Reactions of Thiocarboxylic Acids with Oximes and Nitrones. A New Synthesis of Thiones

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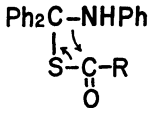
The reactions of ketone derivatives containing carbon-nitrogen double bond such as oximes (**3**), *N*-alkyloximes (nitrones, **11**), oxime *O*-alkyl ethers, phenylhydrazones and semicarbazones with thiocarboxylic acids were studied for the purpose of preparing thioketones. Both **3** and **11** reacted with thiocarboxylic acids to give thioketones in good yields. The reaction did not proceed in the cases of other ketone derivatives, the starting materials being recovered. The reaction of benzophenone oxime with thiobenzoic acid gave thiobenzophenone, dibenzoyl disulfide and ammonium benzoate, while that of benzophenone-*N*-methylnitrone with thioacetic acid gave thiobenzophenone and *N*-acetyl-*N*-methylhydroxylamine. The mechanisms of these reactions are presented.

Various procedures for the preparation of thiones including the thionation of ketones by hydrogen sulfide or phosphorus pentasulfide have been worked out.[1,2] Conversion of ketodichlorides[3] or ketimines[4] (Scheme 1) into thiones by the action of thiocarboxylic acids have been used for preparing diaryl or heterocyclic thiones. We were interested in these simple synthetic methods using thiocarboxylic acids and have examined the reaction of more readily available derivatives of ketones such as oximes, nitrones, hydrazones, and semicarbazones with thiobenzoic (**1**) or thioacetic acid (**2**).

$$Ph_2C{=}NPh + RCOSH \longrightarrow$$



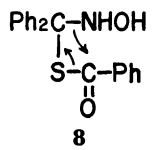
$$\longrightarrow Ph_2C{=}S + RCONHPh \quad (1)$$

Results and Discussion

When benzophenone oxime (**3a**) was mixed with an equimolar amount of **1** in benzene at room temperature, thiobenzophenone (**4a**) was obtained in low yield after being left to stand for 3 days. However, ammonium benzoate (**5**) and dibenzoyl disulfide (**6**) were formed as by-products instead of benzohydroxamic acid (**7**) which was expected to be formed according to the following scheme. Since **7** does not react with **1**, **3a**

$$Ph_2C{=}NOH + PhCOSH \longrightarrow$$

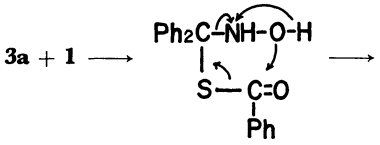
3a **1**



$$\longrightarrow Ph_2C{=}S + PhCONHOH \quad (2)$$

4a **7**

8



$$\longrightarrow$$

$$Ph_2C{=}S + H_2NOCPh \quad (3)$$

4a **9**

or **4a** to form **5** or **6** under the same reaction conditions, another pathway involving intramolecular nucleophilic attack of oxygen to carbonyl carbon followed by proton transfer in the intermediate (**8**) to form **4a** and *O*-benzoylhydroxylamine (**9**) has been considered. *O*-Acylhydroxylamines react readily with various nucleophiles at nitrogen atom to form carboxylate ion.[5,6]

$$RCO_2NH_2 + :Nu \longrightarrow RCO_2^- + NH_2Nu \quad (4)$$

It seems probable that a portion of **1** in the reaction mixture would react as nucleophile with **9** to afford **5** and **6** as follows. If these steps take part in the reaction

$$\mathbf{9} + \mathbf{1} \longrightarrow PhCO_2H + (PhCOSNH_2)$$
$$(PhCOSNH_2) + \mathbf{1} \longrightarrow \mathbf{6} + NH_3$$
$$PhCO_2H + NH_3 \longrightarrow \underset{\mathbf{5}}{PhCO_2NH_4} \quad (5)$$

and proceed relatively rapid, overall reaction would be as follows. Support for this proposal is supplied by the

$$Ph_2C{=}NOH + 3PhCOSH \longrightarrow$$

3a **1**

$$Ph_2C{=}S + PhCO_2NH_4 + PhCOSSCOPh \quad (6)$$

4a **5** **6**

fact that **9** prepared from *p*-nitrophenyl benzoate and hydroxylamine reacts with 2 mol of **1** at room temperature to give **5** and **6** and that the yield of **4a** increases to *ca.* 80% by using over 3 mol of **1** (Table 1). The other ketoximes reacted similarly to give the corresponding thiones in relatively good yields. The results are given in Table 2.

Table 1. Relation of molar ratio (thiobenzoic acid (**1**)/oximes) and yield of thiobenzopehnone (**4a**)

Molar ratio	1	2	3
Yield of **4a** (%)	30	50	78

The reactions of ketoximes with thioacetic acid (**2**) proceeded rapidly to give thioketones and acetamide along with a small amount of diacetyl disulfide. No ammonium acetate was obtained.

No reaction took place with **1** and benzophenone oxime *O*-methyl ether (**10**), which structurally cannot cause proton transfer in the intermediate.

Nitrones were found to react with thiocarboxylic acids much more readily than oximes. When benzo-

TABLE 2. PREPARATION OF THIONES BY THE REACTION OF OXIMES WITH THIOBENZOIC ACID AND THIOACETIC ACID

$R_1-\underset{\underset{S}{\|}}{C}-R_2$

	R_1	R_2	Molar ratio (RCOSH/oxime)	Condition: Solvent	Condition: Time (day)	R (in RCOSH): Ph Yield (%)	R (in RCOSH): CH_3 Yield (%)
4a	C_6H_5	C_6H_5	1	B	4	30	40
			3			78	80
4b	CH_3	C_6H_5	1	B	3		
			3			trace	trace
4c	*p*-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4$	1	B	4	30	36
			3			60	65
4d	*p*-$CH_3OC_6H_4$	C_6H_5	1	B	3	30	30
			3			60	70
4e	*p*-$CH_3C_6H_4$	C_6H_5	1	B–E	3	25	35
			3			60	70
4f	2-Thienyl	*p*-ClC_6H_4	1	B	7	26	30
			3			60	78
4g	*p*-ClC_6H_4	*p*-ClC_6H_4	1	B	4	20	35
			3			50	67
4h	*p*-ClC_6H_4	C_6H_5	1	B–E	3	20	40
			3			70	75

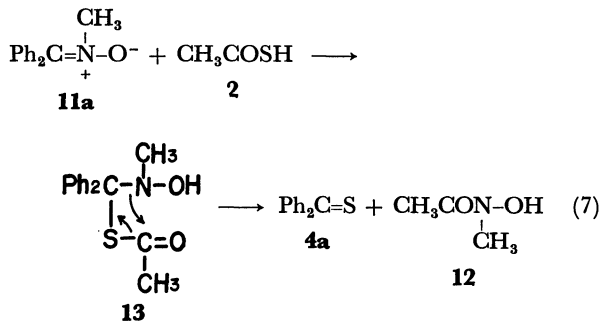
Solvent. B: benzene, B–E: benzene–ether (4: 1)

TABLE 3. PREPARATION OF THIONES BY THE REACTION OF N-METHYLNITRONES WITH THIOACETIC ACID

$R_1-\underset{\underset{S}{\|}}{C}-R_2$

	R_1	R_2	Reaction time (day)	Yield (%)
4a	C_6H_5	C_6H_5	2	76
4b	CH_3	C_6H_5[21]	1	44
4c	*p*-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4$	2	70
4e	*p*-$CH_3C_6H_4$	C_6H_5	2	81
4g	*p*-ClC_6H_4	*p*-ClC_6H_4	2	75

phenone-*N*-methylnitrone (**11a**) was allowed to react with **2**, **4a** and *N*-acetyl-*N*-methylhydroxylamine (**12**) were obtained.* The latter was identified by elementary analyses and comparison of its IR spectra with those of an authentic sample. Thus, the reaction is considered to proceed by intramolecular nucleophilic attack of nitrogen on carbonyl carbon in the intermediate (**13**)

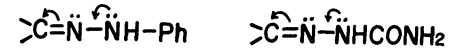


* The reactions of **11** with **1** proceeded similarly, but gave unsatisfactory results in the yield and purity of **4**.

as in the case of Scheme 1. The other thiones were obtained similarly (Table 3).

The cause of such differences in the mechanisms of the reaction of oxides and nitrones has not been clarified.

Phenylhydrazones and semicarbazones did not react with thiocarboxylic acids even in refluxing benzene, the starting materials being recovered. In these compounds, the following resonance effects may markedly lower the reactivity of imino carbon toward uncleophilic addition of thiocarboxylic acids, retarding the reaction.



Experimental

All melting and boiling points were uncorrected. The IR spectra were measured on a Hitachi EPI-21G spectrometer. The mass spectra were obtained on a Hitachi RMU-7M mass spectrometer operating at an ionization energy of 70 eV. Silica gel column chromatography was performed with Wakogel C-200 (Wako Pure Chem.).

Materials. Commercial benzophenone and acetophenone were used without further purification. The other ketones were prepared by the Friedel-Crafts reaction of the corresponding acid chlorides. Oximes were prepared by the usual methods. **3f** was prepared from the corresponding ketone and hydroxylamine hydrochloride in pyridine.[7] *N*-Methylnitrones were prepared by the reaction of the corresponding oximes with dimethyl sulfate[8] or methyl iodide.[9] Acetophenone-*N*-methylnitrone was prepared from acetophenone diethyl acetal and *N*-methylhydroxylamine hydrochloride.[10] *O*-Benzoylhydroxylamine was synthesized from *p*-nitrophenyl benzoate and hydroxylamine hydrochloride in the presences of sodium hydroxide.[11] *N*-Acetyl-*N*-methylhydroxylamine was prepared according to the method given by Exner.[10] Thioacetic and thiobenzoic acid were

prepared according to general methods.[12,13]

Preparation of Thiobenzophenone (4a). *Reaction of Benzophenone Oxime (3a) With Thiobenzoic Acid (1)*: A solution of **1** (12.4 g, 0.09 mol) in bry benzene (30 ml) was added to a solution of **3a** (6 g, 0.03 mol) in dry benzene (140 ml) at room temperature under nitrogen atmosphere. The solution gradually turned blue, white precipitates separating. The reaction mixture was allowed to stand in the dark for 4 days. Filtration of the precipitate gave ammonium benzoate (2.7 g, mp 189—191 °C (from EtOH), lit, mp 190 °C). The blue filtrate was evaporated under reduced pressure. The residue was chromatographed on a silica gel column (80 g) by elution with petroleum ether to afford **4a** (4.7 g, 78%, bp 120—125 °C/1 mmHg, mp 47—50 °C (from petroleum ether (bp 60—80 °C); lit,[14] mp 53—54 °C). Further elution with benzene gave dibenzoyl disulfide (3 g, mp 128 °C (from EtOH); lit,[15] mp 130 °C).

Reaction of 3a with Thioacetic Acid (2): A solution of **2** (6.8 g, 0.09 mol) in dry benzene (15 ml) was added to a solution of **3a** (6 g, 0.03 mol) in dry benzene (140 ml) at room temperature under nitrogen atmosphere and the mixture was allowed to stand in the dark for 4 days. The blue solution obtained was evaporated under reduced pressure. The residue was chromatographed on a silica gel column (80 g) by elution with petroleum ether to afford **4a** (4.8 g, 80%). Further elution with benzene–ethanol (1: 1) gave acetamide (1 g, mp 80—81 °C; lit, mp 81—82 °C) and diacetyl disulfide (0.2 g, bp 72—74 °C/2 mmHg, lit[16] bp 60—61 °C/1 mmHg). Acetamide was identified by its IR spectra and by admixture with an authentic sample. **4b—h** were obtained by a similar procedure. The thiones obtained were identified by their physical constants (**4c**,[3] **4d**,[17] **4e**,[18] **4f**,[19] **4g**,[20] **4h**[18]) and conversion into 2,4-dinitrophenylhydrazone.

Reaction of O-Benzoylhydroxylamine (9) with Thiobenzoic Acid (1). A solution of **9** (2.2 g, 0.016 mol) in dry benzene (15 ml) was added to a solution of **1** (4.4 g, 0.032 mol) in dry benzene (50 ml) with stirring at room temperature under nitrogen atmosphere and allowed to stand for 3 days. The white precipitate separated was removed by filtration to give ammonium benzoate (1.4 g, mp 190—193 °C). The filtrate was evaporated under reduced pressure and the residue was recrystallized from ethanol to give dibenzoly disulfide (2.6 g, mp 127—128 °C).

Reaction of Benzophenone-N-methylnitrone (11a) with Thioacetic Acid (2). A solution of **2** (7.1 g, 0.092 mol) in dry benzene (15 ml) was added to a solution of **11a** (19.5 g, 0.092 mol) in dry benzene (100 ml) at room temperature under nitrogen atmosphere. The reaction mixture which rapidly turned blue was allowed to stand in the dark for 2 days. After removal of the solvent, fractional distillation under reduced pressure gave **4a** (15 g, 76%, bp 120—125 °C/1 mmHg, mp 48—50 °C) and *N*-acetyl-*N*-methylhydroxylamine (5 g, bp 93—95 °C/3 mmHg; lit,[10] bp 80 °C/2 mmHg); IR(liquid): 3150, 2850, and 1630 cm^{-1}; MS *m/e* 73 (M^+—O), 58, and 43. **4b**, **4c**, **4e**, and **4g** were obtained by a similar procedure.

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