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# $CBr_4$-photoirradiation protocol for chemoselective deprotection of acid labile primary hydroxyl protecting groups

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**Abstract**—$CBr_4$-photoirradiation protocol was found to be a mild, highly efficient and selective method for deprotection of isopropylidene, benzylidene, triphenylmethyl and *tert*-butyldimethylsilyl protecting groups on sugar molecules. The conditions of this reaction can also be used to cleave peptides off from acid-labile resin linkers in solid-phase peptide synthesis.


The success of the multi-step synthesis of complex natural products depends on efficient protection–deprotection of the several functional groups involved.[1] Although many methods have been reported for the selective deprotection of protected hydroxyl groups, a great need remains to explore simple, effective and selective ones for carbohydrate chemistry. Of the various protecting groups used for hydroxyl groups in carbohydrate chemistry, isopropylidene, benzylidene, triphenylmethyl (trityl) and *tert*-butyldimethylsilyl groups are those most frequently used for protecting primary hydroxyl due to their availability for selective protection and orthogonal deprotection.[1]

A catalytic amount of carbon tetrabromide ($CBr_4$) in methanol, at a reflux temperature, was demonstrated to successfully deprotect trityl,[2] *p*-methoxybenzyl (PMB),[3] β-(trimethylsilyl)ethoxymethyl,[4] methoxyethoxymethyl,[5] tetrahydropyranyl[6] and trialkylsilyl[7] ethers and *gem*-diacetates,[8] ketals[9] and acetals.[9] However, this method did not exhibit any chemoselectivity for deprotection of the most acid-labile protecting groups from other acid-sensitive groups. Recently, we reported a mild, highly efficient and selective deprotection of primary *tert*-butyldimethylsilyl (TBDMS) ethers in the presence of secondary silyl ethers using a catalytic amount of $CBr_4$ in methanol under photochemical reaction conditions.[10] Our longstanding interest in carbohydrate chemistry prompted us to investigate further the application of this methodology to the deprotection of other acid-labile protecting groups. Here we report the extension of this methodology to the deprotection of isopropylidene, benzelidene, trityl and TBDMS groups on sugar molecules. Moreover, this method is applicable to cleaving some types of acid-labile linkers in solid-phase peptide synthesis.[11]

Although many reagents have been reported to be effective in the cleavage of isopropylidene groups,[1,8,9] lack of selectivity was encountered with most of the methods. Recently, a few of selective isopropylidene deprotection methods were reported.[12] Here, we first examined the selective deprotection of isopropylidene of furanose derivatives with various hydroxyl protecting groups at position C-3 using $CBr_4$-photoirradiation method[10] (Table 1, entries 1–4). The selective removal of the isopropylidene group attached to the primary hydroxyl group was observed in the presence of acetyl, PMB, *p*-toluenesulfonyl and TBDMS, all of which remained intact during the reactions. Although the time required varied widely (24–48 h), uniformly high yields (81–89%) were obtained, indicating the efficiency of the method. Remarkably, the acetyl group migration reported under $CBr_4$/MeOH reflux conditions[2] was not observed when the present protocol was applied (entry 1). Also, the PMB group, reported to be cleaved easily

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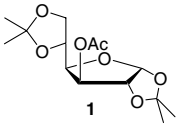
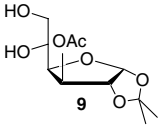
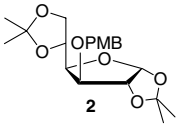
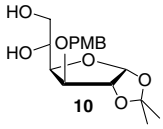
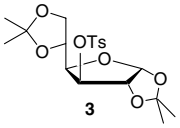
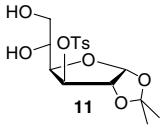
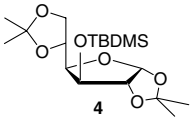
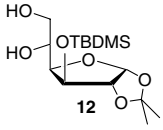
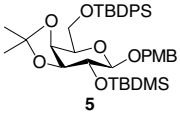
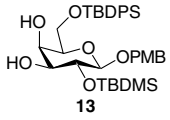
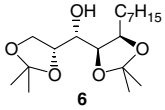
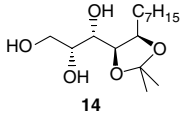
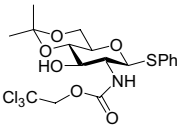
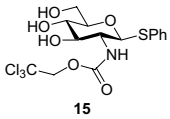
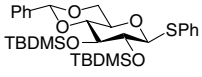
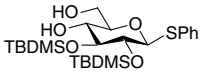
**Table 1.** Selective deprotection of isopropylidene and benzylidene with 5 mol% $CBr_4$/MeOH

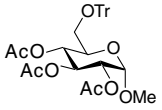
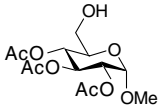
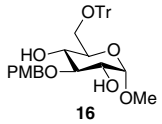
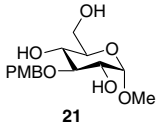
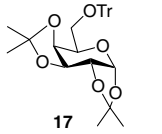
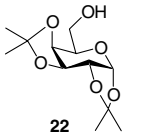
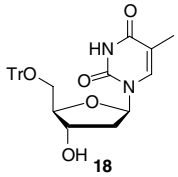
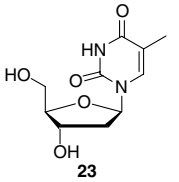
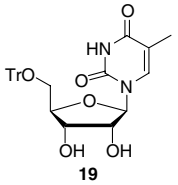
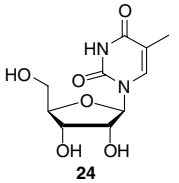
| Entry | Acetonide | Product | Time (h)[a] | Yield (%)[b] |
|---|---|---|---|---|
| 1 |  **1** |  **9** | 24 | 89 |
| 2 |  **2** |  **10** | 35 | 83 |
| 3 |  **3** |  **11** | 48 | 88 |
| 4 |  **4** |  **12** | 45 | 81 |
| 5 |  **5** |  **13** | 22 | 89 |
| 6 |  **6** |  **14** | 43 | 72 |
| 7 |  **7** |  **15** | 5 | 93 |
| 8 |  **8** |  **16** | 32 | 86 |

[a] Irradiated for 0.5 h then stirred at room temperature.
[b] Isolated yield.

under $CBr_4$/MeOH reflux conditions,[3] survived under the present photoirradiation conditions (entry 2). Accordingly, the present protocol is superior to those reported earlier, overcoming some of the disadvantages described above. Moreover, the isopropylidene or benzylidene protecting groups of pyranoses **5**, **7** and **8** were selectively deprotected with high yields (Table 1). Notably, the terminal isopropylidene on the di-isopropylidene-protected compound **6** was selectively deprotected under $CBr_4$/MeOH photoirradiation conditions.

Next, the deprotection of trityl ether, a widely used protecting group in carbohydrate and nucleoside chemistry, was explored. The known methods for deprotecting the trityl group[1,2] have several drawbacks, including the cleavage of glycosidic bond, the migration of acyl groups, tedious work-up procedures and low yields.[13] Monosaccharides **15**–**19** with a trityl group at the primary hydroxyl group position, were prepared[14] and subjected to the $CBr_4$/MeOH photoirradiation conditions. As expected, selective deprotection of trityl group was observed giving high yields of the products. The reaction conditions were tolerated by Ac and PMB groups (entries 1 and 2, Table 2). Notably, the trityl group on compound **17** was selectively cleaved in the presence of isopropylidene groups (cf. entry 5 in Table 1). Furthermore, the present methodology was very effective in the deprotection of trityl groups attached to

**Table 2.** Selective deprotection of trityl protecting group with 5 mol% $CBr_4$/MeOH

| Entry | Trityl ether[a] | Product | Time (h)[b] | Yield (%)[c] |
|---|---|---|---|---|
| 1 |  **15** |  **20** | 6 | 86 |
| 2 |  **16** |  **21** | 38 | 91 |
| 3 |  **17** |  **22** | 9 | 90 |
| 4 |  **18** |  **23** | 13 | 97 |
| 5 |  **19** |  **24** | 12 | 94 |

[a] Tr = Trityl group.
[b] Irradiated for 0.5 h then stirred at room temperature.
[c] Isolated yield.

the primary hydroxyl groups of nucleosides **18** and **19** (Table 2).

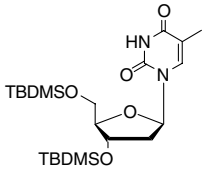
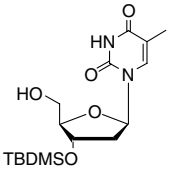
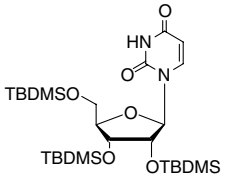
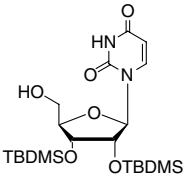
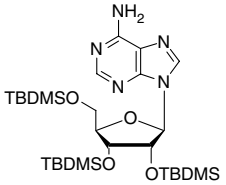
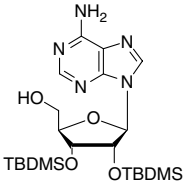
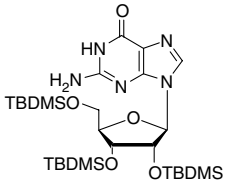
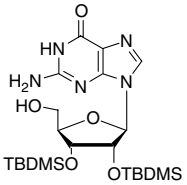
The photoirradition conditions were also applied to the selective deprotection of the primary TBDMS ethers[10] of full TBDMS protected nucleosides (Table 3). The primary TBDMS ethers of deoxythymine **25** and uridine **26** were successfully deprotected in high yields (85% and 92%). In the presence of the amino group of adenosine **27** and guanosine **28**, only moderate yields were obtained after reacting for 3 days (62% and 54%, respectively) even when the amount of $CBr_4$ was increased to 50% equivalent. Carbon tetrabromide in the presence of protic solvent is generally believed to release a hydrobromic acid molecule,[3] which is responsible for cleaving the trialkyl silyl ethers, and the other protecting groups mentioned above. In the presence of a basic amine on the nucleoside base, the acidic hydrobromide would be trapped, making it unavailable for deprotection. Contrary to the expectation, the deprotection of primary TBDMS in nucleosides proceeded smoothly. However, the details of the mechanism of the $CBr_4$/MeOH photoirradiation deprotection would require further investigation.

Finally, this method was also found effective in cleaving amino acids from acid-labile resin linkers (Table 4). Fmoc amino acid-preloaded trityl, HMPB-BHA and Wang resins were subjected to photoirradiation conditions and subsequent stirring for 3 days to yield the corresponding methyl ester amino acid residues in high yields (92–96%). Thus, this method can be applied to cleave peptides off from the resins in solid-phase peptide synthesis.

In summary, a highly selective protocol is developed for deprotection of a wide range of acid-labile protecting groups on primary alcohols. This method was applied in carbohydrate, nucleoside and solid-phase peptide synthesis.

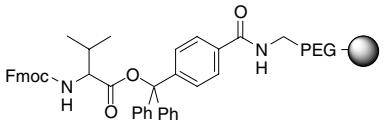
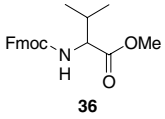
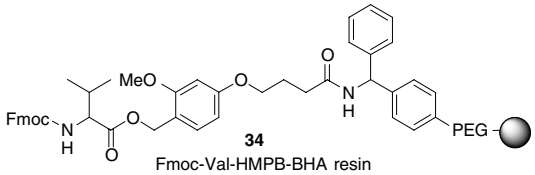
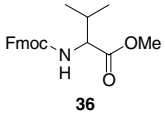
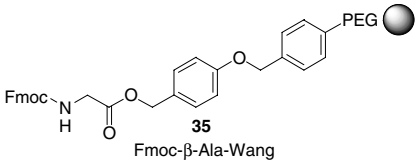
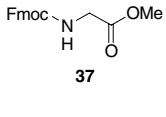
*Experiment:* A typical procedure for the selective cleavage of a protecting group using $CBr_4$ is as follows: A solution of saccharide (1.0 equiv), $CBr_4$ (0.05 equiv) and anhydrous MeOH (10 mL) in a Pyrex round bottom was irradiated by a TLC-lamp (Uvltec Limited, 245 nm, 8 W) for 0.5 h, followed by stirring without irradiation at room temperature. After the reaction was completed (by

**Table 3.** Selective deprotection of TBDMS ether with 20 mol% $CBr_4$/MeOH

| Entry | TBDMS-nucleotides | Product | Time (h)[a] | Yield (%) |
|---|---|---|---|---|
| 1 |  **25** |  **29** | 68 | 85 |
| 2 |  **26** |  **30** | 68 | 92 |
| 3 |  **27** |  **31** | 72 | 62(33)[b] |
| 4 |  **28** |  **32** | 72 | 54(43)[b] |

[a] Irradiated for 0.5 h then stirred at room temperature.
[b] The number in parenthesis indicates the yield of recovery of the starting material.

**Table 4.** Transesterification by 20 mol% $CBr_4$/MeOH

| Entry | Substrate | Product | Time (days)[a] | Yield (%)[b] |
|---|---|---|---|---|
| 1 |  **33** |  **36** | 2.5 | 96 |
| 2 |  **34** Fmoc-Val-HMPB-BHA resin |  **36** | 3 | 92 |
| 3 |  **35** Fmoc-β-Ala-Wang |  **37** | 3 | 95 |

[a] Irradiated for 0.5 h then stirred at room temperature.
[b] Isolated yield.

TLC), the organic solvent was removed directly under reduced pressure. Further purification was achieved by flash chromatograph with silica gel and ethyl acetate/hexane.

## Acknowledgements

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