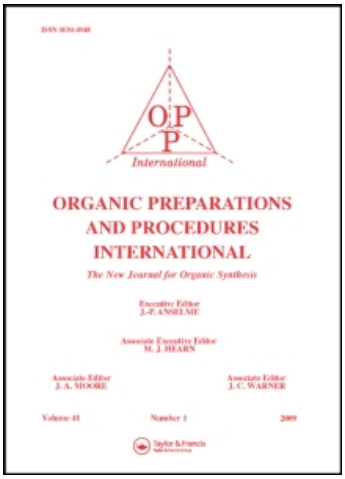

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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To cite this Article Klayman, Daniel L. and Lin, Ai J.(1984) 'THIOCARBONYL-ACTIVATED TRANSAMINATION. A FACILE SYNTHESIS OF N⁴-MONO AND N⁴,N⁴-DISUBSTITUTED THIOSEMICARBAZONES', Organic Preparations and Procedures International, 16: 2, 79 — 83
To link to this Article: DOI: 10.1080/00304948409356169
URL: http://dx.doi.org/10.1080/00304948409356169

ORGANIC PREPARATIONS AND PROCEDURES INT. 16(2), 79-83 (1984)

THIOCARBONYL-ACTIVATED TRANSAMINATION. A FACILE SYNTHESIS OF N^4-MONO AND N^4,N^4-DISUBSTITUTED THIOSEMICARBAZONES

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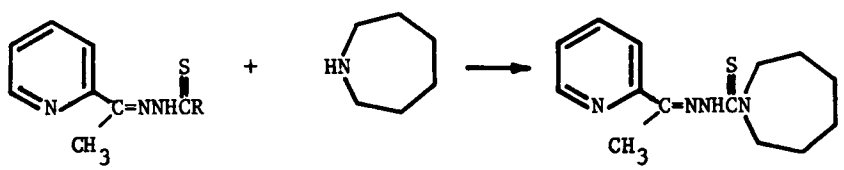
The exchange of the amino function of several thioamides, thioureas, and thiosemicarbazones by ammonia and amines has been reported. For example, thioamides have been found to react with amines to form either amidines, by displacement of the thio function, or other thioamides, by a transamination process.[1-3] Reaction of thiourea[4] or acetone thiosemicarbazone[5] with ammonia or amines requires forcing conditions, i.e., extended heating in toluene or heating in a sealed tube. This communication describes a facile procedure for 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 related 4,4-dimethyl-3-thiosemicarbazones by a primary or secondary amine. Derivatives of methyl 2-pyridinyl ketone (1) were chosen as model compounds for evaluation of this method.

In order to determine the optimum leaving group, the reaction was performed in refluxing CH_3CN with the methyl 2-pyridinyl ketone thiosemicarbazones (1) and one equivalent of hexamethyleneimine for 6 hrs (Eq. 1).

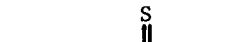


(1)

a) R = NH_2 b) R = NHMe c) R = NMe_2

1 2

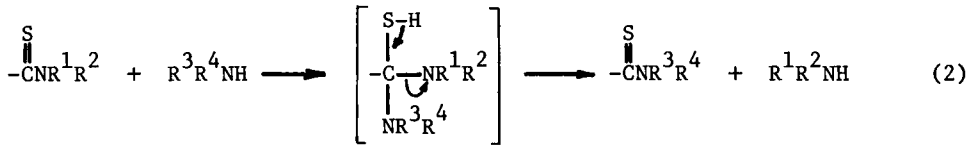
Reactions with the unsubstituted thiosemicarbazone 1a and the monosubstituted thiosemicarbazone 1b, which require the elimination of ammonia and methylamine, respectively, led to the recovery of unchanged starting materials; however, with 1c, which requires the elimination of dimethylamine, there was obtained a good yield of thiosemicarbazone 2. In boiling toluene for 24 hrs, thiosemicarbazones 1a and 1b gave a 14% and 25% yield of 2, respectively. The superiority of the dimethylamino as a leaving group in the transamination reaction was, thus, evident. The scope of the reaction was further probed using several primary and secondary amines with 1c (Table 1) and the thiosemicarbazone, N,N-dimethyl-2-(phenylmethylene)hydrazinecarbothioamide, 3 (Table 2). Over-



3

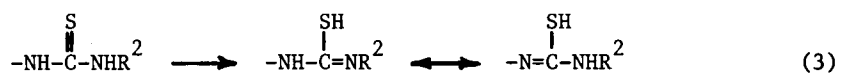
all, it was found that good yields of the desired thiosemicarbazones were obtained by this transamination reaction. However, virtually no reaction occurred when N-methylaniline, p-nitroaniline, or 2,6-dimethylpiperidine were heated with 1c in CH_3CN up to 24 hrs, i.e., when the amine lacked sufficient basicity or was sterically hindered.

The transamination reaction described above may be portrayed as taking place via a tetrahedral intermediate, as shown in Eq. 2. However,



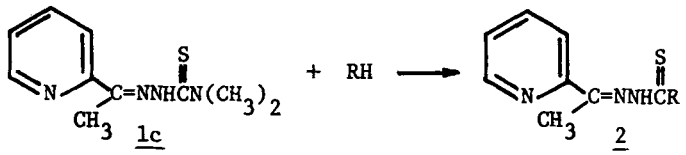
(2)

when R^1 = H or R^1 = R^2 = H, tautomerization is possible (Eq. 3) which



(3)

TABLE 1. Methyl 2-Pyridinyl Ketone Thiosemicarbazones from 1c



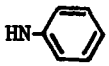
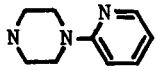
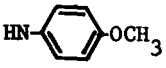
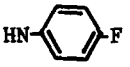
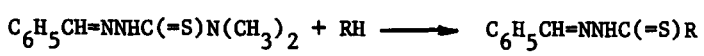
R	mp (C°)	Recryst. solvent	Reaction time (hrs)	Yield (%)
$HNCH_2CH_2OH$	129-131	CH_3CN	6	63
	182-183	EtOH	6	59
	164-166	CH_3CN	6	65
	180-181	CH_3CN	6	75
$HNCH_2C_6H_5$	149-151	CH_3CN	6	75
	192-194	EtOH	24	10
	175-176	CH_3CN	6	67
	170-171	CH_3CN	24	50

TABLE 2. Benzaldehyde Thiosemicarbazones from 3



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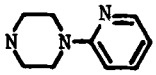
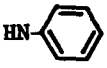
R	mp (C°)	Recryst. solvent	Reaction time (hrs)	Yield (%)
	139-140	EtOH	6	56
	164-166	CH_3CN	6	73
	179-181[12]	EtOH	6	63

can reduce the electrophilicity of the thiocarbonyl carbon atom and, thus, diminish the likelihood of the occurrence of a transamination reaction. Related reactions of thiosemicarbazones, such as the borohydride reduction of the azomethine bond[6] and a cyclodesulfurization reaction,[7] are influenced indirectly by the presence or absence of a proton on the terminal thiosemicarbazone nitrogen atom.

The amine displacement reaction reported here is a useful alternative to the related method for the construction of thiosemicarbazones by the reaction of amines with methyl alkylidenehydrazinecarbodithioates.[8]

EXPERIMENTAL

Melting points were determined on a Hoover-Thomas melting point apparatus and are uncorrected. Elemental analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI. Satisfactory analyses (± 0.3% of the calculated values) were obtained for all new compounds. PMR spectra were recorded in $CDCl_3$ on a JEOL FX90Q spectrometer. Mass spectra were determined on a Finnigan Model 3100D GC/MS Spectrometer.

N,N-Dimethyl-2-(phenylmethylene)hydrazinecarbothioamide (3).- Benzaldehyde (1.8 g, 0.0168 mole) and 4,4-dimethyl-3-thiosemicarbazide (2.0 g, 0.0168 mole)[9] in 25 ml of 95% EtOH was heated at reflux on steam bath for 24 hrs. After cooling, compound 3 (2.5 g, 71%) was collected and recrystallized from $CHCl_3$/EtOH to give fine white crystals, mp. 162-164°, lit.[10,11] mp. 161-162°, 167-168°. NMR ($CDCl_3$): δ 3.44 [s, 6H, $-N(CH_3)_2$], 7.26-7.65 (m, 5H, Ar-H), 7.72 (s, 1H, Ar-CH=N-), 9.08 (s, 1H, -NH-); GC/MS: m/z 208 (M+1).

General Transamination Reaction.- N,N-Dimethyl-2-[1-(2-pyridinyl)ethylidene]hydrazinecarbothioamide (1c)[9] (0.44 g, 2 mmoles) and 2 mmoles of amine in 15 ml of CH_3CN was heated under reflux for 6 hrs. The solution was reduced to one-half volume in vacuo and cooled. The crystals

which separated were collected and recrystallized.

Compound 3 was treated with amines in the identical manner as described above.

REFERENCES

1. R. N. Hurd and G. DeLamater, Chem. Revs., 61, 45 (1961).
2. A. Reissert and K. Brüggemann, Ber., 57, 981 (1924).
3. M. J. Schlatter, J. Am. Chem. Soc., 64, 2722 (1942).
4. T. L. Davis and K. C. Blanchard, ibid., 45, 1816 (1923).
5. W. Baird, K. Burns, and F. J. Wilson, J. Chem. Soc., 2527 (1927).
6. D. L. Klayman, J. P. Scovill, J. F. Bartosevich, and J. Bruce, J. Med. Chem., 26, 35 (1983).
7. A. J. Lin, Manuscript in preparation.
8. D. L. Klayman, J. F. Bartosevich, T. S. Griffin, 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, ibid., 22, 1367 (1979).
10. E. Lieber, C. N. Pillai, and R. D. Hites, Can. J. Chem., 35, 832 (1957).
11. C. Yamazaki, ibid., 53, 610 (1975).
12. K. Miyatake, J. Pharm. Soc. Japan, 73, 460 (1953).

(Received November 21, 1983; in revised form February 14, 1984)