

Chelation-Controlled Selectivity in the Clay-Catalyzed Deprotection of Phenolic Methoxy Methyl Ethers

Jay P. Deville and Victor Behar*

Department of Chemistry MS-60, Rice University,
Houston, Texas 77251-1892

behar@rice.edu

Received February 16, 2001

The use of Montmorillonite clay catalysis to effect organic transformations¹ has increased due to its exceptionally mild conditions, ease of use and recyclability, simplicity of purification, and low cost.² Montmorillonite clays and their ion-exchanged forms have been used in a variety of Lewis acid-catalyzed reactions, including the aldol condensation,³ Prins reaction,^{1c} Claisen rearrangement,⁴ and Diels–Alder reaction.⁵ In connection with studies to develop selective methods to differentiate phenolic groups in naphthoquinone- and anthraquinone-containing antitumor antibiotics with highly oxygenated frameworks, we observed an unexpectedly facile removal of a methoxy methyl (MOM) ether catalyzed by Montmorillonite K 10 clay (Scheme 1). The reaction of MOM-protected naphthol **1**⁶ proceeded at room temperature in

* To whom correspondence should be addressed. Tel: 713-348-6159. Fax: 713-348-5155.

(1) For comprehensive review of clays used in organic synthesis, see: (a) Nikalje, M. D.; Phukan, P.; Sudalai, A. *Org. Prep. Proc. Int.* **2000**, *32*, 1. (b) Balogh, M.; Laszlo, P. In *Organic Chemistry Using Clays*; Springer-Verlag: New York, 1993. For recent examples, see: (c) Yadav, J. S.; Reddy, B. V. S.; Kumar, G. M.; Murthy, Ch. V. S. R. *Tetrahedron Lett.* **2001**, *42*, 89. (d) Choudary, B. M.; Chowdari, N. S.; Kantam, M. L. *Tetrahedron* **2000**, *56*, 7291. (e) Das, B.; Madhusudhan, P.; Venkataiah, B. *Synth. Commun.* **2000**, *30*, 4001.

(2) Montmorillonite K 10 and Montmorillonite KSF clays are both available from Aldrich for \$20.25/kg.

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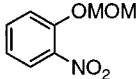
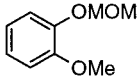
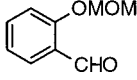
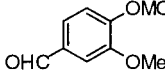
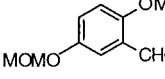
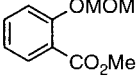
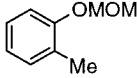
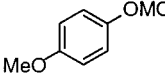
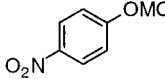
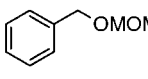
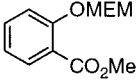
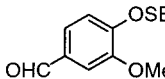
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Table 1. Clay-Catalyzed Deprotection of MOM Ethers^a

Entry	Substrate	Time/h	Temp./°C	Yield ^b %
1		5	25	93
2		1	50	91
3		2.5	25	89
4		1	50	96
5		5	25	74 ^c
6		0.5	25	86
7		14	50	Dec. ^d
8		22	50	Dec. ^d
9		72	50	<20
10		120	50	N. R.
11		1.5	25	96
12		0.5	50	92

^a All entries and their deblocked products are known compounds.⁷ ^b Isolated yield. ^c Only the MOM group ortho to the aldehyde is removed. ^d Complex decomposition occurred with prolonged exposure to the clay at 50 °C. No reaction was observed at 25 °C.

benzene over 45 min, affording 95% isolated yield of phenol **2**.

Recognizing the potential utility of this mild method for removal of the MOM protecting group, we sought to study the scope of this reaction. The results are summarized in Table 1.

The reaction was found to be general for a variety of ortho-substituted MOM-protected phenols (entries 1–6),

Scheme 1. Clay-Mediated Deprotection of MOM Ether 1

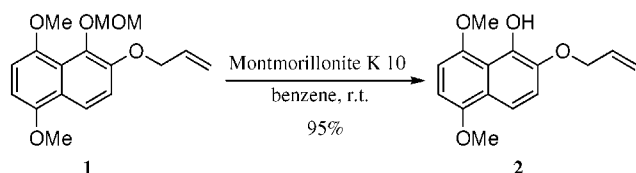


Table 2. Solvent Dependence in Deprotection of MOM-Salicylaldehyde

entry	solvent	% conversion ^a
1	hexanes	9
2	CH ₂ Cl ₂	100
3	PhH	100
4	ether	9
5	THF	2
6	acetone	<1

^a Determined by ¹H NMR at 400 MHz.

though the reaction requires the presence of a heteroatom in this ortho position (cf. entry 7). A substrate that contains two MOM groups can be differentiated if one is ortho to a chelating group and the other is not (entry 5). Some oxidative degradation accounts for the slightly lower yield for this substrate. Electron-withdrawing groups in the ortho position facilitate the reaction, allowing shorter reaction times at room temperature (entries 1, 3, and 6). Electron-donating groups decrease the rate of the reaction, and some substrates required heating to 50 °C for reasonable reaction times (entries 2 and 4). In the absence of an ortho-chelating functionality, the MOM group is not efficiently cleaved by exposure to the clay (entries 7–10). An aliphatic MOM group was also stable under these conditions (entry 10). Finally, the reaction is general for acetal-type protecting groups including MEM and SEM ethers (entries 11 and 12), which are cleaved with comparable efficiency to the MOM ether.

A variety of solvents were screened in the deblocking of MOM-protected salicylaldehyde as shown in Table 2. It is worth noting that the reaction works equally well with methylene chloride and benzene (entries 2 and 3). Not surprisingly, competing Lewis basic solvents attenuate the reactivity of the clay resulting in very low conversions (entries 4–6). Hexanes (entry 1) was

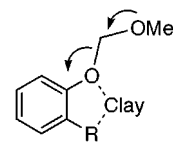


Figure 1. Chelation-assisted cleavage of MOM ether.

not an optimal solvent, and this was due to lack of solubility.

The data presented here are consistent with a mechanism involving chelation-assisted cleavage of the MOM ether by the Lewis acidic Montmorillonite clay (Figure 1).

Electron-withdrawing substituents stabilize the emerging phenoxide anion, hence resulting in a more facile cleavage. Competing Lewis basic solvents are incompatible with the deprotection reaction. Further studies of the Montmorillonite clay catalyzed cleavage of acetal groups are currently underway.

Experimental Section

General Experimental Methods. Montmorillonite K 10 clay was purchased from Aldrich Chemical Co. and was used without any further purification. Benzene, methylene chloride, and hexanes were distilled from calcium hydride under nitrogen. THF and ether were distilled from sodium–benzophenone ketyl. Acetone was dried over calcium sulfate. Reaction progress was monitored by thin-layer chromatography on 250 μm Baker precoated silica gel plates with visualization by UV light.

Representative Procedure. To a solution of MOM-protected naphthol **1** (67 mg, 0.22 mmol) in dry benzene (1.5 mL) was added Montmorillonite K 10 clay (67 mg). After the solution was stirred vigorously for 45 min at room temperature, the clay was filtered and washed with EtOAc. Concentration of the filtrate in vacuo followed by purification by silica gel chromatography (hexanes/EtOAc 8:2) afforded free naphthol **2** (54 mg, 95%) as a white solid. Mp: 123–124 °C. ¹H NMR (400 MHz, CDCl₃): δ 9.48 (s, 1H); 7.66 (d, *J* = 9 Hz, 1H); 7.22 (d, *J* = 9 Hz, 1H); 6.60 (d, *J* = 8 Hz, 1H); 6.48 (d, *J* = 8 Hz, 1H); 6.13 (m, 1H); 5.41 (d, *J* = 16 Hz, 1H); 5.25 (d, *J* = 9 Hz, 1H); 4.7 (d, *J* = 8 Hz, 2H); 3.97 (s, 3H); 3.90 (s, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 152.2, 150.2, 143.1, 142.7, 133.9, 123.3, 117.5, 116.4, 112.9, 109.0, 103.7, 100.9, 71.1, 56.3, 55.5. IR (thin film): 3332 (–OH) cm^{–1}. HRMS (CI): calcd for C₁₅H₁₆O₄ (M + H) 261.1127, found 261.1130.

Acknowledgment. We gratefully acknowledge financial support from the Robert A. Welch Foundation (Grant C-14189) and William Marsh Rice University. J.P.D. is supported in part by the National Science Foundation Graduate Fellowship Program.

JO015578L