

Generation and Reactivity of Oxazolidinone Derived N-Acyl Radicals

Gary E. Keck, Mark C. Grier

Department of Chemistry, University of Utah, Salt Lake City, Utah 84112, USA

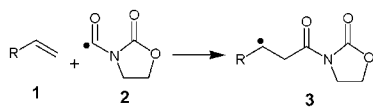
Fax +1 (801) 581-7055; E-mail: keck@chemistry.utah.edu

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Abstract: The N-acyl(phenylseleno)oxazolidinone **5** was prepared (85% yield) by treatment of the lithium salt of oxazolidinone with triphosgene, followed by addition of benzeneselenol. Reduction of **5** with *n*-Bu₃SnH/AIBN gave the N-formyloxazolidinone **6** (99%) and reaction with allyltri-*n*-butylstannane gave **7** (89%). Bimolecular additions to various alkenes using the N-acyl radical derived from oxazolidinone **5** were also studied. Best results were obtained with electron rich olefins, such as enol ether derivatives. Eight such additions are reported, with yields ranging from 51–90%. Two prochiral substrates showed significant levels of diastereoselectivity in reactions with **5**/Bu₃SnH.

Key words: radicals, radical reactions, acylations, stereoselectivity, Lewis acids

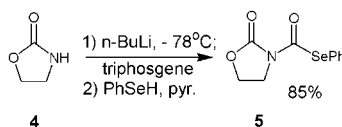
In recent years, free radical based methodology has played an increasingly important role in organic synthesis, and many desirable features of such reactions are now appreciated.¹ One developmental thrust has been directed at methodology which can preserve high levels of functionality in radical additions to unsaturated systems. Among many conceptual approaches to this general problem, the use of acyl radicals,² α -alkoxy radicals,³ and acetal derived radicals⁴ are of considerable interest. It occurred to us that, in view of the many well known chemical transformations of N-acyloxazolidinones developed to support asymmetric aldol technology,⁵ additions of oxazolidinone derived N-acyl radicals to various unsaturations could potentially prove to be of utility in synthesis (Eq 1). We describe herein the first examples of the generation and reactivity of such radicals.



Equation 1

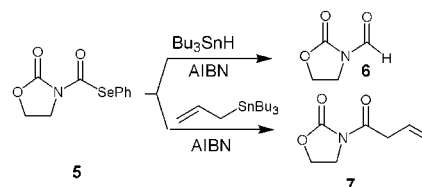
The N-acyl(phenylseleno)oxazolidinone **5** was chosen as a potential precursor to radical **2** and was synthesized by reaction of the lithium salt of oxazolidinone with triphosgene (0.5 eq), followed by addition of a solution of benzeneselenol in pyridine (Eq 2).

Preliminary experiments to examine the potential of **5** as a source of **2**, and also to investigate the viability of **2** in bimolecular free radical reactions, were performed by reduction of **5** with tri-*n*-butyltin hydride and allylation⁶ of **5** using allyltri-*n*-butylstannane. These experiments con-



Equation 2

firmed that, as expected, radical **2** could in fact be generated from **5** and, more importantly, that **2** was sufficiently stable with respect to decarbonylation to function effectively in bimolecular reactions. Thus, reduction of **5** gave the N-formyloxazolidinone **6** in 99% yield, while the allylation afforded **7** in 89% isolated yield (Eq 3).



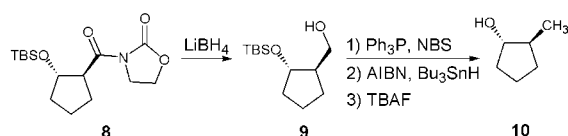
Equation 3

Reactions of **5** with a variety of olefins were then investigated. The standard reaction protocol eventually employed in each case utilized **5** (1.0 eq), tri-*n*-butyltin hydride (1.5 eq), bis(tributyltin) (0.05 eq) or AIBN (0.1 eq), and an excess (5 eq) of olefin, with irradiation *via* a 200 W sunlamp during slow addition (over 12 h) of the tin hydride as a solution in benzene (0.3 M overall). Several trends were noted. The desired addition reactions proceeded very poorly (no isolable amounts of products detected) with α,β -unsaturated esters such as benzylacrylate or benzylcrotonate. In these cases, the reduction product **6** was isolated. Reaction with cyclopentenone did occur, but in general, more electron rich olefins proved superior in reactivity towards **2** (Table 1). Thus, addition to methylenecyclopentane was successful (76% isolated yield) as was addition to α -methylstyrene (51%). Very good results were obtained with various enol ethers including TBS silyl enol ethers. Reaction with *n*-butyl vinyl ether afforded the desired addition product in 72% isolated yield; similar results (77% yield) were obtained with the endocyclic enol ether dihydrofuran. Additions to the TBS enol ethers derived from pinacolone and acetophenone provided excellent results (90% and 85% isolated yields, respectively).

With two prochiral substrates, very intriguing observations were made regarding the potential for diastereoselectivity in these reactions. Reaction with the TBS enol ether derived from cyclopentanone afforded product **8** as largely a single diastereomer by ^1H and ^{13}C NMR analysis, in 83% isolated yield (entry 7). Reductive removal of the oxazolidinone using LiBH_4 gave the corresponding primary alcohol **9**; NMR analysis (methine protons at 4.35 and 3.90 δ for the major and minor diastereomers) indicated a 14:1 mixture of isomers (Eq 4). Assignment of *trans* stereochemistry to the major isomer was made by conversion of alcohol **9** to 2-methylcyclopentanol and comparison of ^1H and ^{13}C NMR data with those previously reported for the *cis* and *trans* isomers.^{7,8}

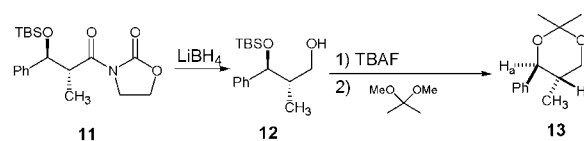
Table 1 Products & Yields for Reactions of **5** with Alkenes.

| Entry | Substrate | Product | Yield (Ratio) |
|-------|-----------|---------|---------------|
| 1 | | | 76 % |
| 2 | | | 51 % |
| 3 | | | 72 % |
| 4 | | | 77 % |
| 5 | | | 90 % |
| 6 | | | 85 % |
| 7 | | | 83 % (14:1) |
| 8 | | | 80 % (30:1) |



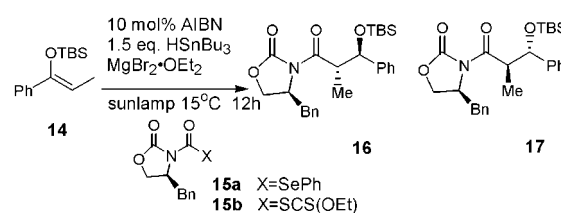
Reaction with another prochiral substrate, the *Z* TBS enol ether derived from propiophenone (entry 8) provided an

even more interesting result. In this case, the addition product **11** (80% isolated yield) was again found to consist of essentially a single diastereomer as judged by ^1H and ^{13}C NMR. Analysis by capillary VPC indicated a *ca.* 40:1 level of diastereoselectivity, but the separation obtained was not adequate for an accurate analysis. Carbonyl reduction with lithium borohydride afforded the corresponding alcohol **12**, which gave a baseline separation by capillary VPC, revealing a 30:1 level of diastereoselectivity (Eq 5). Assignment of stereochemistry to the major diastereomer as *anti* was made by removal of the TBS group from alcohol **12** followed by reaction with dimethoxypropane to give the 1,3-dioxane **13** which exhibited a 10.2 Hz coupling constant between the relevant vicinal protons H_a and H_b .⁹



Equation 5

Preliminary experiments aimed at achieving asymmetric induction in these reactions by the obvious strategy have also been conducted using the Evans chiral oxazolidinone derivatives **15** derived from L-phenylalanine.¹⁰ As expected, no selectivity was observed in the reaction of **14** with **15a** in the absence of additives; at $\sim 80^\circ\text{C}$ a 1:1 mixture of **16** and **17** was obtained in 89% yield (Table 2). It was anticipated that the use of Lewis acids to complex and rigidify the acyloxazolidinone at lower reaction temperatures would be necessary to realize significant levels of diastereoselectivity.¹⁰ However, an unanticipated problem was encountered in that the selenide **15a** proved unreactive at lower temperatures ($\sim 15^\circ\text{C}$) in the presence of $\text{MgBr}_2 \cdot \text{OEt}_2$; at higher temperatures the silyl enol ether substrate **14** suffered extensive decomposition. In an attempt to utilize a more reactive radical precursor, the xanthate **15b** was investigated (Eq 6). This material was easily prepared along the lines previously employed by reaction of lithiated (*S*)-benzyloxazolidinone with triphosgene followed by addition of commercially available potassium O-ethylxanthate to give **15b** in 95% yield. Reaction with **14** in the presence of $\text{MgBr}_2 \cdot \text{OEt}_2$ as a chelating Lewis acid at *ca.* 15°C afforded predominantly the *anti* products **16** and **17** with significant diastereoselectivity (8:1), albeit in low (20%) isolated yield.¹¹



Equation 6

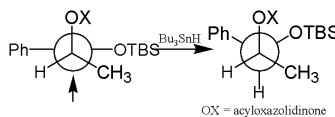
Table 2 Products and Yields For Reactions of **14**.

| acyloxazolidinone | additive | temperature | 16:17 | yield |
|-------------------|-------------------------------------|-------------|--------------|-------|
| 15a | none | 80 °C | 1:1 | 89% |
| 15a | MgBr ₂ ·OEt ₂ | 15 °C | NR | |
| 15b | MgBr ₂ ·OEt ₂ | 15 °C | 8:1 | 20% |

The reactions described herein extend the known chemistry of acyl radicals to bimolecular processes utilizing synthetically versatile N-acyloxazolidinones. Reactions with acyclic enol ethers provide a radical based synthesis of materials commonly envisioned as "aldol products" via an alternative bond construction. Further studies on the reactions of such radicals, particularly with respect to investigations of asymmetric methodology, are in progress.¹²

References and Notes

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- (8) The stereochemical outcome for the reaction described in entry 7 of Table 1 suggests a late, product-like transition state with significant pyramidalization at the radical center, presumably to minimize steric interactions between the acyloxazolidinone and OTBS groups.
- (9) (a) The stereochemical outcome for the reaction described in entry 8 of Table 1 may be rationalized by an extension of stereochemical models set forth independently by Hart^{9b,c} and by Porter, Giese, and Curran.^{9d}



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- (11) The structural assignment made for these materials is based upon independent synthesis.
- (12) Financial assistance provided by the NIH and by Pfizer, Inc. is gratefully acknowledged.

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