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Convenient Synthesis of Thiol Esters from Acyl Chlorides and Disulfides Using Zn/$AlCl_3$

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Summary. Various thiol esters were prepared by condensation of acyl chlorides with disulfides in the presence of Zn/$AlCl_3$. The advantages of this method are high yields under relatively mild conditions, simple work-up, lack of toxicity, and low costs.

Keywords. Thiol esters; Zn/$AlCl_3$; Reductive cleavage of disulfides.

Introduction

Thiol esters have received considerable interest because of their importance as mild acyl transfer agents and intermediates in organic synthesis [1–5]. Among the large number of methods available for the synthesis of thiol esters, those which make use of carboxylic acids or their derivatives as starting materials have been extensively studied [6–14]. However, these methods implicate toxic and hazardous reagents, harsh conditions, or uncommon starting materials.

Acid chlorides have been classically transformed to thiol esters by means of thiols in presence of a base. However, using transition metal mercaptides gives better yields for this transformation [15–18]. Recently, *Zhang et al.* have reported that SmI_2 reduces diphenyl disulfide or thiocyanates to the corresponding samarium mercaptides which mildly react with acyl chlorides in nitrogen atmosphere to produce thiol esters [19–21].

In connection with our previous work on Zn/$AlCl_3$ which revealed to be an efficient reagent for the coupling of disulfides with various halides [22], herein we wish to report a convenient and efficient synthesis of thiol esters from disulfides and acyl chlorides in acetonitrile.

Results and Discussion

As summarized in Table 1, both aromatic and aliphatic acid chlorides are easily coupled with both aromatic and aliphatic disulfides. The reaction of acetyl chloride

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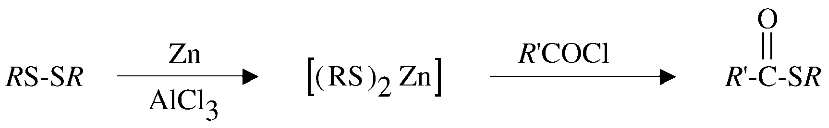
Table 1. Preparation of thiol esters from disulfides and acid chlorides using Zn/$AlCl_3$; yields refer to pure isolated products

Entry	*R*	*R*′	*t*/min	Yield/%	Ref.
1	Ph	CH_3	60	86	[18]
2	4-ClC_6H_4	CH_3	60	84	[24]
3	4-$CH_3C_6H_4$	CH_3	65	85	[25]
4	$PhCH_2$	CH_3	80	82	[26]
5	*n*-Octyl	CH_3	80	79	[27]
6	*n*-Butyl	CH_3	90	80	[27]
7	Cyclohexyl	CH_3	100	77	[28]
8	Ph	Ph	40	92	[18]
9	4-ClC_6H_4	Ph	40	92	[29]
10	4-$CH_3C_6H_4$	Ph	45	91	[25]
11	$PhCH_2$	Ph	50	79	[30]
12	*n*-Butyl	Ph	55	78	[3]



$$RS\text{-}SR \xrightarrow[AlCl_3]{Zn} [(RS)_2Zn] \xrightarrow{R'COCl} R'\text{-}\overset{\overset{\Large O}{||}}{C}\text{-}SR$$

Scheme 1

with various disulfides proceeded quantitatively at 40°C with a molar ratio of $AlCl_3$:acetyl chloride = 1:2; however, the condensation of benzoyl chloride with disulfides required elevated temperatures (65°C) and a higher quantity of aluminum chloride ($AlCl_3$:benzoyl chloride = 1:1) for completion. The presence of aluminum chloride is essential; in the absence of this *Lewis* acid, the reaction slows down considerably. When disulfides primarily reacted with Zn/$AlCl_3$ in acetonitrile, the zinc powder almost disappeared during 30–40 minutes. This indicates that a reductive cleavage of the S–S bond [19] may lead to the zinc thiolate intermediate which further undergoes nucleophilic displacement with acid chloride in the presence of $AlCl_3$ to afford the thiol ester (Scheme 1).

Experimental

Disulfides were prepared according to the method reported by *Rieke et al.* [23]. Zinc powder, $AlCl_3$, and acyl chlorides were purchased from Merck or Fluka. All products were characterized by comparison of their spectroscopic and physical data with those of known samples. IR spectra were obtained using a Shimadzu 470 instrument. ^1H NMR spectra were determined by Jeol JNM-PMX 60 MHz or Bruker 200 MHz NMR spectrometers.

General procedure for the preparation of thiol esters from acetyl chloride

In a round-bottomed flask equipped with a drying tube, a mixture of disulfide (0.5 mmol), zinc powder (2.0 mmol), and finely ground anhydrous aluminum chloride (1.0 mmol) was suspended in acetonitrile (7 cm^3). The mixture was stirred for 30–40 min at 40°C, during which time the zinc powder was almost completely consumed. Then, acetyl chloride (2.0 mmol) was added, and the mixture was stirred for additional 30–70 min at this temperature. Progress of the reaction was monitored by TLC. The solvent was evaporated, and the residue was washed with 10% $NaHCO_3$ and H_2O ($2 \times 10\,cm^3$) to remove the unreacted acetyl chloride. Extraction with diethyl ether ($3 \times 10\,cm^3$), drying ($MgSO_4$) of the combined organic layers, and evaporation of the solvent gave the pure thiol ester.

General procedure for preparation of thiol esters from benzoyl chloride

In a round-bottomed flask equipped with a condenser and drying tube, a mixture of disulfide (0.5 mmol), zinc powder (2.0 mmol), finely ground anhydrous aluminum chloride (2.0 mmol), and acetonitrile ($7\,cm^3$) was stirred at 65°C. When the zinc powder had almost disappeared (30–40 min), benzoyl chloride (2.0 mmol) was added, and the resulting mixture was stirred for additional 10–20 min. After completion of the reaction, the solvent was evaporated *in vacuo*, and the residue was extracted with diethyl ether ($2 \times 10\,cm^3$). The combined organic layers were dried over $MgSO_4$. Evaporation of the solvent gave the desired thiol esters in 78–92% yield. In some cases (Table 1, entries 8–10) the thiol esters were recrystallized from EtOH.

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