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N-Nitroso Compounds. IV.1) Reaction of *N*-Nitrosourea with Thiol. A New Synthesis of Thiocarbamic *S*-Esters

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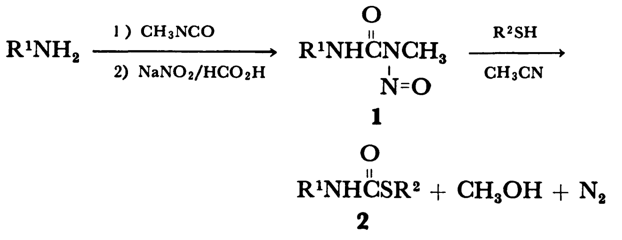
Synopsis. Thirteen thiocarbamic *S*-esters have been synthesized in good yield by the reaction of thiol with substituted *N*-methyl-*N*-nitrosourea in anhydrous acetonitrile.

Although several methods have been reported on the preparation of thiocarbamic *S*-esters, the most commonly used ones are those from alkylcarbamoyl chlorides with sodium alkanethiolates,2a) alkyl thiocyanates with alcohols,2b) or those using carbonyl sulfide with base,2a) or carbon monoxide with selenium as a catalyst.2c) Since the preparation of herbicidal thiocarbamic *S*-esters is of commercial importance, it is significant to explore an alternative route to this class of compounds.

Recently, we have shown that *N'*-substituted *N*-methyl-*N*-nitrosourea readily reacts with aliphatic amines to give "transaminated" urea in substantial yield.1) Similar S_N2 reactions have also been reported for *N*-alkyl-*N*-nitroso amides with aliphatic primary amines in refluxing dichloromethane.3) Furthermore, Challis and his co-workers observed a nucleophilic rather than a general base catalysis of imidazole in the hydrolyses of *N*-nitroso-2-pyrrolidone and related compounds in aqueous buffer solution.4) All of these results are undoubtedly related to an enhanced leaving property of the *N*-nitrosoamino moiety of the substrates. Thus a facile reaction is also expected to occur with other nucleophiles. We have now found that *N*-nitrosourea **1** reacts with various thiols under mild conditions to give the corresponding thiocarbamic *S*-esters **2** in good yields as shown in Scheme 1.



$$R^1NH_2 \xrightarrow[\text{2) NaNO}_2\text{/HCO}_2\text{H}]{\text{1) CH}_3\text{NCO}} R^1NH\overset{O}{\overset{\|}{C}}\underset{N=O}{\underset{|}{N}}CH_3 \xrightarrow[CH_3CN]{R^2SH} R^1NH\overset{O}{\overset{\|}{C}}SR^2 + CH_3OH + N_2$$

1

2

Scheme 1.

We wish to report here a convenient method of the preparation of **2** from primary amines by the use of **1** as a key compound.

Results and Discussion

N-Methylurea ($R^1NHCONHCH_3$) was obtained conventionally5) through the carbamoylation of starting amine with methyl isocyanate. On treatment of the urea with sodium nitrite in formic acid, an *N*-nitrosated urea **1** was produced exclusively; this was the product from the mononitrosation at the less hindered *N*-position.6) The crude product **1** was treated with 2 equiv of thiol in anhydrous acetonitrile at 60 °C. Because of the limited solubility and to avoid the hydrolysis of **1**,7) the use of organic solvent may be of significance. As the reaction proceeded, gas evolution was observed and in most cases, almost all quantity of **1** was consumed within several hours. However, under the same

Table 1. Yields, melting points, and IR data of **2**

Run	R^1(Amine)	R^2(Thiol)	Reaction conditions		**2**		
			Temp/°C	Time/h	Overall Yield/%a)	Mp(θ_m/°C)	IR(C=O)/cm^{-1}
1	*n*-C_4H_9	Ph	reflux	18	39	oil	1660
2	*cyclo*-C_6H_{11}	*n*-C_4H_9	60	21	77	65—66b)	1650
3	1-Adamantyl	*n*-C_4H_9	60	2	99	62—64	1670
4	Ph	C_2H_5	60	1	73	69.5—70.0	1680
5	Ph	*n*-C_4H_9	60	1	83	68—70	1670
6	Ph	*i*-C_4H_9	60	0.5	73	105—107	1670
7	Ph	*t*-C_4H_9	60	0.5	12c)	142—143	1670
8	Ph	$CH_2CH=CH_2$	60	1	91	69—70	1680
9	Ph	CH_2CH_2OH	60	0.5	71	72.5—73.5	1660
10	Ph	*cyclo*-C_6H_{11}	60	0.5	86	115.0—115.5	1660
11	Ph	*n*-$C_{10}H_{21}$	r.t.	72	69	62.5—64.0	1680
12	Ph	Ph	reflux	16	89	120—121d)	1670
13	Ph	*p*-$CH_3C_6H_4$	reflux	16	88	130.0—130.5e)	1670

a) Isolated Yield. b) 68 °C, Ref. 2b). c) Ref. 8). d) 122—124 °C, Ref. 9). e) 130—132 °C, Ref. 9).

conditions, aromatic thiol did not react with **1** even after a prolonged reaction period, so that an elevated temperature was required. After work up, the thiocarbamic *S*-ester **2** was obtained in the yields of 42—100% (39—99% based on the amine used).[8] The results are summarized in Table 1.

For synthetic purposes, the present method has some advantages in that (i) the direct reaction of **1** with alkanethiol (not sodium alkanethiolates) occurs spontaneously under rather mild conditions; (ii) by-products such as methanol and nitrogen arising from the *N*-methyl-*N*-nitrosoamino fragment can readily be eliminated, so that no tedious work up is necessary (see Experimental); (iii) in addition to the current availability of aromatic amines, it becomes possible to utilize aromatic thiols as well. Thus the present study provides an efficient new route to thiocarbamic *S*-esters.

Experimental

Mps are uncorrected. IR spectra were taken in chloroform solution by a Shimadzu IR-400 spectrophotometer. All the reagents were of commercial grade and used without further purification.

Reaction of 1 with Thiol. An *N*′-substituted *N*-methylurea was prepared in a usual fashion.[5] The urea (10 mmol) was treated by sodium nitrite (20 mmol) in formic acid (10 ml) at 0—5 °C for 1 h. The mixture was poured onto ice-water, and the precipitate formed was collected, washed with cold water, and dried under reduced pressure to yield exclusively *N*-nitrosated urea **1** (77—100% from the amine). The crude product **1** and an excess of thiol (20 mmol) were dissolved in anhydrous acetonitrile (20 ml) and the mixture was stirred at 60 °C with monitoring the reaction by TLC analysis. After **1** was consumed, evaporation of the solvent and the excess thiol under reduced pressure gave **2** in almost pure solid. When a thiol of high boiling point was used, isolation by column chromatography (silica gel, $CHCl_3$–hexane or ether–hexane) was carried out. The IR and ^1H NMR spectra of the crude solid **2** were consistent with the assigned structure. In most cases, the analytical sample was obtained by recrystallization to give a satisfactory elemental analysis within ±0.4% for C, H, N, and S. The yields and some of the physical data of **2** are summarized in Table 1.

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