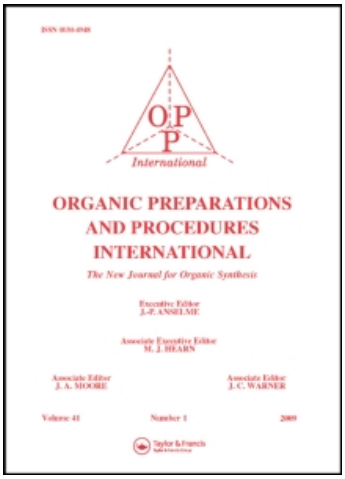

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PREPARATION OF THIOL ACIDS, THIOL ESTERS AND AMIDES BY REACTIONS OF CARBONYL SULFIDE WITH GRIGNARD REAGENTS

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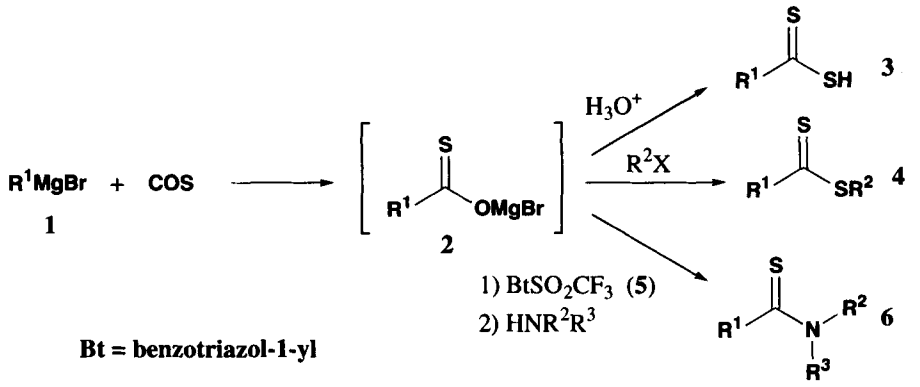
Reactions of Grignard reagents with carbon dioxide are well documented in the literature, and provide a general method for the preparation of carboxylic acids.[1,2] Similarly, dithiocarboxylic acids and esters have been prepared from carbon disulfide.[3] Grignard reagents were reported to react with carbonyl sulfide affording mixtures of thiol acids (9-73%) and tertiary alcohols (22-52%) in ratios which depend on the Grignard reagent used.[4] We recently disclosed a novel, convenient, one-pot synthesis of thioamides involving successive reactions of a Grignard reagent with carbon disulfide, 1-trifluoromethylsulfonylbenzotriazole and an amine.[5] We now describe the reactions of carbonyl sulfide with Grignard reagents and further transformations of the resulting organomagnesium complexes with hydrochloric acid, alkyl halides and 1-trifluoromethylsulfonylbenzotriazole (**5**) and amines (Scheme 1).



Scheme 1

Thiol carboxylic acids are usually prepared by reaction of hydrogen sulfide with acyl halides[6,7] or anhydrides.[8,9] Other procedures may involve cleavage of an amide[10] or sulfur-sulfur bond,[11] or additions of carbonyl sulfide to olefins.[12] Thiol esters are generally synthesized from thiols

and carboxylic acid derivatives.[13-15] Other reported methods include the hydroboration of alkylthioalkynes[16] and the oxidation of thiol ethers.[17] Well documented preparations of amides generally utlilize carboxylic acids or their derivatives and amines.[18]

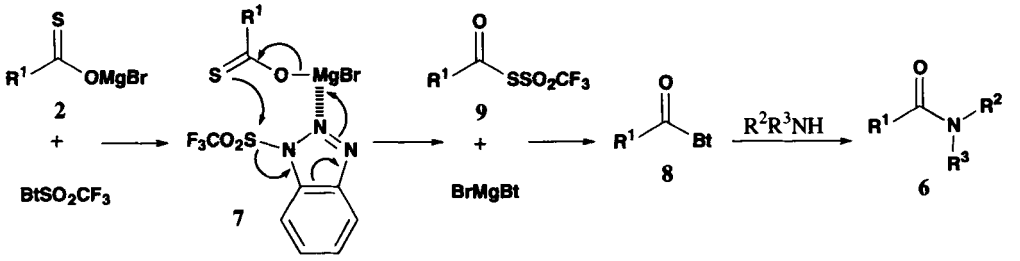
In the present work, carbonyl sulfide was passed through a solution of Grignard reagent at 0°, and the resulting organometallic complex **2** quenched with hydrochloric acid to afford the thiol acids **3** in nearly quantitative yields; no tertiary alcohols were detected using our conditions, in contrast to a previous report.[4] The products **3** were easily purified by a simple basification/acidification technique. Treatment of **2** *in situ* with alkyl halides formed thiol esters **4** in yields of 70-77%. Thiol acids **3** and thiol esters **4** were characterized by ^{1}H and ^{13}C NMR spectroscopy. The carbonyl resonances appear between 190-200 ppm as expected,[19] indicating significant deshielding compared with those of the corresponding carboxylic acids and esters (160-180 ppm).[19] The chemical shifts are also significantly different from those of the more deshielded thiocarbonyl groups of *O*-thiocarboxylic acid esters (210-230 ppm).[19]

When **2** was successively treated with 1-trifluoromethylsulfonylbenzotriazole (**5**) and amines, the corresponding amides **6** were obtained in good yields (Table 1). Zinc bromide was used to improve the yield of amide **6a** derived from phenyl Grignard. The use of carbon dioxide in place of carbonyl sulfide, under the same conditions, did not form amides **6**. The mechanism for the formation of **6** should be similar to that proposed for the formation of thioamides.[5] The 1-acylbenzotriazole intermediates **8**, are electrophilic entities capable of reacting with primary and secondary amines to afford the corresponding amides as suggested in Scheme 2.

TABLE 1. Preparation of Thiol Acids (**3**), Thiol Esters (**4**) and Amides (**6**)

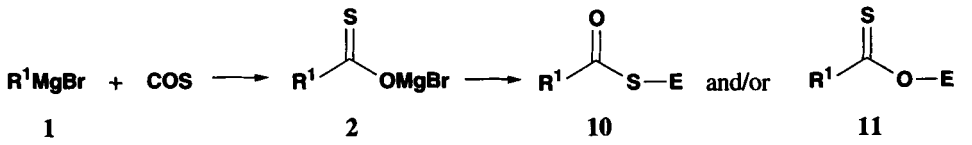
Cmpd	R^1	R^2	R^3	Yield %
3a	Ph	–	–	99
3b	$PhCH_2$	–	–	90
3c	n-C_7H_{15}	–	–	93
4a	Ph	CH_3	–	75
4b	Ph	$PhCH_2$	–	77
4c	$PhCH_2$	n-C_4H_9	–	70
4d	n-C_4H_9	$PhCH_2$	–	76
6a	Ph	n-C_4H_9	H	88[a]
6b	n-C_4H_9	$PhCH_2$	H	68
6c	n-C_7H_{15}	$-CH_2CH_2OCH_2CH_2-$		75

a) $ZnBr_2$ used in the reaction.



Scheme 2

The reaction between COS and a Grignard reagent gives the organomagnesium adduct **2,** which upon treatment with electrophiles could provide carbonyl compounds **10** and/or thiocarbonyl compounds **11** (Scheme 3). However, the formation of thiocarbonyl derivatives **11** was not detected, probably due to the stronger nucleophilicity of sulfur compared to oxygen.[20,21]



Scheme 3

In summary, the reactions of carbonyl sulfide with Grignard reagents have been investigated. Quenching the initially formed organomagnesium adducts with hydrochloric acid or alkyl halides affords the corresponding thiol acids and thiol esters in excellent yields. Successive one-pot treatment of the same adducts with 1-trifluoromethylsulfonylbenzotriazole and amines provides the corresponding amides in good yields. This method appears quite general as it allows direct and convenient transformations of both alkyl and aryl halides into thiol acids, thiol esters and amides with one carbon homologation. This procedure is also attractive due to its simplicity and availability of starting materials compared with other reported preparations of thiol acids and thiol esters.

EXPERIMENTAL SECTION

Melting points were determined on a Bristoline hot-stage microscope and are uncorrected. ^1H (300 MHz) NMR spectra were recorded on a Varian VXR-300 (FT mode) spectrometer with Me_4Si as the internal standard. ^{13}C NMR spectra were recorded at 75 MHz on the same instrument using the $CDCl_3$ solvent peak, δ 77.0 as the reference. Elemental analyses (C,H,N) were carried out using a Carlo Erba 1106 elemental analyzer. Flash chromatography was run on EM Science silica gel 60 (230-400 mesh). Carbonyl sulfide was purchased from Aldrich.

General Procedure for the Preparation of Thiol Acids (3a-c).- Carbonyl sulfide was passed through a solution of Grignard reagent (10 mL, 1 M in ether, 10 mmol) in THF (10 mL) at 0° for 30

min. The mixture was stirred at 20° for 30 min then cooled to 0°. Hydrochloric acid (10 mL, 12 M aqueous solution) was added dropwise, followed by water (10 mL). The mixture was extracted with ether (3 x 30 mL). The combined organic extracts were poured into sodium hydroxide (15 mL, 1 M aqueous solution). The aqueous extract was collected and washed with ether. The aqueous layer was made acidic with hydrochloric acid (20 mL, 12 M aqueous solution), and extracted with ether (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to afford the pure thiol acids **3**.

Thiolbenzoic Acid (3a) obtained as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 4.56 (br, 1H), 7.41-7.47 (m, 2H), 7.55-7.61(m, 1H), 7.87-7.91 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 127.8, 128.6, 133.8, 136.4, 190.2; (previously reported[6] as a yellow oil, bp. 85-87°/10mm).

2-Phenylthiolacetic Acid (3b) obtained as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 3.82 (s, 2H), 4.58 (br, 1H), 7.22-7.38 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 52.0, 127.7, 128.8, 129.6, 133.1, 196.1; (previously reported[22] as an oil, bp. 92°/2mm).

Thioloctanoic Acid (3c) obtained as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H, J = 6.8 Hz), 1.24-1.36 (m, 8H), 1.65 (quintet, 2H, J = 7.4 Hz), 2.61 (t, 2H, J = 7.5 Hz), 4.49 (br, 1H); ^{13}C NMR ($CDCl_3$): δ 13.9, 22.5, 25.3, 28.6, 28.8, 31.5, 45.7, 197.8; (previously reported[23] as an oil, bp. 70°/2mm).

General Procedure for the Preparation of Thiol Esters (4a-d).- Carbonyl sulfide was passed through a solution of Grignard reagent (10 mL, 1 M in ether, 10 mmol) in THF (10 mL) at 0° for 30 min. The mixture was stirred at 20° for 30 min then cooled to 0°. Alkyl halide (5 mmol) was added dropwise, and the mixture refluxed overnight. The mixture was cooled to room temperature, poured into saturated $NaHCO_3$ and extracted with CH_2Cl_2. The organic extract was dried ($MgSO_4$), filtered and evaporated. The crude residue was purified by column chromatography to afford the pure thiol esters **4**.

***S*-Methyl Benzenethiocarboxylate (4a)** obtained as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.46 (s, 3H), 7.43 (t, 2H, J = 7.5 Hz), 7.55 (t, 1H, J = 7.5 Hz), 7.96 (d, 2H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 11.6, 127.1, 128.6, 133.2, 137.1, 192.3; (previouly reported[24] as an oil, bp. 123-124°/20mm).

***S*-Benzyl Benzenethiocarboxylate (4b)** obtained as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 4.28 (s, 2H), 7.17-7.38 (m, 7H), 7.45-7.50 (m, 1H), 7.92-7.95 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 33.4, 127.4, 128.7, 129.1, 133.4, 136.9, 137.6, 191.1; (previously reported,[15] mp. 36-38).

***S*-Butyl 2-Phenylethanethiocarboxylate (4c)** obtained as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H, J = 7.3 Hz), 1.34 (sextet, 2H, J = 7.2 Hz), 2.51 (quintet, 2H, J = 7.4 Hz), 2.84 (t, 2H, J = 7.3 Hz), 3.79 (s, 2H), 7.20-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 13.4, 21.8, 28.9, 31.4, 50.4, 127.2, 128.5, 129.4, 133.7, 197.3; (previously reported[16] and characterized by NMR).

***S*-Benzyl Pentanethiocarboxylate (4d)** obtained as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.91 (t, 3H, J = 7.4 Hz), 1.35 (sextet, 2H, J = 7.4 Hz), 1.66 (quintet, 2H, J = 7.5 Hz), 2.57 (t, 2H, J = 7.5 Hz), 4.11 (s, 2H), 7.20-7.31 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 13.6, 22.0, 27.6, 33.0, 43.5, 127.1, 128.5, 128.7, 137.7, 198.7; (previously reported[25] as an oil, bp. 159°/7mm).

General Procedure for the Preparation of Amides (6a-c).- Carbonyl sulfide was passed through a solution of Grignard reagent (10 mL, 1 M in ether, 10 mmol) in THF (10 mL) at 0° for 30 min. The

mixture was stirred at 20° for 30 min then cooled to 0°. 1-Trifluoromethylsulfonylbenzotriazole (1.26 g, 5 mmol) in THF (10 mL) was added dropwise. In the preparation of **6a**, zinc bromide (1.23 g, 5.5 mmol) was added at this stage. The mixture was stirred at 0° for 30 min then at 20° for 5 hrs. The appropriate amine (5 mmol) was added dropwise and the mixture refluxed for 4 hrs. The solution was cooled to room temperature, poured into water and extracted with chloroform (3 x 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was purified by column chromatography.

***N*-Butylbenzamide (6a)** obtained as a yellow sticky oil. ^{1}H NMR ($CDCl_3$): δ 0.93 (t, 3H, *J* = 7.3 Hz), 1.37 (sextet, 2H, *J* = 7.4 Hz), 1.58 (quintet, 2H, *J* = 7.3 Hz), 3.42 (q, 2H, *J* = 7.2 Hz), 6.51 (br, 1H), 7.35-7.50 (m, 3H), 7.75-7.80 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 13.7, 20.1, 31.7, 39.7, 126.8, 128.4, 131.1, 134.8, 167.5; (previously reported,[26] mp. 41-42°).

***N*-Benzylpentanamide (6b)** obtained as white needles, mp 48°. ^{1}H NMR ($CDCl_3$): δ 0.90 (t, 3H, *J* = 7.3 Hz), 1.33 (sextet, 2H, *J* = 7.3 Hz), 1.60 (quintet, 2H, *J* = 7.5 Hz), 2.18 (t, 2H, *J* = 7.6 Hz), 4.37 (d, 2H, *J* = 5.8 Hz), 6.27 (br, 1H), 7.20-7.33 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 13.7, 22.3, 27.7, 36.3, 43.3, 127.2, 127.6, 128.5, 138.4, 173.1.

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.36; H, 8.96; N, 7.32. Found: C, 75.04; H, 9.05; N, 7.25

***N*-Octanoylmorpholine (6c)** obtained as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H, *J* = 6.8 Hz), 1.24-1.35 (m, 8H), 1.62 (quintet, 2H, *J* = 7.4 Hz), 2.31 (dd, 2H, *J* = 7.9 and 7.5), 3.44-3.49 (m, 2H), 3.58-3.69 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 13.9, 22.5, 25.2, 28.9, 29.3, 31.6, 33.0, 41.8, 46.0, 66.6, 66.8, 171.9; (previously reported[27] as an oil, bp. 150°/0.1mm).

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