

Limitations on the Persistence of Iminoxyls: Isolation of *tert*-Butyl 1,1-Diethylpropyl Ketiminoxyl and Related Radicals

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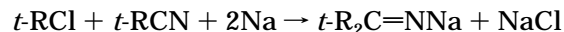
A series of iminoxyl radicals of the general formula R(C=NO•)R¹, with R and R¹ usually tertiary, was synthesized in a search for radicals of increased persistence. Three new radicals were isolated as blue liquids: Et₃C(C=NO•)Bu-*t* (**1**), *t*-C₅H₁₁(C=NO•)Bu-*t* (**2**), and (*t*-C₅H₁₁)₂C=NO• (**3**). Oxidation of oximes Et₃C(C=NOH)Ph (**4H**), PhCH₂CMe₂(C=NOH)Bu-*t* (**5H**), PhCMe₂(C=NOH)Bu-*t* (**6H**), and Me₂CH(C=NOH)C₅H₁₁-*t* (**7H**), among others, did not lead to isolable iminoxyls. A new, convenient synthesis of symmetrical tertiary imines from *tert*-RCl, *tert*-RCN, and Na is described. Radical *t*-Bu₂C=NO• (**8**) and cyclohexene readily gave the allylic substitution product, 2,2,4,4-tetramethyl-3-hexanone *O*-(2'-cyclohexen-1'-yl)oxime.

Iminoxyl radicals, of the general formula R₂C=NO•, are intermediate in reactivity between carbon-centered radicals and nitroxides. Di-*tert*-butyliminoxyl¹ was the first to be isolated in the pure state and has shown modest synthetic utility.² Since it decays slowly by irreversible head-to-tail dimerization, we anticipated that replacement of *tert*-butyl by sterically more demanding substituents would strongly retard all of the known pathways for decay. For instance, the (logarithmic) steric parameter E_S declines from -1.54 for *tert*-butyl to -2.55 for phenyl and -3.8 for Et₃C.³ The preparation of a radical of low molecular weight that could be stored indefinitely at room temperature would greatly facilitate further studies.

Bis(1-adamantyl) ketiminoxyl is the most persistent iminoxyl isolated to date.⁴ We also sought in this study to prepare polyradicals derived from 1,3-dibromoadamantane, with the eventual goal of synthesis of 3D network polyradicals starting from known 1,3,5,7-tetrahaloadamantanes.⁵

The precursors to isolable iminoxyls are sterically hindered oximes. These are accessible from hindered ketones and hydroxylamine under pressure,⁶ and more conveniently by reaction of hydroxylamine with the corresponding ketimine, available in turn by alkylation

of nitriles with alkylolithiums,⁷ or with Grignard reagents in the presence of catalytic Cu(I).⁸ Hartzler showed that di-*tert*-butyl ketimine could be prepared in good yield from pivalonitrile and sodium.⁹ We have improved the economy of this approach by the production of the alkylation agent *in situ* from sodium and the corresponding tertiary chloride:



Synthesis of Oximes and Radicals. The synthesis of ketimines from nitrile, chloride, and sodium conveniently avoids expensive, pyrophoric reagents. The synthesis was accomplished inadvertently in one unsymmetrical case as well. 2',2'-Diethylpropiophenone oxime (**4H**) was isolated from a reaction of sodium with triethylacetonitrile, followed by addition of hydroxylamine. We inferred that the aromatic ring arose from contamination of the starting nitrile with chlorobenzene apparently added as a chaser solvent for distillation. Subsequent attempts to react pure triethylacetonitrile with sodium followed by hydroxylamine did not give products with sensible combustion analyses.

The unsymmetrical oximes other than **4H** were synthesized by the successive reaction of an alkylolithium and hydroxylamine with the appropriate tertiary nitrile. The unsymmetrical oximes displayed ¹H-NMR spectra that indicated a mixture of geometrical isomers, even though the melting points were acceptably sharp. Since *syn*- and *anti*-iminoxyl radicals equilibrate readily,¹⁰ the use of the mixture of oximes in their synthesis was of no consequence.

We encountered mixed success in the conventional oxidation of the oximes to the corresponding radicals by stirring with silver oxide in benzene. The wholly aliphatic, acyclic tertiary oximes gave isolable radicals. The other iminoxyls were not isolable, but their ESR and visible spectra could be measured easily. These details will be reported elsewhere.

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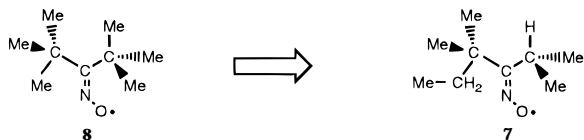
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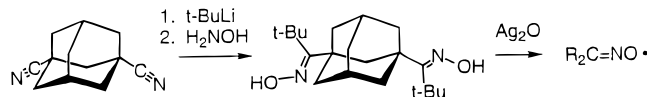
The radical **6** derived from cumyl *tert*-butyl ketoxime lacks easily abstractable H-atoms, and offered the possibility of facile synthesis of iminoxyls substituted on the aromatic ring. However, we were disappointed to observe that **6**, obtained from oxidation of solutions of **6H**, decayed rapidly according to a second-order rate law.

Out of curiosity we also determined the effect of a formal shift of a methylene unit from the (isolable) radical **8** as shown below:

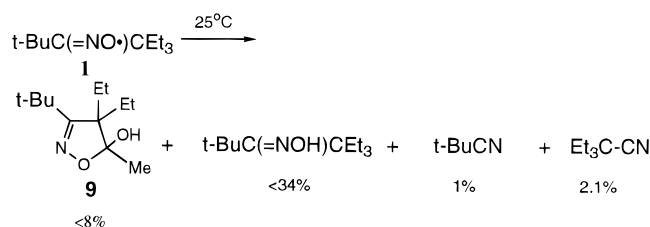


One conformer of the isomer **7** has a "pocket" where the oxygen might be expected to reside, which might lower the tendency for it to abstract an H-atom from the remote methylene group, while at the same time the larger *tert*-pentyl might retard dimerization. However, the stability of **7** was only comparable to that of the related *tert*-butyl isopropyl ketiminoxyl,^{1b} and it could not be isolated.

Attempts to oxidize the difficultly-soluble adamantane dioxime shown below under a variety of conditions always gave colorless solutions that contained small amounts of an unstable iminoxyl (ESR).



The decompositions of the other, isolable iminoxyls were not examined in detail. Radicals *tert*-butyl *tert*-pentyl ketiminoxyl (**2**) and di-*t*-pentyl ketiminoxyl (**3**) decayed slightly faster than the more heavily substituted radical **1**, but the stability of all three was increased by dilution. The kinetics of decay, however, are not second order and will be described elsewhere. Isolation of **9** from **1**, and the virtual absence of nitriles or the parent ketone



among the decomposition products, are consistent with an internal H-abstraction as the dominant mode of decay.

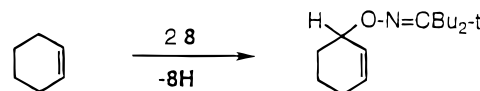
The HRMS (EI) of radical **2** showed a signal agreeing with a value of $M - 2H^+$ within 0.001 amu, while radical **3** showed mass values agreeing both with $M - 2H^+$ and $M + 2H^+$, with the parent ions essentially absent from both radicals. This outcome was consistent with a disproportionation, e.g.



Since the olefinic product of this reaction, like **3H** itself, should be oxidizable to the corresponding iminoxyl radical, and the normal syntheses of the radicals contained silver oxide in excess, we became concerned that the radicals sent for exact mass might actually have contained the olefinic iminoxyls with two less mass units.

For radical **1** this possibility is ruled out by the combustion analysis, which does not agree with values calculated for a radical with two fewer H-atoms. Second, if we reduced samples of **3** with 1,3-cyclohexadiene immediately after preparation, or after standing 30 h at 0 °C, the product after evaporation of volatiles displayed an ¹H-NMR spectrum identical to that of the parent oxime, with no significant resonances in the olefinic region.

Reactions of Di-*tert*-butyl Ketiminoxyl (8**) with Cyclohexene.** The ¹H-NMR spectrum of the adduct between **8** and cyclohexene was virtually identical to that of 2-cyclohexen-1-ol other than the presence of the two *tert*-butyl resonances. We inferred that a 3-cyclohexenyl radical was trapped by the oxygen atom of a second iminoxyl radical. This reaction may be useful for allylic functionalization of olefins under mild conditions.



Experimental Section

Reagent chemicals were purchased from commercial sources. Olefins and oxidizable solvents were passed through a short column of alumina before use.

Exact masses (± 0.5 ppm) were measured by Mr. James Windak, University of Michigan, with a VG Analytical Model VG7250S. Conventional mass spectra were obtained with an HP 5985B instrument. NMR spectra (CDCl_3 unless otherwise noted) were recorded on one of several commercial instruments with ≥ 200 MHz field. Combustion analyses were performed by Spang Laboratories, Eagle Harbor, MI.

Acyclic nitriles in this study were synthesized by alkylation of phenylacetone nitrile or the appropriate butyronitrile (Aldrich) with sodamide and alkyl bromides by the procedure of Newman.¹⁰ 2,2-Dimethyl-3-phenylpropionitrile (HRMS m/z calcd for $\text{C}_{10}\text{H}_{13}\text{N}$ 159.1048, found 159.1040) was reported by Moore¹² but without analytical details. 4,4-Diethyl-2,2-dimethyl-3-hexanone¹³ was prepared by refluxing the corresponding imine (0.60 g, 0.0030 mol, obtained as an intermediate as described below) 4 h with 5 mL of 10% sulfuric acid followed by extraction with hexanes (15 mL). The product was isolated by bulb-to-bulb distillation below 1 torr: IR 2968, 2881, 1680, 1460, 1394, 1382, 1365, 1219, 1194, 1077, 1047, 1010, 992, 923, 856, 808 cm^{-1} . ¹H-NMR δ 0.70 (t, 9H, $J = 7.6$ Hz), 1.212 (s, 9H), 1.67 (q, 6H, $J = 7.4$ Hz).

Symmetrical tertiary imines were prepared by the following representative procedure: Sodium (5.9 g, 0.26 g-atom) was dispersed in the usual way in boiling xylenes, allowed to cool, washed with hexanes, and placed in a 100 mL round-bottomed flask with 65 mL of hexanes under argon. A mixture of pivalonitrile (8.3 g, 0.10 mol) and *tert*-butyl chloride (9.3 g, 0.10 mol) was added dropwise with magnetic stirring, and stirring was continued for a total of 1.5 h. The green mixture was then hydrolyzed with water (20 mL) while maintaining its temperature below 15 °C with an external ice bath. The layers were separated, and the aqueous layer was washed with 30 mL of hexanes. The combined, dried (Na_2SO_4)

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organic layers were concentrated at aspirator pressure to give di-*tert*-butyl ketimine (10.9 g, 77%), ¹H-NMR δ 1.259 (lit.⁹ δ 1.24). Similarly, *tert*-amyl chloride and α,α -dimethylbutyronitrile led to the corresponding imine (59%) which was converted to **3H** in 32% overall yield.

Unsymmetrical ketimines for this study were prepared by reaction^{1b} of a nitrile with *tert*-butyllithium (Aldrich) or isopropyllithium (from the bromide and Li¹⁴). The unpurified imines were converted to oximes by the following representative procedure: Hydroxylamine hydrochloride (5.80 g, 83.5 mmol) and di-*tert*-butyl ketimine (7.30 g, 51.6 mmol) were refluxed in methanol (30 mL) for 3.5 h and then cooled to -40 °C for 15 min. The white oxime **8H** was filtered off and washed with cold water: 7.18 g after drying (88%), mp 156–7 °C (lit.⁶ mp 157.5–8.5 °C). The oximes were purified by crystallization from hexanes or methanol except for **4H**, which was sublimed several times <1 torr. (Additional data given as Supporting Information.)

1,3-Dipivaloyladamantane dioxime was synthesized under N₂ by introducing the corresponding dinitrile¹⁵ (1.01 g, 5.4 mmol) in toluene (8 mL) dropwise to vigorously stirred *tert*-butyllithium (8.6 mL of 1.7 M in pentane). The reaction flask was immersed in water at room temperature. The mixture was stirred 24 h, and the clear yellow solution was then hydrolyzed with ethanol (5 mL) followed by water (5 mL). The organic product was extracted with ether, dried (Na₂SO₄), and concentrated to the pale green bis-imine (1.24 g, 76%, IR 1594 cm⁻¹). The crude bis-imine (1.2 g, 4.1 mmol), methanol (35 mL), and hydroxylamine sulfate (1.16 g, 7.1 mmol) were refluxed 7 h and then allowed to stand 0.5 h at 0 °C: colorless crystals, 0.84 g (61%), after recrystallization mp 237–9 °C (sealed tube). MS (CI, probe) m/z 335 (M⁺ + 1), 261 (M⁺ - C₄H₉O), 234 (M⁺ - C₄H₉CNOH), 160, 57, 41. (Additional characterization in Supporting Information.)

***tert*-Butyl 1,1-diethylpropyl ketiminoxyl (1).** The oxime **1H** (1.8 g, 8.9 mmol) in benzene (50 mL) was stirred vigorously with finely divided silver oxide (2.95 g, 12.7 mmol) for 5 h. The mixture was filtered and the filtrate concentrated at 25 °C under reduced pressure to give a blue liquid that was immediately purified by elution through a short column of silica gel with 3–4 mL of hexanes (alternatively basic alumina/pentanes). Concentration of the hexanes (vacuum line suitable, since the radical has low volatility) gave pure **1**, 1.7 g (96%), $d = 0.93 \pm 0.03$ g/cm³. IR 2980(vs), 2890(sh), 1610 (vs), 1470(vs), 1400, 1390, 1370, 1280, 1230, 1200, 1170, 1090, 1010, 960, 930, 860, 820, 680 cm⁻¹. Anal. Calcd for C₁₂H₂₄NO: C, 72.67; H, 12.20; N, 7.06. Found: C, 72.43; H, 12.06, N, 7.00.

The unstable radicals **2** and **3** were synthesized from their parent oximes in exactly the same way. Since combustion analysis was no longer available locally, their identity was assumed to follow from their mode of formation, characteristic ESR spectra, blue color, and intense IR absorption at 1607 cm⁻¹ and the absence of OH and C=O absorptions.

Analysis of Radical Decomposition Products. Samples of **1** on standing lost their blue color within a few days and deposited colorless crystals that slowly filled

the entire sample volume. A 2.03 g sample of **1** after 7 days was filtered from the solid portion (0.27 g), which was crystallized successively from methanol and hexane to give 0.20 g of a white solid, mp 101–103 °C, shown by LCMS (HP 5988 equipped with thermospray interface, 90:10 MeCN:water, 45 °C, 1.0 mL/min, 2.1 × 200 mm C-18) to contain 96% **1H**. The presence of **1H** in decomposed **1** was also confirmed by HPLC (4.6 × 250 mm Rainin microsorb-MV C-18, 1 mL hexane/min, RI detection), with one peak eluting at the same time (3.79 min) as authentic **1H**.

The first of about nine other peaks from the decomposed sample of **1** eluting from the column was collected repeatedly. Concentration of the combined fractions gave a few milligrams of colorless crystals, ascribed structure **9**, mp 89–90 °C. HRMS (CI-CH₄) m/z calcd for C₁₂H₂₄NO₂⁺ (M + H⁺) 214.1807, found 214.1801; other m/z at 196 (M - OH)⁺, 140 (M - OH - C₄H₂)⁺, and 98 (Et₂-CCHMe⁺). ¹H-NMR δ 0.74 (t, $J = 7.5$ Hz, 3H), 0.94 (t, $J = 7.5$ Hz, 3H), 1.21 (s, 9H), 1.49 (s, 3H), 1.52 (s, OH + water impur), two diastereotopic CH₂ groups appeared as a series of partially obscured multiplets ($J \sim 7.5$ Hz) centered approximately at 1.4, 1.7, 1.8, and 2.1. Decoupling experiments showed that the triplet at 0.74 was coupled to the multiplets at 1.4 and 1.8, and the triplet at 0.94 to those at 1.7 and 2.1. IR 3490 (s, br) 2995, 1590 (w), 1690, 1450, 1580, 1370, 1180, 1170, 1110, 900, 880, 830, 790 cm⁻¹.

The liquid portion of the decomposed radical in the original experiment was analyzed by GC (1% in pentane, HP 5985B GCMS, with a JW Scientific DB-5 capillary column, 30 m × 0.32 mm × 0.25 μ m film thickness, 170 °C; also for other analyses below). Comparison of peak areas with standards revealed the presence of triethylacetone nitrile (2.1% based on original weight of radical) and pivalonitrile (1%). (The presence of these nitriles was confirmed by the presence of minor signals in both ¹³C- and ¹H-NMR spectra of the decomposed radical which increased after spiking with authentic samples.) No 4,4-diethyl-2,2-dimethyl-3-hexanone (<0.4% present) was detected upon injection of the pentane solution of the liquid fraction of decomposed **1** on the same column (5 min at 35 °C, followed by ramping to 245 °C at 10 °C/min). The authentic ketone eluted after 14 min under these conditions.

A sample of pure **1** that was allowed to decompose at room temperature in a sealed tube subsequently displayed a ¹H-NMR spectrum (CDCl₃) from which, after integration, we calculated maximum yields of **1H** (34%) and **9** (8%). The remaining material consists in part of high molecular weight aggregates, since the LCMS of a recrystallized fraction of the mixture displayed a peak with m/z 394 in addition to those of **9** and **1H**.

Oxidation of Other Oximes. A 0.1 M solution of **3** that had decomposed at 25 °C in benzene was concentrated to a white solid that was submitted for CI-MS (probe). At the point of peak total ion current, masses were observed corresponding to dimer m/z 368 (2M - 1)⁺, 367, 200 (M + CH₄⁺), 186 (M + H⁺), 98 (C₅H₁₁CHN⁺), and 71 (C₅H₁₁⁺), among others.

A solution of α,α -diethylbutyrophenone oxime (**4H**, 66.2 mg, 0.269 mmol) in benzene (5 mL) was stirred 22 h with silver oxide (318 mg, 1.37 mmol), filtered, and concentrated to 0.06 g of a red oil. A GCMS trace of the material revealed eight peaks, with the largest eluted peak ascribed to starting oxime (9.2 min). The next largest (7.1 min) was ascribed to α,α -diethylbutyrophenone: m/z

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204 (M^+), 189 ($M^+ - CH_3$), 175 ($M^+ - Et$), 105 ($PhCO^+$), 99 (Et_3C^+), 98 ($Et_3C^+ - H$), 77 (Ph^+), 57 ($C_4H_9^+$).

The crude oxidation product from cumyl *tert*-butyl ketoxime (**6H**) and silver oxide, obtained similarly, displayed m/z (CIMS probe) 220 (oxime + H^+), 437 (dimer + H^+), and 119 (cumyl $^+$), among other minor signals.

Reaction of 8 with Cyclohexene. A stock solution of the radical (0.13 M) in pentane was concentrated at aspirator pressure to a blue liquid. The neat radical (222 μ L, 1.17 mmol) was mixed with redistilled cyclohexene (277 μ L, 2.73 mmol) and allowed to react for 1 h at 25 °C during which a portion of **8H** crystallized. The mixture was diluted with 0.5 mL pentane and allowed to stand at -60 °C for 1 h. The supernatant was pipetted off and passed through a short column of basic alumina contained in a disposable pipette to remove any remaining **8H**, and the column was washed with pentane. The eluate and washings were concentrated to give 78.9 mg (60%; upon repetition, 83%) of 2,2,4,4-tetramethyl-3-hexanone *O*-(2'-cyclohexen-1'-yl)oxime as a colorless, fragrant liquid (97% pure by GC/column 160 °C). 1H -NMR: δ 5.85 (m, 2H), 4.46 (m, 1H), 1.59–1.93 (m, 6H), 1.34 (s, 9H), 1.21 (s, 9H). IR (neat): 2950, 1490, 1450, 1400, 1370, 1320, 1250, 1200, 1180, 1040, 970, 920, 750 cm^{-1} . MS (EI): m/z 236, 158, 140, 97, 84, 57, 41; HRMS (CI/ NH_3) m/z calcd for $C_{15}H_{28}NO$ ($M + H^+$) 238.2171, found 238.2164.

Summary

1. The seven new monooximes of this study gave isolable radicals when both alkyl groups were tertiary and not aromatic.

2. Di-*tert*-butyl ketiminoxyl effects facile allylic substitution on cyclohexene to give the corresponding *O*-substituted allylic oxime ether.

3. Although groups larger than *tert*-butyl can prevent head-to-tail dimerization of iminoxylys, internal H-abstraction can limit their kinetic stability, even when an α -CH is lacking.

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Supporting Information Available: A table of melting points, combustion analyses or exact mass values, and 1H -NMR data for new oximes described herein (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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