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Bu_3SnH-mediated radical cyclisation onto azoles

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ABSTRACT

Alkyl radicals have been cyclised onto pyrroles, imidazoles and pyrazoles, and acyl radicals cyclised onto pyrroles, using Bu_3SnH-, $(TMS)_3SiH$- and Bu_3GeH-mediated aromatic homolytic substitution for the synthesis of bicyclic *N*-heterocycles. The reactions yield intermediate π-radicals that lose hydrogen in the rearomatisation step of the aromatic homolytic substitution. Mechanistic studies of these rearomatisation steps indicate aromatic homolytic substitution in which the initiator or breakdown products from the inhibitor are responsible for the H-abstraction step.

1. Introduction

Synthesis using aromatic homolytic substitution has advanced rapidly in the last 20 years with the development of modern free radical chemistry and the application of Bu_3SnH and $(Me_3Sn)_2$ as reagents. The use of aromatic homolytic substitution in synthesis has been recently reviewed in detail.[1,2]

One of the recent synthetic advances has been the cyclisation of radicals onto azole moieties as shown in Scheme 1. The application of *N*-(ω-phenylselenyl)-alkyl and *N*-(ω-bromo)alkyl building blocks have been used for aromatic homolytic substitution with loss of hydrogen for the cyclisation of *N*-(ω-alkyl)-radicals onto a range of azole rings, which include pyrroles,[3–5] indoles,[5–7] imidazoles,[3,8] benzimidazoles,[3] pyrazoles[8,9] and 1,2,3-triazoles.[10] These building blocks contain a radical leaving group and another leaving group that can be used to facilitate attachment to azoles by N-alkylation. Different chain lengths can be incorporated but in general only five-, six-, and seven-membered ring cyclisations give useful yields. The cyclisations are most successful when electron-withdrawing substituents are present on the azole rings, i.e., nucleophilic alkyl radicals prefer to attack electron deficient rings. These reactions are therefore the *umpolung* of the normal Friedel–Crafts alkylation onto electron rich azoles and have useful synthetic application. These intramolecular radical reactions are regioselective, which facilitate the design of syntheses to desired target molecules.

Aromatic homolytic *ipso* substitution with loss of *S*-centred radicals (phenyl-sulfonyl, -sulfoxyl and -thiyl leaving groups) has provided another avenue of synthesis and has been reported for indoles,[11] imidazoles[12] and benzimidazoles.[12,13] *N*-Alkyl(ω-acyl) radicals have also been cyclised onto pyrroles[14,15] and indoles.[15] Isoelectronic *N*-alkyl(ω-imidoyl) radicals have also been cyclised onto pyrroles and indoles.[16] Buildings blocks, which generate aryl

Scheme 1. Aromatic homolytic substitution on azoles with loss of hydrogen.

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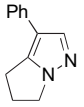
radicals have also proved useful for five- and six-membered ring cyclisation onto indoles[5,17–19] and pyrroles[5,17] and imidazoles.[20] Cyclisations of *N*-(ω-alkyl) and *N*-(ω-aryl) radicals onto six-membered ring heteroarenes (e.g., quinolin-4-ones,[21] quinol-2-ones,[22] 5-amino- and 5-hydroxy-uracils,[23] 3*H*-quinazol-4-ones[24] and pyridones[25]) has also proved synthetically useful.

Our initial studies showed that cyclisations of alkyl radicals onto imidazole and pyrroles was a useful synthetic procedure.[3] In this paper we report full details and further studies of our preliminary results of cyclisation of alkyl radicals onto pyrazoles[9] and acyl radicals onto pyrroles[14] and further studies of cyclisation of alkyl radicals onto imidazoles and pyrroles. We also report further studies of our preliminary results on the mechanisms of the aromatic homolytic substitution on azoles.[26]

2. Discussion

2.1. Alkyl radical cyclisation onto pyrazoles

At the outset of this study, alkyl radicals had been cyclised onto pyrroles, indoles, imidazoles and triazoles. Pyrazoles are an obvious target of study especially because of the importance of their biological activity to the pharmaceutical industry. Our protocol provides a route for the synthesis of [1,2-*b*]-fused bicyclic pyrazoles, an example of which is the natural product withasomnine **1**.[27] Very few pyrazoles have been isolated as natural products but withasomnine from *Withania somnifera* is used in ayurvedic alternative medicine. Various syntheses have been reported but none using radical reactions.[28]



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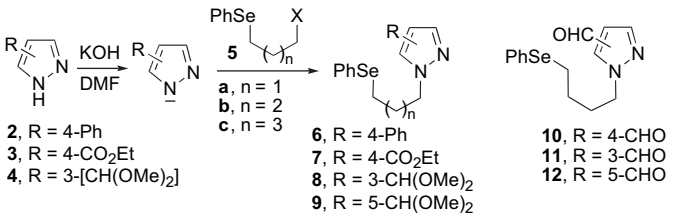
A range of substituted pyrazoles were synthesised by standard procedures. The 4-phenylpyrazole **2** was synthesised using a Suzuki coupling with tosyl-protected 4-bromopyrazole. Our standard protocol[3] using N-alkylation of ω-halogeno-alkyl phenylselenides was applied to introduce the required side chains for generating the alkyl radical precursors **6**–**12** for cyclisation (Scheme 2). The phenylselenide moiety, a poor leaving group in S_N2 substitutions, was used as the radical leaving group instead of bromine or iodine to avoid attack by the 'pyridine' nitrogen atom during alkylation. High yields were obtained except for the 4-esters because some hydrolysis took place under the reaction conditions. The 3-dimethylacetal **3** gave a mixture of isomeric products **8** and **9** as expected because of the ambident anion intermediate. Aldehyde precursors were prepared by conversion of the 4-ester **7** to the 4-aldehyde **10** by reduction ($LiAlH_4$) and Swern oxidation and hydrolysis of the dimethyl acetals **8** and **9** to yield the 3-aldehyde **11** and 5-aldehyde **12**, respectively.



Scheme 2. Synthesis of pyrazole radical precursors.

The precursors **6**–**12** were subjected to standard radical reactions using Bu_3SnH or $(TMS)_3SiH$ and results of the cyclisations are shown in Table 1. The pyrazoles **6** and **7** (R=Ph and CO_2Et) gave good yields for the six-membered ring cyclisation, more favourable than the five- and seven-membered ring cyclisations. This is commonly observed because of the strain for the five-membered ring cyclisation and the greater entropy problems for the seven-membered ring cyclisation.[2] Cyclisation of the pyrazole **6b** using Bu_3GeH and Et_3B also gave only cyclisation and no reduced uncyclised product **15b** (R=Ph) but some of the unexpected uncyclised alkene was obtained.[8] For R=CO_2Et, the use of Bu_3SnH gave only the alkene products **17**. However, with use of $(TMS)_3SiH$ and Et_3B, the alkene products **17** were obviated, the six-membered ring cyclisation was favourable but the five- and seven-membered ring cyclisations gave only reduced products **15** (R=CO_2Et). This indicates that phenyl substituents are more effective than CO_2Et for facilitating cyclisation. We have no explanation for the formation of the unexpected elimination by-product **17** in the Bu_3SnH- and Bu_3GeH-mediated reactions. The intermediate radicals **13** (R=Ph and CO_2Et) showed complete regioselectivity of cyclisation onto the 5-C on the pyrazole ring and no products resulting from cyclisation onto the 2-N were observed.

Cyclisation of the 3-dimethoxymethyl precursors **8a**–**c** all failed and only uncyclised reduced material was obtained. This functional group is neither electron-withdrawing nor stabilising of the intermediate π-radical **14** and the results provide further evidence that such groups are normally required to facilitate cyclisation onto the electron rich azole rings. Cyclisation of the 4-aldehyde **10b** gave cyclisation only as expected for an electron-withdrawing group and the favoured six-membered ring cyclisation. Cyclisation of the 3-aldehyde **11b** was also successful but the cyclised product **16b** (R=3-CHO) could not be separated from unaltered starting material and was not fully characterised. Cyclisation of the 5-aldehyde **12b** gave an intractable oil.

These results indicate that there is little difference in mechanism between the use of Bu_3SnH, Bu_3GeH and $(TMS)_3SiH$ as radical-mediators and ACCN [1,1′-azobis(cyclohexanecarbonitrile)] and Et_3B as initiators. Both initiators were used in greater than equimolar excess indicating that they participate in the H-abstraction step from the π-radicals **14** to cyclised products **16** (Scheme 3).

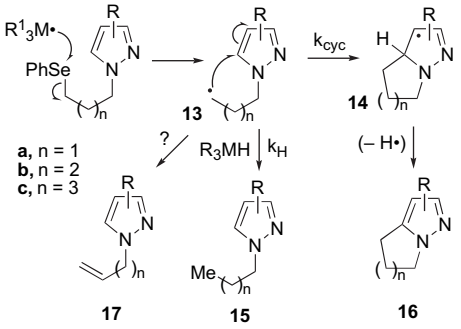
The structure of withasomnine was confirmed by X-ray crystallography (Fig. 1). The structure clearly shows the strain in the new five-membered ring, which is completely planar facilitating a flat molecule. Five-membered ring cyclisation onto a substituted imidazole to give 6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazole-1-carbaldehyde also yielded a similarly strained flat bicyclic ring structure as determined by X-ray crystallography.[3] However, six-membered ring cyclisation onto substituted imidazoles to yield 5,6-dihydroimidazo[2,1-*a*]isoquinoline-3-carboxylate and methyl 5,6-dihydroimidazo[5,1-*a*]isoquinoline-1-carboxylate gives new six-membered ring, which is not strained and not planar.[17] This use of X-ray crystallography provides further evidence that the five-membered ring cyclisation onto heteroarenes is strained and not as favourable as the six-membered ring cyclisation which in general proceeds in much better yields with little reduced uncyclised products.

The use of solid-phase synthesis in radical reactions has been of increasing interest and has been reviewed.[29] Solid-phase radical reagents have also been developed and show promise. For example, we have recently demonstrated that solid-phase triorganogermanium hydride gives good results for a wide range of radical reactions and compares very well with the corresponding solution-phase use of tributyltin- or tributylgermanium-hydride.[30] We have carried out the only examples of aromatic homolytic substitutions on solid phase. The first of these involved *ipso* substitution on benzimidazole moieties in which the radical leaving group (arylsulfanyl) was attached to the solid phase, i.e., the cyclised product comes off the resin during aromatic homolytic substitution and leaves unaltered starting material

Table 1
Cyclisation studies of pyrazole radical precursors

Starting material	Conditions[a] (h)	% Yields		
		Cyclised	Reduced	Other
6a	4.5	**1** (R=4-Ph), 38	**15a** (R=4-Ph), 17	0
6b	4.5	**16b** (R=4-Ph), 63	**15b** (R=4-Ph), 0	0
6b	26[b]	**16b** (R=4-Ph), 44	**15b** (R=4-Ph), 0	**17b** (R=4-Ph), 16
6c	4.5	**16c** (R=4-Ph), 37	**15c** (R=4-Ph), 48	0
7a	4	**16a** (R=4-CO_2Et), 0	**15a** (R=4-CO_2Et), 38	**17a** (R=4-CO_2Et), 11
	28[c]	**16a** (R=4-CO_2Et), 0	**15a** (R=4-CO_2Et), 73	**17a** (R=4-CO_2Et), 0
7b	4	**16b** (R=4-CO_2Et), 0	**15b** (R=4-CO_2Et), 0	**17b** (R=4-CO_2Et), 67
	28[c]	**16b** (R=4-CO_2Et), 36	**15b** (R=4-CO_2Et), 0	**17b** (R=4-CO_2Et), 0
7c	4	**16c** (R=4-CO_2Et), 0	**15c** (R=4-CO_2Et), 0	**17c** (R=4-CO_2Et), 41
	28[c]	**16c** (R=4-CO_2Et), 0	**15c** (R=4-CO_2Et), 62	**17c** (R=4-CO_2Et), 0
8a	4	**16a** [R=3-CH$(OMe)_2$], 0	**15a** [R=3-CH$(OMe)_2$], 75	0
8b	28[c]	**16b** [R=3-CH$(OMe)_2$], 0	**15b** [R=3-CH$(OMe)_2$], 57	0
8c	4	**16c** [R=3-CH$(OMe)_2$], 0	**15c** [R=3-CH$(OMe)_2$], 35	0
11b	12[d]	**16b** (R=4-CHO), 37	**15b** (R=4-CHO), 0	0
10b	12[d]	**16b** (R=3-CHO)[e]	**15b** (R=3-CHO), 0	0
12b	12[d]	*Intractable oil with no identifiable products*		

[a] Reactions were carried out under reflux and N_2 using Bu_3SnH and ACCN unless otherwise stated.
[b] Bu_3GeH and Et_3B (4 equiv, in two aliquots at 0 h and 8 h) and room temperature, Ref. 8.
[c] $(TMS)_3SiH$ and BEt_3 (4 equiv, in four aliquots at 0 h, 8 h and 20 h) and room temperature.
[d] $(TMS)_3SiH$ and BEt_3 (4 equiv, in four aliquots at 0 h, 2 h, 4 h and 6 h) and room temperature.
[e] The cyclised product could not be separated.



Scheme 3. Radical cyclisation of pyrazole precursors. $R^1{}_3M$=Bu_3Sn, $(TMS)_3Si$, Bu_3Ge.

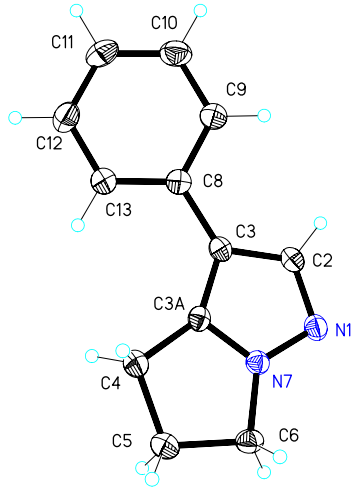


Figure 1. X-ray crystal structure of withasomnine **1**.

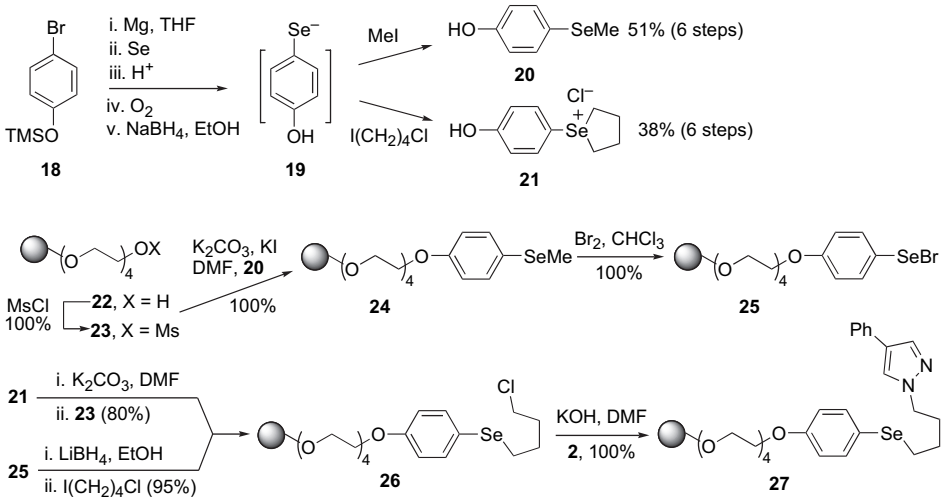
and reduced uncyclised products on the resin.[13] The second example involved aryl radical cyclisation onto a pyrazole-4-ester using solid-phase synthesis in good yield.[17] The pyrazole ring was attached to Wang resin via the ester and the cyclised pyrazole needed to be removed from the resin after cyclisation.

Arylselenyl traceless linkers have been developed in several solid-phase protocols whereby the resin-bound selenyl bromide is used for a synthetic procedure and the product removed from the resin by Bu_3SnH-mediated radical reduction.[31–33] These solid-phase resins have not been used for carrying radical reactions other than removing the products from the resin. The synthesis of the arylselenyl linker used by Nicolaou used the volatile, expensive and toxic dimethyl diselenide, which we wished to avoid.[32] However, since our study the Nicolaou resin has become available commercially.

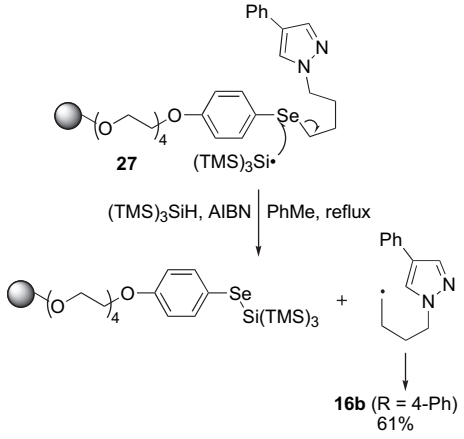
Our aim was to develop a new solid-phase methodology in which the radical leaving group was attached to a Quadragel® resin as shown in Scheme 4. The Quadragel® resin has several advantages, which include solubility and the ability to measure good quality NMR and IR spectra. Quadragel® is a polystyrene resin cross-linked with divinylbenzene and with PEG grafts containing four oxyethyl repeat units with a free terminal hydroxyl group. Tentagel®, a similar resin, has been reported using arylselenyl linkers for asymmetric selenyl reactions.[34] In our study the arylselenyl group is attacked by the radical reagent in an S_H2 reaction thereby generating an alkyl radical, cleaved from the resin, which facilitates the aromatic homolytic substitution (Scheme 5).

In order to attach the *N*-alkyl ω-arylselenide to the resin, a new linker was synthesised using selenium metal rather than the unpleasant and toxic dimethyl diselenide (Scheme 4). The yield of the selenium addition was higher and cleaner using the THP-protected 4-bromophenol as opposed to the TMS-protected 4-bromophenol but both were satisfactory. The protocol proceeds via the diselenide, which is reduced to yield the intermediate anion **19**. Unfortunately the diaryl selenide ether was also produced as an impurity, which needed to be separated. The required radical precursor was obtained by two routes. The first route was to alkylate the selenide anion **19** with methyl iodide to yield the methylselenyl ether **20**, which was attached to the mesylated Quadragel® resin **23** to yield a selenyl methyl ether **24** similar to the Nicolaou polystyrene resin. Bromination gave the selenyl bromide **25** in quantitative yield. The selenyl bromide **25** was reduced to the anion and alkylated with 1-chloro-4-iodobutane to yield the common intermediate **26**. 1-Chloro-3-iodopropane and 1-chloro-5-iodopentane were added in the same way in quantitative yield but not further pursued.

The second route involved attaching the chloroalkyl chain to the linker before attachment to the resin. Interestingly, the 4-chlorobutyl group cyclised to form the salt **21** but did not do so when attached to the resin. Both routes gave the intermediate **26** to which 4-phenylpyrazole was added in quantitative yield. All the reactions



Scheme 4. Synthesis of arylselenyl Quadragel® resin and attachment of 4-phenylpyrazole **2**.



Scheme 5. Solid-phase radical cyclisation.

involving the resin went in high yield, most were quantitative. All the resin intermediates were characterised by NMR and IR spectroscopy. Azoles other than 4-phenylpyrazole were also attached in very high yield but not further pursued. The methodology using the Quadragel® resin shows excellent potential for further exploitation.

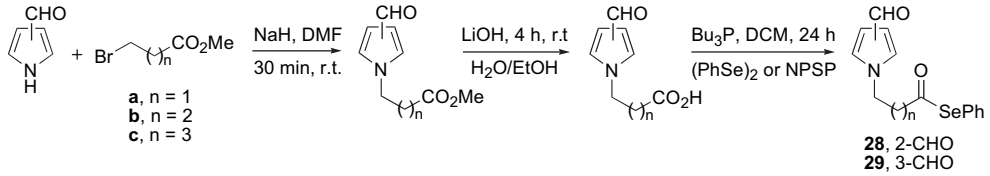
Quadragel® *N*-butyl-4-phenylpyrazole **27** was submitted to standard radical cyclisation conditions and yielded the expected 3-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine **16b** (R=4-Ph) in 61% yield (Scheme 5). The yield was similar to that obtained from solution-phase synthesis indicating the applicability of the solid-phase protocol. However, when the analogous five-membered ring cyclisation was attempted using Quadragel® *N*-propyl-4-phenylpyrazole no cyclised material (withasomnine **1**) was obtained. Further studies using the resin system are required to fully evaluate the synthetic potential.

2.2. Acyl radical cyclisation onto pyrroles

Acyl radicals have been widely used in organic synthesis and well reviewed.[35] Our initial results of acyl radical cyclisation onto pyrroles have been reported earlier and we now report full details.[14] Other examples in the literature have shown that acyl radicals can be used for aromatic homolytic substitution onto arenes and heteroarenes.[15,21,36] We have since shown that imidoyl radicals, isoelectronic to acyl radicals, also cyclise onto azoles.[16]

Initial studies using an atmosphere of nitrogen showed large amounts of decarbonylation and this protocol proved unsatisfactory for synthesis.[14] Studies using alkylacyl radicals are commonly carried out under a high pressure of carbon monoxide to either add CO on or to prevent decarbonylation.[15,35] Arylacyl radicals do not undergo decarbonylation and high pressure of CO is not required.[21,36] Fortunately the rate of CO loss (2×10^2 M^{-1} s^{-1} at 80 °C to yield primary alkyl radicals) is considerably slower than CO addition to primary alkyl radicals (6.3×10^5 M^{-1} s^{-1} at 80 °C). This difference in rate allowed us to generate the alkylacyl radicals under an atmosphere of CO without appreciable decarbonylation. Nitrogen in the reactions was replaced by CO using the freeze–thaw technique. Various reaction conditions were investigated and we determined that the use of a two-phase solvent system of acetonitrile and cyclohexane and reflux at 80 °C gave optimal yields. The precursors **28** and **29** and AIBN were insoluble in cyclohexane but soluble in acetonitrile whereas the Bu_3SnH is soluble in the cyclohexane. This also helps keep [Bu_3SnH] low, which helps to facilitate cyclisation over reduction.

Acyl radical precursors were synthesised as shown in Scheme 6. The key selenation step was carried out by the literature procedures.[35,37] Both diphenyl diselenide and *N*-(phenylselenyl)-phthalimide (NPSP)[38] in the formation of the acyl selenides but the latter gave cleaner reactions. The alkylation and hydrolysis steps were high yielding and the ester was not normally purified prior to hydrolysis to the carboxylic acid. The acyl selenides **29a–c** formed

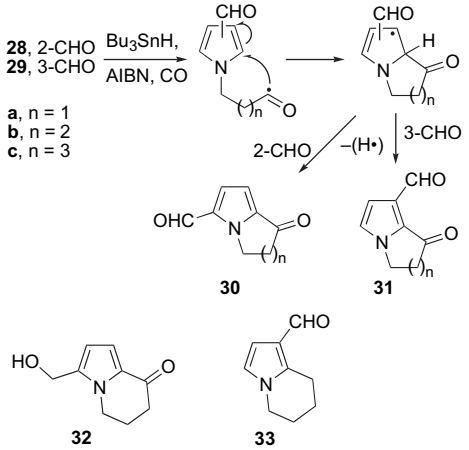


Scheme 6. Synthesis of acyl selenide radical precursors. Selenation step: **28a** (59%), **28b** (57%), **28c** (63%), **29a** (40%), **29b** (40%), **29c** (35%).

from pyrrole-3-carbaldehydes were formed in high yield but were unstable to chromatography resulting in lower yields than for the corresponding pyrrole-2-carbaldehydes. Attempts to selenate (3-acetyl-1*H*-pyrrol-1-yl)-propanoic, -butanoic and -pentanoic acid failed and the diseleno acetals were formed instead.

A number of differing conditions were investigated using an atmosphere of CO. Syringe pump addition of Bu_3SnH and the initiator, AIBN or AIBMe [2-(1-methoxycarbonyl-1-methylethylazo)-2-methylpropionic acid methyl ester], gave better yields than sealed tube reactions when all the reagents were added at the beginning. In the 2-carbaldehyde series, **28a** and **28c** gave the expected cyclised products **30a** and **30c** in reasonable yields (55% and 31%, respectively). In the latter reaction, **28c** also yielded 46% of the uncyclised aldehyde [1-(5-oxopentyl)-1*H*-pyrrole-2-carbaldehyde] indicating the slower rate of cyclisation for seven-membered rings. Precursor **28b** gave a reduced product, 3-(hydroxymethyl)-5,6,7,8-tetrahydroindolizin-8-one **32** (65%, reagents added at the beginning of the reaction and carried out in a sealed tube). In the earlier studies using an atmosphere of nitrogen instead of CO, the expected cyclised ketone **30b** was obtained in low yield (20%) and none of the reduced product **32** suggesting that reduction took place after cyclisation because of the longer reaction time in the sealed tube.

In the 1*H*-pyrrole-3-carbaldehyde series, all three precursors **29a–c** gave cyclisation as expected [**31a** (32%), **31b** (50%), **31c** (38%). As normally observed for cyclisation onto heteroarenes,[2] the six-membered ring cyclisation was most favourable with no other products. In the slower five- and seven-membered ring cyclisations some decarbonylation took place with **31a** yielding 1-ethyl-1*H*-pyrrole-3-carbaldehyde (17%) and **31c** yielding the alkyl cyclised product **33**. In the latter reaction, the intermediate alkyl radical formed by decarbonlyation undergoes a fast and favourable six-membered ring cyclisation. All the cyclisations proceeded with complete regioselectivity to the 2-position on the pyrrole (Scheme 7).



Scheme 7. Cyclisation of acyl radicals.

The structures of 8-oxo-5,6,7,8-tetrahydroindolizine-1-carbaldehyde **31b** and 9-oxo-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-3-carbaldehyde **31c** were confirmed by X-ray crystallography (Fig. 2). In contrast to the planar and strained five-membered alicyclic ring present in withasomnine **1**, the six- and seven-membered rings in **31b** and **31c** show the expected non-planarity. The lack of strain in the six-membered ring helps to explain why the six-membered ring cyclisations are more favourable than five-membered ring cyclisations. While the seven-membered ring in **31c** is not strained, the rate of cyclisation is slower than the six-membered ring cyclisation due to entropy effects.

The success of the cyclisation of *N*-alkylacyl radicals onto the 2-C position of pyrrole-2- and 3-carbaldehydes prompted us to investigate 2- and 3-alkylacyl radicals as shown in Scheme 8. The precursors were easily prepared using standard procedures. The mild Lewis acid BF_3 facilitated α-acylation whereas the stronger Lewis acid $AlCl_3$ facilitated β-acylation. However, radical cyclisation gave loss of CO yielding reduced products. Normal radical conditions gave mainly the reduced uncyclised **36** (58%) and only traces of the expected cyclised product **37** (GC–MS analysis). When the cyclisation was repeated using our sealed tube procedure with an atmosphere of CO and a two-phase MeCN/cyclohexane solvent system, intractable mixtures of products were obtained. The 3-acyl analogue **35** gave similarly disappointing reactions. 6-*endo* Cyclisation onto the electron deficient position β to the carbonyl group or 5-*exo* cyclisation onto the position α to the carbonyl group followed by neophyl rearrangement are possible mechanisms but clearly neither are favoured.

With this failure, we investigated alkyl radical cyclisation onto acyl pyrroles, i.e., making use of the electron-withdrawing acyl group to lower the electron density of the pyrrole ring to favour attack by the nucleophilic alkyl radicals (Scheme 9). The *N*-phenylsulfonyl derivatives were used to further lower electron density on the pyrrole ring and to lower aromaticity. The precursors **38** and **42** were synthesised by Friedel–Crafts acylations as before. The radical reactions were carried out using standard syringe pump conditions with Bu_3SnH to give unexpected 5-*endo* cyclisation onto the oxygen atoms of the carbonyl groups (**41** and **43**, respectively). The 5-*endo* cyclisation is obviously faster than the cyclisation onto the pyrrole ring. While unexpected, the cyclised radicals, e.g., **40**, are strongly stabilised by both the oxygen atom and the pyrrole ring. These 5-*endo trig* cyclisations onto oxygen are not unusual and a number have been reported in the literature.[39] The intermediate radical **39** has several options for cyclisation: 5-*endo* onto oxygen, 5-*exo* onto the 2-C of the pyrrole ring followed by neophyl rearrangement or 6-*endo* cyclisation onto the electron deficient 3-C of the pyrrole ring. In the cyclisation of **38** ca. 10% of the 6-*endo* product, 1-(phenylsulfonyl)-1,4,5,6-tetrahydroindol-7-one, was isolated but not fully characterised. Attempts to use $(TMS)_3SiH$ with BEt_3 as initiator to facilitate cyclisation with **42** as the precursors gave only the reduced uncyclised product 1-(1-benzenesulfonyl-1*H*-pyrrol-3-yl)butan-1-one in 70% yield. It is possible that the BEt_3 coordinates with the ketone oxygen atom thereby blocking cyclisation but still not facilitating cyclisation onto the ring was observed. In conclusion, cyclisation of acyl or alkyl radicals on a side chain attached to the α- or β-carbons are unfavourable unlike the successful cyclisation of acyl or alkyl radicals attached on the pyrrole *N*-atom.

2.3. Effect of functional groups on cyclisation onto azoles

In general, the cyclisation by nucleophilic alkyl radicals onto azoles is not successful and an electron-withdrawing group is normally needed to facilitate cyclisation. The presence of phenyl group (e.g., the synthesis of withasomnine) also helps to facilitate cyclisation presumably by lowering the energy of the transition state for cyclisation. Our earlier studies of cyclisation onto pyrroles had used aldehyde and ketone functional groups and we sought to expand this study by cyclisation using ester functional groups (Scheme 10 and Table 2) as for our studies on pyrazoles. The results for reactions with 2-ester and 2-carbaldehyde functional groups are similar indicating similar electron-withdrawing effects. The 2-ester **44a** requires a longer time than 3 h to react with all the starting material. The use of sub-stoichiometric amounts of tributyltin chloride to keep the concentration of Bu_3SnH low during the reaction gave reasonable yields but not as good as the use of syringe pump addition in the Bu_3SnH reactions. The use of *tert*-butanol is superior to that of ethanol because of the lack of easily abstracted hydrogens.

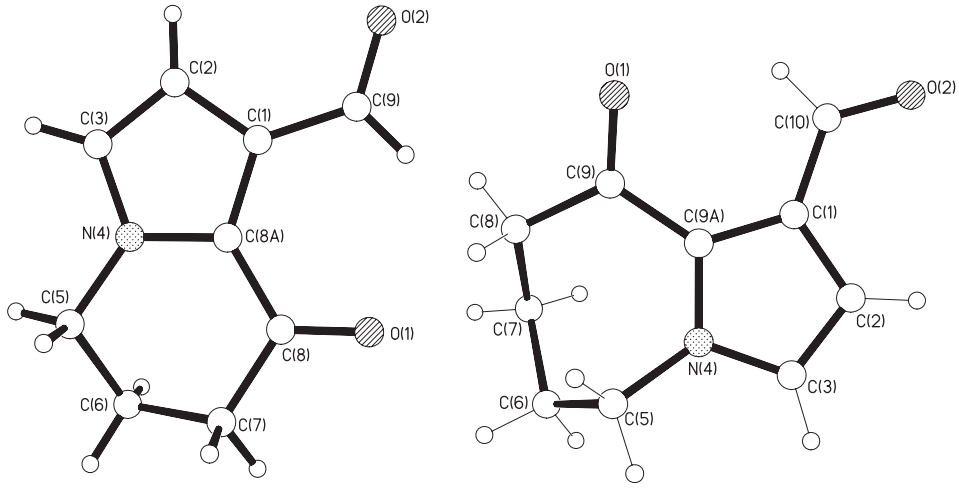
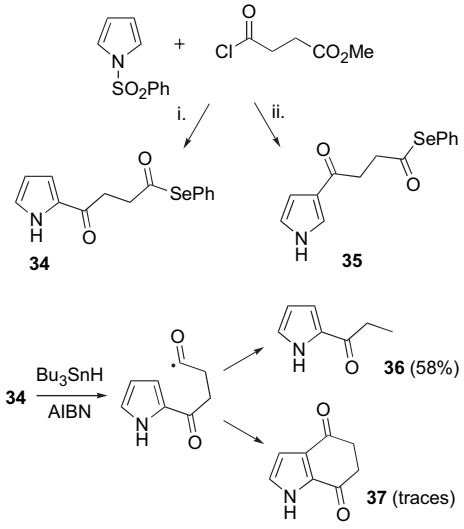
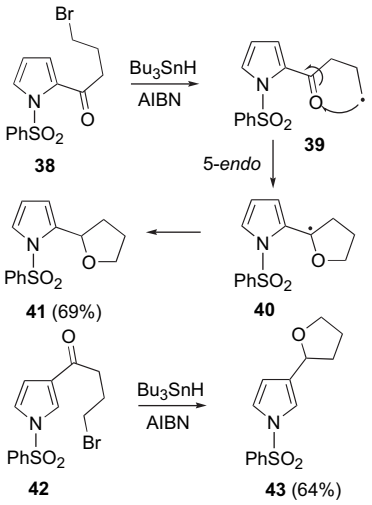


Figure 2. X-ray crystal structures of 8-oxo-5,6,7,8-tetrahydroindolizine-1-carbaldehyde **31b** and 9-oxo-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-1-carbaldehyde **31c**.

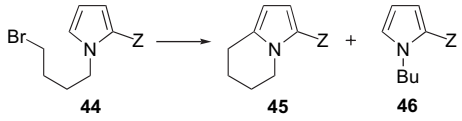


Scheme 8. (i) $BF_3{\cdot}Et_2O$, CH_2Cl_2 (61%); (ii) NaOH, MeOH/H_2O (100%); $(PhSe)_2$, PBu_3, CH_2Cl_2 (93%); (i) $AlCl_3$, CH_2Cl_2; (ii) NaOH, MeOH/H_2O (63%%); $(PhSe)_2$, PBu_3, DCM (77%).



Scheme 9. Cyclisation of α- and β-pyrrole-acylalkyl radicals.

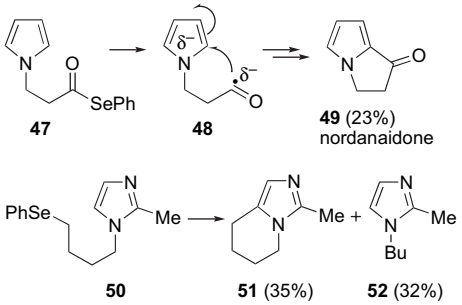
Although the absence of an electron-withdrawing or aryl group on the azole ring normally prevents cyclisation of nucleophilic alkyl and acyl radicals we have observed a few examples where this is not the case (Scheme 11). In the first of these examples, acyl radicals were cyclised onto pyrrole to yield the butterfly (Lepidoptera family, *Danainae* genus) pheromone nordanaidone **49**.[40] A recent synthesis using radical cyclisation has also been published.[15] The nucleophilic acyl radical intermediate **48**, generated from the acyl selenide **47**, is able to cyclise onto the electron rich pyrrole ring in low yield. In the second example, alkyl radical cyclisation from precursor **50** also gave a low yield of cyclisation onto the imidazole ring to yield **51** (35%) and also the uncyclised reduced product **52** (32%). This latter reaction was unexpected because other cyclisations on unactivated imidazoles[3] and pyrazoles (see earlier) had failed.



Scheme 10. Alkyl radical cyclisation onto pyrroles; **a**, Z=CO_2Et; **b**, Z=CHO.

Table 2
Alkyl radical cyclisation onto pyrroles

Precursor	Conditions	% Yield
44a	Bu_3SnH, AMBN, 6 h, cyclohexane, reflux	**45a** (61), **46a** (0), **44a** (0)
	Bu_3SnH, AMBN, 3 h, cyclohexane, reflux	**45a** (37), **46a** (13), **44a** (51)
44b	Bu_3SnH, AIBN, 3 h, toluene, reflux[3]	**45b** (55), **46b** (0), **44b** (0)
44a	Bu_3SnCl (0.1 equiv), AIBN, $NaCNBH_3$, *t*-BuOH, reflux	**45a** (40), **46a** (23), **44a** (0)
44b	Bu_3SnCl (0.1 equiv), AIBN, $NaCNBH_3$, *t*-BuOH, reflux	**45b** (91), **46b** (0), **44b** (0)
44b	Bu_3SnCl (0.1 equiv), AIBN, $NaCNBH_3$, EtOH, reflux	**45b** (40), **46b** (60), **44b** (0)

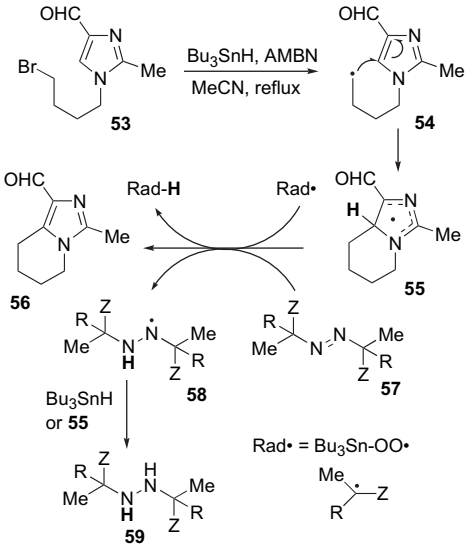


Scheme 11. Cyclisation onto non-substituted azoles.

2.4. Mechanistic studies

The mechanisms involved in Bu_3SnH-mediated aromatic homolytic substitution have been widely debated and recently reviewed.[1,2] In the mechanism of aromatic homolytic substitution the radical adds to the aromatic ring to form a stabilised π-radical intermediate. This mechanism is illustrated in Scheme 1 for intramolecular cyclisation onto azoles. The formation of the radical is facilitated by halide or phenylselenyl abstraction with Bu_3SnH or analogous radical reagents such as Bu_3GeH and $(TMS)_3SiH$. The difficulty with these reactions is the explanation of the loss of hydrogen from the aromatic ring. Bu_3SnH-mediated cyclisations are normally expected to yield a reduced product but in these reactions aromatic products are obtained. The central point of the mechanism is that the intermediate π-radical is stable and reacts too slowly with Bu_3SnH to yield a cyclised reduced product. Therefore, other radicals or H-acceptors present in the solution abstract the hydrogen to complete the aromatic homolytic substitution to yield the aromatic product.

Initially one of us proposed a pseudo-$S_{RN}1$ mechanism involving single electron transfer (SET),[41] which is also further discussed in a later reference.[2] However, in a joint study with Beckwith and Storey this SET mechanism was clearly disproved and evidence suggested aromatic homolytic substitution.[26] Several other potential mechanisms were also excluded in these studies. Most of the Bu_3SnH-mediated aromatic homolytic substitutions involved AIBN, which was clearly involved in the mechanism because greater than 1 equiv of the initiator was required.[1,2] These initial studies suggested that AIBN was directly involved with a H-abstraction mechanism for the rearomatisation step because only a small amount of nitrogen gas (from breakdown of AIBN) was measured.[26] Up to 25% of 2-cyanopropane was measured in certain aromatic homolytic substitutions showing that the 2-cyanoprop-2-yl radical (rad•) from breakdown of AIBN could act as a H-abstractor in the rearomatisation step (e.g., Scheme 12).[26] The 2-cyanoprop-2-yl radical is not a good acceptor of hydrogen but rearomatisation is a strong driving force.



Scheme 12. Putative mechanism involving the diazene initiator; AMBN (R=Et, Z=CN), AIBMe (R=Me, Z=CO_2Me).

A putative mechanism is illustrated in Scheme 12 in which the diazene initiator **57** acts as a hydrogen acceptor to yield an intermediate and stable hydrazyl radical **58**. Reduction of diazenes by abstraction of hydrogen from benzhydryl radicals to yield the corresponding hydrazines also supports the conjecture that diazene initiation can directly abstract hydrogen from π-radical intermediates in an aromatisation step.[42] Bu_3SnH is able to reduce hydrazyl radicals in chain reactions.[43] Therefore, reduction of the hydrazyl intermediate **58** by Bu_3SnH would complete a chain reaction. Our studies were focused in determining the mechanism of the involvement of the diazene initiator.

We chose a Bu_3SnH-mediated aromatic homolytic substitution reaction, which gave near quantitative yield[3] and used AIBN or AMBN [2-(1-cyano-1-methyl-propylazo)-2-methyl-butyronitrile] (**57**, R=Et, Z=CN) (Scheme 12). Studies with AIBN are complicated by the fact that measured efficiency is not 100% and the literature reports indicate between 50 and 70%.[44] A definitive study indicates an efficiency of 0.69 for AIBN in acetonitrile at 75 °C.[45] The aim was to isolate a reduced form of AIBN (**59**, R=Me, Z=CN) or AMBN (**57**, R=Et, Z=CN). However, even after considerable attempts and altered conditions no products could be isolated. ^{1}H NMR spectral and GC–MS analysis failed to indicate even small traces. Both compounds were synthesised to use as reference compounds in the analysis of reaction mixtures but were found to be unstable to both the reaction and work-up conditions. The reduced compounds were also unstable to column chromatography or even standing in a solution of CH_2Cl_2.

With the failure to isolate products from the initiator as an indication of mechanism, the next part of our investigation was to show that the initiator was required as suggested by the putative mechanisms in Scheme 12. 'Normal' Bu_3SnH-mediated cyclisation are reductive and only require sub-stoichiometric amounts of initiator and hence the requirement for larger amounts would indicate further involvement in the mechanism of aromatic homolytic substitution. We therefore repeated our chosen reaction (Scheme 12) with varying amounts of Bu_3SnH and AMBN to determine optimum yields and conditions. The results are shown in Table 3. AMBN was used in place of AIBN because of its full solubility in acetonitrile to obviate possible problems due to insolubility of AIBN.

The results show some variation of yield but clearly show the overall requirements of Bu_3SnH and initiator. Some of the variation in yields can be assigned to losses in the isolation of the product and unaltered starting material but also to variation in rates of initiation in this non-chain reaction. The requirement for at least 1 equiv of the initiator AMBN clearly indicates that this initiator is

Table 3
Cyclisation of 1-(4-bromobutyl)-2-methyl-1*H*-imidazole-4-carboxaldehyde **53** under differing conditions

Time	Bu_3SnH (equiv)	AMBN (equiv)	% Yield	
			Starting material **53**	Cyclised **56**
3 h	2.2	2.0	12	88
3 h	2.2	1.0	0	92
3 h	2.2	0.75	20	80
3 h	2.2	0.5	53	43
3 h	2.2	0.25	92	8
3 h	2.2	0.05	74	0
1 h	2.2	2.0	0	64
1 h	2.2	1.0	0	49
1 h	2.2	0.75	9	52
1 h	2.2	0.5	28	33
1 h	2.2	0.25	34	20
30 min	2.2	1.0	55	28
15 min	2.2	2.0	89	0
3 h	2.2	1.0	0	92
3 h	1.2	1.0	55, 46[a]	25, 25[a]
3 h	0.75	1.0	71, 56[a]	0, 40[a]
3 h	0.5	1.0	75	7
3 h	0.25	1.0	54	7

Reactions were carried out in refluxing acetonitrile under an atmosphere of nitrogen.
[a] Bu_3SnH was added in a solution of 30 cm^3 of acetonitrile instead of 50 cm^3.

involved in the mechanism other than initiating the formation of $Bu_3Sn^{\bullet}$ radicals. The most obvious conclusion is that the AMBN, or breakdown products there from, acts as an oxidant in the conversion of the cyclised π-radical intermediate **55** to the cyclised product **56** as shown in Scheme 12. The decline in yield of cyclised material with lowering the amount of Bu_3SnH also indicates that greater than 1 equiv of Bu_3SnH is required.

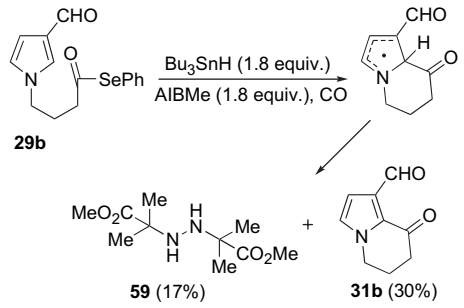
Interestingly, no uncyclised reduced material, 1-butyl-2-methyl-1*H*-imidazole-4-carboxaldehyde, was formed in any of the reactions indicating that the rate of cyclisation of the intermediate alkyl radical **54** is faster than reduction by Bu_3SnH under the reaction conditions. However, a more encompassing explanation has been reported in the literature.[26] The conversion of the cyclised π-radical intermediate **55** to the cyclised product **56** is a chain terminating step and therefore terminates potential chain reactions that could take place, i.e., reduction of **53** via the alkyl radical intermediate **54** to 1-butyl-2-methyl-1*H*-imidazole-4-carboxaldehyde. This explanation also provides further evidence for the putative mechanisms in Scheme 12.

If Bu_3SnH is only required for bromine abstraction as indicated in Scheme 12 then hexamethylditin [$Me_3(Sn)_2$] should be a suitable substitute. Reactions were carried out with hexamethylditin in refluxing propanonitrile and *tert*-butylbenzene in order to get a high enough temperature to cleave the tin–tin bond. Photolysis was also used to ensure cleavage. The yields were as follows: 3 days (4%), 24 h (65%) and 16 h (23%) in propanonitrile and 16 h in *tert*-butylbenzene in place of propanonitrile (53%). The reactions gave extensive decomposition, which was worse at longer reaction times. The nature of the abstracting radical required for the rearomatisation step is unknown but methyl radicals from the breakdown of trimethyltin radicals ($Me_3Sn^{\bullet}$) have been proposed.[46] The results give further evidence that the trialkyltin radicals ($R_3Sn^{\bullet}$) are required for abstraction of bromine in the first step of the mechanism and the initiator or breakdown products there from are required for the rearomatisation step.

With the failure to isolate any adducts from AIBN or AMBN we decided to use AIBMe [dimethyl 2,2′-azodiisobutyrate or by IUPAC nomenclature, 2-(1-methoxycarbonyl-1-methylethylazo)-2-methyl-propionic acid methyl ester] (**57**, R=Me, Z=CO_2Et), which has a similar profile to AIBN in radical reactions but the resulting hydrazine (**58**, R=Me, Z=CO_2Et) was predicted to be more stable. Whereas loss of CN from the α-hydrazino-nitrile (**59**, R=Me, Z=CN) in work-up could be expected, the α-hydrazino-ester (**59**, R=Me, Z=CO_2Et) should not undergo elimination. The latter was synthesised and tested for stability. In contrast to α-hydrazino-nitrile (**59**, R=Me, Z=CN), the α-hydrazino-ester (**57**, R=Me, Z=CO_2Et) was found to be stable to acid/base work-up conditions, reflux in toluene for 5 h and solution in CH_2Cl_2 at room temperature for 48 h but decomposed in a solution of sodium carbonate in MeOH (72 h).

We used AIBMe in several Bu_3SnH-mediated aromatic homolytic substitutions but again in most reactions failed to isolate any products relating to reduction of AIBMe except in one of the acyl radical cyclisations (Scheme 11). The same reactions conditions (Scheme 7) for the cyclisation of **29b** were repeated and the crude product mixture analysed by ^{1}H NMR spectroscopy using an internal standard. The cyclised product **31b** (30%) as obtained before and dihydro-AIBMe **59** (17%) indicating that AIBMe could be partly responsible for the oxidative step (Scheme 13).

The general lack of success using AIBMe was compounded by further blank studies, which showed that the α-hydrazino-ester (**59**, R=Me, Z=CO_2Et) was unstable in a solution of Bu_3SnH or Bu_3GeH in refluxing toluene (3 h). No traces of adducts could be detected by ^{1}H NMR spectroscopy or GC–MS analysis and only ca. 1% of **59** remained unaltered. We have no explanation for this unexpected lack of stability to Bu_3SnH or Bu_3GeH. Therefore, although



Scheme 13. Isolation of α-hydrazino-ester (**59**, R=Me, Z=CO_2Et).

evidence clearly shows the requirement for greater than 1 equiv of diazene initiators and Bu_3SnH, evidence for the mechanism involving H-abstraction directly by the diazene has proved difficult, possibly because of the lack of stability of the resulting hydrazines to the reaction conditions.

Our results and those of others[2] clearly indicate that other group XIV hydrides other than Bu_3SnH, e.g., Bu_3GeH and $(TMS)_3SiH$, behave similarly and therefore are likely to proceed by similar mechanisms. Triethyl borane (Et_3B) is now commonly used as an initiator in place of AIBN and can also be successfully used in Bu_3SnH-mediated aromatic homolytic substitutions. We have suggested that the mechanism of the rearomatisation step is similar, i.e., the initiator is crucial and that the ethyl radicals formed from the breakdown of Et_3B in the presence of oxygen abstract the hydrogen to yield ethane and the aromatic product.[16,21,47]

3. Experimental

3.1. General

Commercial dry solvents were used in all reactions except for light petroleum and ethyl acetate (EtOAc), which were distilled from $CaCl_2$, and dichloromethane (DCM) was distilled over phosphorus pentoxide. Light petroleum refers to the bp 40–60 °C fraction. Sodium hydride was obtained as 60% dispersion in oil and was washed with light petroleum. Mps were determined on an Electrothermal 9100 melting point apparatus and are uncorrected. Elemental analyses were determined on a Perkin Elmer 2400 CHN Elemental Analyser in conjunction with a Perkin Elmer AD-4 Autobalance. IR spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer on NaCl plates. NMR spectra were recorded on a Bruker DPX 400 (^{1}H, 400 MHz; ^{13}C, 100 MHz) spectrometer in solutions of deuteriochloroform using tetramethylsilane as an internal standard. Except where otherwise stated, ^{1}H NMR spectra were run on a Bruker AC-250 (^{1}H, 250 MHz). Chemical shifts are given in parts per million (ppm) and *J* values in hertz (Hz). Mass spectra were recorded on a JEOL SX102 mass spectrometer or carried out by the EPSRC Mass Spectrometry Service at University of Wales, Swansea. All mass spectra are electron impact spectra (EI) unless otherwise stated. TLC using silica gel as adsorbent was carried out with aluminium backed plates coated with silica gel (Merck Kieselgel 60 F_{254}). Column chromatography was carried out using silica gel as adsorbent and light petroleum/EtOAc as eluent unless otherwise specified. Extractions solvents were used in ca. 30 cm^3 quantities unless otherwise specified. Organic solutions were evaporated to dryness under reduced pressure using a rotary evaporator. Organic solutions were dried using anhydrous magnesium sulfate and filtered prior to evaporation.

1-Chloro-3-(phenylselenyl)propane, 1-iodo-3-(phenylselenyl)-propane, 1-chloro-4-(phenylselenyl)-butane, 1-iodo-4-(phenylselenyl)butane, 1-chloro-5-(phenylselenyl)pentane and 1-iodo-5-(phenylselenyl)-pentane were prepared by the literature procedures.[3]

3.2. 4-Phenyl-1-(3-(phenylselenyl)propyl)-1*H*-pyrazole 6a. General procedure for alkylation of pyrazoles

4-Phenylpyrazole (0.15 g, 1.0 mmol) was added to a stirred suspension of crushed potassium hydroxide (0.17 g, 3.0 mmol) in DMF (15 cm^3) and stirring was continued for 30 min. 1-Iodo-3-(phenylselenyl)-propane (0.65 g, 2.0 mmol) was added slowly to the stirred suspension and stirring was continued overnight. The crude reaction mixture was partitioned between water and ethyl acetate and the aqueous layer separated and extracted with ethyl acetate. The combined organic extracts were washed twice with water and brine, dried and evaporated to dryness. The crude off-white oily solid was purified by column chromatography to yield 4-phenyl-1-[3-(phenylselenyl)propyl]-1*H*-pyrazole **6a** (0.34 g, 100%) as a white solid, mp 48–50 °C. (Found: $(M+H)^+$, 343.0717. $C_{18}H_{19}N_2Se$ requires 343.0713.) ν_{max} (KBr)/cm^{-1} 1607, 760 and 693; δ_H 2.23–2.37 (2H, m, 2-H), 2.91 (2H, t, *J* 7.1, 3-H), 4.31 (2H, t, *J* 6.5, 1-H), 7.24–7.32 (4H, m, phenyl–H), 7.37–7.52 (6H, m, phenyl–H), 7.53 (1H, s, pyrazole 3-H) and 7.77 (1H, s, pyrazole 5-H); δ_C 24.4 (2-C), 30.4 (3-C), 51.3 (1-C), 122.9 (pyrazole 4-C), 125.5 (CH), 125.7 (pyrazole 3-C), 126.4 (CH), 127.1 (CH), 128.8 (CH), 129.2 (CH), 129.5 (C), 132.5 (C), 132.8 (CH) and 136.9 (pyrazole 5-C); *m*/*z* 343 [$(M+H)^+$, 29%] and 187 (100).

3.3. 1-[4-(Phenylselenyl)butyl]-1*H*-pyrazole-3-carbaldehyde 11b. General method for hydrolysis

3-(Dimethoxymethyl)-1-[4-(phenylselenyl)butyl]-1*H*-pyrazole (0.36 g, 1.0 mmol) was dissolved in ethanol (30 cm^3) and *p*-TSA (19 mg, 0.1 mmol) was added and the solution was stirred overnight. The crude material was evaporated to dryness, partitioned between aqueous sodium bicarbonate and dichloromethane and the organic layer removed. The aqueous layer was further extracted with dichloromethane and the combined organic layers evaporated to dryness to yield 1-[4-(phenylselenyl)butyl]-1*H*-pyrazole-3-carbaldehyde **11b** (0.28 g, 91%) as a colourless oil. (Found: M^+, 308.0428. $C_{14}H_{16}N_2OSe$ requires 308.0432.) ν_{max} (thin film)/cm^{-1} 2936, 2827, 1693, 1578, 760, 737; δ_H 1.66–1.75 (2H, m, 3-H), 1.99–2.10 (2H, m, 2-H), 2.90 (2H, t, *J* 7.2, 4-H), 4.20 (2H, t, *J* 7.0, 1-H), 6.77 (1H, d, *J* 2.4, pyrazole 4-H), 7.22–7.27 (3H, m), 7.37 (1H, dd, *J* 2.4, 0.8, pyrazole 2,6-H), 7.44–7.48 (2H, m) and 9.94 (1H, d, *J* 0.8, CHO); δ_C 26.9 (3-C), 27.0 (2-C), 30.1 (4-C), 52.4 (1-C), 106.0 (pyrazole 4-C), 127.1 (phenyl 4-C), 129.1 (CH), 129.75 (C), 131.1 (pyrazole 5-C), 132.8 (CH), 151.5 (pyrazole 3-C) and 186.4 (CHO); *m*/*z* 308 (M^+, 17%) and 155 (17).

3.4. Cyclisation of 4-phenyl-1-[3-(phenylselenyl)propyl]-1*H*-pyrazole 6a. General procedure for radical cyclisation

A solution of tributyltin hydride (0.11 cm^3, 0.38 mmol) and ACCN (0.15 g, 0.58 mmol) in toluene (50 cm^3) was added to a solution of 4-phenyl-1-[3-(phenylselenyl)propyl]-1*H*-pyrazole **6a** (0.10 g, 0.29 mmol) in toluene (200 cm^3) heated under reflux over 4 h under an atmosphere of nitrogen. The reaction mixture was heated at reflux for a further 30 min following complete addition, cooled to room temperature and evaporated to dryness. Purification by column chromatography yielded 3-phenyl-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole **1** (withasomnine) (19 mg, 38%) as a white solid. (Found: M^+, 184.1000. $C_{12}H_{12}N_2$ requires 184.1005.) ν_{max} (thin film)/cm^{-1} 2937, 1607, 1470, 1356, 762 and 694; δ_H 2.66–2.73 (2H, m, 5-H), 3.10 (2H, t, *J* 7.2, 4-H), 4.18 (2H, t, *J* 7.4, 6-H), 7.14–7.21 (1H, m, phenyl 4-H), 7.34–7.38 (2H, m, phenyl 3,5-H), 7.42–7.46 (2H, m, phenyl 2,6-H) and 7.81 (1H, s, 2-H); δ_C 23.8 (5-C), 26.4 (4-C), 47.6 (6-C), 116.3 (3-C), 125.0 (CH), 125.6 (CH), 128.8 (CH), 130.9 (phenyl 1-C), 133.8 (3a-C) and 140.9 (2-C); *m*/*z* 184 (M^+, 100%), 128 (15) and 159 (18).

Further elution yielded the reduced product **15a** (R=4-Ph), 3-phenyl-1-propyl-1*H*-pyrazole 208 (9 mg, 17%) was isolated as a colourless oil. (Found: M^+, 186.1154. $C_{12}H_{14}N_2$ requires 186.1157.) ν_{max} (thin film)/cm^{-1} 3131; δ_H 0.95 (3H, t, *J* 7.4, Me), 1.89–1.98 (2H, m, 2-H), 4.11 (2H, t, *J* 7.2, 1-H), 7.19–7.25 (1H, m), 7.34–7.38 (2H, m), 7.47–7.49 (2H, m), 7.63 (1H, s, 3-H) and 7.78 (1H, s, 5-H); δ_C 11.1 (Me), 23.7 (CH_2), 54.0 (NCH_2), 122.6 (4-C), 125.4 (CH), 125.9 (3-C), 126.2 (CH), 128.8 (CH), 132.7 (C) and 136.5 (5-C); *m*/*z* 186 (M^+, 87%), 157 (100) and 144 (64).

3.5. Solid-phase study

*3.5.1. 4-(Methylselenyl)phenol **20***

A 2 cm^3 aliquot of (4-bromophenoxy)trimethylsilane **18** (10.00 g, 40.8 mmol) dissolved in THF (20 cm^3) was added to magnesium (1.27 g, 52.4 mmol) in a three-necked flask fitted with reflux condenser and potassium hydroxide scrubbing train. A single crystal of iodine was added to the stirred suspension and heated gently until reflux was self-sustaining, the remainder of the THF solution was added dropwise to maintain reflux. The suspension was heated under reflux for 45 min, cooled to room temperature and grey selenium powder (3.06 g, 38.8 mmol) was added in one portion. The dark suspension was heated under reflux for a further 3 h, cooled to 0 °C and quenched cautiously with saturated ammonium chloride solution. The mixture was filtered through Celite and the solid was washed with saturated ammonium chloride and diethyl ether, the ethereal layer was separated and the aqueous layer extracted twice with ether, washed with brine, dried and evaporated to dryness to yield a viscous orange oil (6.21 g), which solidified on standing. NMR spectroscopic analysis indicated that noticeable desilylation had occurred.

Sodium borohydride (74 mg, 1.96 mmol) was added slowly to a stirred solution of the crude diselenide (0.40 g) in ethanol (50 cm^3) at 0 °C. The solution was stirred for 30 min and iodomethane (0.23 g, 1.62 mmol) was added, stirring was maintained at room temperature for 16 h, evaporated to dryness and treated with hydrochloric acid (2 M, 10 cm^3). The aqueous layer was extracted with diethyl ether. The organic fractions were washed with aqueous sodium carbonate and brine, dried and evaporated to dryness, yielding 4-(methylselenyl)phenol **20** (0.25 g, 51%) as an off-white solid. (Found: M^+, 187.9741. C_7H_8OSe requires 187.9740.) ν_{max} (KBr disc)/cm^{-1} 3386, 2950, 1251 and 817; δ_H 2.30 (3H, s, Me), 4.88 (1H, s, OH), 6.73–6.78 (2H, m, 2,6-H) and 7.34–7.39 (2H, m, 3,5-H); δ_C 8.7 (Me), 116.3 (2,6-C), 121.7 (4-C), 133.7 (3,5-C) and 154.7 (1-C); *m*/*z* 188 (M^+, 71%), 173 (71) and 151 (100).

*3.5.2. 4-(Tetrahydroselenophen-1-yl)phenol chloride **21***

(4-Bromophenoxy)trimethylsilane **18** (9.00 g, 36.7 mmol) was dissolved in THF (20 cm^3) and an aliquot of this solution (2 cm^3) was added to magnesium (1.14 g, 47.0 mmol) in a three-necked flask fitted with reflux condenser and potassium hydroxide scrubbing train. A single crystal of iodine was added to the stirred suspension and heated gently until reflux was self-sustaining, the remainder of the THF solution was added dropwise to maintain reflux. The suspension was heated under reflux for 45 min, cooled to room temperature and grey selenium powder (2.75 g, 34.9 mmol) was added in one portion. The dark suspension was then heated under reflux for a further 3 h, cooled to 0 °C and quenched cautiously with saturated ammonium chloride solution. The mixture was filtered through Celite and the solid was washed with saturated ammonium chloride and ether, the ether layer was separated and the aqueous layer extracted twice with ether, washed with brine, dried and evaporated to dryness to yield a viscous orange oil (6.70 g), which solidified on standing. Sodium borohydride (0.74 g, 19.6 mmol) was added slowly to a stirred solution of the crude diselenide (4.00 g) in ethanol (250 cm^3) at 0 °C. The solution was stirred for 30 min and 1-chloro-4-iodobutane (4.28 g, 19.6 mmol) was added, stirring was maintained at room temperature for 16 h and treated with hydrochloric acid (2 M, 10 cm^3). The

reaction mixture was concentrated to a viscous slurry and the solid was collected, washed with ether and dried under vacuum to yield 4-(tetrahydroselenophen-1-yl)phenol chloride **21** (0.81 g, 38%) as an off-white solid. (Found: M^+, 229.0129. $C_{10}H_{13}OSe$ requires 229.0132.) ν_{max} (KBr disc)/cm^{-1} 1592, 1277 and 826; δ_H 2.37–2.50 (4H, m, $SeCH_2CH_2$), 3.55–3.65 (2H, m, $SeCH_2$), 3.79–3.90 (2H, m, $SeCH_2$), 6.97–7.03 (2H, m, 2,6-H) and 7.60–7.66 (2H, m, 3,5-H); δ_C 32.3 ($SeCH_2CH_2$), 48.7 ($SeCH_2$), 117.4 (4-C), 119.2 (2,6-C), 133.2 (3,5-C) and 163.3 (phenyl 1-C); *m*/*z* 229 (M^+, 100%).

3.5.3. *Methylselenyl Quadragel® **24***

Quadragel® mesylate **23** (1.383 g, 2.60 mmol) was swollen in DMF (30 cm^3) and 4-methylselenylphenol (0.80 g, 4.3 mmol), sodium iodide (1.30 g, 8.7 mmol) and potassium carbonate (1.20 g, 8.7 mmol) were added and the suspension was heated at 60 °C for 30 h. The reaction was quenched with aqueous THF and the resin was washed with DMF, water, aqueous THF, THF/DCM/methanol alternately with a final washing with DCM. The resin was dried under vacuum to give methylselenyl Quadragel® **24** (1.69 g, 100%) as a colourless resin (1.54 mmol g^{-1}); ν_{max} (thin film)/cm^{-1} 2916, 1243 and 1094; δ_H 2.26 (SeMe), 3.32–3.80 (CH_2O) and 7.63–8.19 (phenyl–H); δ_C 8.56 (SeMe), 67.5–71.9 (CH_2–O), 115.5 (phenyl 2,6-C), 116.3 (phenyl 4-C) and 133.2 (phenyl 3,5-C).

3.5.4. *Quadragel® 4-phenoxyselenyl bromide **25***

4-Methylselenylphenoxy Quadragel® **24** (2.55 g, 3.9 mmol) was swollen in chloroform (50 cm^3) and cooled to 0 °C. Bromine (0.67 g, 3.9 mmol) was added in chloroform (2 cm^3) and the mixture was agitated for 10 min, warmed to room temperature and the resin was collected by filtration. Some of the resin beads were already turning dark red/brown following the elimination of methyl bromide. The resin was swollen in ethanol and heated at reflux for 1 h. The resultant dark red resin was collected by filtration and washed with water/THF (1:1), THF, DCM and methanol. The resin was dried at the pump prior to drying overnight under vacuum to yield Quadragel® 4-phenoxyselenyl bromide **25** (2.806 g, 100%) as a dark red resin (1.40 mmol g^{-1}). (Found: Br, 10.5; Se, 8.4%.) Elemental analysis indicates approximately 1.25 mmol g^{-1}; ν_{max} (thin film)/cm^{-1} 2920, 1247 and 1108; δ_H 3.71 (CH_2O) and 6.89–7.81 (phenyl–H); δ_C 62.1–71.1 (CH_2–O), 116.2 (phenyl 2,6-C) and 139.5 (phenyl 3,5-C).

3.5.5. *4-(4-Chlorobutylselenyl)phenoxy Quadragel® **26** (mesylate route)*

Quadragel® mesylate **23** (0.800 g, 1.47 mmol) was swollen in DMF (10 cm^3) and 4-tetrahydroselenoniumphenol chloride **21** (0.66 g, 2.50 mmol) and potassium carbonate (0.69 g, 5.00 mmol) were added and the suspension was heated at 60 °C for 48 h. The reaction was quenched with aqueous THF and the resin was washed with DMF, water, aqueous THF and THF/DCM/methanol alternately with a final washing of DCM. The resin was dried under vacuum to give 4-(4-chlorobutylselenyl)phenoxy Quadragel® **26** (1.16 g, 100%) as a colourless resin (1.38 mmol g^{-1}). Slightly greater mass than expected indicates some ion exchange may have occurred; ν_{max} (KBr disc)/cm^{-1} 2925, 1243 and 1111; δ_H 1.84 (4H, br, 2,3-H), 2.85 (2H, br, 1-H), 3.72–4.33 (br, PEG and 4-H), 6.78 (2H, br, phenyl 2,6-H) and 7.45 (2H, br, phenyl 3,5-H); δ_C 26.7 (2-C), 28.6 (3-C), 29.1 (1-C), 44.4 (4-C), 115.3 (phenyl 2,6-C), 119.7 (phenyl 4-C), 135.6 (phenyl 3,5-C) and 158.6 (phenyl 1-C).

3.5.6. *4-(4-Chlorobutylselenyl)phenoxy Quadragel® **26** (selenyl bromide route)*

Quadragel® 4-phenoxyselenyl bromide **25** (1.27 g, 1.8 mmol) was swollen in ethanol/THF (1:1, 40 cm^3) and lithium borohydride (2.0 M, 4.0 cm^3) was added. The reaction mixture was agitated for 1 h and 1-chloro-4-iodobutane (2.18 g, 10 mmol) was added. The reaction was agitated for 24 h and quenched by the addition of water, the resin was collected by filtration and washed with aqueous THF, THF, DCM and methanol. The resin was dried at the pump for 30 min and then thoroughly dried under vacuum overnight to yield 4-(4-chlorobutylselenyl)phenoxy Quadragel® **26** (1.24 g, 95%) as a pale yellow resin (1.38 mmol g^{-1}); the data matched that of the alternate synthetic route.

3.5.7. *Quadragel® N-butyl-4-phenylpyrazole **27***

4-(4-Chlorobutylselenyl)phenoxy Quadragel® **26** (1.083 g, 1.50 mmol) was swollen in DMF (15 cm^3) and 4-phenylpyrazole (0.48 g, 3.30 mmol) and crushed potassium hydroxide (0.28 g, 5.0 mmol) was added. The polymer was agitated for 15 min and sodium iodide was added. The polymer was agitated at room temperature for 24 h and the resin was collected by filtration, washed with aqueous THF, methanol, THF and DCM. The resin was dried at the pump for 15 min and dried overnight under vacuum to yield the Quadragel® bound pyrazole **27** (1.32 g, 100%) as a yellow resin (1.24 mmol g^{-1}). (Found: C, 62.1; H, 6.5; N, 2.15%.) ν_{max} (KBr disc)/cm^{-1} 2915, 1607, 1245, 1106 and 826; δ_H 1.82 (4H, br, 2,3-H), 2.84 (2H, br, 4-H), 3.66–4.28 (br, PEG and 1-H), 6.76 (2H, br, phenyl 2,6-H), 7.44 (3H, br, phenyl 3,5-H and pyrazole 3-H) and 7.76 (1H, br, pyrazole 5-H); δ_C 26.7 (2-C), 28.6 (3-C), 29.1 (4-C), 51.7 (1-C), 115.3 (phenol 2,6-C), 119.7 (phenol 4-C), 122.8 (pyrazole 4-C), 125.4 (phenyl 2,6-C), 125.8 (pyrazole 3-C), 126.3 (phenyl 4-C), 128.8 (phenyl 3,5-C), 132.6 (phenyl 1-C), 135.6 (phenol 3,5-C), 136.6 (pyrazole 5-C) and 158.7 (phenol 1-C).

3.5.8. *Radical cyclisation using Quadragel® N-butyl-4-phenylpyrazole **27***

Quadragel® *N*-butyl-4-phenylpyrazole **27** (0.203 mg) was swollen in toluene (15 cm^3) and AIBN (0.13 g, 0.8 mmol, 3.0 equiv) and $(TMS)_3SiH$ (0.36 cm^3, 1.45 mmol, 5.4 equiv) were added. The reaction mixture was refluxed for 8 h. The resin was collected by filtration, washed with toluene and DCM. The solution was evaporated to dryness under reduced pressure and purified by column chromatography to yield 3-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine **16b** (R=4-Ph) (61%).

3.6. Acyl radical cyclisations

3.6.1. *Synthesis of phenyl (formyl-1H-pyrrol-1-yl)alkaneselenoates*

*General procedure. Phenyl 3-(2-formyl-1H-pyrrol-1-yl)propaneselenoate **28a**.* Diphenyl diselenide (2.40 g, 7.5 mmol) was stirred in dichloromethane (100 cm^3) at room temperature and tributylphosphine (2.5 cm^3, 10 mmol) was added dropwise over 2 min. The reaction mixture was stirred for a further 5 min and 3-(2-formyl-1*H*-pyrrol-1-yl)propanoic acid (0.80 g, 5.0 mmol) was added. The reaction mixture was stirred for 4 h, washed with water and brine and back extracted with dichloromethane. The organic layers were combined, dried and evaporated to dryness. The crude material was purified by column chromatography to yield phenyl 3-(2-formyl-1*H*-pyrrol-1-yl)propaneselenoate **28a** (0.90 g, 59%) as a coloured solid, mp 59–61 °C. (Found: $(M+H)^+$, 308.0195. $C_{14}H_{14}NO_2Se$ requires 308.0190.) ν_{max} (KBr disc)/cm^{-1} 3056, 1716, 1661, 739 and 689; δ_H (400 MHz) 3.21 (2H, t, *J* 6.0, 2-H), 4.55 (2H, t, *J* 6.0, 3-H), 6.20 (1H, m, pyrrole 4-H), 6.94–6.97 (3H, m, pyrrole 3,5-H), 7.33–7.39 (3H, m, phenyl 3,4,5-H), 7.42–7.45 (2H, m, phenyl 2,6-H) and 9.52 (1H, s, CHO); δ_C 44.6 (2-C), 48.0 (3-C), 109.7 (pyrrole 4-C), 125.4 (pyrrole 5-C), 125.9 (phenyl 1-C), 129.1, 129.2 (phenyl 2,6-C), 129.4 (phenyl 3,5-C), 130.9 (pyrrole 2-C), 132.6 (pyrrole 3-C), 135.7 (phenyl 4-C), 179.3 (CHO) and 198.7 (COSePh).

3.6.2. *Cyclisation of phenyl 3-(2-formyl-1H-pyrrol-1-yl)propaneselenoate **28a***

General method. Phenyl 3-(2-formyl-1*H*-pyrrol-1-yl)propaneselenoate **28a** (122 mg, 0.40 mmol) and AIBN (130 mg, 0.80 mmol)

were dissolved in acetonitrile (50 cm^3) and following and the reaction vessel was subjected to CO saturation using the freeze–thaw technique and was fitted with a three-way tap linked independently to a high vacuum source and a balloon of carbon monoxide. The vessel was subjected to liquid nitrogen temperatures and upon complete freezing was evacuated for 10 min, after which time the evacuated flask was allowed to fill with carbon monoxide and warmed to room temperature with the CO balloon attached. The freeze–thaw technique was repeated further two times. The reaction mixture was warmed slowly to room temperature, placed in an oil bath at 80 °C and a solution of tributyltin hydride (0.16 cm^3, 0.60 mmol) in cyclohexane (20 cm^3) was added dropwise over 2 h. Heating was maintained overnight. The reaction mixture was cooled to room temperature, evaporated to approximately 30 cm^3 total volume and washed with light petroleum. The crude material was purified by gradient elution column chromatography to yield 1-oxo-2,3-dihydro-1*H*-pyrrolizidine-5-carbaldehyde **30a** (33 mg, 55%) as the major product. (Found: M^+, 149.0478. $C_8H_7NO_2$ requires 149.0477.) ν_{max} (neat)/cm^{-1} 1711; δ_H 3.13 (2H, t, *J* 6.1, 2-H), 4.63 (2H, t, *J* 6.1, 3-H), 6.73 (1H, d, *J* 4.4, 7-H), 7.12 (1H, d, *J* 4.4, 6-H) and 9.75 (1H, s, CHO); δ_C 38.8 (2-C), 43.9 (3-C), 107.3 (7-C), 125.1 (6-C) and 186.8 (CHO); *m*/*z* 150 (MH^+, 100%), 122 (100) and 80 (100).

Cyclisation of phenyl 4-(2-formyl-1H-pyrrol-1-yl)butaneselenoate ***28b***.The general procedure was used except that the reaction solution under an atmosphere of CO was heated at 95 °C for 12 h in a sealed Schlenk tube to yield 3-(hydroxymethyl)-5,6,7,8-tetrahydroindolizin-8-one **32** (16 mg, 65%) as a colourless oil. (Found: M^+, 165.0787. $C_9H_{11}NO_2$ requires 165.0790.) ν_{max} (thin film)/cm^{-1} 3387, 1641, 1341 and 1180; δ_H 2.27–2.32 (2H, m, 6-H), 2.57–2.62 (2H, m, 7-H), 4.14–4.19 (2H, m, 5-H), 4.67 (2H, s, CH_2OH), 6.21 (1H, d, *J* 4.0, 2-H) and 6.96 (1H, d, *J* 4.0, 1-H); δ_C 23.4 (6-C), 36.0 (7-C), 42.5 (5-C), 56.7 (CH_2OH), 110.2 (2-C), 113.3 (1-C), 131.8 (3-C), 136.5 (8a-C) and 187.6 (8-C); *m*/*z* 165 (M^+, 90%), 148 (100) and 57 (55).

Cyclisation of phenyl 5-(2-formyl-1H-pyrrol-1-yl)pentaneselenoate ***28c***. The general procedure was used except that the tributyltin hydride and AIBN were added over 5 h. 9-Oxo-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-3-carbaldehyde **30c** (31%), white solid, mp 79–81 °C. (Found: M^+, 177.0794. $C_{10}H_{11}NO_2$ requires 177.0790.) ν_{max} (KBr disc)/cm^{-1} 1663; δ_H 1.88–1.96 (2H, m, 7-H), 2.03–2.10 (2H, m, 6-H), 2.78–2.82 (2H, m, 8-H), 4.80–4.85 (2H, m, 5-H), 6.89–6.93 (2H, m, 1,2-H) and 9.71 (1H, s, CHO); δ_C 19.5 (7-C), 26.1 (6-C), 39.9 (8-C), 44.3 (5-C), 115.2 (1-C), 122.9 (2-C), 133.8 (9a-C), 141.3 (3-C), 181.8 (CHO) and 194.1 (9-C); *m*/*z* 177 (M^+, 73%) and 148 (42). 1-(5-Oxopentyl)-1*H*-pyrrole-2-carbaldehyde (46%), colourless oil. (Found: M^+, 179.0945. $C_{10}H_{13}NO_2$ requires 179.0946.) ν_{max} (thin film)/cm^{-1} 1722 and 1661; δ_H (400 MHz) 1.60–1.65 (2H, m, 3-H), 1.78–1.82 (2H, m, 2-H), 2.47 (2H, t, *J* 8.0, 4-H), 4.33 (2H, t, *J* 8.0, 1-H), 6.20–6.23 (1H, m, pyrrole 4-H), 6.92–6.94 (2H, m, pyrrole 3,5-H), 9.52 (1H, s, pyrrole CHO) and 9.75 (1H, s, 5-C); δ_C 18.9 (3-C), 30.7 (2-C), 43.3 (4-C), 48.9 (1-C), 109.7 (pyrrole 4-C), 125.0 (pyrrole 5-C), 131.3 (pyrrole 3-C), 179.3 (CHO) and 201.8 (5-C); *m*/*z* 179 (M^+, 20%), 150 (100), 134 (45), 122 (91), 108 (52), 94 (57) and 80 (50).

The reaction was repeated using the sealed tube procedure and heated at 90 °C for 6 h to yield the reduction product 1-(5-oxopentyl)-1*H*-pyrrole-2-carbaldehyde as the major compound and 9-oxo-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-3-carbaldehyde **30c** (20%).

3.6.3. Phenyl 4-oxo-4-(1H-pyrrol-2-yl)butaneselenoate *34*

Methyl 4-oxo-4-[1-(phenylsulfonyl)-1H-pyrrol-2-yl]butanoate. Methyl 4-chloro-4-oxo butyrate (3.7 cm^3, 30.0 mmol) was added to a stirred solution of boron trifluoride etherate (7.40 cm^3, 60.0 mmol) in dichloromethane (50 cm^3). Stirring was maintained at room temperature for 10 min and *N*-(phenylsulfonyl)-1*H*-pyrrole (2.14 cm^3, 10.0 mmol) in dichloromethane (10 cm^3) was added over 20 min and the reaction mixture was stirred for 4 days. The reaction was quenched with ice-water (100 cm^3) and the aqueous phase was extracted with further portions of dichloromethane. The combined organic extracts were washed with sodium hydroxide solution (0.1 M), water and dried (Na_2SO_4). Evaporation of solvent yielded methyl 4-oxo-4-[1-(phenylsulfonyl)-1*H*-pyrrol-2-yl]butanoate (1.95 g, 61%) as a white solid. (Found: M^+, 321.0671. $C_{15}H_{15}NO_5S$ requires 321.0671.) (Found: C, 56.0; H, 4.7; N, 4.4. $C_{15}H_{15}NO_5S$ requires: C, 56.1; H, 4.7; N, 4.35.) ν_{max} (KBr disc)/cm^{-1} 1736, 1681 and 1356, 1166; δ_H 2.62 (2H, t, *J* 7.1, 2-H), 3.03 (2H, t, *J* 7.1, 3-H), 3.61 (3H, s, Me), 6.34–6.37 (1H, m, pyrrole 4-H), 7.12 (1H, dd, *J* 1.6, 3.9, pyrrole 3-H), 7.47–7.62 (3H, m), 7.80 (1H, dd, *J* 1.6, 3.0, pyrrole 5-H) and 7.96–7.99 (2H, m); δ_C 28.0 (2-C), 33.9 (3-C), 51.7 (Me), 110.5 (pyrrole 4-C), 123.7 (pyrrole 5-C), 128.2 (phenyl 3,5-C), 128.7 (phenyl 2,6-C), 130.3 (pyrrole 3-C), 132.8 (pyrrole 2-C), 133.6 (phenyl 4-C), 138.8 (phenyl 1-C), 173.0 (1-C) and 186.2 (4-C); *m*/*z* 321 (M^+, 29%), 234 (95), 160 (60) and 141 (55).

4-Oxo-4-(1H-pyrrol-2-yl)butanoic acid. Methyl 4-oxo-4-[1-(phenylsulfonyl)-1*H*-pyrrol-2yl]butanoate (1.90 g, 5.9 mmol) was dissolved in methanol (20 cm^3) and aqueous sodium hydroxide (5 M, 20 cm^3) was added. The reaction mixture was heated under reflux for 5 h and cooled to room temperature, acidified to pH 3 with hydrochloric acid and thoroughly extracted with dichloromethane. The organic layers were washed with water, dried and evaporated to dryness to give 4-oxo-4-(1*H*-pyrrol-2-yl)butanoic acid (0.99 g, 100%) as an off-white solid. (Found: M^+, 167.0580. $C_8H_9NO_3$ requires 167.0582.) ν_{max} (KBr disc)/cm^{-1} 3322, 2960, 1714, 1643; δ_H (400 MHz, $CO(CD_3)_2$) 2.67 (2H, t, *J* 8.0, 2-H), 3.10 (2H, t, *J* 8.0, 3-H), 6.22–6.24 (1H, m, pyrrole 4-H), 7.01–7.03 (1H, m, pyrrole 3-H) and 7.10–7.12 (1H, m, pyrrole 5-H); δ_C 28.3 (2-C), 33.1 (3-C), 110.6 (pyrrole 4-C), 116.5 (pyrrole 5-C), 125.2 (pyrrole 3-C), 132.6 (pyrrole 2-C), 174.1 (1-C) and 188.6 (4-C); *m*/*z* 167 (M^+, 60%), 100 (73) and 94 (83).

Phenyl 4-oxo-4-(1H-pyrrol-2-yl)butaneselenoate ***34***. 4-Oxo-4-(1*H*-pyrrol-2-yl)butanoic acid (1.00 g, 6.0 mmol) and diphenyl diselenide (2.80 g, 9.0 mmol) were stirred in dichloromethane (25 cm^3) at −30 °C and tributylphosphine (2.2 cm^3, 9.0 mmol) was added dropwise over 5 min. The reaction mixture was stirred at −30 °C for 30 h after which time the reaction mixture was diluted with dichloromethane, washed with water and brine and back extracted with dichloromethane. The organic layers were combined, dried and evaporated to dryness. Purification by column chromatography using gradient elution yielded phenyl 4-oxo-4-(1*H*-pyrrol-2-yl)butaneselenoate **34** (1.70 g, 93%) as a white solid, mp 94–95 °C. (Found (ESI): $(M+H)^+$, 308.0184. $C_{14}H_{14}NO_2Se$ requires 308.0189.) ν_{max} (KBr disc)/cm^{-1} 3295, 1720, 1636, 1403, 1107 and 1042; δ_H 3.12–3.19 (4H, s, 2,3-H), 6.26–6.27 (1H, m, pyrrole 4-H), 6.94–6.94 (1H, m, pyrrole 3-H), 7.02–7.03 (1H, m, pyrrole 5-H), 7.36–7.37 (3H, m, phenyl 3-5-H) and 7.51–7.54 (2H, m, phenyl 2,6-H); δ_C 32.5 (2-C), 41.6 (3-C), 110.8 (pyrrole 4-C), 116.4 (pyrrole 5-C), 124.9 (pyrrole 3-C), 126.3 (phenyl 1-C), 128.9 (phenyl 3,5-C), 129.4 (phenyl 4-C), 131.2 (pyrrole 2-C), 135.9 (phenyl 2,6-C), 187.4 (4-C) and 199.4 (1-C).

3.6.4. Radical reaction of phenyl 4-oxo-4-(1H-pyrrol-2-yl)butaneselenoate *34*

Tributyltin hydride (0.75 cm^3, 2.8 mmol) and AMBN (0.88 g, 4.6 mmol) in cyclohexane (20 cm^3) was added over 7 h to a solution of phenyl 4-oxo-4-(1*H*-pyrrol-2-yl)butaneselenoate **34** (0.70 g, 2.3 mmol) in acetonitrile (250 cm^3) heated under reflux. The reaction mixture was heated under reflux for 9 h after which time it was cooled to room temperature and evaporated to dryness. Purification using gradient elution column chromatography yielded 1-(1*H*-pyrrol-2-yl)-propan-1-one **36**[48] (0.164 g, 58%) as a colourless oil; ν_{max} (thin film)/cm^{-1} 3287 and 1640; δ_H (400 MHz) 1.22 (3H, t, *J* 7.5, Me), 2.82 (2H, q, *J* 7.5, $COCH_2$), 6.26 (1H, ddd, *J* 2.5, 3.8, 2.5,

pyrrole 4-H), 6.92 (1H, ddd, *J* 3.8, 2.5, 1.3, pyrrole 3-H) and 7.04 (1H, ddd, *J* 2.5, 2.9, 1.3, pyrrole 5-H).

3.6.5. 4-Bromo-1-[1-(phenylsulfonyl)-1H-pyrrol-2-yl]butan-1-one **38**

4-Bromobutyryl chloride (2.8 cm^3, 24.0 mmol) was added to a stirred solution of boron trifluoride etherate (3.0 cm^3, 24.0 mmol) in dichloromethane (50 cm^3). Stirring was maintained at room temperature for 10 min and *N*-(phenylsulfonyl)-1*H*-pyrrole (2.48 cm^3, 12.0 mmol) in dichloromethane (10 cm^3) was added over 20 min and the reaction mixture was stirred for 4 days The reaction was quenched with ice-water (100 cm^3), the aqueous phase was extracted with further portions of dichloromethane. The combined organic extracts were washed with sodium hydroxide solution (0.1 M), water and dried (Na_2SO_4). Evaporation of solvent yielded 4-bromo-1-[1-(phenylsulfonyl)-1*H*-pyrrol-2-yl]butan-1-one **38** (2.25 g, 53%) as a white solid, mp 68–69 °C. (Found: M^+, 354.9884. $C_{14}H_{14}BrNO_3S$ requires 354.9878.) ν_{max} (thin film)/cm^{-1} 1676, 1364 and 1174; δ_H 2.07–2.18 (2H, m, 2-H), 2.88 (2H, t, *J* 7.0, 3-H), 3.37 (2H, t, *J* 6.4, 1-H), 6.35–6.37 (1H, m, pyrrole 4-H), 7.11–7.12 (1H, m, pyrrole 3-H), 7.50–7.54 (2H, m), 7.59–7.61 (1H, m), 7.81–7.83 (1H, m, pyrrole 5-H) and 7.97–8.00 (2H, m); δ_C 27.0 (2-C), 33.2 (3-C), 37.1 (1-C), 110.5 (pyrrole 4-C), 123.7 (pyrrole 5-C), 128.1 (CH), 128.7 (CH), 130.4 (pyrrole 3-C), 133.0 (pyrrole 2-C), 133.7 (CH), 138.8 (C) and 187.1 (4-C); *m*/*z* 355 (M^+, 4%), 234 (100), 185 (38), 141 (65), 94 (46) and 77 (100).

3.6.6. Cyclisation of 4-bromo-1-[1-(phenylsulfonyl)-1H-pyrrol-2-yl]butan-1-one **38**

Tributyltin hydride (0.59 cm^3, 2.2 mmol) and AIBN (0.36 g, 4.6 mmol) in toluene (50 cm^3) was added over 7 h to a solution of 4-bromo-1-[1-(phenylsulfonyl)-1*H*-pyrrol-2-yl]butan-1-one **38** (0.39 g, 1.1 mmol) in acetonitrile (250 cm^3) heated under reflux. The reaction mixture was heated under reflux for 9 h, cooled to room temperature and evaporated to dryness under reduced pressure. Purification using gradient elution column chromatography yielded 1-(phenylsulfonyl)-1,4,5,6-tetrahydro-indol-7-one (10% by ^{1}H NMR spectral correlation to reported data[49]) and 1-phenylsulfonyl-2-(tetrahydrofuran-2-yl)-1*H*-pyrrole **41** (0.210 g, 69%) as a colourless oil. (Found: M^+, 277.0768. $C_{14}H_{15}NO_3S$ requires 277.0773.) ν_{max} (thin film)/cm^{-1} 1368 and 1178; δ_H (400 MHz) 1.60–1.66 (1H, m, 4-H), 1.92–1.96 (2H, m, 3-H), 2.24–2.29 (1H, m, 4-H), 3.77–3.81 (1H, m, 5-H), 3.87–3.90 (1H, m, 5-H), 5.27–5.28 (1H, m, 2-H), 6.22–6.26 (2H, m, pyrrole 3,4-H), 7.26–7.28 (1H, m, pyrrole 5-H), 7.46–7.49 (2H, m), 7.55–7.57 (1H, m) and 7.80–7.82 (2H, m); δ_C 25.5 (3-C), 32.8 (4-C), 68.1 (5-C), 73.5 (2-C), 111.7 (pyrrole 4-C), 112.0 (pyrrole 5-C), 123.4 (pyrrole 3-C), 126.8 (CH), 129.2 (CH), 133.7 (CH), 137.0 (pyrrole 2-C) and 139.5 (C).

Cyclisation of 4-bromo-1-[1-(phenylsulfonyl)-1H-pyrrol-3-yl]butan-1-one ***42***. 1-Phenylsulfonyl-3-(tetrahydrofuran-2-yl)-1*H*-pyrrole **43** (0.193 g, 64%), colourless oil. (Found: M^+, 277.0775. $C_{14}H_{15}NO_3S$ requires 277.0773.) ν_{max} (thin film)/cm^{-1} 1370, 1175; δ_H (400 MHz) 1.73–1.76 (1H, m, 4-H), 1.88–1.93 (2H, m, 3-H), 2.11–2.14 (1H, m, 4-H), 3.74–3.80 (1H, m, 5-H), 3.89–3.94 (1H, m, 5-H), 4.72–4.74 (1H, m, 2-H), 6.25–6.26 (1H, m, pyrrole 4-H), 7.11–7.13 (2H, m, pyrrole 2,5-H), 7.41–7.45 (2H, m), 7.51–7.54 (1H, m) and 7.82–7.84 (2H, m); δ_C 25.8 (3-C), 32.9 (4-C), 68.0 (5-C), 74.7 (2-C), 112.4 (pyrrole 4-C), 117.3 (pyrrole 5-C), 121.3 (pyrrole 2-C), 126.4 (CH), 129.4 (CH), 131.4 (pyrrole 3-C), 133.9 (CH) and 138.9 (C); *m*/*z* 277 (M^+, 33%), 276 (26), 234 (22), 141 (37), 136 (57), 94 (42) and 77 (100).

3.6.7. Cyclisation of ethyl 1-(4-bromobutyl)-1H-pyrrole-2-carboxylate ***44a***

The general procedure for radical cyclisations with cyclohexane as solvent was used with 6 h reaction time. AMBN was added independently every hour. Purification by column chromatography using light petroleum and DCM as eluents gave ethyl 5,6,7,8-tetrahydroindolizine-3-carboxylate **45a** as a clear, colourless liquid (61%). (Found: M^+, 193.1104. $C_{11}H_{15}NO_2$ requires 193.1102.) ν_{max} (neat)/cm^{-1} 3374, 2940, 1701, 1541, 1489, 1444, 1428, 1401, 1368, 1347, 1304, 1230, 1187, 1142, 1092, 1068, 1042, 996, 922, 872 and 751; δ_H 1.31 (3H, t, *J* 4.3, Me), 1.76–1.83 (2H, m, 7-H), 1.90–1.99 (2H, m, 6-H), 2.80 (2H, t, *J* 6.3, 8-H), 4.25 (2H, q, *J* 4.3, OCH_2), 4.32 (2H, t, *J* 6.1, 5-H), 5.86 (1H, d, *J* 4.0, 1-H) and 6.92 (1H, d, *J* 4.0, 2-H); δ_C (62.5 MHz) 14.6 (Me), 20.1 (7-C), 23.0 (6-C), 24.2 (8-C), 45.6 (5-C), 59.4 (OCH_2), 106.0 (1-C), 117.5 (2-C), 128.8 (3-C), 137.0 (8a-C) and 161.3 (C=O); *m*/*z* 194 (M+1, 11%), 193 (M^+, 73%), 192 (9), 165 (17), 164 (45), 148 (54), 121 (54), 120 (100), 118 (19), 106 (16), 91 (20), 82 (14), 65 (16), 55 (14) and 49 (17).

A repeat reaction for 3 h afforded ethyl 5,6,7,8-tetrahydro-3-indolizinecarboxylate **45a** as a clear liquid (37%), ethyl 1-butyl-1*H*-pyrrole-2-carboxylate **46a** as an orange liquid (13%) and unaltered ethyl 1-(4-bromobutyl)-1*H*-pyrrole-2-carboxylate **44a** (51%). The TLC, ^{1}H NMR and IR spectra were identical to those of the authentic materials.

Ethyl 1-(4-bromobutyl)-1*H*-pyrrole-2-carboxylate **44a** (0.20 g, 0.73 mmol), sodium cyanoborohydride (68.76 mg, 1.09 mmol) and tri-*n*-butyltin chloride (24 mg, 0.1 equiv) were dissolved in *tert*-butanol (100 cm^3) and stirred under reflux for 3 h. AIBN was added independently every hour. After cooling to room temperature and evaporating to dryness, the crude yellow oil was subjected to flash column chromatography using light petroleum and DCM as eluents to yield ethyl 5,6,7,8-tetrahydro-3-indolizinecarboxylate **45a** (57 mg, 40%) and ethyl 1-butyl-1*H*-pyrrole-2-carboxylate **46b** (32 mg, 23%).

Cyclisation of 1-(4-bromobutyl)pyrrole-2-carboxaldehyde ***44b***. The same procedure was used to yield 5,6,7,8-tetrahydro-3-indolizinecarbaldehyde **45b** (91%). The reaction was repeated using EtOH in place of *tert*-butanol and gave 5,6,7,8-tetrahydro-3-indolizinecarbaldehyde **45b** (40%) and 1-butylpyrrole-2-carboxaldehyde **46b** (60%).

3.6.8. Cyclisation of phenyl 3-(1H-pyrrol-1-yl)propaneselenoate ***47***[15]

The standard procedure for acyl radical cyclisations under an atmosphere of CO yielded 2,3-dihydro-1*H*-pyrrolizidin-1-one **49** (23%) as a clear semi-solid. (Found: M^+, 121.0529. C_7H_7NO requires 121.0528.) ν_{max} (thin film)/cm^{-1} 1697; δ_H 3.09 (2H, t, *J* 6.2, 2-H), 4.34 (2H, t, *J* 6.2, 3-H), 6.51–6.54 (1H, m, 6-H), 6.73–6.75 (1H, m, 7-H) and 7.04–7.07 (1H, m, 5-H); δ_C 39.4 (2-C), 42.1 (3-C), 107.6 (6-C), 117.0 (7-C), 122.8 (5-C) and 130.3 (7a-C); *m*/*z* 121 (M^+, 81%) and 93 (100).

3.6.9. Cyclisation of 2-methyl-1-[4-(phenylselenyl)butyl]-1H-imidazole ***50***

The standard procedure for azole radical cyclisation using Bu_3SnH (added by syringe pump over 3 h) and AMBN in refluxing cyclohexane gave 1-butyl-2-methyl-1*H*-imidazole **52** as a yellow oil (32%) (characterised by comparison with independently synthesised material) and 3-methyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine **51** as a pungent smelling yellow oil (35%). (Found: M^+, 136.1000. $C_8H_{12}N_2$ requires 136.1000.) ν_{max} (neat)/cm^{-1} 3052, 2953, 1419, 1388, 1265, 736 and 703; δ_H 1.73–1.78 (2H, m, 6-H), 1.80–1.83 (2H, m, 7-H), 2.34 (3H, s, Me), 2.74 (2H, t, *J* 6.3, 8-H), 3.79 (2H, t, *J* 6.1, 5-H) and 6.64 (1H, s, 1-H); δ_C 12.6 (Me), 20.3 (6-C), 21.2 (7-C), 23.2 (8-C), 42.6 (5-C), 121.7 (1-C), 127.6 (8a-C) and 142.7 (3-C); *m*/*z* 137 (M+1, 56%), 136 (M^+, 81%), 135 (100), 121 (14), 108 (25), 95 (21), 94 (14), 91 (34), 81 (12), 67 (17), 56 (19), 55 (21), 41 (17) and 40 (11).

3.7. Mechanistic investigations

3.7.1. Dimethyl 2,2′-hydrazinobisisobutyrate (***59***, *R*=Me, *Z*=CO_2Et)

Hydrazine hydrate (0.26 g, 4.4 mmol) in ethanol (10 cm^3) was added to a stirred solution of dimethyl 2,2′-azobisisobutyrate (**57**,

R=Me, Z=CO_2Et) (0.25 g, 1.1 mmol) in ethanol (20 cm^3) and the reaction was stirred in air for 24 h at room temperature [Cu(I)I accelerates reaction rate, addition of catalytic quantities gives complete reaction in minutes]. The white precipitate was removed and the reaction mixture evaporated to dryness. The resulting colourless oil was partitioned between ethyl acetate and hydrochloric acid (2 M), the organic layer was separated and the aqueous layer extracted again with ethyl acetate. The aqueous layer was basified to pH 9 with aqueous sodium hydroxide (2 M) and extracted with ethyl acetate. The combined organic layers were dried and evaporated to dryness to yield dimethyl 2,2′-hydrazinobisisobutyrate (**59**, R=Me, Z=CO_2Et) (0.119 g, 47%) as a pale yellow oil. (Found: M^+, 232.1423. $C_{10}H_{20}N_2O_4$ requires 232.1423.) ν_{max} (thin film)/cm^{-1} 3435 and 1728; δ_H (400 MHz) 1.24 (12H, s, Me) and 3.71 (6H, s, CO_2Me); δ_C 23.9 (Me), 51.9 ($CO_2\mathit{Me}$), 61.3 ($\mathit{C}Me_2CO_2Me$) and 177.6 ($\mathit{C}O_2Me$); *m*/*z* 232 (M^+, 17%), 113 (65) and 102 (100).

3.7.2. *Radical cyclisation of 1-(4-bromobutyl)-2-methyl-1H-imidazole-4-carboxaldehyde* ***53***

3-Methyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine-1-carbaldehyde ***56***. A solution of Bu_3SnH (1.19 cm^3, 4.49 mmol) was added dropwise via a syringe pump over 6 h to a solution of 1-(4-bromobutyl)-2-methyl-1*H*-imidazole-4-carboxaldehyde **53** (0.54 g, 2.04 mmol) and excess AMBN in refluxing acetonitrile (500 cm^3) under an atmosphere of nitrogen. AMBN was added independently every 30 min. After cooling to room temperature, the solvent was evaporated under reduced pressure, aqueous HCl (1 M) added and washed with light petroleum. The aqueous layer was neutralised, basified to pH 14 and extracted into DCM. ^1H NMR spectral analysis using an internal standard indicated a quantitative yield. Column chromatography using neutral alumina and ethyl acetate and methanol as eluents gave 3-methyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine-1-carbaldehyde **56** as a yellow solid (0.29 g, 82%), mp 110–114 °C. (Found: M^+, 164.0951. $C_9H_{12}N_2O$ requires 164.0949.) ν_{max} (DCM)/cm^{-1} 1670 and 1265; δ_H 1.80–1.89 (2H, m, 7-H), 1.97–2.07 (2H, m, 6-H), 2.95 (3H, s, Me), 3.09 (2H, t, *J* 6.4, 8-H), 3.84 (2H, t, *J* 6.0, 5-H) and 9.85 (1H, s, CHO); δ_C 13.2 (Me), 19.4 (7-C), 22.52 (6-C), 22.9 (8-C), 43.1 (5-C), 135.5 (3-C), 137.6 (8a-C), 145.1 (1-C) and 186.8 (CHO); *m*/*z* 164 (M^+, 100%), 163 (94), 152 (21), 135 (20), 123 (13), 109 (11) and 97 (26).

Repeat reactions using differing conditions. The reactions were carried out using the above conditions with Bu_3SnH and AMBN in refluxing acetonitrile. The time of reaction, amounts of Bu_3SnH and AMBN and yields are indicated in Table 3. The yields refer to isolated pure material. The Bu_3SnH was added as a solution in acetonitrile (50 cm^3) except where otherwise indicated.

Cyclisation using hexamethylditin. 1-(4-Bromobutyl)-2-methyl-1*H*-imidazole-4-carboxaldehyde **53** (0.20 g, 0.82 mmol) and hexamethylditin (0.32 g, 0.82 mmol) were dissolved in propanonitrile (5 cm^3) and heated under reflux for varying times under irradiation from two sunlamps and a halogen lamp. After cooling to room temperature and removing the solvent by flash column chromatography using neutral alumina and light petroleum as eluent, ^1H NMR spectroscopic analysis with an internal standard showed the sole imidazole product in each case to be 3-methyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyridine-1-carbaldehyde **56**. Large amounts of decomposed and polymeric material were also observed.

3.8. X-ray crystallography

For all three samples, light petroleum in a sealed flask was allowed to diffuse into a solution of the sample in DCM at room temperature. After 6 days, the small crystals that had formed were used for X-crystallographic analysis. Data were collected at 150(2) K on a Bruker SMART 1000 diffractometer.[50] The structures were solved by direct methods and refined by full-matrix least-squares on F^2 using the SHELXTL suite of programs.[51] All the non-hydrogen atoms were refined with anisotropic atomic displacement parameters and hydrogen atoms were inserted at calculated positions using a riding model. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 668021–668023. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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Supplementary data

Supplementary data includes syntheses of compounds in which the general method and a representative example has been included in the paper. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.06.014.

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