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A Refined Method for the Removal of the Methoxymethyl (MOM) Protecting Group for Carbinols with Acidic Ion-Exchange Resin

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A REFINED METHOD FOR THE REMOVAL OF THE METHOXYMETHYL (MOM) PROTECTING GROUP FOR CARBINOLS WITH ACIDIC ION-EXCHANGE RESIN

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ABSTRACT: The methoxymethyl protecting group for carbinols is best removed from acid-sensitive substrates by hydrolysis in aqueous methanol using a cationic exchange resin (Dowex-50W).

The methoxymethyl (MOM) function has been extensively used as a protecting group for hydroxy groups,[1] especially in multistep syntheses of functionally complex molecules. It is stable towards a wide range of reaction conditions, including organometals, reducing and oxidizing reagents, and mild acids, but unlike many acetal functions it does not introduce a further stereogenic center into chiral molecules with all the attendant problems associated with the inevitable formation of diastereomers. Unfortunately, its removal often requires relatively harsh acidic conditions because of its chemical stability, which has

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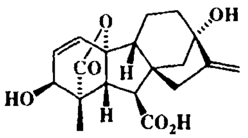
somewhat restricted its utilization in molecules containing other acid-sensitive functionality. For example, it was not possible to avoid a Wagner-Meerwein rearrangement of the acid-sensitive C/D ring moiety[2] (*i.e.* **2**→**4**) in the product from a simple acid-catalyzed hydrolysis of the 13-MOM group in **2**, an advanced intermediate in the synthetic conversion of gibberellic acid **1** into the rare bamboo gibberellin **3**.[3] This was initially found to be a serious constraint in some recent synthetic work on gibberellins ("GAs")[4] and other reagents[5] were also found to be inadequate for the task. We can now report that the MOM protecting group for carbinols is best removed from acid-sensitive substrates by hydrolysis in aqueous methanol using a cationic exchange resin (Dowex-50W).[6]



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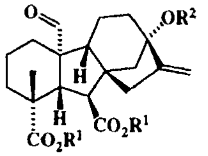
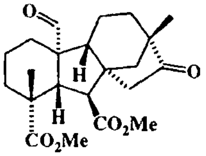


2 R^1 = Me, R^2 = MOM
3 R^1 = H, R^2 = H



4

The results from the hydrolysis of MOM ethers derived from a variety of GA derivatives are summarized in Table 1. The structures of all compounds listed here were confirmed either by direct comparison with authentic materials or of ^{1}H-NMR spectra. In each case, the work-up was reduced to mere filtration and the yields were excellent. Skeletal rearrangements of the C/D ring system were completely eliminated, which was in contrast to the results from hydrolysis using *p*-toluenesulfonic acid as a catalyst, where a considerable amount of the rearrangement products formed. In the absence of water longer reaction times were necessary (6 hours instead of 3). In the case of the aldehydes **2** and **5** inclusion of water was necessary to prevent formation of a cyclic methyl acetal between the 4α-

Table 1. Deprotection of MOM ethers in GA Derivatives

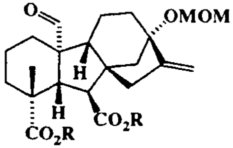
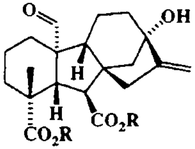
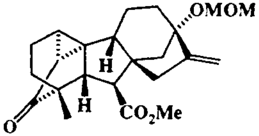
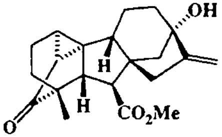
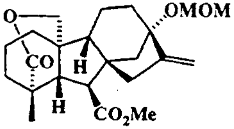
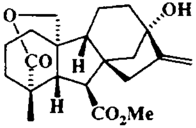
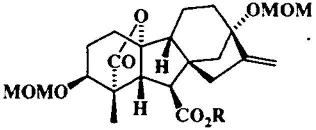
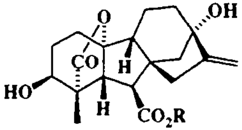
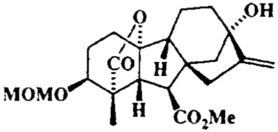
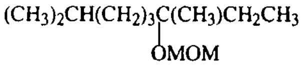
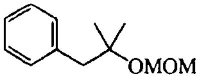
Entry	MOM ether		Time (hr)	Product	Isolated Yield (%)
1		**2** R=Me	3		**10** R=Me (93)
2		**5** R=H	3		**3** R=H (90)
3		**6**	3		**11** (93)
4		**7**	3		**12** (96)
5		**8** R=Me	6		**13** R=Me (96)
6		**9** R=H	6		**14** R=H (91)
7	**8**		3		**15** (42) [+ **13** (51)]

Table 2. Deprotection of MOM group in Acyclic Substrates

Entry	MOM ether	Time (hr)	Isolated Yield (%) of Alcohol
1	$CH_3(CH_2)_{12}CH_2OMOM$ **16**	30	96
2	$CH_3(CH_2)_{11}CH(CH_3)OMOM$ **17**	8	94
3	 $(CH_3)_2CH(CH_2)_3C(OMOM)(CH_3)CH_2CH_3$ **18**	2	94
4	 **19**	0.5	97

carboxyl and the 20-formyl group. The outcome for the 3β,13-bisMOM ether (**8**) (entry 7) shows that a tertiary MOM ether is cleaved faster than a secondary one, suggesting that steric congestion promotes removal.

Although many examples of the removal of MOM protecting groups from alcohols through acid catalyzed solvolysis have been reported,[1,8] there has been no comment on the influence of steric factors on the reaction rate. So, to clarify this aspect, our reaction conditions were applied to the MOM ethers derived from a series of simple acyclic alcohols.

The results summarized in Table 2 show that the relative reaction rate of the solvolysis of MOM ethers in methanol increases in the order, primary (**16**) < secondary (**17**) < tertiary, **18** < **19**, where **19** is sterically more congested than **18**. Therefore, it is apparent that increasing steric congestion facilitates the solvolytic cleavage of MOM ether under acidic conditions. In addition, the clean regeneration of tertiary alcohols (entries 3 and 4) without elimination to the olefin provides a further demonstration of the mildness of these reaction conditions.

Experimental

Typical Procedure for the removal of MOM protecting group: Resin[9] (500 mg) was added to a solution of 13-MOM-GA_{19} dimethyl ester (**2**) (500 mg) in a mixture of methanol (10 ml) and water (2 ml) and the heterogeneous mixture refluxed with stirring until a t.l.c. monitor indicated complete reaction (*ca.* 3 hr). The resin was filtered off through a glass-filter and washed with methanol. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel using a mixture of *n*-hexane and ethyl acetate (2:1) as eluting solvent, giving GA_{19} dimethyl ester (**10**) in 93% yield.

References and Notes

1. Greene, T.W. "Protective Groups in Organic Syntheses," John Wiley and Sons, Inc., New York, 1981; p. 16 and references cited therein.
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6. This kind of acidic ion-exchange resin, Amberlyst H-15 or Dowex-50W-X8, was already used as a catalyst for protection of alcohols with the tetrahydropyranyl group and its removal at room temperature.[7]

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8. (a) Kieczykowsky, G.R., Quesada, M.L. and Schlessinger, R.H. *J. Am. Chem. Soc.*, **1982**, *102*, 782. (b) Kametani, T.; Katoh, T.; Tsubuki, M. and Honda, T. *J. Am. Chem. Soc.*, **1986**, *108*, 7055.
9. Purchased resin, Dowex-50W-X2 (H^+ form) was used after successive washing with dist. H_2O, 2N NaOH, dist. H_2O and 2N HCl, then dist. H_2O on a glass-filter until the filtrate was neutral. Without this conditioning, the reactions were complicated by side-reactions resulted from strongly acidic conditions (see text).

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