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SmI_2-Promoted Radical Addition of Nitrones to α,β-Unsaturated Amides and Esters: Synthesis of γ-Amino Acids via a Nitrogen Equivalent to the Ketyl Radical

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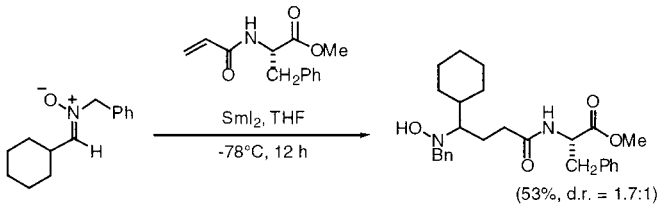
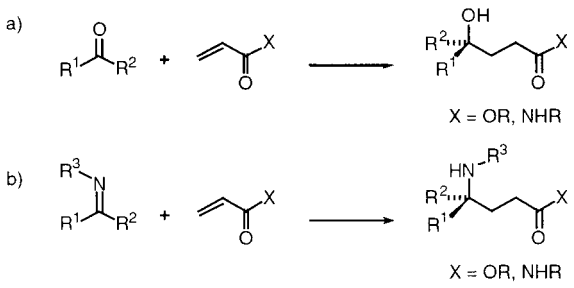
ABSTRACT



Alkyl nitrones undergo radical addition reactions to a series of α,β-unsaturated amides and esters when subjected to samarium diiodide via a nitrogen equivalent to a ketyl radical anion. This reaction conveniently provides access to a variety of functionalized γ-amino acids. The methodology was extended to the asymmetric synthesis of 4-substituted γ-amino acids, via the nitrone radical addition reaction to acrylates/amides possessing a chiral auxiliary.

The reduction of aldehydes or ketones by low-valent transition-metal complexes to ketyl radicals and their subsequent intra- or intermolecular addition to α,β-unsaturated esters or amides is well-documented and therefore a useful synthetic organic transformation (Scheme 1a).[1] Above all, the lanthanide-based one-electron reducing agent, samarium diiodide, has been found to be one of the most effective reagents for promoting such reactions under mild reaction conditions, and in many cases leads to products with high diastereoselectivities.[2] On the other hand, analogous reactions with imines or related systems possessing a carbon−nitrogen double bond are scarce, largely due to the difficulties in reducing such functionalities to their corresponding ketyl-type radical intermediate under mild conditions.[3−7]

Scheme 1



Recently, alkyl and aryl nitrones were reported to undergo low-temperature pinacol-type heterocoupling with carbonyl compounds promoted by samarium diiodide.[8] Evidence was

(1) Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771 and references therein.

(2) For recent reviews on the application of SmI_2 in organic synthesis, see: (a) Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727. (b) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745. (c) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307. (d) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321. (e) Skrydstrup, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 345. (f) Molander, G. A. *Org. React.* **1994**, *46*, 211.

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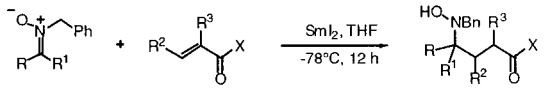
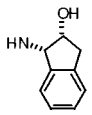
provided for the preferential reduction of the C=N bond, suggesting the presence of an intermediate α-heteroatom-substituted carbon radical. If this mechanism is indeed valid, it should be possible to intercept the carbon radical species with electron-deficient alkenes. In this report, we reveal our preliminary efforts in this area demonstrating the ability of alkyl *N*-benzylnitrones to undergo intermolecular radical addition to α,*β*-unsaturated amides and esters when treated with SmI_2, thereby providing a useful entry to 4-substituted *γ*-amino acids alone or as constituents of small mixed α,*γ*-peptides (Scheme 1b). This work represents the first practical application of a nitrogen equivalent of the intermolecular ketyl radical addition reaction.

Initial experiments were carried out with the cyclohexyl *N*-benzylnitrone and the methyl ester of *N*-acryloylglycine, as illustrated in Table 1. A 0.1 M etheral solution of SmI_2 was added dropwise to a 1:1 solution of the nitrone and acrylamide in THF cooled to −78 °C. After stirring for 12 h, work up and column chromatography led to a 65% yield of the *N*-hydroxylated dipeptide analogue possessing a *γ*-amino acid unit (entry 1).[9] Inclusion of a proton source (e.g. *t*-BuOH) did not lead to an improvement. At higher temperatures competitive reduction and dimerization of the acrylamide was observed indicating the close reactivity of the two substrates with the low-valent lanthanide reagent and the fine balance of selectivity that is achieved at lower temperatures.

Other examples are illustrated in Table 1. With the *N*-acryloylphenylalanine derivative as shown in entry 2, the *γ*,α-dipeptide was obtained in a 53% yield as an approximately 2:1 diastereomeric mixture. Other alkyl nitrones also provided peptide analogues under similar conditions (entries 3 and 4). Even coupling to the *N*-acryloyl derivative of LeuPheOMe proved feasible, as illustrated in entry 5, furnishing the tripeptide analogue in 47% yield. A dipeptide possessing a 2,4-disubstituted *γ*-amino acid unit was obtained with good diastereoselectivity from the addition of the cyclohexyl nitrone to *N*-methacryloylglycine (entry 6). The successful coupling of the same nitrone with the *N*-acryloyl derivative of (2*R*,3*S*)-aminohydroxydihydroindane (entry 7) provides entry to a new class of compounds possessing structural similarities to the potent HIV protease inhibitor, indinavir.[10] Extrapolation of the same radical addition

Table 1. SmI_2-Promoted Addition of Nitrones to α,*β*-Unsaturated Amides and Esters[a]



entry	R, R^1	R^2, R^3	X	product (yield)[b]
1	*c*-C_6H_{11}, H	H, H	Gly(OMe)	(65%)
2	*c*-C_6H_{11}, H	H, H	Phe(OMe)	(53%, d.r. = 1.7:1)
3	Et, H	H, H	Gly(OMe)	(40%)
4	*i*-Pr, H	H, H	Gly(OMe)	(53%)
5	*c*-C_6H_{11}, H	H, H	LeuPhe(OMe)	(47%, d.r. = 2:1)
6	*c*-C_6H_{11}, H	H, Me	Gly(OMe)	(40%, d.r. = 8:1)
7	*c*-C_6H_{11}, H	H, H		(40%, d.r. = 5:1)
8[c]	*c*-C_6H_{11}, H	H, H	O*n*-Bu	(70%)
10[c]	*c*-C_6H_{11}, H	Me, H	OEt	(70%, d.r. = 10:1)
10[c]	*c*-C_6H_{11}, H	H, Me	OMe	(43%, d.r. = 10:1)
11[c]	-$(CH_2)_5$-	H, H	O*n*-Bu	(34%)

[a] For full experimental details, see the Supporting Information. [b] Isolated yields after column chromatography. [c] Reaction performed in the presence of 2 equiv of *t*-BuOH.

(3) Only imines prepared from aryl aldehydes or ketones have so far been reported to undergo reduction by SmI_2. For some examples, see: (a) Machrouhi, F.; Namy, J.-L. *Tetrahedron Lett.* **1999**, *40*, 1315. (b) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondo, L. *Tetrahedron Lett.* **1998**, *39*, 3333. (c) Taniguchi, N.; Uemura, M. *Synlett* **1997**, 51. (d) Imamoto, T.; Nishimura, S. *Chem. Lett.* **1990**, 1141. (e) Enholm, E. J.; Forbes, D. C.; Holub, D. P. *Synth. Commun.* **1997**, *27*, 1483.

(4) Hydrazones or oximes prepared from alkyl aldehydes are not reduced by SmI_2 even in the presence of HMPA. See: (a) Fallis, A. G.; Sturino, C. F. *J. Am. Chem. Soc.* **1994**, *116*, 7447. (b) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543. (c) Riber, D.; Hazell, R.; Skrydstrup, T. *J. Org. Chem.* **2000**, *65*, 5382 and references therein.

(5) The electroreductive coupling of two closely related aromatic imines to methyl acrylate represents the only examples previously reported for this reaction, Shono, T.; Kise, N.; Kunimi, N.; Nomura, R. *Chem. Lett.* **1991**, 2191.

(6) Surrogates to imines for generating α-amino radicals with SmI_2 and their application in intramolecular cyclizations have been reported. (a) Katritzky, A. R.; Feng, D. M.; Qi, M.; Aurrecoechea, J. M.; Suero, R.; Aurrekoetxea, N. *J. Org. Chem.* **1999**, *64*, 3335. (b) Aurrecoechea, J. M.; Fernandez, A.; Gorgojo, J. M.; Saornil, C. *Tetrahedron* **1999**, *55*, 7345.

(7) For other work on the generation and application of α-amino radicals, see: Renaud, P.; Giraud, L. *Synthesis* **1996**, 913.

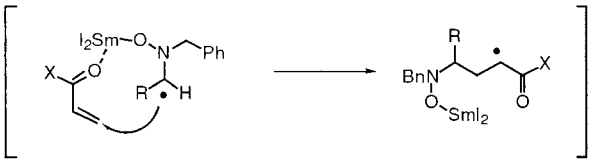
(8) Masson, G.; Py, S.; Vallée, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 1772.

(9) For other applications of SmI_2 for the synthesis of modified peptides, see: Ricci, M.; Blakskjær, P.; Skrydstrup, T. *J. Am. Chem. Soc.* **2000**, *122*, 12413.

reactions to α,β-unsaturated esters was more rewarding (entries 8−10) with yields up to 70% in two examples. In contrast to the acrylamides, *t*-BuOH is required in these couplings for successful C−C bond formation.[11] In the latter two cases, the diastereoselectivity proved even higher than seen with the methacyrlamide in entry 6. Even generation of a quaternary carbon center is feasible, though in somewhat reduced yield (entry 11).

The products obtained from this reaction suggest the formation of a ketyl-like intermediate as illustrated in Scheme 2. Coordination of the lanthanide metal center to the carbonyl

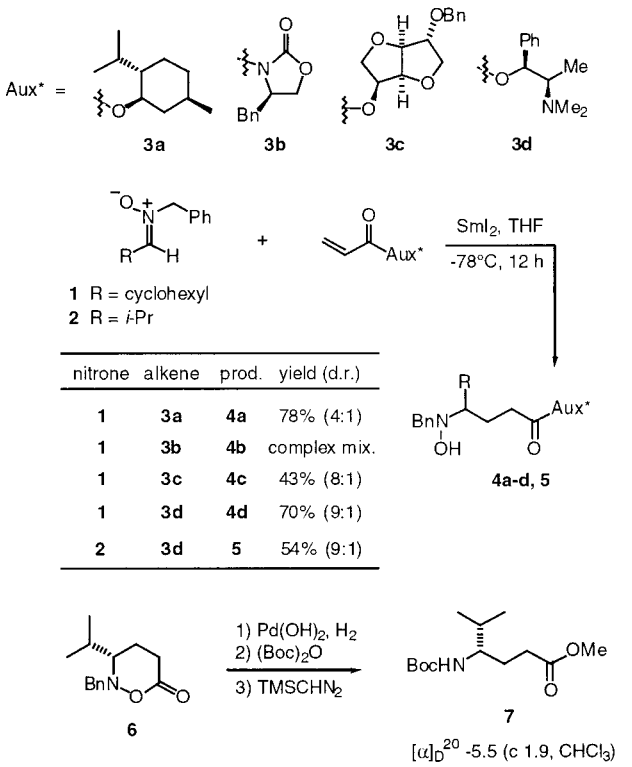
Scheme 2



group and activation is followed by the 1,4-addition step. There is also the possibility that the good Lewis acid ability of SmI_2 or other salts formed under the reaction conditions catalyzed the cycloaddition of the nitrone to the C−C double bond followed by SmI_2-mediated deoxygenation at the α-position. However, deoxygenation at the α-position of esters with SmI_2 in general requires the presence of strongly coordinating solvents such as HMPA, which augments the reducing power of the divalent lanthanide reagent.[2f] In addition, the nitrone cycloaddition step would be expected to afford products of the opposite regioisomer.[12]

Finally, attempts were made to extend this methodology for the preparation of optically active 4-substituted γ-amino acids, by initially examining the addition of nitrone **1** to acrylates/acrylamides **3a**−**d** possessing a chiral auxiliary (Scheme 3). Of the four chiral auxiliaries tested, (1*R*,2*S*)-*N*-methylephedrine proved to be the most effective leading to a 9:1 diastereomeric ratio of the γ-amino acid derivative **4d**. The same high diastereoselectivity could be obtained for the nitrone **2** leading to derivative **5**.[13] Compound **5** was

Scheme 3



found to undergo predominant cyclization to **6** upon chromatography; however, a three-step transformation led to the quantitative formation of the Boc-protected γ-amino acid derivative **7**.[14]

In conclusion, we have demonstrated that alkyl nitrones undergo addition reactions to α,β-unsaturated amides and esters upon reduction with SmI_2, providing an imine equivalent to the well-known radical addition reactions of aldehydes and ketones. This reaction provides access to variously substituted γ-amino acids and preliminary studies have revealed that such amino acids can be prepared with high enantiomeric excesses. Efforts are underway to examine the efficiency of other chiral auxiliaries, as well as their generality.

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

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(10) For a recent and extensive review on protease inhibitors, see: Leung, D.; Abbenante, G.; Fairlie, D. P. *J. Med. Chem.* **2000**, *43*, 305.

(11) In the addition reactions to the acrylamides, the amide proton may serve as the protonation source for the resulting enolate formed, hence explaining the observation that the presence of *t*-BuOH does not affect the yields of these reactions.

(12) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.

(13) Fukuzawa and co-workers reported this chiral auxiliary to be the most effective in the asymmetric preparation of γ-lactones with high enantiomeric excesses by SmI_2-promoted ketyl radical addition reactions. Fukuzawa, S.-i; Seki, K.; Tatsuzawa, M.; Mutoh, K. *J. Am. Chem. Soc.* **1997**, *119*, 1482.

(14) Schmidt, U.; Riedl, B.; Haas, G.; Griesser, H.; Vetter, A.; Weinbrenner, S. *Synthesis* **1993**, 216.