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# Nafion-H mediated selective deprotection of terminal isopropylidene acetals and trityl ethers. Application in the synthesis of a substituted piperidone

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**Abstract**—A facile chemoselective hydrolysis of terminal isopropylidene acetals has been achieved in good to excellent yields within 2–4 h using Nafion-H in methanol at ambient temperature. This procedure has been employed to synthesize a substituted piperidone derivative. Similarly, trityl ethers are also deprotected to the corresponding alcohols in excellent yields using Nafion-H at room temperature.


## 1. Introduction

The usefulness of isopropylidene acetals (or acetonides) as protecting groups for 1,2- and 1,3-diols in organic synthesis, in general, and in carbohydrate and nucleoside chemistry, in particular, has been well documented.[1] Various reagents used for the regioselective hydrolysis of terminal isopropylidene acetals in the presence of internal ones include both protic and Lewis acids. The protic acids employed include aq HCl,[2a] aq HBr,[2b] 60% aq $CH_3CO_2H$,[2c] 8% $H_2SO_4$ in MeOH,[2d] Dowex $H^+$ in MeOH:$H_2O$ (9:1),[2e] trifluoroacetic acid,[2f] camphorsulfonic acid,[2g] and *p*-TsOH,[2h] whereas the Lewis acids include $CuCl_2\cdot 2H_2O$ in EtOH,[3a] $Zn(NO_3)_2\cdot 6H_2O$,[3b] $Yb(OTf)_3\cdot H_2O$,[3c] $CeCl_3\cdot 7H_2O/(COOH)_2$,[3d] $La(NO_3)_3\cdot 6H_2O$[3e] and $VCl_3$.[3f] Clearly, some of these acids are strong enough to allow non-selective hydrolysis leading to lower yields of the desired products, particularly in the presence of water. In addition to this, a neutral method employing thiourea[4] has been reported for this purpose. A few supported reagents such as $FeCl_3\cdot 6H_2O/SiO_2$,[5a] $NaHSO_4\cdot SiO_2$,[5b] $PMA/SiO_2$,[5c] polymer supported $FeCl_3$[5d] and $H_2SO_4\cdot SiO_2$[5e] have also been reported to address the issues of ease of work-up and environmental factors.

Similarly, the benefits of trityl ethers as protecting groups in organic synthesis, especially in carbohydrate chemistry[1] are also well known and the reagents employed for their deprotection include formic acid,[6a] acetic acid,[6b] trifluoroacetic acid,[6c] 1% methanolic solution of iodine,[6d] $BCl_3$,[6e] $Yb(OTf)_3$,[6f] $AlClEt_3$,[6g] $ZnBr_2$,[6h] ceric ammonium nitrate[6i] and $CBr_4$–MeOH.[6j] Recently, 5% trifluoroacetic acid[7a] and $NaHSO_4$[7b] adsorbed on column silica gel have also been reported for the deprotection of trityl ethers. More recently, we reported $HClO_4$ supported on silica gel[8] for the selective deprotection of terminal isopropylidenes and trityl ethers.

Nafion-H (a perfluorinated resin sulfonic acid) has attracted significant attention[9] and has been useful in various organic transformations as a solid catalyst. We have also reported a few organic transformations catalyzed by Nafion-H[10] such as acetylation of alcohols,[10a] Mukaiyama aldol condensations[10b] and deprotection of *tert*-butyldimethylsilyl ethers.[10c] Due to the ease of handling and reusability of Nafion-H and our continued interest in developing new methods in carbohydrate chemistry,[11] we now report that Nafion-H in methanol effectively deprotects terminal isopropylidene groups and trityl ethers at room temperature in good to excellent yields. Under these conditions several functional groups such as benzoyl, *p*-nitrobenzoyl (PNB), tosyl and TBDMS ethers remained unaffected. Our results are summarized in Tables 1 and 2. Interestingly, methyl 4-acetoxy-2,3-di-*O*-benzyl-6-*O*-trityl glucopyranose **44**

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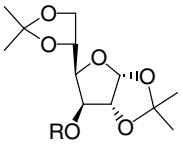
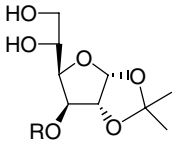
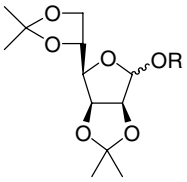
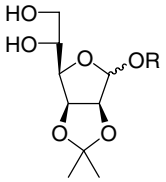
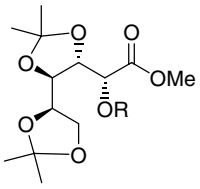
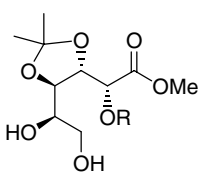
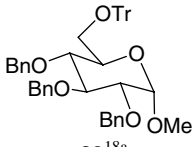
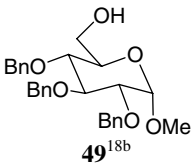
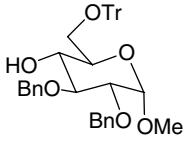
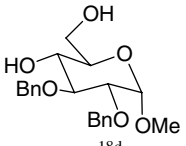
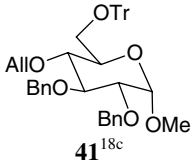
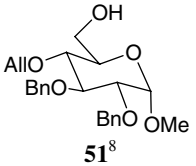
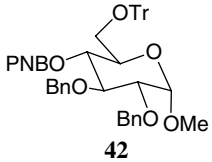
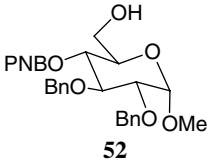
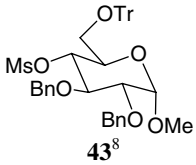
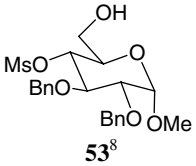
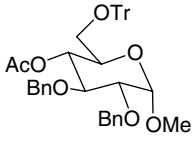
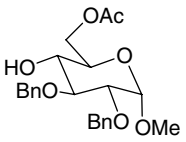
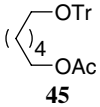
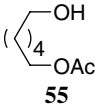
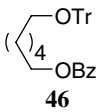
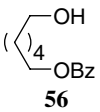
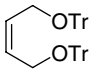
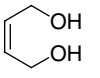
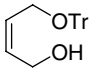
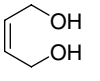
**Table 1.** Deprotection of isopropylidene acetals

| Diisopropylidene | Product 1,2-diol | Time (h) | Yield (%) |
|---|---|---|---|
|  |  | | |
| **1**: R = OH[15a] | **20**[15b] | 3 | 96 |
| **2**: R = Bn[15c] | **21**[15c] | 3 | 94 |
| **3**: R = Allyl[15d] | **22**[15d] | 3 | 91 |
| **4**: R = Ms[15e] | **23**[15f] | 2.5 | 87 |
| **5**: R = Ts[15e] | **24**[5b] | 3 | 88 |
| **6**: R = Bz[8] | **25**[5b] | 3 | 96 |
| **7**: R = PNB[8] | **26**[8] | 4 | 89 |
| **8**: R = TBDMS[5a] | **27**[15g] | 2 | 68 |
| **9**: R = OAc[15h] | **28**[15i] | 4 | 80 |
|  |  | | |
| **10**: R = Ac[16a] | **29**[16a] | 3 | 92 |
| **11**: R = Allyl[16b] | **30**[16b] | 3 | 83 |
|  |  | | |
| **12**: R = H[17a] | **31**[17a] | 3 | 82 |
| **13**: R = Ts[8] | **32**[8] | 3 | 84 |
| **14**: R = Bz[8] | **33**[8] | 2 | 88 |
| **15**: R = Ms[17a] | **34** | 2.5 | 86 |
| **16**: R = Ac | **35** | 4 | 90 |
| **17**: R = Bn[17b] | **36** | 5 | 92 |
| **18**: R = TBS[17c] | **37**[17c] | 2 | 74 |
| **19**: R = PNB | **38** | 3.5 | 92 |

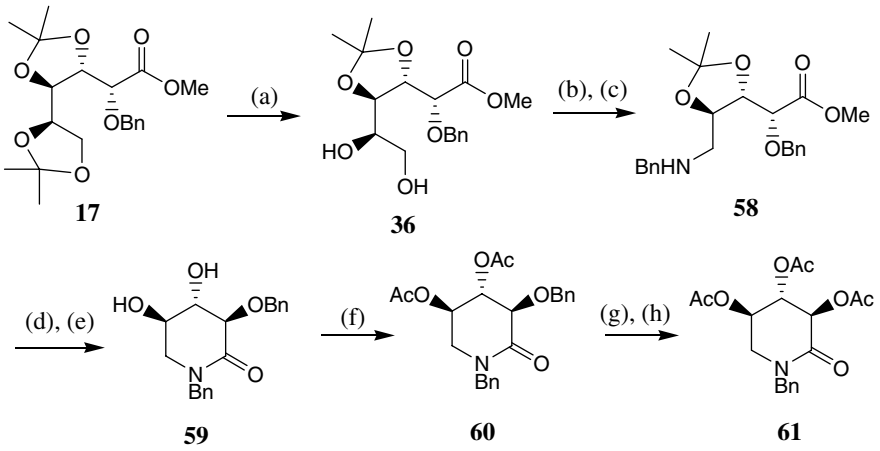
underwent migration[12] of the acetyl group from C-4- to C-6.

Our current interest[11d,13] in the synthesis of glycosidase inhibitors and other biologically important compounds led us to explore the utility of this method in the synthesis of piperidinone derivative **61** which is a potential glycosidase inhibitor.[14] Treatment of gluconolactone derived compound **17** with Nafion-H gave the corresponding diol **36** (see the Supplementary data for experimental details and data), which on subsequent treatment with sodium periodate followed by reductive amination with benzylamine led to the open chain amino ester **58**. The internal acetonide moiety was then cleaved with 0.5% HCl in methanol and subsequent treatment with Hunig's base in $CH_2Cl_2$ readily gave the cyclized piperidinone derivative **59**, which was acetylated to give diacetyl derivative **60** in good yield. Debenzylation followed by acetylation gave triacetoxypiperidinone **61** (Scheme 1).

**Table 2.** Deprotection of trityl ethers

| Trityl ether | Product | Time (h) | Yield (%) |
|---|---|---|---|
|  **39**[18a] |  **49**[18b] | 7 | 90 |
|  **40**[18c] |  **50**[18d] | 9 | 92 |
|  **41**[18c] |  **51**[8] | 12 | 86 |
|  **42** |  **52** | 10 | 75 |
|  **43**[8] |  **53**[8] | 14 | 82 |
|  **44**[18e] |  **54** | 9 | 85 |
|  **45** |  **55** | 16 | 88 |
|  **46** |  **56** | 15 | 89 |
|  **47** |  **57** | 18 | 91 |
|  **48** |  **57** | 16 | 90 |

See Refs. 8 and 18.




**Scheme 1.** Reagents and conditions: (a) Nafion-H, methanol, rt, 5 h, 92%; (b) $NaIO_4$, $CH_3CN$:$H_2O$ (3:1), rt; (c) $BnNH_2$, $NaCNBH_3$, AcOH, MeOH, two steps 61%; (d) 0.5% HCl in methanol; (e) Hunig's base, DCM, two steps 62%; (f) $Ac_2O$, $Et_3N$, DCM 94%; (g) 10% Pd/C, ammonium formate, MeOH and (h) $Ac_2O$, $Et_2N$, DCM two steps 72%.

Since Nafion-H is cheap, easy to handle and reusable and the work-up merely involves decantation followed by purification, it would be expected that this method would find application in organic synthesis.

## 2. General experimental procedures

Nafion-H was prepared from Nafion-K by the following procedure:[9h] Nafion-K (10 g) was treated with boiling deionized water (30 mL) for 2 h and filtered. The resin was then stirred in 20–25% nitric acid (40 mL) for 4–5 h at room temperature and filtered. This acid treatment was repeated three to four times to obtain maximum exchange of potassium ions in the resin with protons. The resin was finally washed several times with deionized water until the filtrate was neutral to litmus. It was then dried under vacuum at 105 °C for 24 h. This Nafion-H was stored in an air-tight vial and used as such throughout.

### 2.1. Deprotection of isopropylidene acetals

To a solution of a diisopropylidene compound (1 mmol) in methanol (2 mL) was added Nafion-H (an amount equal to the weight of the starting isopropylidene acetal). The heterogeneous mixture was stirred at room temperature for the appropriate time. After completion of the reaction (TLC monitoring), the mixture was filtered and the recovered Nafion-H was washed with methanol. The combined filtrate was concentrated under vacuum and the crude product purified by column chromatography to afford the pure 1,2-diol.

### 2.2. Detritylation

To a solution of trityl ether (1 mmol) in 2 mL of methanol, an amount equal to half the weight of the starting trityl ether of Nafion-H was added and the reaction was stirred at room temperature for the required time (Table 2). After completion of the reaction (TLC monitoring), it was filtered over cotton wool, washed with methanol and the combined organic extract was concentrated and the residue purified by column chromatography to give pure detritylated products.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.10.067.

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