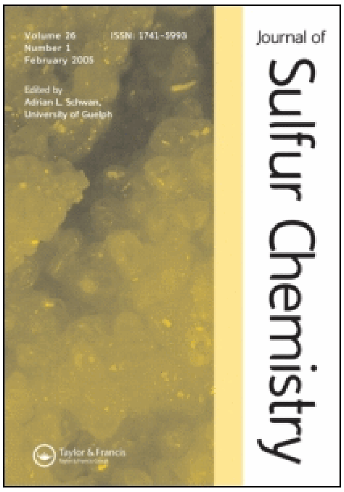

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Synthesis of thiol esters by the use of carbonyl sulfide as a thiocarboxylation agent

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This paper is dedicated to Professor Juzo Nakayama on the occasion of his 65th birthday and retirement.

A simple and efficient procedure for the synthesis of thiol esters **3** has been developed by utilizing carbonyl sulfide (S=C=O, **1**) as a thiocarboxylation agent. Treatment of **1** with organolithium reagents at −78 °C for 5 min yielded lithium thiocarboxylates **2**. Trapping of **2** with alkyl iodides gave the corresponding thiol esters **3** in good to excellent yields. Similarly, the reaction of **1** with cyanoarylcuprates followed by alkylation under similar conditions afforded **3**.

Keywords: thiol ester; carbonyl sulfide; aryllithium; cuprate; regioselectivity

1. Introduction

Thiol esters (**3**) can be converted to aldehydes (*1–5*) and ketones (*6–9*), and also utilized as precursors of acyl radicals (*10*) and as a protecting group of thiol (*11*). Methods for the synthesis of lactones (*12*) and decarbonylative addition to alkynes (*13*) have also been developed. Silyl enol ethers of thiol esters (**3**) have also been used in asymmetric aldol reaction (*14*), as well as in asymmetric Michael addition (*15*) and Mannich reaction (*16*, *17*). Until the mid-1980s, thiol esters (**3**) were prepared by conventional methods, *i.e.* condensation of thiols with the parent carboxylic acids in the presence of an activating agent or substitution of acid chlorides or acid anhydrides with metal thiolates (*6a*, *7*, *18*). However, in proportion with growing interests in organic transformations of thiol esters (**3**), the following synthetic methods are now available: (i) transition metal catalyzed carbonylation (*19*); (ii) reaction of acyllithiums with disulfides (*20*); (iii) hydration of thioacetylenes (*21*); (iv) Tishchenko-type reaction (*22*); and (v) coupling of thiol chloroformate with organotin compounds (*23*). Here, we disclose that the reaction of thiocarbonyl with organometallic reagents provides a general method for the synthesis of thiol esters.

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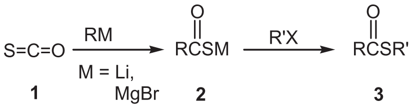
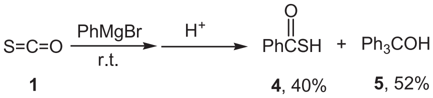
2. Results and discussion

Carbonyl sulfide (**1**) has been used for introduction of a thiocarboxyl unit into stabilized carbon nucleophiles such as enolates (*24*), phosphorous ylides (*25*), an acyllithium (*26*), lithium acetylides (*27*), and a trifluoromethyl anion (*28*), as well as heteroatom nucleophiles such as amines (*29*) and alcohols (*30*).



Scheme 1.

Although it is expected that a variety of organometallic reagents react with **1** to form the corresponding metal thiocarboxylates **2** (Scheme 1), little attention has been paid to the reaction with non-stabilized organolithiums and Grignard reagents, probably due to the following two reports. First, Weigert (*31*) showed in 1903 that the reaction of **1** with PhMgBr at room temperature followed by protonation afforded the corresponding thiocarboxylic acid **4**; however, this was along with significant amounts of overreaction product, triphenylcarbinol **5** (Scheme 2). Second, in 1995, Katrizky *et al.* (*32*) found that the reaction of **1** with Grignard reagents at 0 °C and successive treatment with ethyl iodide afforded the corresponding thiol esters in good yields; however, the authors misdrew the product as dithioester.



Scheme 2.

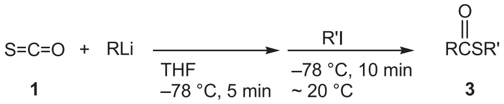
During the course of our study on the siteselectivity in the reaction of carbonyl selenide ($Se{=}C{=}O$) with organometallic reagents, we found that PhLi attacked selenium of carbonyl selenide but, in contrast, preferred the attack at the central carbon of carbonyl sulfide (*33*). We here examined the reaction of carbonyl sulfide **1** with organometallic reagents in detail, aiming at the development of convenient methods for synthesis of thiol esters. Treatment of carbonyl sulfide (**1**, 2 mmol) with 1 equiv of PhLi at −78 °C for 5 min, and the trapping of the resulting thicarboxylate **2** (R=Ph, M=Li) with MeI, gave the desired thiol ester **3a** in 95% yield without overreaction product (Table 1, Run 1). When PhMgBr was used instead of PhLi, **3a** was also obtained, albeit in lower yield.

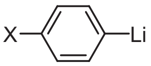
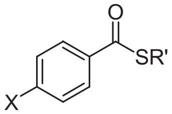
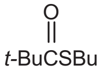
In a similar manner, thiol esters **3b–d** were prepared in high yields from aryllithiums having an electron-releasing or -withdrawing substituent at the *para* position (Runs 2–4). Treatment of **1** with *t*-BuLi also afforded the corresponding thiol ester **3e** after trapping with BuI (Run 5).

As for other organometallic reagents, organocopper reagents were found to be useful. For example, the reaction of **1** with cyanophenylcuprate afforded **3a** in 98% yield under similar conditions (Scheme 3). Thiolesters **3b–d** were also synthesized in high yields from the corresponding cyanoarylcuprates.

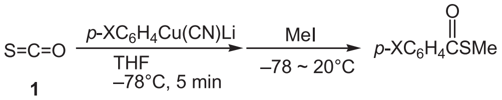
In summary, the reaction of carbonyl sulfide with organometallic reagents at low temperature for short reaction period followed by alkylation was found to be useful and efficient for the synthesis of thiol esters.

Table 1. Synthesis of thiol esters 3.



Run	RLi	R′I	Product	Yield (%)[a]
				
1	X=H	MeI	**3a**	95
2	X=Me	MeI	**3b**	72
3	X=MeO	MeI	**3c**	98
4	X=Cl	MeI	**3d**	70
5	*t*-BuLi	BuI	 $t\text{-Bu}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{SBu}$ **3e**	60

Notes: Reagents: RLi (2 mmol), SCO (0.11 M in THF, 18.5 mL, 2 mmol), R′ (4 mmol). [a]Isolated yield.



3a: X = H 98%
3b: X = Me 79%
3c: X = MeO 83%
3d: X = Cl 65%

Scheme 3.

3. Experimental

3.1. *General*

Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. PhLi (1.04 M solution in cyclohexane-diethyl ether) and *t*-BuLi (1.62 M solution in pentane) were used as purchased. Other aryllithiums (*34*) and cyanoarylcuprates (*35*) were prepared according to the reported procedure. MeI and BuI were distilled from P_2O_5. Carbonyl sulfide (0.11 M solution in THF) was prepared by dissolving 224 ml of carbonyl sulfide (SCO) gas in 100 ml of THF at −78 °C, and its concentration was determined by measuring the amount of *S*-methyl diethylcarbamate formed by the reaction with excess diethylamine and subsequent trapping with methyl iodide.

^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-GSX-270 (270 and 68 MHz, respectively) spectrometer using Me_4Si as an internal standard. Purification of products was performed on a preparative thin-layer chromatography (TLC) with Wakogel B-5F silica gel (325 mesh). Melting points were determined on a Yanagimoto Micro Melting Point apparatus.

3.2. *S-Methyl benzothioate (3a)*

PhLi (2 mmol, 1.01 M in Et_2O, 2.0 ml) was added dropwise to 2 mmol of SCO in THF (18.5 ml, 0.11 M) at −78 °C. After stirring for 5 min, methyl iodide (4 mmol, 568 mg) was added and the stirring was continued for an additional 10 min. After the mixture was warmed up to 20 °C, the mixture was poured into aqueous saturated NH_4Cl solution (100 ml), and extracted with Et_2O (50 ml). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by preparative TLC (hexane-Et_2O, 30:1) to give a pale yellow liquid. IR, ^1H and ^{13}C NMR data of **3a** are identical to the reported values (*36*, *37*).

3.2.1. *General procedure for the reaction of carbonyl sulfide with ArLi*

ArLi, prepared by the reaction of the appropriate *para*-substituted ArI (2 mmol) with *t*-BuLi (4 mmol, 1.62 M in *n*-pentane, 2.5 ml) in THF (5 ml) at −78 °C, was added dropwise to a THF solution of SCO (2 mmol) at −78 °C. After stirring for 5 min, methyl iodide (4 mmol, 568 mg) was added and the stirring was continued for an additional 10 min. A similar workup as described above afforded **3b–d**. Only the unreported analytical data are given below.

*S-Methyl 4-methylbenzothioate (**3b**)*

A pale yellow liquid. IR, ^1H and ^{13}C NMR data of **3b** are identical to the reported values (*36*, *38*).

*S-Methyl 4-methoxybenzothioate (**3c**)*

The product was recrystallized from hexane to give a white solid; mp 40.5–42.0 °C (*c.f.* (*39*) mp 41–42 °C). IR and ^1H NMR data of **3c** are identical to the reported values (*36*).

^{13}C NMR ($CDCl_3$) δ 11.6, 55.5, 113.8, 129.3, 130.0, 163.7, 190.9.

*S-Methyl 4-chlorobenzothioate (**3d**)*

A pale yellow liquid. IR and ^1H NMR data of **3d** are identical to the reported values (*36*). ^{13}C NMR ($CDCl_3$) δ 11.8, 128.5, 128.9, 135.4, 139.6, 191.2.

*S-Butyl 1,1-dimethylethanecarbothioate (**3e**)*

t-BuLi (2 mmol, 1.62 M in *n*-pentane, 1.3 ml) was added dropwise to 18.5 ml of 0.11 M SCO in THF (2 mmol) at −78 °C. After stirring for 5 min, butyl iodide (4 mmol, 736 mg) was added and the stirring was continued for an additional 10 min. After the mixture was warmed up to 20 °C, the mixture was poured into aqueous saturated NH_4Cl solution (100 ml) and extracted with Et_2O (50 ml). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by preparative TLC (hexane-Et_2O, 30:1) to give a pale yellow liquid. IR, ^1H, and ^{13}C NMR data of **3b** are identical to the reported values (*22*, *40*).

3.2.2. *General procedure for the reaction of carbonyl sulfide with cyanoarylcuprates*

A slurry of CuCN (2 mmol, 183 mg) and THF (5 ml) was cooled to −78 °C, and ArLi, prepared as described above, was added. The mixture was warmed until a bright yellow homogeneous solution was obtained, and it was recooled to −78 °C. The solution was then transferred via a cannula to 18.5 ml of 0.11 M SCO in THF (2 mmol) at −78 °C. After stirring for 5 min, methyl iodide (4 mmol, 568 mg) was added and the stirring was continued for an additional 10 min, and then the mixture was warmed up to 20 °C. After the mixture was filtered through Celite using Et_2O (80 ml), the filtrate was washed with aqueous saturated NH_4Cl solution (100 ml), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by preparative TLC (hexane-Et_2O, 30:1).

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