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A radical cyclization route to cyclic imines

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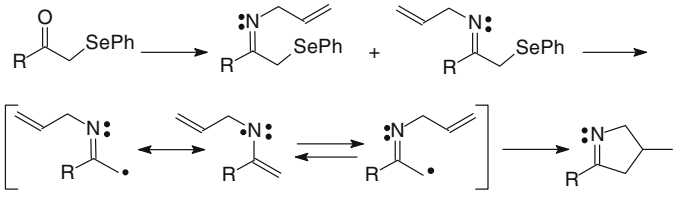
ABSTRACT

A novel route to cyclic imines based on 5-*exo* radical cyclization is explored. The radical precursors are imines prepared from allylamine and readily available α-phenylselenenyl ketones.

Cyclic imines form an important class of nitrogen-containing heterocycles found in several pharmacologically important alkaloids. Thus, many methods are available for their synthesis[1] including addition of organometallics to lactam derivatives[2] or to ω-bromo nitriles,[3] transition metal-catalyzed intramolecular oxidative amination of alkenes[4] or hydroamination of alkynes,[5] cyclization of ω-amino ketones,[6] 1,3-dipolar cycloaddition of münchnones to alkenes,[7] thermally-induced C–H nitrene insertion in *trans*-oximes,[8] and transition metal-catalyzed cyclization of γ-olefinic oximes.[9]

Free radical cyclization methodologies have been used extensively in the synthesis of heterocycles and natural products.[10] However, their use for cyclic imine synthesis has received only scant attention. Thus, 5-*exo* radical cyclization of iminyl radicals was used for Δ^1-pyrroline synthesis.[11] In our search for novel radical-based methodology, it occurred to us that readily available α-phenylselenenyl ketones, after condensation with allylic amines, could serve as precursors of 3-aza-2,5-hexadienyl radicals (Scheme 1). It was our hope that such radicals, despite increased stability due to resonance stabilization, would cyclize at a decent rate in a 5-*exo* fashion to provide cyclic imines. In the event, the imine-forming reaction would result in a mixture of *E*- and *Z*-isomers, resonance in the radical intermediate would in turn allow for conversion of the unreactive (in cyclization) *Z*-isomer into the reactive *E*-isomer (Scheme 1).

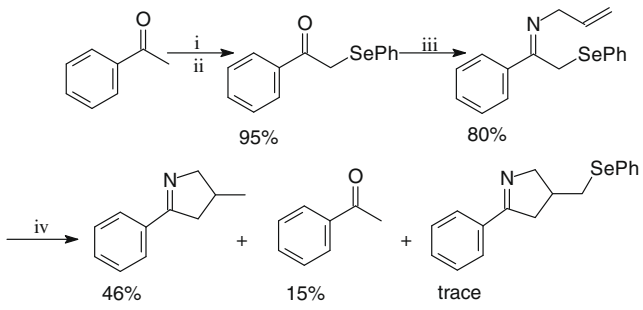
A variety of methods are available for the introduction of a PhSe-group into the α-position of ketones. We found the two-step procedure involving reaction of ketones with $PhSeCl_3$, followed by the reduction of the resulting crystalline organyl phenyl selenium



Scheme 1.

dichloride, convenient for large scale preparation[12] of such compounds (as exemplified in Scheme 2).

The PhSe-group is an excellent precursor of carbon-centred radicals, but a poor leaving group. Thus, reaction of α-phenylselenenyl acetophenone with excess allylamine in the presence of $TiCl_4$



Scheme 2. Reagents and conditions: (i) $PhSeCl_3$, dry Et_2O, rt, overnight, (ii) $Na_2S_2O_5$, H_2O, Et_2O, (iii) allylamine, $TiCl_4$, dry Et_2O, −78 °C to rt overnight, (iv) AIBN, TTMSS, C_6H_6, reflux, 8 h.

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afforded the corresponding imine in good yield (80%) and purity according to ^{1}H NMR analysis, as an *E*/*Z*-mixture.[13] In contrast, phenacyl bromide, when subjected to the conditions for imine formation, produced a complex mixture where nucleophilic displacement of bromide had occurred.

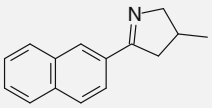
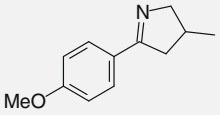
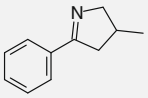
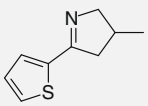
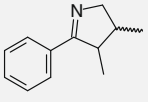
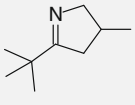
Due to the lability of the imine towards chromatographic purification, radical cyclization had to be attempted using the crude reaction mixture. Addition of Bu_3SnH with AIBN initiation afforded, after work-up, an 18% yield (based on starting α-phenylselenenyl acetophenone) of cyclic imine together with reduced, hydrolyzed, starting material (acetophenone; 57%). Slow addition of tris(trimethylsilyl)silane (TTMSS) and AIBN over 8 h in refluxing benzene afforded an overall 37% isolated yield of the desired cyclic imine along with 8% of the reduced product. Another by-product (10%) in this reaction was the corresponding group transfer product which could be hydrodeselenated by treatment with Bu_3SnH (Scheme 2). By adding TTMSS-AIBN slowly over 2–3 h, the yield of the cyclic imine increased to 46% (51% by NMR), the group transfer product was hardly seen and the amount of reduced product increased to 15%.[14]

Table 1 shows the cyclic imines prepared and the yields obtained over two steps (imine formation and cyclization).

Unfortunately, our efforts to extend the methodology to cyclic α-phenylselenenylketones and α-phenylselenenyl aldehydes failed at the imine-forming step. As observed for pinacolone and 2-acetylthiophene (Table 1), pyrrolines from low molecular weight aliphatic ketones were volatile and difficult to isolate. Imines prepared in situ from α-phenylselenenyl ketones and allylamine were obtained as *E*/*Z*-mixtures (isomeric ratios were in the range of 100/0–70/30 according to ^{1}H NMR analysis). However, the structures of the predominating isomers were not known. Therefore we do not know if *E*/*Z*-isomerisation in the carbon-centred radical as outlined in Scheme 1 occurs rapidly enough that both isomers of the starting material can indeed be converted into cyclized product.

In summary we have described a novel radical cyclization route to substituted Δ^1-pyrrolines using readily available organoselenium radical precursors. Considering the biological and synthetic (for face selective addition of nucleophiles to the C=N bond) utility of pyrrolines, we feel our methodology should be useful for the preparation of cyclic imines.

Table 1
Structures of the cyclic imines prepared

Product	Yield[a] Crude[b] (%)/isolated (%)
 **1**	52/47
 **2**	50 /46
 **3**	51/46
 **4**	33/—
 **5**	49/38 *cis*/*trans*=82/18
 **6**	18/—

[a] Yield over two steps (imine formation and cyclization).
[b] As determined by ^{1}H NMR spectroscopy using DMAP as an internal standard.

Acknowledgements

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13. *General procedure for imine formation*: The α-phenylselenenyl ketone (1 mmol), allylamine (5 mmol) and dry Et_2O (10 mL) were cooled to −78 °C. $TiCl_4$ (0.5 mmol) in C_6H_6 (2 mL) was then added dropwise to the mixture. The cold-bath was removed after 30 min and the reaction was left to stir overnight at room temperature. After work-up with saturated aqueous $NaHCO_3$, drying and evaporation, the crude imine was obtained, sometimes as a mixture of isomers.
14. *General procedure for cyclization*: To the crude imine (1 mmol) in refluxing C_6H_6 (30 mL) under N_2 were added TTMSS (1.5 mmol) in C_6H_6 (10 mL) and AIBN (0.5 mmol) in C_6H_6 (10 mL) at a rate of 1 mL per 10 min. The mixture was then refluxed overnight. After evaporation, the crude yield was determined by ^{1}H NMR using DMAP as an internal standard. Pure imine was obtained by flash chromatography on silica (ether–pentane, 0–30% v/v; 1.5% pyridine).
3-Methyl-5-(2-naphthyl)-3,4-dihydro-2H-pyrrole (**1**): ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (s, 1 H), 8.09 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.86 (m, 3H), 7.51 (m, 2H), 4.24 (dddd, *J* = 16.0, 8.0, 1.8, 1.8 Hz, 1H), 3.71 (dddd, *J* = 16.0, 5.0, 1.85, 1.85 Hz, 1H), 3.24 (dddd, *J* = 16.0, 8.0, 1.9, 1.9 Hz, 1H), 2.71 (dddd, *J* = 16.0, 5.0, 1.85, 1.85 Hz, 1H), 2.60 (m, 1H), 1.15 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.9, 134.4, 133.1, 132.3, 128.7, 128.2, 127.8, 127.1, 126.4, 124.4, 69.1, 43.2, 31.6, 20.5. HRMS (ESI) for $C_{15}H_{16}N$; found (210.1280 $[M+H]^+$), calcd (210.1283 $[M+H]^+$).
5-(4-Methoxyphenyl)-3-methyl-3,4-dihydro-2H-pyrrole (**2**): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 4.15 (dddd, *J* = 15.0, 8.0, 1.8, 1.8 Hz, 1H), 3.84 (s, 3H), 3.61 (dddd, *J* = 15.0, 5.0, 2.0, 1.8 Hz, 1H), 3.09 (dddd, *J* = 16.0, 8.0, 1.8, 1.8 Hz, 1H), 2.55 (dddd, *J* = 16.0, 5.5, 2.0, 2.0 Hz, 1H), 2.52 (m, 1 H), 1.10 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.2, 161.4, 129.2, 127.8, 113.8, 68.9, 55.5, 43.2, 31.6, 20.5. HRMS (ESI) for $C_{12}H_{16}NO$; found (190.1229 $[M+H]^+$), calcd (190.1232 $[M+H]^+$).

3-Methyl-5-phenyl-3,4-dihydro-2H-pyrrole (**3**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (m, 2H), 7.40 (m, 3H), 4.17 (dddd, J = 16.0, 9.5, 2.4, 2.4 Hz, 1H), 3.65 (dddd, J = 16.0, 7.0, 2.4, 2.4 Hz 1H), 3.12 (dddd, J = 16.0, 9.5, 2.4, 2.4 Hz, 1H), 2.59 (dddd, J =16.0, 7.0, 2.4, 2.4 Hz, 1H), 2.55 (m, 1H), 1.11 (d, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8, 135.0, 130.4, 128.5, 127.6, 69.1, 43.3, 31.6, 20.5. HRMS (EI) for $C_{11}H_{13}N$; found (159.1049 $[M]^+$), calcd (159.1048 $[M]^+$).

3-Methyl-5-(2-thienyl)-3,4-dihydro-2H-pyrrole (**4**): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (dd, J = 5.0, 1.2 Hz, 1H), 7.29 (dd, J = 3.6, 1.2 Hz, 1H), 7.06 (dd, J = 5.0, 3.6 Hz, 1H), 4.14 (dddd, J = 16.0, 8.0, 1.9, 1.9 Hz, 1H), 3.61 (dddd, J = 16.0, 4.8, 1.9, 1.9 Hz, 1H), 3.11 (dddd, J = 16.0, 10.0, 1.9, 1.9 Hz, 1H), 2.57 (m, 2 H), 1.11 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.6, 140.0, 131.0, 129.0, 127.5, 68.8, 43.9, 32.0, 20.4. HRMS (EI) for $C_9H_{11}NS$; found (165.0613 $[M]^+$), calcd (165.0612 $[M]^+$).

cis-3,4-Dimethyl-5-phenyl-3,4-dihydro-2H-pyrrole (**5**): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (m, 2H), 7.41 (m, 3H), 4.12 (ddd, J = 15.0, 7.0, 2.0 Hz, 1H), 3.63 (ddd, J = 15.0, 3.7, 1.0 Hz, 1H), 2.96 (m, 1H), 2.08 (m, 1H), 1.17 (d, J = 7.0 Hz, 3H), 1.07 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.1, 134.3, 130.3, 128.7, 128.0, 66.7, 50.0, 40.4, 20.3, 17.8. HRMS (EI) for $C_{12}H_{15}N$; found (173.1210 $[M]^+$), calcd (173.1204 $[M]^+$).

5-tert-Butyl-3-methyl-3,4-dihydro-2H-pyrrole (**6**): ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.88 (dddd, J = 15.0, 7.5, 1.6, 1.6 Hz, 1H), 3.38 (dddd, J = 15.0, 5.0, 1.6, 1.6 Hz, 1H), 2.67 (dddd, J = 15.0, 7.5, 1.6, 1.6 Hz, 1H), 2.34 (m, 1H), 2.15 (dddd, J = 15.0, 5.0, 1.6, 1.6 Hz, 1H), 1.15 (s, 9H), 0.98 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 184.4, 67.9, 41.5, 35.7, 31.6, 27.9, 20.0. HRMS (EI) for $C_9H_{17}N$; found (139.1354 $[M]^+$), calcd (139.1361 $[M]^+$).