

ACTIVATION OF NITROSO GROUP WITH THIOLS. A NEW TRANSFORMATION
OF PRIMARY AMINES TO ORGANIC SULFIDES OR THIOLS

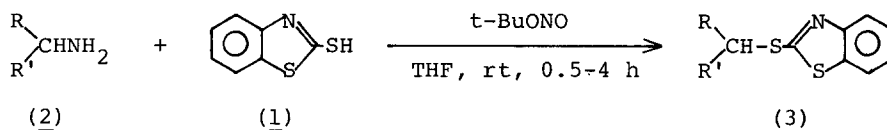
Yoshio Ueno,* Chie Tanaka, and Makoto Okawara
Research Laboratory of Resources Utilization, Tokyo Institute
of Technology, Nagatsuta, Midoriku, Yokohama 227, Japan

Summary: Aliphatic primary amines reacted with 2-mercaptobenzothiazole in the presence of *t*-butylnitrite at room temperature to give condensation products, 2-(alkylthio)benzothiazole.

An aliphatic deamination (either reductive, oxidative, or without change in the oxidation state) is an attractive approach in synthetic chemistry or in a manipulation of amino-containing natural products.¹ One serious problem in such deamination chemistry seems to arise from the fact that aliphatic diazonium ions unlike aromatic ones are very unstable and give complex mixtures of products.² Moreover, only limited numbers of nucleophiles are successfully employed to trap such unstable diazonium ions, because of the competitive nitrosation of nucleophiles themselves.

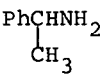
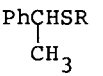
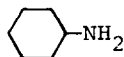
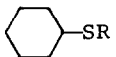
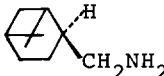
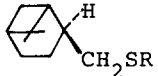
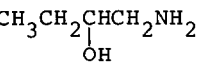
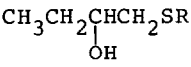
For example, our first attempt to trap aliphatic diazonium ion with a thiol by the nitrosation of aliphatic amines in the presence of thiophenol resulted in the formation of diphenyl disulfide.³

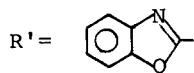
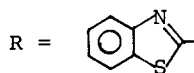
We found, however, 2-mercaptobenzothiazole (1) was a special thiol, which was able to trap aliphatic diazonium ions. We wish to report here a synthetically useful and mechanistically interesting method for the aliphatic deamination, which consists of a new type of direct transformation of amines to organic sulfides.



Thus, we found amines (2) reacted with (1) in the presence of *t*-butylnitrite (isopentyl- or *n*-pentylnitrite was equally effective) in tetrahydrofuran (THF) at room temperature to afford the condensation products, 2-(alkylthio)benzothiazoles (3) as major products in respectable yields (Table 1).⁴

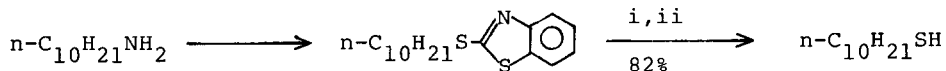
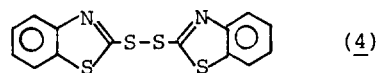
Table 1. Sulfides (3) from amines (2)

Amines (2)	Sulfides (3)	Yield (%)
a PhCH ₂ NH ₂	PhCH ₂ SR	80
b PhCH ₂ CH ₂ NH ₂	PhCH ₂ CH ₂ SR	79
c n-C ₁₀ H ₂₁ NH ₂	n-C ₁₀ H ₂₁ SR	73
d MeN(CH ₂ CH ₂ CH ₂ NH ₂) ₂	MeN(CH ₂ CH ₂ CH ₂ SR) ₂	71
e 		56
f 		63
g 		60
h 		42
i n-C ₁₀ H ₂₁ NH ₂	n-C ₁₀ H ₂₁ SR'	62



When the above reaction was carried out in the absence of amines, the rapid and quantitative formation of disulfide (4) was observed (t-BuONO, rt, 15 min).

The present reaction, when coupled with the facile manipulation of organosulfur compounds, opens a new useful approach to the modification of aliphatic amino-function. For example, the reaction provides a new method for the replacement of amino group with mercapto one via N-methylbenzothiazolium salt.

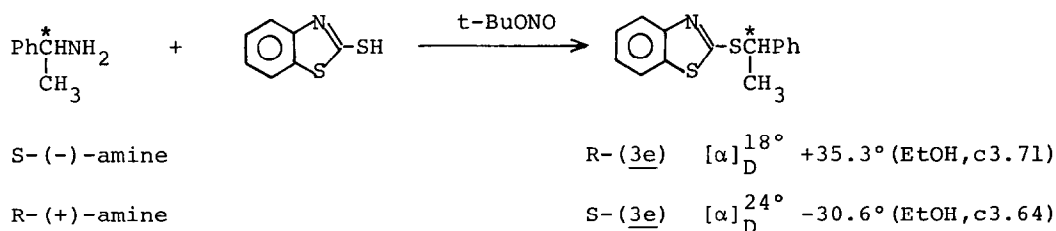


i: Me₂SO₄, 90°C, 5 h. ii: NH₂NH₂, EtOH, ref., 2 h.

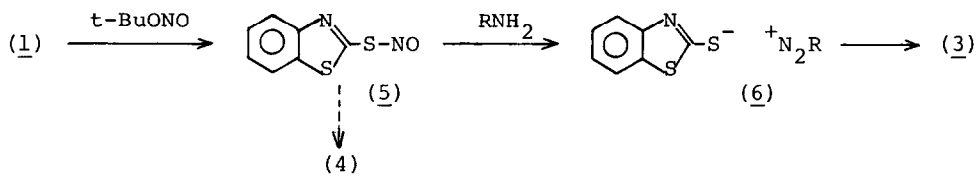
In addition, aliphatic reductive deamination (RNH₂ → RH) is also promising, since organosulfur compounds are well known to be reductively desulfurized to hydrocarbons with Raney Ni.⁵

The characteristic points of the present mechanistically interesting reaction are as follows; [1]. Only 2-mercaptobenzothiazole or 2-mercaptobenzoxazole is effective. Other thiols such as thiophenol, thiolbenzoic acid, or 2-mercaptobenzothiazoline gave no expected sulfides.⁶ [2]. Amines do not react with *t*-butylnitrite under similar conditions in the absence of thiol (1). [3]. A very small amount or no amount of disulfide (4) is detected in the presence of amines.

These facts indicate 2-mercaptobenzothiazole (1) activates a nitroso group. In order to clarify the mechanism, we examined the reaction using a very susceptible benzylic chiral amine. Thus, *S*- or *R*- α -methylbenzylamines gave the sulfide (3e) with a partial inversion of the chiral center, respectively [*R*-(3e) ee 10%, *S*-(3e) ee 8.7%].⁷



The results suggest the following reaction scheme. Thus, thionitrite (5) is a key intermediate,⁸ which is a powerful nitrosation reagent unlike the ordinary thionitrites. The efficient nitroso transfer from thionitrite (5) to amines yielding diazonium ions (6) may prevent the reaction from the self-decomposition of (5) leading to disulfide (4). The resulting diazonium ion (6) decomposes rapidly with liberation of nitrogen gas yielding sulfide (3) in both S_N1 and S_N2 manners with a partial inversion.



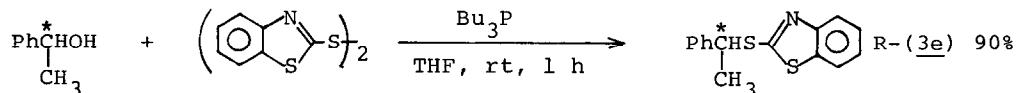
The efficient nitroso transfer from oxygen to sulfur, then to nitrogen may lead to the successful present reaction. On the other hand, thionitrite (PhS-NO) derived from thiophenol is a poor nitroso transfer reagent towards amines, yielding disulfide (PhSSPh).

A typical experimental procedure is as follows. To a solution of (1) (0.46 g, 2.74 mmol) and benzylamine (0.3 ml, 2.74 mmol) in dry THF (8 ml), was added a solution of *n*-pentylnitrite (0.41 ml, 3.0 mmol) in dry THF (5 ml) at room temperature during ten min. Gas evolution and slight exothermic

reaction was observed in a few minutes. After stirring for 3 h, sulfide (3a) was obtained by the usual work up in 87% yield. The NMR spectrum showed a contamination of N-benzyl benzothiazoline-2-thione in 7% yield. In a separate experiment using t-butyl nitrite under the similar conditions, pure (3a) was obtained after purification by column chromatography (alumina, benzene) in 74% yield.

References and notes

- 1) G. A. Doldourous, J. Kollonitsch, J. Am. Chem. Soc., 100, 341 (1980).
- 2) D. S. Wulfman, "The chemistry of diazonium and diazo groups" S. Patai, Ed., John Wiley, New York, 1978, Chap. 8.
- 3) Thiols react with nitrosating reagents to give unstable thionitrites (RS-NO), which decompose spontaneously to disulfides. S. Oae, K. Shinhama, K. Fujimori, Y. H. Kim, Bull. Chem. Soc. Jpn., 53, 775 (1980) and cited references.
- 4) A small amount of N-alkyl benzothiazoline-2-thione (7) or disulfide (4) was isolated in some cases.
- 5) J. S. Pizey, "Synthetic Reagents, Vol. II" John Wiley, New York, 1974, p 175-311.
- 6) Other than the disulfide formation, sulfenamide (8) was isolated in 39% yield in the case of thiolbenzoic acid.
A related sulfenamide formation has been $\left[\text{PhCH}(\text{CH}_3)\text{NH-SCOPh} \right]$ (8) reported in the reaction of thionitrates (RSNO₂) with amines. S. Oae, K. Shinhama, Y. H. Kim., Bull. Chem. Soc. Jpn., 53, 1065 (1980).
- 7) The authentic chiral sulfide R-(3e) [mp. 65-66°C, $[\alpha]_D^{25} = +352.4^\circ$ (EtOH, c 2.87, 28°C)], prepared using (S)- α -methylbenzylalcohol, seems to be almost optically pure, since no change in the optical rotation after repeated recrystallization was observed.



For a related reactions, see, I. Nakagawa, T. Hata, Tetrahedron Lett., 1975, 1409. K. H. M. Walker, *ibid*, 1977, 4475.

- 8) An attempt to isolate (5) failed owing to its rapid decomposition. A possibility of N-nitroso-benzothiazoline-2-thione (9) as a key intermediate is not completely excluded. We feel, however, a somewhat similarity between thionitrite (5) and 2-(acylthio)benzothiazole (10). The latter compound (10) is known as an effective acylating reagent towards amines.

M. Ueda, A. Sato, Y. Imai, J. Poly. Sci., Polym. Chem. Ed., 16, 475 (1978).

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