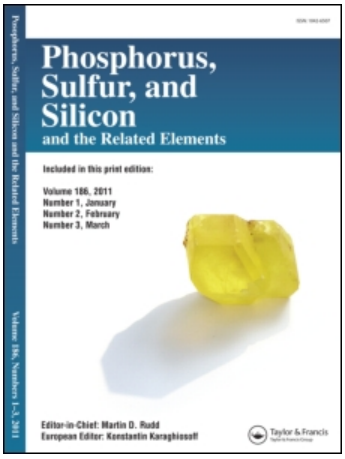

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John P. Scovill[a]
[a] Department of Chemistry, United States Military Academy, West Point, NY

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A FACILE SYNTHESIS OF THIOSEMICARBAZIDES AND THIOSEMICARBAZONES BY THE TRANSAMINATION OF 4-METHYL-4-PHENYL-3-THIOSEMICARBAZIDE

JOHN P. SCOVILL

Department of Chemistry, United States Military Academy, West Point, NY 10996

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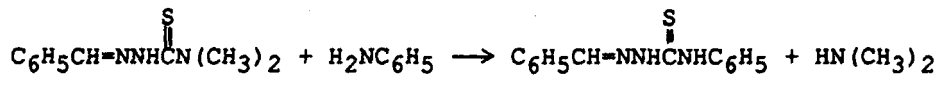
Key words: Thiosemicarbazones; thiosemicarbazides; 4-Methyl-4-phenyl-thiosemicarbazide, activated transamination reactions.

Thiosemicarbazones of α-(N)-heterocyclic ketones and aldehydes possess a broad spectrum of potentially useful chemotherapeutic activities. Thus, the antimalarial, antibacterial, and antiviral properties of this class have been explored by Klayman, et al.[1] The antileishmanial activity of a series of acetyl β-carboline thiosemicarbazones was recently described by Dodd and coworkers.[2] The α-(N)-heterocyclic thiosemicarbazones act as tridentate ligands for transition metals[3]; this property has been implicated in their biological mechanism of action.[4] The synthesis thiosemicarbazone-transition metal complexes and the spectroscopic investigation of structure and bonding in these complexes is being actively pursued.[5] In order to facilitate these investigations, an improved method of synthesizing thiosemicarbones is desirable. Such a synthesis should be efficient (high yield), general (afford thiosemicarbazones of N^4-monosubstitution or N^4,N^4-disubstitution patterns), safe (avoids toxic or unpleasant reagents and byproducts) and direct (a single step reaction which does not require the isolation of any intermediates). Klayman and Lin described the preparation of a variety of N^4-mono and N^4,N^4-disubstituted thiosemicarbazones by the displacement of the dimethylamino function of the corresponding thiosemicarbazones by a primary or secondary amine.[6] Thus, refluxing a solution of benzaldehyde 4,4-dimethyl-3-thiosemicarbazone (**A**) in acetonitrile (bp 82°C) for 6 h with two equivalents of aniline gave a 63% yield of benzaldehyde 4-phenyl-3-thiosemicarbazide (**B**). When the thiosemicarbazone substrate bore a hydrogen atom as an N^4-substitutient, low yields (ca. 20%) of thiosemicarbazones could only be obtained under forcing conditions (24 h at 109°C in toluene). This clearly established the requirement for a secondary amine as a leaving group for facile transamination at the thiocarbonyl carbon atom. With this observation in mind, the reaction might be improved further by the substitution of a phenylmethylamino group for a dimethylamino group. Substitution of the electron withdrawing pheny group for one of the methyl groups should enhance the electrophilicity of the thiocarbonyl group. Furthermore, the aromatic amine, being a

Reprint requests to: John P. Scovill, Virology Division, U.S. Army Medical Research Institute of Infectious Diseases, Ft. Detrick, Frederick, MD 21701-5011 USA.

weaker base, ought to serve as a better leaving group. In this communication, I describe the facile preparation of thiosemicarbazides (**1**) by transamination of 4-methyl-4-phenyl-3-thiosemicarbazide (**1a**), and thiosemicarbazones (**2**), by transamination of **1a** in the presence of the requisite aldehyde or ketone.



A **B**

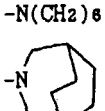
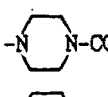
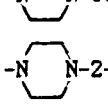
1 **2**

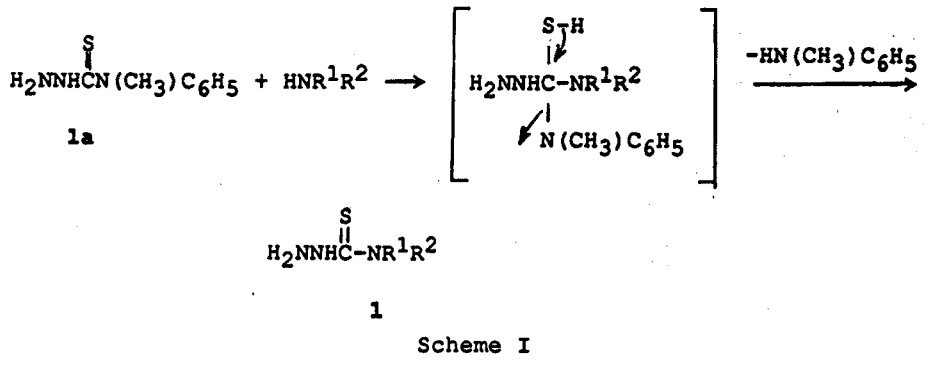
Thiosemicarbazides. Transamination of **1a** with highly nucleophilic amines proceeds readily at low temperature. Thus, refluxing a solution of **1a** in MeCN (bp 82°C) with an equivalent of pyrrolidine for 15 min gave a 72% yield of pyrrolidino-1-thiocarboxylic acid hydrazide **1b**. The morpholino analog **1c** was obtained similarly in 53% yield. Less basic amines, such as benzylamine, required a longer reaction period. The yields of the N^4-monosubstituted and N^4,N^4-disubstituted thiosemicarbazides are summarized in Table I.

The transamination reaction probably follows the standard addition-elimination mechanism (Scheme I). Nucleophilic addition of an amine to the thiocarbonyl group of **1a** produces a tetrahedral intermediate. Elimination of N-methylaniline from this intermediate reforms the thiocarbonyl group and yields a new N^4-substituted thiosemicarbazide, **1**.

TABLE I

N^4-substituted thiosemicarbazides

No.	R (S ‖ H_2NNHC-R)	mp (°C)	lit. mp	lit. ref.	Recryst. solvent	Formula	Yield (%)
1b	$-N(CH_2)_4$	172-4	173-4	7	EtOH	$C_5H_{11}N_3S$	72
1c	morpholino	174-6	175-7	7	EtOH	$C_5H_{11}N_3OS$	53
1d	$-NCH_2C_6H_5$	126-8	126-7	7	MeOH	$C_8H_{11}N_3S$	50
1e	$-N(CH_2)_6$	114-6	117	7	MeOH	$C_7H_{15}N_3S$	51
1f		164-5	164-5	1	EtOH	$C_8H_{17}N_3S$	61
1g		156-158	158-9	1	EtOH	$C_8H_{16}N_4SO_2$	63
1h		184-5	184-5	1	EtOH	$C_{10}H_{15}N_5S$	47



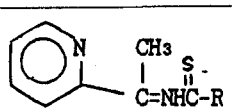
Scheme I

Thiosemicarbazones. Derivatives of 2-acetylpyridine were chosen as model compounds for evaluation of this method. Thus, reaction of 2-acetylpyridine with one equivalent each of **1a** and the requisite amine in refluxing MeOH or MeCN (15 min) gave good yields of the desired N^4-substituted 2-acetylpyridine 3-thiosemicarbazones, **2** (cf. Table II). Presumably, the mechanism of this reaction resembles that described for the formation of thiosemicarbazides. Condensation of 2-acetylpyridine with 4-methyl-4-phenyl-3-thiosemicarbazide (**1a**) results in the formation of 2-acetylpyridine 4-methyl-4-phenyl thiosemicarbazide (**C**). Attack of the thiocarbonyl group of **C** by an amine gives a tetrahedral intermediate, **D**. Loss of N-methylaniline from this intermediate results in reformation of the thiocarbonyl group and completes the transamination process (cf. Scheme II).

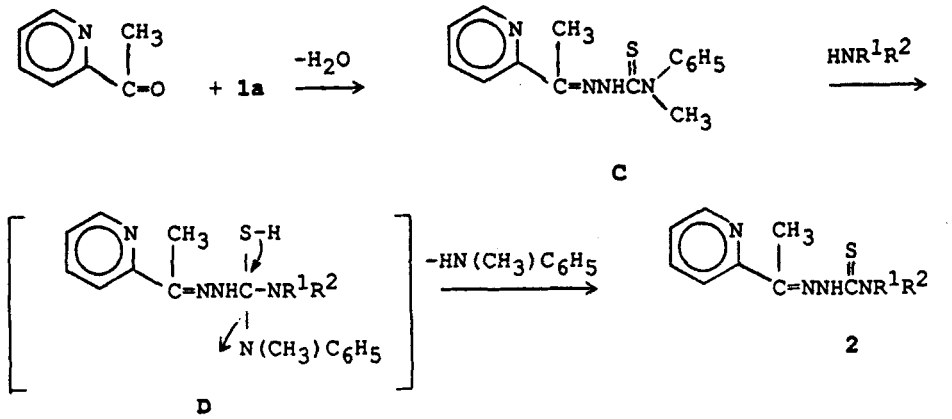
It is interesting to note that the attempted synthesis of 2-acetylpyridine 4-phenyl-3-thiosemicarbazone (**3**) by this transamination reaction resulted in the formation of aminobiurea **4**. Compound **4** can also be obtained simply by heating a solution of 2-acetylpyridine and **2a**. Evidently, the terminal amino group of 4-methyl-4-

TABLE II

N^4-Substituted 2-acetylpyridine 3-thiosemicarbazones

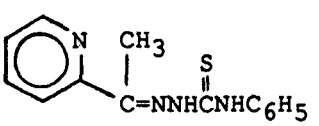


No.	R	mp, (°C)	lit. mp	lit. ref.	recryst. solvent	Formula	Yield (%)
2a	-NHCH$_2$CH$_2$NH-	214-6	214-6	8	EtOH	$C_{18}H_{22}N_8S_2$	45
2b	-NHCH$_2$CH$_2$OH	130-3	130-3	8	EtOH	$C_{10}H_{14}N_4OS$	40
2c	morpholino	187-9	182-5	9	MeOH	$C_{12}H_{16}N_4OS$	58
2d	-N(CH$_2$)$_4$	147-8	147-8	9	MeOH	$C_{12}C_{16}N_4S$	60
2e	-N(CH$_2$)$_5$	152-3	152-3	9	MeOH	$C_{13}H_{18}N_4S$	47
2f	-N(CH$_2$)$_6$	161-2	161-2	9	MeOH	$C_{14}H_{20}N_4S$	65



Scheme II

phenyl-3-thiosemicarbazide is a better nucleophile than the aromatic amino group in aniline. The scope and limitation of this reaction and its application to the synthesis of heterocycles will be discussed in subsequent papers.



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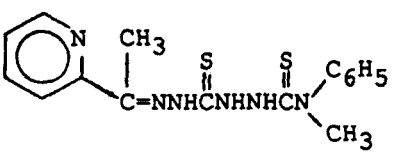

4

The results reported in this communication illustrate the utility of 4-methyl-4-phenyl-3-thiosemicarbazide (**1a**) as a reagent in the synthesis of thiosemicarbazides and thiosemicarbazones. As the methylphenylamino group of **1a** is readily replaced by aliphatic amines, this reactive thiosemicarbazide may be regarded as a transfer reagent for the thiocarbohydrizido group, **5**.

5

EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are uncorrected. PMR spectra were recorded in $CDCl_3$ with a Varian FX200 spectrometer. IR spectra were recorded on a Perkin-Elmer Model 383 spectrophotometer.

Carboxymethyl N-methyl-N-phenyldithiocarbamate. This procedure is a modification of the method of Holmberg and Psilanderhielm.[10] A mixture consisting of 12.0 mL (15.2 g, 0.20 mol) of CS_2 and 21.6 mL (21.2 g, 0.20 mol) of N-methylaniline was treated with a solution of 8.4 g (0.21 mol) of NaOH in 250 mL. After stirring at room temperature for 4 h, the organic layer had disappeared. At this point, the straw colored solution was treated with 23.2 g (0.20 mol) of sodium chloroacetate and allowed to stand overnight (17 h). The solution was acidified with 25 mL of conc. HCl and the solid which separated was collected and dried. This afforded 39.7 g (82%) of the pale buff colored carboxymethyl N-methyl-N-phenyldithiocarbamate, mp 197–198°C.

4-Methyl-4-phenyl-3-thiosemicarbazide (**1a**). This procedure is an improvement of the method of Stanovnik and Tisler.[11] A solution of 17.7 g (0.0733 mol) of carboxymethyl N-methyl-N-phenyldithiocarbamate in 20 mL of 98% hydrazine hydrate and 10 mL of water was heated on the rings of the steam bath (85°C). After 3 min crystals began to separate. Heating was continued an additional 22 min. The crystals were collected by filtration, washed well with water and dried under a heat lamp. The crude product was recrystallized from a mixture of 50 mL of EtOH and 25 mL of water (norit). This gave 10.8 g (81%) of stout colorless rods of 4-methyl-4-phenyl-3-thiosemicarbazide (**1a**), mp 124–125°C. It is interesting to note that this compound resolidifies with continued heating at 130°C.

Pyrrolidine-1-thiocarboxylic acid hydrazide (**1b**). The general method for the synthesis of thiosemicarbazides is exemplified in this preparation: a solution of 1.00 g (5.52 mmol) of 4-methyl-4-phenyl-3-thiosemicarbazide (**1a**) in 5 mL of MeCN was treated with 392 mg (5.52 mmol) of pyrrolidine and the solution heated at reflux for 15 min. The solution was chilled and the crystals which separated were collected and washed well with MeCN. This afforded 574 mg (72%) of colorless needles of pyrrolidine-1-thiocarboxylic acid hydrazide (**1b**), mp 172–174°C dec.

Morpholine-4-thiocarboxylic acid 2-[1-2-pyridinyl)ethylidene]hydrazide (**2c**). The general method for the synthesis of thiosemicarbazones is exemplified in this preparation: A solution 1.00 g (5.52 mmol) of 4-methyl-4-phenyl-3-thiosemicarbazide (**1a**) in 5 mL of MeCN was treated with 480 mg (5.52 mmol) of morpholine and 668 mg (5.52 mmol) of 2-acetylpyridine. The solution was heated at reflux for 15 min. The solution was chilled and the crystals which separated were collected and washed well with MeCN. This afforded 850 mg (58%) of stout yellow rods of morpholine-4-thiocarboxylic acid 2-[1-(2-pyridinyl)ethylidene]hydrazide (**2c**), mp 187–189°C dec.

1-Methyl-1-phenyl-6-[1-(2-pyridinyl)ethylidene]amino-2,5-dithiobiurea (**4**). A solution of 1.83 g (10 mmole) of 4-methyl-4-phenyl-3-thiosemicarbazide **2a** and 660 mg (5 mmole) of 2-acetylpyridine in 6 mL of MeCN was heated at 60°C for 45 min. The solution was chilled and the crystals which separated were recrystallized from MeCN. This afforded 1.62 g (89%) of pale yellow needles of **4**, mp 154–155°C: ir (KBr) 3260, 3210, 1595, 1588, 1562, 1485, 1436, 1412, 1343, 1272, 1215, 1105, 884 and 700 cm^{-1}; nmr ($CDCl_3$) ppm 8.86 (s, 1H, NH), 8.64, (s, 1H, NH), 8.57 ("d", J = 4.5 Hz, H_6), 8.18 ("d", J = 8 Hz, H_3), 7.72 ("t of ds", 1H, J = 8 Hz, J = 2 Hz), 7.45 (m, 6H), 3.69 (s, 3H, N—CH_3), 2.39 (s, 3H, C—CH_3).
Anal. Calc'd for $C_{16}H_{18}N_6S_2$: C, 53.61; H, 5.06; N, 23.44; S, 17.89. Found: C, 53.67; H, 5.06; N, 23.28; S, 18.01.

REFERENCES AND NOTES

1. For the most recent paper in this series, see D. L. Klayman, A. J. Lin, J. M. Hoch, J. P. Scovill, C. Lambros and A. S. Dobeck, *J. Pharm. Sci.*, **73,** 1763 (1984).
2. R. H. Dodd, C. Ouannes, M. Robert-Gero and P. Potier, *J. Med. Chem.*, **32,** 1272 (1989).
3. J. P. Scovill, D. L. Klayman and C. Franchino, *J. Med. Chem.*, **25,** 1261 (1982).
4. E. C. Moore, M. S. Zadek, K. C. Agrawal and A. C. Sartorelli, *Biochemistry*, **23,** 4492 (1970).
5. For recent papers, see B. S. Garg, M. R. P. Kurup, S. K. Jain and Y. K. Bhoon, *Trans. Met. Chem.*, **13,** 247 (1988); B. S. Garg, M. R. P. Kurup, S. K. Jain and Y. K. Bhoon, *Trans. Met. Chem.*, **13,** 309 (1988); D. X. West, C. S. Carlson, A. C. Whyte and A. Lamberta, *Trans. Met Chem.*, **15,** 43 (1990).
6. D. L. Klayman and A. J. Lin, *Org. Prep. Proc. Int.*, **16,** 79 (1984).
7. R. S. McElhinney, *J. Chem. Soc. (C)*, 950 (1966).
8. D. L. Klayman, J. F. Bartosevich, T. Scott Griffen, C. J. Mason and J. P. Scovill, *J. Med. Chem.*, **22,** 855 (1979).
9. D. L. Klayman, J. P. Scovill, J. F. Bartosevich and C. J. Mason, *J. Med. Chem.*, **22,** 1367 (1979).
10. B. Holmberg and B. Psilanderhielm, *J. Prakt. Chem.*, **82,** 440 (1910).
11. B. Stanovnik and M. Tisler, *J. Org. Chem.*, **25,** 2234 (1960).