Communications to the Editor

Generation of Alkoxy Radicals from *N*-Alkoxypyridinethiones

Athelstan L. J. Beckwith* and Benjamin P. Hay

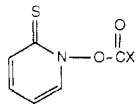
Research School of Chemistry
Australian National University
Canberra, A.C.T. 2601, Australia
Received February 4, 1988

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.

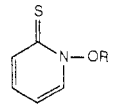
There are relatively few reliable absolute kinetic data available for alkoxy radical reactions. In principle they could be determined by a competitive method similar to those used for intramolecular reactions of alkyl radicals, e.g., the interaction of alkyl halides and tributylstannane.[8] Unfortunately, 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 chemistry[11] which meet these criteria.

Unlike carbamates of the general type **1** which are suitable precursors of alkylamino radicals, $RR'N^{\bullet}$,[12] via generation and decarboxylation of $RR'NCO_2^{\bullet}$, the carbonates **2** do not afford alkoxy radicals, $RO^{\bullet}$. 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 cyclopentyloxy radicals under these conditions undergo ring opening, they cannot be intermediates in this reaction.

Whilst the N–O bond strength in *N*-alkoxypyridine-2-thiones (e.g., **3**) would be expected to be stronger than those in the thiohydroxamates **1** or **2**, the formation of the strong Sn–S bond[13]



1. X = R_2N
2. X = RO



3. R = $(CH_2)_3CH{=}CH_2$
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-pentenyloxy 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 cyclopentyloxy radical[17] competes with hydrogen atom transfer from stannane (Scheme I). The cyclohexyloxy 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.

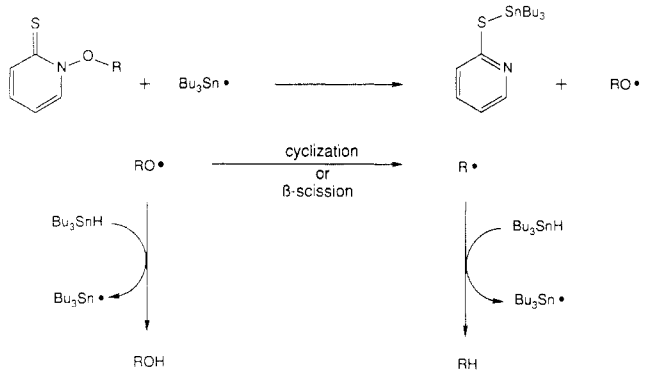
When the cyclopentyloxy compound **4** was heated with bromotrichloromethane and AIBN in benzene, the sole product (≥95%) was 5-bromopentanal. Its formation is consistent with a mechanism involving (i) generation of the cyclopentyloxy radical, (ii) β-fission to give $^{\bullet}CH_2(CH_2)_3CHO$, (iii) S_H2 attack on bromine to give 5-bromopentanal and $CCl_3^{\bullet}$, and (iv) chain propagation by attack of $CCl_3^{\bullet}$ on **4**.

Since they can be readily prepared, are relatively stable, and undergo clean chain decomposition under suitable conditions, the *N*-alkoxypyridine-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 (≤1%) indicates that the 4-pentenyloxy 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*; Abromovitch, 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 cyclopentyloxy 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.; Kretzschmar, 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 R_3Sn–SR bonds is unavailable, it is known that Sn–S bonds are stronger than Sn–O bonds.[9] For comparison, Me_3Sn–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. Kabasakalian, 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.
(18) Takagi, H.; Washida, N.; Bandow, H.; Akimoto, H.; Okuda, M. *J. Phys. Chem.* **1981**, *85*, 2701. Druliner, J. D.; Kitson, F. G.; Rudat, M. A.; Tolman, C. A. *J. Org. Chem.* **1983**, *48*, 4951. Choo, K. Y.; Benson, S. W. *Int. J. Chem. Kinet.* **1981**, *13*, 833 and references therein.

0002-7863/88/1510-4415$01.50/0

Scheme I



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

The propensity of the ring-opened radicals to undergo ring closure and other rearrangements[22] 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 ≫ cyclohexyloxy ≫ *tert*-butoxy.

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

(21) Other reactive radicals abstract H• from tributylstannane with similar pre-exponential factors, e.g., benzoyloxy (log A = 10.0 ± 0.2) and $(CH_3)_2C{=}CH^•$ (log A = 9.7 ± 0.3): Johnston, L. J.; Lusztyk, 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 benzoyloxy radical.)

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

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

Makoto Ubukata and Kiyoshi Isono*

Antibiotics Laboratory, RIKEN (The Institute of Physical and Chemical Research) Wako-shi, Saitama 351-01, Japan

Ken-ichi Kimura

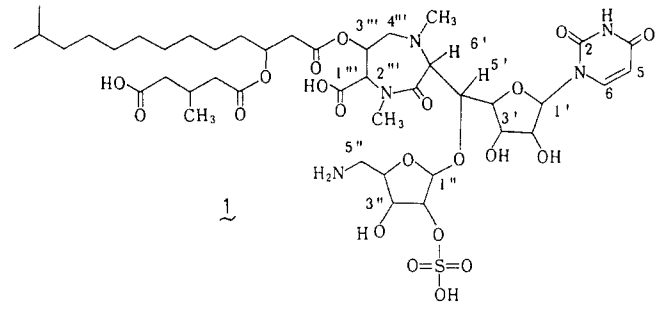
Research Institute of Life Science Snow Brand Milk Products Co., Ltd. Ishibashi-machi, Shimotsuga-gun, Tochigi 329-05, Japan

Chad C. Nelson and James A. McCloskey

Departments of Medicinal Chemistry and Biochemistry University of Utah, Salt Lake City, Utah 84112

Received December 4, 1987

The liposidomycins are a family of nucleoside antibiotics, recently isolated from *Streptomyces griseosporeus*,[1] which strongly inhibit bacterial peptidoglycan synthesis. Liposidomycins inhibit formation of the lipid intermediate in peptidoglycan synthesis (unpublished data), as does tunicamycin,[2] but with three orders of magnitude greater activity (ID_{50} 0.03 μg/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]



1

Liposidomycin B (mol wt 1009, $C_{42}H_{67}N_5O_{21}S$)[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/MS[8] 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 [$(M\text{-}C_3H_5O_2)^+$, m/z 185; $C_4H_7O_3^+$, m/z 103].[11]

Acid hydrolysis of **1** also gave nucleoside **2** (mol wt 426, $C_{17}H_{22}N_4O_9$)[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 (-COOH) and basic (-N<) groups. Presence of a sulfate group in **1** was established from IR spectroscopy (KBr,

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

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

(3) (a) Ghuysen, 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; $(M-H)^-$, m/z 1008.403 (calcd 1008.397); **2**, as tetratrimethylsilyl (TMS) derivative, M^+, m/z 714.2961 (calcd 714.2968); **3**, $(TMS)_5$, 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 CD_3OD(TMS): uracil moiety, δ 7.82 (1 H, d, J = 8 Hz), 5.76 (1 H, d, J = 8 Hz); 3-methylglutaryl moiety, 1.0 (3 H, d, J = 6.4 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 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 Hz, J = 15.7 Hz), 2.69 (1 H, dd, J = 4.4 Hz, J = 15.7 Hz), 1′, 5.64 (1 H, d, J = 1.5 Hz), 2′, 4.14 (1 H, overlapping), 5′, 4.42 (1 H, brd, J = 10.7 Hz), 6′, 3.79 (1 H, d, J = 10.7 Hz), 1″, 5.45 (1 H, s), 2″, 4.67 (1 H, d, J = 4.8 Hz), 3″, 4.30, (1 H, overlapping), 4″, 4.16 (1 H, overlapping), 5″, 3.43 (1 H, dd, J = 2.7 Hz, J = 12 Hz), 3.24 (1 H, dd, J = 3.7 Hz, J = 12 Hz), 3‴, 5.45 (1 H, m). **1**, ^{13}C NMR CD_3OD(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 ^2H 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.

(10) *Mass Spectra of Compounds of Biological Interest*; Markey, S. P., Urban, W. G., Levine, S. P., Eds.; U.S. Atomic Energy Commission, TID-26553-P2: Oak Ridge, TN, Vol. II, Part 1, p 425.

(11) Ryhage, R.; Stenhagen, E. *Arkiv. Kemi.* **1960**, *15*, 545.

0002-7863/88/1510-4416$01.50/0