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M. P. Kaushik[a]; Hemlata Rana[a]
[a] Process Technology Development Division, Defence R & D Establishment, Gwalior, India

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RESEARCH ARTICLE

An efficient and practical *O*-methylation of dithiaalkanediols

M. P. KAUSHIK* and HEMLATA RANA

Process Technology Development Division, Defence R & D Establishment, Jhansi Road, Gwalior-474002 (MP), India

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A very simple method for the *O*-Methylation of thiodiglycol and dithiaalkanediols has been developed. Dimethyl ethers were prepared using stoichiometric amounts of dimethyl sulfate in tetrahydrofuran in the presence of solid crushed potassium hydroxide. This method is suitable for the synthesis of methyl ethers in high yields and with high selectivity.

Keywords: Dithiaalkanediols; *O*-Methylation; Thiodiglycol; Chemical warfare agents; Sesquimustard; Sulfur mustard; Dimethyl sulfate

1. Introduction

Dithiaalkanediols [1] are important intermediates for the synthesis and degradation of the chemical warfare agents (CWA) such as sesquimustard (Q) [2, 3] and sulfur mustard (HD) [3, 4], the strong organic sulfur vesicants. They also serve as potential biomarkers as well as suitable models for verifying the use of sulfur vesicants either in war or by any terrorist group. Dithiaalkanediols with the general formula $(CH_2)_n[SC_2H_4X]_2$ where $n = 1$–6, 8, 10 are of special interest owing to their real and potential industrial [5–10] and biomedical applications. The alkylation of alcohols is one of the most important and routinely utilized transformations in organic synthesis [11], especially in the synthesis of complicated natural products and glycosylation of sugars [12]. Alkylation is also used for derivatisation of the precursors and degradation products of chemical warfare agents; the more polar analytes and some of the more reactive or highly volatile agents [13] are usually derivatized to facilitate chromatography and to impart properties beneficial for detection. Alkyl groups also play a pivotal role as protecting groups of hydroxyls [11]. Despite a number of precedents, new efficient methodologies for the alkylation are still in strong demand. Several methods have been reported for the *O*-methylation of alcohols and derivatives [14]. Most commonly used methods involve *O*-methylation using methyl iodide [15–21], dimethyl carbonate [22], and diazomethane [23]. However, these methods have some drawbacks and limitations. Handling

*Corresponding author. Email: mpkaushik@rediffmail.com

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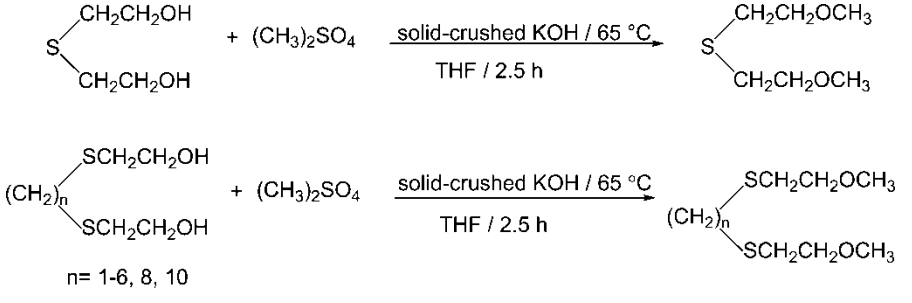
an excess of the low boiling methyl iodide and diazomethane during work up of the reaction mixture present air emission and health safety problems for large-scale workup.

In our ongoing development program, we needed a practical method for the *O*-methylation of diols. Dimethyl sulfate was selected for the *O*-methylation of diols, because it is high boiling and any excess reagent can be safely destroyed in ammonium hydroxide. Herein, we report an efficient and practical method for the *O*-methylation of diols using dimethyl sulfate in the presence of potassium hydroxide.

2. Results and discussion

Dimethyl sulfate is a powerful alkylating agent and has been quite useful as a reagent for methylation of hydroxyl groups [24]. We have found that a stoichiometric amount of dimethyl sulfate reacts smoothly with dithiaalkanediols in tetrahydrofuran in the presence of solid potassium hydroxide to give the corresponding methyl ethers as shown in the scheme 1. Various dithiaalkanediols were converted to the corresponding dimethyl ethers using dimethyl sulfate in high yields. The results are summarized in the table 1.

Most probably the diol-containing substrates are chemisorbed on potassium hydroxide in a manner that positions the hydroxyl groups remote from the potassium hydroxide surface. This means that the hydroxyl groups of the diols are easily available to react with dimethyl sulfate by absorption on solid potassium hydroxide. Dimethyl sulfate is a strong methylating agent and has been used for the methylation of a wide variety of nucleophiles. Usually a base is required, either (1) to make the reaction site more reactive, e.g., convert OH group of the



SCHEME 1

Table 1. O-Methylation of dithiaalkanediols with dimethyl sulfate.

Substrate[a]	$(CH_3)_2SO_4$/mol eq.	Yield (%)[b]	B.P (°C/mmHg)
$S(CH_2CH_2OH)_2$	2	98	80–90/10
$CH_2(SCH_2CH_2OH)_2$	2	93	120/2
$(CH_2)_2(SCH_2CH_2OH)_2$	2	92	122/2
$(CH_2)_3(SCH_2CH_2OH)_2$	2	90	110/1
$(CH_2)_4(SCH_2CH_2OH)_2$	2	88	120/0.4
$(CH_2)_5(SCH_2CH_2OH)_2$	2	85	150/2
$(CH_2)_6(SCH_2CH_2OH)_2$	2.5	80	160/2
$(CH_2)_8(SCH_2CH_2OH)_2$	2.5	80	190/2
$(CH_2)_{10}(SCH_2CH_2OH)_2$	2.5	75–80	Undistilled

[a]Substrate (0.01 mol), potassium hydroxide (0.07 mol), dimethyl sulfate (0.02 mol) and THF (10 ml) were refluxed for 2–2.5 h.
[b]Isolated yield. All products gave satisfactory spectral data (details are given in the experimental section).

alcohol into the salt form before reaction with that of dimethyl sulfate, or (2) to neutralize the monomethyl sulfuric acid or sulfuric acid that is produced, e.g. in the methylation of aliphatic alcohols. Under the conditions described, the free hydroxyl groups of the dithiaalkanediols become reactive and generate a strong oxygen nucleophile in comparison to that of sulfur which is attached to that of two carbon atom with covalent bonds and do not get polarized. Because of the strong polarization of the bond, dithiaalkanediols became more reactive towards dimethyl sulfate and results in the formation of diethers of the corresponding dithiaalkanediols. The methylation of the sulfides [25] and sulfur containing oximes, hydroxamic acids and hydroxylamines [26] has also proven that alkylation takes place selectively at oxygen atom and not on the sulfur atom, when the methylation is carried out in the presence of a base.

Many factors such as solvent, base and the structure of the alkyl group profoundly influence the course of the reaction. For example, use of acetone and dioxane as solvent gave poor yields and requires long reaction time. Tetrahydrofuran proved to be the reaction solvent of choice, being low boiling in comparison to high boiling dioxane, and could be removed easily from the reaction mixture. Sodium hydroxide was also used and it was observed that pure sodium hydroxide is not as reactive as potassium hydroxide, perhaps due to lower solubility in tetrahydrofuran. Use of aqueous potassium hydroxide gave a mixture of mono and diether derivatives. In all cases the reaction was faster in the presence of powdered potassium hydroxide as compared to powdered sodium hydroxide yielding the *O*-methylated products in more then 80% yield. Several investigations have been carried out to understand the influence of structural variations of the alkyl moiety. The reactivity order is $(CH_2)_n[SC_2H_4X]_2$ where $n = 1$–5, 6, 8, 10. While thiodiglycol and dithiaalkanediols of general formula $(CH_2)_n[SC_2H_4X]_2$ where $n = 1$–5 react faster comparatively to where $n = 6$, 8, 10 may be because of the solubility difference of the dithiaalkanediols in tetrahydrofuran.

3. Conclusion

In conclusion, a powerful and versatile methylation method by virtue of base catalysis has been developed. This method includes a lot of unique merits, namely, a cheap and easy to handle alkylating reagent, operational simplicity and no need for absolute dry reaction conditions, work up and isolation of the product are quite easy, base (KOH) is removable at ease by washing with water and often a simple filtration through a thin pad of silica gel of the crude products furnished pure methylated products. Although a slight excess amount of methylating reagent should be used for the complete conversion of the diols in question, it some times causes tedious separation of the methylated products from the remaining methylating reagent. To overcome such an obstacle, excess reagent can be safely destroyed in ammonium hydroxide and the desired products were obtained by vacuum distillation.

4. Experimental

4.1 *General*

To a vigorously stirred mixture of diol (0.01 mol) in tetrahydrofuran (50 ml) at 60–65 °C (oil bath temperature) was added crushed solid commercial potassium hydroxide (0.07 mol) over a period of 10 min while maintaining an internal temperature of 60–65 °C. The mixture was stirred at the same temperature for 10 min, and dimethyl sulfate (0.02 mol) was added drop wise over a period of 20 min while maintaining the internal temperature mentioned above. The reaction mixture was stirred/refluxed at 70–80 °C for 2–2.5 h. The stirring was continued at the

same temperature for additional 30 min and the reaction was monitored by TLC (chloroform: acetone, 80:20). After completion of reaction, the mixture was filtered to remove the solid material, solvent was removed by evaporation and the residue was distilled to get the pure dimethyl ethers. All the compounds gave satisfactory spectroscopic data.

4.1.1 Bis(2-methoxyethyl)sulfide (1). IR (KBr): υ_{max} 2924, 2876, 2824, 1457, 1380, 1185, 1115, 1046, 957, 767 cm^{-1}: ^1H NMR ($CDCl_3$ 400 MHz): δ 3.5 (t, $J = 8.2$ Hz, 4H), 3.29(s, 6H) 2.68 (t, $J = 8.1$ Hz, 4H); MS(EI) *m/z* (%) 150 (M^+,3), 118 (56), 75 (90), 72 (26), 59 (65), 58 (88), 45 (100).

4.1.2 Bis(2-methoxyethylthio)methane (2). IR (KBr): υ_{max} 2981, 2923, 2826, 1459, 1382, 1189, 1116, 958, 726 cm^{-1}: ^1H NMR ($CDCl_3$ 400 MHz): δ 3.70 (s, 2H), 3.53 (t, $J = 8.2$ Hz, 4H), 3.29 (s, 6H), 2.74 (t, $J = 8.1$ Hz, 4H); MS (EI) *m/z* (%) 196 (M^+,12), 164 (22),138 (57),105 (42), 75 (100), 59 (58), 45 (82).

4.1.3 1,2-Bis(2-methoxyethylthio)ethane (3). IR (KBr): υ_{max} 2923, 2893, 2822, 1448, 1189, 1116, 956, 915, 765 cm^{-1}: ^1H NMR ($CDCl_3$ 400 MHz): 3.50 (t, $J = 4.1$ Hz, 4H), 3.29 (s, 6H), 2.71 (s, 4H), 2.66 (t, $J = 4.2$ Hz, 4H); MS(EI) m/z(%) 210 (M^+,3), 178 (42), 152 (60), 119 (93), 118 (69), 93 (24), 75 (74), 59 (99), 58 (69), 45 (100).

4.1.4 1,3-Bis(2methoxyethylthio)propane (4). IR (KBr): υ_{max} 2921, 2823, 1449, 1189, 1114, 956, 766 cm^{-1}: ^1H NMR ($CDCl_3$ 400 MHz): δ 3.53 (t, $J = 4.1$ Hz, 4H), 3.35 (s, 6H), 2.65 (m, 8H), 1.85 (m, 2H); MS (EI) m/z(%) 224 (M^+,10), 92 (35), 165 (100), 133 (23), 107 (26), 73 (33), 59 (91), 45 (78).

4.1.5 1,4-Bis(2-methoxyethylthio)butane (5). IR (KBr): υ_{max} 2923, 2823, 1450, 1189, 1114, 957, 768 cm^{-1}: ^1H NMR ($CDCl_3$ 400 MHz): δ 3.48 (t, $J = 4.2$ Hz, 4H), 3.29 (s, 6H), 2.63 (t, $J = 4.1$ Hz, 4H), 2.5 (m, 4H), 1.6 (m, 4H); MS(EI) m/z(%) 238 (M^+,5), 206 (45), 179 (85), 147 (55), 115 (90), 87 (85), 75 (60), 59 (100), 45 (90).

4.1.6 1,5-Bis(2-methoxyethylthio)pentane (6). IR (KBr): υ_{max} 2924, 2822, 1454,1183, 1114, 956, 769 cm^{-1}: ^1H NMR ($CDCl_3$ 400 MHz): δ 3.5 (t, $J = 4.1$ Hz, 4H), 3.3 (s, 6H), 2.64 (t, $J = 4.2$ Hz, 4H), 2.5 (t, $J = 4.2$ Hz, 4H), 1.53 (m, 4H), 1.41 (m, 2H); MS(EI) m/z(%) 252 (M^+,2), 220 (92), 161 (100), 129 (90), 102 (76),101 (70), 75 (84), 59 (72), 45 (64).

4.1.7 1,6-Bis(2-methoxyethylthio)hexane (7). IR (KBr): υ_{max} 2924, 2856, 2821, 1455, 1183, 1115, 957 cm^1: ^1H NMR ($CDCl_3$ 400 MHz): δ 3.47 (t, $J = 8.2$ Hz, 4H), 3.28 (s, 6H), 2.62 (t, $J = 8.2$ Hz, 4H), 2.47 (t, $J = 8.2$ Hz, 4H) 1.57 (m, 4H), 1.31 (m, 4H); MS (EI) m/z (%) 266 (M^+, 8), 234 (51), 175 (57), 143 (100), 115 (85), 81 (72), 61 (71), 55 (66), 45 (72).

4.1.8 1,8-Bis(2-methoxyethyl thio)octane (8). IR (KBr): υ_{max} 2924, 2855, 1456, 1183, 1115, 957, 724 cm^{-1}: ^1H NMR($CDCl_3$ 400 MHz): δ 3.65 (t, $J = 4.1$ Hz, 4H), 3.47 (s, 6H), 2.80 (t, $J = 4.1$ Hz, 4H), 2.64 (t, $J = 4.2$ Hz, 4H), 1.67 (m, 4H), 1.47 (m, 4H), 1.40 (m, 4H); MS(EI) m/z(%) 293 (M^+, 5), 262 (16), 171 (100), 143 (76), 141 (42), 101 (30), 87 (60), 61 (46), 59 (42), 45(62).

4.1.9 1,10-Bis(2-methoxyethylthio)decane (9). IR (KBr): υ_{max} 2924, 2853, 1457, 1114, 957, 617 cm^{1}: ^{1}H NMR ($CDCl_3$ 400 MHz): δ 3.5 (t, $J = 4.2$ Hz, 4H), 3.30 (s, 6H), 2.64 (t, $J = 4.2$ Hz, 4H), 2.47 (t, $J = 4.2$ Hz, 4H), 1.53 (m, 4H) 1.27 (m, 12H); MS (EI) m/z (%) 321(M^+, 4), 290 (14), 203 (42), 199 (80), 171 (100), 169 (40), 115 (26), 101 (56), 87 (98), 61 (64), 55 (82), 45 (89).

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