleavage of benzyl ethers located *ortho* to an aldehydic carbonyl group in various benzene and naphthalene derivatives without affecting other benzyl groups present.[5,6]

Results and discussion

Treatment of 1-*O*-benzyl-2,3-*O*-isopropylideneglycerol **1** with magnesium bromide in a diethyl ether–benzene solution (2:1) resulted in only partial deprotection. For instance, with 2.5 equiv. of magnesium bromide under reflux for 72 h, only 80% deprotection took place. When the ether was removed from the reaction mixture, **1** underwent complete deprotection with 1.5 equiv. of magnesium bromide to afford **4** in refluxing benzene in less than 24 h, leaving the benzyl ether group unaffected (Scheme 1). The reflux was found to be imperative since stirring at r.t. in the presence of 4 equiv. of magnesium bromide for 24 h resulted in the complete recovery of unchanged starting material, whereas after 11 days only 15% deprotection took place under the same conditions. As had been expected the mild magnesium bromide cleaving agent was passive toward the benzyl ether group, cleavage of which usually requires more powerful deblocking agents such as aluminium and boron trichloride.[7,8]

These results clearly demonstrate that a chelating solvent such as diethyl ether diminishes the cleaving power of the reagent and can, presumably, together with temperature control, be used as a mean to mediate the reaction and control the selectivity of the reagent. This behaviour is believed to be related to coordination of the chelating solvent to the Lewis acid cleaving agent in competition with the protected glycerol derivative.

The bulky TBDMS and TIPS ethers were also found to be completely resistant to 4 equiv. of magnesium bromide in refluxing benzene, as became evident for compounds **2** and **3**, respectively, but the isopropylidene group was readily cleaved. Tetrabutylammonium fluoride is generally employed to cleave the TBDMS and TIPS groups without affecting the isopropylidene group.[9] Therefore, magnesium bromide can be used comple-



Scheme 1.

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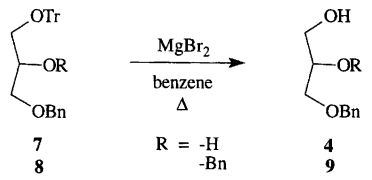
mentarily to that reagent selectively to cleave isopropylidene derivatives, leaving TBDMS and TIPS ethers unaffected. There are some examples of more powerful Lewis acids used to deprotect TBDMS ethers,[10,11] under which conditions the isopropylidene group would certainly not survive. Nevertheless, the selective deblocking of the TBDMS group by ferric chloride adsorbed on silica gel in acetone has been reported.[12] With chloroform as the solvent the reverse selectivity was observed and the isopropylidene group was cleaved leaving the TBDMS group unaffected. The reason for this behaviour was the effect of using an excess of acetone as the solvent to suppress isopropylidene group deprotection. The necessity selectively to deprotect an isopropylidene group in the presence of a TBDMS group became a reality, for example in the synthesis of phyllanthocin.[13]

It was interesting to observe that the isopropylidene protecting group was more resistant to magnesium bromide in the TIPS protected isopropylideneglycerol **3** compared with the TBDMS-protected isopropylidene glycerol **2**. When the TBDMS-protected isopropylidene glycerol **2** was treated with 4 equiv. of magnesium bromide in refluxing benzene, complete deprotection of the isopropylidene protecting group took place in only 24 h. The corresponding TIPS-protected isopropylidene glycerol **3**, on the other hand, underwent only 85% deprotection after 24 h and 90% after 48 h under the same conditions. This can be rationalized by the increased steric effect of the more bulky TIPS group compared with TBDMS, limiting the ready approach of the reagent to coordinate to the isopropylidene moiety, the stability thus being quite dependent upon the local steric environment.

Magnesium bromide was also found readily to cleave the trityl protecting group highly selectively in the presence of the far more stable and unaffected benzyl group. 1-*O*-Benzyl-3-*O*-tritylglycerol **7**, when treated with 2 equiv. of magnesium bromide in refluxing benzene, underwent complete deprotection of the trityl group in less than 24 h. Similar results were obtained for the dibenzyl adduct **8** to afford **9** (Scheme 2). At r.t. with 4 equiv. of magnesium bromide in benzene 90% removal of the trityl group in **7** took place after 6 days. These results indicate that the trityl group is more prone to cleavage with magnesium bromide than is the isopropylidene group. Selective cleavage of the former group in the presence of the latter may stand a good chance. There is a report of such selective removal of the trityl group, leaving the isopropylidene group unaffected, using



7 R = -H **4**
8 -Bn **9**

Scheme 2.

ferric chloride adsorbed on silica gel in acetone as the solvent, under which conditions the stable TBDMS group was cleaved (*vide supra*).[12] Trityl ethers are very sensitive to most Lewis acids and readily cleaved.[10,11] Selective cleavage of trityl ethers in the presence of the unaffected TBDMS group by diethylaluminium chloride in dichloromethane has been reported.[14]

Experimental

Preparation of glycerol derivative precursors. The 1-*O*-benzylisopropylideneglycerol derivative **1** was prepared in high yield (87% after distillation *in vacuo*) from isopropylideneglycerol (Aldrich) by benzylation with benzyl chloride in dry refluxing THF after treatment with sodium hydride as a base. The silyl protected derivatives **2** and **3** were also made highly efficiently (88 and 91% yield, respectively, after distillation *in vacuo*) from isopropylideneglycerol using TBDMS and TIPS chlorides, respectively, under standard conditions at r.t. in DMF in the presence of imidazole. The tritylglycerol derivative **7** was prepared in a good yield (70% after silica gel chromatography, not optimized) from the diol **4** by a standard procedure using trityl chloride in pyridine at r.t. All these compounds were obtained in a highly pure state as was established by high-field ^1H and ^{13}C NMR and IR spectroscopy. 1,2-*O*-Dibenzyl-3-*O*-tritylglycerol **8** was prepared by benzylation of **7** by the same procedure as used for the preparation of **1**. It was used crude, but fairly pure, for the deblocking experiments.

Deblocking experiments. Anhydrous magnesium bromide in a 2:1 diethyl ether–benzene solution was prepared in accordance with a previously described procedure[6] and was used as a 0.42 M stock solution in the deblocking experiments. An ether-free benzene solution of magnesium bromide was obtained by carefully distilling off the ether after adding the equivalent amount of benzene to the solution. All transfers took place via a syringe under a dry nitrogen atmosphere.

In a typical deblocking procedure the glycerol derivative (0.5–1.0 g) was added to magnesium bromide in dry benzene and the resulting mixture stirred at r.t. or refluxed under a nitrogen atmosphere for the appropriate length of time. The reaction mixture was allowed to cool to r.t. after which it was poured into an aqueous solution of sodium bicarbonate and the resulting mixture extracted with diethyl ether or chloroform. In case of the more polar diol derivatives **4**, **5** and **6**, which are partially soluble in water, an aqueous solution of sodium chloride was added to the aqueous phase to aid separation and extraction into the organic phase. The combined organic phase was dried over magnesium sulfate and the solvent was removed *in vacuo* by rotary evaporation and the product analysed by high-field NMR spectroscopy to investigate the progress of the deblocking reaction. The final products were afforded in a pure state in good yields (usually 70–80%, not optimized) after silica gel

purification, as was established by high-field ^{1}H and ^{13}C NMR and IR spectroscopy.

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