Synthesis of Indoles Using Cyclization of Imidoyl Radicals

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Abstract: Imidoyl radicals, generated from imidoyl phenylselanide precursors, have been used for the synthesis of 2,3-disubstituted indoles. A facile high yielding synthesis of imidoyl phenylselanides has been developed. The potential for neophyl rearrangement of 5-*exo* radical intermediates to 6-*endo* radical intermediates is discussed.

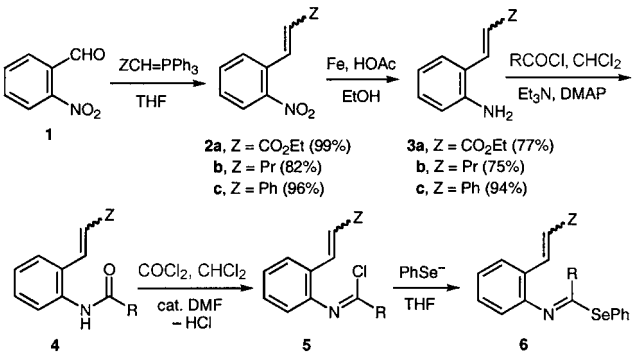
Key words: radicals, radical reactions, indoles, cyclizations, rearrangements

Procedures have been developed for converting a wide range of functional groups into radicals for synthesis.[1] One of the functional groups that has been little studied is the use of amides. We were attracted to the use of amides because of the wide diversity facilitated by joining different carboxylic acids and amines. The aim of our study was to use amides as precursors for the generation of imidoyl radicals. We report our initial results, which test the protocol on the synthesis of 2,3-disubstituted indoles using imidoyl phenyl selanides (N-substituted-selenoacylimidic acid phenyl esters) as imidoyl radical precursors.

Carboxamides have been used in previous studies as starting materials for radicals.[2–4] In these studies, the carboxamides are easily converted using Lawesson's reagent into thioamides which act as the radical precursors. Radicals add onto the S-atom of the thioamides to yield intermediate C-centered radicals which are able to undergo cyclization onto alkenes,[2,3] and under more forcing conditions, onto alkynes.[4] These radicals are considered to act as 'imidoyl equivalents' and have been successfully used for the synthesis of indoles.[3] Indoles have also been synthesized using imidoyl radicals, generated by addition of radicals onto isonitriles.[5] We considered that these studies on indoles provided a good initial model for testing our protocol.

Other methodologies have also been used for generating intermediate imidoyl radicals.[6] A notable application of the addition of radicals to isonitriles are the studies reported by Curran for the syntheses of camptothecin and analogues.[7]

We considered that imidoyl selanides which have been reported[8–10] to act as precursors for imidoyl radicals would be most facile for developing our synthetic protocols. Radical reagents such as tributyltin hydride (via $Bu_3Sn\cdot$) are able to abstract the phenylselanide group in S_H2 reactions. The amides were converted into the respective α-chloro-imines using phosgene.[11] Safe use of phosgene was facilitated by purchase as a sealed made-up solution in toluene. The α-chloro-imines were used without purification. A variety of methods[8–10,12] have been used to introduce the selanide group and we wished a facile reliable method. In order to avoid use of foul smelling phenylselanol, diphenyl diselanide was reduced in situ with K-Selectride® to the potassium salt of phenylselanide and added directly to the imidoyl chloride. The imidoyl selanides were formed in ca. quantitative yields but lower yields of pure isolated precursors were obtained after the required purification by rapid chromatography to remove unreacted diphenyl diselanide. Some hydrolysis takes place on both silica and alumina.



Scheme 1 Synthesis of imidoyl phenyl selanides **6** as precursors for imidoyl radicals

The required starting amides **4** were prepared by standard procedures from *o*-nitrobenzaldehyde (**1**) in high yields (Scheme 1). The stereochemistry of the alkenes was a mixture of *E*/*Z* isomers throughout. The amides were converted in good yields into the corresponding imidoyl selanides except for R = Bn (Table 1). For **6** (R = Bn), large amounts of the starting amides **4** (R = Bn) were recovered from chromatographic purification suggesting some tautomerism to the respective ketimines followed by hydrolysis.

A representative range of imidoyl selanides were prepared in order to observe the effect of different groups on the cyclization; **6a** with Z = CO_2Et (electron-withdrawing), **6b** with Z = propyl (electron-donating) and **6c** with

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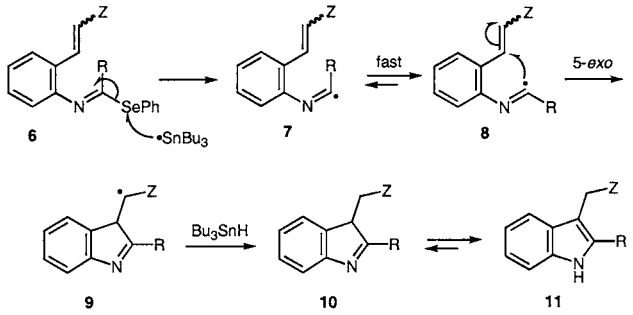
Table 1 Synthesis of Imidoyl Selanide Radical Precursors

Aniline	Amide	Yield[a]	Imidoyl selanide	Yield[a]
3a	**4a**, R = *p*-Tol	42%	**6a**, R = *p*-Tol	64%
	R = *p*-Cl-C_6H_4	25%	R = *p*-Cl-C_6H_4	67%
	R = Bn	56%	R = Bn	23%
	R = Me	68%	R = Me	50%
3b	**4b**, R = *p*-Tol	89%	**6b**, R = *p*-Tol	52%
	R = Bn	66%	R = Bn	27%
	R = Me	72%	R = Me	43%
3c	**4c**, R = *p*-Tol	64%	**6c**, R = *p*-Tol	41%
	R = Me	71%	R = Me	68%

[a] Yields were not optimized.

Z = phenyl (aromatic); R = electron-rich and electron-poor arenes, benzyl and methyl groups.

The reactions with imidoyl selanide precursors were performed under standard Bu_3SnH radical conditions. Syringe pump addition was used to provide a low [Bu_3SnH] to ensure cyclization over reduction of the imidoyl radicals. Later studies indicated that the reactions were very fast, and that the Bu_3SnH could be added in one portion at the start. No traces of uncyclized reduced products (imines) were detected. The reaction mechanisms are shown in Scheme 2 and the results in Table 2. Most reactions were not optimized but moderate to excellent yields of indoles were obtained. Although never detected, we assume that the 3*H*-indole intermediates **10** are first formed and rapidly tautomerize to the indoles **11**. Imidoyl radicals, as for acyl radicals, are nucleophilic and cyclize fastest onto the electron-deficient α,β-unsaturated esters but also cyclize onto the electron-rich propyl- and phenyl-alkenes.



Scheme 2 Cyclization of imidoyl phenyl selanides **6** to yield 2,3-disubstituted indoles **11**

The use of triethylborane (Et_3B) in place of AIBN as the radical initiator was investigated. A sample reaction with **6b** (R = Me) was carried out at room temperature using Et_3B instead of AIBN as initiator and resulted in equally good yields [81% (Et_3B), 73% (AIBN)].

The stereochemistry of the imidoyl radicals, which contain the unpaired electron in a sp^2 orbital, is of importance.[13,14] NOESY NMR studies indicate that the phenylselanide group is *anti* to the N-substituent in the imidoyl selanides (e.g. **6**, in Scheme 2). Therefore, the imidoyl radicals will initially have the two substituents in the *syn* position **7**, which is not favorable for cyclization. Although the literature[13] indicates that the barrier to inversion between *syn* and *anti* imidoyl radicals is higher than that for vinyl radicals, the rate of inversion and cyclization must be more rapid than the rate of the bimolecular reaction with Bu_3SnH, even at high [Bu_3SnH].

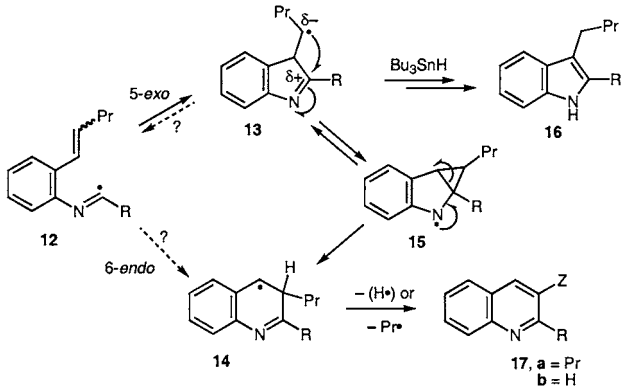
Table 2 Radical Cyclizations to 2,3-Disubstituted Indoles

Precursor	Products	Yields	Conditions[a]
6a, R = *p*-Tol	**11a**, R = *p*-Tol	95%	[b]
6a, R = *p*-Cl-C_6H_4	**11a**, R = *p*-Cl-C_6H_4	92%	[b]
6a, R = Bn	**11a**, R = Bn	98%	[b]
6a, R = Me	**11a**, R = Me	98%	[b]
6b, R = *p*-Tol	**11b**, R = *p*-Tol	10%[d]	[b]
	17a, R = *p*-Tol	39%	
	17b, R = *p*-Tol	6%	
6b, R = *p*-Tol	**11b**, R = *p*-Tol	66%	[c]
6b, R = Bn	**11b**, R = Bn	15%[d]	[b]
	17a, R = Bn	22%	
6b, R = Bn	**11b**, R = Bn	52%	[c]
6b, R = Me	**11b**, R = Me	9%	[b]
	17a, R = Me	35%	
6b, R = Me	**11b**, R = Me	73%	[c]
6c, R = *p*-Tol	**11c**, R = *p*-Tol	70%	[c]
6c, R = Me	**11c**, R = Me	80%	[c]

[a] All reactions were carried out in toluene as the solvent under an atmosphere of nitrogen with [imidoyl selanide] = 10 mM.
[b] Syringe pump addition of Bu_3SnH (2.2 equiv) and portion-wise addition of AIBN (1.0 equiv) over 6 h.
[c] Bu_3SnH (2.2 equiv, 20 mM) added and AIBN (0.1 equiv) in one portion at the beginning of the reaction.
[d] The% yield was calculated using ^1H NMR spectroscopy.

The observation of quinoline products for the alkyl (Pr) substituted alkenes **6b** requires explanation (Scheme 3). When the reactions were carried out at low [Bu_3SnH] using a syringe pump in order to facilitate cyclization over reduction of the intermediate imidoyl radical, the main products were the quinolines **17a** and **17b**. These results suggest a competition between 5-*exo*- and 6-*endo* cyclization or a rapid neophyl rearrangement of the 5-*exo* intermediate **13** via **15** to the more stable 6-*endo* intermediate **14**. At high [Bu_3SnH], when all the Bu_3SnH was added in one portion at the beginning of the reaction, only high yields of the indole resulting from 5-*exo* cyclization were observed. We suggest that this indicates that the increased rate of trapping of the 5-*exo* radical **13** prevents the neophyl rearrangement (see Scheme 3).

These results could also be explained by a reversible ring-opening of the 5-*exo* radical **13** to allow a slower 6-*endo* cyclization to the stable benzylic radical **14** (Scheme 3). However, this would require the breaking of a strong sp^2



Scheme 3 Mechanism of the cyclization of imidoyl selanide **6** to yield 5-*exo* and 6-*endo* products

hydridized bond, which suggests reversibility is unlikely, but cannot be ruled out.

No quinoline products were observed for the ester- and aryl-substituted alkenes **6a** and **6c**, respectively. In the former, the 5-*exo* radical **9a** is electrophilic and will react rapidly with the nucleophilic Bu_3SnH. Compound **9a** will also react very slowly via 3-*exo* cyclization onto the electrophilic α-carbon atom of the imine required for a neophyl rearrangement, thereby preventing rearrangement. In the aryl substituted reaction, a benzylically stabilized 5-*exo* radical **9c** results and hence there is no driving force for a neophyl rearrangement.

In the reactions of **6b** at low [Bu_3SnH], a number of unidentified products also were observed. Overall, the yields were less favorable, indicating a number of different side reactions. Surprisingly, aromatization of the 6-*endo* radical **14** (R = *p*-tol) has sufficient driving force to eliminate propyl radicals to yield **17b** (R = *p*-tol). The aromatization by loss of hydrogen [H] to yield the aromatic 2,3-disubstituted quinolines **17a** is a now well-known phenomenon in Bu_3SnH-facilitated reactions.[15]

Our preliminary results indicate that imidoyl selanides are good easily accessible precursors for generating imidoyl radicals and provide a useful protocol for the synthesis of 2,3-disubstituted indoles. We are extending our studies to more complex systems and cascade reactions for the synthesis of natural products.

Preparation of Imidoyl Phenyl Selanides. 3-{2-[(Phenylselanyl-*p*-tolyl-methylene)-amino]-phenyl}acrylic Acid Ethyl Ester [6a, (R = *p*-tol)].

Phosgene [20% w/w toluene solution] (6.39 mL, 12.13 mmol) and DMF (5 drops) were added to a solution of 3-[2-(4-methyl-benzoylamino)phenyl]acrylic acid ethyl ester **4a** (R = *p*-tol) (1.50 g, 4.85 mmol) in anhyd CH_2Cl_2 (40 mL). The reaction mixture was stirred at r.t. for 4 h. The solution of the imidoyl chloride was evaporated to dryness and the product re-dissolved in anhyd THF (50 mL). A solution of 'potassium phenylselanate' was prepared by adding K-Selectride® (1 M THF solution; 4.60 mL, 4.60 mmol) to diphenyl diselanide (0.68 g, 2.18 mmol) in anhyd THF (50 mL). This solution was added to the solution of the imidoyl chloride in THF. The reaction was stirred for 2 h at r.t., H_2O and CH_2Cl_2 added and separated. The CH_2Cl_2 solution was dried and evaporated to dryness. The residue was purified by flash silica column chromatography to yield the imidoyl selanide **6a** (R = *p*-tol) as a yellow oil (1.24 g, 64%). IR (neat): 3056, 2976, 1707, 1628, 1592, 1474, 1314, 1267, 1172, 1092, 910 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 7.2 Hz, 3 H, Me), 2.29 (s, 3 H, Me), 4.26 (q, *J* = 7.2 Hz, 2 H, C*H*$_2$O), 6.38 (d, *J* = 15.9 Hz, 1 H, C*H*CO_2Et), 6.89 (d, *J* = 7.9 Hz, 1 H, Ar-H), 7.53–7.01 (m, 9 H, Ar-H), 7.59 (d, *J* = 8.1 Hz, 2 H, Ar-H), 7.86 (d, *J* = 16.1 Hz, 1 H, C*H*=CHCO$_2$Et). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3 (Me), 21.3 (Me), 60.2 (CH_2), 118.7 (*C*HCO$_2$Et), 119.8 (Ar-*C*H), 124.6 (Ar-*C*), 124.7 (Ar-*C*H), 127.2 (Ar-*C*H), 127.7 (Ar-*C*H), 128.7 (Ar-*C*H), 128.8 (Ar-*C*H), 128.9 (Ar-*C*), 129.1 (Ar-*C*H), 130.5 (Ar-*C*H), 135.2 (Ar-*C*H), 135.5 (Ar-*C*), 140.7 (Ar-*C*), 140.8 (Ar*C*H=CH), 150.3 (Ar-*C*-N), 165.2 (C=O or C=N), 167.0 (C=O or C=N). HRMS (FAB): $C_{25}H_{13}NO_2Se$ + H requires: 450.0972; found: 450.0970; *m/z* (%) = 450 (10) $[M + H]^+$, 366 (4), 292 (42), 248 (42), 220 (90), 128 (19), 119 (100), 91 (25), 77 (15), 65 (5).

Cyclization Reactions. (2-*p*-Tolyl-1*H*-indol-3-yl)acetic Acid Ethyl Ester [11a (R = *p*-tol)].

The reaction was carried out under an atmosphere of nitrogen. A deoxygenated solution of Bu_3SnH in toluene (20 mL) was added using a syringe pump over 5 h to a solution of 3-{2-[(phenylselanyl-*p*-tolylmethylene)amino]-phenyl}acrylic acid ethyl ester [**6a** (R = *p*-tol), 0.469 g, 1.046 mmol] in anhyd toluene (100 mL) under reflux. AIBN (0.086 g, 0.523 mmol) was added portion-wise over 5 h. The reaction mixture was refluxed for a further hour, cooled and evaporated to dryness. The crude mixture was purified by flash silica column chromatography using light petroleum:EtOAc (6:1) as eluant to yield the indole **11a** (R = *p*-tol) as a pale yellow oil (0.290 g, 95%). IR (thin film): 3373, 3053, 3024, 2976, 2921, 2869, 1718, 1506, 1457, 1342, 1306, 1176, 1029, 822 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.1 Hz, 3 H, Me), 2.38 (s, 3 H, Me), 3.80 (s, 2 H, C*H*$_2$CO$_2$Et), 4.14 (q, *J* = 7.1 Hz, 2 H, C*H*$_2$O), 7.30–7.12 (m, 5 H, Ar-H), 7.52–7.49 (m 2 H, Ar-H), 7.66–7.64 (m, 1 H, Ar-H), 8.18 (br s, 1 H, N*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 (Me), 21.2 (Me), 31.2 (CH_2), 60.8 (O*C*H$_2$), 105.3 (Ar-*C*), 110.8 (Ar-*C*H), 119.2 (Ar-*C*H), 119.9 (Ar-*C*H), 122.3 (Ar-*C*H), 128.1 (Ar-*C*H), 129.1 (Ar-*C*), 129.5 (Ar-*C*), 129.6 (Ar-*C*H), 135.7 (Ar-*C*), 136.3 (Ar-*C*), 137.9 (Ar-*C*), 172.3 (C=O). HRMS (EI): $C_{19}H_{19}NO_2$ requires: 293.1415; found: 293.1419; *m/z* (%) = 292 (40) $[M^+]$, 269 (20), 220 (100), 204 (22), 177 (5), 155 (4), 91 (4).

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