

TRIMETHYLSELENONIUM HYDROXIDE: A NEW METHYLATING AGENT

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Trimethylselenonium hydroxide is very useful for methylating COOH, SH, aromatic OH, ring NH groups in aromatic heterocycles, etc.

Onium hydroxides ($R_nX^+ OH^-$) may be considered as potent alkylating agents. Tetraalkylammonium hydroxides, however, are not practical alkylating agents. Only trimethylanilinium hydroxide has been used for methylation of carboxylic acids, phenolic alkaloids, xanthine bases and nucleosides, etc.¹ Previously we introduced trimethyloxosulfonium hydroxide $[(CH_3)_3S^+(=O) OH^-]$ ² and trimethylsulfonium hydroxide, $[(CH_3)_3S^+ OH^-]$ ³ as new methylating agents for methylation of carboxylic acids, phenols, mercaptans, nucleic acid-bases, etc.

As the extension of the study, we wish to report the synthesis of trimethylselenonium hydroxide $[(CH_3)_3Se^+ OH^-, Me_3SeOH]$ and novel methylation of various kinds of compounds using the reagent, which was found to be most reactive of all known onium hydroxides.

Me_3SeOH was prepared by addition of silver oxide (6.0 g, 25.9 mmol) to the solution of trimethylselenonium iodide⁴ (8.2 g, 32.6 mmol) in methanol - water (100 ml - 1 ml) with stirring at room temperature. The supernatant was checked occasionally for iodide with nitric acid-silver nitrate solution. After completion of the reaction, the reaction mixture was filtered and the solution was concentrated to 40 ml. The titration of the reagent solution with 0.1 N hydrochloric acid indicated 0.67 N as the concentration of Me_3SeOH (yield, 82 %). When the titrated solution was concentrated, trimethylselenonium chloride was obtained as crystals in the yield of 92 %. The NMR of the solution : δ 2.75 [s, $(CH_3)_3Se^+$]. The reagent solution is strongly alkaline and stable considerably at below 10 °C, undergoing only ca. 5 % decomposition after one month.

Methylation reactions were carried out generally as follows. Reaction

conditions and results are summarized in Tables 1 and 2. A mixture of the Me_3SeOH solution and a substrate in a round-bottom flask was concentrated by a rotary evaporator. The flask was then equipped with a short distillation apparatus and heated with stirring by a magnetic device. For methylation reactions of succinimide, uridine and xanthine, the concentrated reaction mixtures were heated in dimethylformamide (DMF). During the reactions, dimethylselenide was distilled (bp. 56 - 57 °C), which was reused by converting quantitatively to trimethylselenonium iodide by a reaction with methyl iodide.^{4,5} All products except 3-methyluridine⁶ were isolated by direct distillation or recrystallization of the reaction mixtures. They had correct physical constants including IR and NMR spectra as well as mp, bp, retention times in gas chromatography, etc.

Table 1. Methylation of Various Compounds with Me_3SeOH

Compound	Compd./ Me_3SeOH mole ratio	React. Temp. (°C)	React. Time (min)	Product	Yield (%)
$(\text{CH}_3)_3\text{CCOOH}$	1.2	100	15	$-\text{CO}_2\text{CH}_3$	quant.
$\text{HOCH}_2\text{CH}_2\text{SH}$	"	"	"	$-\text{SCH}_3$	"
$\text{C}_6\text{H}_5\text{OH}$	"	"	"	$-\text{OCH}_3$	"
$\text{C}_6\text{H}_5\text{SH}$	1.1	70	"	$-\text{SCH}_3$	"
$\text{C}_6\text{H}_5\text{NH}_2$	3	100	60	$-\text{NHCH}_3$	5
$\text{CH}_3(\text{CH}_2)_5\text{CH}_2\text{OH}$	5	"	"	$-\text{OCH}_3$	trace
succinimide	2 ^a	"	"	$>\text{NCH}_3$	10
imidazole	1.2	80	15	$>\text{NCH}_3$	93
pyrazole	"	"	"	$>\text{N}^1-\text{CH}_3$	quant.
xanthine	4.8 + 2.4 ^{a,b}	100	15 + 15	caffeine ^c	85

a) DMF (12 ml) was used as a solvent. b) The reaction mixture of xanthine and Me_3SeOH (4.8 mmol) in DMF was heated for 15 min. The reagent solution (2.4 mmol) was then added to the reaction mixture and, after rough removal of methanol from the mixture, it was heated for another 15 min. c) 1,3,7-Trimethylxanthine.

Me_3SeOH is apparently useful for methylation of COOH , SH , aromatic OH , ring NH groups in aromatic heterocycles, etc. The reagent, however, was not suited for methylation of aromatic and aliphatic NH_2 groups and aliphatic OH and amido groups. Methylation reactions may proceed most likely by the following scheme.

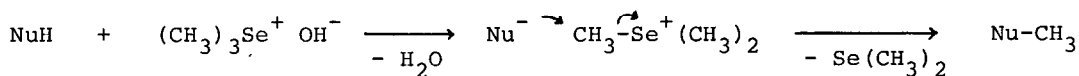


Table 2 shows methylation of uridine using various onium hydroxides. These results and the time-course of the yield of 3-methyluridine revealed the following order of reactivity of onium hydroxides as methylating agents:

$\text{Me}_3\text{SeOH} > (\text{CH}_3)_3\text{S}^+ \text{OH}^- > (\text{CH}_3)_3\text{S}^+(\text{=O}) \text{OH}^- > (\text{CH}_3)_3\text{N}^+\text{C}_6\text{H}_5 \text{OH}^- > (\text{CH}_3)_4\text{N}^+ \text{OH}^-$
 The very high reactivity of Me_3SeOH may be attributed to the weak C-Se bond.

Table 2. Methylation of Uridine with Various Onium Hydroxides ^a

Onium Hydroxide	The Hydroxide/ Uridine Mole Ratio	React. Temp. (°C)	UV-Spectroscopic Yield (%) of 3-Methyluridine ^b
$(\text{CH}_3)_3\text{Se}^+ \text{OH}^-$	1.05	50	70
"	"	65	90 (73°C)
$(\text{CH}_3)_3\text{S}^+ \text{OH}^-$	1.1	"	82
$(\text{CH}_3)_3\text{S}^+(\text{=O}) \text{OH}^-$	1.3	"	67
$(\text{CH}_3)_3\text{N}^+\text{C}_6\text{H}_5 \text{OH}^-$	1.1	75	73
$(\text{CH}_3)_4\text{N}^+ \text{OH}^-$	5	100	2 - 3

a) Reaction conditions: uridine / DMF = 2 mmol / 8 ml; Reaction time, 1 hr. b) UV-spectroscopic yield of 3-methyluridine in reaction mixtures was obtained by the procedure similar to that mentioned previously.⁷ c) The yield of 3-methyluridine isolated.

Advantages of Me_3SeOH as a methylating agent are: rapid and nearly quantitative methylation at moderate temperature for compounds above mentioned which have pK_a values smaller than about 12, and easy isolation and purification of products since byproducts of Me_3SeOH (water and dimethylselenide) can be removed easily. The similar advantages were observed in methylation using

trimethylsulfonium hydroxide.³ At contrast, trimethylanilinium hydroxide requires rather longer reaction time and high reaction temperature, while other common alkylating agents⁸ such as methyl iodide, diethylsulfate, methyl p-toluenesulfonate coproduce hydroiodic acid, methylsulfate, p-toluenesulfonic acid, respectively, or their sodium or potassium salts, which are difficult to remove especially when products are soluble in water. Although diazomethane may be as useful as Me_3SeOH , it and its starting materials (N-nitroso-N-methylamino compounds) must be handled carefully because they are strong carcinogens.⁹

References and Notes

- 1) E. Brochmann-Hanssen and T. O. Oke, *J. Pharm. Sci.*, **58**, 370 (1969); I. Gan J. Korth and B. Halpern, *Synthesis*, 494 (1973); G. R. Pettit et al., *Synthetic Commun.*, **7**, 449 (1977).
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- 4) T. Hashimoto, et al., *Nippon Kagaku Zasshi*, **88**, 991 (1967); *C. A.*, **69**, 2655r (1968).
- 5) Methylation reactions must be conducted in a draft chamber to avoid inhalation of dimethylselenide.
- 6) 3-Methyluridine was isolated as crystals by treating the concentrated reaction mixture with a silica gel column (2 cm x 50 cm) and washing the column with a mixture of chloroform and methanol (10 : 1 v/v), 0.37 g (73 %), mp 115 - 116 °C (ethyl acetate - methanol) (lit. 115 - 116 °C; K. Yamauchi and M. Kinoshita, *J. Chem. Soc. Perkin I*, 762 (1978)).
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- 9) B. Singer in "Progress in Nucleic Acid Research and Molecular Biology," Vol. 15, W. E. Cohn Ed., Academic Press, New York, 1975, p. 219. Biological study of Me_3SeOH is now under study.

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