Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 45 (2004) 5395–5398

Tetrahedron Letters

Mild and facile procedure for clay-catalyzed acetonide protection and deprotection of *N*(Boc)-amino alcohols and protection of 1,2-diols

Nadim S. Shaikh, Santosh S. Bhor, Anil S. Gajare, Vishnu H. Deshpande and Radhika D. Wakharkar*

Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune 411 008, India

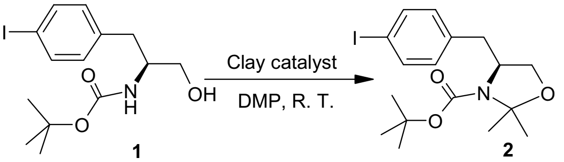
Received 16 February 2004; revised 10 May 2004; accepted 17 May 2004

Abstract—The application of clay as a catalyst for acetonide protection of *N*(Boc)-amino alcohols and 1,2-diols to obtain good to excellent yields of the acetonide derivatives is described. Acetonide deprotection to obtain the parent amino alcohol was carried out using a similar catalyst in the presence of methanol as solvent. The reaction takes place at room temperature within 2 h to give the parent amino alcohol in quantitative yield keeping the *N*(Boc) group intact.

The acetonide functionality is frequently used as a protecting group for 1,2-amino alcohols and 1,2-diols in carbohydrate and peptide chemistry[1] due to its stability to mildly acidic as well as basic conditions. During the course of a synthetic sequence, it usually becomes necessary to protect free hydroxyl or amino groups. Many syntheses fail because the protecting groups give poor results or are difficult to cleave.[2] Hence, in effecting efficient conversion of functional groups present in the side chain of 1,2-amino alcohols and 1,2-diols, appropriate protection of the amine and alcohol functionality is highly desirable.

Classical acetonation of diols in carbohydrates has been achieved using acetone with various mineral acids, such as concd sulfuric acid or fuming HCl or phosphoric acid, in the presence or absence of copper(II) sulfate or zinc chloride.[3] The use of 2,2-dimethoxypropane (DMP) in the presence of CSA (camphorsulfonic acid) or a catalytic amount of *p*-TsOH in combination with an appropriate solvent such as DMF has been employed for the conversion of 1,2-diequatorial hydroxyl groups of carbohydrates into isopropylidene derivatives.[4,5] 1,2-Amino(Boc) alcohols can be protected as oxazolidines using DMP and PPTS (pyridinium *p*-toluenesulfonate) at ambient temperature,[6] while dil HCl, TFA (trifluoroacetic acid) and methanolic *p*-TsOH[2] are the reagents generally used for the deprotection of acetonides to obtain the parent diol or amino alcohol.

Several methods are available for the protection of 1,2-diols as isopropylidenes in sugars and for 1,2-amino alcohols as oxazolidine derivatives.[1] However, the development of mild and efficient methods is still required. Recently, in the course of our studies directed towards the synthesis of 4-borono-L-phenylalanine[7] compound **2** was an important intermediate. The acetonide protection of *N*(Boc)-protected amino alcohol **1** to give the protected derivative of phenylalanol **2** (as shown in Scheme 1) was unsatisfactory with $BF_3 \cdot OEt_2$,[8] *p*-TsOH and $CuSO_4$ in the presence of acetone and/or DMP. A decomposed material was obtained in the first case whereas a mixture of products or a low yield of **2** was observed in the latter case.



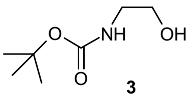
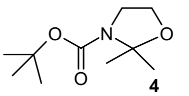
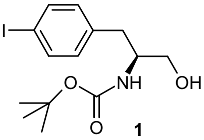
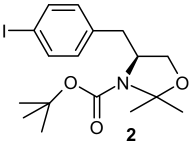
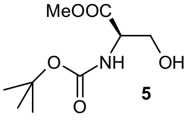
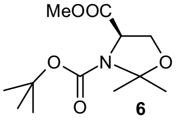
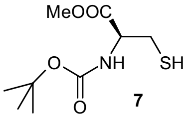
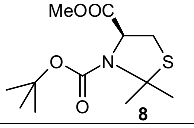
Scheme 1. Clay-catalyzed protection of amino alcohol **1**.

Keywords: Clay catalyst; Acetonide; Protection; Deprotection; Amino alcohols; Diols.

* Corresponding author. Tel./fax: +91-20-25893614; e-mail: rdw@dalton.ncl.res.in

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.05.079

Table 1. Clay-catalyzed acetonide protection (A) and deprotection (B)

Entry	Substrate	Product	Yield (%) A	Yield (%) B
1	 **3**	 **4**	95 91[a] 93[b] 15[c]	98 95[a] 97[b] 20[c]
2	 **1**	 **2**	94 0[c] 92[d]	95 10[c] 98[d]
3	 **5**	 **6**	85	82
4	 **7**	 **8**	82	81

[a] Using EPZG®.

[b] Using natural kaolinitic clay.

[c] Without catalyst for 24 h.

[d] With recycled catalyst.

Recently, clay minerals have become available for organic syntheses as heterogeneous acid catalysts.[9] Commercially available Montmorillonite K 10 clay has been used successfully in many important organic transformations. Experimental procedures using clay are simple with regard to treatment and removal of the catalyst because of its non hygroscopic and heterogeneous nature. As the application of clay in Lewis acid catalyzed reactions is of ongoing interest to us,[10] we applied Montmorillonite K 10 clay in acetone, under reflux to convert **1** into **2**. Only a negligible amount of **2** was isolated, however, when acetone was replaced with excess DMP, complete conversion of **1** was observed, and compound **2** was isolated as the only product in excellent yield (95%).

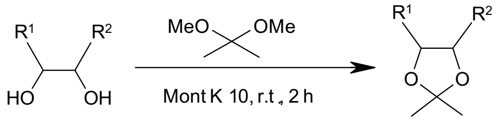
In a typical experiment derivative **1** was stirred in a mixture of dry acetone and DMP (3 equiv) in the presence of Montmorillonite K 10 clay (20% w/w) to afford 75% of the desired product **2** in 3 h.

Selective isopropylidene deprotection using methanolic *p*-TsOH at room temperature was incomplete even after 14 h. Furthermore, when the reaction mixture was refluxed for 1 h in methanolic *p*-TsOH, partial deprotection of the *N*-Boc group was observed. The clay catalyst was examined for selective cleavage of acetonide **2** in order to obtain **1**. Using methanol as solvent, the reaction proceeded to completion within 2 h to give compound **1** in quantitative yield without affecting the Boc group.[10f] These results prompted us to develop a simple catalytic system for different substrates for protection (A) and deprotection (B) as summarized in Table 1.

As a model, *N*(Boc) protected ethanolamine underwent acetonation using Montmorillonite K 10 clay in the presence of DMP to give 95% of the corresponding protected compound within 2 h. Natural kaolinitic clay and envirocat EPZG® also showed comparable results in both acetonide protection and deprotection. In a blank experiment (without catalyst), after 24 h, only a poor yield (Table 1, entry 1) of the desired protected compound (15%) was obtained. The methyl ester of *N*(Boc) protected L-serine demonstrated excellent yields for both protection and deprotection (Table 1, entry 3). Such a fully protected serine derivative has many potential synthetic applications including the preparation of valuable unnatural α-amino acids.[11a] The optical rotation for **6** was in good agreement with the reported value indicating no loss in optical purity during the transformation. Similarly the methyl ester of *N*(Boc) L-cysteine gave thiazolidine **8**[11b] (entry 4). In all the cases studied, protection and deprotection occurred smoothly keeping the *N*(Boc) group intact. However, acetonide protection of free 1,2-amino alcohols such as L-phenylalanol and ethanolamine failed.

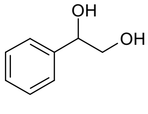
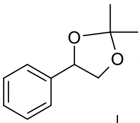
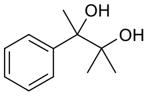
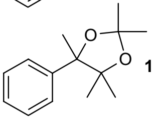
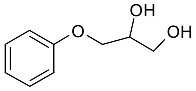
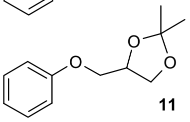
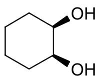
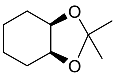
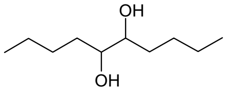
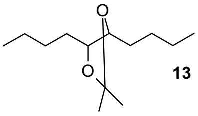
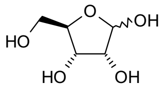
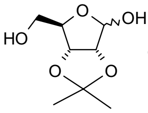
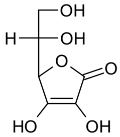
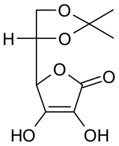
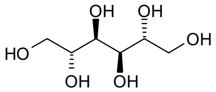
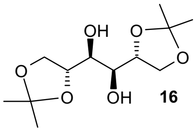
A similar strategy was applied for the acetonide protection of 1,2-diols to convert them into the corresponding isopropylidene ketals (Scheme 2).

Various 1,2-diols were studied and the results are summarized in Table 2. The 1,2-diol of styrene, when stirred with DMP in the presence of the clay catalyst (40%



Scheme 2. Montmorillonite K 10 catalyzed protection of 1,2-diols.

Table 2. Montmorillonite K 10 catalyzed acetonide protection of 1,2-diols

Entry	Substrate	Product[a]	Yield (%)[b]
1		 **9**	87
2		 **10**	80
3		 **11**	84
4		 **12**	92
5		 **13**	74
6		 **14**	90
7		 **15**	52[c]
8		 **16**	60[d]

[a] All the products were characterized by spectral analysis.
[b] Isolated yields.
[c] Reaction time of 8 h.
[d] The triacetonide (25%) was also isolated.

w/w), gave the corresponding isopropylidene derivative **9** (Table 2, entry 1) in 87% isolated yield. As shown in Table 2, satisfactory yields were obtained in all the cases including cyclic, linear aliphatic and sugar diols. In the case of D-mannitol along with the diacetonide (Table 2, entry 8) triacetonide formation was observed with 25% isolated yield.

Unfortunately the reaction did not work for D-glucose even after heating for 12 h. Also, the reaction failed in the case of catechol. Deprotection of the acetonides of 1,2-diols was also studied and it was found that the substrates were stable under these conditions (clay in methanol) even at reflux temperature.

Thus, a mild and efficient method for the protection and deprotection of *N*-Boc protected 1,2-amino alcohols, 1,2-amino thiols and acetonide formation from 1,2-diols has been developed using a heterogeneous catalyst. Short reaction times, high yields and simple work up procedures are the main features of this method.

Acknowledgements

N.S.S. and A.S.G. are grateful to CSIR, New Delhi, for research fellowships.

References and notes

1. Green, T. W.; Wuts, P. G. M. *Protecting Groups in Organic Synthesis*, 2nd ed.; John Wiley & Sons Inc: New York, 1991.
2. Chhabra, S. R.; Mahajan, A.; Chan, W. C. *J. Org. Chem.* **2002**, *67*, 4017–4029.

3. (a) Foster, A. B. In *The Carbohydrates: Chemistry and Biochemistry*; Pigman, W., Horton, D., Eds.; Academic: New York, 1972; Vol. 1A, p 391; (b) De Belder, A. N. *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 179; (c) Clode, D. M. *Chem. Rev.* **1979**, *79*, 491–513, and references cited therein.
4. He, D. Y.; Li, Z. J.; Liu, Y. Q.; Qiu, D. X.; Cai, M. S. *Synth. Commun.* **1992**, *22*, 2653–2658.
5. (a) Evans, M. E.; Parrish, F. W.; Long, L., Jr. *Carbohydr. Res.* **1967**, *23*, 453–462; (b) Hasegawa, A.; Fletcher, H. G., Jr. *Carbohydr. Res.* **1973**, *29*, 209–222; (c) Hasegawa, A.; Nakajima, M. *Carbohydr. Res.* **1973**, *29*, 239–245.
6. Ali, S. M.; Hoemann, M. Z.; Aube, J.; Mitscher, L. A.; Georg, G. I.; McCall, R.; Jayasinghe, L. R. *J. Med. Chem.* **1995**, *38*, 3822–3828.
7. (a) Snyder, H. R.; Reedy, A. J.; Lennarz, W. J. *J. Am. Chem. Soc.* **1958**, *80*, 835–838; Malan, C.; Morin, C. *J. Org. Chem.* **1999**, *63*, 8019–8020; Malan, C.; Morin, C. *Synlett* **1996**, 167–168; Barth, R. F.; Soloway, A. H.; Tjarks, W.; Barnum, B. A.; Rong, F.-G.; Wyzlic, I. M.; Wilson, J. G. *Chem. Rev.* **1998**, *98*, 1515–1562; Coderre, J. A.; Glass, R. G.; Fairchild, P. L.; Micca, P. L.; Fand, I.; Joel, D. D. *Cancer Res.* **1990**, *50*, 138; (b) Synthesis of 4-borono-L-phenylalanine: Unpublished results from our group.
8. McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Synthesis* **1994**, 31–33.
9. (a) Laszlo, P. *Pure Appl. Chem.* **1990**, *62*, 2027–2030; (b) Laszlo, P. *Science* **1987**, *235*, 1473–1477; (c) Nikalje, M. D.; Phukan, P.; Sudalai, A. *Org. Prep. Proced. Int.* **2000**, *32*, 1; (d) Verma, R. S. *Tetrahedron* **2002**, *58*, 1235–1255.
10. (a) Gajare, A. S.; Shaikh, N. S.; Jnaneshwara, G. K.; Deshpande, V. H.; Ravindranathan, T.; Bedekar, A. V. *J. Chem. Soc., Perkin Trans. 1* **2000**, 999–1001; (b) Shaikh, N. S.; Deshpande, V. H.; Bedekar, A. V. *Tetrahedron* **2001**, *57*, 9045–9048; (c) Gajare, A. S.; Shaikh, N. S.; Bonde, B. K.; Deshpande, V. H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 639–640; (d) Ponde, D. E.; Deshpande, V. H.; Bulbule, V. J.; Sudalai, A.; Gajare, A. S. *J. Org. Chem.* **1998**, *63*, 1058–1063; (e) Jnaneshwara, G. K.; Barhate, N. B.; Sudalai, A.; Deshpande, V. H.; Wakharkar, R. D.; Gajare, A. S.; Shingare, M. S.; Sukumar, R. *J. Chem. Soc., Perkin Trans. 1* **1998**, 965–968; (f) Shaikh, N. S.; Gajare, A. S.; Deshpande, V. H.; Bedekar, A. V. *Tetrahedron Lett.* **2000**, *41*, 385–387.
11. (a) Koskinen, A. M. P.; Hassila, H.; Myllymaki, V. T.; Rissanen, K. *Tetrahedron Lett.* **1995**, *36*, 5619–5622; (b) Threadgill, M. D.; Gledhill, A. P. *J. Org. Chem.* **1989**, *54*, 2941–2949.