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Imidoyl Radicals as Synthons of Unstable Acyl Radicals

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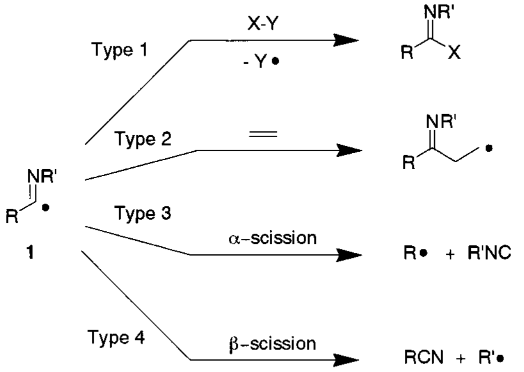
Imidoyl radicals ($R\dot{C}{=}NR'$, **1**), which have the isoelectronic structures of acyl radicals, have been used as important intermediates in organic synthesis. They can be generated by the addition of carbon radicals to isocyanides,[2−5] by the abstraction of H, X, SeR, and TeR groups from aldimines,[6] imidoyl halides,[7] selenoimidates,[8] and telluroimidates,[9] respectively, or by thermal decomposition of appropriate azo compounds.[10,11] Reactions of imidoyl radicals can be classified into four types (Scheme 1). One is the atom[2] or group[12] transfer reaction onto the imidoyl carbon as exemplified by hydrogen abstraction with imidoyl radicals to give the corresponding aldimines (Type 1). A second type is the addition to unsaturated bonds which have been employed for the synthesis of various heterocycles[3a−c,6e−i,8] as well as natural products.[4] The other two reactions are fragmentation of imidoyl radicals, i.e., α-scission (Type 3) and *β*-scission (Type 4). For example, imidoyl radicals **1** having a *tert*-butyl or benzyl group on the nitrogen atom are prone to undergo *β*-scission, giving nitriles and the corresponding carbon radicals ($R' = t\text{-Bu}, PhCH_2$).[5] Although α-scission of imidoyl radicals is much less common than decarbonylation of acyl radicals, Nanni et al. reported that an imidoyl radical possessing a triphenylmethyl group on the imidoyl carbon atom, derived by hydrogen abstraction from the corresponding aldimine, underwent α-scission to afford a triphenylmethyl radical ($R = Ph_3C$, $R' = p\text{-}MeOC_6H_4$).[6i]

Scheme 1. Reaction Pathways of Imidoyl Radicals



We have developed a variety of transformations based on the radical carbonylation methodology in which acyl radicals, formed by reaction of carbon radicals with carbon monoxide, play important roles as key intermediates.[13] However, this methodology cannot be applied to a system involving acyl radicals having radical-stabilizing

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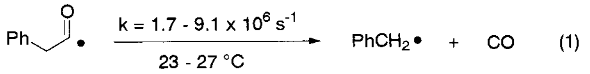
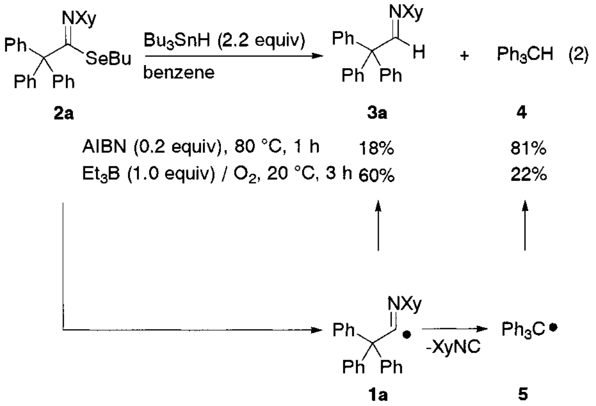
substituent(s) on the α-carbon due to their rapid carbon monoxide elimination. For example, rate constants of decarbonylation of phenylacetyl radical were reported to be on the order of 10^6 s^{-1} (eq 1).[14,15]

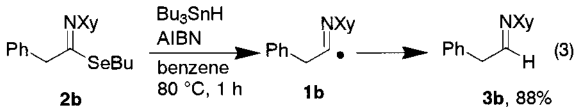


Recently, we revealed novel synthetic methods of selenoimidates having various substituent(s) on the adjacent carbon of the imidoyl carbon.[16] These successful results prompted us to examine the behavior of imidoyl radicals generated from the selenoimidates, aiming at the synthetic use of imidoyl radicals as synthons of unstable acyl radicals.

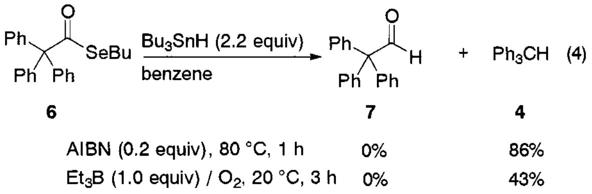
First, we attempted to trap triphenylacetimidoyl radical **1a** (Xy = 2,6-xylyl) using Bu_3SnH as a hydrogen source (eq 2). When a benzene solution of triphenylacetoselenoimidate **2a**, 2.2 equiv of Bu_3SnH,[17] and 0.2 equiv of AIBN was refluxed for 1 h, triphenylmethane (**4**) was formed in 81% yield as a major product, and the expected aldimine **3a** was obtained only in 18% yield. This result indicated that α-scission of **1a** was faster than the trapping with Bu_3SnH under these conditions. To suppress this α-scission, the reaction was then carried out at lower temperature. Thus, treatment of **2a** with 2.2 equiv of Bu_3SnH at 20 °C by using Et_3B-O_2 as a radical initiator[18] resulted in efficient trapping of **1a**, giving rise to **3a** in 60% yield.



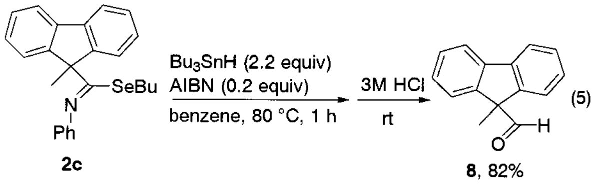
Similarly, phenylacetimidoyl radical **1b** generated from selenoimidate **2b** was trapped efficiently with Bu_3SnH under AIBN conditions to afford the corresponding aldimine **3b** in high yield (eq 3).



To compare more clearly the fragmentation of **1a** with that of its acyl analogue, we conducted the reaction of selenolester **6** under the same conditions. As shown in eq 4, decarbonylation predominated exclusively, affording triphenylmethane (**4**) without any formation of triphenylacetaldehyde (**7**) even at 20 °C.



These results suggested that imidoyl radicals possess highly potential synthetic utility as synthons of unstable acyl radicals. This was demonstrated clearly by the following successful one-pot conversion from selenoimidates to aldehydes, wherein selenoimidate **2c** was subjected to hydrogenative deselenation using the Bu_3SnH/AIBN system and the resulting mixture was then treated with aqueous 3 M HCl solution without purification to give the corresponding aldehyde **8** in 82% yield (eq 5).



When a similar selenoimidate **2d** was allowed to react with Bu_3SnH under AIBN conditions, indole derivative **9** was isolated in 74% yield. This result indicates that 5-exo cyclization of imidoyl radical **1d** leading to **10** is faster than both α-scission and hydrogen abstraction from Bu_3SnH (eq 6).

In conclusion, imidoyl radicals possessing radical-stabilizing aromatic substituent(s) have been generated from selenoimidates and trapped efficiently with Bu_3SnH or by intramolecular cyclization. α-Scission of imidoyl radicals leading to benzylic radicals and isocyanides was found to be much slower than analogous decarbonylation of the corresponding acyl radicals. The synthetic utility of imidoyl radicals as synthons of kinetically unstable acyl radicals has been demonstrated by the successful one-pot transformation of a fluorene-substituted sele-

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(15) Rate constants of decarbonylation of phenylmethylacetyl and phenyldimethylacetyl radicals at 27 °C in isooctane were reported to be 4.9×10^7 and 1.5×10^8 s^{-1}, respectively: see ref 14g.

(16) (a) Reaction of organolithiums with isoselenocyanates followed by alkylation: Maeda, H.; Kambe, N.; Sonoda, N.; Fujiwara, S.; Shin-ike, T. *Tetrahedron* **1996**, *52*, 12165–12176. (b) Imidoylation of organolithiums with selenium and isocyanides followed by alkylation: Fujiwara, S.; Maeda, H.; Matsuya, T.; Shin-ike, T.; Kambe, N.; Sonoda, N. *J. Org. Chem.* **2000**, *65*, 5022–5025.

(17) Requirement of 2.2 equiv of tributyltin hydride is due to the competition for the tin radical between selenium group abstraction from selenoimidates and $Bu_3SnSeBu$. See: Schwartz, C. E.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 9272–9284.

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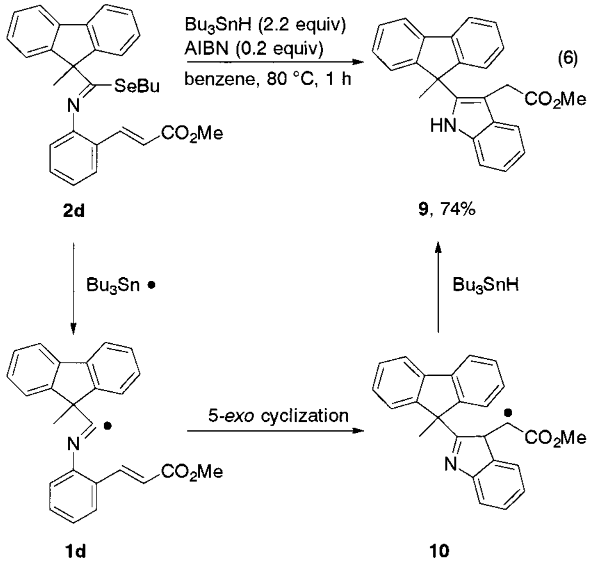

noimidate (**2c**) to the corresponding aldehydes (**8**) via an imine intermediate (eq 5).

Experimental Section

Benzene was fractionally distilled and dried over calcium hydride. Bu_3SnH, AIBN, and Et_3B (1.0 M solution in hexane) were used as purchased. Selenoimidates **2**[16] and selenolester **6**[19] were prepared according to our previously reported procedure. NMR yields were determined by ^{1}H NMR using trioxane as a standard.

Generation and Trapping of Imidoyl Radical (1a): AIBN Condition. A mixture of **2a** (245 mg, 0.48 mmol), Bu_3SnH (338 mg, 1.16 mmol), and AIBN (16 mg, 0.10 mmol) in benzene (5 mL) was heated at 80 °C for 1 h. Brine (50 mL) was added, and the product was extracted with ether (50 mL), dried over $MgSO_4$, and concentrated, and the NMR yield (18%) of **3a** was determined.

Generation and Trapping of Imidoyl Radical (1a): Et_3B Condition. A mixture of **2a** (253 mg, 0.50 mmol), Bu_3SnH (323 mg, 1.11 mmol), and Et_3B (0.1 M solution in hexane, 0.50 mL, 0.50 mmol) in benzene (5 mL) was stirred at 20 °C for 3 h. Brine (50 mL) was added, and the product was extracted with ether (50 mL), dried over $MgSO_4$, and concentrated, and the NMR yield (60%) of **3a** was determined. Purification by recycling preparative HPLC and the following recrystallization from hexane afforded 85 mg (51%) of *N*-(2,2,2-triphenylethylidene)-2,6-xylidine (**3a**) as a white solid: mp 155.0 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.04 (s, 6 H), 6.88 (t, J = 6.4 Hz, 1 H), 6.98 (d, J = 7.3 Hz, 2 H), 7.20−7.37 (m, 15 H), 8.46 (s, 1 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 18.90, 64.08, 123.63, 126.84, 127.13, 127.98, 128.14, 130.54, 143.57, 150.95, 169.79. HRMS (EI): calcd for $C_{28}H_{25}N$ 375.1967; found 375.1975.

Generation and Trapping of Phenylacetimidoyl Radical. A mixture of **2b** (245 mg, 0.48 mmol), Bu_3SnH (338 mg, 1.16 mmol), and AIBN (16 mg, 0.10 mmol) in benzene (5 mL) was heated at 80 °C. After 1 h, removal of the solvent and ^{1}H NMR measurement showed the formation of aldimine **3b** (88%). Purification by column chromatography eluting with *n*-hexane−ether (15:1 v/v%) afforded phenylacetoaldehyde (43%), a hydrolyzed product, instead of **3b**.

One-Pot Synthesis of Aldehyde (8) from Selenoimidate (2c). A mixture of **2c** (209 mg, 0.50 mmol), Bu_3SnH (341 mg, 1.17 mmol), and AIBN (16 mg, 0.10 mmol) in benzene (5 mL) was heated at 80 °C for 1 h. After cooling to room temperature, an aqueous 3 M HCl solution (50 mL) was added and the product was extracted with ether (50 mL), washed with brine (50 mL), dried over $MgSO_4$, and concentrated. Purification by column chromathography eluting with *n*-hexane−ether (20:1 v/v%) followed by preparative TLC eluting with *n*-hexane−ether (5:1, v/v%) afforded 85 mg (82%) of 9-formyl-9-methyl-9*H*-fluorene (**8**) as a colorless liquid: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.67 (s, 3 H), 7.33−7.49 (m, 6 H), 7.80 (d, J = 7.8 Hz, 2 H), 8.78 (s, 1 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 16.88, 63.09, 120.39, 124.68, 127.94, 128.76, 141.81, 143.94, 196.97; IR (NaCl) 1716 cm^{-1}. HRMS (EI): calcd for $C_{15}H_{12}O$ 208.0888; found 208.0885.

Intramolecular Cyclization of an Imidoyl Radical from Selenoimidate (2d). A mixture of **2d** (144 mg, 0.29 mmol), Bu_3SnH (194 mg, 0.67 mmol), and AIBN (9 mg, 0.055 mmol) in benzene (5 mL) was heated at 80 °C for 1 h. A pale yellow solid was deposited by removal of the solvent. Purification by preparative HPLC afforded 79 mg (74%) of 2-(9-methyl-9*H*-fluorenyl)-3-(methoxycarbonylmethyl)indole (**9**) as a white solid: mp 209.0−211.0 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.00 (s, 3 H), 3.30 (s, 2 H), 3.42 (s, 3 H), 7.06−7.44 (m, 10 H), 7.79 (d, J = 7.8 Hz, 2 H), 7.97 (s, 1 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 25.62, 29.84, 51.40, 51.66, 104.97, 110.49, 118.28, 119.69, 120.34, 121.83, 124.18, 127.79, 127.94, 129.54, 134.49, 136.83, 139.18, 151.59, 172.07. HRMS (EI): calcd for $C_{25}H_{21}NO_2$ 367.1572; found 367.1596.

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Supporting Information Available: Full compound characterization data and ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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