

THE CONVERSION OF CARBOXYLIC ACIDS TO AMIDES VIA TIN(II) REAGENTS

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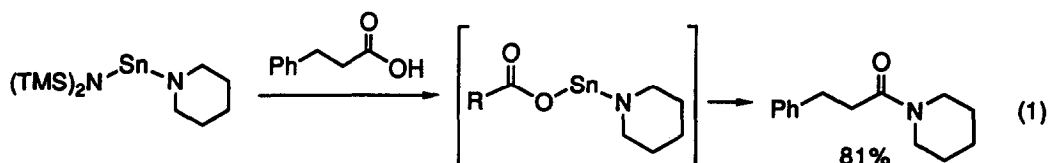
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Abstract: Unsymmetrical tin(II) amides can be generated, *in situ*, by adding one equivalent of an amine to bis(bis(trimethylsilylamino) tin, $\text{Sn}[\text{N}(\text{TMS})_2]_2$). Treatment of carboxylic acids with these tin(II) reagents derived from alkyl or aryl amines results in smooth conversion to the corresponding N-alkyl or N-aryl amides.

Carboxylic acids can be converted to amides by a variety of methods.^{1,2} The most common methods involve either conversion of the carboxylic acid to a more reactive functional group such as an acid chloride, mixed anhydride, acyl azide, or active ester, or via an *in situ* activation of the carboxylic acid by reagents such as dicyclohexyl carbodiimide (DCC). The DCC methodology and mixed anhydride approach are widely used for the synthesis of peptides.^{3,4}

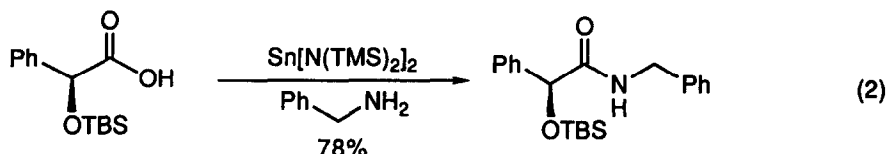
During the course of our research on the chemistry of divalent tin, we discovered a fundamentally new and useful method for converting carboxylic acids to amides. We were aware from our previous work with unsymmetrical tin(II) compounds of type $\text{SnN}(\text{TMS})_2\text{NR}_2$, that the alkyl amino group can be selectively transferred to carbonyl groups to give N,N-dialkyl enamines.⁵ This reaction was highly chemoselective and we found no evidence for formation of N,N-bis(trimethylsilyl) enamines. More recently, we developed a procedure for the direct conversion of esters to amides using these unsymmetrical tin(II) amides.⁶ Once again, only the alkyl amino group was transferred.

Unsymmetrical tin(II) amides can be prepared *in situ* by addition of an amine to bis(bis(trimethylsilylamino) tin.⁷ Further reaction of $\text{SnN}(\text{TMS})_2\text{NR}_2$ with a carboxylic acid generates a tin(II) amido carboxylate via displacement of the remaining silazane ligand. This intermediate, upon further stirring at room temperature, undergoes a facile intramolecular rearrangement to give an amide with concomitant expulsion of tin oxide. For example, addition of hydrocinnamic acid to $\text{Sn}(\text{piperidinyl})\text{N}(\text{TMS})_2$ yields an intermediate tin(II) piperidinyl carboxylate. When this piperidinyl carboxylate was allowed to stir at room temperature overnight or was heated at reflux for one hour, we obtained the piperidinyl amide in 81% yield (eq 1).



When we examined the scope of this reaction using a variety of amines and carboxylic acids, we found it to be fairly general.⁸ The tin(II) reagent can be derived from primary or secondary amines, such as benzylamine, pyrrolidine, piperidine, and morpholine (Table 1). In the case of aromatic amines, such as *p*-methoxy aniline, we obtained slightly better yields using two equivalents of the tin(II) reagent. The reaction also worked well using phenylacetic acid, hydrocinnamic acid, cinnamic acid, and citronellic acid as test substrates. No conjugate addition products were formed in the case of cinnamic acid. Furthermore, the absence of [2+2] cycloadducts in the case of citronellic acid suggests that the reaction does not proceed via dehydration of the carboxylic acid to a ketene, followed by addition of the amine.

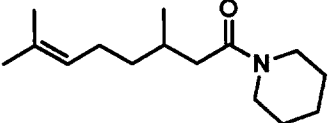
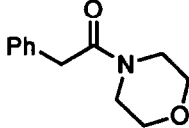
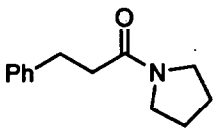
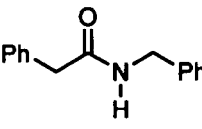
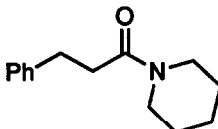
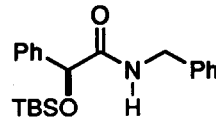
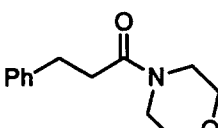
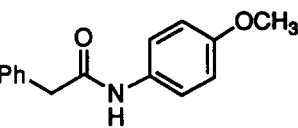
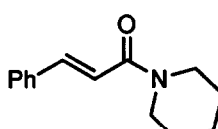
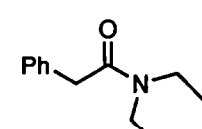
We were also pleased to find that carboxylic acids with α -chiral centers can be converted to amides without racemization. Specifically, reaction of *S*-2-(*tert*-butyldimethylsilyloxy)phenylacetic acid with the tin(II) amide generated from $\text{Sn}[\text{N}(\text{TMS})_2]_2$ and benzylamine gave the *N*-benzyl amide in 78% yield (eq 2). An optical rotation of the desilylated material, *S*-(+)- α -hydroxy-*N*-(phenylmethyl)-benzeneacetamide,⁹ established that no racemization had occurred during formation of the amide.



While optimizing the reaction conditions for this transformation, we evaluated the effect of modifying the order of addition of reagents. We found that the same results and yields can be achieved regardless of whether the amine or acid is added first to bis(bis(trimethylsilyl)amino) tin. Addition of a carboxylic acid to $\text{Sn}[\text{N}(\text{TMS})_2]_2$ generates an *N,N*-disilyl tin(II) carboxylate, which is converted to an *N*-alkyl or *N*-aryl tin(II) carboxylate when treated with an alkyl or aryl amine. Thus, one can use whichever order of addition of acid and amine to $\text{Sn}[\text{N}(\text{TMS})_2]_2$ is most convenient.

In summary, acids can be converted to amides under mild conditions and in good to excellent yield using tin(II) reagents. This method can be used for a wide variety of substrates, including saturated and unsaturated carboxylic acids, and both primary and secondary amines. Finally, carboxylic acids with α -chiral centers are converted to amides without racemization.

Table I. Conversion of Carboxylic Acids to Amides.

Entry	Amide	Yield (%)	Entry	Amide	Yield (%)
1		99	6		93
2		89	7		82
3		81	8		78
4		72	9		65 (83) ^a
5		81	10		73

a) Two equivalents of tin reagent were used.

The following procedure is representative: To a THF solution of $\text{Sn}[\text{N}(\text{TMS})_2]_2$ (0.350 g, 0.796 mmol, 0.079 M) at room temperature and under a nitrogen atmosphere, was added citronelic acid (0.134 g, 0.789 mmol) in a THF solution (ca. 1 mL). Piperidine (0.079 mL, 0.80 mmol) was then added neat to the stirring solution. The reaction was monitored by GC and after 14 h the reaction mixture was concentrated under reduced pressure. The crude product was purified by Kugelrohr distillation (ca. 100 °C, 0.2 mmHg) to give 0.186 g (99%) of 1-(3,7-dimethyl-1-oxo-6-octenyl)-piperidine as a colorless oil; IR (neat) cm^{-1} 2926 (s), 2859 (s), 1640 (s), 1445 (s), 1254 (m), 1223 (m); ^1H NMR (CDCl_3) δ 4.99-5.13 (m, 1 H), 3.47 (t, 2 H, J = 5.4 Hz), 3.32 (t, 2 H, J = 5.5 Hz), 2.24 (dd, 1 H, J = 5.9, 14.3 Hz), 2.05 (dd, 1 H, J = 8.3, 14.3 Hz), 1.43-1.59 (m, 13 H), 1.27-1.35 (m, 1 H), 1.09-1.18 (m, 1 H), 0.87 (d, 3 H, J = 6.6 Hz); ^{13}C NMR (CDCl_3) δ 170.5, 131.0, 124.3, 46.4, 42.3, 40.4, 36.8, 29.8, 26.4, 25.2, 24.3, 19.5, 17.4; MS (70eV, EI) 238(44), 237(M⁺, 89), 168(18), 155(43), 154(71),

140(41), 127(100), 126(20), 112(43), 86(24), 85(31), 84(46), 70(17), 69(49), 56(19), 42(20), 41(62), 39(16).

An alternative workup for less volatile amides such as α -*tert*-butyldimethylsiloxy-N-(phenylmethyl)-benzeneacetamide (Table 1, entry 8, 1.7 mmol scale) involves the addition of 2 mL methanol to the crude amide reaction mixture to precipitate tin. After stirring for several minutes, the reaction mixture was concentrated under reduced pressure. The resulting slurry was diluted with 75 mL of ethyl acetate, poured into a separatory funnel, and washed with 5% KOH (3 x 15 mL) and brine (1 x 15 mL). The organic layer was then dried over anhydrous MgSO₄ and concentrated under reduced pressure to yield 0.471 g (78%) of α -*tert*-butyldimethylsiloxy-N-(phenylmethyl)-benzeneacetamide as a pale yellow oil.

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8. Thus far, it appears that the only limitation of this methodology is low yields in reactions with hindered acids, such as pivalic acid.
9. Observed, $[\alpha]_D^{25} = 82.2^\circ$ (c = 1.05, CHCl₃), lit. $[\alpha]_D^{25} = 79.9^\circ$ (c = 1.09, CHCl₃) Tani, K.; Ise, T.; Tatsuno, Y.; Saito, T. *J. Chem. Soc., Chem. Commun.* 1984, 1641.