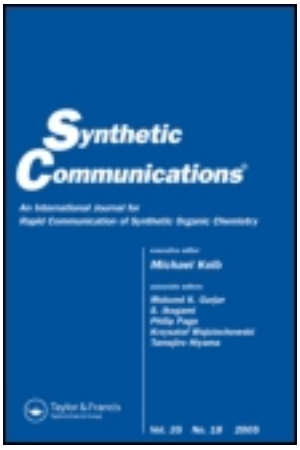

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Aminolysis of 3-Phenyl Propylthiol Esters Leading to Diverse Sets of Amides

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Abstract: 3-Phenyl propylthiol esters were investigated as "activatable" solution phase linkers. These linkers can be activated with silver salts and upon treatment with amines can be converted to the corresponding amides. Under unactivated conditions, the linker is stable to a variety of reagents and reaction conditions including treatment with amines.

Keywords: Activatable linkers, amides synthesis, solid phase synthesis, thioesters

INTRODUCTION

A powerful means of achieving diverse combinatorial libraries is to introduce structural diversity concomitant with cleaving the product from the resin. For example, tetrafluorophenol esters,[1] oximes,[2] and Marshal linker[3] are all solid-supported linkers for tethering acids to a solid support that can afford a number of different amides upon cleavage with amines. Treatment of these solid supports with amines cleaves the linker and affords the desired amide products; however, the use of amines or other nucleophiles in steps other than the cleavage step is precluded because of the activated nature of these linkers. Barn and coworkers[4]

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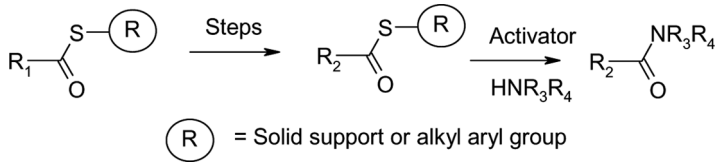


Scheme 1. Catch and release process on solid support.

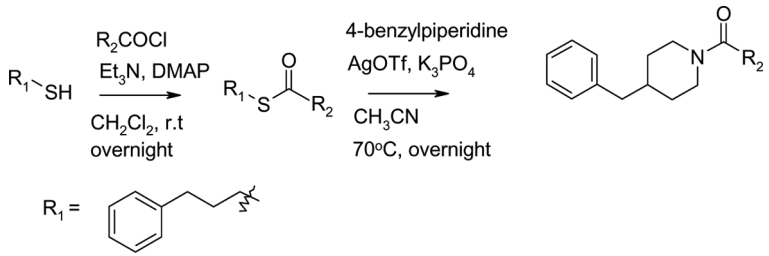
have shown that a Wang ester linkage, which is stable to a number of nucleophiles including amines, can be activated with $AlCl_3$ and can afford the corresponding amides upon addition of amines. Because strong Lewis acids are not compatible with a number of functional groups typically found in heavily functionalized molecules, we were interested in developing a stable linker system that can afford amides under more mild conditions.

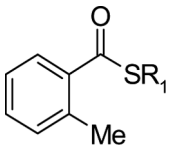
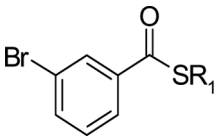
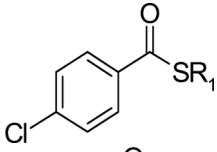
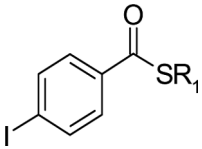
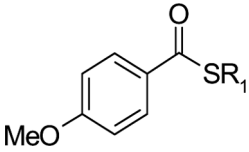
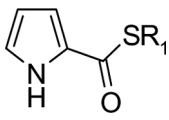
There are literature reports that thioesters can be converted into amides in the presence of silver[5] or mercury salts,[6] and this linker has been utilized in the solid-phase synthesis of peptides.[7] We were interested in further exploring the potential of this linker in the synthesis of diverse sets of amides. Our initial studies with thioesters on solid support were hampered because of the labile nature of these linkers to amines even under unactivated conditions. We thereby undertook a systematic study to evaluate the potential of thioesters as activatable linkers. Our plan was to first study the thioester linkage in solution, wherein convenient methods of quantification exist, and then apply it to solid-phase synthesis as illustrated in Scheme 1. Herein, we report our solution-phase studies.

RESULTS AND DISCUSSION

After screening a variety of thioesters, we were pleased to find that 3-phenyl propylthiol esters possessed the sought-after linker qualities. 3-Phenyl propylthiol ester can be activated with $AgOTf/K_3PO_4$ and undergo a smooth reaction with amines, affording the corresponding amides. Importantly, however, in the absence of the activator, the thiol esters do not react with amines. The best conversions to amides were obtained by treating 3-phenyl propylthiol ester with amines in the presence of AgOTf (3 eq.) and K_3PO_4 (3 eq.) in acetonitrile at 70°C for 24 h. Silver triflate turned out to be the activator of choice from a number of thiophilic reagents including Ag_2CO_3, Ag_2O, $FeSO_4$, $FeCl_3$, $FeBr_3$, $HgCl_2$, and $Cu(OAc)_2$. Although AgOAc was found to be as equally effective as AgOTf, the better solubility profile of AgOTf meant that this particular

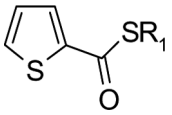
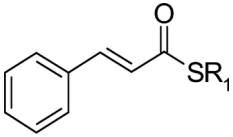
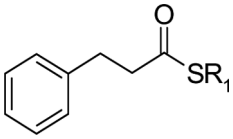
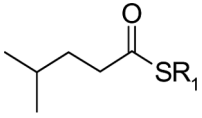
Table 1. Variation of carboxy group in thioesters



Thioester	Yield (%)
	84
	89
	98
	88
	92
	89

(*Continued*)

Table 1. Continued

Thioester	Yield (%)
	83
	91
	87
	74

silver salt was selected for further study. Meanwhile, K_3PO_4 in acetonitrile was determined to be the best base/solvent combination.

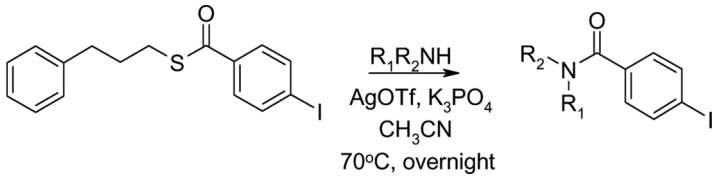
Other solvents tried were tetrahydrofuran (THF), dimethylformamide (DMF), dimethylsulfoxide (DMSO), and dioxane; other bases tried were K_2CO_3, Cs_2CO_3, NEt_3, and diisopropylethyl amine (DIPEA).

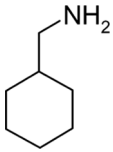
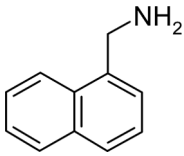
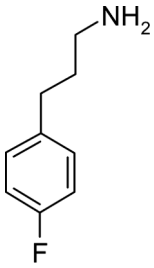
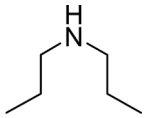
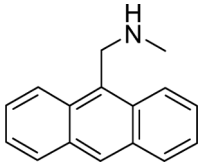
We were interested in determining the scope of the reaction by varying the carboxy group. Using 4-benzyl piperidine as a representative secondary amine, a variety of 3-phenyl propylthiol esters were studied as summarized in Table 1. Aliphatic, electron-deficient and electron-rich aromatic, and hetero aromatic 3-phenyl propylthiol esters were efficiently converted to the corresponding amides under the condition developed. Although some substrates reacted even at room temperature, it was most convenient to run the reactions at 70°C to ensure complete conversions.

The scope of amines tolerated in this reaction was studied next. Using p-iodophenyl thioester as the common substrate, primary amines and both cyclic and acyclic secondary amines were found to be good substrates for converting thioesters into amides (Table 2).

We also investigated the compatibility of 3-phenylpropanethiol linker to four different reactions: reductive amination, amide formation, and Stille and Suzuki coupling reactions. The reductive amination of benzaldehyde thioester with primary and secondary amines using $NaBH(OAc)_3$ in CH_2Cl_2 at room temperature overnight is summarized

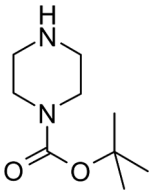
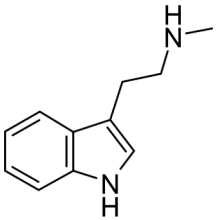
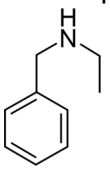
Table 2. Amidation of thioester with a variety of amines



Amine	Yield (%)
	79
	74
	89
	84
	88

(*Continued*)

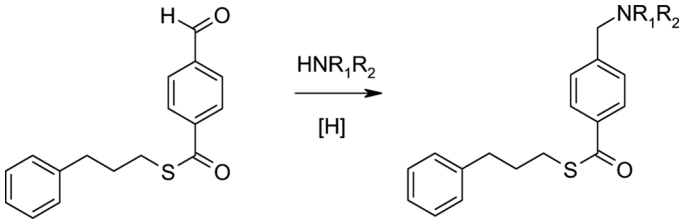
Table 2. Continued

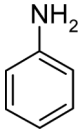
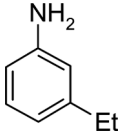
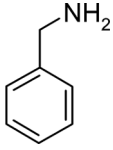
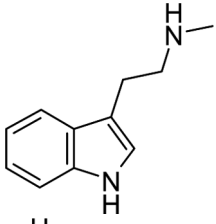
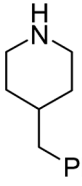
Amine	Yield (%)
	79
	90
	81

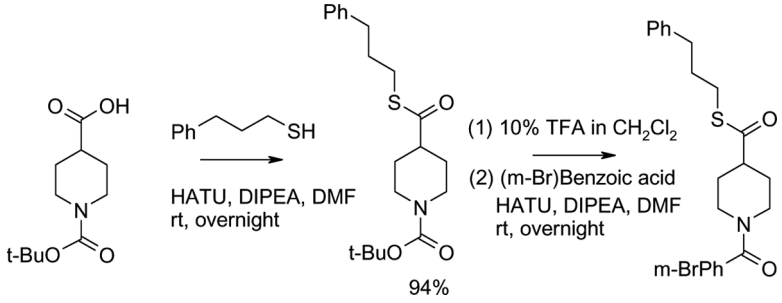
in Table 3. There was no premature cleavage of the thioester linker under these conditions.

The stability of 3-phenyl propylthiol ester was then investigated under the standard amide coupling reaction. As shown in Scheme 2, 3-phenyl propylthiol ester was treated with trifluoroacetic acid (TFA) to give the corresponding amine, which was subjected to standard peptide coupling conditions, affording the desired amide in 92% yield. Once again, the thioester linker remained intact during this transformation. 3-Phenyl propylthiol esters were also found to be compatible with Stille and Suzuki cross-coupling reactions (Scheme 3). p-Iodobenzoyl thioester ester undergoes a Stille cross-coupling reaction with $PhSnBu_3$, affording the biaryl product. This same thiol ester participated in an efficient Suzuki cross-coupling reaction with p-tolyl boronic acid in the presence of a palladium catalyst. The product from the Suzuki coupling reaction, obtained in 93% yield, was treated with 4-benzyl piperidine under the activated condition developed to give the corresponding amide in quantitative yield. Interestingly, Liebeskind and coworkers[8] have reported that thioesters can be converted into the corresponding ketones with aryl boronic acids in the presence of a palladium catalyst and copper salts. In

Table 3. Reductive amination reaction displaying the stability of thioester linker to treatment with amines under "unactivated" conditions



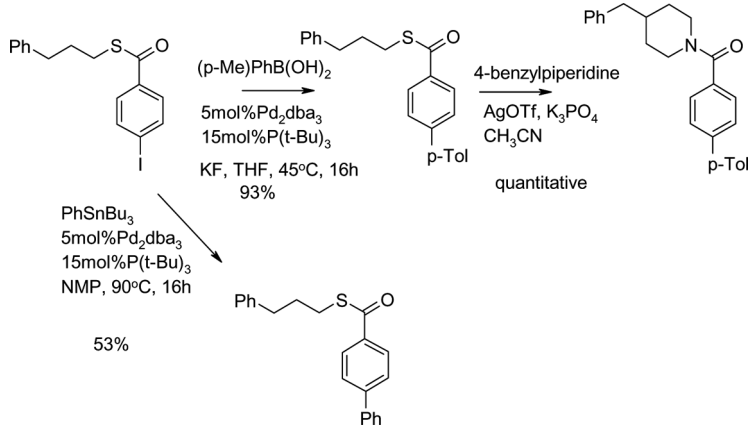
Amine	Yield (%)
	52
	88
	68
	79
	57



Scheme 2. Amide coupling reaction.

our case, no ketone product was observed, presumably because of the absence of copper salt.

In conclusion, we have demonstrated that 3-phenyl propane thiol esters can be utilized as stable linkers in solution-phase chemistries. This linker tolerates a number of reaction conditions including reductive amination, Stille and Suzuki coupling, Boc cleavage, and amide coupling. Equally importantly, these thiol esters can be activated with silver acetate at the appropriate point in the synthesis and be efficiently converted to the corresponding amides. Further exploration of the solid-supported version of this work using silica-bound propylthiol is in progress and will be reported in due course.



Scheme 3. Suzuki and Stille coupling reactions.

EXPERIMENTAL

Representative Procedure for the Synthesis of Thiocarbamates (Tables 1 and 2)

Triethyl amine (10 mmol) and dimethylaminopyridine (25 mg) were added to a solution of acid chloride (3.6 mmol) in dichloromethane (25 mL) at 0°C followed by 3-phenypropyl thiol (3.6 mmol), and the resulting mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography.

Representative Procedure for the Synthesis of Amides from Thiocarbamates (Tables 1 and 2)

Amine (0.36 mmol), anhydrous silver trifluoromethanesulfonate (0.9 mmol), and potassium phosphate (0.9 mmol) were added to a stirred solution of 3-phenylpropyl thiocarbamate (0.3 mmol) in acetonitrile (3 mL). After 16 h at 70°C, the reaction mixture was filtered through a plug of silica gel (5 g), eluted with acetonitrile (10–15 mL), and concentrated under reduced pressure. Then the crude product was purified by column chromatography to afford the corresponding amide.

Representative Procedure for the Reductive Amination Reactions (Table 3)

The amine (1 mmol) was added to a solution of the S-(3-phenylpropyl) 4-formylbenzenecarbothioate (0.3 mmol) in dichloromethane (5 mL) and stirred at room temperature overnight. $NaCN(BH)_3$ (1.5 mmol) was added to the reaction mixture and heated at reflux overnight. After the usual aqueous workup, the crude product was purified by flash chromatography.

Synthesis of tert-Butyl 4-(3-Phenylpropylsulfanylcarbonyl)piperidine-1-carboxylate

O-(7-Azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate (HATU) (5 mmol) was added to a solution of 1-tert-butoxycarbonylpiperidine-4-carboxylic acid (5 mmol), 3-phenylpropane thiol (4 mmol), and diisopropylethyl amine (10 mmol) in dimethyl acetamide

(10 mL), and the resulting mixture was stirred at room temperature overnight. After the usual aqueous workup, the residue was purified by flash chromatography eluting with 10% ethyl acetate in hexane to give tert-butyl 4-(3-phenylpropylsulfanylcarbonyl)piperidine-1-carboxylate (91%).

Synthesis of 4-(3-Phenylpropylsulfanylcarbonyl)piperidine

A solution of tert-butyl 4-(3-phenylpropylsulfanylcarbonyl)piperidine-1-carboxylate (0.3 mmol) in 5% trifluroacetic acid in dichloromethane (10 mL) was stirred at room temperature overnight. Solvent was removed under reduced pressure, and the residue was used for the subsequent step without further purification.

Synthesis of S-(3-Phenylpropyl) 1-(3-Bromobenzoyl)piperidine-4-carbothioate

HATU (0.5 mmol) was added to a solution of 4-(3-phenylpropylsulfanylcarbonyl)piperidine (0.5 mmol), 3-bromobenzoic acid (0.5 mmol), and diisopropylethyl amine (1.5 mmol) in dimethyl acetamide (5 mL), and the resulting mixture was stirred at room temperature overnight. After the usual aqueous workup, the residue was purified by flash chromatography eluting to give S-(3-phenylpropyl) 1-(3-bromobenzoyl) piperidine-4-carbothioate (92%).

Synthesis of S-(3-Phenylpropyl) 4-(p-Tolyl)benzenecarbothioate

p-Tolyl boronic acid (0.7 mmol) was added to a solution of S-(3--phenylpropyl) 4-iodobenzenecarbothioate (0.5 mmol), $Pd_2(dba)_3$ (5 mol%) tributylphosphine (15 mol%), and potassium fluoride (KF) (1.5 mmol) in THF (5 mL), and the resulting mixture was heated at 45 °C overnight. After the usual aqueous workup, the residue was purified by flash chromatography eluting to give S-(3-phenylpropyl) 4-(p-tolyl)benzenecarbothioate (93%).

Synthesis of (4-Benzyl-1-piperidyl)-[4-(p-tolyl)phenyl]methanone

Following the general procedure described previously for the synthesis of amides from thiocarbamates, (4-benzyl-1-piperidyl)-[4-(p-tolyl)phenyl]

methanone was made starting from S-(3-phenylpropyl) 4-(p-tolyl) benzenecarbothioate.

S-(3-Phenylpropyl) 4-Phenylbenzenecarbothioate

Phenyltributyl tin (0.6 mmol) was added to a solution of S-(3--phenylpropyl) 4-iodobenzenecarbothioate (0.5 mmol), $Pd_2(dba)_3$ (5 mol%), and tributylphosphine (15 mol%) in N-methyl pyrolidinone (NMP) (5 mL), and the resulting mixture was heated at 90°C overnight. After the usual aqueous workup, the residue was purified by flash chromatography eluting to give S-(3-phenylpropyl) 4-phenylbenzenecarbothioate (53%).

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