

Highly Efficient and Convenient Deprotection of Methoxymethyl Ethers and Esters Using Bismuth Triflate in an Aqueous Medium

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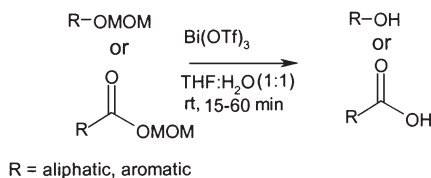
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A simple and efficient method has been developed for the hydrolysis of methoxymethyl (MOM) ethers and esters to the corresponding alcohols and acids employing a catalytic amount of bismuth triflate in an aqueous medium. The conversions occur at ambient temperature and the yields of the deprotected alcohols are very good. The reaction was highly selective in the presence of other protecting groups such as TBDMS, TBDPS, benzyl, and allyl ethers.

Selective protection and deprotection of hydroxy and carboxyl groups is often a challenging task in multistep synthesis of complex natural products.^{1,2} Among various methods available for the protection of hydroxy groups most widely used is transformation into methoxymethyl ethers as they can easily be introduced and are stable under a variety of reaction conditions including strongly basic and weakly acidic media.^{3,4} Deprotection is usually effected under acidic conditions. Normally the reaction is carried out in protic solvents and is catalyzed by acids such as HCl⁵ and pyridinium *p*-toluenesulfonate.⁶ Several Lewis acids have also been used for this purpose such as, LiBF₄,⁷ Me₂BBr,⁸ Ph₂BBr,⁹ catechol boron bromide,¹⁰ ZnBr₂,¹¹ and TiCl₄. These methods suffer drawbacks such as harsh reaction conditions including the use of mineral acids, high reaction temperatures, and reaction times. There was a report recently on the deprotection of MOM ethers with CBr₄¹² whose use is toxic and not environmentally friendly.

Herein we wish to report a new method for the deprotection of MOM ethers and esters using bismuth triflate in a biphasic aqueous medium (THF and water) (Scheme 1). The method takes advantage of the highly stable, cheap, and environmental-friendly nature of Bi(OTf)₃. Bismuth triflate has been employed, as an efficient catalyst in organic synthesis in a variety of reactions¹³ and is known to exhibit stronger activity than other known corresponding Bi(III) Lewis acids¹⁴ as well as Lanthanide metal triflates.¹⁵ Lewis acids like, TiCl₄, ZnBr₂ requires aprotic solvents¹¹ whereas the reactions with Bi(OTf)₃ can be carried out effectively in aqueous media. Although bismuth triflate is not commercially available, it can be easily prepared in the laboratory in large quantities at relatively low cost.¹⁶

Initially we attempted to hydrolyze aromatic MOM ethers in



Scheme 1.

anhydrous THF. The reaction went to completion within 30–40 min. In order to reduce the use of organic solvents, the reaction was carried out in the presence of minor amounts of water. To our surprise, the yields of the deprotected alcohols were higher with reduced reaction times. Optimal results were observed when the reaction was carried out with equal volumes of THF and water.

A series of aromatic MOM ethers were deprotected under the similar conditions (Table 1). The reaction was extended to

Table 1. Deprotection of MOM ethers and esters using Bi(OTf)₃

Entry	Substrate	Product ^a	Time / min	Yield ^b / %
1			10	92
2			15	95
3			30	90
4			60	80
5			50	88
6			55	85
7			35	90
8			30	95
9			65	86
10			25	90
11			15	95
12			40	86
13			45	90
14			50	87
15			55	90

^a All the products were characterized by ¹HNMR and mass spectroscopy. ^b Isolated yields.

aliphatic MOM ethers and esters, which required slightly higher reaction temperatures and time.

Finally we examined the chemoselective deprotection of aliphatic MOM ethers and esters in the presence of other protecting groups such as phenolic TBDMS, TBDPS, and benzyl ethers (Entries 7–9). The results were very satisfactory as shown in Table 1. Similar chemoselective deprotection was also achieved in the presence of aliphatic TBDPS, benzyl, and allyl ethers (Entries 13–15).

Typical procedure: To a stirred solution of the methoxymethyl ether of ferulic acid methyl ester (100 mg, 0.44 mmol, Entry 1) in THF and water (1:1) was added Bi(OTf)₃ (1–2 mol %) at room temperature. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was filtered, and the filtrate concentrated and subjected to column chromatography on silica gel using hexane:ethyl acetate (97:3) to afford the pure product.

In summary the present procedure of deprotection of MOM ethers and esters offers salient features such as ease of operation, high efficiency, environmental-friendly and chemoselectivity. The deprotection described here adds a new and convenient method, which may find extensive application in organic synthesis where selective deprotection of MOM ethers is required at ambient conditions in large scale.

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