Methoxymethylation of Alcohols, Phenols, and Avermectin Aglycones Using MOM-2-pyridylsulfide

Benjamin F. Marcune,* Sandor Karady, Ulf-H. Dolling, and Thomas J. Novak

Department of Process Research, Merck Research Laboratories, Merck & Co., P.O. Box 2000, Rahway, New Jersey 07065

Received November 13, 1998

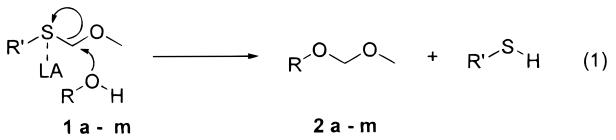
Methoxymethyl-2-pyridylsulfide (MOM-ON) is an effective methoxymethylating reagent when used in conjunction with AgOTf, NaOAc, and THF. A wide range of MOM ethers are produced from corresponding phenols and alcohols, including tertiary and allylic alcohols, in good yields and under mild, neutral conditions. This method is also effective for the methoxymethylation of avermectin aglycones.

Introduction

The methoxymethyl moiety (MOM) is a frequently used protecting group for alcohols, phenols, and carboxylic acids.[1−3] We became interested in methoxymethylations during the preparation of antiparasitic ivermectin derivative **2l**.[4]

MOM derivatives are usually prepared by alkylation with an excess of chloromethyl methyl ether.[2] Because of the potent carcinogenic properties of chloromethyl methyl ether,[5] the task of finding alternate methods for the preparation of MOM ethers was undertaken.

The ideal reagent would have no alkylating activity until it is activated by a suitable Lewis acid (eq 1). This



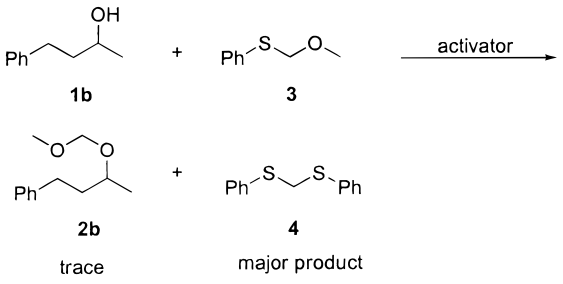
(1)

principle has been extensively explored in transacetalization reactions of dimethoxymethane with alcohols, utilizing various catalysts such as P_2O_5,[6] *p*-toluenesulfonic acid,[7] Nafion-H,[8] iodotrimethylsilane,[9] molybdenum(VI) acetylacetonate,[10] and BF_3.[11] Though these methods have their advantages over using chloromethyl methyl ether, the strong acid catalysts limit their use. Complex, acid-sensitive molecules, such as avermectin aglycones, and easily ionizable alcohols, such as tertiary, allylic, and benzylic alcohols, are not suitable for methoxymethylation under these conditions. Therefore, these methods have not been proven to have general applications. When applying these conditions to avermectin aglycone **1l** (Table 1), rapid desilylation followed by slow indiscriminate methoxymethylation ensued.

Herein, we report a new method for the methoxymethylation of avermectin aglycones, alcohols, and phenols under very mild and neutral conditions. Inspired by work showing that thioglycosides are effective glycosyl donors in the presence of thiophilic silver salts,[12] we prepared and tested a variety of MOM-thiol reagents. We now present MOM-2-pyridylsulfide (**5**), MOM-ON, as an efficient methoxymethylating reagent of alcohols and phenols, including acid-sensitive allylic and tertiary alcohols.

Results and Discussion

Our search for an effective MOM-thiol reagent began with commercially available MOM-phenyl sulfide (**3**). Reaction of **3** with alcohol **1b** and a Lewis acid such as TMSOTf, $Cu(OTf)_2$, $BF_3{\cdot}Et_2O$, $Sn(OTf)_2$, or AgOTf in methylene chloride resulted in the production of **4** with only a trace or poor yield of the desired product **2b** (eq 2). Nucleophilic attack by thioether **3** or the thiol



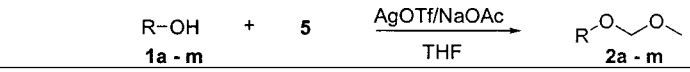
(2)

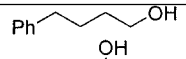
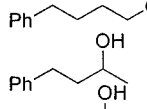
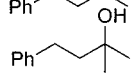
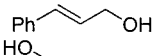
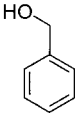
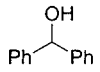
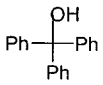
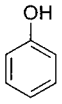
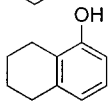
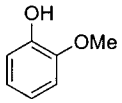
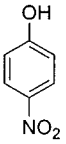
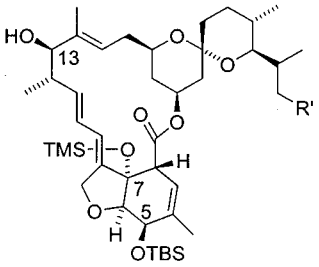
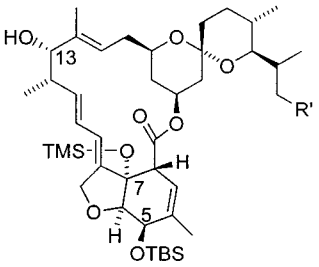
analogue of **3** on the metal−oxygen complex of **3** is a likely mechanism. This result alerted us to the need for a reagent with a more sulfur-selective coordinating capability and reduced thio nucleophilicity, thereby eliminating the competing reaction with itself. With this in mind, reagents **5**−**14** were prepared from the corre-

(1) Greene, T. W. *Protective Groups in Organic Chemistry*; Wiley-Interscience: New York, 1981; p 10.
(2) McComie, J. F. W. *Advances in Organic Chemistry*; Wiley-Interscience: New York, 1963; p 232 and references therein.
(3) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; John Wiley & Sons: New York, 1967; Vol. 1, p 132.
(4) Mrozik, H.; Linn, B. O. U. S. Patent 4,587,247, May 6, 1986.
(5) Occupational Safety and Health Administration, U.S. Department of Labor, Federal Register 39 (20); U.S. Government Printing Office: Washington, DC, 1974.
(6) Fuji, K.; Nakano, S.; Fujita, E. *Synthesis* **1975**, 276−277.
(7) Yardley, J. P.; Fletcher, H. *Synthesis* **1976**, 244.
(8) Olah, G. A.; Husain, A.; Gupta, B. G. B.; Narang, S. C. *Synthesis* **1981**, 471−472.
(9) Olah, G. A.; Husain, A.; Narang, S. C. *Synthesis* **1983**, 896−897.
(10) Kantam, M. L.; Santhi, P. L. *Synlett*. **1993**, 429−430. Although this method employs mildly acidic conditions, in our hands it failed to yield any desired product when attempting to methoxymethylate **1l**.
(11) Danheiser, R. L.; Romines, K. R.; Koyama, H.; Gee, S. K.; Johnson, C. R.; Medich, J. R. *Org. Synth*. **1992**, *71*, 133−139.
(12) Toshima, K.; Tatsuta, K. *Chem. Rev*. **1993**, *93*, 1503−1531.

10.1021/jo9822582 CCC: $18.00
Published on Web 03/17/1999

Table 1

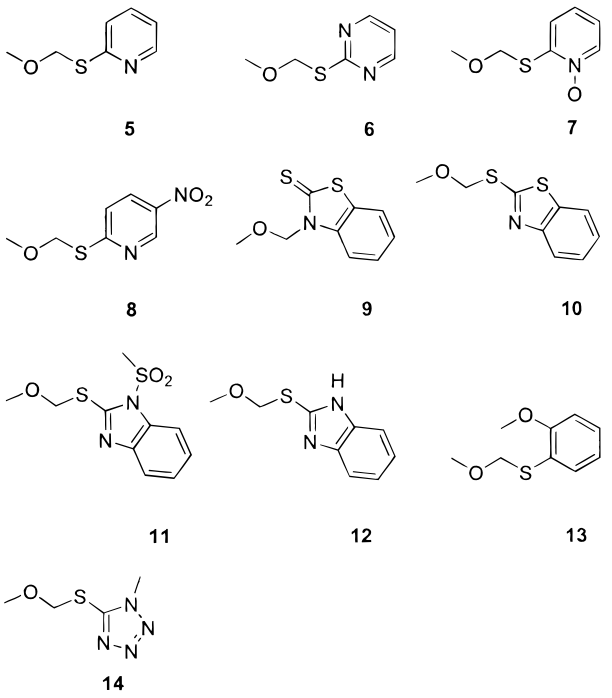


Entry	1	(5) eqs.	AgOTf eqs.	[a] L.C. % Yield
a		1.8	1.63	92
b		1.8	1.6	90
c		2.44	2.14	84
d[14]		2.4	2.2	79
e[14]		1.8	1.6	79
f		1.8	1.6	75
g		8.3	7.3	47
h[14]		4.0	3.7	98
i		4.0	3.68	92
j		4.0	3.7	82
k		4.0	3.7	14
l[4]		3.54	3.08	82
m[4]		4.42	3.75	83

[a] LC response factors of the alcohols and their corresponding MOM ethers are essentially identical. Therefore, the LC assay yields of the MOM ethers were calculated using the pure alcohols as standards.

sponding commercially available thiols, dimethoxymethane, and $BF_3{\cdot}Et_2O$.

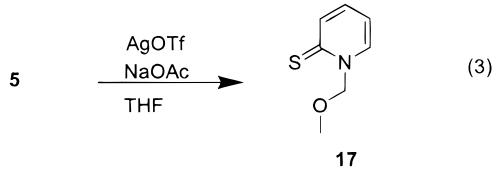
With the exception of **9** and **14,** which exhibited no reaction, the thioamidate heterocycles **5**−**8** and **10**−**12** and thioether **13**, in combination with AgOTf and THF, all produced **2b** with yields in excess of 40%. Thioacetal byproducts analogous to **4** were not detected. Because MOM-ON (**5**) gave the highest yields, it was selected for



further development. Reaction of this reagent with **1b** resulted in a 5:95 ratio of **1b** to **2b**, with a yield of only 53%. The major byproduct was identified as acetal **16**. We hypothesized that production of **16** was caused by an indiscriminate complexation of **5** allowing either the methoxy moiety or the sulfide moiety to be the leaving group. In the case of the former, intermediate **15** would form, leading to **16** (Scheme 1). Alternatively, **16** could form from the reaction of **1b** with product **2b**. To facilitate formation of the sulfur−silver complex, we tested various additives (Ag_2O, acetic acid, silver acetate, and sodium acetate), of which the acetates were shown to produce dramatic improvement of yield with minimal formation of **16**.

With our model secondary alcohol **1b**, optimal results were obtained when 1.8 equiv of **5**, 1.6 equiv of AgOTf, and 1.2 equiv of NaOAc in THF were used. Numerous solvents were tested, with THF giving the highest yields.

Excess **5** was required because of a rearrangement of **5** to **17** which competed with the main pathway. Isomer **17** and the analogous **9**, both N-methoxymethylated, are completely nonreactive in this reaction. Reacting **5** with AgOTf and NaOAc in THF (eq 3) directly generated

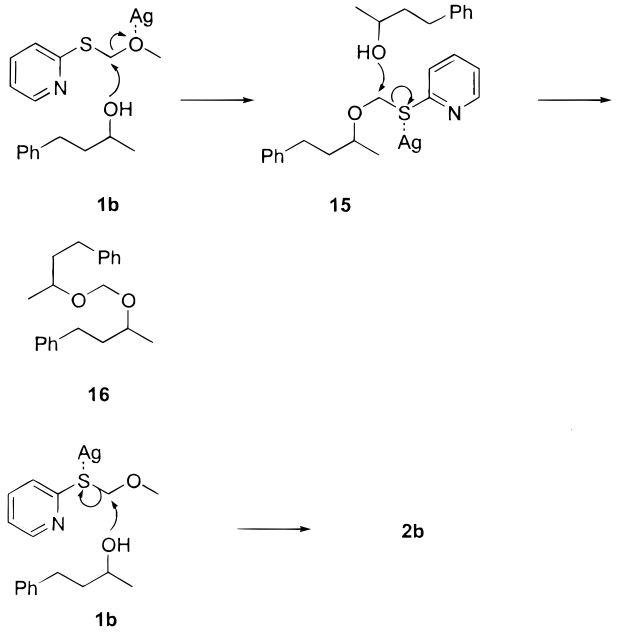


(3)

isomer **17**. Upon standing neat at ambient temperature for a few weeks, **17** reverted to a mixture of **5** and **17** in a ratio of 80:20. Likewise, **5** under similar conditions converted to a mixture of **5** and **17** in a ratio of 70:30. To verify this apparent thermodynamic equilibrium, **5** and **17** were each subjected to 100 °C temperatures for 48 h. As expected, each sample resulted in the same mixture of **5** and **17** in a ratio of 65:35.

As shown in Table 1, MOM-ON produced high yields of methoxymethyl ethers when used with a variety of

Scheme 1



alcohols and phenols. Tertiary alcohols, though slower to react than primary and secondary alcohols, still produced high yields. With only a slight increase of reagents needed, allylic and benzylic alcohols also gave good yields. Even the highly ionizable and hindered trityl alcohol (**1g**) was methoxymethylated in modest yield. Phenol gave an exceptionally high yield when 4.0 equiv of MOM-ON was used. Finally, the method was tested on the avermectin aglycones, which are prone to acid-catalyzed rearrangements.[13] Good yields of MOM-ethers **2l** and **2m** were produced with no desilylation or rearrangement products detected. In contrast, the Lewis acid catalyzed reactions of **1l** with dimethoxymethane produced mainly desilylation products.

Relative rates of reaction were tested by mixing equimolar amounts of two given alcohols, 1 equiv of each, with 0.5 equiv of MOM-ON. The results showed very little difference between primary, secondary, and tertiary alcohols. However, phenols reacted much slower than alcohols.

The experimental procedure is quite simple. A solution of AgOTf in THF is added very quickly to a solution of the alcohol, NaOAc, and **5**, resulting in the immediate precipitation of the silver salts. After a few minutes, brine solution and toluene are added to complete the precipitation, and the solids are removed by filtration. The basic byproducts are removed by acidic extractions. After solvent removal, MOM ethers are left with little to no byproducts detectable by NMR.

Rapid addition of the silver triflate solution is imperative. Slow addition results in incomplete transformations. The excess reagents required for optimal yield with various alcohols and phenols are shown in Table 1. As a rule, the ratio of **5** to AgOTf should remain 1.1:1.

Conclusion

MOM-ON is an effective reagent for the methoxymethylation of a wide range of alcohols and phenols. The

(13) Mrozik, H.; Eskola, R. L.; Arison, B. H.; Fisher, M. H.; Albers-Schonberg, G. *J. Org. Chem.* **1982**, *47*, 489−492.

(14) Goff, D. A.; Harris, R. N., III; Bottaro, J. C.; Bedford, C. D. *J. Org. Chem.* **1986**, *51*, 4711−4714.

conditions are extremely mild, resulting in very quick and clean reactions. We have shown this method to be broadly applicable. Even highly ionizable and nonnucleophilic compounds such as triphenylmethanol and *p*-nitrophenol react to some extent.

Experimental Section

^{1}H and ^{13}C NMR were run at 250 MHz. HPLC was carried out with a Zorbax SB phenyl column (4.6 mm × 15 cm). MS data was obtained by a Finnigan TSQ 7000 instrument with an atmosphere pressure ionization interface. Ionization was accomplished with atmosphere pressure chemical ionization. Alcohols and phenols **1a**−**k** and thiols used to produce reagents **5**−**14** were purchased from Aldrich Chemical Co.

MOM-ON (5). To a 0 °C solution of 2-mercaptopyridine (24.7 g, 222 mmol) in dimethoxymethane (100 mL) under N_2 was added $BF_3{\cdot}Et_2O$ (34.7 g, 245 mmol). The mixture was allowed to warm to room temperature and was stirred for 4 h. In an open flask, 100 mL of saturated $NaHCO_3$ was added slowly, followed by extraction with CH_2Cl_2 (1 × 100 mL, 1 × 50 mL). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by vacuum distillation (66 °C at 0.28 mmHg) yielding 26 g of **5** (75% yield) as a clear yellow oil. Quick, low-pressure distillation is necessary because of rearrangement of **5** to **17** at elevated temperatures. ^{1}H NMR ($CDCl_3$) δ 3.29 (s, 3H), 5.22 (s, 2H), 6.91 (m, 1H), 7.17 (d, J = 8.7 Hz, 1H), 7.40 (m, 1H), 8.35 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 56.51, 73.48, 120.14, 122.73, 136.36, 149.48, and 157.71; MS (APCI) *m*/*e* 155.

General Procedure for the Methoxymethylation of Alcohols and Phenols (2a−m). Preparation of (3-methoxymethoxy-butyl)-benzene (2b). To a rapidly stirred solution of **1b** (0.106 g, 0.706 mmol), **5** (0.212 g, 1.37 mmol), and NaOAc (0.716 g 0.873 mmol) in 6.0 mL of THF under N_2 at room temperature was added all at once a solution of AgOTf (0.3 g, 1.17 mmol) in THF (5.0 mL). After 5 min, saturated brine (1.3 mL) and toluene (13 mL) were added. The precipitates were filtered, and the filtrate was washed with 1 N HCl (3 × 25 mL), saturated $NaHCO_3$ (25 mL), and saturated brine solution (25 mL). After drying with Na_2SO_4, the solvent was removed in vacuo leaving **2b** as a yellowish oil with an HPLC assay yield of 90%: ^{1}H NMR ($CDCl_3$) δ 1.24 (d, J = 6.2 Hz, 3H), 1.84 (m, 2H), 2.73 (m, 2H), 3.42 (s, 3H), 3.75 (m, 1H), 4.71 (q, J = 13.3, 6.9 Hz, 2H), 7.26 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.45, 31.96, 38.95, 55.37, 72.91, 95.11, 125.79, 128.39, and 142.28; MS (APCI) *m*/*e* 194. The crude products can be further purified by distillation or silica gel chromatography.

(4-Methoxymethoxy-butyl)-benzene (2a): ^{1}H NMR ($CDCl_3$) δ 1.70 (m, 4H), 2.67 (t, J = 7.2 Hz, 2H), 3.37 (s, 3H), 3.56 (t, J = 6.3 Hz, 2H), 4.63 (s, 2H), 7.24 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 28.14, 29.40, 35.72, 55.11, 67.59, 96.41, 125.74, 128.30, 128.43, and 142.40; MS (APCI) *m*/*e* 194.

(3,3-Methoxymethoxy-methyl-butyl)-benzene (2c): ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 6H), 1.83 (m, 2H) 2.69 (m, 2H) 3.42 (s, 3H), 4.77 (s, 2H), 7.24 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 12.21, 30.44, 43.90, 55.21, 75.99, 91.06, 125.67, 128.49, and 142.78; MS (APCI) *m*/*e* 208.

Diphenyl-methoxymethoxymethane (2f): ^{1}H NMR ($CDCl_3$) δ 3.45 (s, 3H), 4.74 (s, 2H), 5.80 (s, 1H), 7.37 (m, 10H); ^{13}CNMR ($CDCl_3$) δ 55.68, 78.75, 94.04, 127.29, 127.55, 128.45, and 141.83; MS (APCI) *m*/*e* 228.

Triphenyl-methoxymethoxymethane (2g): ^{1}H NMR ($CDCl_3$) δ 3.31 (s, 3H), 4.63 (s, 2H), 7.28 (m, 3H), 7.45 (dd, 2H); ^{13}C NMR ($CDCl_3$) δ 56.06, 92.53, 86.65, 127.11, 127.80, 128.59, and 144.41; MS (APCI) *m*/*e* 304.

5,6,7,8-Tetrahydro-1-methoxymethoxynaphthylene (2i): ^{1}H NMR ($CDCl_3$) δ 1.78 (m, 4H), 2.73 (m, 4H), 3.49 (s, 3H), 5.21 (s, 2H), 6.77 (d, J = 7.6 Hz, 1H), 6.87 (d, J = 7.7 Hz, 1H), 7.05 (t, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.82, 23.25, 26.53, 29.67, 55.96, 94.28, 110.45, 122.54, 125.72, 126.65, 138.71, and 154.95.

1-Methoxy-2-methoxymethoxybenzene (2j): ^{1}H NMR ($CDCl_3$) δ 3.48 (s, 3H), 5.20 (s, 2H), 6.88 (m, 3H), 7.13 (d. J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 55.77, 56.12, 95.45, 111.77, 116.51, 120.86, 122.52, and 149.74; MS (APCI) *m*/*e* 168.

***N*-Methoxymethyl-2-mercaptopyridine (17).** To a solution of **5** (0.534 g, 3.44 mmol) in THF (8 mL) under N_2 was added a solution of AgOTf (0.982 g, 3.82 mmol) in THF (7 mL). After 15 min, the usual work up was applied: ^{1}H NMR ($CDCl_3$) δ 3.45 (s, 3H), 5.75 (s, 2H), 7.71 (dd, J = 8.9, 1.0 Hz, 1H), 6.75 (td, J = 6.8, 1.4 Hz, 1H), 7.22 (ddd, J = 8.5, 5.3, 1.7 Hz, 1H), 7.86 (dd, J = 6.8, 1.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 58.23, 84.66, 114.11, 134.93, 136.27, 137.10, and 179.01; MS (APCI) *m*/*e* 155.

Acknowledgment. We gratefully acknowledge Dr. Guo Jie Ho for insightful discussions and Mr. Bob Reamer for his assistance with NMR interpretations.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra are available for compounds **2a**−**c**, **2f**,**g**, **2i**,**j**, **5**, **16**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9822582