

Communications to the Editor

Generation of Alkoxy Radicals from *N*-Alkoxy-pyridinethiones

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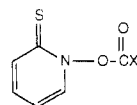
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β -Fission and hydrogen-atom abstraction, both inter- and intramolecular, are important characteristic reactions of alkoxy radicals.^{1,2} Such processes play a key role in various synthetically important transformations including, inter alia,³⁻⁷ the Barton reaction,³ the ring opening of cyclic compounds by regioselective C-C bond fission,⁴ and the formation of cyclic ethers.^{5,6} Also, by such reactions alkoxy radicals act as initiators for vinyl polymerization and other radical chain processes.

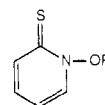
There are relatively few reliable absolute kinetic data available for alkoxy radical reactions. In principle they could be determined by a competitive method similar to those used for intramolecular reactions of alkyl radicals, e.g., the interaction of alkyl halides and tributylstannane.⁸ Unfortunately, the usual precursors for alkoxy radicals, viz peroxides, peresters, hyponitrites, nitrites, nitrates, and hypohalites,² do not interact with tributylstannane by clean chain processes involving alkoxy radical intermediates.^{9,10} Our aim, therefore, was to devise procedures for the generation of alkoxy radicals which utilize readily prepared and relatively stable precursors, which are suitable for kinetic experiments involving tributylstannane and which can be effectively employed in synthesis. We now describe methods based on Barton chemistry¹¹ which meet these criteria.

Unlike carbamates of the general type **1** which are suitable precursors of alkylamino radicals, RR'N[•],¹² via generation and decarboxylation of RR'NCO₂[•], the carbonates **2** do not afford alkoxy radicals, RO[•]. Thus, **2** (R = cyclopentyl), prepared in the usual way,^{11,12} gave cyclopentanol as the only product (GC) when heated in benzene with tributylstannane 0.030 M and AIBN. Since the experiments described below show that cyclopentyl radicals under these conditions undergo ring opening, they cannot be intermediates in this reaction.

Whilst the N-O bond strength in *N*-alkoxy-pyridine-2-thiones (e.g., **3**) would be expected to be stronger than those in the thi-hydroxamates **1** or **2**, the formation of the strong Sn-S bond¹³



1. X = R₂N
2. X = RO



3. R = (CH₂)₃CH=CH₂
4. R = cyclopentyl
5. R = cyclohexyl
6. R = *tert*-butyl

and the restoration of pyridine aromaticity should provide sufficient driving force to effect generation of alkoxy radicals by attack of tributyltin radicals on **3-6**. The latter compounds were prepared by treatment of the sodium salt of 2-mercaptopyridine-*N*-oxide with 1 molar equiv of a suitable alkyl halide in DMF at 80 °C. Although they decompose slowly in light, the yellow *N*-alkoxy compounds are stable in the dark at room temperature and are not sensitive to oxygen or moisture. When heated in dilute solution (0.030 M) in benzene at 80 °C under argon in the dark for periods up to 1 h, they underwent no observable reaction. However, when tributylstannane (0.030 M) and AIBN (0.003 M) were present the yellow color rapidly faded, and the reaction was complete within 20 min. The products were as follows: 2-methyltetrahydrofuran (80%) from **3**; cyclopentanol (23%) and pentanal (63%) from **4**; cyclohexanol (73%) and hexanal (8%) from **5**; and *tert*-butyl alcohol (86%) and acetone (2%) from **6**.¹⁵

These products are consistent with the intermediacy of alkoxy radicals in a chain mechanism (Scheme I). Thus, the formation of 2-methyltetrahydrofuran from the *N*-alkoxy compound **3** accords with known propensity of 4-pentenyl radical to undergo rapid endo cyclization.^{1,16} Similarly, the formation of cyclopentanol and pentanal from precursor **4** indicates that under these conditions the characteristic β -fission of the cyclopentyl radical¹⁷ competes with hydrogen atom transfer from stannane (Scheme I). The cyclohexyl and *tert*-butoxy radicals generated from **5** and **6**, respectively; behave in much the same way.¹⁸ It is noteworthy that the formation of such products cannot reasonably be reconciled with any polar mechanism or with the formation of ionic intermediates.

When the cyclopentyl radical compound **4** was heated with bromotrichloromethane and AIBN in benzene, the sole product ($\geq 95\%$) was 5-bromopentanal. Its formation is consistent with a mechanism involving (i) generation of the cyclopentyl radical, (ii) β -fission to give [•]CH₂(CH₂)₃CHO, (iii) S_H2 attack on bromine to give 5-bromopentanal and CCl₃[•], and (iv) chain propagation by attack of CCl₃[•] on **4**.

Since they can be readily prepared, are relatively stable, and undergo clean chain decomposition under suitable conditions, the *N*-alkoxy-pyridine-2-thiones should be useful additions to the list of alkoxy radical precursors. In particular, they are very suitable for kinetic work. For example, the failure of the reaction of **3** to afford 4-pentenol in detectable yield ($\leq 1\%$) indicates that the 4-pentenyl radical has $k_C/k_H \geq 1.5$ M, where k_C is the rate

(1) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic: New York, 1980.

(2) Kochi, J. In *Free Radicals*; Kochi, J., Ed.; Wiley: New York, 1973; Vol. 2, Chapter 24.

(3) For reviews, see: Akhtar, M. *Adv. Photochem.* **1964**, *2*, 263. Hesse, R. H. *Adv. Free Radical Chem.* **1969**, *3*, 83.

(4) For a review, see: Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541.

(5) Kraus, G. A.; Thurston, J. *Tetrahedron Lett.* **1987**, *28*, 4011 and references therein.

(6) Kalvoda, J.; Heusler, K. *Synthesis* **1971**, 501.

(7) Brun, P.; Waegell, B. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum: New York, 1979; Vol. 3, p 367. Brun, P.; Waegell, B. *Tetrahedron* **1976**, *32*, 517.

(8) See, for example: Beckwith, A. L. J.; Lawrence, T. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1535.

(9) Davies, A. G.; Smith, P. J. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon: Oxford, 1982; Chapter 11.

(10) Separate experiments have shown that the photolysis of cyclopentyl nitrite in the presence of tributylstannane in low concentration does not give free cyclopentyl radicals.

(11) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1983**, 939; *Tetrahedron* **1985**, *41*, 3901. Barton, D. H. R.; Crich, D.; Kretschmar, G. *J. Chem. Soc., Perkin Trans. 1* **1986**, 39.

(12) Newcomb, M.; Deeb, T. M. *J. Am. Chem. Soc.* **1987**, *109*, 3163. Newcomb, M.; Park, S.-U.; Kaplan, J.; Marquardt, D. *J. Tetrahedron Lett.* **1985**, *26*, 5651.

(13) Although thermochemical data for R₃Sn-SR bonds is unavailable, it is known that Sn-S bonds are stronger than Sn-O bonds.⁹ For comparison, Me₃Sn-OEt has a bond dissociation energy of 84 kcal/mol.¹⁴

(14) Jackson, R. A. *J. Organomet. Chem.* **1979**, *166*, 17.

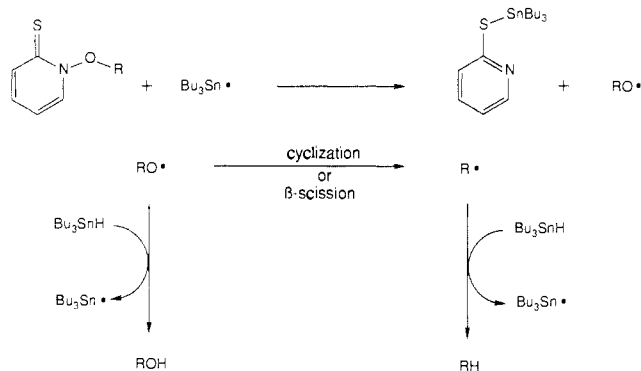
(15) Yields of 90-95% have been observed at higher tributylstannane concentrations (≥ 0.20 M).

(16) Rieke, R. D.; Moore, N. A. *Tetrahedron Lett.* **1969**, 2035; *J. Org. Chem.* **1972**, *37*, 413.

(17) Nussbaum, A. L.; Robinson, C. H. *Tetrahedron* **1962**, *17*, 35. Kabisakalian, P.; Townley, E. R.; Yudis, M. D. *J. Org. Chem.* **1962**, *27*, 2918. Walling, C.; Clark, R. T. *J. Am. Chem. Soc.* **1974**, *96*, 4530.

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Scheme 1



constant for cyclization and k_H that for hydrogen atom transfer from tributylstannane. As the value of k_H for 4-pentyloxy radicals should be very similar to that for *tert*-butoxy radicals (estimated to be $4 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ at 80°C)^{19,20} it follows that $k_C \geq 6 \times 10^8 \text{ s}^{-1}$ at 80°C .

The propensity of the ring-opened radicals to undergo ring closure and other rearrangements²² complicates the estimation of the rate constants for β -fission of the cycloalkoxy radicals generated from **4** and **5**. Nevertheless, it is clear that the relative ease of β -fission is in the order cyclopentyloxy \gg cyclohexyloxy \gg *tert*-butoxy.

N-Alkoxy-pyridine-2-thiones should also be useful precursors of alkoxy radicals for synthetic work. Details of such applications and of kinetic studies now in progress will be reported shortly.

(19) Scaiano, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 5399.

(20) On the basis of the reasonable assumption that H^\bullet abstraction from tributylstannane by alkoxy radicals has a pre-exponential factor of $\log A \approx 10$,²¹ it follows from the value of the rate constant for *tert*-butoxy radical at 25° ($k_H = 2 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$)⁹ that $E_a \approx 2.3 \text{ kcal/mol}$. These Arrhenius parameters allow the estimation of $k_H = 4 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ at 80°C .

(21) Other reactive radicals abstract H^\bullet from tributylstannane with similar pre-exponential factors, e.g., benzyloxy ($\log A = 10.0 \pm 0.2$) and $(\text{CH}_3)_2\text{C}=\text{CH}^\bullet$ ($\log A = 9.7 \pm 0.3$): Johnston, L. J.; Luszyk, J.; Wayner, D. D. M.; Abeywickrema, A. N.; Beckwith, A. L. J.; Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 4594 (Due to the slow rate of decarboxylation, the data reported in this reference for the phenyl radical actually pertain to the benzyloxy radical.)

(22) Beckwith, A. L. J.; Hay, B. P., unpublished results.

The Structure of Liposidomycin B, an Inhibitor of Bacterial Peptidoglycan Synthesis

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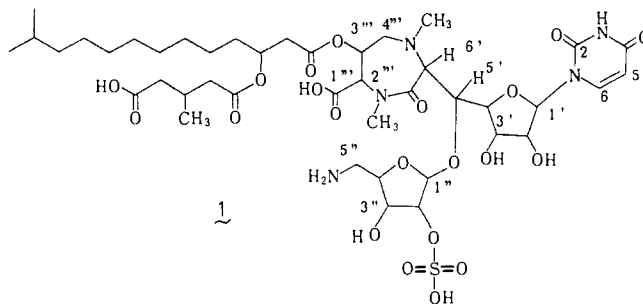
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The liposidomycins are a family of nucleoside antibiotics, recently isolated from *Streptomyces griseosporus*,¹ which strongly inhibit bacterial peptidoglycan synthesis. Liposidomycins inhibit formation of the lipid intermediate in peptidoglycan synthesis

(1) Isono, K.; Uramoto, M.; Kusakabe, H.; Kimura, K.; Izaki, K.; Nelson, C. C.; McCloskey, J. A. *J. Antibiot.* **1985**, *38*, 1617.

(unpublished data), as does tunicamycin,² but with three orders of magnitude greater activity ($\text{ID}_{50} 0.03 \mu\text{g/mL}$) and extremely high specificity. For liposidomycin B, one of the principal constituents, we propose structure **1**, a novel lipid-containing nucleoside of unusual complexity. Compound **1** resembles the reaction intermediate between UDP-*N*-acetylmuramylpentapeptide and undecaprenyl phosphate in the lipid cycle of peptidoglycan synthesis.³



Liposidomycin B (mol wt 1009, $\text{C}_{42}\text{H}_{67}\text{N}_5\text{O}_{21}\text{S}$)⁴ contains nine active hydrogen atoms,⁵ is amphoteric, and gives a positive ninhydrin test. Uracil, 3-methylglutaric acid, and 3-hydroxy-12-methyltridecanoic acid were identified in an acid hydrolyzate of **1** (e.g., 3 M HCl, 100°C , 3 h) by NMR spectroscopy and by GC/MS⁸ of the trimethylsilylated hydrolyzate, including comparison with authentic uracil and 3-methylglutaric acid.^{9,10} The methyl ester derivative of isolated 3-hydroxy-12-methyltridecanoic acid (M^+ , m/z 258) showed ions characteristic of β -hydroxylation [$(\text{M}-\text{C}_3\text{H}_5\text{O}_2)^+$, m/z 185; $\text{C}_4\text{H}_7\text{O}_3^+$, m/z 103].¹¹

Acid hydrolysis of **1** also gave nucleoside **2** (mol wt 426, $\text{C}_{17}\text{H}_{22}\text{N}_4\text{O}_9$)⁴ and a small amount of **3** (mol wt 444). The complete structure of **3** is undetermined but was shown by EI mass spectrometry to differ from **2** by 18 mass units in the seven-membered heterocycle, from which it was concluded that **2** is a dehydrated form of **3**. The structure of **2** was determined by ^1H NMR and in comparison with the anhydrodeacylliposidomycin **4** (see below). High voltage paper electrophoresis of **2** showed presence of acidic ($-\text{COOH}$) and basic ($-\text{N}^<$) groups. Presence of a sulfate group in **1** was established from IR spectroscopy (KBr,

(2) *Tunicamycin*; Tamura, G., Ed.; Japan Scientific Press: Tokyo, 1981; p 32.

(3) (a) Ghuyssen, J.-M. In *Topics in Antibiotic Chemistry*; Sammes, P. G., Ed.; Ellis Horwood Ltd.: England, 1980; Vol. 5, p 35. (b) Mirelman, D. In *Bacterial Outer Membranes*; Inouye, M., Ed.; Wiley: New York, 1979; p 116.

(4) High resolution and FAB mass spectra, VG 70-SEQ and MAT 731 instruments; **1**, MH^+ , m/z 1010; $(\text{M}-\text{H})^-$, m/z 1008.403 (calcd 1008.397); **2**, as tetrakis(trimethylsilyl) (TMS) derivative, M^+ , m/z 714.2961 (calcd 714.2968); **3**, $(\text{TMS})_5$, M^+ , m/z 804; **4**, MH^+ , m/z 558.2053 (calcd 558.2048); **5**, MH^+ , m/z 638; **6**, MH^+ , m/z 656. NMR spectra were measured by using JEOL GX 400, GSX 400, GSX 270 instruments; **1**, ^1H NMR $\text{CD}_3\text{OD}(\text{TMS})$: uracil moiety, δ 7.82 (1 H, d, $J = 8 \text{ Hz}$), 5.76 (1 H, d, $J = 8 \text{ Hz}$); 3-methylglutaryl moiety, 1.0 (3 H, d, $J = 6.4 \text{ Hz}$), 2.37 (1 H, m), 2-2.4 (4 H, m); 3-hydroxy-12-methyltridecanoyl moiety, 0.88 (6 H, d, $J = 6.8 \text{ Hz}$), 1.51 (1 H, m), 1.3 (12 H, m), 1.6 (1 H, m), 5.2 (1 H, m), 2.61 (1 H, dd, $J = 8.5 \text{ Hz}$, $J = 15.7 \text{ Hz}$), 2.69 (1 H, dd, $J = 4.4 \text{ Hz}$, $J = 15.7 \text{ Hz}$), 1', 5.64 (1 H, d, $J = 1.5 \text{ Hz}$), 2', 4.14 (1 H, overlapping), 5', 4.42 (1 H, brd, $J = 10.7 \text{ Hz}$), 6', 3.79 (1 H, d, $J = 10.7 \text{ Hz}$), 1'', 5.45 (1 H, s), 2'', 4.67 (1 H, d, $J = 4.8 \text{ Hz}$), 3'', 4.30 (1 H, overlapping), 4'', 4.16 (1 H, overlapping), 5'', 3.43 (1 H, dd, $J = 2.7 \text{ Hz}$, $J = 12 \text{ Hz}$), 3.24 (1 H, dd, $J = 3.7 \text{ Hz}$, $J = 12 \text{ Hz}$), 3''', 5.45 (1 H, m). **1**, ^{13}C NMR $\text{CD}_3\text{OD}(\text{TMS})$: COOR, CON (176.7, 173.8, 172.9, 172.6, 171.1 each s), 4 (166.5, s), 2 (152, s), 6 (142.5, d), 1'' (110.2, s), 5 (102.4, d), 1' (92, d), 4' (83.6, d), 2'' (81.6, d), 6' (64.6, d).

(5) Determined by FAB mass spectrometry with a ^3H exchange method.^{6,7}

(6) Sethi, S. K.; Smith, D. L.; McCloskey, J. A. *Biochem. Biophys. Res. Commun.* **1983**, *112*, 126.

(7) Verma, S.; Pomerantz, S. C.; Sethi, S. K.; McCloskey, J. A. *Anal. Chem.* **1986**, *58*, 2898.

(8) EI mass spectra of TMS derivatives, VG 70-SEQ: uracil-(TMS)₂, M^+ m/z 256; 3-methylglutaric acid-(TMS)₂, M^+ m/z 290; 3-hydroxy-12-methyltridecanoic acid-(TMS)₂, M^+ m/z 388.

(9) White, E., V.; Krueger, P. M.; McCloskey, J. A. *J. Org. Chem.* **1972**, *37*, 430.

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