A New Method for Alkoxymethyl (MOM or EOM) Protection of Thiol Functionality in Heterocyclic Compounds

Hyung Jae Jeong, Eun-Young Yoon, Min Kyu Kim, Ji-Hyun Lee, Yong-Jin Yoon,* and Sang-Gyeong Lee*

Department of Chemistry and Research Institute of Life Science, Gyeongsang National University, Jinju 660-701, Korea
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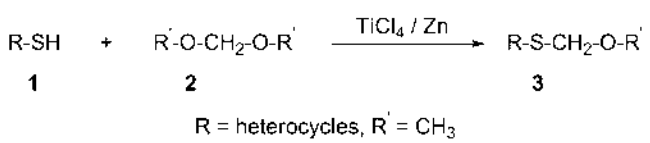
Numerous methods have been used to protect hydroxyl groups in organic compounds. One of these involves formation of methoxymethyl (MOM) ethers.[1] In contrast, by far the fewer methods have been tried for the selective protection of thiol groups,[2] even though the thiol group is more sensitive than the hydroxyl function to acidic and basic conditions and oxidizing agents. Included among the few thiol protecting groups described so far is the MOM group. However, to date few procedures have been reported for the preparation of MOM-protected thiols that do not require basic conditions and chloromethyl methyl ether (a carcinogen) as the substrate. Although there are a few exception37 s, an equimolar amount of an acyl halide is needed as an activating agent[3,4] or require a base for the preparation of MOM group during the reaction.[5]

In a joint research program[6] investigating low-valent titanium species [Ti], we developed a new method of preparing MOM and ethoxymethyl (EOM) protected thiols. Our method of forming the methoxymethyl thioether with dimethoxymethane/[Ti] can avoid the use of a base and the carcinogen37 ic chloromethyl methyl ether. In addition, the MOM protected thiols are obtained in a short reaction time and also in high yields. According to our results, the condition of dimethoxymethane/[Ti] is more effective for the protection of thiol than other Lewis acids[7] such as $AlCl_3$, $ZnCl_2$, $TiCl_4$ and $SnCl_4$. Below, we describe the new procedure, which uses dimethoxymethane (DMM) or diethoxymethane (DEM) for the source of the alkoxymethyl moiety, providing the examples of its application to selected heterocyclic thiols.

The low-valent titanium species [Ti] was prepared[8] under the conditions of $TiCl_4$ and zinc powder (1 : 2 molar equivalent ratio) in dimethoxymethane at 0 °C for 30 min. To the reaction mixture were added the heterocyclic thiol compounds, which gave the MOM protected thiols in good yields (Scheme 1). Under these conditions, the heterocyclic compounds have two protective functional groups such as carboxylic acid and thiol (entry 5), dithiols (entry 6), amino and thiol (enthry 10), hydroxy and thiol (enthry 11) were not protected selectively. However, in the case of the secondary amine and thiol can be protected selectively (entry 7).

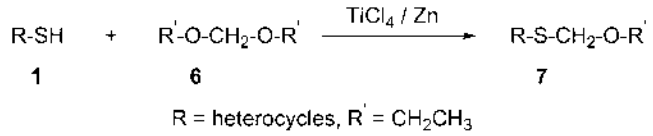


Scheme 1

Under the conditions described above, it is possible for $TiCl_4$ to serve as a Lewis acid catalyst for the thiol protection process. To test this possibility, reactions of the thiols with dimethoxymethane in the presence of 1 equivalent of $TiCl_4$ were investigated. Reaction under these conditions for 1.0 h resulted less than 40% conversion of the thiol to its MOM-protected derivative. In addition, thiols were found not to react with DMM in the presence of Zn alone. We also investigated the use of other Lewis acids (1 equivalent) such as $ZnCl_2$ and $AlCl_3$, and the results were almost the same as when only $TiCl_4$ was used. The conversion of thiols to their MOM-protected derivatives by using $ZnCl_2$ and $AlCl_3$ proceeded less than 40% in 1.0 h. According to our results, the rate order to protect the thiol with MOM in the presence of Lewis acids was $TiCl_4$/Zn [Ti] > $AlCl_3$ > $ZnCl_2$ > $SnCl_4$, and the reaction times were not differentiated according to their structures. Therefore, the MOM-protection reactions under the conditions described above appear not to be the simple $TiCl_4$ catalyzed acetal exchange processes because they also proceed by different mechanism with other simple Lewis acids.

Our results suggest that the reaction occurs *via* a radical pathway together S_N2 routes. A general reaction mechanism of the thiols and DMM in the presence of Lewis acids occurs through S_N2 pathway. But, in our conditions, it was difficult to jump to a conclusion that the reaction proceeded through S_N2 pathway only. The results presented in entries 8 and 9 of Table 1 support this line of reasoning. The major products of the reactions of imidazole **11** and thiazole **12** are the S-MOM protected thiols **22** and **24**, respectively. However, in both of these reactions, significant amounts of the (methoxy)methoxymethyl derivatives (**23** and **25**) are formed. The minor products **23** and **25** could be generated through reaction pathways involving either the cation or radical intermediates, $^{+}CH_2OCH_2OCH_3$ and $\cdot CH_2OCH_2OCH_3$. The reaction conditions are not suitable for the formation of the cation $^{+}CH_2OCH_2OCH_3$. On the other hand, generation of the radical $\cdot CH_2OCH_2OCH_3$ by reaction of $CH_3OCH_2OCH_3$ with a strongly electron donating[9] low valent titanium species [Ti] seems more plausible.

EOM-protected thiols are prepared by substituting diethoxymethane for dimethoxymethane in this procedure (Scheme 2). As expected from the reaction of the thiol and

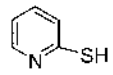
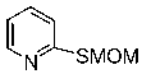
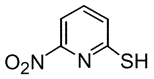
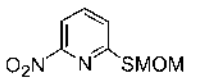
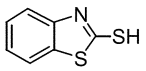
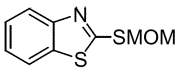
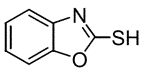
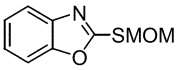
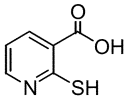
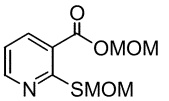
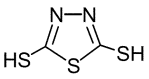
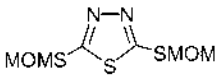
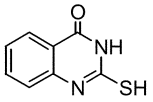
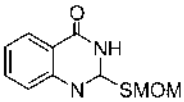
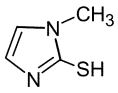
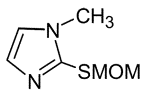
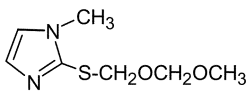
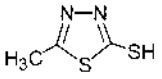
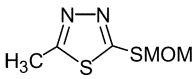
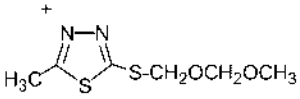
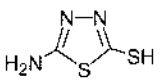
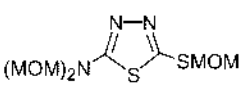
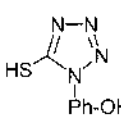
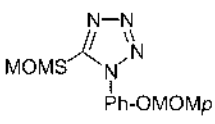


Scheme 2

dimethoxymethane, we obtained EOM-protected thiols with a moderate yield. In the case of EOM-protected thiol, the reaction time took slightly longer.

In conclusion, a new method has been developed for protection of thiols via formation of their MOM- or EOM-ethers that does not require the use of the carcinogenic reagent, chloromethyl methyl ether or strongly acidic or basic conditions. By using this method, the MOM protected thiols can be obtained cleanly without such by-product as disulfides. Additional studies for aromatic and aliphatic thiols are underway, probing the use of low valent titanium species [Ti] with MOMCl or EOMCl, and the results of this effort will be the subjects of future publications.[10]

Table 1. The Yield of RS-MOM Obtained from The Reaction of R-SH and $TiCl_4$/Zn in DMM

Entry	R-SH		Product		Time (h)	Yield (%)
1		(4)		(15)	1	89
2		(5)		(16)	1	91
3		(6)		(17)	2	89
4		(7)		(18)	1.5	90
5		(8)		(19)	2	86
6		(9)		(20)	1	89
7		(10)		(21)	1	94
8		(11)		(22)	1	75
			+			
				(23)		17
9		(12)		(24)	1	58
			+			
				(25)		21
10		(13)		(26)	1	89
11		(14)		(27)	1	91

1) All reaction caried out under the same conditions. 2) Isolated Yields.

Experimental Section

All non-aqueous reactions were carried out under nitrogen. THF was distilled from Na/benzophenone; methanol was distilled from Mg; methylene chloride was distilled from CaH_2. Melting points were determined with Electrothermal melting point apparatus IA 9000 and are uncorrected. NMR spectra were measured on a Bruker ARX-300 (500 MHz) spectrometer in $CDCl_3$ solution used as an internal standard unless otherwise noted (value in ppm); coupling constants are reported in Hz. IR spectra were taken on a Hitachi 270-50 FT/IR spectrophotometer (ν_{max}, cm^{-1}). The elemental analyses were performed with LECO Micro Carbon Hydrogen Determinator (CHN-800). Mass spectra were obtained by using JEOL JMS-700 spectrophotometer. TLC was run on Merck precoated silica gel plates. Merck silica gel 60 (230-400 mesh) was used for column chromatography.

The following general procedure is used to carry out MOM protection of thiols. To a pre-stirred (30 min, 0 °C) mixture of $TiCl_4$/Zn (powder, 100 mesh) in a 1 : 2 molar equivalent ratio (modified the McMurry and Mukaiyamas conditions for low valent [Ti] formation)[6] in 25 mL of dimethoxymethane is added the thiol (entry 1-6, 2.8×10^{-4} mol). The resulting solution is stirred for 1-2 h at 25 °C, poured into water (50 mL), and extracted with EtOAc (50 mL × 3). The EtOAc extracts are washed with water and brine, dried ($MgSO_4$), and concentrated in-vacuo. Silica gel column chromatography (*n*-Hexane/EtOAc = 10/1, v/v) of the residue then provides the pure MOM-protected thiol product (see Table 1). The products obtained in these processes are characterized by using spectroscopic methods.[11]

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References and Notes

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10. The reaction of aromatic and aliphatic thiols with MOMCl or EOMCl under the low valent titanium species [Ti] gives different products in the same process. For example, the reaction of RSH and MOMCl with low valent titanium species [Ti] gives methylene inserted RS-CH_2-SR. These results will be submitted in our next paper.
11. All products were characterized by ^{1}H- and ^{13}C-NMR spectroscopy and mass spectrometry. The spectral data for products **15-21**, **26** and **27** consisted of the results we had expected.