# Carboxyl activation via silylthioesterification: one-pot, two-step amidation of carboxylic acids catalyzed by non-metal ammonium salts

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## ARTICLE INFO

## ABSTRACT

The first organo-catalyzed silylthioesterification of a carboxylic acid and a commercially available mercaptoorganosilane results in the in situ production of an *O*-silylthionoester. Subsequent amine addition forms amides in an operationally simple one-pot procedure without removal of water. The scope and efficiency of these reactions with respect to the catalyst, carboxylic acid, amine, [Si–S] moiety, and solvent are investigated. A number of functionalities are tolerated in the two-step amidation including alkene, alkyne, alkyl and aryl halides, benzylic ethers, and heterocycles with free coordinating sites.

Much effort has been dedicated to amide bond construction, especially in attempts to address problems concerning cost and atom-economy.[1] Several systems have recently been employed to catalyze a direct amidation of ~1:1 ratios of RCOOH and RNH₂ (including B(III) reagents, metal salts, inorganic acids, and other heterogeneous materials), though many of these systems require long reaction times, high temperatures, high dilution (at lower temperatures), and/or the removal of water either azeotropically in high boiling solvents or with molecular sieves.[2,3] However, the most widely employed coupling methods require a stoichiometric activating agent.[4] These reactions are frequently hindered by the use of an excess of reagent and/or strictly anhydrous conditions, and are accompanied by the formation of by-products and large amounts of chemical waste which can be difficult to separate.

From a synthetic perspective, silylthiols have been largely unexplored as reagents when compared to analogous organic thiols. The relatively weak Si–S bond (~300 kJ/mol)[5] and the oxophilicity of silicon lead to highly reactive molecules with intriguing potential in organic synthesis. To date, the [Si–S] moiety has been used primarily in the production of silanethiolato complexes of main group elements and transition-metals for the synthesis of heterometallic clusters.[6] Only a few examples of the utilization of [Si–S] units as reagents for functional transformations have been reported. For example, thiosilanes have been used for C–O bond cleavage (oxirane ring-opening),[7] as masking agents of carbonyl groups,[8] and in reactions with acid halides to form thiol esters.[9]

Recently, our research group has discovered that *O*-silylthionoesters, generated by silylation of thiol acids (prepared in two steps from carboxylic acids using traditional coupling agents), serve as a functionally unique, activated carboxyl unit compared to analogous *O*-alkylthionoesters (Scheme 1).[10] The kinetically formed *S*-silylthiol ester undergoes a thermodynamically driven tautomerization of the triorganosilicon group from sulfur to oxygen to form an *O*-silylthionoester. These *O*-silylthionoester species react with amines to generate *oxoamides* exclusively due to a subsequent *O*- to *S*-silatropic migration, while *O*-alkylthionoesters react with amines to produce *thioamide* linkages. Following this finding, we aimed to explore the use of thiosilane units as a direct and atom-economical means of generating these unique functionalities from carboxylic acids (Scheme 2).

Intrigued by the possibility of a *silylthio*esterification of a carboxylic acid, we were inspired by the bulky diarylammonium (DPAT) and pentafluorophenyl ammonium (PFPAT) (thio)esterification catalysts of Ishihara,[11] Tanabe,[12] and others[2c] (Fig. 1). Though sterically encumbered alcohol substrates have been shown to be far less reactive with these catalysts in esterifications,[2c] the elongated Si–SH bond[13] (as compared to C–OH) may increase the nucleophilic viability of the bulky silylthiols in silylthioesterification attempts. Herein we report the employment of a commercially available mercaptoorganosilane for an

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**Scheme 1.** Differential reactivity of thionoesters.
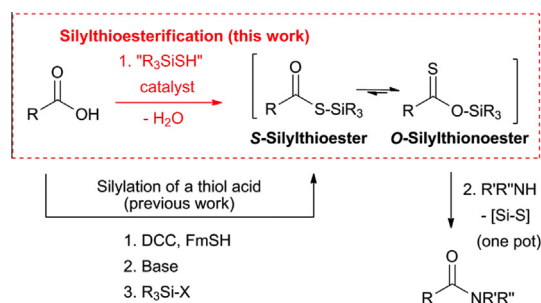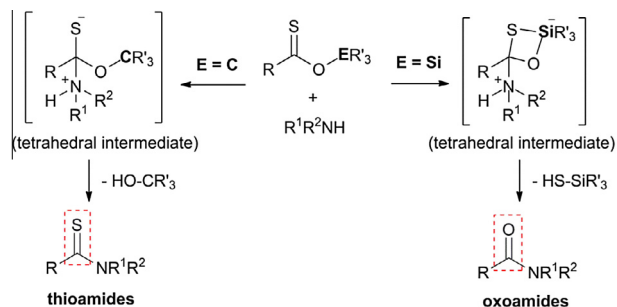


**Scheme 2.** Direct formation of a reactive O-silylthionoester species via silylthioesterification of a carboxylic acid.



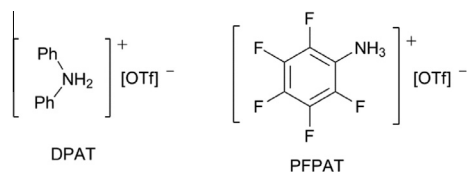**Figure 1.** Examples of ammonium salt esterification catalysts.



**Scheme 3.** Formation of O-silylthionoester.[14]

**Table 1**
Survey of [Si–S] reagents and catalysts



| Entry | [Si–S] | Solvent | Catalyst (10 mol %) | % yield[a] |
|---|---|---|---|---|
| 1 | None | Xylenes | None | 5[b] |
| 2 | None | Xylenes | PFPAT | Trace |
| 3 | Ph$_3$SiSH | Xylenes | None | 12 |
| 4 | Ph$_3$SiSH | Xylenes | PFPAT | 4[c] |
| 5 | Ph$_3$SiSH | Xylenes | PFPAT | 47[d] |
| 6 | Ph$_3$SiSH | Xylenes | PFPAT[e] | 21 |
| 7 | Ph$_3$SiSH | Xylenes | PFPAT[f] | 40 |
| 8 | Ph$_3$SiSH | C$_6$H$_5$CF$_3$ | PFPAT | 20 |
| 9 | Ph$_3$SiSH | Toluene | PFPAT | 15 |
| 10 | Ph$_3$SiSH | Heptane | PFPAT | 8 |
| 11 | Ph$_3$SiSH | Cyclohexane | PFPAT | Trace |
| 12 | Me$_3$Si–S–SiMe$_3$ | Xylenes | PFPAT | 0[g] |
| 13 | Ph$_2$MeSiSH | Xylenes | PFPAT | Trace[g] |
| 14 | $^i$Pr$_3$SiSH | Xylenes | PFPAT | 9 |
| 15 | ($^t$BuO)$_3$SiSH | Xylenes | PFPAT | Trace |
| 16 | Ph$_3$SiOH | Xylenes | PFPAT | Trace |
| 17 | Ph$_3$SiSH | Xylenes | [C$_6$F$_5$NH$_3$]$^+$[OTos]$^-$ | 6 |
| 18 | Ph$_3$SiSH | Xylenes | DPAT | 18 |
| 19 | Ph$_3$SiSH | Xylenes | [Mes$_2$NH$_2$]$^+$[OTf]$^-$ | 21 |
| 20 | Ph$_3$SiSH | Xylenes | [Ph$_2$NH$_2$]$^+$[OTos]$^-$ | 3 |

[a] Determined by GCMS using (4-$^t$BuPh)$_2$ as internal standard.
[b] BnNH$_2$ was added in the first step and heated 24 h at 60 °C.
[c] All reagents added at once, refluxed for 2 h then at 60 °C for an additional 8 h.
[d] Similar yield obtained using 'wet' xylene.
[e] 5 mol % PFPAT.
[f] 20 mol % PFPAT.
[g] Only hydrolysis of [Si–S] was observed.

intermediary production of an O-silylthionoester from a carboxylic acid with organic ammonium salt catalysts and subsequent atom-economical amidation with a nearly equimolar amount of amine. This represents the first example of O-silylthionoester formation directly from a carboxylic acid via silylthioesterification, and the first usage of a silylthiol as an amidation coupling agent.

In our initial investigations, we sought to isolate O-silylthionoesters from carboxylic acids prior to amine addition (Scheme 3). Though evidence of formation of O-silylthionoester and expulsion of water was observed by $^{13}$C NMR and IR (see Supporting Information), purification and quantification of these compounds proved challenging. For this reason, an in situ reaction with an amine (1 pot, 2-step) was envisioned as a proof of concept in order to quantify the resulting isolable amide product.

To begin our investigation of amide formation, c-C$_6$H$_{11}$-COOH was chosen as a modestly encumbered test substrate (Table 1). In a series of control experiments (entries 1–4), the exclusion of silylthiol and/or catalyst from the reaction in Step 1 resulted in minor yield of amide formation, presumably due to catalyst quenching upon amine addition and a negligible background direct condensation reaction at 60 °C over ~8 h. The reaction was then optimized by varying the stoichiometry of substrates, as well as the solvent (xylenes, trifluoromethyltoluene, toluene, heptane, cyclohexane), temperature, and reaction time to produce the following operationally simple condition: RCOOH/Ph$_3$SiSH/ ammonium salt catalyst (1:1:0.1, respectively), 2 h in refluxing
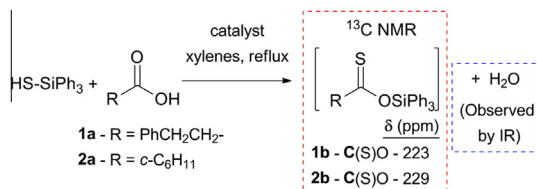
xylenes without removal of water, followed by BnNH$_2$ addition and heating at 60 °C for 4–12 h (1 pot).

Under the best conditions found in the study, a series of different 'Si–S' units were tested using known pentafluorophenylammonium triflate (PFPAT)[12] as catalyst (Table 1, entries 12–15). Since it has been shown that thiosilanes are prone to hydrolysis or alcoholysis under acidic conditions,[15,16] and that sterically bulky silyl groups are known to enhance stability of the silylthiol to hydrolysis,[16–18] we tested $^i$Pr$_3$SiSH and ($^t$BuO)$_3$SiSH.[16] As expected, the less sterically hindered 'Si–S' substrates that were tested hydrolysed immediately in the acidic conditions (entries 12 and 13), whereas the bulky $^i$Pr$_3$SiSH and hydrolytically stable ($^t$BuO)$_3$SiSH[16] were not as effective as the air stable, commercially available solid Ph$_3$SiSH, implying a balance for the silylthiol substrate between stability to undesired hydrolysis and S-nucleophilicity to generate S-silyl thioesters. A reaction time of two hours in Step 1 proved to be important, as hydrolysis of Ph$_3$SiSH (and the resulting thionoester) increased over time as observed by GCMS, but was sufficiently low at shorter reaction times even in undried solvent. The observed triphenylsilanol by-product was also tested as a possible activating agent in the reaction, but no amide formation resulted (entry 16).