Tetrahedron Letters 50 (2009) 4318–4320

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

$NbCl_5$ mediated deprotection of methoxy methyl ether

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ARTICLE INFO

Article history:
Received 30 January 2009
Revised 20 March 2009
Accepted 26 March 2009
Available online 29 March 2009

ABSTRACT

An efficient cleavage of methoxy methyl ether using $NbCl_5$ is described. This protocol works efficiently with MOM ethers of alkyl, allyl, propargyl, benzyl alcohol and phenol derivatives. MOM esters are also found to be effectively cleaved under the present conditions.

The selective introduction and removal of protective groups is an important tool which plays a significant role in the area of total synthesis of complex, biologically potent molecules.[1] Hydroxyl groups are the major functionalities found in large no. of intermediate compounds utilized in multi step synthesis. Of the several protective groups developed so far to proceed ahead in the target synthesis, methoxymethyl chloride can be considered as one of the most commonly used acid labile hydroxyl protective group, since it is easily introduced and forms the stable product. However, deprotection of the same is very often tedious as strong acidic conditions are utilized for deprotection of MOM moiety. The most commonly employed reagents known till date for MOM deprotection are HCl,[2] catechol boron bromide,[3] *p*TSA, pyridinium *p*-toluenesulfonate[4] and CBr_4/TPP.[5] Even Lewis acids $LiBF_4$,[6] Me_2BBr,[7] Ph_2BBr,[8] $(i\text{-Pr})_2BBr$,[9] Me_3SiBr,[10] $TiCl_4$,[11] $ZrCl_4$[12] and I_2 in methanol,[13] solid catalysts such as clay, Wells–Dawson acid ($H_6P_2W_{18}O_{62}$. aq)[14] and $NaHSO_4$–SiO_2[15] have been utlized for this transformation. Deprotection of MOM moiety under neutral conditions is also reported.[16] However, many of these procedures suffer from severe drawbacks such as lack of selectivity and lower yields. Also, the utility of strong acid becomes the barrier for the substrates with acid sensitive functionalities. Thus the scope for further development of new reagents for MOM deprotection is still persisting. In this Letter, we herein, report the utility of $NbCl_5$ as a reagent for MOM deprotection (Scheme 1).

$$\text{R—OMOM} \xrightarrow[\text{0 °C to rt}\\ \text{1-2 h, 70-93\%}]{\text{NbCl}_5\text{ (1 eq.)}\\ \text{acetonitrile,}} \text{R—OH}$$

R = Ar, alkyl, allyl, benzyl, propargyl

Scheme 1.

In continuation of a program directed toward the investigations of Lewis acid mediated/catalyzed organic transformations with $NbCl_5$,[17] we have recently demonstrated that $NbCl_5$ works efficiently for Knoevenegal condensation. While studying different examples, incidentally, we observed the cleavage of phenolic MOM ether with $NbCl_5$.[18] This result has encouraged us to optimize the conditions for MOM deprotection with $NbCl_5$.

We started with substrate **1a** (1 mmol), which was treated with $NbCl_5$ (0.5 equiv) in acetonitrile (3 mL) at room temperature. The complete consumption of the starting material was observed within 1 h to yield a single product. The product was isolated, characterized by ^{1}H NMR, ^{13}C NMR and mass spectroscopy as the hydrolyzed product **1b**. To further optimize the reaction conditions, the reaction was studied with several other solvents such as DCM, THF, MeOH and DMF. It was found that the reaction proceeds well in all the solvents. However acetonitrile was found to be the best in terms of the reaction time and yield.

For quantification of the catalyst/reagent, series of experiments were conducted with different concentrations of $NbCl_5$. It was observed that by increasing the amount of $NbCl_5$ (0.5–1.0 equiv) the reaction time was decreased (6–1 h). When excess $NbCl_5$ (1.5 or 2 equiv) was used there was no significant enhancement in yield.[19] Thus 1 equiv of $NbCl_5$ was necessary to get the optimum yield with minimum reaction time. Similarly, substrate **2a** when subjected to the present protocol produced the corresponding phenol **2b** as the only product in 89% yield. With these results, we moved ahead to investigate further generality of the reaction. Thus several MOM ethers of primary (**13a**, **14a**), benzylic (**4a**, **6a**, **8a**) propargylic (**9a**–**12a**) and allylic alcohols (**3a**, **5a**) were treated with $NbCl_5$ to obtain their corresponding hydrolysed products (Table 1) in good yields.

Substrates that are protected with both benzyl and MOM ethers (**7a** and **13a**) responded well with this new procedure yielding the desired products (**7b** and **13b**) with benzyl groups intact. However, TBS deprotection was observed for substrate **14a** to result in diol **14b**. All the products obtained were compared with the authentic samples and characterized by ^{1}H NMR, ^{13}C NMR and mass spectroscopy.[20] Gratifyingly, the MOM esters (**15a** and **16a**) also responded well to the present protocol yielding the corresponding acids (**15b** and **16b**, Table 2).

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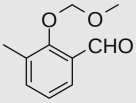
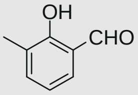
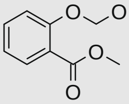
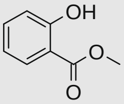
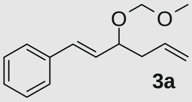
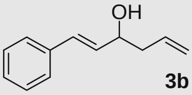
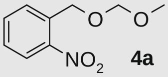
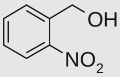
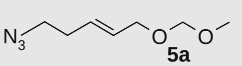
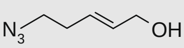
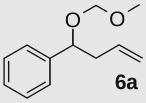
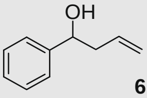
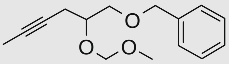
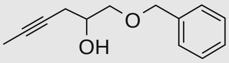
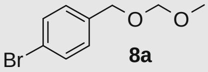
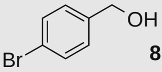
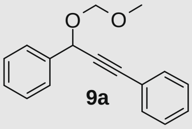
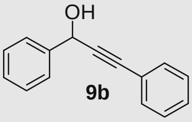
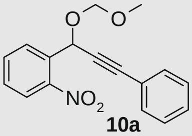
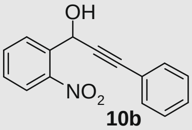
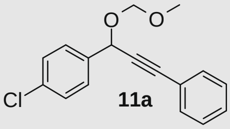
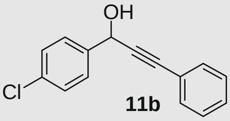
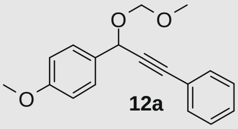
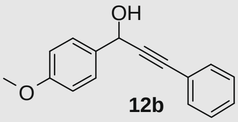
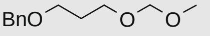
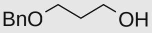
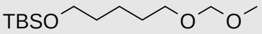
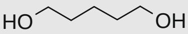
0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.03.171

Table 1
Deprotection of MOM ether with $NbCl_5$ in acetontitrile

Entry	Substrate	Product[a]	Time (h)	Yield[b] (%)
1	 **1a**	 **1b**	1	92
2	 **2a**	 **2b**	1	89
3	 **3a**	 **3b**	1.5	80
4	 **4a**	 **4b**	1	88
5	 **5a**	 **5b**	2	90
6	 **6a**	 **6b**	2	91
7	 **7a**	 **7b**	2	77
8	 **8a**	 **8b**	1	81
9	 **9a**	 **9b**	2	90
10	 **10a**	 **10b**	2	89
11	 **11a**	 **11b**	2	92
12	 **12a**	 **12b**	2	91

(*continued on next page*)

Table 1 (*continued*)

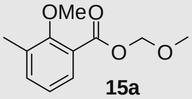
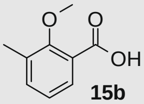
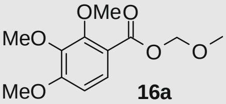
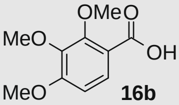
Entry	Substrate	Product[a]	Time (h)	Yield[b] (%)
13	 **13a**	 **13b**	1.5	75
14	 **14a**	 **14b**	1	70

[a] Products were characterized by ^{1}H NMR, ^{13}C NMR and mass spectroscopy.

[b] Isolated yields after column chromatography.

Table 2

Deprotection of MOM ester with $NbCl_5$ in acetontitrile

Entry	Substrate	Product[a]	Time (h)	Yield[b] (%)
15	 **15a**	 **15b**	1	91
16	 **16a**	 **16b**	1	93

[a] Products were characterized by ^{1}H NMR, ^{13}C NMR and mass spectroscopy.

[b] Isolated yields after column chromatography.

In conclusion, we have demonstrated the utility of $NbCl_5$ as a Lewis acid for an efficient cleavage of MOM ether to the corresponding alcohol and MOM ester to the corresponding acid. This protocol with milder reaction conditions (0 °C to room temperature) and high yield with shorter reaction times may find wide application in the field of synthetic organic chemistry.

Acknowledgements

Two of us (B.G.) and (D.C.B.) thank CSIR, New Delhi for financial assistance.

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18. Yadav, J. S.; Bhunia, D. C.; Singh, V. K.; Srihari, P. *Tetrahedron Lett*, **2009**, *50*, 2470–2473.
19. Compound **3a** was studied with different concentrations of the catalyst.
20. General procedure: To the MOM ether (1 mmol) dissolved in acetonitrile (3 mL) at 0 °C was added $NbCl_5$ (1 equiv) and stirred against the time mentioned in the table allowing the reaction mixture to warm to room temperature. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with satd aq $NaHCO_3$ solution. The product was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 then evaporated to give the crude product which was purified by silica gel column chromatography. Analytical data of few examples. 1,3-Diphenylprop-2-yn-1-ol (**9a**): Yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.91 (br s, 1H) 5.64 (s, 1H), 7.22–7.40 (m, 6H), 7.41–7.50 (m, 2H), 7.55–7.63 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 64.8, 86.4, 88.7, 122.3, 126.6, 128.1, 128.2, 128.4, 128.5, 131.6, 140.5. IR (neat): γ_{max} 3385, 3061, 2198, 1488, 1449, 1028, 757, 693 cm^{-1}. ESI-MS: *m/z* 231 $(M+Na)^+$. HRMS for $C_{15}H_{12}ONa$: calcd 231.0780, found 231.0789. (Benzyloxy)propan-1-ol (**13a**): Yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.80 (t, *J* = 5.8 Hz, 2H), 3.34 (br s, 1H), 3.56 (t, *J* = 5.8 Hz, 2H), 3.66 (t, *J* = 5.8 Hz, 2H), 4.45 (s, 2H), 7.17–7.39 (m, 5H), ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.9, 60.2, 68.1, 72.7, 127.3, 128.1, 137.8. IR (neat): γ_{max} 3413, 2930, 2862, 1736, 1453, 1364, 1079, 1024, 739 cm^{-1}, ESI-MS: *m/z* 167 $(M+H)^+$, HRMS for $C_{10}H_{16}O_2$: calcd 167.1066, found 167.1064. 2-Methoxy-3-methylbenzoic acid (**15a**): White solid Mp 72 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H), 3.89 (s, 3H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 7.3 Hz, 1H), 7.85 (d, *J* = 7.5 Hz, 1H), 11.08 (br s, 1H), ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.8, 61.8, 122.3, 124.3, 130.2, 132.0, 136.5, 158.2, 168.65. IR (neat): γ_{max} 2949, 2706, 2588, 1701, 1591, 1471, 1305, 1225, 1004, 768 cm^{-1}. ESI-MS: *m/z* = 167 $(M+H)^+$. HRMS for $C_9H_{11}O_3$: calcd 167.0703, found 167.0711.