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Reactions of Phenylhydrazinium Thiocyanate with Ketones and Aldehydes

Isamu ARAI
Department of Chemistry, College of Science, Rikkyo (St. Paul's) University,
Nishi-Ikebukuro, Toshima-ku, Tokyo 171

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Reactions of phenylhydrazinium thiocyanate with various ketones and aldehydes gave 1-phenyl-3-alkyl-5-mercapto-Δ^4-1,2,4-triazoline compounds in 80—90% yield by the cycloaddition of thiocyanic acid to the phenylhydrazones intermediately formed from phenylhydrazine and the ketones or aldehydes. Their structure were determined by elemental analyses, spectral data (IR, NMR, and MS) and chemical reactions. Many 2-phenylthiosemicarbazone and 1-phenyl-1,2,4-triazole derivatives were synthesized in good yields.

We have reported that hydrazinium thiocyanate (I') reacts with aldehydes and ketones to give 1,2,4-triazolidine (II') and triazolo-triazole (III') compounds.[1]

We considered that the 1,2,4-triazolidine compounds (II') were produced by the cycloaddition of thiocyanic acid to the hydrazones intermediately formed from ketones or aldehydes with hydrazine. Attempts to isolate these intermediate hydrazones from the reaction mixture failed because the hydrazones were not stable and readily changed to the corresponding azines.[2]

In this paper we deal with the formation of 1,2,4-

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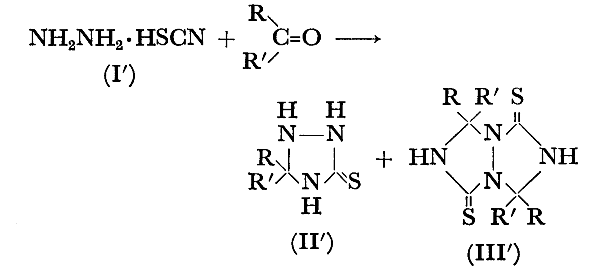
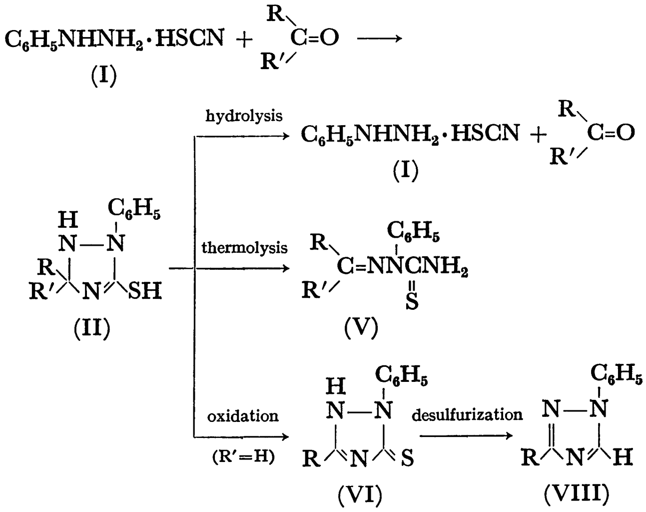
[1] I. Arai, S. Abe, and A. Hagitani, This Bulletin, **46**, 677 (1973).

[2] H. H. Szmant and C. Mc Ginnis, *J. Amer. Chem. Soc.*, **72**, 2890 (1950).





triazolidine compounds and their derivatives, using phenylhydrazine as the starting material instead of hydrazine. New useful methods are given for the preparation of 2-phenylthiosemicarbazone and 1-phenyl-1,2,4-triazole derivatives.

Results and Discussion

When a ketone or aldehyde was added to an aqueous solution of phenylhydrazinium thiocyanate (I) and the mixture was allowed to stand at room temperature, 1-phenyl-3-alkyl-5-mercapto-Δ^4-1,2,4-triazoline (II) was obtained in an 80—90% yield. Elemental analyses (Table 1) and mass spectral data of (II) gave a reasonable molecular formula. The IR spectra of (II) showed absorption bands at 3135—3136 (NH) and 1590—1595 (C=N) cm^{-1}, and the NMR spectral data of (II) also gave a reasonable structure (see Experimental). From these data and the results of chemical reactions (hydrolysis, thermolysis, oxidation, and desulfurization) of (II), the structure was assigned to be 1-phenyl-3-alkyl-5-mercapto-Δ^4-1,2,4-triazoline.

This was also supported by the mass spectral data of (II); *i.e.*, peaks of $C_6H_5NCS^+$ and $C_6H_5NH^+$ at *m/e* 135 and 92 respectively. Fragmentations resulting from the loss of R, R' or HSCN from the molecular ion were also observed.

The yields of the products are given in Table 2 and those of (IIa) *versus* reaction time in Fig. 1.

From the above results and those of previous work,[1] the following path is proposed for the formation of (II). First the ketone or aldehyde reacts with phenylhydrazine in the presence of an acid catalyst to produce phenylhydrazone (IV). The intermediate then reacts with thiocyanic acid to form (II). Formation of this

Table 1. 1-Phenyl-3-alkyl-5-mercapto-Δ^4-1,2,4-triazoline (II)

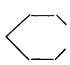
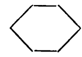
II	R	R'	Mp (decomp) (°C)	Formula	Analysis (%) Found (Calcd) C	H	N	S
IIa	CH_3	CH_3	134.0	$C_{10}H_{13}N_3S$	57.85	6.71	20.25	15.19
					(57.96)	(6.32)	(20.28)	(15.44)
IIb	C_2H_5	CH_3	113.5	$C_{11}H_{15}N_3S$	59.92	6.85	19.38	14.43
					(59.71)	(6.83)	(18.99)	(14.46)
IIc	*n*-C_3H_7	CH_3	112.0	$C_{12}H_{17}N_3S$	61.18	7.94	17.80	
					(61.24)	(7.28)	(17.85)	
IId	*iso*-C_3H_7	CH_3	130.5	$C_{12}H_{17}N_3S$	61.13	6.70	18.26	
					(61.24)	(7.28)	(17.85)	
IIe	*t*-C_4H_9	CH_3	167.0	$C_{13}H_{19}N_3S$	61.99	7.95	16.81	
					(62.62)	(7.68)	(16.85)	
IIf	*iso*-C_4H_9	CH_3	136.5	$C_{13}H_{19}N_3S$	62.69	7.30	16.58	
					(62.62)	(7.68)	(16.85)	
IIg	C_2H_5	C_2H_5	119.0	$C_{12}H_{17}N_3S$	61.22	7.40	17.64	13.35
					(61.24)	(7.28)	(17.85)	(13.16)
IIh			148.8	$C_{13}H_{17}N_3S$	62.91	6.70	16.99	
					(63.12)	(6.93)	(16.99)	
IIi	CH_3	H	96.5	$C_9H_{11}N_3S$	55.71	6.15	21.35	
					(55.93)	(5.74)	(21.74)	
IIj	C_2H_5	H	125.0	$C_{10}H_{13}N_3S$	58.31	6.30	20.06	
					(57.96)	(6.32)	(20.28)	
IIk	*n*-C_3H_7	H	125.5	$C_{11}H_{15}N_3S$	59.51	7.21	18.76	
					(59.71)	(6.83)	(18.99)	
IIl	*iso*-C_3H_7	H	130.0	$C_{11}H_{15}N_3S$	59.98	7.11	18.79	
					(59.71)	(6.83)	(18.99)	

Table 2. Reactions of phenylhydrazinium thiocyanate (I) with ketones and aldehydes

Ketone	Yield (%) of (II)	Aldehyde	Yield (%) of (II)
CH_3COCH_3	78.7	CH_3CHO	78.3
$C_2H_5COCH_3$	83.5	C_2H_5CHO	84.6
n-$C_3H_7COCH_3$	77.4	n-C_3H_7CHO	87.6
iso-$C_3H_7COCH_3$	80.7	iso-C_3H_7CHO	92.6
t-$C_4H_9COCH_3$	70.3		
iso-$C_4H_9COCH_3$	53.6		
$C_2H_5COC_2H_5$	90.2		
=O	93.4		

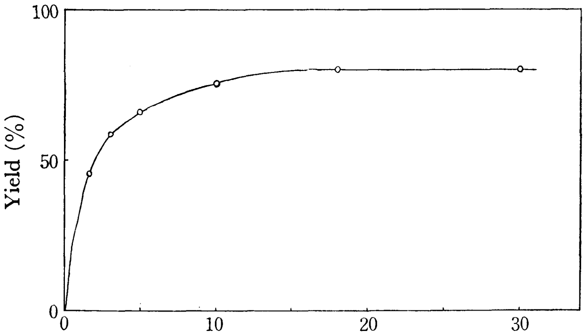
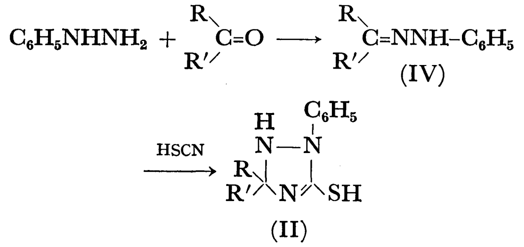


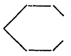
Fig. 1. Yield of (IIa) *versus* reaction time, $C_6H_5NHNH_2\cdot HSCN$ (0.05 mol), acetone (0.05 mol), and water (200 ml)



intermediate (IV) was detected by tlc[3] and confirmed by isolating it from the reaction mixture.

Reactions (IV)+HSCN→(II) were carried out to confirm the above path. (II) was obtained in higher yields (Table 3) than in the original reactions ((I)+$\genfrac{}{}{0pt}{}{R'}{R}\!>\!C{=}O$→(II)). The results reveal that the reactions of (I) with ketones or aldehydes pass through phenylhydrazone (IV) as an intermediate, and those of (I') also pass through hydrazone.

Table 3. Reactions of phenylhydrazones(IV) with thiocyanic acid

IV	$\genfrac{}{}{0pt}{}{R}{R'}\!>\!C{=}NNH\text{-}C_6H_5$ (IV)		Yield (%) of (II)
	R	R'	
IVa	CH_3	CH_3	91.2
IVb	C_2H_5	CH_3	93.7
IVc	n-C_3H_7	CH_3	92.8
IVd	iso-C_3H_7	CH_3	89.9
IVe	t-C_4H_9	CH_3	94.6
IVf	iso-C_4H_9	CH_3	81.2
IVg	C_2H_5	C_2H_5	91.1
IVh			92.7
IVi	CH_3	H	80.0
IVj	C_2H_5	H	88.9
IVk	n-C_3H_7	H	95.0
IVl	iso-C_3H_7	H	90.2

Thermolysis of (II) gave 2-phenyl-thiosemicarbazone (V) almost quantitatively. This is a convenient method for synthesizing thiosemicarbazone derivatives since to synthesize them by the conventional method requires several steps.[4]

Oxidation of (IIi—l) gave 1-phenyl-3-alkyl-Δ^3-1,2,4-triazoline-5-thione (VI). This is also a new method to synthesize Δ^3-1,2,4-triazoline-5-thione derivatives and demonstrates the interesting fact that the hydrogen atom attached to a ring carbon of an saturated heterocyclic compound is easily released under mild conditions. Table 4 shows the yields and elemental analyses of (VI).

(VI) was readily methylated with dimethyl sulfate or methyl iodide to give 1-phenyl-3-alkyl-5-methylthio-1,2,4-triazole (VII). (VII) was further desulfurizated with Raney nickel to give 1-phenyl-3-alkyl-1,2,4-triazole (VIII). (VIII) was also prepared by desulfurization of (VI) with Raney nickel. (VIII) was identified by comparison (mp and UV) with an authentic sample.[5] The reactions indicated the presence of a 1,2,4-triazoline skeleton in (II). They also represent a new

Table 4. 1-Phenyl-3-alkyl-Δ^3-1,2,4-triazoline-5-thione (VI)

VI	R	Mp (°C)	Yield (%)	Formula	Analysis (%) Found (Clacd)		
					C	H	N
VIi	CH_3	177.0—178.0	58.62	$C_9H_9N_3S$	56.47 (56.52)	4.73 (4.74)	21.96 (21.97)
VIj	CH_3	147.0—147.5	57.56	$C_{10}H_{11}N_3S$	58.49 (58.51)	5.40 (5.40)	20.47 (20.47)
VIk	n-C_3H_5	135.5—136.5	62.57	$C_{11}H_{13}N_3S$	60.19 (60.25)	5.99 (5.97)	19.25 (19.16)
VIl	iso-C_3H_7	161.5—162.2	79.08	$C_{11}H_{13}N_3S$	60.29 (60.25)	5.98 (5.97)	19.17 (19.16)

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[3] On silica gel with methanol–chloroform (1: 100 v/v).

[4] "Beilsteins Handbuch der Organischen Chemie," Vol. 15, 281.

[5] M. R. Atkinson, E. A. Parkes, and J. B. Polya, *J. Chem. Soc.*, **1954**, 4256.

useful method for the preparation of 1,2,4-triazole derivatives.

Experimental

All melting and boiling points are uncorrected. The IR spectra were recorded from KBr pellets, using a 215 Hitachi grating infrared spectrophotometer. The NMR spectra were measured in a solution of deuteriochloroform with a JNM C-60HL spectrometer using tetramethylsilane as an internal standard. The mass spectra were obtained on a CEC 21-110B spectrometer at 70 eV.

Reaction of Phenylhydrazinium Thiocyanate (I) with Ketone and Aldehyde. Ketone or aldehyde (0.05 mol) was added dropwise to a solution of phenylhydrazine hydrochloride (7.23 g, 0.05 mol) and sodium thiocyanate (4.05 g, 0.05 mol) in 0.25 M hydrochloric acid (200 ml) with stirring. The solution was stirred at room temperature for 18 hr under shield from light. A white precipitate formed which was filtered and washed with water several times. It was recrystallized with 1,2-dichloroethane to give 1-phenyl-3-alkyl-5-mercapto-Δ^4-1,2,4-triazoline (II).

(IIa): IR; 3150, 2970, 1595, 1490, 1380, 1170, 745 cm^{-1}. NMR; δ 1.50 (s, $-CH_3$), 4.80 (s, -SH), 7.18—8.20 ($-C_6H_5$ and -NH-). Mass spectra; *m/e* 207 ($C_{10}H_{13}N_3S^+$), 192 ($C_9H_{10}N_3S^+$), 148 ($C_9H_{12}N_2^+$), 135 ($C_6H_5NCS^+$), 92 (C_6H_5-NH^+).

(IIi): IR; 3150, 2960, 1590, 1475, 1400, 1239, 760 cm^{-1}. NMR; δ 1.45 (d, J=6.0 Hz, $-CH_3$), 4.75 (broad s, -SH) 4.92 (q, J=6.0 Hz, =CH-), 7.00—8.20 ($-C_6H_5$ and -NH-). Mass spectra; *m/e* 193 ($C_9H_{11}N_3S^+$), 191 ($C_9H_9N_3S^+$), 178 ($C_8H_8N_3S^+$), 135 ($C_6H_5NCS^+$), 134 ($C_8H_{10}N_2^+$), 92 (C_6H_5-NH^+).

Phenylhydrazone (IV). To a cooled solution of 0.1 mol of phenylhydrazine in ether (100 ml) were added 0.1 mol of ketone or aldehyde and a few drops of acetic acid and the solution was heated for several minutes. Sodium hydroxide was added to the solution, and it was allowed to stand at room temperature overnight. The ethereal solution was separated from the sodium hydroxide by decantation and then evaporated. The residue was distilled under reduced pressure to give ketone or aldehyde phenylhydrazone (IV).

(IVa); bp 127.0 °C/9.5 mmHg, (IVb); bp 136.5—137.5 °C/7.5 mmHg, (IVc); bp 158.0—160.0 °C/18.5 mmHg, (IVd); bp 156.0—157.0 °C/21.0 mmHg, (IVe); bp 111.8—113.8 °C/1.5 mmHg, (IVf); bp 127.0—128.7 °C/3.0 mmHg, (IVg); bp 157.0—158.0 °C/20.0 mmHg, (IVh); mp 73.0—75.0 °C, (IVi); bp 110.0—111.0 °C/3.5 mmHg, (IVj); bp 126.0—128.5 °C/7.0 mmHg, (IVk); bp 110.0—111.5 °C/2.0 mmHg, (IVl); bp 142.5—144.0 °C/16.0 mmHg.

Reaction of Phenylhydrazone(IV) with Thiocyanic Acid. Sodium thiocyanate (8.10 g, 0.05 mol) was added in one portion to a solution of 0.05 mol of (IV) in acetic acid (40 ml) with stirring. The solution was stirred at room temperature for 18 hr with a light shield. A white precipitate formed which was filtered and washed with water. It was recrystallized with dichloroethane to give 1-phenyl-3-alkyl-5-mercapto-Δ^4-1,2,4-triazoline (II).

Hydrolysis of 1-Phenyl-3,3-dimethyl-5-mercapto-Δ^4-1,2,4-triazoline (IIa). A mixture of 1.0 g of (IIa) in water (30 ml) was refluxed for a few minutes, and distilled at atmospheric pressure until 5 ml of a solution was collected. The distillate was poured into a solution of 2,4-dinitrophenylhydrazine in 6 M hydrochloric acid. A yellow precipitate formed which was filtered and recrystallized from ethanol to give acetone 2,4-dinitrophenylhydrazone, mp 125 °C. The liquor remaining on distillation was evaporated under reduced pressure, and chloroform was added to the residue. An insoluble material (0.40 g) was recrystallized with methanol–ether to give phenylhydrazinium thiocyanate (I), mp 108 °C (decomp). The products were identified by comparison (IR spectra and mp) with an authentic sample.

Thermolysis of 1-Phenyl-3,3-dimethyl-5-mercapto-Δ^4-1,2,4-triazoline (IIa). A solution of 1.0 g of (IIa) in 2-butanol (50 ml) was refluxed for 1.5 hr, and then evaporated under reduced pressure. The residue (1.0 g) was recrystallized from 75 vol% ethanol to give acetone 2-phenylthiosemicarbazone (Va), mp 133.0—134.0 °C (lit,[4] mp 135.0 °C).

Found: C, 57.94; H, 6.32; N, 20.27%. Calcd for $C_{10}H_{13}$-N_3S: C, 58.18; H, 6.41; N, 20.23%.

Oxidation of 1-Phenyl-3-alkyl-5-mercapto-Δ^4-1,2,4-triazoline (IIi—l). Oxygen was passed into a mixture of 1.0 g of (IIi—l) in 1 M sodium hydroxide (100 ml) with stirring until (IIi—l) was dissolved. The solution was then acidified with 1 M hydrochloric acid. A white precipitate formed which was filtered and recrystallized from 50 vol% ethanol to give 1-phenyl-3-alkyl-Δ^3-1,2,4-triazoline-5-thione (VI).

IR of (VIi): 3000, 2890, 2700, 1610, 1490, 1225, 1010, 755, 687 cm^{-1}. NMR of (VIi): δ 2.36 (s, $-CH_3$), 7.30—8.25 ($-C_6H_5$ and -NH-).

Methylation of 1-Phenyl-3-methyl-Δ^3-1,2,4-triazoline-5-thione (VIi). 1) With methyl iodide. A solution of 2.0 g of (VIi) and methyl iodide (1.48 g) in ethanol (50 ml) was refluxed for 3.5 hr, and then evaporated under reduced pressure. Fifty milliliters of 1 M sodium hydroxide was added to the residue, and the mixture was extracted with chloroform. The extract was evaporated. The residue (2.07 g) gave 1-phenyl-3-methyl-5-methylthio-1,2,4-triazole (VIIi). (VIIi) was an oil and formed a hydrochloride, mp 141 °C decomp. (from tetrahydrofuran).

Found: C, 49.60; H, 4.87; N, 17.73%. Calcd for $C_{10}H_{12}$-N_3SCl: C, 49.69; H, 5.01; N, 17.38%. IR: 2990, 2600, 2470, 1595, 1585, 1505, 1480, 1245, 1025, 770, 690 cm^{-1}. NMR: δ 2.78 (s, $-CH_3$), 3.20 (s, $-SCH_3$), 7.68 (s, $-C_6H_5$).

2) With dimethyl sulfate. To a cooled solution of 0.5 g of (VIi) in 1 M sodium hydroxide (20 ml) was added dropwise dimethyl sulfate (0.33 g). The mixture was then stirred at room temperature for 24 hr and extracted with chloroform. The extract was evaporated and the residue (0.34 g) gave (VIIi).

1-Phenyl-3-methyl-1,2,4-triazole (VIIIi). 1) A mixture of 0.5 g of 1-phenyl-3-methyl-Δ^3-1,2,4-triazoline-5-thione (VIi) and *ca.* 5 g of Raney nickel (W-2) in ethanol (25 ml) was refluxed for 24 hr. The solution of ethanol was then separated from Raney nickel by filtration and evaporated. The residue (0.34 g) was recrystallized with *n*-hexane to give (VIIIi), mp 89.5 °C (lit,[5] mp 89.0 °C).

Found: C, 68.10; H, 6.00; N, 26.27%. Calcd for C_9H_9-N_3: C, 67.91; H, 5.70; N, 26.40%. IR: 3100, 1600, 1530, 1500, 1310, 765, 695 cm^{-1}. UV λ_{max}^{EtOH} 244 nm (lit,[5] 244 nm). NMR: δ 2.53 (s, $-CH_3$), 7.35—7.90 ($-C_6H_5$), 8.59 (s, =CH-).

2) A mixture of 1.0 g of 1-phenyl-3-methyl-5-methylthio-1,2,4-triazole (VIIi) and *ca.* 10 g of Raney nickel (W-2) was refluxed for 24 hr. It was worked up as in the previous experiment to give (VIIIi), 0.70 g.

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