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Amides as precursors of imidoyl radicals in cyclisation reactions

W. Russell Bowman,[a,*] Anthony J. Fletcher,[a] Jan M. Pedersen,[a] Peter J. Lovell,[b] Mark R. J. Elsegood,[a] Elena Hernández López,[a] Vickie McKee[a] and Graeme B. S. Potts[a]

[a]*Department of Chemistry, Loughborough University, Loughborough, Leicestershire LE11 3TU, United Kingdom*
[b]*Psychiatry Medicinal Chemistry II, GlaxoSmithKline, New Frontier Science Park North, Harlow, Essex CM19 5AW, United Kingdom*

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Abstract—Amides have been successfully used as precursors of imidoyl radicals for radical cyclisation. The amides have been converted to imidoyl selanides via reaction with phosgene to yield imidoyl chlorides followed by reaction with potassium phenylselanide. Imidoyl selanides were reacted with tributyltin hydride (Bu_3SnH) as the radical mediator with triethylborane or AIBN as initiators to yield imidoyl radicals for cyclisation reactions. Imidoyl radicals have been cyclised onto alkenes to yield 2,3-substituted-indoles and -quinolines and also onto pyrroles and indoles to give bi- and tricyclic heteroarenes.

1. Introduction

Carboxamides have not been widely used as precursors of *C*-centred free radicals in contrast to many other functional groups. Amides are attractive precursors of synthetic protocols because a wide range of diversity can easily be incorporated by the coupling of carboxylic acids and amines. The aim of our study was to develop the use of amides as precursors for the generation of imidoyl radicals, i.e., *C*-centred radicals with an α-*N*-atom. The potential of the synthetic use of imidoyl radicals was envisaged by cyclisation onto unsaturated bonds to yield nitrogen heterocycles. We report our results in which secondary amides have been converted to imidoyl phenyl selanides (*N*-substituted-selenoacylimidic acid phenyl esters) as imidoyl radical precursors and the use of these radicals in cyclisation reactions. Preliminary studies of cyclisation onto alkenes to yield 2,3-disubstituted indoles[1] and cyclisation onto alkynes in domino reactions to yield aryl-annulated[*b*]carbazoles[2] including the anticancer alkaloid ellipticine have been reported.

Carboxamides have been used as precursors of *C*-centred radicals via conversion to thioamides and use of the thioamides in radical reactions.[3,4] The carboxamides are converted using Lawesson's reagent into thioamides. The thioamides act as 'pseudo' imidoyl radicals by a mechanism, which is not fully established but involves addition of radicals onto the *S*-atom of the thioamides to yield intermediate *C*-centred radicals, which undergo cyclisation onto alkenes[3] and alkynes.[4] Cinnamamides have also been used as precursors in synthetic studies by the addition of tributyltin radicals to the amide oxygen atom.[5] Other methodologies have also been used for generating intermediate imidoyl radicals; the main protocol involves addition of radicals to isonitriles.[6,7]

2. Discussion

2.1. Synthesis of radical precursors from carboxamides

The use of xanthates as precursors for radicals has been developed by Zard and proved very useful.[8] An obvious new precursor for our studies was imidoyl thioxanthates. We proposed to add the potassium xanthate to intermediate imidoyl chlorides as shown in Scheme 1. Use of oxalyl chloride gave cyclic 1,4-oxazolin-2,3-dione products.[9] Therefore, the amides were converted into the respective α-chloro-imines using phosgene.[10] Phosgene is toxic but was purchased as sealed made-up solutions in toluene and could thus be safely used. However, reactions between the imidoyl chlorides and xanthate did not yield the expected imidoyl xanthates **2** (Scheme 1). Instead, thioacyl-thiocarbamic acid *O*-ethyl esters **3** were obtained in good yields via a rearrangement of the intermediate addition compounds (Scheme 1). The structures were determined with the help of X-ray crystallography (Fig. 1). A sub-structure search of databases indicated that this rearrangement was first observed over a hundred years ago.[11] Unfortunately, this interesting rearrangement precludes the use of imidoyl xanthates as radical precursors. We then planned to synthesise imidoyl phenylselanides in which rearrangement would not be possible.

Keywords: Imidoyl radicals; Radical cyclisation; Imidoyl selanides; Indoles; Quinolines.
* Corresponding author. Tel.: +44 1509 222569; fax: +44 1509 223925; e-mail: w.r.bowman@lboro.ac.uk

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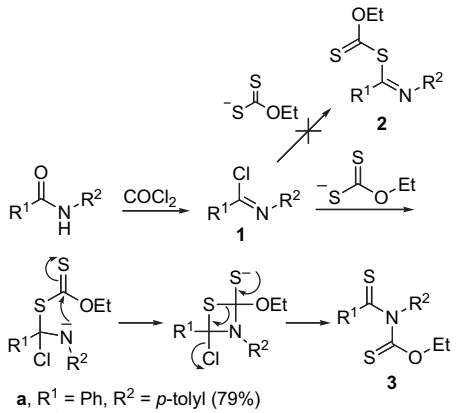


Scheme 1. Formation of thioacyl-thiocarbamic acid *O*-ethyl esters **3**.

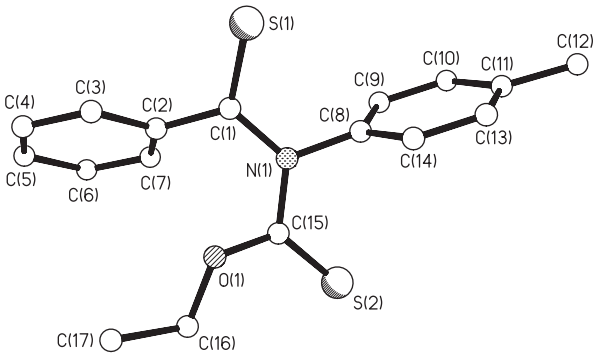
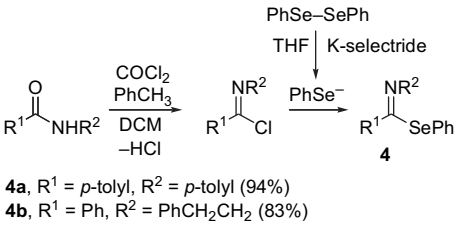


Figure 1. X-ray crystal structure of thiobenzoyl-(*p*-tolyl)thiocarbamic acid *O*-ethyl ester **3a** with H atoms omitted for clarity.

Imidoyl selanides (e.g., **4**, Scheme 2) have been reported to act as precursors for imidoyl radicals[12–14] and we considered these precursors would be suitable for developing our synthetic protocols. However, the imidoyl selanides would require reductive radical procedures unlike that of the imidoyl xanthates, which would potentially be more efficient proceeding by group transfer and preventing termination reactions.[8] Radical reagents such as tributyltin hydride (via $Bu_3Sn^{\bullet}$) are well known to be able to abstract the phenylselanide group in S_H2 reactions and in these precursors would yield the required imidoyl radicals.



Scheme 2. Synthesis of imidoyl selanides via imidoyl chlorides.

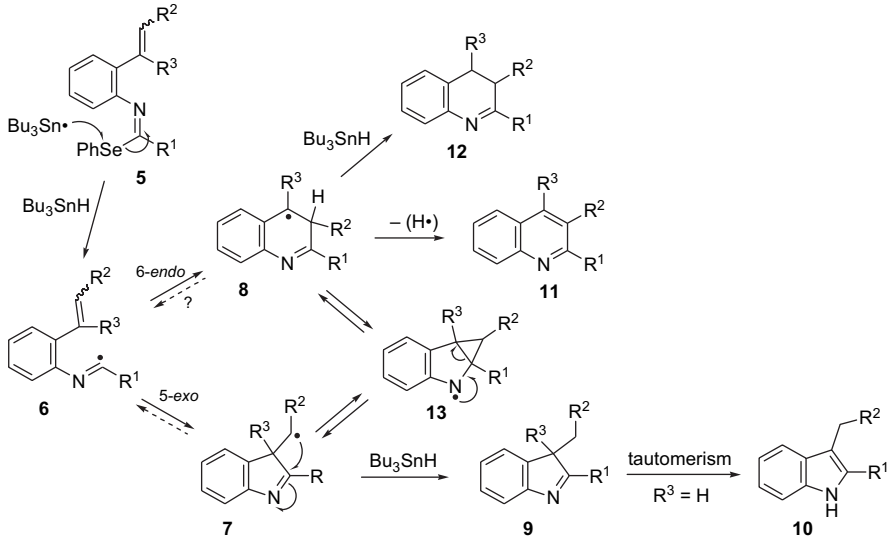
A variety of methods[12–14] have been used to introduce the phenylselanide group but had varied yields and we wished a facile reliable method. A number of test compounds were investigated in order to optimise the conditions for the synthesis of both imidoyl phenylselanides (Scheme 2). The amides were converted into the respective α-chloroimines using phosgene. Initial studies of simple amides showed that the imidoyl chlorides were quantitatively formed and from thereon were used without purification. In order to ensure a clean solution of phenylselanide and to avoid use of foul smelling phenylselanol, diphenyl diselanide was reduced in situ with K-Selectride® to potassium phenylselanide and added directly to the imidoyl chloride. The imidoyl selanides **4a**,**b** were formed in approximately quantitative yields but lower yields of pure isolated precursors were obtained after the required purification. Even with rapid chromatography to remove unreacted diphenyl diselanide, some hydrolysis took place on both silica and alumina columns. The corresponding imidoyl sulfides (**4a**,**b** with Se=S) were also synthesised in high yield using sodium phenylthiolate, freshly prepared from phenylthiol and sodium methoxide. However, the imidoyl sulfides were found to be essentially unreactive under normal Bu_3SnH conditions and were not further investigated.

2.2. Synthesis of 2,3-disubstituted-indoles and -quinolines

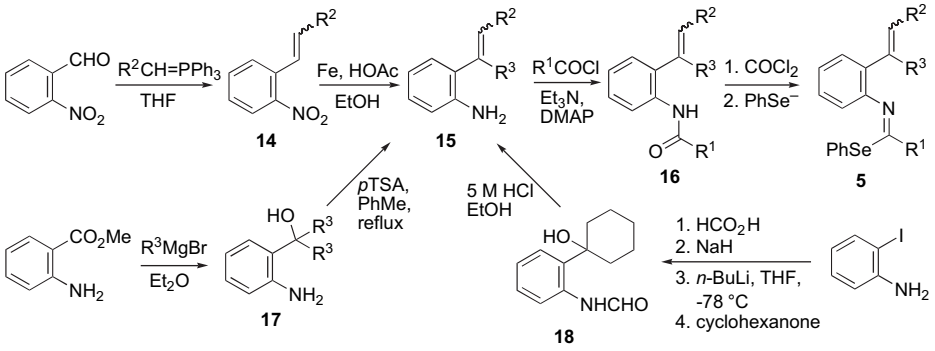
In order to assess the usefulness of our protocol using imidoyl radicals generated from imidoyl selanides, we investigated cyclisation onto alkenes to yield 2,3-disubstituted-indoles and -quinolines, cyclisation onto alkynes (reported elsewhere[2]) and cyclisation onto arenes and heteroarenes. Indoles have been previously synthesised using imidoyl radicals by the bimolecular addition of radicals onto isonitriles, which yield imidoyl radicals.[15] Thioamides react with Bu_3SnH to yield intermediate radicals, which are considered to act as 'imidoyl equivalents' and have been successfully used for the synthesis of indoles.[4] The synthesis of indoles and/or quinolines provided a good initial model for testing our protocol.

Suitable imidoyl selanide precursors **5** can be envisaged to undergo cyclisation by 5-*exo* (to indoles) or 6-*endo* (to quinolines) regioselectivity as shown in Scheme 3. The competition between 5-*exo* and 6-*endo* cyclisation is likely to depend on the nature of the substituents. Rearrangements via 3-*exo* cyclisation onto imines are known[16] and present a possible reaction route as shown in Scheme 3, i.e., 5-*exo* to **7** followed by rearrangement to the 6-*endo* intermediate **8** via **13**. In order to fully investigate the parameters of these potential cyclisations, we synthesised a wide range of radical precursors.

The syntheses of the imidoyl radical precursors **5** were carried out by standard procedures as shown in Scheme 4. The yields of amides and imidoyl selanides are shown in Table 1. Use of initial Wittig reactions with 2-nitroacetophenone for the synthesis of the amides **16j–16l** proved low yielding and were abandoned in favour of the use of Grignard reactions with methyl anthranilate as shown in Scheme 4. The cyclohexenyl analogue **16m** was synthesised by a procedure based on literature protocols.[17] The yields of most reactions were not optimised. Most of the alkenes were mixtures of *E*- and *Z*-isomers and were carried through as mixtures. This was not a problem because the alkene stereochemistry is lost on cyclisation.



Scheme 3. Cyclisation of imidoyl radicals by 5-*exo* versus 6-*endo* regioselectivity.

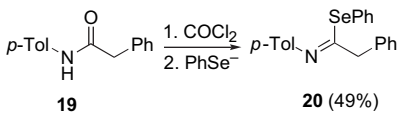


Scheme 4. Synthesis of imidoyl selanides for cyclisation to indoles and quinolines.

The imidoyl selanides were prepared from the respective amides by our procedure in moderate to good yields. When R^2 was benzyl (**16c**,**f** to **5c**,**f**) some difficulties were experienced, which suggested that tautomerism to the respective ketimines followed by hydrolysis upon column chromatographic purification. The isolation of starting amides **16c**,**f** in respective reactions provided evidence for this hydrolysis. In order to study this problem, we investigated the conditions for the synthesis of a simpler imidoyl selanide **20** from the benzyl amide **19** (Scheme 5). We observed that not only was hydrolysis more rapid than the other analogues but that imidoyl chloride formation did not proceed to completion. However, with careful optimisation yield of 49% could be obtained. The yields of the imidoyl selanides **5j**–**5m** were also generally low. The isolation of quinoline **11m** in 55% yield during the one-pot imidoyl chloride and imidoyl selanide syntheses indicates that the low yields are possibly due to the formation of quinolines **11** via attack of the electron-rich alkenes onto the imidoyl chlorides. This side reaction was not observed in the other imidoyl selanide syntheses. These imidoyl selanides were stable and once formed did not convert to the respective quinolines. Optimisation of these reactions was not undertaken.

Table 1. Synthesis of imidoyl selanide precursors

16, **5**	R^1	R^2	R^3	**16** (% yield)	**5** (% yield)
a	*p*-tolyl	CO_2Et	H	42	64
b	*p*-Cl-C_6H_4	CO_2Et	H	25	67
c	Bn	CO_2Et	H	56	23
d	Me	CO_2Et	H	68	50
e	*p*-tolyl	Pr	H	89	52
f	Bn	Pr	H	66	27
g	Me	Pr	H	72	43
h	*p*-tolyl	Ph	H	64	41
i	Me	Ph	H	71	68
j	Me	H	Me	72	26
k	*p*-tolyl	H	Me	67	42
l	*p*-tolyl	Me	Et	55	10
m	Me		$(CH_2)_4$	75	27



Scheme 5. Study of imidoyl selanide formation with benzyl groups.

The stereochemical configuration of the imidoyl selanides could be crucial in the cyclisation reactions because the *E*-configuration of the imidoyl radical **6** is required for cyclisation to take place. Vinyl radicals are well known to equilibrate rapidly between cis and trans isomers, with an interconversion barrier of less than 5 kcal/mol. Therefore,

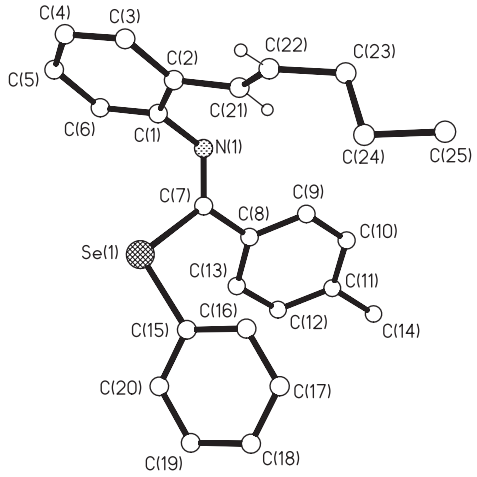


Figure 2. X-ray crystal structure of *Z*-4-methyl-*N*-[(2-pent-1-enyl)phenyl]-selenobenzimidic acid phenyl ester **5e** with most H atoms and the minor disorder component omitted for clarity.

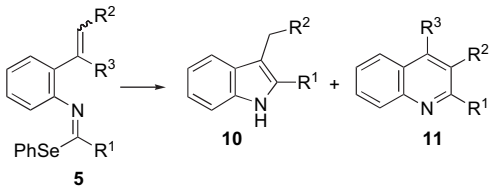
equilibration to the required conformation for cyclisation can be assumed to take place. However, little has been reported on the conformational stability of imidoyl radicals. Calculations based on the unsubstituted imidoyl radical •CH=NH indicate that the *E*-configuration is preferred by ca. 2.5 kcal/mol and that the barrier of interconversion is approximately 10 kcal/mol.[18] Based on steric grounds it would be expected that the same preference is observed for our substituted imidoyl radicals **6**. To clarify whether the imidoyl selanides are in an *E*- or *Z*-configuration with respect to the C=N bond, a crystal structure of selanide **5e** was obtained (Fig. 2). As shown, the imidoyl selanide prefers the *Z*-configuration. This means that on formation of the imidoyl radicals **6** (Scheme 3), no rotation around the C=N bond is necessary. A second crystal structure of an imidoyl selanide also showed the *Z*-configuration.[2] This configuration is perhaps surprising because prediction would suggest that the bulky phenylselanide group to be trans to the *N*-aryl group. However, the steric bulk close to the imine bond is considerably reduced because of the length of the C–Se bond (1.947(2) Å) as compared to the corresponding C–C bond between the imine carbon and toluoyl group (1.482(3) Å). Another explanation could be an electronic effect, where the selenium electron lone pairs repel the lone pair on the imine nitrogen, thereby increasing the energy of the *E*-configuration.

2.3. Cyclisations

The imidoyl selanides **5a**–**5m** were reacted under standard radical conditions using Bu_3SnH with AIBN as the initiator, and the results are summarised in Table 2.

The cyclisation of the α,β-unsaturated esters **5a**–**5d** proceeded in very high yield to the respective indoles **10a**–**10d**. The nucleophilic imidoyl radical undergoes rapid 5-*exo* cyclisation onto the electron deficient β-position of the α,β-unsaturated ester. The cyclised radical is strongly electrophilic and is rapidly trapped by the nucleophilic Bu_3SnH. Although initially we kept the [Bu_3SnH] very low, subsequent studies showed that the cyclisations are rapid and syringe pump addition of the Bu_3SnH was unnecessary.

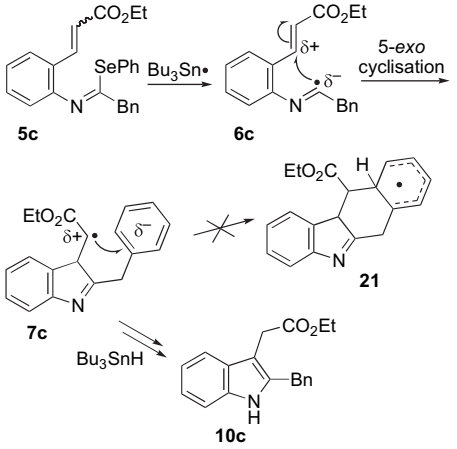
Table 2. Synthesis of indoles and quinolines by radical cyclisation of imidoyl selanides



Imidoyl selanide	Indole, yield (%)	Quinoline, yield (%)	Conditions[a]	R^1	R^2	R^3
5a	**10a**, 95	**11a**, 0	[b]	*p*-tolyl	CO_2Et	H
5b	**10b**, 92	**11b**, 0	[b]	*p*-Cl-C_6H_4	CO_2Et	H
5c	**10c**, 98	**11c**, 0	[b]	Bn	CO_2Et	H
5d	**10d**, 98	**11d**, 0	[b]	Me	CO_2Et	H
5e	**10e**, 10	**11e**, 39[c]	[b]	*p*-tolyl	Pr	H
5f	**10f**, 15	**11f**, 22	[b]	Bn	Pr	H
5g	**10g**, 9	**11g**, 35	[b]	Me	Pr	H
5e	**10e**, 66	**11e**, 0	[d]	*p*-tolyl	Pr	H
5f	**10f**, 52	**11f**, 0	[d]	Bn	Pr	H
5g	**10g**, 73	**11g**, 0	[d]	Me	Pr	H
5g	**10g**, 81	**11g**, 0	[e]	Me	Pr	H
5h	**10h**, 70	**11h**, 0	[d]	*p*-tolyl	Ph	H
5i	**10i**, 80	**11i**, 0	[d]	Me	Ph	H
5j	**10j**, 0[f]	**11j**, 80	[g]	Me	H	Me
5k	**10k**, 0[f]	**11k**, 73	[g]	*p*-tolyl	H	Me
5l	**10l**, 0[f]	**11l**, 76	[g]	*p*-tolyl	Me	Et
5m	**10m**, 0	**11m**, 10	[g]	Me		$(CH_2)_4$

[a] Reactions were carried out in toluene under reflux and a nitrogen atmosphere with [imidoyl selanide]=10 mM.
[b] Syringe pump addition of Bu_3SnH (2.2 equiv) and portion wise addition of AIBN (1.0 equiv) over 6 h.
[c] Quinoline **11** (R^1=*p*-Tol, R^2=R^3=H) (6%) isolated.
[d] Bu_3SnH (2.2 equiv) and AIBN (0.1 equiv) were added at the beginning of the reaction.
[e] Et_3B (0.15 equiv) and room temperature instead of AIBN and reflux.
[f] No spiro-3*H*-indoles observed.
[g] Bu_3SnH (2.2 equiv) was added at the beginning of the reaction and Et_3B (3.0 equiv) was added at 0, 16 and 32 h. The reaction time was 48 h at room temperature with an oxygen bleed.

We had hoped that the intermediate electrophilic radical **7c** would cyclise onto the benzene ring but no traces of a tandem product was observed (Scheme 6). In contrast, studies of cyclisation of the analogous alkyne (alkyne bond in place of the alkene bond) gave high yields of the tandem cyclisation via the more reactive vinyl radicals.[2]

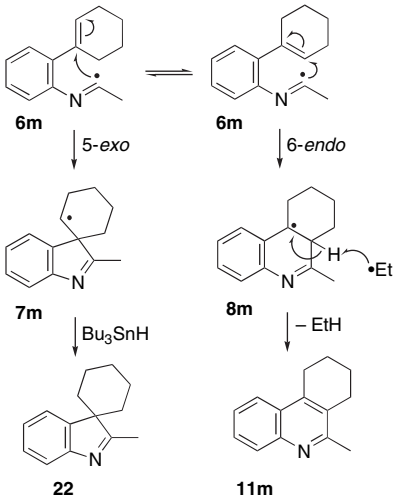


Scheme 6. Cyclisation of imidoyl selanide **5c** to indole **10c**.

Cyclisations of the propyl alkenes **5e**–**5g** gave unexpected results. When slow addition of Bu_3SnH was carried out, quinoline products were also obtained. For instance, in the cyclisation of selanide **5e**, the quinoline formation indicates that either 6-*endo* cyclisation (**6e** to **8e**) or rearrangement (**7e** via **13e** to **8e**) (Scheme 3) takes place. The radical formed on initial 5-*exo* cyclisation **7e** is now nucleophilic and the rate of H-abstraction from the nucleophilic Bu_3SnH is much slower. The slow rearrangement via 3-*exo* cyclisation onto the electrophilic α-C of the imine (**7e** to **13e**) becomes competitive and neophyl rearrangement to the 6-*endo* radical (**8e**) takes place. This stabilised π-radical, which is similar to the intermediates found in aromatic homolytic substitution, undergoes loss of hydrogen to yield quinoline **11e**. To our knowledge, this is only the second example of π-radical formation and subsequent aromatisation not generated by aromatic electrophilic substitution.[19] This hydrogen is abstracted by the AIBN initiator or breakdown products there from. This mechanism has been widely observed and studied in aromatic homolytic substitutions facilitated by Bu_3SnH and AIBN.[20] More surprising is the loss of a propyl radical (or propene) in the aromatisation to yield the quinoline **11** (R^1=*p*-Tol, R^2=R^3=H). Loss of *iso*-propyl radicals (or *iso*-propene) has been reported in rearomatisation.[3] If rearrangement was taking place, the intermediate 5-*exo* cyclised radical should be trapped by higher concentrations of Bu_3SnH because the rate of 3-*exo* cyclisation is slow and unaffected by [Bu_3SnH] (Table 2). This proved to be the case when the [Bu_3SnH] was increased by not using a syringe pump and adding the Bu_3SnH in one portion at the beginning of the reaction. These results strongly suggest that 6-*endo* cyclisation is not taking place.

Cyclisation of precursors **5h** and **5i** proceeded as expected to give good yields of the respective 2,3-disubstituted indoles **10h** and **10i**, respectively, with no traces of quinoline products. The intermediates after 5-*exo* cyclisation (**7h** and **7i**) would be stabilised benzylic radicals and not expected to undergo neophyl rearrangement.

All three of the alkenes (R^2=CO_2Et, *n*-Pr and Ph; R^3=H) gave 5-*exo* cyclisation. We set out to determine the effect of a substituent on the other end of the alkene, i.e., R^3. A shift from 5-*exo* towards 6-*endo* was expected.[21] The imidoyl selanides **5j**–**5l** were reacted with Bu_3SnH using triethylborane (Et_3B) initiation at room temperature. In order to obtain good yields of quaternary 3*H*-indoles, the reactions were carried out using high [Bu_3SnH] to avoid neophyl rearrangements. However, to our surprise the alkene cyclisations resulted in complete 6-*endo* regioselectivity to the quinolines **11j**–**11l**, respectively, in high yields. No 3*H*-indole products could be detected in the crude reaction mixtures by ^{1}H NMR spectroscopic analysis. These oxidative cyclisations were also very slow at room temperature and a 48 h reaction time was required for the starting materials to be consumed. The 6-*endo* cyclisations are non-chain reactions and the addition of 5–10 equiv of Et_3B during the reaction was a necessity. The large amount of initiator required indicates a non-chain mechanism and participation of the initiator in the aromatisation of the products. We suggest that the ethyl radicals generated from Et_3B are responsible for generating $Bu_3Sn^{\bullet}$ radicals by H-abstraction from Bu_3SnH as well as H-abstraction from the π-radical intermediate[2] (see Scheme 7). The imidoyl selanide starting materials **5j**–**5m** were stable to reaction conditions in the absence of Et_3B indicating that the formation of quinolines is a radical reaction and not a thermal cyclisation. This complete shift from 5-*exo* to 6-*endo* cyclisation is unprecedented to our knowledge. For instance, Beckwith et al.[21] have shown that in the cyclisation of 5-hexen-1-radicals the 5-*exo*/6-*endo* ratio=43. When a 5-methyl group is introduced the ratio changes to 0.46 indicating that substituents in the '5-*exo*' position push the cyclisation towards 6-*endo* but not regioselectively.



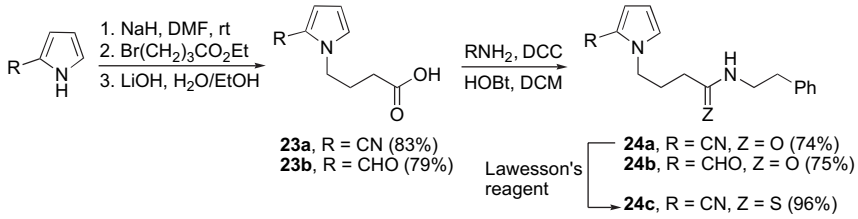
Scheme 7. Cyclisation of cyclohexenyl imidoyl selanide **5m**.

The reaction of the selanide **5m** which involves cyclisation onto a cyclohexene moiety resulted in a complex mixture of products (Scheme 7). The quinoline **11m** was known as it was a by-product in the previous step to make the imidoyl selanide. It was therefore recognisable during ^{1}H NMR spectroscopic analysis of the crude reaction mixture, and the yield was estimated to be approximately 10%. Column chromatography resulted in a 1:2 mixture of quinoline **11m** and another product, which had a ^{1}H NMR spectrum compatible with the spiro-3*H*-indole **22**. Unfortunately, further column chromatography resulted in the breakdown of this compound to other products, and thus, it was not isolated and fully characterised.

2.4. Cyclisation onto arenes and heteroarenes

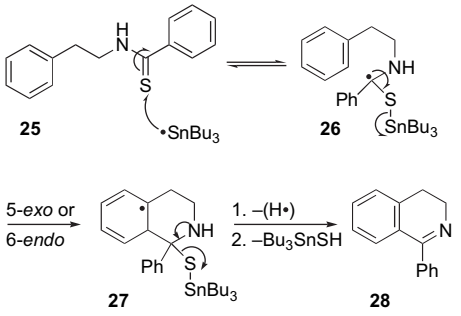
Finally we also wished to determine if imidoyl radicals could cyclise onto heteroarene rings. We first considered thioamides, which have been successfully used to cyclise onto alkenes and alkynes as 'pseudo imidoyl' radicals and suggested a useful method of cyclisation in our studies.[3,4,22] A suitable pyrrole precursor **24c** was synthesised by standard procedures as shown in Scheme 8. Attempts to convert the pyrrole-2-carbaldehyde **24b** to the corresponding thioamide failed and gave an intractable mixture. A suitable precursor **25** for cyclisation onto an arene was also prepared.

The attempted cyclisations using the thioamide **24c** and **25** failed completely and only unaltered starting materials were obtained in both reactions (Scheme 9). Bu_3SnH, TTMSS and Bu_3GeH all failed to give any results. As shown in Scheme 9, we suggest that although the triorganometal radicals add



Scheme 8. Synthesis of pyrrole precursors.

onto the thioamides, the resulting radicals are not reactive enough to attack the benzene or pyrrole ring, nor does this radical intermediate breakdown to give and imidoyl radical as has been suggested in the literature.[22] For example, radical **26** could be predicted to undergo 5-*exo* cyclisation followed by neophyl rearrangement (or 6-*endo* cyclisation) to yield a π-radical **27**. Aromatisation[20] and elimination to the imine would yield the dihydroquinoline **28**. The pyrrole precursor **24c** was also well set up for 6-*exo* cyclisation, which has been most successful for the cyclisation of other radicals onto pyrrole rings.[20,22–24] This supports reported observations that thioamides do not cyclise onto arenes.[25]

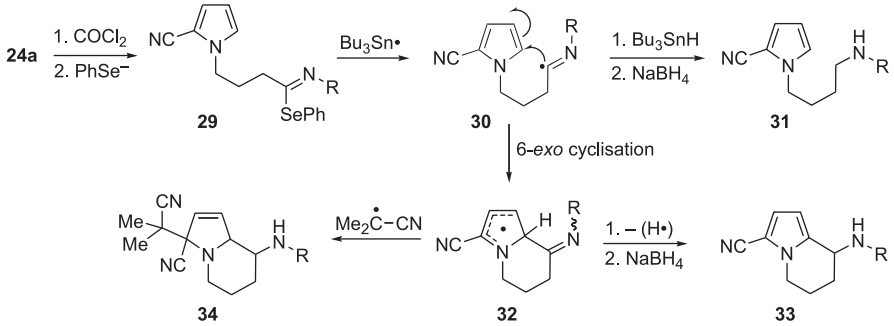


Scheme 9. Attempted cyclisation of thioamides.

With the failure of thioamides, we studied the use of imidoyl selanides as radical precursors of imidoyl radicals for cyclisations onto arenes and heteroarenes. As an initial test reaction, the imidoyl selanide **4b** (Scheme 2) derived from *N*-phenethylbenzamide was prepared and subjected to standard radical conditions using Bu_3SnH. An excess of AIBN was used to promote aromatisation at the end of any possible cyclisation. All of the starting material **4b** was consumed and no identifiable products were isolated from the crude reaction mixture. However, we did find evidence for the formation of PhSe–$SnBu_3$ from analysis of the GC–MS data obtained for the crude mixture. This indicates that $Bu_3Sn^{\bullet}$ radicals abstracted the phenylselanyl group and formed the imidoyl radical. These results indicate that imidoyl radicals are insufficiently reactive to cyclise onto unactivated arenes.

Studies in the literature show that cyclisation onto activated heteroarenes with electron withdrawing groups or radical stabilising groups such as phenyl is more successful than that of arenes. For example, cyclisation has been reported for pyrroles,[22–24] imidazoles,[22,26] indoles,[23,26,27] pyrazoles,[26,28] pyridinium salts,[29] 1,2,3-triazoles[30] and quinolones.[31] Acyl radicals which are isoelectronic with imidoyl radicals have been successfully cyclised onto activated pyrroles and indoles and were an obvious target for our studies.[24] We therefore decided to investigate suitable pyrrole and indole precursors with electron withdrawing groups (CN, CHO) to activate the rings for attack by the nucleophilic imidoyl radicals.

Firstly, a pyrrole radical precursor was prepared. The amide **24a** was successfully converted to the required imidoyl selanide for study. However, the corresponding pyrrole-2-carbaldehyde **24b** gave an intractable mixture and was not further studied. The precursor **29** was designed so that intermediate radical could cyclise onto either the pyrrole or arene ring (Scheme 10). However, no products resulting from cyclisation onto the arene were detected. The precursor to give 6-*exo* cyclisation was also chosen because in cyclisation onto five-membered ring heteroarenes the 5-*exo* cyclisation is less favourable than 6-*exo* cyclisation due to ring strain.[22–28] The selanide **29** was treated to standard Bu_3SnH conditions (Scheme 10). Attempts to isolate imine products directly and to hydrolyse the imines to isolate the corresponding ketone products both failed. Therefore, the crude reaction mixture was reduced with $NaBH_4$ before isolation of products. The yield of products was high (70–80%) giving a mixture of three products, which could only be separated



Scheme 10. Preparation and cyclisation of imidoyl selanide **29** (R=phenethyl).

with difficulty. The desired 8-(phenethylamino)-5,6,7,8-tetrahydroindolizine-3-carbonitrile **33** (7%), a 2-cyano-2-propyl adduct, 3-[(cyanodimethyl)-methyl]-8-(phenethylamino)-3,5,6,7,8,8a-hexahydroindolizine-3-carbonitrile **34** (6%) and a reduced uncyclised amine, 1-[4-(phenethylamino)-butyl]-1*H*-pyrrole-2-carbonitrile **31** (13%). The product ratio was determined by ^{1}H NMR spectroscopic analysis of the crude basic products to be **33**:**34**:**31**, 1.6:1.0:4.3.

The imidoyl radical **30** was more readily reduced by Bu_3SnH than cyclised even though the [Bu_3SnH] was kept low by the use of a syringe pump, indicating that rate of cyclisation of the imidoyl radical is slow. The rearomatised product was expected and the mechanism of this aromatic homolytic substitution has been extensively studied.[20] The intermediate π-radical **32** is very stable and does not react with Bu_3SnH to give a dihydropyrrole product. This allows time for hydrogen to be abstracted in an aromatisation step to **33** or for 2-cyano-2-propyl radicals to trap the radical to yield the adduct **34**. It is possible that the adduct eliminates 2-cyanopropane to yield **33**. These adducts have been previously observed in radical reactions using AIBN but are not the normal products whereas the product of homolytic aromatic substitution is normal.[32]

In order to facilitate more cyclisation over reduction we studied reagents, which react more slowly with radicals than Bu_3SnH. When the reaction was repeated using TTMSS in the place of Bu_3SnH, the product ratio was determined by ^{1}H NMR spectroscopic analysis of the crude basic products to be **33**:**34**:**31** was 2:1:7.8, i.e., no improvement. Use of hexamethylditin which has no available hydrogen for trapping radicals gave an intractable mixture, probably due to decomposition due to the higher temperature used.

Cyclisation onto indole rings is normally more successful than onto pyrrole owing to the weaker aromaticity of the pyrrole ring in indole.[23,26,27] Reduced cyclised products are also often obtained. The indole imidoyl selanide precursor **37** was prepared in good yield as shown in Scheme 11 from the amide **36**, which in turn was prepared from 3-cyanoindole via the carboxylic acid **35**. Cyclisation was carried out under standard Bu_3SnH reaction conditions to yield a complex mixture of products. In order to simplify the product mixture, the procedure using $NaBH_4$ reduction at the end of the reaction was carried out but also gave a multitude of products with at least four major products as shown by TLC and ^{1}H NMR spectroscopic analysis which were not separable by column chromatography. However, when the reaction was repeated with hydrolysis at the end of the reaction a cleaner mixture was obtained. ^{1}H NMR spectral analysis of the mixture indicated 2:1 mixture of the expected ketone **39** (isolated in 14%) and hydrolysed starting material (amide **36**, isolated in 5% yield). The yield of products was generally high (60–70%) but purification was difficult. Cyclisation yielded the cyclised imine **38**, which on hydrolysis gave the ketone **39**. The results indicate that imidoyl radical cyclisation onto activated heteroarenes is possible but further studies are required to optimise procedures and yields.

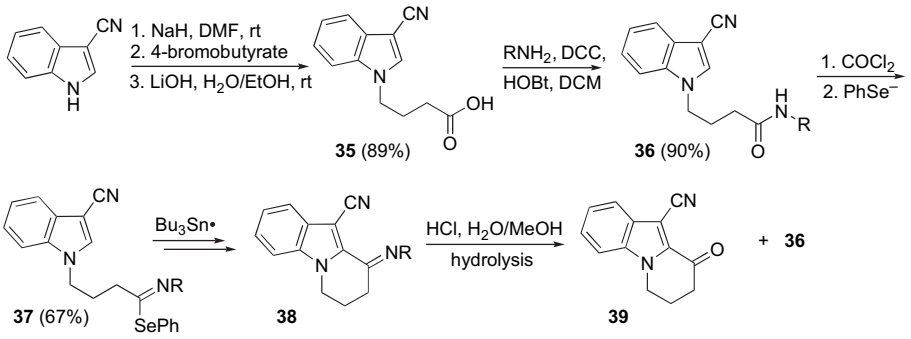
3. Conclusions

Imidoyl selanides are easily prepared from secondary amides and have proved to be useful precursors of imidoyl radicals. Imidoyl radicals have been successfully cyclised onto alkenes (to yield 2,3-disubstituted-indoles and -quinolines), alkynes and heteroarenes. We have shown that amides can be used in synthetic protocols via imidoyl radicals to a wide range of heterocyclic compounds by incorporation of the C═N moiety.

4. Experimental

4.1. 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 un-corrected. 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. When 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



Scheme 11. Cyclisation of imidoyl selanide **37** (R=phenethyl).

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 F254). Column chromatography was carried out using silica gel as adsorbent and light petroleum–EtOAc as eluent unless otherwise specified.

Phosgene was purchased as a 20% w/w solution in toluene. Phosgene is very toxic and suitable precautions must be taken for containment and destruction at the end of experiments.

4.2. 4-Methyl-*N*-(*p*-tolylseleno)benzimidic acid phenyl ester 4a. General method for the synthesis of imidoyl selanides from amides

DMF (3/4 drops) and phosgene (20% w/w toluene solution) (4.7 cm^3, 8.88 mmol) were added to a solution of 4-methyl-*N*-(*p*-tolyl)benzamide (1.00 g, 4.44 mmol) in dry dichloromethane (40 cm^3). The reaction mixture was stirred for 4 h at room temperature. The resultant mixture was evaporated to dryness under reduced pressure, redissolved in anhydrous THF (30 cm^3) and added via a cannular to a solution of diphenyl diselenide (0.900 g, 2.886 mmol), K-Selectride® (1 M THF solution) (6.4 cm^3, 6.40 mmol) and anhydrous THF (40 cm^3). The combined reaction mixture was stirred for 3 h at room temperature. The reaction mixture was washed with water and extracted into dichloromethane. The combined organic fractions were dried and concentrated under reduced pressure. The crude residue was purified by flash silica column chromatography using light petroleum–diethyl ether as the eluent to yield the imidoyl selanide **4a** as a yellow oil (1.51 g, 94%) [HRMS (FAB). Found: 366.0759. $C_{21}H_{20}NSe$ (M^++H) requires 366.0760]; ν_{max}(thin film)/cm^{-1} 3052, 3022, 2917, 2863, 1603, 1575, 1506, 1437, 1251, 1162, 1020 and 902; δ_H(250 MHz, $CDCl_3$) 2.25 (3H, s, CH_3), 2.35 (3H, s, CH_3), 6.87 (2H, d, *J* 7.8), 6.97–7.09 (5H, m), 7.16 (2H, d, *J* 8.1), 7.25–7.26 (2H, m) and 7.49 (2H, d, *J* 8.1); δ_C 21.4 (Me), 21.7 (Me), 120.0 (CH), 127.8 (CH), 128.9 (CH), 129.1 (CH), 129.6 (CH), 129.9 (CH), 134.6 (C), 135.5 (CH), 140.4 (C), 149.2 (C) and 163.9 (C) [two quaternary-C signals could not be observed]; *m/z* 366 (49%), 322 (5), 264(8), 208 (100), 194 (17) and 91 (87).

4.3. Synthesis of precursors for cyclisations to indoles and quinolines

4.3.1. 3-(2-Nitrophenyl)acrylic acid ethyl ester 14 (R^2=CO_2Et). General method for Wittig reactions. (Triphenyl-phosphanylidene)-acetic acid ethyl ester (35.5 g, 102 mmol) was added to a solution of 2-nitrobenzaldehyde (15.40 g, 102 mmol) in anhydrous tetrahydrofuran (200 cm^3). The reaction mixture was stirred overnight at room temperature. The solution was evaporated under reduced pressure and the residue purified by flash silica column chromatography using light petroleum–EtOAc as eluent to yield the ester **14** (R^2=CO_2Et) as a light yellow oil (10:1 *E*/*Z*-mixture of alkene isomers) (21.77 g, 97%) (Found: 221.0691. $C_{11}H_{11}NO_4$ requires 221.0688); ν_{max}(thin film)/cm^{-1} 3072, 2981, 2937, 2903, 1717, 1636, 1570, 1525, 1442, 1345, 1183, 1033 and 974; δ_H(250 MHz, $CDCl_3$) 1.10 (3H, t, *J* 7.1, minor), 1.34 (3H, t, *J* 7.1 major), 4.03 (2H, q, *J* 7.1, minor), 4.29 (2H, q, *J* 7.1, major), 6.10 (1H, d, *J* 11.9, minor), 6.36 (1H, d, *J* 15.8, major), 7.39–7.71 (3H, m), 8.02–8.06 (1H, m) and 8.10 (1H, d, *J* 15.8, major); δ_C (*E* isomer): 14.2 (Me), 60.9 (CH_2), 123.3 (CH), 124.9 (CH), 129.1 (CH), 130.2 (CH), 130.6 (C), 133.5 (CH), 139.8 (CH), 148.3 (C) and 165.8 (C). (*Z*-isomer): 13.9 (Me), 60.3 (CH_2), 121.3 (CH), 124.3 (CH), 128.9 (CH), 131.1 (CH), 132.6 (C), 133.0 (CH) and 1 CH and 2 C signals could not be seen; *m/z* 221 (M^+, 1%), 176 (68), 147 (62), 130 (100), 120 (65), 102 (65), 92 (96), 77 (48), 65 (63) and 51 (33).

4.3.2. 3-(2-Aminophenyl)acrylic acid ethyl ester 15 (R^2=CO_2Et, R^3=H). General method for the reduction of nitro groups. Glacial acetic acid (40 cm^3) and iron powder (9.22 g, 164.70 mmol) were added to a solution of 3-(2-nitro-phenyl)acrylic acid ethyl ester **14** (R^2=CO_2Et) (9.10 g, 41.77 mmol) in absolute ethanol (40 cm^3). The mixture was heated under reflux for 2 h. The crude mixture was cooled, filtered through a pad of Celite and evaporated under reduced pressure. The residue was dissolved in diethyl ether and extracted with 2 M hydrochloric acid. The aqueous fraction was basified using concentrated aqueous sodium hydroxide solution and the product amine extracted into dichloromethane. The combined organic fractions were dried and evaporated under reduced pressure to yield the ester **15** (R^2=CO_2Et, R^3=H) as yellow crystals; mp 69–70 °C (4.53 g, 58%) (Found: 191.0948. $C_{11}H_{13}NO_2$ requires 191.0946); ν_{max}(thin film)/cm^{-1} 3467, 3369, 3059, 3030, 2990, 2903, 1680, 1616, 1489, 1463, 1306, 1188, 1162, 1031 and 977; δ_H(250 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.0 Me), 4.02 (2H, br s, NH_2), 4.26 (2H, q, *J* 7.0, OCH_2), 6.35 (1H, d, *J* 15.9), 6.68 (1H, d, *J* 8.0), 6.75 (1H, dd, *J* 7.7, 7.7), 7.16 (1H, dt, *J* 1.5, 7.7), 7.37 (1H, dt, *J* 1.5, 7.7) and 7.83 (1H, d, *J* 15.9); δ_C 14.3 (Me), 60.4 (CH_2), 116.7 (CH), 118.1 (CH), 118.9 (CH), 119.9 (C), 128.1 (CH), 131.2 (CH), 140.0 (CH), 145.5 (C) and 167.3 (C); *m/z* 191 (M^+, 35%), 146 (100), 128 (31), 118 (80), 91 (25), 77 (5) and 65 (9).

4.3.3. 3-[2-(4-Methylbenzoylamino)phenyl]acrylic acid ethyl ester 16a. General method for the synthesis of amides. Triethylamine (4.2 cm^3, 30.34 mmol), a catalytic quantity of dimethylaminopyridine and *p*-tolylchloride (3.1 cm^3, 23.34 mmol) were added to a solution of 3-(2-aminophenyl)acrylic acid ethyl ester **15** (R^2=CO_2Et, R^3=H) (4.46 g, 23.34 mmol) in dry DCM (200 cm^3) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The organic solution was washed with 2 M hydrochloric acid and saturated aqueous sodium hydrogen carbonate. The combined organic fractions were dried and concentrated under reduced pressure. The residue was purified by alumina column chromatography. The resultant solid was recrystallised from hot dichloromethane–hexane to yield the ester **16a** as a white powder (3.07 g, 42%), mp 147–148 °C (Found: 309.1367. $C_{19}H_{19}NO_3$ requires 309.1364); ν_{max}(thin film)/cm^{-1} 3268, 2983, 1711, 1644, 1613, 1523, 1504, 1302, 1264, 1178, 1030 and 988; δ_H(250 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.1, Me), 2.42 (3H, s, Me), 4.23 (2H, q, *J* 7.1, CH_2O), 7.20–7.34 (3H, m), 6.42 (1H, d, *J* 15.9, C*H*CO_2Et), 7.42 (1H, ddd, *J* 1.5, 7.9, 7.9),

7.58 (1H, dd, *J* 1.5, 7.9) and 7.77–8.00 (5H, m); δ_C 14.2 (Me), 21.4 (Me), 60.6 (CH_2), 120.7 (CH), 125.3 (CH), 125.8 (CH), 127.2 (CH), 127.3 (CH), 128.0 (C), 129.4 (CH), 130.7 (CH), 131.4 (C), 136.1 (C), 139.3 (CH), 142.6 (C), 166.0 (C) and 166.6 (C); *m/z* 309 (13%), 236 (3), 190 (16), 119 (100) and 91 (28).

4.3.4. 3-[2-(Phenylacetylamino)phenyl]acrylic acid ethyl ester 16c. General method for the synthesis of amides using dicyclohexylcarbodiimide. Phenylacetic acid (4.523 g, 33.26 mmol), dicyclohexylcarbodiimide (6.851 g, 33.26 mmol) and HOAT (0.334 g, 2.46 mmol) were added to a solution of 3-(2-aminophenyl)acrylic acid ethyl ester **15** (R^2=CO_2Et, R^3=H) (4.705 g, 24.63 mmol) in anhydrous DCM (100 cm^3). The reaction mixture was stirred for 36 h. The crude mixture was then filtered and washed successively with 2 M hydrochloric acid and saturated aqueous sodium hydrogen carbonate solution. The combined organic fractions were dried and concentrated under reduced pressure. The crude product was purified by flash silica column chromatography to yield the ester **16c** as a white solid (4.30 g, 56%), mp 117–118 °C (Found: 309.1360. $C_{19}H_{19}NO_3$ requires 309.1364); ν_{max}(thin film)/cm^{-1} 3263, 3027, 2978, 2929, 2853, 1713, 1661, 1634, 1579, 1527, 1454, 1316, 1260, 1177 and 972; δ_H(250 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.2, Me), 3.79 (2H, s, CH_2Ph), 4.25 (2H, q, *J* 7.2, CH_2O), 6.25 (1H, d, *J* 15.9, C*H*CO_2Et), 7.47–7.12 (8H, m), 7.54 (1H, d, *J* 15.9, C*H*=CHCO_2Et) and 7.75 (1H, d, *J* 8.1); δ_C 14.3 (CH_3), 44.5 (CH_2), 60.6 (CH_2), 121.0 (CH), 124.6 (CH), 125.8 (CH), 127.2 (CH), 127.5 (C), 127.8 (CH), 129.4 (CH), 129.5 (CH), 130.6 (CH), 134.2 (C), 135.5 (C), 138.9 (CH), 168.4 (C) and 169.6 (C); *m/z* 309 (M^+, 23%), 268 (7), 240 (11), 191 (14), 146 (55), 118 (38), 91 (100) and 65 (13).

4.3.5. 3-{2-[(Phenylselanyl-*p*-tolylmethylene)amino]phenyl}acrylic acid ethyl ester 5a. The general procedure for the synthesis of imidoyl selanides was used. Yellow oil (64%) [HRMS (FAB) Found: 450.0968. $C_{25}H_{24}NO_2Se$ (M^++H) requires 450.0972]; ν_{max}(thin film)/cm^{-1} 3056, 2976, 1707, 1628, 1592, 1474, 1314, 1267, 1172, 1092 and 910; δ_H(250 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.2, Me), 2.29 (3H, s, Me), 4.26 (2H, q, *J* 7.2, CH_2O), 6.38 (1H, d, *J* 16.0, C*H*CO_2Et), 6.89 (1H, d, *J* 8.0), 7.53–7.01 (10H, m), 7.59 (2H, d, *J* 8.0) and 7.86 (1H, d, *J* 16.0, C*H*=CHCO_2Et); δ_C 14.3 (CH_3), 21.3 (CH_3), 60.2 (CH_2), 118.7 (CH), 119.8 (CH), 124.6 (C), 124.7 (CH), 127.2 (CH), 127.7 (CH), 128.7 (CH), 128.8 (CH), 128.9 (C), 129.1 (CH), 130.5 (CH), 135.2 (CH), 135.5 (C), 140.7 (C), 140.8 (CH), 150.3 (C), 165.2 (C) and 167.0 (C); *m/z* (FAB) 450 (M^++H, 10%), 366 (4), 292 (42), 248 (42), 220 (90), 128 (19), 119 (100), 91 (25), 77 (15) and 65 (5).

4.3.6. (*Z*)-Phenyl *N*-2-cyclohexenylphenylethaneselenoimidate 5m. The general method for the synthesis of imidoyl selanides was used and yielded after purification the imidoyl selanide **5m** (27%) as a yellow oil and 6-methyl-7,8,9,10-tetrahydrophenanthridine **11m** (55%) as colourless crystals, mp 84–86 °C.

Compound **5m**: ν_{max}(neat)/cm^{-1} 3055, 2925, 2853, 2831, 1644, 1117, 740 and 692; δ_H(400 MHz, $CDCl_3$) 1.64–1.76 (4H, m), 2.14 (3H, s, Me), 2.14–2.21 (2H, m), 2.32–2.36 (2H, m), 5.80 (1H, m, cyclohexenyl 2-H), 6.81–6.83 (1H, m), 7.09–7.13 (1H, m), 7.19–7.23 (2H, m), 7.31–7.41 (3H, m) and 7.62–7.63 (2H, m); δ_C 22.3 (CH_2), 23.2 (CH_2), 25.8 (CH_2), 28.5 (Me), 28.7 (CH_2), 119.4 (CH), 124.7 (CH), 127.1 (CH), 127.2 (CH), 128.2 (C), 128.9 (CH), 129.1 (CH), 129.3 (CH), 135.3 (C), 136.8 (C), 137.2 (CH), 148.2 (C) and 163.32 (C=N); *m/z* [(LSIMS) Found: 356.0907. $C_{20}H_{22}NSe$ ($M+H)^+$ requires 356.0912], 355 (79%), 314 (37), 260 (68), 232 (100) and 214 (50).

Compound **11m**:[33] ν_{max}(neat)/cm^{-1} 3059, 2934, 2864, 1588, 1423, 763 and 746; δ_H(400 MHz, $CDCl_3$) 1.87–1.93 (4H, m, 8,9-H), 2.62 (3H, s, CH_3), 2.73–2.76 (2H, m, 7- or 10-H), 3.06–3.08 (2H, m, 7- or 10-H), 7.45 (1H, ddd, *J* 8.3, 6.9, 1.0, 2- or 3-H), 7.59 (1H, ddd, *J* 8.3, 6.9, 1.2, 2- or 3-H), 7.87 (1H, dd, *J* 8.3, 1.2, 1- or 4-H) and 7.98 (1H, dd, *J* 8.3, 1.0, 1- or 4-H); δ_C 22.0 (8,9-C), 22.5 (8,9-C), 23.3 (Me), 25.5 (7,10-C), 26.8 (7,10-C), 122.4 (CH), 125.4 (CH), 126.7 (C), 128.0 (CH), 128.0 (CH), 128.9 (C), 141.1 (C), 145.3 (C) and 158.6 (C); *m/z* (ESI) [Found: 198.1279. $C_{14}H_{16}N$ ($M+H)^+$ requires 198.1277], 197 (100%), 182 (30), 169 (58) and 77 (20).

4.4. Radical cyclisation reactions for the synthesis of indoles and quinolines

4.4.1. [2-(*p*-Tolyl)-1*H*-indol-3-yl]acetic acid ethyl ester 10a. General method for the radical cyclisation of imidoyl selanides using syringe pump addition of Bu_3SnH. 3-{2-[(Phenylselanyl-*p*-tolyl-methylene)-amino]-phenyl}-acrylic acid ethyl ester **5a** (0.469 g, 1.05 mmol) was dissolved in anhydrous toluene (100 cm^3). The reaction mixture was deoxygenated and heated to reflux. A solution of Bu_3SnH (0.61 cm^3, 2.31 mmol, 2.2 equiv) in toluene (20 cm^3) was added via a syringe pump over 5 h and AIBN (0.164 g, 1.05 mmol) was added over 5 h as five equal aliquots. The reaction mixture was cooled and the solvent removed under reduced pressure. The crude mixture was purified by flash silica column chromatography using an eluent system of light petroleum and EtOAc to yield the indole **10a** as a pale yellow oil (0.293 g, 95%) (Found: 293.1419. $C_{19}H_{19}NO_2$ requires 293.1415); ν_{max}(thin film)/cm^{-1} 3373, 3053, 3024, 2976, 2921, 2869, 1718, 1506, 1457, 1342, 1306, 1176, 1029 and 822; δ_H(250 MHz, $CDCl_3$) 1.23 (3H, t, *J* 7.1, CH_3), 2.38 (3H, s, CH_3), 3.80 (2H, s, CH_2CO_2Et), 4.14 (2H, q, *J* 7.1 CH_2O), 7.12–7.30 (5H, m), 7.49–7.52 (2H, m), 7.64–7.66 (1H, m) and 8.18 (1H, br s, N*H*); δ_C 14.2 (CH_3), 21.2 (CH_3), 31.2 (CH_2), 60.8 (CH_2), 105.3 (C), 110.8 (CH), 119.2 (CH), 119.9 (CH), 122.3 (CH), 128.1 (CH), 129.1 (C), 129.5 (C), 129.6 (CH), 135.7 (C), 136.3 (C), 137.9 (C) and 172.3 (C=O); *m/z* 292 (M^+, 40%), 269 (20), 220 (100), 204 (22), 177 (5), 155 (4) and 91 (4).

4.4.2. Cyclisation of (*Z*)-phenyl 4-methyl-*N*-[(2-penten-1-yl)phenyl]benzoselenoimidate 5e. The general method for the radical cyclisation of imidoyl selanides using syringe pump addition of the imidoyl selanide **5e** gave a crude mixture, which was analysed by ^1H NMR spectroscopy as **10e**:**11e**:2-(*p*-tolyl)quinoline, 1:4:3, along with other minor unknown products. 3-Propyl-2-(*p*-tolyl) quinoline **11e** (39%), the indole **10e** (10%) and 2-(*p*-tolyl) quinoline (6%) were isolated using column chromatography.

4.4.2.1. 3-Propyl-2-(*p*-tolyl)-quinoline 11e. Brown oil [Found: 262.1585 $(M+H)^+$. $C_{19}H_{20}N$ requires 262.1590]; ν_{max}(neat)/cm^{-1} 2950, 1600, 810 and 755; δ_H(250 MHz, $CDCl_3$) 1.08 (3H, t, *J* 7.4, Me), 1.79–1.91 (2H, m, propyl 2-H), 2.44 (3H, s, Me), 3.10 (2H, t, *J* 7.7, propyl 1-H), 7.31–7.36 (2H, m), 7.49–7.55 (1H, m), 7.67–7.76 (2H, m), 7.70 (1H, s, quinoline 4-H), 8.02–8.10 (2H, m) and 8.16–8.22 (1H, m); δ_C 14.3 (Me), 21.38 (Me), 23.4 (propyl 2-C), 34.6 (propyl 1-C), 118.7 (CH), 123.4 (CH), 125.8 (CH), 126.5 (C), 127.5 (CH), 129.6 (CH), 130.4 (CH), 136.7 (CH), 137.1 (C), 139.2 (C), 148.5 (C), 148.9 (C) and 157.0 (C); *m*/*z* (EI), 262 (30%), 234 (100) and 221 (75).

4.4.2.2. 2-(*p*-Tolyl)quinoline. Mp 80–82 °C (lit.,[34] 81–82 °C) (Found: 220.1120 $(M+H)^+$. $C_{16}H_{14}N$ requires 220.1121); ν_{max}(neat)/cm^{-1} 2925, 1596 and 813; δ_H(250 MHz, $CDCl_3$) 2.43 (3H, s, CH_3), 7.33 (2H, d, *J* 7.9), 7.47–7.54 (1H, m, quinoline 6- or 7-H), 7.68–7.75 (1H, m, quinoline 6- or 7-H), 7.81 (1H, dd, *J* 8.2, 1.2, quinoline 5- or 8-H), 7.86 (1H, d, *J* 8.7, quinoline 3- or 4-H), 8.07 (2H, d, *J* 7.9) and 8.14–8.21 (2H, m, quinoline-H); δ_C 21.38 (CH_3), 118.89 (CH), 125.75 (C), 126.10 (CH), 127.11 (CH), 127.45 (CH), 129.53 (C), 129.60 (CH), 129.67 (CH), 136.69 (C), 136.89 (C), 139.42 (CH), 148.30 (CH), 157.36 (2-C); *m*/*z* 220 (M^+, 100%) and 91 (38). The data were identical to that reported in the literature.[34]

4.4.3. 3-Butyl-2-(*p*-tolyl)-1*H*-indole 10e. General method for the cyclisation with Bu_3SnH and AIBN added at the beginning of the reaction. (*Z*)-Phenyl 4-methyl-*N*-[(2-penten-1-yl)phenyl] benzoselenoimidate **5e** (173 mg, 0.41 mmol), tributyltin hydride (220 μL, 0.83 mmol) and AIBN (7 mg, 0.04 mmol) were dissolved in dry toluene (150 cm^3) and the solution was flushed with nitrogen for 15 min followed by heating to reflux. The reaction mixture was stirred at reflux for 1 h, evaporated under reduced pressure. ^{1}H NMR spectroscopic analysis of the crude mixture showed the indole **10e** as the only product from the imidoyl selanide. The crude product was purified by column chromatography yielding 3-butyl-2-(*p*-tolyl)-1*H*-indole **10e** (73 mg, 66%) as a brown oil.

4.4.3.1. 3-Butyl-2-(*p*-tolyl)-1*H*-indole 10e. Yellow oil, ν_{max}(neat)/cm^{-1} 3411, 2954, 1457 and 741; δ_H(250 MHz, $CDCl_3$) 0.92 (3H, t, *J* 7.3, butyl 4-H), 1.34–1.49 (2H, m, butyl 3-H), 1.64–1.74 (2H, m, butyl 2-H), 2.41 (3H, s, Me), 2.87 (2H, t, *J* 7.9, butyl 1-H), 7.09–7.46 (6H, m), 7.61–7.64 (1H, m), 7.96 (1H, br s, NH) and 8.19–8.23 (1H, m). Compound **18e** was unstable in solution and was only partially characterised.

4.4.4. Cyclisation of (*Z*)-phenyl *N*-[2-(penten-1-yl)phenyl]-ethaneselenoimidate 5g. The general method for the radical cyclisation of imidoyl selanides using syringe pump addition of Bu_3SnH gave a crude mixture, which was analysed by ^{1}H NMR spectroscopy as **10g**:**11g**, 1:2, along with other minor unknown products. Purification using column chromatography gave 3-butyl-2-methyl-1*H*-indole **10g** (9%) and 2-methyl-3-propylquinoline (35%).

4.4.4.1. 3-Butyl-2-methyl-1*H*-indole 10g. Yellow oil, ν_{max}(neat)/cm^{-1} 3405, 2955, 2928 and 741; δ_H(250 MHz, $CDCl_3$) 0.92 (3H, *J* 7.2, butyl 4-H), 1.29–1.44 (2H, m, butyl 3-H), 1.54–1.63 (2H, m, butyl 2-H), 2.36 (3H, s, 2-Me), 2.68 (2H, t, *J* 7.5, butyl 1-H), 7.02–7.13 (2H, m), 7.22–7.27 (1H, m), 7.48–7.52 (1H, m) and 7.68 (1H, br s, NH); δ_C 11.66 (2-Me), 14.05 (butyl 4-C), 22.65, 23.84, 32.99 (butyl 1-, 2- and 3-C), 110.06 (CH), 112.48 (C), 118.16 (CH), 118.91 (CH), 120.73 (CH), 128.87 (C), 130.54 (C) and 135.25 (C). The data were the same as those reported in the literature.[35]

4.4.4.2. 2-Methyl-3-propylquinoline 11g. Yellow oil, ν_{max}(neat)/cm^{-1} 2957, 2929 and 750; δ_H(250 MHz, $CDCl_3$) 1.05 (3H, t, *J* 7.3, propyl 3-H), 1.66–1.81 (2H, m, propyl 2-H), 2.73 (3H, s, 2-methyl), 2.76 (2H, t, *J* 6.9, propyl 1-H), 7.45 (1H, ddd, *J* 8.1, 6.9, 1.2), 7.62 (1H, ddd, *J* 8.4, 6.9, 1.5), 7.73 (1H, dd, *J* 8.1, 1.5), 7.84 (1H, s, quinoline 4-H), 7.99 (1H, br d, *J* 8.4); δ_C 14.01 (propyl 3-C), 22.80 (propyl 2-C), 23.16 (2-Me), 34.91 (propyl 1-C), 125.62, 126.91 (quinoline CH), 127.39 (4a-C), 128.24, 128.44 (CH), 134.28 (3-C), 134.50 (CH), 146.36 (8a-C) and 158.64 (2-C). The data were the same as those reported in the literature.[36]

The general method for the cyclisation with Bu_3SnH and AIBN added at the beginning of the reaction gave 2-benzyl-3-butyl-1*H*-indole **10g** (73%) as a yellow oil.

4.4.4.3. General procedure for cyclisation using Et_3B as initiator. The imidoyl selanide **5g** (300 mg, 0.88 mmol) and tributyltin hydride (520 μL, 1.93 mmol) were dissolved in dry toluene (150 cm^3) and the solution was flushed with nitrogen for 15 min followed by the addition of triethylborane (1 M solution in hexanes, 0.13 cm^3, 0.13 mmol). A needle was used to allow O_2 to bleed into the reaction vessel. The reaction mixture was stirred at room temperature for 1 h, evaporated under reduced pressure. ^{1}H NMR spectroscopic analysis of the crude mixture showed only 3-butyl-2-methyl-1*H*-indole **10g**. The crude product was purified by column chromatography yielding 3-butyl-2-methyl-1*H*-indole **10g** (133 mg, 81%) as a yellow oil.

4.4.5. Cyclisation of (*Z*)-phenyl *N*-2-(prop-1-en-2-yl)phenylethaneselenoimidate 5j. The general method for cyclisation using Et_3B with 48 h reaction time and Et_3B added in three equal portions during 48 h. The crude which was analysed by ^{1}H NMR spectroscopic to show only 2,4-dimethylquinoline **11j**. The crude was dissolved in DCM and extracted with hydrochloric acid (1 M) HCl. A strong aqueous NaOH solution was added to the aqueous layer until the solution was basic and extracted with DCM. The solvent was evaporated under reduced pressure to give 2,4-dimethylquinoline **11j** (80%) as a clear oil (Found: 157.0891. $C_{11}H_{11}N$ requires 157.0891); ν_{max}(neat)/cm^{-1} 3059, 2953, 2920, 1617, 1603 and 859; δ_H(250 MHz, $CDCl_3$) 2.68 (3H, s, 4-Me), 2.71 (3H, s, 2-CH_3), 7.16 (1H, s, 3-H), 7.51 (1H, m), 7.68 (1H, m), 7.96 (1H, dd, *J* 8.2, 1.0), 8.05 (1H, d, *J* 7.7); δ_C 18.7 (4-Me), 25.0 (2-CH_3), 122.8 (CH), 123.6 (CH), 125.6 (CH), 126.6 (C), 128.8 (CH), 129.3 (CH), 144.7 (C), 147.3 (C) and 158.6 (C); *m*/*z* 158 (14%), 157 (100), 156 (11), 142 (6), 116 (5), 115 (13) and 77 (6). The data were the same as authentic commercial material.

4.4.6. 4-(2-Cyanopyrrol-1-yl)-*N*-(phenethyl)-selenobutyrimidic acid phenyl ester 29. The general procedure for the synthesis of imidoyl selanides was used employing

4-(2-cyanopyrrol-1-yl)-*N*-(phenethyl)-butyramide **24a** (2.00 g, 7.11 mmol). This gave 4-(2-cyanopyrrol-1-yl)-*N*-(phenethyl)-selenobutyrimidic acid phenyl ester **29** as a yellow oil (1.91 g, 64%), *m/z* (LSIMS) [Found: 422.1121. $C_{23}H_{24}N_3Se$ $(M+H)^+$ requires 422.1130]; ν_{max}(neat)/cm^{-1} 2925, 2215, 1644, 739 and 693; δ_H(250 MHz, $CDCl_3$) 1.88–1.99 (2H, m, 3-H), 2.12 (2H, t, *J* 7.1, 2-H), 3.07 (2H, t, *J* 7.4, *N*-phenethyl 2-H), 3.70 (2H, t, *J* 7.4, *N*-phenethyl 1-H), 3.87 (2H, t, *J* 6.9, 4-H), 6.07 (1H, dd, *J* 4.0, 2.7, pyrrole 4-H), 6.56 (1H, dd, *J* 2.7, 1.6), 6.70 (1H, dd, *J* 4.0, 1.6), 7.19–7.43 (8H, m) and 7.54–7.58 (2H, m); δ_C 28.6 (3-C), 37.0 (CH_2), 47.9 (CH_2), 57.3 (CH_2), 57.5 (CH_2) 103.7 (C), 109.5 (pyrrole C-4), 114.2 (C), 120.3 (CH), 126.6 (CH), 127.0 (CH), 127.1 (C), 128.8 (CH), 129.4 (CH), 129.4 (CH), 129.9 (CH), 137.5 (CH), 140.4 (C) and 160.7 (C═N).

The same procedure failed to yield the imidoyl selanide 4-(2-formylpyrrol-1-yl)-*N*-(phenethyl)-selenobutyrimidic acid phenyl ester from 4-(2-formylpyrrol-1-yl)-*N*-(phenethyl)-butyramide **24b**. Only diphenyl diselenide could be isolated from an intractable mixture.

4.4.7. Cyclisation of 4-(2-cyanopyrrol-1-yl)-*N*-(phenethyl)-selenobutyrimidic acid phenyl ester 29.

4.4.7.1. Using Bu_3SnH and AIBN. 4-(2-Cyanopyrrol-1-yl)-*N*-(phenethyl)-selenobutyrimidic acid phenyl ester **29** (300 mg, 0.71 mmol) was dissolved in dry toluene (150 cm^3) and the solution was flushed with nitrogen for 15 min followed by heating to reflux. A solution of tributyltin hydride (420 μL, 1.43 mmol) in toluene (20 cm^3) was added over 5 h via syringe pump, while AIBN (221 mg, 1.43 mmol) was added portion wise (37 mg) for every 45 min (six portions). The reaction mixture was heated under reflux for 5 h and cooled to room temperature. Methanol (5 cm^3) and sodium borohydride (83 mg, 2.20 mmol) were added followed by stirring for 16 h at room temperature. The reaction mixture was evaporated under reduced pressure, dissolved in EtOAc and extracted with dilute aqueous HCl. The aqueous phase was washed with light petroleum, basified with sodium carbonate and aqueous NaOH solution and extracted with diethyl ether. Both solutions containing, respectively, neutral and basic organic products were evaporated under reduced pressure. The neutral products were separated by column chromatography and were diphenyl diselanide and AIBN residues. Three basic products were isolated using column chromatography, namely the desired 8-(phenethylamino)-5,6,7,8-tetrahydroindolizine-3-carbonitrile **33** (12 mg, 7%) as a brown oil, 3-[(cyanodimethyl)methyl]-8-(phenethylamino)-3,5,6,7,8,8a-hexahydroindolizine-3-carbonitrile **34** (12 mg, 6%) as colourless crystals, and 1-[4-(phenethylamino)-butyl]-1*H*-pyrrole-2-carbonitrile **31** (25 mg, 13%) as a brown oil. The product ratio was determined by ^1H NMR spectroscopic analysis of the crude basic products to be **33**:**34**:**31**, 1.6:1:4.3. These three products are characterised as follows:

Compound **33**: (Found: 265.1583 M^+. $C_{17}H_{19}N_3$ requires 265.1579); ν_{max}(neat)/cm^{-1} 3330, 2932, 2209, 750 and 700; δ_H(250 MHz, $CDCl_3$) 1.65–1.76 (1H, m), 1.84–1.96 (1H, m), 1.99–2.10 (1H, m), 2.14–2.25 (1H, m), 2.82 (2H, t, *J* 6.7, *N*-phenethyl 2-H), 2.96 (2H, t, *J* 6.7, *N*-phenethyl 1-H), 3.86 (1H, dd, *J* 7.2, 5.5, 8-H), 3.99 (2H, t, *J* 5.9, 5-H), 5.98 (1H, d, *J* 3.9, 1-H), 6.74 (1H, d, *J* 3.9, 2-H), 7.19–7.35 (5H, m, Ph-H); δ_C 19.98 (6-C), 26.95 (7-C), 36.32, 44.45, 48.01 (5-C and phenethyl 1- and 2-C), 51.6 (8-C), 102.3 (3-C), 107.1 (1-C), 114.0 (CN), 119.5 (CH), 126.4 (CH), 128.5 (CH), 128.7 (CH), 132.5 (C) and 139.5 (C); *m/z* (EI) 265 (3%), 174 (14), 160 (5), 145 (100), 118 (4), 105 (10), 91 (9), 77 (4).

Compound **34**: ν_{max}(neat)/cm^{-1} 3356, 2915, 2230, 1693, 738 and 700; δ_H(250 MHz, $CDCl_3$) 1.62–2.28 (4H, 6- and 7-H), 1.71 (3H, s, Me), 1.73 (3H, s, Me), 2.78–2.85 (2H, m, phenethyl 2-H), 2.95–3.02 (2H, m, phenethyl 1-H), 3.80–3.90 (2H, m, 8- and 9-H), 4.06–4.12 (2H, m, 5-H), 5.89 (1H, d, *J* 3.8), 5.97 (1H, d, *J* 3.8) and 7.18–7.33 (5H, m); δ_C 15.8 (Me), 20.9 (CH_2), 27.3 (CH_2), 27.9 (Me), 30.7 [*C*(CN)Me_2], 36.5 (CH_2), 44.6 (CH_2), 48.2 (CH_2), 52.0 and 57.4 (8- and 9-C), 64.1 (3-C), 104.5 and 105.6 (1- and 2-C), 123.4 (CN), 126.2 (CH), 126.6 (CH), 128.5 (CH), 129.5 (CN) and 138.1 (C); *m/z* 307 (4%, loss of HCN), 239 (4), 187 (100), 172 (11), 105 (5) and 91 (17).

Compound **31**: [Found: 266.1655 $(M-H)^+$. $C_{17}H_{20}N_3$ requires 266.1657]; ν_{max}(neat)/cm^{-1} 3383, 2927, 2214, 1653, 742 and 701 (Ar); δ_H(250 MHz, $CDCl_3$) 1.70–2.05 (4H, m, 2- and 3-H), 2.64 (2H, t, *J* 7.2, 4-H), 2.75–2.91 (4H, m, phenethyl 1- and 2-H), 4.03 (2H, t, *J* 7.2, 1-H), 6.15 (1H, dd, *J* 3.9, 2.6, pyrrole 4-H), 6.77 (1H, dd, *J* 3.9, 1.5), 6.81 (1H, dd, *J* 2.6, 1.5) and 7.01–7.33 (5H); δ_C 26.9 (3-C), 29.0 (2-C), 36.3 (phenethyl 2-C), 48.8 (CH_2), 48.9 (CH_2), 51.0 (CH_2), 103.6 (pyrrole 2-C), 109.5 (pyrrole 4-C), 113.9 (CN), 119.9 (CH), 126.2 (CH), 126.3 (CH), 128.5 (CH), 128.7 (CH) and 139.90 (C); *m/z* (EI), 266 (6%), 176 (100), 132 (39), 105 (46), 91 (15).

4.4.7.2. Using $Me_3Sn–SnMe_3$, hν. 4-(2-Cyanopyrrol-1-yl)-*N*-(phenethyl)-selenobutyrimidic acid phenyl ester **29** (107 mg, 0.26 mmol) was dissolved in dry *tert*-butylbenzene (7 cm^3) in a flat two-necked flask and hexamethylditin (500 mg, 1.43 mmol) was added. The solution was deoxygenated with nitrogen followed by heating to reflux and irradiation with UV light. After 48 h stirring at reflux, the reaction mixture was cooled to room temperature. The rest of the work-up was the same. The yield of crude basic reaction products was only 10 mg and there were no identifiable products by TLC and ^1H NMR spectroscopic analysis.

4.4.8. 4-(3-Cyanoindol-1-yl)-*N*-phenethyl-selenobutyrimidic acid phenyl ester 37.

Standard selanation conditions were employed to give imidoyl selanide **37** (67%) as yellow crystals, mp 95–98 °C [Found: 472.1289 $(M+H)^+$. $C_{27}H_{26}N_3Se$ requires 472.1292]; ν_{max}(neat)/cm^{-1} 2925, 2215, 1645 and 741; δ_H(250 MHz, $CDCl_3$) 1.90 (4H, m, 3- and 2-H), 3.10 (2H, t, *J* 7.1, phenethyl 2-H), 3.72 (2H, t, *J* 7.1, phenethyl 1-H), 3.99 (2H, t, *J* 6.4, 4-H), 7.16–7.38 (12H, m), 7.40–7.45 (2H, m) and 7.69–7.75 (1H, m); δ_C 26.8 (3-C), 36.6 (CH_2), 36.7 (CH_2), 45.6 (CH_2), 56.8 (CH_2), 85.3 (indole 3-C), 110.6 (indole 2-C), 116.0 (CN), 119.8 (CH), 122.0 (CH), 123.6 (CH), 126.3 (CH), 126.5 (C), 127.8 (C), 128.5 (CH), 128.9 (CH), 129.1 (CH), 129.4 (CH), 134.8 (CH), 135.1 (C), 137.0 (CH), 139.9 (C) and 160.4 (C═N); *m/z* (LSIMS) [Found: 472.1289 $(M+H)^+$. $C_{27}H_{26}N_3Se$ requires 472.1292], 472 (27%).

4.4.9. Cyclisation of 4-(3-cyanoindol-1-yl)-*N*-phenethylselenobutyrimidic acid phenyl ester 37 followed by hydrolysis. The standard procedure for Bu_3SnH mediated cyclisations was used followed by hydrolysis. MeOH was added to the crude product until the solution was homogeneous and the solution was stirred for 4 h at room temperature. ^1H NMR spectral analysis of the crude products revealed a 2:1 mixture of ketone **39** and hydrolysed starting material (amide **36**, isolated in 5% yield). The crude product was purified by column chromatography yielding 9-oxo-6,7,8,9-(tetrahydropyrido)-[1,2-*a*]indole-10-carbonitrile **39** (14%) as colourless crystals, decomposed at 170 °C (Found: 210.0792 M^+. $C_{13}H_{10}N_2O$ requires 210.0793); ν_{max}(neat)/cm^{-1} 2923, 2221, 1672, 1526 and 750; δ_H(250 MHz, $CDCl_3$) 2.43–2.53 (2H, m, 7-H), 2.83 (2H, t, *J* 6.5, 8-H), 4.35 (2H, t, *J* 5.9, 6-H), 7.32 (1H, ddd, *J* 8.2, 5.7, 2.5), 7.43–7.52 (2H, m) and 7.76 (1H, m); δ_C 22.7 (7-C), 36.7 (8-C), 42.1 (6-C), 87.7 (10-C), 111.3 (CH), 114.6 (CN), 121.3 (CH), 123.8 (CH),127.1 (CH), 127.5 (C), 135.9 (C), 136.3 (C) and 187.8 (C═O); *m/z*, 210 (100%), 182 (20) and 154 (41).

4.5. X-ray crystallography

Data were collected at 150(2) K on a Bruker SMART 1000 diffractometer.[37] The structures were solved by direct methods and refined by full-matrix least squares on F^2 using the SHELXTL suite of programs.[38] All the non-hydrogen atoms were refined with anisotropic atomic displacement parameters and hydrogen atoms were inserted at calculated positions using a riding model. In **5e** atoms C(22), C(23) and C(24) were disordered over two sets of positions with approximately equal occupancy {major sites: 50.9(7)%}. This side chain was modelled with restraints on displacement parameters and geometry. 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 616265–616267. 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 have been included in the paper. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.10.030.

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