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Reductive removal of methoxyacetyl protective group using sodium borohydride

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ABSTRACT

Herein, we have developed a mild and selective reductive deprotection method for the MAc protected alcohols using sodium borohydride. The new deprotection conditions provide a complete orthogonality between *O*-MAc and other protecting groups such as *tert*-butyl ester, *N*-Boc, Fmoc, Cbz, *O*-TBDMS, *N*-benzyl, *O*-benzyl, *O*-acetyl, *N*-acetyl, *N*-MAc, etc. In addition to *O*-MAc deprotection, this method is also applicable for *S*-MAc deprotection.

The methoxyacetyl (MAc) group has been used for quite some time as a protecting group for the alcohols.[1] It has been conventionally used to protect the hydroxyl functional group of nucleoside derivatives. MAc can be deprotected using methanolic ammonia solution and its removal is much faster than the corresponding acetyl moiety.[1] In spite of its apparent utility, the MAc group has not found widespread use probably because of the lack of effective, mild and selective deprotection techniques. Typical deprotection methods include strongly basic conditions such as ammonia or other amines,[2] lanthanide triflates,[3] KO^{t}Bu,[4] enzymatic cleavage[5] and ZnI_2/MeOH.[6] Herein we report a mild and selective reductive method of deprotection of MAc protected alcohols using sodium borohydride (Fig. 1).

In order to explore the scope of deprotection methodology, a set of diverse alcohols was converted into their corresponding MAc esters and then subjected to deprotection using sodium borohydride. The protection was achieved using methoxyacetyl chloride in DCM at room temperature in quantitative yields.[1] These MAc protected alcohols were purified before this deprotection methodology. It was observed that these compounds were deprotected using 1–2 equiv of sodium borohydride in ethanol at room temperature

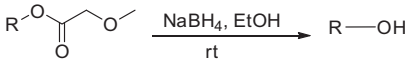

Figure 1. Reductive deprotection of MAc group.

in 1–4 h in high to excellent yields (Table 1–4). This Letter details the scope and limitation of this deprotection methodology.

We incorporated MAc on several substrates that include various primary and secondary aliphatic alcohols, phenols, thiols and amines.[7] It was desirable to demonstrate the efficiency of the reductive deprotection on different aromatic alcohols (Table 1, entries 1 and 2), aliphatic alcohols (Table 1, entries 3 and 4) and compounds bearing both phenolic and aliphatic groups (Table 1, entry 6). However, using these deprotection conditions, we did not observe any selectivity between primary and secondary alcohols (Table 1, entry 5). Similarly no selectivity was observed between phenol and aliphatic hydroxyl functionalities present within the same molecules (Table 1, entry 6) under different reaction conditions. In addition to the above examples we also wanted to expand the scope of MAc deprotection to nucleoside and carbohydrate compounds. Thus we synthesized compounds **7** and **8** (Table 1) from commercially available starting materials. Subjecting compound **7** (Table 1) to the optimized deprotection protocol led to global deprotection of both primary and secondary alcohols as also observed, for compound **5** (Table 1). In case of compound **8** (Table 1), MAc was deprotected successfully in the presence of

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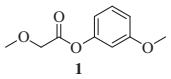
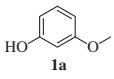
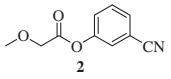
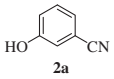
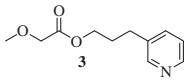
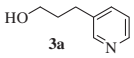
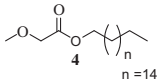
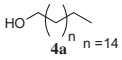
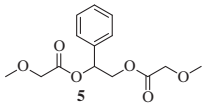
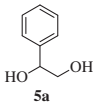
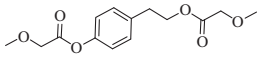
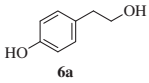
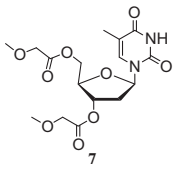
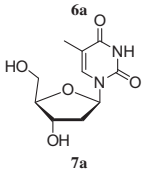
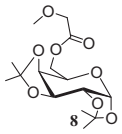
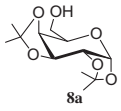
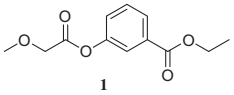
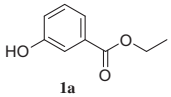
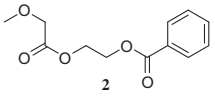
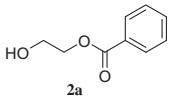
Table 1
Deprotection of different phenols, aliphatic primary and secondary alcohols

Entry[a]	Substrate	Product	Yield (%)
1	 1	 1a	95
2	 2	 2a	76
3	 3	 3a	79
4	 4 n =14	 4a n =14	66
5	 5	 5a	89
6	 6	 6a	81
7	 7	 7a	84
8	 8	 8a	79

[a] Reaction condition: ethanol, $NaBH_4$ (1 equiv), rt, 1 h.[8]

Table 2
Deprotection of MAc in the presence of esters

Entry[a]	Substrate	Product	Yield (%)
1	 1	 1a	85
2	 2	 2a	73

[a] Reaction condition: ethanol, $NaBH_4$ (1 equiv), rt, 1 h.[8]

acetonides. We also tried deprotection of 6-*O*-MAc protected 1,2,3,4-tetra-*o*-acetyl-beta-D-glucopyranose but deprotection using sodium borohydride led to concomitant loss of both MAc and acetyl protecting groups (data not shown).

MAc protection of alcohols entails the generation of an ester moiety so it was important to evaluate its deprotection selectivity in the presence of another ester group. For this we synthesized compounds **1** and **2** (Table 2) possessing an aromatic ester moiety. Thus we carried out deprotection of **1** and **2** (Table 2) under optimized deprotection conditions to achieve 85% and 73% yields, respectively. This extends the use of MAc as an orthogonal protecting group in the presence of these ester moieties.

Having achieved a mild and effective deprotection technique for MAc, we diverted our attention towards selective deprotection of MAc in the presence of other commonly used protecting groups (Table 3, entries 1–11). In this respect we wanted to establish orthogonality of MAc deprotection in the presence of *tert*-butyl ester, *N*-Boc, Fmoc, Cbz, *O*-TBDMS, *N*-benzyl, *O*-benzyl, *O*-acetyl, *N*-acetyl and *N*-MAc. Since deprotection of MAc was under reductive conditions we did not envisage any major hurdles in achieving orthogonality. As depicted in Table 3 (entries 1–11), we successfully established reaction conditions for the deprotection of MAc in the presence of other protecting groups in 72–95% yields.

However, for *O*Ac functionality this deprotection strategy, (Table 3, entry 9) had to be modified. In case of compound **9** (Table 3), selectivity was obtained only when the reaction mixture was stirred at rt for 1 h with 0.5 equiv of sodium borohydride. An increase in relative proportion of sodium borohydride and reaction time, led to the deprotection of both groups. As expected *N*-acetyl was not affected during the reductive deprotection by sodium borohydride (Table 3, entry 10) and similarly the *N*-MAc was not affected (Table 3, entries 1 and 11).

Since thiols and alcohols are chemically similar, we explored the scope of our deprotection on such functionalities. Protection for the thiol group is important in many areas of organic research, mainly in peptide and proteins synthesis, which often involves amino acids such as cysteine. A free SH group, can be protected as a thioether or thioester.[9] The alkyl thio ethers are difficult to cleave and have not been used extensively as protecting group.[10] Another commonly used protection strategy for thiols is the conversion into thioesters. The *S*-acetyl group is deprotected under base catalysed conditions which leads to β elimination products thus generating olefinic side products[11] and low yields.[12] We