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# In Situ Carboxyl Activation Using a Silatropic Switch: A New Approach to Amide and Peptide Constructions

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Supporting Information

**ABSTRACT:** The novel reactivity of *O*-silylthionoesters with amine nucleophiles to generate oxoamides (rather than thioamides) is described. A straightforward first-generation trimethylsilylation protocol using bistrimethylsilylacetamide (BSA) combined with the unique reactivity of the *O*-silylthionoesters toward 1° and 2° amines to generate oxoamides provides the simplest means of activating a thiol acid for peptide bond formation at neutral pH. Excellent stereoretention is observed.

The mild and chemoselective formation of amide bonds, in particular from the context of racemization-free peptide ligations, remains a focus of much modern research activity.[1] In fact, the development of new amide-forming reactions tops a recent priority list of process improvements desired by the pharmaceutical industry.[2]

We disclose herein a novel, pH-neutral method for in situ activation of the carboxyl function that underpins a surprisingly simple system for room-temperature amide and peptide bond construction. This unique carboxyl activation relies upon the known spontaneous formation of *O*-silylthionoesters from their *S*-silylthiol ester isomers by a thermodynamically driven tautomerization of the triorganosilicon group from sulfur to oxygen (Scheme 1).[3] *Surprisingly, the efficient reaction of O-silylthionoesters with amines to generate amide rather than thioamide linkages is unknown.*[4] The latter are formed exclusively when the analogous *O*-alkylthionoesters are substrates (Scheme 2).[5] Since thionoesters are significantly more reactive toward nucleophiles than thiol esters,[5c] the S-to-O silatropy and the attendant formation of oxoamides serves as a novel and mild in situ activation of the carboxyl function for nucleophilic addition.

Our first efforts focused on the stoichiometric preparation of *O*-silylthionoesters through direct silylation of thiol acids.[6] The silylation of thiol acids occurs kinetically at sulfur to generate the *S*-trimethylsilylthiol ester, but a rapid silatropic equilibration to the more stable *O*-silylthionoester ensues.[3] With this simple silylative chemistry, the key reactivity principles underscoring the amidic and peptidic coupling of *O*-silylthionoesters with amines were defined and are described herein.

With thiobenzoic acid serving as a model, in situ silylation with bistrimethylsilylacetamide (BSA) generated the *O*-trimethylsilylthionoester within 4 min at room temperature (Scheme 3).[7] Upon addition of *i*-PrNH$_2$, a reaction ensued at room temperature to provide the corresponding amide in 70% yield after 3 h. The free thiol acid itself is poorly reactive with *i*-PrNH$_2$.[8] Almost identical isolated yields of the amide resulted from a silylative activation reaction run under an argon atmosphere (64%) and one conducted open to air (70%).

The amide yields observed from the silylative activation protocol open to air are a function of the reactivity of the *O*-silylthionoester and are not caused by oxidation of the thiol acid to its corresponding diacyldisulfide, which then reacts with the amine.[9] A variety of observations support this analysis: (1) a $CDCl_3$ solution of thiobenzoic acid (1.0 equiv), BSA (1.1 equiv), and $Et_3N$ (1.3 equiv) exposed to air showed no evidence of the formation of dibenzoyldisulfide after 2 days at room temperature, and (2) the reaction rates were essentially identical for experiments run under argon after freeze−thaw degassing or open to air (1.0 equiv thiobenzoic acid, 1.3 equiv *i*-PrNH$_2$, 1.0 equiv BSA in $CDCl_3$). In other control studies, PhCOSEt remained intact after treatment with *i*-PrNH$_2$ in THF for 24 h at room temperature, both in the presence and in the absence of BSA, reaction conditions under which the *O*-silylthionoester is converted completely to the amide. Furthermore, treating 0.5 equiv of PhCOSEt and 0.5 equiv of 4-$CH_3C_6H_4COSH$ with 0.5 equiv of BSA and 1 equiv of *i*-PrNH$_2$ in THF at room temperature provided the "unscrambled" reaction product (4-$CH_3C_6H_4CONH$*i*-Pr) in 88% isolated yield with recovery of PhCOSEt in 99% yield, further supporting the mechanistic framework suggested herein. Of additional mechanistic interest, an authentic sample of bisbenzoyldisulfide did react rapidly with *i*-PrNH$_2$, but the rate of amide formation stalled at 50% conversion (see the Supporting Information).

With this background in hand, a study of the BSA activation of thiol acids for amide and peptide bond formation was undertaken. Results for amide formation are gathered in Table 1. The thiol acids were either commercially available or prepared from the corresponding 9-fluorenylmethyl thiol esters via a standard piperidine deprotection/acidification protocol[10] and were used without further purification. When the silylation of the thiol acid was carried out at room temperature in the presence of a primary or secondary amine, amide linkages were generated in very good yields within a matter of hours. Both aromatic thiol acids (entries 1−5) and aliphatic thiol acids (entries 6−10) reacted effectively with primary and secondary amines to produce secondary and tertiary amides, respectively. The hydroxyl group was well-tolerated under the reaction conditions (entry 4). Even aniline, which has low nucleophilicity, reacted smoothly with *N*-Boc-Glu thiol acid to produce the corresponding anilide (entry 7). Sterically hindered thiol acids and amines also reacted to provide the sterically congested amides in quite good yields (entries

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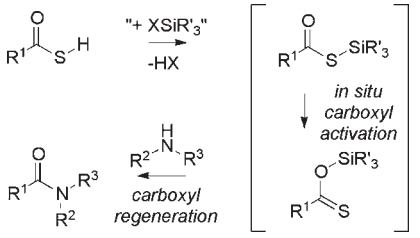
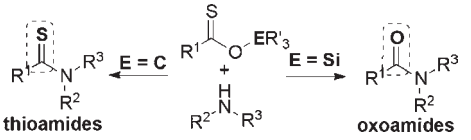
**Scheme 1. In Situ Carboxyl Activation Using a Silicon Switch**




**Scheme 2. Differential Reactivity of Thionoesters**




**Scheme 3. Exploratory Reactions Using Thiobenzoic Acid**

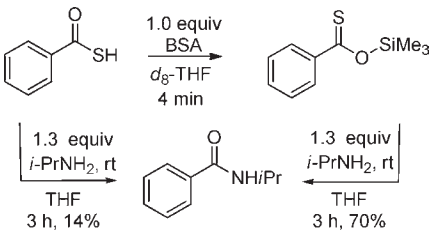
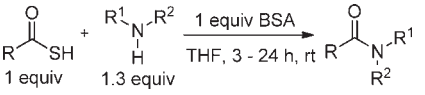
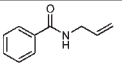
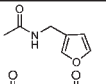
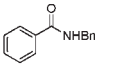
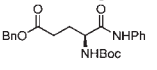
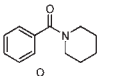
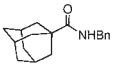
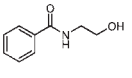
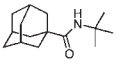
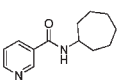
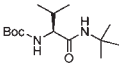



**Table 1. S-to-O Silylative Switch-Induced Amide Formation**




| entry | amide | hr *yld*[a] (%) | entry | amide | hr *yld*[a] (%) |
|---|---|---|---|---|---|
| 1 |  | 3 *91* | 6 |  | 3 *82* |
| 2 |  | 3 *89* | 7[b] |  | 24 *69* |
| 3 |  | 3 *76* | 8 |  | 5 *65* |
| 4 |  | 5 *74* | 9 |  | 23 *81* |
| 5 |  | 24 *62* | 10[b] |  | 24 *71* |

[a] General procedure: 1 equiv of thiol acid, 1.3 equiv of amine, and 1 equiv of BSA were stirred at room temperature in THF. Isolated yields are shown. [b] No racemization was observed.

8−10). Remarkably, doubly hindered amides were also obtained in good yields (entries 9 and 10), although longer reaction times were required at room temperature. No racemization was observed for entries 7 and 10.

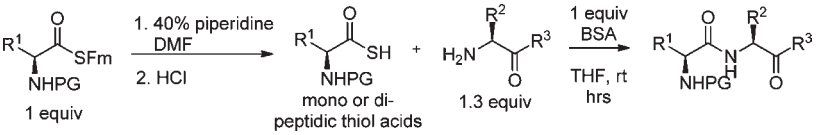
Peptide bond formation was also easily accomplished using the silylative activation of N-protected α-amino thiol acids (Table 2). The peptidic thiol acids were generated from the corresponding 9-fluorenylmethyl thiol esters by the method of Crich[10] and used without further purification. As shown in Table 2, Gly, Met, Phe, Glu, and Pro thiol acid residues reacted easily to give the corresponding dipeptides (entries 1−9). It is noteworthy that sterically hindered α-amino thiol acids such as Val (entries 10 and 11) and even 2-aminoisobutyric thiol acid (entry 12) were effectively coupled using this method, although longer reaction times were required to achieve acceptable yields at room temperature. The amino acids, Phe, Tyr, Val, Ala, Gly, Met, Trp, and Pro were all equally effective as N-terminal coupling partners (entries 1−15). The formation of Cbz-Gly-L-Tyr-OMe indicates that phenolic residues do not interfere with the coupling reaction (entry 2). Cbz-Gly-L-Phe-OMe, which was formed as a single dipeptide in 78% yield from Cbz-Gly-SH and L-Phe-OMe under the general coupling conditions (entry 1), was generated in an almost identical isolated yield (71%) when an equimolar amount of Cbz-L-Arg-OH was added to the reaction mixture. This simple experiment confirms the compatibility of this method with both carboxylic acid and guanidine functionalities.

Even prior to any extensive studies of the influence of electronic and steric effects of the silicon reagent, epimerization of sensitive stereocenters using the pH-neutral "silylative switch" protocol for peptide coupling was found to be competitive with or better than existing technologies. For example, the absence of epimerization at both coupling partners was verified by HPLC analysis for the dipeptides shown in entries 1 and 3−5 of Table 2 and for the tripeptide Boc-L-Phe-L-Pro-L-Ala-OEt in entry 13. Furthermore, both the Anderson (entry 14) and Anteunis (entry 15) tests were conducted to evaluate epimerization-prone linkages during the peptide formation process.[1a] Of significance for future systematic studies of the influence of the silylating agent, $PhSiH_2Cl$ gave lower levels of epimerization than BSA in the few cases preliminarily investigated. In the Anteunis test, this method gave less than 5% epimerization, which is superior to results using *N*,*N*′-dicyclohexylcarbodiimide (18.8% DL) and PyBOP (6.6% DL) to facilitate the coupling between Z-Gly-L-Phe-OH and L-Val-OMe·HCl, as reported in the literature.[11]

A comparison of the reaction of Boc-L-Glu(O-*t*Bu)-SH and Gly-OMe using a traditional peptide-coupling protocol with the new silylative activation is both illustrative and compelling, demonstrating the unique reactivity of the *O*-silylthionoester approach to peptide construction. A 1:1.3 mixture of Boc-L-Glu(O-*t*Bu)-SH and Gly-OMe·HCl was first exposed to $Et_3N$ to liberate the amine and then to 1 equiv of BSA in THF at room temperature to produce the peptide in 74% yield within 8 h. In contrast, traditional activation of the thiol acid with PyBop and diisopropylethylamine (DIEA) gave a mixture of the desired peptide (40%) and the thioamide (28%), as depicted in Scheme 4.

The origin of the different reactivities of *O*-alkylthionoesters and *O*-silylthionoesters toward amines is suggested in Scheme 5. The mechanism of the known reaction of *O*-alkylthionoesters with amines to give thioamides is straightforward.[5c] Attack by the nucleophilic amine at the C═S bond of the thionoester generates tetrahedral intermediate **A**, which can only collapse to create a thioamide or revert back to starting materials. Without cleavage of the strong R−O bond of **A** in Scheme 5, an oxoamide cannot be formed from the tetrahedral intermediate generated from the

**Table 2. Activation of Thiol Acids for Peptide Synthesis via the "Silylative Switch"[a]**



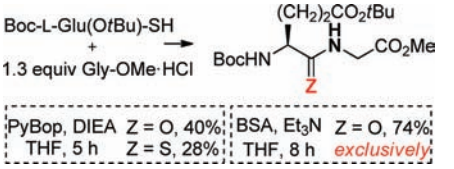

| entry | amino thiol acid | amino ester | di- or tripeptide | time (h) | yield (%)[b] | epimerization[c] |
|---|---|---|---|---|---|---|
| 1 | Cbz-Gly-SH | L-Phe-OMe·HCl | Cbz-Gly-L-Phe-OMe | 10 | 78 | L/D = 100:0 |
| | | | | 10 | 71[d] | |
| 2 | Cbz-Gly-SH | L-Tyr-OMe·HCl | Cbz-Gly-L-Tyr-OMe | 10 | 69 | |
| 3 | Boc-L-Met-SH | L-Val-OEt·HCl | Boc-L-Met-L-Val-OEt | 10 | 83 | LL/DL > 99:1 |
| 4 | Boc-L-Phe-SH | L-Ala-OEt·HCl | Boc-L-Phe-L-Ala-OEt | 12 | 72 | LL/DL > 99:1 |
| 5 | Boc-L-Glu(O*t*Bu)-SH | L-Val-OMe·HCl | Boc-L-Glu(O*t*Bu)-L-Val-OMe | 10 | 71 | LL/DL > 99:1 |
| 6 | Boc-L-Glu(OBn)-SH | Gly-OEt·HCl | Boc-L-Glu(OBn)-Gly-OEt | 8 | 76 | |
| 7 | Boc-L-Glu(OBn)-SH | L-Met-OMe·HCl | Boc-L-Glu(OBn)-L-Met-OMe | 10 | 68 | |
| 8 | Boc-L-Glu(OBn)-SH | L-Trp-OMe·HCl | Boc-L-Glu(OBn)-L-Trp-OMe | 8 | 74 | |
| 9 | Boc-L-Pro-SH | L-Val-OMe·HCl | Boc-L-Pro-L-Val-OMe | 10 | 65 | |
| 10 | Boc-L-Val-SH | L-Pro-OMe·HCl | Boc-L-Val-L-Pro-OMe | 48 | 70 | |
| 11 | Boc-L-Val-SH | L-Phe-OMe·HCl | Boc-L-Val-L-Phe-OMe | 63 | 67 | |
| 12 | Boc-Aib-SH | L-Trp-OMe·HCl | Boc-Aib-L-Trp-OMe | 54 | 74 | |
| 13 | Boc-L-Phe-L-Pro-SH | L-Ala-OEt·HCl | Boc-L-Phe-L-Pro-L-Ala-OEt | 8 | 65[e] | LLL/LDL > 99:1 |
| 14 | Cbz-Gly-L-Phe-SH | Gly-OEt·HCl | Cbz-Gly-L-Phe-Gly-OEt | 15 | 80 | L/D > 96:4 |
| | | | | | 60[e] | L/D > 96:4 |
| | | | | | 73[f] | L/D = 97:3 |
| 15 | Cbz-Gly-L-Phe-SH | L-Val-OMe·HCl | Cbz-Gly-L-Phe-L-Val-OMe | 15 | 74 | LL/DL > 95:5 |
| | | | | | 50[e] | LL/DL > 96:4 |
| | | | | | 55[f] | LL/DL = 97:3 |

[a] General procedure: A solution containing 1 equiv of the N-protected α-amino thiol acid (generated from the corresponding 9-fluorenylmethyl thiol ester via piperidine deprotection/HCl acidification) and 1 equiv of BSA in THF was added to a solution containing 1.3 equiv of the amino acid hydrochloride salt and 1.3 equiv of triethylamine or DIEA in THF. The mixture was then stirred at room temperature for 8−63 h. [b] Isolated yields. [c] Epimerization ratios were determined by HPLC. [d] A solution containing 1 equiv of Cbz-Gly-SH and 1 equiv of BSA in THF was added to a solution containing 1 equiv of Cbz-L-Arg-OH, 1.3 equiv of L-Phe-OMe·HCl, and 1.3 equiv of triethylamine. The reaction mixture was stirred at room temperature for 10 h. [e] To a $CH_3CN$ solution containing 1 equiv of dipeptidic thiol acid, 1.1 equiv of $PhSiH_2Cl$, and 1.3 equiv of amino ester hydrochloride salt was added 2.3 equiv of DIEA, and the mixture was stirred at room temperature for 8 or 15 h. [f] To a $CH_3CN$ solution containing 1 equiv of dipeptidic thiol acid, 1.1 equiv of $PhSiH_2Cl$, and 2 equiv of amino acid ester hydrochloride salt was added 3.0 equiv of DIEA, and the mixture was stirred at room temperature for 15 h.

*O*-alkylthionoester. In contrast, however, the tetrahedral intermediate formed by attack of an amine on an *O*-silylthionoester can participate in a tautomeric migration of silicon from oxygen to sulfur, possibly via the pentavalent Si intermediate **B**.

In conclusion, *O*-silylthionoesters, generated in situ from thiol acids via a straightforward and simple sequence of S-silylation followed by S-to-O silatropy, have been shown to react with 1° and 2° amines in a mild, ambient temperature construction of amides and mono-, di-, and tripeptides. Both unhindered and highly hindered substrates participated in room-temperature amide and peptide bond formation, although longer reaction times were required for the sterically encumbered entities. Stereocenter epimerization was absent for most substrates and very low for substrates known to be problematic in traditional peptide-coupling protocols. Although a thorough study of the influence of the nature of the silane on the reaction rate and epimerization level of the amide/peptide coupling has yet to be undertaken, a single example probing variation of the silane structure suggested that unwanted epimerization can be positively influenced by the nature of the silylating agent. At present, this straightforward first-generation trimethylsilylation protocol combined with the unique reactivity of *O*-silylthionoesters

**Scheme 4. Silylative versus Traditional Activation of a Thiol Acid**




toward 1° and 2° amines to generate oxoamides provides the simplest means of activating a thiol acid for peptide bond formation at neutral pH.[12] The tolerance of hydroxylic and phenolic groups to the reaction conditions holds promise for the extension of the silylative protocol to glycopeptide synthesis. This and experiments to understand how the nature of the triorganosilyl moiety influences the reactivity of the *O*-triorganosilylthionoester toward various nucleophiles are planned. Finally, in its most compelling conception, the formation of amides would take place directly from carboxylic acids and amines via in situ-generated *O*-silylthionoesters using only catalytic quantities of a thiosilylating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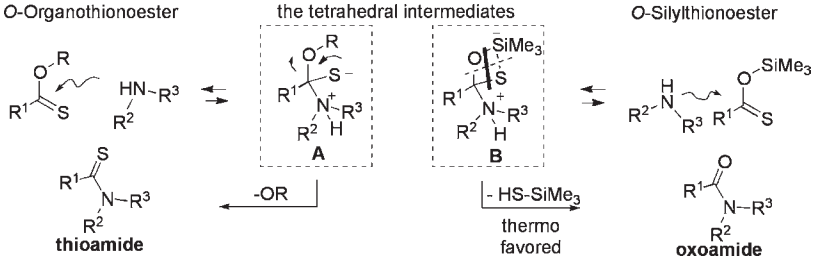
**Scheme 5. S-to-O Silylative Switch Amidation Mechanism**




agent. Experiments to achieve this forward-looking goal are in progress.

## ■ ASSOCIATED CONTENT

**Supporting Information.** Experimental procedures, synthesis and characterization of all new compounds, and scanned spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) As a control reaction to assess the mechanism of the reaction of thiol acids with azides to generate amides, Williams and co-workers investigated the reaction of *O*-trimethylsilylthionobenzoate with benzyl azide, which generated only trace amounts of corresponding amide (see ref 12h). In footnote 24 within that manuscript, false coupling results obtained with unpurified and unsparged thiol acid were assumed to be caused by impurities and/or incomplete formation of the thionoester.

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(6) Tautomerization of an *S*-silylthioester to an *O*-silylthionoester functions as a novel in situ activation of the carboxyl function for reaction with nucleophiles. Therefore, any synthetic method that can directly generate an *S*-silylthioester under mild reaction conditions can serve as an entry to the *O*-silylthionoester.

(7) Thiobenzoic acid: $^{1}$H NMR: $\delta$ 7.91 ($H_{ortho}$, dd, $J$ = 1.2, 8.4 Hz, 2H), 7.61 ($H_{para}$, dt, $J$ = 1.2, 8.0 Hz, 1H), 7.47 ($H_{meta}$, t, $J$ = 7.8 Hz, 2H), 4.58 (S−*H*, br s, 1H). IR: 2567(sh), 1660, 1594, 1580 cm$^{-1}$. *O*-Trimethylsilylthionoester (see ref 12h): $^{1}$H NMR: $\delta$ 8.21 ($H_{ortho}$, d, $J$ = 8.4 Hz, 2H), 7.54 ($H_{para}$, t, $J$ = 7.2 Hz, 1H), 7.37 ($H_{meta}$, t, $J$ = 7.8 Hz, 2H), 0.5 ($Me_3Si$, s, 9H). $^{13}$C NMR: $\delta$ 212.6 (S═*C*−O), 139.6, 133.0, 128.9, 128.1, 0.3.

(8) From the recent focus on reagent-based methods to activate thiol acids for reaction with amines to give amides (see refs 10 and 12 in this manuscript), one might infer that thiol acids are unable to directly acylate amines. Examples of amine acylation by thiol acids without special activation have appeared in the literature for decades (see: Cronyn, M. W.; Jiu, J. *J. Am. Chem. Soc.* **1952**, *74*, 4726. Sheehan, J. C.; Johnson, D. A. *J. Am. Chem. Soc.* **1952**, *74*, 4726. Hawkins, P. J.; Tarbell, D. S.; Noble, P. *J. Am. Chem. Soc.* **1953**, *75*, 4462. Hirabayashi, Y.; Mizuta, M.; Kojima, M.; Horio, Y.; Ishihara, H. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 791. ). However, some caution in interpreting the published results is appropriate, since the direct reaction of thioacids with amines is highly dependent on the purity of the thioacid.

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