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

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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 RNH_2 (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-silyl*thionoester species react with amines to generate *oxoamides* exclusively due to a subsequent *O*- to *S*-silatropic migration, while *O-alkyl*thionoesters 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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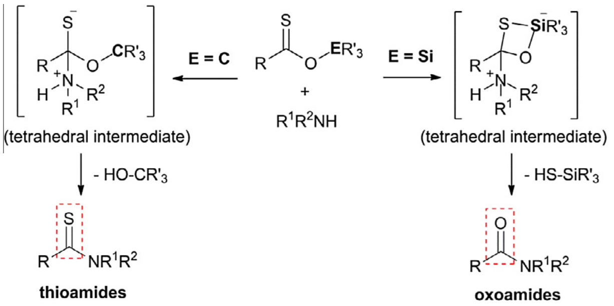
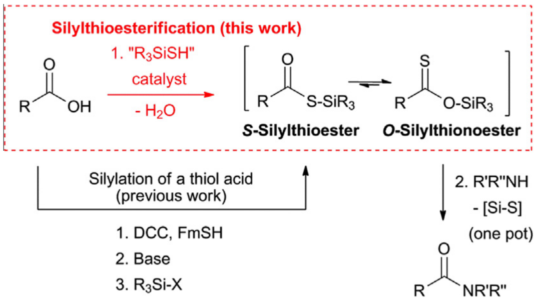


Scheme 1. Differential reactivity of thionoesters.



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

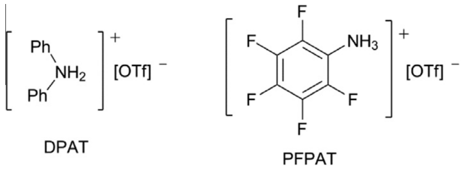
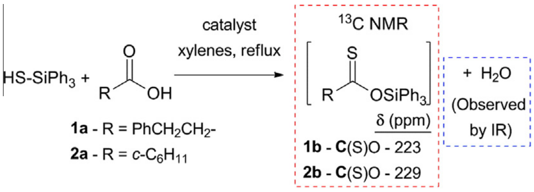
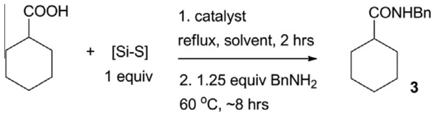


Figure 1. Examples of ammonium salt esterification catalysts.



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_3SiSH	Xylenes	None	12
4	Ph_3SiSH	Xylenes	PFPAT	4[c]
5	Ph_3SiSH	Xylenes	PFPAT	47[d]
6	Ph_3SiSH	Xylenes	PFPAT[e]	21
7	Ph_3SiSH	Xylenes	PFPAT[f]	40
8	Ph_3SiSH	$C_6H_5CF_3$	PFPAT	20
9	Ph_3SiSH	Toluene	PFPAT	15
10	Ph_3SiSH	Heptane	PFPAT	8
11	Ph_3SiSH	Cyclohexane	PFPAT	Trace
12	Me_3Si–S–$SiMe_3$	Xylenes	PFPAT	0[g]
13	$Ph_2MeSiSH$	Xylenes	PFPAT	Trace[g]
14	$^{i}Pr_3SiSH$	Xylenes	PFPAT	9
15	$(^{t}BuO)_3SiSH$	Xylenes	PFPAT	Trace
16	Ph_3SiOH	Xylenes	PFPAT	Trace
17	Ph_3SiSH	Xylenes	$[C_6F_5NH_3]^+[OTos]^-$	6
18	Ph_3SiSH	Xylenes	DPAT	18
19	Ph_3SiSH	Xylenes	$[Mes_2NH_2]^+[OTf]^-$	21
20	Ph_3SiSH	Xylenes	$[Ph_2NH_2]^+[OTos]^-$	3

[a] Determined by GCMS using $(4\text{-}^{t}BuPh)_2$ 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_6H_{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_3SiSH/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 $^{i}Pr_3SiSH$ and $(^{t}BuO)_3SiSH$.[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 $^{i}Pr_3SiSH$ and hydrolytically stable $(^{t}BuO)_3SiSH$[16] were not as effective as the air stable, commercially available solid Ph_3SiSH, 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_3SiSH (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).

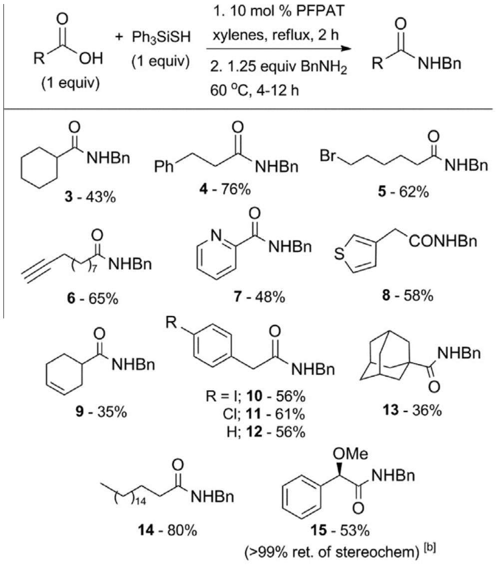
Several ammonium catalysts (entries 17–20) were then synthesized[11,12] and tested with Ph_3SiSH. An attractive feature of the ammonium salt catalysts is their ability to promote esterifications without azeotropic or chemical removal of water. PFPAT was found to be the most effective catalyst tested, even in the presence of undried solvent. Bulky diarylammonium salts (entries 18–20) were less effective than PFPAT, but all of the $[OTf]^-$ containing catalysts were more effective than the background reaction in which catalyst was excluded (entry 3). Catalysts containing the $[OTos]^-$ counteranion in the ammonium salt proved to be less efficient than the background.

The substrate scope of carboxylic acid of the reaction was then investigated using $BnNH_2$ employing the best conditions revealed in Table 1 (Table 2).

The best yields (56–80%) were obtained from sterically accessible 1° alkyl and benzylic carboxylic acids. As steric bulk increases in 2° and 3° carboxylic acids, the efficiency of the 2-step amidation sequence decreases. A number of functionalities are tolerated including alkene, alkyne, alkyl and aryl halides, benzylic ethers, and heterocycles. The enantiopure (*R*)-(−)-α-methoxyphenylacetic acid was tested to determine if racemization would occur during the reaction pathway, and complete retention of configuration (>99%) of the amide product **15** was observed by comparison to the isolated racemate using chiral HPLC. In addition, the nature of the amine nucleophile was briefly examined (Table 3). As expected, sterically hindered 2° and 3° amines (entries 2 and 3) resulted in lower yields than 1° $BnNH_2$ (entry 1), and the electron deficient and less nucleophilic 2-pyridylamine (entry 4) resulted in a lower yield over the same standard reaction time.

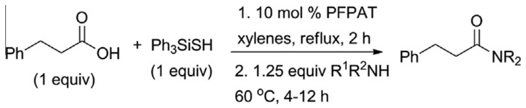
The mechanistic pathway (Scheme 4) is believed to proceed in a similar fashion to analogous PFPAT-catalyzed (thio)esterifications of carboxylic acids and alcohols/thiols. The catalyst is presumed to produce a hydrophobic environment[2c,12] in order to promote the silylthioesterification of the carboxylic acid with Ph_3SiSH, resulting in a *S*-silylthioester (not observed) which rapidly tautomerizes to the *O*-silylthionoester isomer through *S*- to *O*-silatropy. Upon amine addition, a tetrahedral intermediate is presumed formed from which a second silyl migration occurs from O to S to expel a [Si–S] unit and produce the oxoamide.

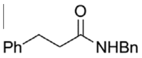
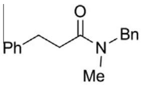
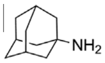
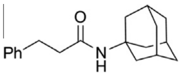
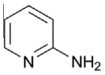
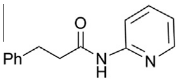
Table 2
2-Step amidation of carboxylic acids[19]

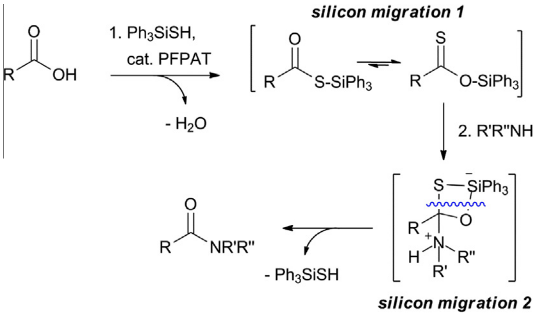


[a] Isolated yields [b] Determined by chiral HPLC from comparison with racemic product

Table 3
Effect of amine in 2-step amidation of hydrocinnamic acid[19]



Entry	R^1R^2NH	Product	Isol. % yield
1	$BnNH_2$		**4**—76
2	BnMeNH		**16**—63
3			**17**—42
4			**18**—42



Scheme 4. Presumed mechanistic pathway.

In conclusion, the first example of silylthioesterification of a carboxylic acid to produce a *O*-silylthionoester via silatropic migration has been described. This reactive intermediate was used as a proof of concept to form amides in an operationally convenient 2-step, 1-pot method without removal of water with a range of amines and carboxylic acids. Although the yields of the product amides are not competitive with the best systems currently available for amidation, this work represents a novel usage of a class of [Si–S]-containing molecules that may presage the development of more uniquely selective and efficient reactions that include, and extend beyond, the formation of amide bonds. The commercially available Ph_3SiSH reagent, while susceptible to hydrolysis over longer reaction times, is sufficiently stable in the reaction, even in undried solvent, and serves as a good nucleophile despite the steric bulk of the triarylsilyl group. Attempts were not made to recover Ph_3SiSH upon completion of the reaction, however, the hydrolysed Ph_3SiOH was observed in examples following purification by chromatography. Further explorations into the utility of silylthiols as reagents for other organic transformations as well as investigations toward an enhanced and/or recyclable silylthiol for amidation are currently underway.

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Supplementary data

Supplementary data (procedural and characterizational data for all products (^{1}H NMR and ^{13}C NMR; crude IR of *O*-silylthionoester intermediate; and HPLC chromatogram of racemic and enantiopure 15)) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.09.050.

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14. *General procedure for preparation of O-silylthionoester:* to a flame-dried flask was added NaSSiR$_3$ (0.33 mmol) and dry toluene (2-4 mL). The mixture was stirred at rt under argon for 15 min. Then R'COCl (0.33 mmol) was added via syringe and a reflux condenser was attached. The solution was heated to reflux under argon with stirring overnight. The reaction was then cooled to room temperature and solvent was removed under vacuum. Dry hexanes were added, solids were removed via filtration and washed with hexanes, and the combined filtrate was concentrated under vacuum. The *O*-silylthionoester products were analyzed without additional purification.
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19. *General procedure for 2-step synthesis of amides:* to a flame-dried flask was added carboxylic acid (0.4 mmol), Ph$_3$SiSH (116 mg; 0.4 mmol), PFPAT (14 mg; 0.04 mmol), and xylenes (2 mL). The flask was purged with argon, and a reflux condenser was attached. The solution was refluxed under argon with stirring for 2 h. The reaction was then cooled to 60 °C and amine (0.5 mmol; 1.25 equiv) was added at once (via gas-tight syringe for liquid amines) and the reaction was stirred under argon at 60 °C for approximately 8 hours (typically 6–14 h). The reaction was then cooled to room temperature, solvent was removed under vacuum, and the crude was purified directly via flash chromatography (typically using an eluant of DCM, then increasing polarity gradually to 20% EtOAc/DCM unless otherwise stated). Products **3**,[20a] **4**,[20b] **5**,[20c] **7**,[20d] **8**,[20e] **9**,[3e] **11**,[20f] **12**,[20g] **13**,[10] **14**,[20h] **15**,[20i] **16**,[20j] **17**,[20k] and **18**[20l] are all known compounds, and all were judged pure (>95%) by comparison to reported data.
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