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Chemoselective Deprotection of Cyclic *N*,*O*-Aminals Using Catalytic Bismuth(III) Bromide in Acetonitrile

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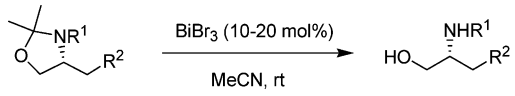
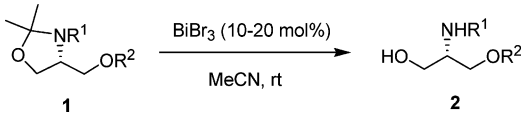


R^1=Boc, Cbz;
R^2=OMOM, OAc, OTBDPS, unsaturated ester or cyc-*O*,*O*-acetals.

Cyclic *N*,*O*-aminals can be chemoselectively and efficiently deprotected using a catalytic amount of bismuth(III) bromide in acetonitrile at room temperature. This selectivity was also achieved in the presence of terminal *O*,*O*-acetal functionality. The susceptibility of various other groups to cleavage was also investigated. This method has advantages of ease of operation and use of nontoxic and inexpensive reagents in catalytic amounts.

Serine and its derivatives are frequently used in the course of many syntheses as *N*,*O*-aminal-protected chirons such as the Garner aldehyde.[1] However, the related cyclic *O*,*O*-acetals are also commonly used protecting groups for 1,2- or 1,3-diols. To our knowledge, cyclic acetals are usually more resistant to cleavage than the corresponding acyclic acetals. Methods of deprotecting cyclic *O*,*O*-acetals can often be applied to cleaving cyclic *N*,*O*-aminals and acyclic acetals as well. Although numerous approaches have been developed for deprotection of cyclic *O*,*O*-acetals,[2] few examples[3] have been reported where *N*,*O*-aminals are selectively deprotected in the presence of *O*,*O*-acetals. Typical conditions for acid-catalyzed deprotection of acetals include DOWEX 50 W (H^+) resin/methanol,[4] trifluoroacetic/H_2O,[5] *p*-TsOH/methanol,[6] aqueous 60−80% AcOH,[7] Amberlyst 15/methanol, or Amberlyst 15/acetone/H_2O.[8] However, many of these involve strong acids, corrosive reagents, and elevated temperatures. Under such conditions, selectivity in cleavage between cyclic *O*,*O*-acetals and *N*,*O*-aminals would be difficult.

SCHEME 1



Recently, considerable effort has been focused on developing mild, selective methods for acetal deprotection. Several methods have been reported for cleaving acetals and ketals under nearly neutral conditions, wherein mild Lewis acids are often adopted instead of strong acids. For example, $PdCl_2$(MeCN) in moist acetonitrile or in acetone can deprotect acetals and ketals efficiently. However, these hydrolyses are not consistently reproducible and must be shielded from light.[9] Selective deprotection of acyclic acetals has been reported using $Bi(NO_3)_3 \cdot 5H_2O$ in CH_2Cl_2.[10] Several cyclic *O*,*O*-acetals have been deprotected utilizing catalytic $Bi(OTf)_3 \cdot 4H_2O$ in refluxing THF/H_2O (4:1).[11] Bismuth(III) compounds are attractive because they have suitable acidity yet are nontoxic, easy to handle, and inexpensive.[12]

We report herein that bismuth(III) bromide in acetonitrile is a highly efficient catalytic system for selective deprotection of cyclic *N*,*O*-aminals (Scheme 1). Since few mild methods exist for the selective deprotection of *N*,*O*-aminals, we examined the use of this system on a variety of other functionalities. It was found that the method proved to be highly efficient and easy to apply; furthermore, chemoselective deprotection of cyclic *N*,*O*-aminals was achieved in the presence of cyclic *O*,*O*-acetals. The reactions proceeded very well in acetonitrile with a catalytic amount of bismuth(III) bromide at room temperature.

Protected cyclic *N*,*O*-aminals were conveniently prepared from L-Garner's aldehyde[13] through reduction and protection of the resultant primary alcohols. As shown

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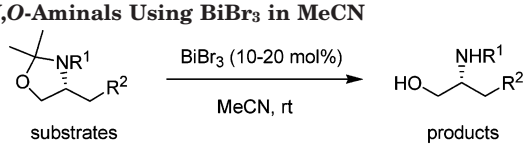
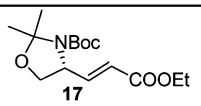
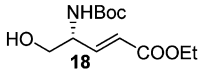
TABLE 1. Deprotection of Cyclic *N,O*-Aminals Using $BiBr_3$ in MeCN



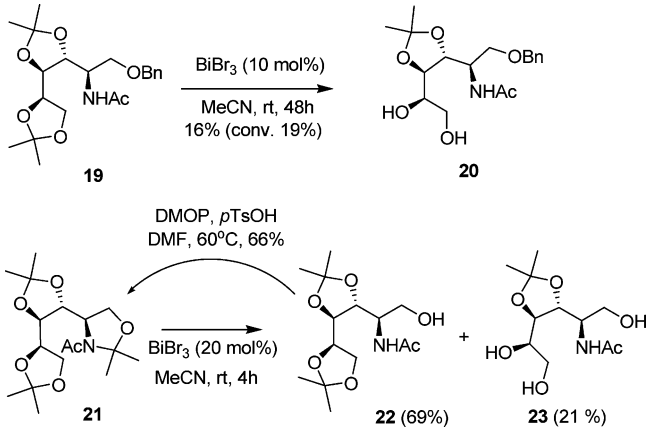
Entry	Substrate[a]	$BiBr_3$ (mol%)/Time[b]	Product[a]	Yield (%)[c]
1	**3**: R^1=Cbz; R^2=OMOM	10%/5h	**4**: R^1=Cbz; R^2=OMOM	97%
2	**5**: R^1=Cbz; R^2=OTBDMS	10%/8h	**6**: R^1=Cbz; R^2=OH	85%
3	**7**: R^1=Cbz; R^2=OAc	10%/4h	**8**: R^1=Cbz; R^2=OAc	97%
4	**9**: R^1=Boc; R^2=OMOM	10%/7h	**10**: R^1=Boc; R^2=OMOM	99%
5	**11**: R^1=Boc; R^2=OTBDMS	10%/7h	**12**: R^1=Boc; R^2=OH	85%
6	**13**: R^1=Boc; R^2=OAc	10%/1h	**14**: R^1=Boc; R^2=OAc	94%
7	**15**: R^1=Boc; R^2=OTBDPS	10%/6h	**16**: R^1=Boc; R^2=OTBDPS	92%
8	 **17**	20%/7h	 **18**	90%

[a] All substrates and products were fully characterized by spectroscopic methods (see Supporting Information). [b] Reaction was carried out following the general procedure described in this paper. [c] Isolated yields.

in Table 1, deprotection of the cyclic *N*,*O*-aminals was achieved in excellent yields. Amine protecting groups such as Boc and Cbz were stable under the conditions used. MOM (entries 1 and 4) and TBDPS (entry 7) groups, as well as acetate (entries 3 and 6) and unsaturated ester functionalities (entry 8), were also stable under the reaction conditions. However, the TBDMS groups (entries 2 and 5) were simultaneously cleaved using this protocol.[13] The reaction rate decreased when the preferred solvent (MeCN) was replaced with acetone or CH_2Cl_2. In the latter cases, significant quantities of unreacted starting materials were indicated by TLC monitoring. It is noteworthy here that the reaction rates could be accelerated by adding a catalytic amount of H_2O such that reaction times could be reduced to 1 h. However, under these conditions the reaction system becomes weakly acidic.[14]

To ascertain the reactivity of *O*,*O*-acetals under the above conditions, the reaction of cyclic *O*,*O*-acetal **19** was examined (Scheme 2). Treatment of **19** with 10 mol % $BiBr_3$ in MeCN at room temperature for 48 h afforded only 16% yield of diol **20**. The results were slightly improved (up to 35% yield) when 20 mol % $BiBr_3$ was used at room temperature. However, the reactions led

SCHEME 2



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to more complex mixtures if the amount of $BiBr_3$ was increased to 50 mol % or the reaction temperature was elevated to reflux. These results indicated that selective deprotection of the cyclic *N*,*O*-aminals using a lower amount of $BiBr_3$ in MeCN at room temperature might be achieved in the presence of cyclic *O*,*O*-acetals. Thus, substrate **21** embodying both a cyclic *N*,*O*-aminal and a cyclic *O*,*O*-acetal was prepared from alcohol **22**[15] and examined (Scheme 2). Treatment of **21** with 20 mol % $BiBr_3$ in MeCN for 4 h at room temperature afforded alcohol **22** (69%) and triol **23** (21%). These results indicate that $BiBr_3$ in MeCN may be a practical choice for selective removal of *N*,*O*-aminals in the presence of *O*,*O*-acetals.

In summary, we have demonstrated that the use of catalytic amounts (10−20 mol %) of bismuth(III) bromide in acetonitrile at room temperature provides a mild and effective method for selective deprotection of cyclic *N*,*O*-aminals. These cyclic *N*,*O*-aminals can be converted to the corresponding amino alcohols in satisfactory to excellent yields in the presence of MOM, TBDPS, acetate, and cyclic *O*,*O*-acetal groups. Advantages of this method include the simplicity of procedure and the use of inexpensive, nontoxic reagents in catalytic amounts.

Experimental Section

General Procedure for Deprotection of Cyclic *N*,*O*-Aminals. To a solution of cyclic *N*,*O*-aminal **1** (1.0 mmol) in MeCN (10 mL) was added bismuth(III) bromide (45 mg, 0.1 mmol) at room temperature. The reaction mixture was stirred at room temperature, and the progress of the reaction was monitored by TLC. When all starting material had disappeared, the reaction mixture was quenched by adding saturated aqueous $NaHCO_3$ (5 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel to afford the pure product **2**.

Benzyl (*S*)-1-Hydroxy-3-(methoxymethoxy)propan-2-ylcarbamate (4). To a solution of (*S*)-benzyl 4-((methoxymethoxy)methyl)-2,2-dimethyloxazolidine-3-carbomate (**3**) (56 mg, 0.18 mmol) in MeCN (1.8 mL) was added bismuth(III) bromide (8 mg, 0.018 mmol) at room temperature. The reaction mixture was stirred at room temperature for 5 h. When all starting material had disappeared, the reaction mixture was quenched by adding saturated aqueous $NaHCO_3$ (2 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give the crude product, which was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 2:1) to give **4** (47 mg, 97%) as a white wax. $[\alpha]^{22}_D$: 1.4 (*c* 1.18, CH_2Cl_2). IR (neat): 3360, 1945, 2883, 1719, 1561, 1500, 1213, 1147, 1030 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.69 (br, 1H), 3.34 (s, 3H), 3.63−3.89 (m, 5H), 4.61 (s, 2H), 5.10 (brs, 2H), 5.45 (d, J = 7.2 Hz,1H), 7.31−7.37 (m, 5H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.1, 55.4, 63.2, 66.9, 67.9, 96.81, 128.1 (2C), 128.2, 128.5 (2C), 136.3, 156.4 ppm. ESIMS (*m*/*z*, %): 292.2 ($M + Na^+$, 100%). HR-ESI-MS calcd for $C_{13}H_{19}NO_5Na$ ($M + Na^+$), 292.1155; found, 292.1151.

***N*-((*R*)-2-Hydroxy-1-((4*R*,5*S*)-2,2-dimethyl-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1,3-dioxolan-4-yl)ethyl)acetamide (22)[15] and Triol 23.** Compound **21** (100 mg, 0.29 mmol) was converted to amino alcohol **22** and triol **23** by the above general procedure using 20 mol % $BiBr_3$. The crude products were separated by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1) to give pure alcohol **22** (61 mg, 69%) as a colorless oil and triol **23** (16 mg, 21%) as a colorless wax. Data for **22**: $[\alpha]^{24}_D$: 14.4 (*c* 1.36, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 6H), 1.41 (s, 3H), 1.43(s, 3H), 2.02 (s, 3H), 3.20 (br, 1H), 3.84−3.93 (m, 4H), 4.01−4.06 (m, 1H), 4.08−4.10 (m, 2H), 4.18 (dd, J = 8.4 Hz, 1H) ppm. Data for **23**: $[\alpha]^{24}_D$: 15.6 (*c* 1.30, CH_3OH). IR (neat): 3318, 2988, 2939, 2887, 1653, 1555, 1374, 1239, 1214, 1081, 1060 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ 1.36 (s, 3H), 1.38 (s, 3H), 1.98 (s, 3H), 3.51−3.81 (m, 5H), 3.92 (dd, J = 7.2 Hz, 1H), 4.02−4.08 (m, 1H), 4.13 (dd, J = 7.5 Hz, 1H), 6.42 (brs, 1H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ 23.2, 27.9, 28.0, 56.6, 62.4, 65.0, 75.1, 80.2, 80.5, 111.3, 173.8 ppm. ESI-MS (*m*/*z*, %): 264.1 ($M + H^+$, 20%), 286.1 ($M + Na^+$, 100%). HR-ESI-MS calcd for $C_{11}H_{21}NO_6Na$ ($M + Na^+$), 286.1261; found, 286.1260.

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Supporting Information Available: Detailed experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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