Alkenylthioimidoyl Radicals: Competition between β-Scission and Cyclization to Dihydrothiophen-2-ylidene-amines

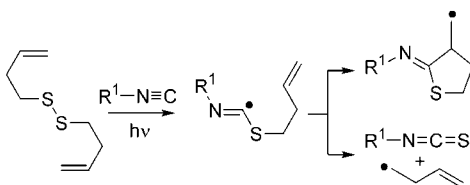Matteo Minozzi,[†] Daniele Nanni,[†] and John C. Walton*,[‡]

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ABSTRACT

But-3-enylthioimidoyl radicals were shown by EPR spectroscopy and end product analysis to ring-close predominantly in the 5-*exo* mode with a rate constant of 2.4×10^4 s^{-1} at 300 K to afford substituted dihydrothiophenylmethyl radicals. This ring closure was in competition with dissociation to but-3-enyl radicals and an isothiocyanate. The dissociation predominated at temperatures above ca. 300 K.

Interest in imidoyl radicals ($R^1-N=C^\bullet X-R^2$) as synthetic intermediates has been stimulated by the discovery of their mediation of several useful annulations[1,2] and also as a consequence of their formation from sulfanyl radical additions to alkenyl isonitriles and subsequent cyclizations.[3,4] Recently, arylthioimidoyl radicals, made by addition of either arylsulfanyl radicals to aryl isonitriles or of aryl radicals to isothiocyanates, have been exploited in cascade syntheses of benzothieno-quinoxalines[5] and -quinolines[6] and thio-chromenoindoles.[7] Alkanethioimidoyl radicals (X = S, R^2 = alkyl) undergo rapid scission of the S−R^2 bond to produce isothiocyanates, together with the corresponding alkyl radicals ($R^2\bullet$).[8] Despite competition from this dissociation, Bachi and co-workers successfully exploited ring closures of thioimidoyls, onto unsaturated N-substituents (R^1 = alkenyl), to afford a variety of *N*-heterocycles, including kainic acid.[3b−d]

The rate of dissociation of alkanesulfanylimidoyl radicals is high when the released C-centered radical is tertiary or resonance stabilized but moderate for primary radicals.[9] We reasoned, therefore, that ring closure onto the alkenesulfanyl moiety should be observable in some circumstances leading

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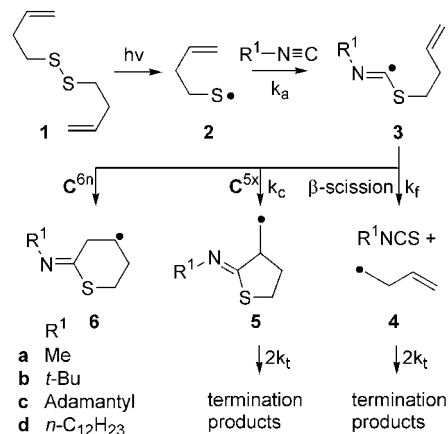(8) (a) Blum, P. M.; Roberts, B. P. *J. Chem. Soc., Chem. Commun.* **1976**, 535. (b) Blum, P. M.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 2* **1978**, 1313.
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to formation of dihydrothiophen-2-ylidene-amines (**5**) and hence to γ-butyrothiolactones.

The feasibility of this ring closure route was tested by examination of the system shown in Scheme 1. But-3-

enylsulfanyl radicals **2** were generated by photolysis of the corresponding disulfide **1**,[10,11] in the presence of various isonitriles in liquid cyclopropane as a solvent. When **1** (15 mg) was photolyzed at 265 K with *tert*-butyl isonitrile (15 mg), the EPR spectrum shown in Figure 1 (upper panel) was
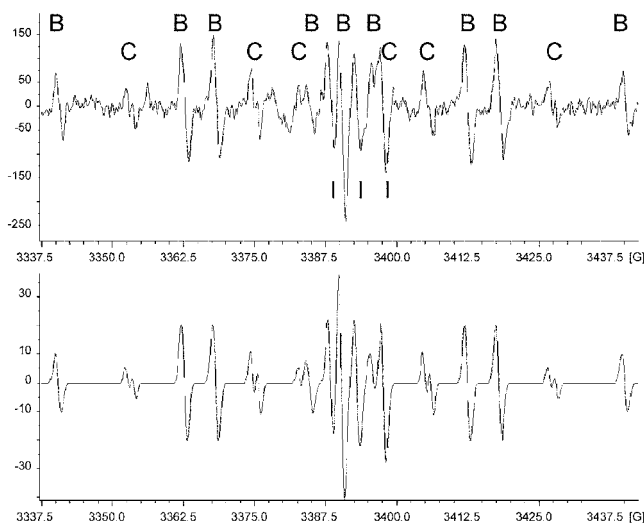
Figure 1. Top: 9 GHz EPR spectrum obtained on photolysis of a cyclopropane solution of dibut-3-enyl disulfide (**1**) and *tert*-butyl isonitrile at 265 K; "I" indicates thioimidoyl radical **3b**, "B" indicates butenyl radical **4**, and "C" indicates cyclized radical **5b**. Bottom: computer simulation.

obtained. The three-line signal marked "I" dominated the spectrum at lower temperatures. This was easily identified as the thioimidoyl radical **3b** by comparison of its EPR parameters with those in the literature[8] and with computed

Table 1. Experimental and Computed EPR Parameters for Thioimidoyl and Dihydrothiophenylmethyl Radicals[a]

radical	T(K) [theor]	g-factor	a(N)	$a(2H_\alpha)$	$a(H_\beta)$	a(other)
3a	[DFT][b]		3.8			2.0(CH₃)
3b	235	2.0011	4.6			
3c	245	2.0012	4.5			
5a	[DFT][b]			−21.5	37.7	−0.8(Hᶜ)
						1.3(Hᵗ)
5b	265	2.0027			21.9	30.2	1.0(1H)
5c	245	2.0027			21.8	30.9	0.9(1H)
2-oxo[c]	210				22.6	30.4	

[a] Spectra in cyclopropane solution; hfs in Gauss. [b] Computed by the UB3LYP method with a 6-311+G(d,p) basis set. [c] Experimental data for the 2-oxocyclopentylmethyl radical (ref 13).

hyperfine splitting (hfs) values (Table 1). The triplet of triplets marked "B" corresponded to the but-3-enyl radical[12] (**4**) formed by β-scission of **3b**. A third signal consisting of a doublet of triplets "C" was also present. The EPR parameters of "C" were very similar to those of the related 2-oxocyclopentylmethyl radical[13] (Table 1), and we identified "C" as the 2-substituted dihydrothiophenylmethyl radical **5b**. This identification was supported by a UB3LYP computation [6-311+G(d,p) basis set][14] on the *N*-methyl analogue **5a** that gave very similar hfs (Table 1). Note that because the β-H hfs has been computed at the lowest point of the rotational potential of the CH₂• group, it is larger than the experimental value, which is an average over the populated energy levels of the rotation.

An interesting feature of the spectrum was the small doublet long-range splitting on each resonance line C. The two γ-H atoms of **5** are nonequivalent and interact with the unpaired electron to different extents. The DFT computation indicated that the H-atom *trans* to the CH₂•, i.e., Hᵗ (structure **5a**), had the larger hfs (Table 1).
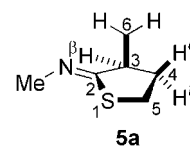
Very similar spectra containing signals from the three analogous radicals (**3c**, **5c**, and **4**) were obtained (Table 1) when disulfide **1** was photolyzed together with adamantane-1-isonitrile.[15] However, when dodecane-1-isonitrile was used, broad unidentified spectra were obtained.

The observation of radicals **5b** and **5c** showed that cyclization onto the but-3-enylsulfanyl moiety of thioimidoyl

(10) Prepared in 75% yield by oxidation of but-3-en-1-thiol[11] with a mixture of KMnO₄ and CuSO₄: ¹H NMR (CDCl₃) δ 2.45 (2 H, m), 2.76 (2 H, t, *J* = 7.5 Hz), 5.03−5.14 (2 H, m), 5.83 (1 H, m); ¹³C (CDCl₃) δ 34.1, 38.8, 117.0, 136.9; CIMS found (MH)⁺ 175.0616, calcd for C₈H₁₅S₂ 175.0615.
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radicals could indeed take place. None of the spectra showed detectable quantities of the thiacyclohex-4-yl radical **6**. It follows that the main cyclization mode is 5-*exo-trig* (C^{5x}) rather than 6-*endo* (C^{6n}).[16]

The concentrations of the three radicals were determined using the usual EPR method[17] and are shown as a function of temperature in Figure 2. Thioimidoyl **3b** decreased in
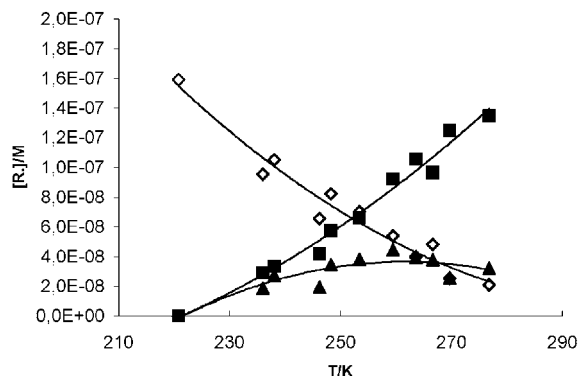
Figure 2. Concentrations of radicals derived from **1** and *tert*-butyl isonitrile in cyclopropane as a function of temperature. Symbols: ◇, [thioimidoyl radical **3b**]; ■, [but-3-enyl radical **4**]; ▲, [dihydrothiophenylmethyl radical **5b**].

concentration as the temperature increased and was essentially all converted to but-3-enyl and dihydrothiophenylmethyl **5b** above ca. 280 K. In the range 230−260 K, cyclization of **3b** competed satisfactorily with β-scission. However, at higher temperatures, the β-scission process dominated.

Several photoinitiated reactions of disulfide **1** with *t*-butyl isonitrile in cyclopropane solution were analyzed by GC-MS. This technique indicated that the main products were compounds **7**−**9** formed by disproportionations of radicals **3**−**5** (Scheme 2) together with dimers and cross-coupled products (e.g., **11**) from the same radicals (others not shown, see Supplementary Information). Cyclopropane is a very poor H-atom donor because of its strong C−H bonds, and therefore radical−radical reactions are the expected outcome

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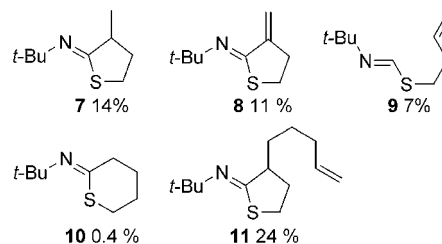
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in this solvent. A small amount of a second product having $M^+ = 171$ ($C_9H_{17}NS$) was also present. The fragmentation pattern that this could be *tert*-butyl-(tetrahydro-thiopyran-2-ylidene)amine, i.e., **10**, the product from 6-*endo* cyclization. If this identification is correct, the ratio of 5-*exo* to 6-*endo* cyclization is ca. 35:1 at 0 °C. The product analysis confirmed the mechanism of Scheme 1, except that minor amounts (<10% total) of products derived from coupling reactions of the butenylthiyl radical **2** were also implicated (see Supplementary Information).

Neglecting the minor amount of termination involving radical **2**, and assuming, as is usual for small transient radicals in solution,[18] that the termination steps involving the three radicals are diffusion controlled and have identical rate constants ($2k_t$), it can easily be shown that

$$k_c/2k_t = [\mathbf{5b}] + [\mathbf{5b}]^2/[\mathbf{3b}] + [\mathbf{4}][\mathbf{5b}]/[\mathbf{3b}] \qquad (1)$$

and that a similar expression for $k_f/2k_t$ also holds, in which [**4**] replaces [**5b**] in the first two terms on the right side of eq 1. Applying the concentrations from Figure 2 to eq 1 and using the usual $2k_t$ value [$\log(2k_t$ (M^{-1} s^{-1})) = 11.63−2.25/θ in *n*-heptane][19] corrected for the difference in *n*-heptane and cyclopropane viscosities as described previously[20] gave k_c (300 K) = 2.4 × 10^4 s^{-1}, $\log(A_c$ (s^{-1})) = 10.2, and E_c (kcal/mol) = 8.0. To our knowledge, these values are the first kinetic parameters available for cyclization of an imidoyl radical. The analogous rate parameters for the β-scission were k_f (300 K) = 1.6 × 10^5 s^{-1}, $\log(A_f$ (s^{-1})) = 13.7, and E_f (kcal/mol) = 11.7.

Roberts and Blum reported k_f (183 K) = 2 × 10^3 s^{-1} for extrusion of the *t*-Bu• radical from the analogous thioimidoyl radical.[8] Extrapolation with our Arrhenius parameters gave a k_f for butenyl 3 orders of magnitude lower at 183 K, and this seems very reasonable for the more difficult loss of this primary radical.

Our findings indicate that the regioselectivity of ring closure of thioimidoyl radical **3b** is strongly in favor of the 5-*exo*-mode. Thus, **3b** follows the norm for hex-5-enyl-type species. In particular, 2-thiahex-5-enyl radicals, that also bear a sulfur atom α-to the radical center, also prefer the 5-*exo*-

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mode, the *exo/endo* ratio being 5.4 at 80 °C.[21] The rate constant for cyclization of butenylthioimidoyl radical **3b** is approximately 1 order of magnitude smaller than the rate constants for cyclizations of the archetype hex-5-enyl radical [k_c (300 K) = 2 × 10^5 s^{-1}][22] and the related acyl radical, hex-5-enoyl [k_c (300 K) = 2.2 × 10^5 s^{-1}].[23] Replacement of the α-methylene group of hex-5-enyl with a SiMe$_2$ group leads to a significant reduction in k_c.[24] Thus, the lower k_c for **3b** indicates that a trend toward slower cyclization rates may be general for radicals with second row groups α to the radical center.

Supporting Information Available: Experimental procedures for preparation of di(but-3-enyl) disulfide, adamantyl isonitrile, and dodecyl isonitrile and for the photochemical reaction of **1** with *tert*-butyl isonitrile; kinetic data and Arrhenius plots for cyclization and β-scission of butenyl-thioimidoyl radical **3b**; and computational methods and Gaussian98 archive files for radicals **3a** and **5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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