A New Synthesis of Thioamides and Dithiocarbamates from Organolithium Derivatives

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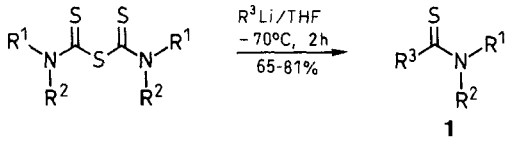
The reaction of organolithium derivatives with thiuram monosulfides gives a convenient method for the synthesis of both aromatic and aliphatic thioamides in good yields. In our hands, the reaction of organolithium derivatives with tetramethylthiuram disulfide gave only dithiocarbamates and not a mixture of these and thioamides.

Organolithium derivatives are among the most versatile reagents in organic synthesis (for reviews cf Ref.[1,2]) and we have now discovered that they can be used for the direct synthesis of thioamides. Most standard procedures for their preparation consist of the conversion of amides[3-9] and nitriles[10] by refluxing with excess phosphorus pentasulfide or other sulfurating agents in various solvents. We have now found that thiuram monosulfides react with organolithium derivatives to yield thioamides (Scheme 1).



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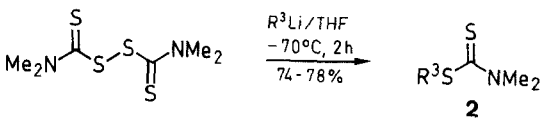
Scheme 1

Typically, one equivalent of thiuram monosulfide is added in one portion to a solution of lithium derivative in tetrahydrofuran at −70 °C, under nitrogen. When after about two hours no more thiuram monosulfide was detected by GLC the reaction mixture was worked up (see experimental part). Both aromatic and aliphatic thioamides were obtained in good yields.

The ^{1}H NMR spectra of the products were consistent with proposed structures and in the case of the *N,N*-dimethylthioamides nonequivalent methyl groups were observed at room temperature.

The corresponding Grignard reagents are not as useful. Both phenylmagnesium bromide and 2-thienylmagnesium bromide had to be reacted at room temperature and for longer times (18–24 hours) and low yields, 26 and 28% respectively, were obtained.



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Scheme 2

Similar differences in reactivity between lithium reagents[13] and Grignard reagents[14] have previously been observed in the reaction with a thiuram disulfide. However, Grignard reagents only yield dithiocarbamates,[14] organolithium reagents are claimed to give mixtures of about equal amounts of dithiocarbamates and the corresponding thioamides in the reaction with tetramethylthiuram disulfide (TMTD).[13] We have therefore studied the reaction of the lithium derivatives given in Table 1 with TMTD. In our hands no detectable amounts of thioamides were formed and good yields of dithiocarbamates were obtained (Scheme 2).

Table 1. Yields and Physical Properties for Thioamides **1a–h**

Product	R^3Li	R^1	R^2	Yield (%)	mp (°C) bp (°C/Torr)
1a	3-Th[a]	Me	Me	75	39–40 124–127/0.2[11]
1b	3-Th	Ph	Me	66	91–92
1c	2-Th	Me	Me	71	42–43 45–46[11]
1d	2-Th	Ph	Me	65	93–94
1e	Ph	Me	Me	78	67–68 68–69[4]
1f	Ph	Ph	Me	70	96–97 96–97[3]
1g	Bu	Me	Me	81	72–74/0.2 70–75/0.25[12]
1h	Bu	Ph	Me	74	106–108/0.2

[a] Th = thienyl.

Table 2. Yields and Physical Properties of Dithiocarbamates **2**

Product	R^3Li	Yield (%)	mp (°C) bp (°C/Torr)
2a	3-Th[a]	77	80–81
2b	2-Th	75	82–83
2c	Ph	74	93–94 92–93[15]
2d	Bu	78	83–85/0.25 157–159/20[16]

[a] Th = thienyl.

Melting points are uncorrected. The ^{1}H NMR spectra were recorded on a Varian XL-300 spectrometer and $CDCl_3$ was used as solvent. The mass spectra were recorded on a JEOL-SX 102 spectrometer. GLC analysis were carried out on a Varian 3300 gas chromatograph using an OV 17, 3% column. BuLi and PhLi were purchased from Merck.

Thioamides 1a–h and *N,N*-Dimethyldithiocarbamates 2a–d; General Procedure:

The lithium compounds were prepared from the corresponding bromo derivative (20 mmol) and BuLi (11 mL, 2.0 N in hexane, 22 mmol) in THF (150 mL) under N_2 at −70 °C. For compounds **1e–h** and **2c–d** PhLi (11.5 mL, 1.90 N in cyclohexane, 0.22 mmol) or BuLi (11 mL 2.0 N in hexane, 0.22 mmol) was diluted with THF (150 mL) and cooled to −70 °C. To these solutions 1 equiv of *N,N'*-dimethyl-,[17] *N,N'*-diphenylthiuram sulfide[17], tetramethylthiuram sulfide[17] or tetramethylthiuram disulfide[17] was added in one portion. After stirring at −70 °C for 2 h, (when Et_2O was used as solvent for **2a** and **2b** the reaction was left overnight) the mixture was allowed to reach r. t. and poured into cold sat. aq NH_4Cl. The phases

were separated and the organic phase dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel 60 using heptane/EtOAc (95:5) as eluent.

N-Methyl-N-phenyl-3-thiophenecarbothioamide **(1b)** was obtained as yellow crystals (3.07 g) from EtOH (Table 1).

$C_{12}H_{11}NS_2$	calc.	C 61.75	H 4.75	N 6.00
(233.2)	found	61.82	4.87	6.02

MS: $m/z = 233$.

^{1}H NMR: δ = 3.90 (3 H, s), 6.68 (1 H, dd, J = 5.08, 1.26 Hz), 6.95 (1 H, dd, J = 5.08, 2.96), 7.17 (1 H, dd, J = 2.96, 1.26), 7.08 (3 H, m), 7.23 (2 H, M).

N-Methyl-N-phenyl-2-thiophenethioamide **(1d)** was obtained as yellow crystals (3.03 g) from EtOH (Table 1).

$C_{12}H_{11}NS_2$	calc.	C 61.75	H 4.75	N 6.00
(233.2)	found	61.65	4.88	5.98

MS: $m/z = 233$.

^{1}H NMR: δ = 3.90 (3 H, s), 6.55 (1 H, dd, J = 3.98, 0.97), 6.68 (1 H, dd, J = 5.08, 3.90), 7.27 (1 H, dd, J = 5.08, 0.97), 7.18 (2 H, m), 7.30–7.41 (3 H, m).

N-Methyl-N-phenylpentanethioamide **(1 h)** was obtained as a yellow oil (3.06 g) (Table 1).

$C_{12}H_{17}NS$	calc.	C 69.51	H 8.26	N 6.75
(207.3)	found	69.48	8.35	6.78

^{1}H NMR: δ = 0.75 (3 H, t, J = 7.35), 1.16 (2 H, hex, J = 7.35), 1.67 (2 H, tt, J = 7.82, 7.35), 2.50 (2 H, t, J = 7.82), 3.72 (3 H, s), 7.17 (2 H, m), 7.43 (3 H, m).

3-Thienyl N,N-Dimethyldithiocarbamate **(2a)** was obtained as yellow crystals (3.13 g) from EtOH (Table 2).

HRMS: m/z, $C_7H_9NS_3$, calc.: 202.9897; found: 202.9907.

^{1}H NMR: δ = 3.49 (3 H, s), 3.55 (3 H, s), 7.12 (1 H, dd, J = 4.68, 1.21), 7.42 (1 H, dd, J = 4.68, 2.80), 7.53 (1 H, dd, J = 2.80, 1.21).

2-Thienyl N,N-Dimethyldithiocarbamate **(2b)** was obtained as yellow crystals (3.04 g) from EtOH (Table 2).

HRMS: m/z, $C_7H_9NS_3$, calc.: 202.9897; found: 202.9887.

^{1}H NMR: δ = 3.50 (3 H, s), 3.56 (3 H, s), 7.15 (1 H, dd, J = 5.30, 3.60), 7.25 (1 H, dd, J = 3.60, 1.27), 7.64 (1 H, dd, J = 5.30, 1.25).

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