Communication

Can Decarbonylation of Acyl Radicals Be Overcome in Radical Addition Reactions? En Route to a Solution Employing *N*-Acyl Oxazolidinones and SmI/HO

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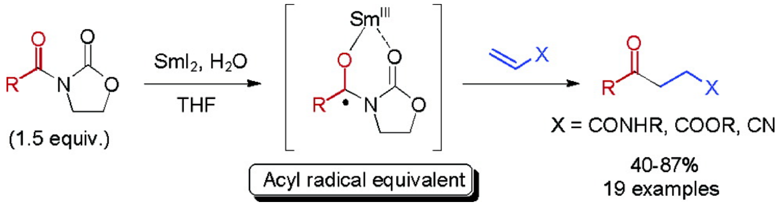

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Can Decarbonylation of Acyl Radicals Be Overcome in Radical Addition Reactions? En Route to a Solution Employing *N*-Acyl Oxazolidinones and SmI_2/H_2O

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The addition of acyl radicals to olefins is a key carbon−carbon bond forming step in the synthesis of natural products and other complex compounds.[1,2] However, acyl radicals possess the sometimes undesirable ability to undergo decarbonylation generating a new carbon-centered radical and carbon monoxide (Scheme 1). The facility of this degradation step can be correlated to the stability of the newly generated radical upon decarbonylation. Hence, inter- and intramolecular radical addition reactions have, in general, been restricted to either aryl or α-unsubstituted alkyl acyl radicals, cases in which the addition step successfully competes with a slow decarbonylation step (k_d typically less than $10^4\ s^{-1}$). In contrast, attempts to promote addition reactions with α-mono- or disubstituted alkyl acyl radicals with decarbonylation rate constants greater than $10^4\ s^{-1}$, as depicted in Scheme 1, commonly lead to products subjected to loss of CO.[3,4] Ryu and co-workers have elegantly demonstrated that decarbonylations can be overridden if the reaction is performed under CO pressure.[1,5,6]

In this paper, we disclose our efforts directed toward developing a useful solution for promoting difficult intermolecular acyl radical additions in the absence of a CO atmosphere *even in cases where the decarbonylation rate constant exceeds $10^8\ s^{-1}$*. Our approach takes advantage of the ability of the single electron transfer agent, samarium diiodide,[7] to reduce appropriately functionalized acyl derivatives to their corresponding ketyl radical anions, which subsequently react with acrylamides, acrylates, or acrylonitrile, providing products arising from a formal acyl radical addition.[8,10]

As a suitable precursor to an acyl radical equivalent, we considered the use of *N*-acyl oxazolidinones based on (a) the considerable literature precedence demonstrating the capacity of the low-valent lanthanide reagent to reduce imides,[11] and (b) an anticipated regioselective reduction of the *N*-acyl carbonyl group by samarium diiodide due to its lower lying π^*_{CO} orbital in comparison to the same π^*_{CO} orbital of the oxazolidinone. To examine the suitability of such compounds, initial experiments were performed to couple the oxazolidinone-bearing amino acid **1** with *N*-benzyl acrylamide (Table 1), a situation where decarbonylation of the corresponding acyl radical is sufficiently rapid to precede the addition step.[1,4] Whereas treatment of a solution of **1** and the radical acceptor with samarium diiodide alone at low temperature was not sufficient to initiate the reduction of the *N*-acyl group required for the C−C bond forming step (entry 1), the addition of cosolvents or additives had an alternative effect. However, only in the case of entry 2, employing an aqueous THF solution of samarium diiodide,[12] was the product **2** from a formal acyl radical addition obtained in a satisfactory yield of 57%.[9a] With other systems involving SmI_2 and H_2O/Et_3N,[13] LiCl, or LiBr,[14] the reactions were either less clean or nonproductive (entries 3−5).

Scheme 1

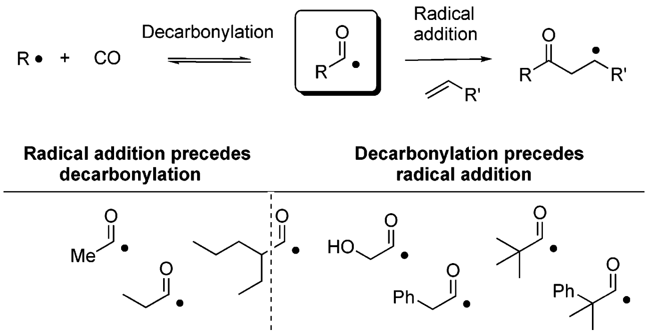
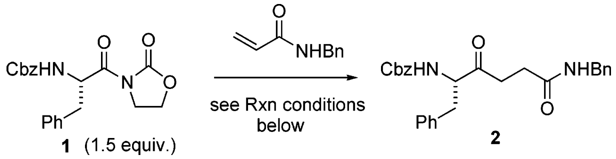


Table 1. Initial Optimization Studies on SmI_2-Promoted Radical Addition Reactions with *N*-Acyl Oxazolidinone **1**[a]



entry	reducing agent	temp	reaction time	yield of **2**[b]
1	SmI_2 (4.5 equiv)	−78 °C	48 h	0%
2	SmI_2 (4.5 equiv), H_2O (8 equiv)	−78 °C	4 days	57%
3	SmI_2 (4.5 equiv) Et_3N (11.3 equiv) H_2O (9 equiv)	−78 °C	24 h	decomp
4	SmI_2 (4.5 equiv) LiCl (10 equiv)	−78 °C	24 h	traces
5	SmI_2 (4.5 equiv) LiBr (11.5 equiv)	−78 °C	24 h	43%[c]

[a] For full experimental detail, see Supporting Information. [b] Isolated yields after column chromatography. [c] Considerable decomposition was observed.

To determine whether this methodology could successfully be applied to other acyl derivatives, we examined the coupling protocol between a diverse array of *N*-acyl oxazolidinones with several acrylamides, *n*-butyl acrylate, and acrylonitrile. Specifically, the examples were chosen to cover the complete range of stable and unstable acyl radicals exhibited in Scheme 1.

As revealed by the results in Table 2, the coupling protocol proved successful for all of the *N*-acyl derivatives tested, even with the examples represented in entries 17 and 18 where the decarbonylation rate constants of the corresponding acyl radicals surpass $10^8\ s^{-1}$. Several additional comments can also be made concerning these results. First, these intermolecular radical addition reactions proved remarkably efficient furnishing the γ-ketoamide products in yields up to 87%, *even though approximately equimolar equivalents of the radical acceptor and donor were employed.* For the ketoester and ketonitrile synthesis (entries 5, 12, 15, and 16),

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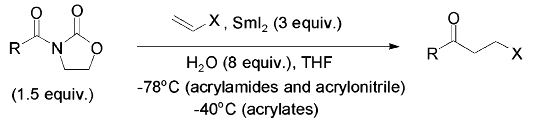
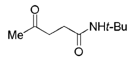
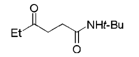
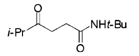
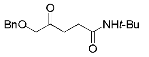
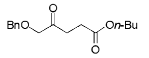
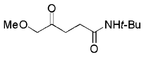
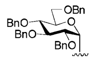
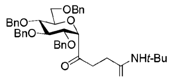
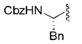
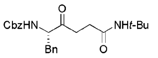
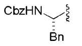
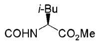
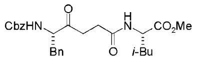
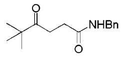
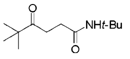
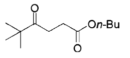
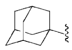
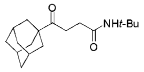
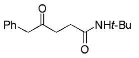
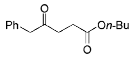
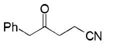
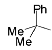
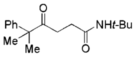
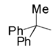
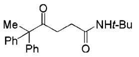
Table 2. Radical Addition of *N*-Acyl Oxazolidinones to Acrylamides and Acrylates Promoted by SmI_2/H_2O[a]



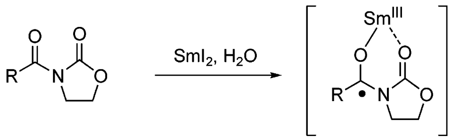
Entry	R	X	Time	Product	Yield
1	Me	CONH*t*-Bu	18 h		46%
2	Et	CONH*t*-Bu	24 h		59%
3	*i*-Pr	CONH*t*-Bu	24 h		43%
4	$BnOCH_2$	CONH*t*-Bu	24 h		75%
5	$BnOCH_2$	COO*n*-Bu	24 h		60%
6	$MeOCH_2$	CONH*t*-Bu	24 h		82%
7		CONH*t*-Bu	48 h		40%
8		CONH*t*-Bu	4 days		41%
9			4 days		58%
10	*t*-Bu	CONHBn	24 h		50%
11	*t*-Bu	CONH*t*-Bu	24 h		87%
12	*t*-Bu	COO*n*-Bu	24 h		81%
13		CONH*t*-Bu	24 h		64%
14	$PhCH_2$	CONH*t*-Bu	3 h		64%
15	$PhCH_2$	COO*n*-Bu	24 h		75%
16	$PhCH_2$	CN	18 h		52%
17		CONH*t*-Bu	18 h		65%
18		CONH*t*-Bu	18 h		62%

[a] For full experimental detail, see Supporting Information.

3 equiv of the acrylate or acrylonitrile was required to ensure satisfactory yields.[15]

Second, bulky alkyl acyl derivatives also afforded coupling products in good yields, as seen in entries 10−13, 17, and 18, implying that sterical hindrance is not a significant factor for these reactions. Finally, as all the coupling products retained the carbonyl group of the starting *N*-acyl oxazolidinone, we propose that a metalated ketyl radical anion intermediate is the species generated under the reaction conditions (Scheme 2) and not an acyl radical, in a manner similar to that postulated for the SmI_2-mediated reduction and radical additions of amino acid thioesters.[9] The addition of this ketyl intermediate to the unsaturation eventually leads to a metalated hemiaminal, which subsequently hydrolyzes upon workup, affording the ketone.[16]

Scheme 2



In conclusion, we have disclosed an indirect approach for overcoming decarbonylations encountered in certain difficult acyl radical addition reactions where the acyl radical intermediates are susceptible to rapid decarbonylation. Further studies directed to the generality of the reaction are currently underway.

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Supporting Information Available: General experimental methods for the radical addition reactions and spectroscopic data for the coupling products, including copies of ^1H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Aryl thioesters of amino acids were earlier found to undergo addition reactions with acrylamides and acrylates upon treatment with samarium diiodide to provide products of a formal acyl radical addition reaction.[9] Attempts to expand this protocol to other alkyl acyl derivatives other than amino acids, including α-oxyacyl derivatives, were met with failure, limiting the general applicability of this methodology.

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(15) No coupling products were observed in the attempted addition to styrene.

(16) The presence of H_2O most likely rules out the possibility of an alternative mechanistic pathway involving the reduction of the acrylamide to a dianion followed by a nucleophilic acyl substitution step.

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