

# S-Transmethylation on Sulfur of Heterocycles with S-Methylmethioninemethyl Ester Iodide

Jai Moo Shin and Yong Hae Kim †

Department of Chemistry, Korea Advanced Institute of Science and Technology, P. O. Box 150 Chongryangni, Seoul, Korea (Received February 17, 1983)

In mammalian systems, S-adenosylmethionine (**1**) has been known to be one of the most versatile methyl donors<sup>1</sup> and the specific methylation of nucleophiles by **1** has been considered to be catalyzed by methyltransferases<sup>2</sup>. S-methyl-methionine (**2**) isolated in cabbage<sup>3</sup> has also been used for S-methylation of heterocycles such as thiopyrimidines and thiopyrimidines in the presence of enzyme of biological systems<sup>4</sup>. Direct methylation on sulfur or on nitrogen atom of heterocycles without using enzymes has been an important problem for the syntheses of alkylated heterocyclic compounds such as pyridine, pyrimidine or purine derivatives. As a model compound for the nonenzymic transmethylation, **3** was prepared from methionine and has been found to be an excellent S-methylation reagent under mild conditions for the heterocyclic-thiols or-thions of 2-thiouracil, 2-thiopyrimidine, 6-methyl-2-thiouracil, 4, 6-dimethyl-2-thiopyrimidine and 2-imidazolidinethione.

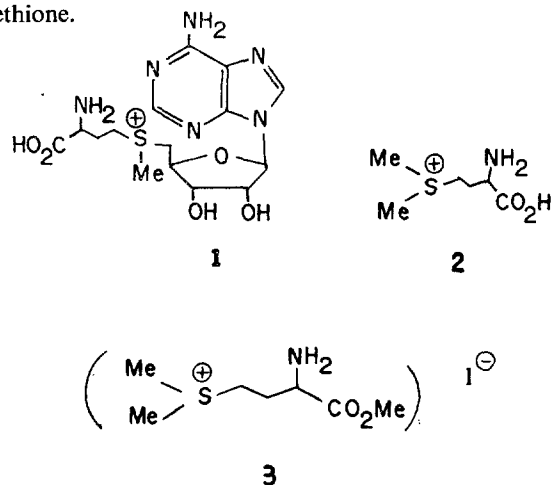


TABLE 1: S-Methylation<sup>a</sup> by **3**<sup>b</sup> in the Presence of Na<sub>2</sub>CO<sub>3</sub>

Run	Substrates	Reaction Temp. (°C)	Reaction Time (h)	Product yields (%) <sup>c</sup>
1		45	1	99
2		50	1	100
3		50	24	95 <sup>d</sup>
4	"	(50)	(10)	(75) <sup>d</sup>
5		50	24	82.7 <sup>d</sup>
6		50	10	90
7		25	1	98

<sup>a</sup>All the reactions were carried out in the presence of sodium carbonate as a base. <sup>b</sup>The methylation reagent, **3** was converted to methioninemethyl ester quantitatively. <sup>c</sup>Isolated yields. <sup>d</sup>Heterogeneous reaction.

In a typical run, sodium carbonate (106 mg, 1 m mole) was added to the 2-thiopyrimidine solution (56 mg, 0.5 m mole, methanol: 10 ml) with stirring, and then **3** (200 mg, 0.54 m mole) was added to 45°C. After stirring for 1 h, white solid (NaI) appeared was removed by filtration. The filtrate was concentrated and purified by preparative thin layer chromatography (Wako-gel GF254, solvent: CH<sub>2</sub>Cl<sub>2</sub>/MeOH=15/1) to give 2-(methylthio)-pyrimidine [63 mg, 99.8 %, <sup>1</sup>H NMR D<sub>2</sub>O δ7.95 (d, J=7 Hz, 2H), 7.75 (d, J=7 Hz, 2H), 2.5 (s, 3H)] The products obtained are identified by comparing their mp., <sup>1</sup>H NMR, IR and UV spectra with those of authentic samples. The results are summarized in Table 1.

S-methylations of 2-thiouracil and its derivatives were carried out in heterogeneous state in methanol and required longer reaction time and higher reaction temperature probably

due to the low solubility of the substrates. It is well known that methylations on heteroatoms is assisted by bases or achieved under the aid of substrate-specific enzymes in biological systems<sup>1,2</sup>. Trialkylsulfonium hydroxide which is strong base were reported to be effective for the O- or N-methylations of nucleic acids<sup>5</sup>. However, S-methyl methionine methyl ester hydroxide was observed to decompose readily to S-methyl methionine at 25°C, and to convert<sup>6</sup> to unidentified materials at 60°C for 1h. The new S-methylation reagent, **3** was stable enough in sodium carbonate-methanol solution to results in the excellent S-methylations. Alkylsulfonium salts were used for the intramolecular or intermolecular alkylations as a O-methylation model compounds for catechol O-methyltransferase<sup>7</sup> and for the phase transfer alkylation reagents.<sup>8</sup> The mechanism of methyl transfer from **3** to the sulfur atom is probably initiated by the nucleophilic attack of the sulfur on the methyl carbon of **3** where methylsulfide is a good leaving group as described in the previous works<sup>7</sup>.

## References and notes

- (1) V. Zappia, E. Usdin and F. Salvatore, "Biochemical and Pharmacological Roles of Adenosylmethionine and the Central Nervous System" P. 2. Pergamon Press, New York, 1979.
- (2) (a) F. Salvatore, E. Borek, V. Zappia, H. G. Williams-Ashman, and F. Schlenk, "The Biochemistry of Adenosylmethionine." Columbia Univ. Press, P. 31. New York, 1977; (b) Woonki Paik, and Sangduk Kim, "Protein Methylation Biochemistry; A Series of Monographs," Vol. I. p. 83-97, John Wiley & Sons, New York, 1980; (c) George Weber, "Advances in Enzyme Regulation," Vol. 9. p. 340-383, Pergamon Press, New York, 1970.
- (3) R. A. McRorie, G. L. Surtherland, M. S. Lewis, A. D. Barton and W. Shive, *J. Amer. Chem. Soc.*, **76**, 115 (1954).
- (4) C. N. Remy, *J. Biol. Chem.*, **238**, 1078 (1963).
- (5) K. Yamauchi, T. Tanabe and M. Kinoshita, *J. Org. Chem.*, **43**, 1593 (1978); *ibid.*, **44**, 638 (1979).
- (6) S-Methylmethionine has been known to be readily decomposed in basic media: (a) A. Meister, "Biochemistry of the Amino Acids," 2nd ed., Academic Press, 1965. (b) F. Ramirez, J. L. Finnan and M. Carlson, *J. Org. Chem.*, **38**, 2597 (1973). (c) W. B. Lawson, E. Gross, C. M. Flotz and B. Witkop, *J. Amer. Chem. Soc.*, **84**, 1715 (1962).
- (7) (a) J. O. Knipe, and J. K. Coward, *J. Amer. Chem. Soc.*, **101**, 4399 (1979). (b) M. F. Hegazi, R. T. Borchardt, and R. L. Schowen, *ibid.*, **101**, 4359 (1979). (c) C. H. Gray, J. K. Coward, K. B. Schowen and R. L. Schowen, *ibid.*, **101**, 4351 (1979). (d) J. K. Coward and W. D. Sweet, *J. Org. Chem.*, **36**, 2337 (1971).
- (8) (a) B. Badet and M. Julia, *Tetrahedron Lett.*, 1101, **1979**. (b) B. Badet, M. Julia, and M. Ramirez-Munoz, *Synthesis*, 926, **1980**.

## Lithium Diisobutyl-*n*-butylaluminum Hydride. An Exceptionally Powerful and Selective Reducing Agent in Reduction of Organic Halides

Sungak Kim<sup>†</sup> and Kyo Han Ahn

Department of Chemistry, Korea Advanced Institute of Science and Technology, Seoul 131, Korea

(Received March 7, 1983)

The reductive dehalogenation of organic halides is one of the fundamental reaction which is frequently used in organic synthesis. Complex hydride reducing agents are the most effective and convenient for this conversion.<sup>1,2</sup>

Although lithium diisobutylmethylaluminum hydride was originally utilized for the facile *trans*-hydroalumination of disubstituted alkynes by Zweifel,<sup>3</sup> relatively few reports on the reducing properties of lithium trialkylaluminum hydrides have appeared in the literature<sup>4</sup>. We wish to report on the interesting reducing characteristics of lithium diisobutyl-*n*-butylaluminum hydride, the ate complex generated from equimolar amounts of diisobutylaluminum hydride and *n*-butyllithium, toward organic halides.

Reductions were usually carried out in tetrahydrofuran-*n*-hexane (4:1) at room temperature under nitrogen using equimolar amounts of the reagent and the substrate,<sup>5</sup> and reaction mixtures were maintained at 0.20M in the substrate and 0.21M in the reagent. The rate of reduction was followed by GLC at appropriate intervals of time and the yield was determined by isolation or GLC using a suitable internal standard.

Figure 1 shows the results obtained in the reaction of structurally different alkyl bromides with a stoichiometric amount of the reagent. Simple primary alkyl bromide, 1-bromodo-

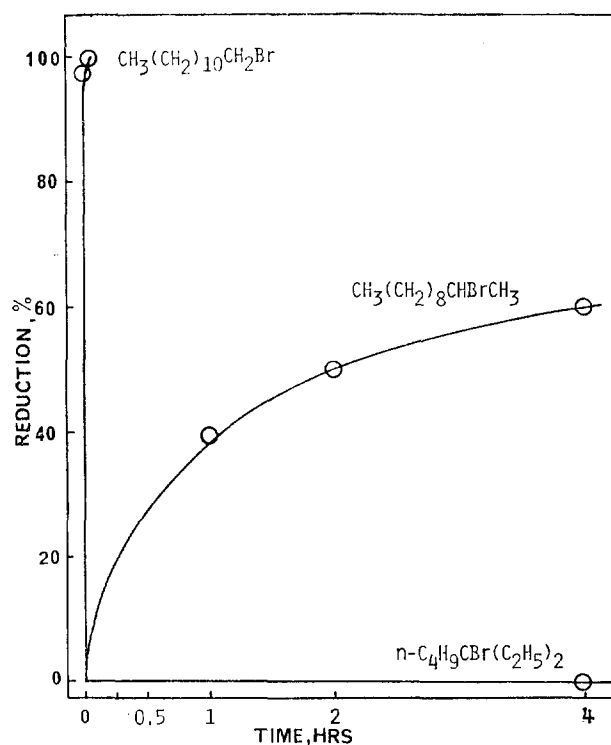


Figure 1. Rates of reduction of alkyl bromides with 1 molar equiv. of LiAl(i-Bu)<sub>2</sub>(n-Bu)H at room temperature.