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N-ACYL-*N*-ALKYLCARBAMOYLOXY RADICALS: ENTRIES TO AMIDYL RADICALS BY DECARBOXYLATION AND TO α-AMIDE RADICALS BY RADICAL TRANSLOCATION

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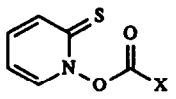
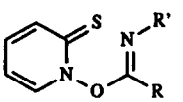
Abstract. *N'*-Acyl-*N*-hydroxypyridine-2-thione carbamates react in radical chain reactions to give the title radicals which can decarboxylate or react by intramolecular hydrogen atom transfer; the competing reaction pathways are controlled by the structure of the alkyl group and the conformation of the precursor which can be influenced by addition of a Lewis acid.

The PTOC esters (**1**) developed by Barton and colleagues comprise one of the more important classes of radical precursors for synthetic applications.[1] Extensions of Barton's chemistry to related PTOC precursors to heteroatom-centered radicals have been reported. Thus, PTOC carbamates (**2**),[2] carbonates (**3**)[3] and imidate esters (**4**)[4] react in chain reactions to give aminyl radicals (after decarboxylation of the first formed radical), alkoxycarbonyloxy radicals and amidyl radicals, respectively. We now report another group of PTOC radical precursors, *N'*-acyl PTOC carbamates (**5**), which react in chain reactions to give *N*-acyl-*N*-alkylcarbamoyloxy radicals (**6**), to our knowledge a new class of radicals. Radicals **6** can decarboxylate thus providing a new entry to amidyl radicals. Alternatively, intramolecular 1,5-hydrogen atom transfer in **6** results in highly regioselective formation of a carbon-centered, α-amide radical. In the latter case, the abstracting element is eliminated as CO_2 without further chemical processing.



1: X = alkyl
2: X = NR_2
3: X = OR



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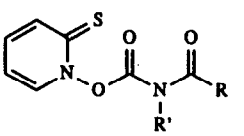
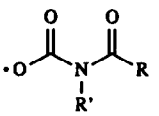


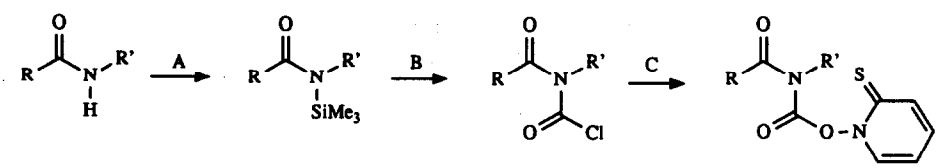
5: = PTOC-N(R')C(=O)R



6

Acyl PTOC carbamates are available in high yield from the reaction sequence in Scheme 1.[5] Thus, reactions of secondary amides with trimethylsilyl triflate gave *N*-(trimethylsilyl)amides that reacted with phosgene to give *N*-acylcarbamoyl chlorides. Subsequent reaction of these intermediates with the sodium salt of *N*-hydroxypyridine-2-thione gave precursors **5** in 80-90% isolated yield from the starting amide. Most of the precursors **5** were oils that were characterized by ^1H and ^{13}C NMR spectroscopy. The *N*-methylacetamide derivative **5a** (mp 112-113 °C) was further characterized by elemental analysis. Precursors **5** generally were prepared immediately before use; however, they could be stored for periods up to 30 days. They were more stable than the PTOC imidate esters[4] and of comparable stability to the PTOC carbamates.[2]

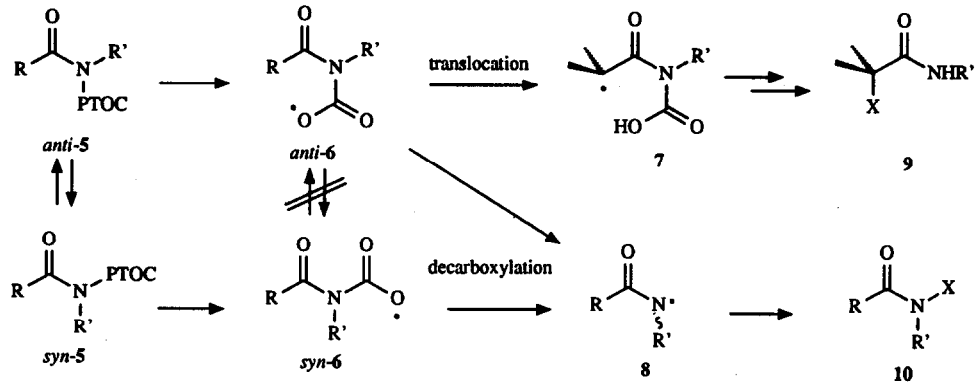
Scheme 1



Reagents: A: $CF_3SO_3SiMe_3$, TEA,; B: $COCl_2$; C: *N*-hydroxypyridine-2-thione sodium salt
Structures: **a**: R = R' = CH_3; **b**: R = R' = *n*-C_4H_9; **c**: R = $(CH_3)_2CH$, R' = *n*-C_4H_9;
d: R = $PhCH_2$, R' = *n*-C_4H_9; **e**: R = Ph, R' = CH_3

The conformation of precursor **5** as it reacts in the initial radical chain propagation step was expected to be a critical feature affecting the partitioning of the first formed radical intermediate **6**. NMR spectra of precursors **5** at 30 °C contained only one set of signals suggesting either that one conformation highly predominated or that rotation about the acyl C-N bond was rapid on the NMR time scale. Low temperature NMR spectra of **5a** also were simple. The *N*-methylbenzamide derivative **5e** (mp 125.0-125.5 °C) was characterized by X-ray crystallography[6] which showed an anti-coplanar arrangement for acyl oxygen and the PTOC moiety as shown in the drawing in Scheme 1. Such an arrangement is also expected in solution in low dielectric solvents on the basis of both electronic (dipole minimization) and steric considerations. From this evidence and reasoning and the results discussed below, we conclude that precursors **5** exist in solution largely in the anti conformation.

Scheme 2



Precursors **5** were allowed to react in radical chain reactions initiated by visible light irradiation.[7] The reaction sequences shown in Scheme 2 are possible. The first formed radical **6** can exist in the syn or anti conformation depending upon the conformation of precursor **5**. It is expected that the rate of decarboxylation of **6** will exceed that of acyl C-N bond rotation, and, therefore, that *anti*-**6** will partition between α-amide radical **7** and amidyl radical **8** whereas *syn*-**6** can only lead to **8**. In the absence of added radicophiles, radicals **7** and **8** will react with precursor **5** to give an α-(2-thiopyridyl)amide (**9**, X = S-2-pyridyl) (after decarboxylation of the first formed product) and an *N*-(2-thiopyridyl)amide (**10**, X = S-2-pyridyl), respectively. In practice, both products **9** and **10** were isolated in most cases and characterized by NMR spectroscopy.

The Table lists the results of reactions of precursors **5**. The method is excellent for the production of acetamidyl radicals. In the series **5a**-**5c** (R = CH_3, 1° alkyl and 2° alkyl), there was a regular increase in the amount of α-substituted product arising from radical translocation. With the reasonable assumption that the rates of decarboxylation of the radicals *anti*-**6** in this series were similar, these results suggest that *anti*-**6** predominated over the syn conformer in each case and that the product distribution was mainly controlled by the competition between translocation and decarboxylation of the anti species. The benzyl-substituted precursor (**5d**) reacted to give a lower than expected ratio of α- to *N*-substituted products. The amount of translocation in **6d** actually was greater than indicated from the yield of **9d** because the dimer formed from coupling of α-radicals (*N,N'*-dibutyl-2,3-diphenylsuccinic diamide) was detected in 11% yield by NMR spectroscopy. However, the relatively high yield of decarboxylation product **9d** from **5d** suggests that there was poor overlap of the phenyl group with the incipient radical center during the translocation reaction.

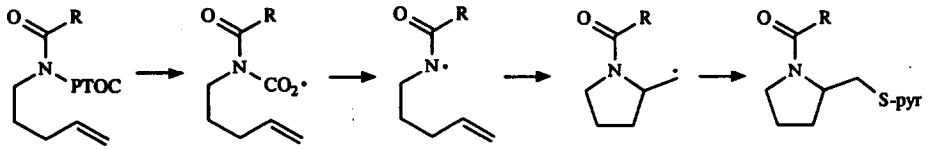
Table. Product Yields from Reactions of **5**

Precursor	Rel. % Yield		Total % Yield
	9	**10**	
5a	1	99	75
5b	44	56	84
5c	73	27	83
5d	60	40	74

In the presence of the efficient radicophile Ph_2Se_2, the results with precursors **5c** and **5d** were similar to those described above. The products from the radical translocation reaction, α-(selenophenyl)amides (**9**, X = SePh) were obtained in 60% and 30% yield, respectively. In addition, unsubstituted amides (**10**, X = H) were formed in these reactions. The absence of *N*-(selenophenyl)amides (**10**, X = SePh), the putative products from trapping of the amidyl radicals by Ph_2Se_2, was expected because the related *N*-thioamines are demonstrated aminyl radical precursors.[8] We presume that *N*-(selenophenyl)amides were produced but continued to react under visible irradiation to give amidyl radicals that ultimately reacted with solvent or disproportionated.

One of the reasons for the increasing interest in radical reactions for organic synthesis is the importance of 5-*exo* radical cyclizations. When the acetamido derivative **11** was allowed to react under visible irradiation, pyrrolidine **13** was produced in 65% isolated yield. The likely reaction sequence is shown in Scheme 3. The yield of pyrrolidine product **13** is similar to that previously obtained when the analogous amidyl radical **14** was produced from its PTOC imidate ester precursor.[4]

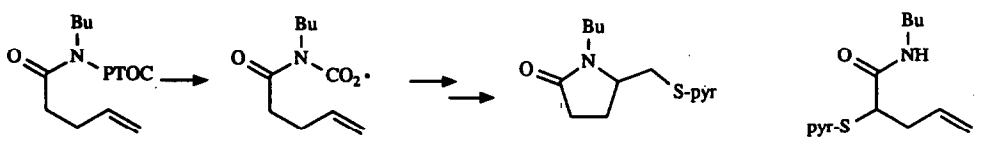
Scheme 3



11: R = CH_3 **12**: R = CH_3; **14**: R = $(CH_2)_3CH_3$ **13**: R = CH_3

In attempts to employ precursors **5** for entry to amidyl radicals, the radical translocation process would be an unwanted side-reaction. In the reaction sequence we propose in Scheme 2, with slow N-acyl rotation and a predominance of the anti conformer, the efficiency of the radical translocation process is determined by substitution at the α-carbon. In principle, it should be possible to attenuate the translocation reaction by favoring the syn radical (*syn*-**6**) which can only decarboxylate. This was demonstrated in reactions of **15** (Scheme 4). A typical reaction[7] of **15** gave lactam product **16** and α-substituted product **17** in a 1.9:1 ratio. However, reaction of **15** in CH_3CN in the presence of $MgBr_2$ at 60 °C gave **16** (isolated in 50% yield) and **17** in a ratio of 22:1. Apparently, the Lewis acid was chelated by the two carbonyl groups in **15** at the instant of radical formation. The reduction in the relative yield of translocation product **17** from 35% (in the absence of $MgBr_2$) to 4% (in the presence of $MgBr_2$) suggests that the anti radical conformer population was no greater than 10% in the latter case.

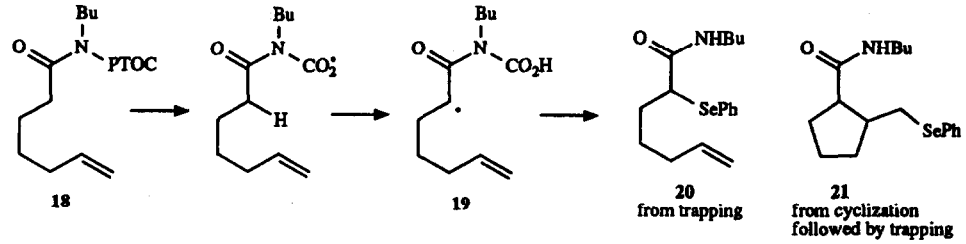
Scheme 4



15 **16** **17**

Radical translocation followed by cyclization also was possible (Scheme 5). Precursor **18** reacted in the presence of Ph_2Se_2 to give the cyclopentylcarboxamide **21** in 37% isolated yield along with the α-(selenophenyl)amide product **20** (8% isolated yield). When one considers that the α-amide radical was formed in only about 50% yield in reaction of the structurally related precursor **5b**, it is seen that the cyclization reaction was reasonably efficient. It is especially noteworthy that the cyclization to a mono-substituted alkene moiety was achieved under these conditions. In cases where α-amide radicals were produced by translocation from *o*-iodoanilide precursors, reactions conducted in the presence of Bu_3SnH, cyclizations onto mono-substituted alkene moieties did not compete favorably against reaction of the α-amide radicals with the tin hydride.[9]

Scheme 5



In summary, *N'*-acyl PTOC carbamates (**5**) are practical precursors for amidyl radicals. The precursors are readily prepared under mild conditions, and the radical translocation reaction can be suppressed to a large extent by employing $MgBr_2$ in the reaction medium. In selected cases with highly substituted α-positions, precursors **5** can also be employed for α-amide radicals, but one's inability to suppress the decarboxylation reaction of radicals **6** limits their utility in this regard.

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References and Notes

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4. Newcomb, M.; Esker, J. L. *Tetrahedron Lett.* **1991**, *32*, 1035.
5. Procedure for preparations of **5**: To a solution of the amide (2.0 mmol) in dry ether (20 mL) was added 2.2 mmol of Et_3N and 2.1 mmol of Me_3SiOTf; the mixture was stirred for 12 h, and the oil layer was removed. The trimethylsilylamide was treated with $COCl_2$ (2.5 mmol) in 5 mL of ether at -78 °C by a reported method.[10] Benzene (10 mL) was added, and the solution was concentrated *in vacuo*. The mixture was shielded from light, and benzene (15 mL) was added followed by *N*-hydroxypyridine-2-thione sodium salt (2.1 mmol). After stirring for 1.5 h, the resulting yellow solution was washed with water, saturated $NaHCO_3$ soln and saturated NaCl soln. The mixture was dried ($MgSO_4$), and solvent was distilled *in vacuo*. Compounds **2a** and **2e** were recrystallized from CH_2Cl_2-hexanes. Compounds **2b-2d**, **11**, **15** and **18** were oils.
6. Heeg, M. J., to be submitted for publication. Inquiries regarding the crystallography may be sent to Dr. M. J. Heeg, Department of Chemistry, Wayne State University, Detroit, MI 48202, U.S.A.
7. Procedure for reactions of **5**: Self-trapping reactions were conducted at room temperature with 0.07 M solutions of **5** in degassed benzene. The solutions were irradiated with a 150 W tungsten filament lamp until colorless or until TLC showed that no **5** remained (2-3 h). Ph_2Se_2 trapping reactions were conducted similarly with 0.05 M solutions of **5** containing 0.10 M Ph_2Se_2 which were irradiated for 12 h. Solvents were removed, and products were separated by radial chromatography on silica gel with hexanes-ethyl acetate elution. Products were analyzed by ^1H and ^{13}C NMR spectroscopy and high resolution mass spectrometry.
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