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SmI_2 Reduced Thioesters as Synthons of Unstable Acyl Radicals: Direct Synthesis of Potential Protease Inhibitors via Intermolecular Radical Addition

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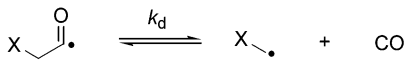
The synthetic utility of reactions involving the addition of acyl radicals to carbon carbon double bonds is well established.[1] The successful application of such reactions is, however, dependent on the kinetic stability of acyl radicals toward decarbonylation where the rate constant (k_d) for the decarbonylation step is greatly influenced by the nature of substituent X (Scheme 1). For example, intermolecular addition reactions involving acyl radical intermediates possessing a heteroatom substituent in the α-position undergo decarbonylation prior to the addition step due to the radical stabilizing effect of such substituents.[1] Whereas acyl radical equivalents have been devised, only few examples exist, and their application has mainly been limited to ring closing reactions where none represent examples with an α-heteroatom substituent.[2,3]

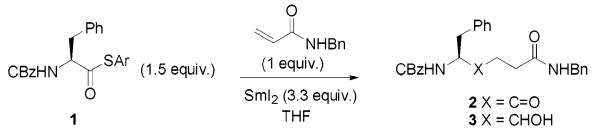
Scheme 1



The one electron reducing agent, samarium diiodide, has demonstrated its versatility in a broad range of synthetic transformations.[4] In the course of our studies on the use of this reagent for the preparation of amino acid and peptide analogues,[5] we recently attempted to prepare 4-substituted γ-amino acids via the SmI_2-promoted reduction of arylthioesters of *N*-protected α-amino acids in the presence of acrylates or acrylamides.[6] Anticipating the formation of an acyl radical intermediate with concomitant decarbonylation, as previously observed for the corresponding acid chlorides,[7] we were surprised to find that all of the products obtained from the reaction still retained the C−O entity. We have now optimized these reactions and reveal in this report a novel SmI_2-mediated radical reaction generating a formal acyl radical species of an amino acid which does not undergo decarbonylation. Interception of such intermediates with a variety of acrylamides provides for a simple and alternative access to γ-ketoamides and -esters directly incorporated into small peptide strands that represent a series of potential protease inhibitors.

Initial experiments were carried out with the 2-pyridyl thioester of CBz-protected phenylalanine and *N*-benzyl acrylamide, as illustrated in Table 1. A solution of the acrylamide and the thioester (1.5 equiv) in THF was added dropwise to a 0.1 M solution of SmI_2 cooled to −20 °C. After the mixture was stirred for 1 h, oxidation of the excess SmI_2 with oxygen and standard workup led to the isolation of the γ-ketoamide **2** and the γ-hydroxyamide **3** in 37 and 13% yield (entry 1). Lowering the temperature suppressed the reduction of the ketone **2**, and at −78 °C only the ketone was obtained (entry 3).[8] Quenching the excess SmI_2 with O_2 before workup was also essential for preventing reduction of the ketone to the corresponding alcohol. Performing the reaction in the presence of a proton source (MeOH) and warming to room temperature afforded more of the alcohol **3**, although the reduction was not completed (entry 4).

Table 1. Initial Optimization Studies on SmI_2-Promoted Addition of Thioesters to *N*-Benzyl Acrylamide[a]

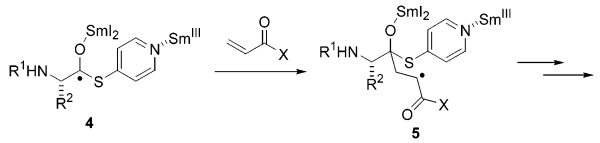


1

Entry	Ar	Temp.	Reaction time	Yield of **2**[b]	Yield of **3**[b]
1	2-pyridyl	-20°C	1 h	37%	13%
2	2-pyridyl	-30°C	24 h	50%	16%
3	2-pyridyl	-78°C	24 h	49%	0%
4[c]	2-pyridyl	-78°C to 25°C	1.5 h	27%	33%
5	phenyl	-78°C	24 h	17%	0%
6	pyrimidyl	-78°C	24 h	21%	0%
7		-78°C	24 h	53%	0%
8	4-pyridyl	-78°C	24 h	66%[d]	0%

[a] For full experimental details, see Supporting Information. [b] Isolated yields after column chromatography. [c] Reaction performed in the presence of MeOH. [d] Equimolar amounts of the alkene and the thioester gave ketone **2** in 60% yield.

Scheme 2



With the conditions optimized for yielding only the ketone, a small series of aromatic thioesters were tested to examine their influence on the product yield (entries 5−8). Both of the thioesters **1** of *N*-methyl 2-thioimidazole (entry 7) and 4-thiopyridine (entry 8) produced the ketone **2** in the best yields (53 and 66%). However, only the 4-pyridine derivative proved sufficiently stable toward chromatographic purification, whereas in all other cases the crude thioesters were used in the coupling step.

That decarbonylation is not observed implies that the reacting species is not an acyl radical. Instead, electron transfer into the carbonyl group could generate a ketyl radical anion equivalent of the structure **4** complexed to samarium(III) (Scheme 2).[9] The low-temperature stability of the metalated *S*,*O*-hemiketal **5** produced after the addition to an alkene prevents the formation of the ketone under the reaction conditions and hence its subsequent reduction. Further investigations to confirm these hypotheses are currently underway in our lab.

With the identification of the 4-pyridyl thioester as a suitable acyl radical equivalent, extrapolation of the reaction to more complex substrates was undertaken, as illustrated in Table 2. Addition of the thioester of CBz-protected phenylalanine to a series

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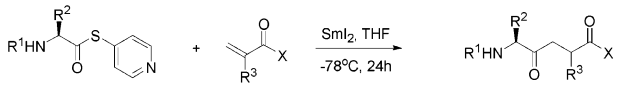
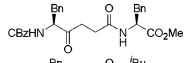
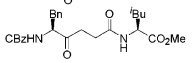
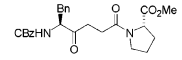
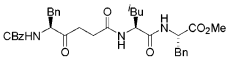
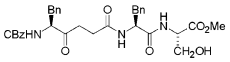
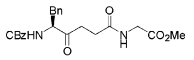
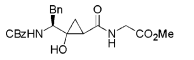
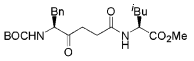
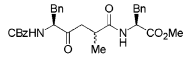
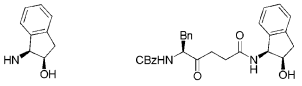
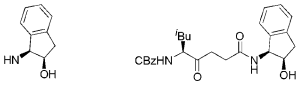
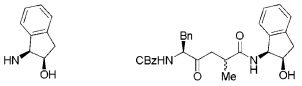
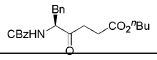
Table 2. SmI_2-Promoted Addition of Amino Acid Derived Thioesters to α,β-Unsaturated Amides and Esters[a]



Entry	R^1,R^2,R^3	X	Product	Yield[b] (d.r.)
1	CBz,Bn,H	PheOMe		63%
2	CBz,Bn,H	LeuOMe		90%
3	CBz,Bn,H	ProOMe		85%
4	CBz,Bn,H	LeuPheOMe		61%
5	CBz,Bn,H	PheSerOMe		54%
6	CBz,Bn,H	GlyOMe		7%[c]
				28% (1:1)
7	BOC,Bn,H	LeuOMe		44%
8	CBz,Bn,Me	PheOMe		51% (1:3)
9	CBz,Bn,H			71%
10	CBz,^{t}Bu,H			40%
11	CBz,Bn,Me			42% (1:2)
12	CBz,Bn,H	O^{n}Bu		51%[d]

[a] For full experimental details, see Supporting Information. [b] Isolated yields after column chromatography. [c] Yield is estimated by NMR studies as the product could not be separated from byproducts. [d] Reaction performed with excess alkene in the presence of 2 equiv of ^{t}BuOH.

of acryloyl containing amino acids and dipeptides proceeded well with yields up to 90% (entries 1−5). As illustrated with the tetrapeptide mimic in entry 5, protection of the primary alcohol is not necessary. The example in entry 3 represents a rapid and efficient synthesis of the potent inhibitor of the angiotensin converting enzyme.[10] Surprisingly, synthesis of a tripeptide analogue via the addition to the *N*-acryloylglycine derivative, shown in entry 6, proved more difficult. In this case, competitive formation of a cyclopropyl derivative was observed possibly arising from attack onto the ketone of the resulting enolate after reduction of the intermediate **5**. Such cyclopropyl derivatives were not found in any of the other examples for reasons that still remain unclear to us.

Other variations such as the use of the BOC-protected phenylalanine (entry 7) or a methacrylamide as in entry 8 proved feasible for such radical reactions as well. Structures related to the potent HIV-protease inhibitor Indinavir[11] were easily synthesized using this protocol by addition to 1-(*N*-acryloyl)-2-hydroxyindene (entries 9 and 10). The product obtained from the corresponding methacrylamide was isolated in an approximately 2:1 diastereomeric mixture (entry 11).

Extension of this methodology to an α,β-unsaturated ester was likewise possible, but it required the presence of a suitable proton source and excess alkene (entry 12). In this way, a satisfactory yield of 51% was obtained. The absence of epimerization at the α-carbon of the amino acids used for this study illustrates the mild conditions characteristic for these reactions.

In conclusion, we have demonstrated that aromatic thioesters derived from α-amino acids undergo addition to α,β-unsaturated amides upon reduction with SmI_2, demonstrating their utility as a synthetically useful acyl radical equivalent. This reaction provides facile access to peptide mimics containing a γ-ketoamide moiety in place of an amino acid residue, under mild conditions. Efforts are underway to examine the generality of this reaction.

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Supporting Information Available: Experimental procedure and spectral data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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