Pergamon

Tetrahedron Letters 41 (2000) 819–822

TETRAHEDRON LETTERS

A modified procedure for the deprotection of methoxymethyl ether

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Received 28 October 1999; revised 22 November 1999; accepted 22 November 1999

Abstract

A new modified procedure using a combination of catechol boron bromide with acetic acid was developed to deprotect methoxymethyl group to form 1,3-diols and 1,3-aminoalcohols.

Keywords: methoxymethyl ether; catechol boron bromide; deprotection; formyl acetal.

Alkoxymethyl ethers are widely used to protect hydroxyl groups in organic synthesis. They are easily introduced under very mild conditions and are quite stable even in the presence of strong acids and bases. Methoxymethyl ether (MOM) group is the most robust of the alkoxymethyl ethers and plays a pivotal role in protecting group chemistry. A variety of conditions are available for MOM cleavage;[1] however, there are often problems deprotecting MOM due to the unique structural features and functionalities in the substrate. One such problem is the formation of cyclic formyl acetals when a nucleophilic hydroxy or amino group is nearby.[2]

During our study of anticancer prodrug cyclophosphamides, we wanted to prepare 1,3-aminoalcohol **2** by removing the MOM protecting group in **1**. A number of common conditions were attempted but failed to afford the desired product **2**. Instead, compound **3**[3] was found to be the major product after flash silica gel column chromatography. The conditions we tried include: (a) catechol boron bromide (CBB), CH_2Cl_2, −78°C→0°C, 2 h, 87%; (b) HCl, MeOH, 0°C→rt, 30 min, complex; (c) $(CH_3)_3SiBr$, CH_2Cl_2, 0°C, 1.5 h, 67%; (d) PhSH, $BF_3 \cdot OEt_2$, CH_2Cl_2, 1 h, 61%; (e) $TsOH \cdot 2H_2O$, toluene, reflux, 45 min, 55% (yields given are for compound **3** only). The difficulty in obtaining the 1,3-aminoalcohol **2** prompted us to develop a new procedure to cleave MOM protected 1,3-aminoalcohols or mono-MOM protected 1,3-diols.

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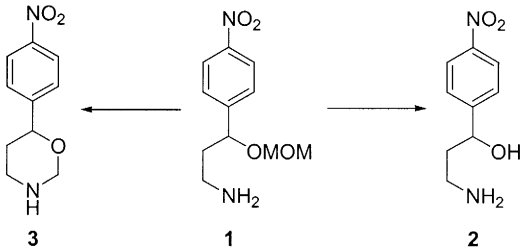
0040-4039/00/$ - see front matter
PII: S0040-4039(99)02200-5

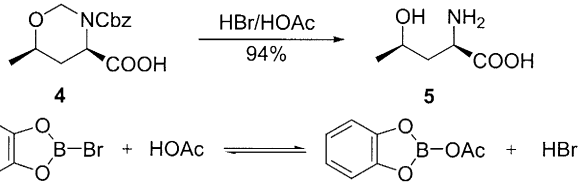


3 1 2

Under common deprotection conditions, the formation of **3** could be the result of a facile acetal–acetal exchange process where the primary amino group at the β position relative to the MOM ether was nucleophilic and could attack the methylene electrophilic carbon forming the entropically-favored six-membered ring. Similar examples reported in the literature showed that this could also occur when cleaving MOM groups with nearby hydroxyl groups.[2]

To our knowledge, the only method that can circumvent this problem is using $(i\text{-PrS})_2$BBr in methanol.[4] Deprotection with $(i\text{-PrS})_2$BBr affords 1,2 and 1,3-diols without forming the formyl acetals in a single step. Catechol boron halides, particularly the bromide, are similar to $(i\text{-PrS})_2$BBr and have been shown to be more effective in cleaving MOM ethers in recent reports.[5] They are also more selective in multifunctional substrates. According to our experimental results, treatment of **1** using catechol boron bromide gave compound **3** with the highest yield (87%). Therefore, it was reasonable for us to focus on this reagent and explore further the conditions needed to effect the desired deprotection and at the same time convert the cyclic formyl acetal to the desired product.

From the literature, we found a procedure using hydrogen bromide in acetic acid to cleave benzyloxycarbonyl (Cbz) protecting group while concurrently hydrolyzing the formyl acetal functionality in compound **4** to produce the erythro-ɣ-hydroxynorvaline **5**.[6] We reasoned that if acetic acid was added to a mixture of **1** and excess catechol boron bromide, hydrogen bromide would be formed quickly (as depicted below), due to the affinity of electrophilic boron(III) species for acetate anion. In this instance, the reactive hydrogen bromide might cleave the formyl acetal in **3** to produce the desired product **2**.

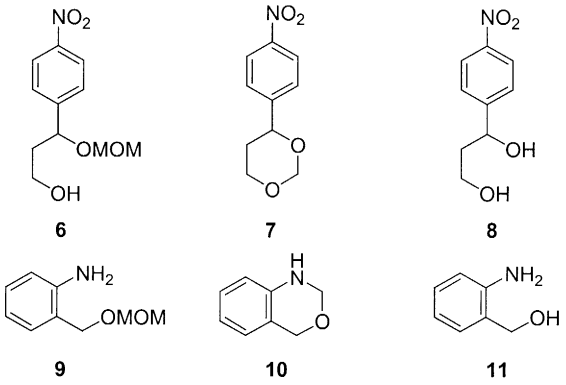


4 5

Based upon this hypothesis, we reinvestigated the deprotection of **1** and found that the deprotection worked very well using the following one-pot procedure: (i) a solution of substrate **1** (1.0 g, 4.2 mmol) in dry methylene chloride (25 mL) was cooled down to −78°C and treated with catechol boron bromide (2.5 equiv., 2.1 g) in methylene chloride (25 mL); (ii) the reaction proceeded for 2 h at −78°C and was allowed to warm up to −20°C before glacial acetic acid (5 equiv., 1.2 mL) was added. The reaction mixture was stirred at ambient temperature for an additional 5 h; (iii) chloroform (100 mL) and 3N aqueous sodium hydroxide (50 mL) were added to quench the reaction, the organic phase was washed with 3N aqueous sodium hydroxide (3×30 mL) until the aqueous phase became colorless and clear. The organic phase was then washed with brine and dried over anhydrous magnesium sulfate. After removal of organic solvents under vacuum, the crude product was purified by flash silica gel column chromatography (chloroform saturated with ammonium hydroxide: methanol, 9:1→8:1) to give **2** (0.63 g, 77%) as a colorless oil, whose structure was confirmed by ^{1}H NMR, IR and high resolution FAB-MS.[7] Using thin layer chromatography to monitor the reaction process, we clearly observed that **3** was formed in step (i) and then disappeared quickly in step (ii) with the concomitant appearance of the more polar compound **2**.

This result suggests that the formyl acetal formed during the Lewis acid-catalyzed deprotection of MOM can be completely hydrolyzed by enhancing the acidity of the medium through the addition of acetic acid and excess CBB. It is believed that acetic acid reacted with CBB to produce hydrogen bromide, which is the reagent responsible for the eventual cleavage of cyclic formyl acetal intermediates.

To demonstrate the capability of our new procedure, we compared the two conditions (CBB/CH_2Cl_2, $-78°C \rightarrow 0°C$ versus CBB/CH_2Cl_2 followed by HOAc, $-78°C \rightarrow$rt) in the deprotection of compounds **6** and **9**. It was found that CBB deprotection of **6** gave cyclic formal acetal **7** in 25% yield and 1,3-diol **8** in 74% yield while our modified procedure using CBB followed by the addition of acetic acid gave compound **8** as the only product in 96% yield after isolation. Similarly, CBB deprotection of **9** gave a mixture of **10** (28%) and **11** (71%) while CBB followed by acetic acid afforded compound **11** as the only product in 91% yield after isolation.[8] The difference between these parallel experiments indicates that our modified procedure is better than CBB alone in deprotecting MOM groups when there is another nucleophilic functional group situated nearby.



In conclusion, the combination of catechol boron bromide with acetic acid effectively cleaves MOM groups, especially in cases where a neighboring hydroxy or amino group might prevent the formation of the desired product using commonly available procedures. Our one-pot procedure presented here is mild and convenient and should be useful in the synthesis of complex natural products.

Acknowledgements

We gratefully acknowledge the financial support of grant DAMD 17-98-1-8544 from the US Army Department of Defense Prostate Cancer Research Program. We thank Dr. Larry Russon (OU Mass Spec. Lab.) for providing MS spectral analysis. Part of this work was done at the University of Oklahoma College of Pharmacy.

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3. Selected physical and spectral data for compound **3**: IR (neat): ν/cm^{-1} 3200, 2870, 1575, 1485, 1405, 1360, 1300, 1250, 1080, 1000, 920, 750, 675; ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm 8.22–8.20 (m, 2H), 7.70–7.65 (m, 2H), 5.00–4.95 (m, 1H), 4.61 (d, J=6.8 Hz, 1H), 4.50 (d, J=6.8 Hz, 1H), 3.40–3.10 (m, 2H), 2.10–1.85 (m, 2H); MS (FAB, 3NBA): *m/z* 209.0 (MH^+, 3.8).

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7. Selected physical and spectral data for compound **2**: mp ($CHCl_3$–MeOH): 126–127.5°C; IR (KBr): ν/cm^{-1} 3330, 3260, 3100, 2880, 2850, 1575, 1490, 1400, 1330, 1300, 1275, 1085, 1075, 1050, 1000, 935, 810, 730, 680; ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm 8.13 (dd, J=2.0, 6.9 Hz, 2H), 7.52–7.47 (m, 2H), 5.03 (dd, J=2.7, 8.7 Hz, 1H), 3.12–3.06 (m, 1H), 3.07–2.92 (m, 1H), 1.99–1.81 (m, 1H), 1.67–1.41 (m, 1H); MS (FAB, 3NBA): *m/z* 197.1 (MH^+, 30.5), 181.0 (M−OH, 1.8); HR FAB-MS: calcd for $C_9H_{13}N_2O_3$ (M+1) 197.0926, found 197.0939.
8. Yields were not optimized.