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# Synthesis of heteroarenes using cascade radical cyclisation *via* iminyl radicals†

**W. Russell Bowman,* Martin O. Cloonan, Anthony J. Fletcher and Tobias Stein**

*Department of Chemistry, Loughborough University, Loughborough, Leicestershire, UK LE11 3TU. E-mail: w.r.bowman@lboro.ac.uk; Fax: +44 (0)1509 223925; Tel: +44 (0)1509 22256*

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Cascade radical cyclisation involving homolytic aromatic substitution has been used to synthesise new tetracycles. Treatment of vinyl iodide radical precursors with $Me_3Sn^{\bullet}$ radicals (from hexamethylditin) yielded intermediate vinyl radicals which undergo 5-*exo* cyclisation onto suitably placed nitrile groups to yield intermediate iminyl radicals. The iminyl radicals undergo aromatic homolytic substitution *via* 6-*endo* cyclisation (or 5-*exo* cyclisation followed by neophyl rearrangement) with loss of hydrogen ($H^{\bullet}$) in a H-abstraction step. We propose that this abstraction was facilitated by *tert*-butoxyl (*t*-$BuO^{\bullet}$) radicals from di-*tert*-butyl peroxide or methyl radicals, generated from breakdown of trimethylstannyl radicals ($Me_3Sn^{\bullet}$). The biologically active alkaloids mappicine and luotonin A were synthesised using the new methodology. A novel radical conversion of nitriles to primary amides is proposed.

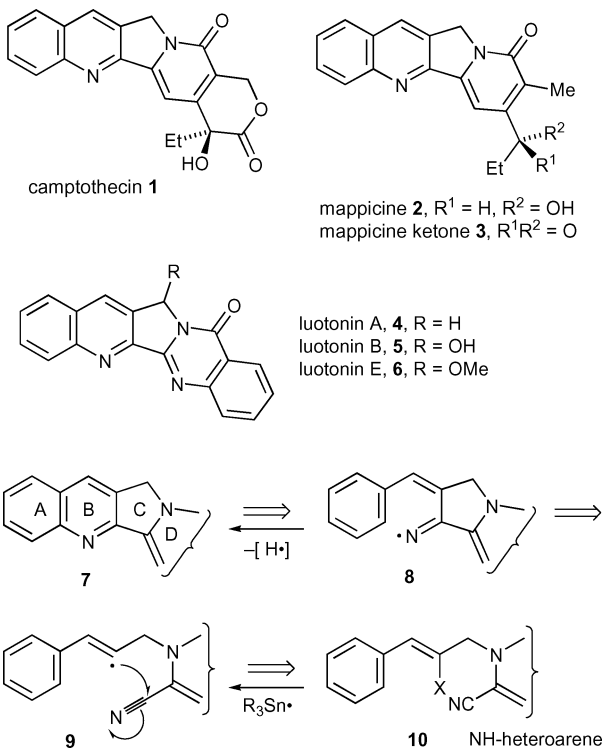


## Introduction

Tetracyclic and pentacyclic alkaloids with the 2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoline ring system making up rings A–C have been of intense interest in recent years. In particular, interest has centred around the anticancer and antiviral camptothecin **1** and analogues mappicine **2** and mappicine ketone (nothapodytine B) **3**.[1] The chemistry and pharmacology of camptothecins and analogues have been fully reviewed.[1] Camptothecin[1,2] and mappicine[1,2*f*,3] have been popular targets of synthesis and a wide variety of protocols have been reported including hetero Diels–Alder reactions, condensation to form the pyridone ring in the synthesis and biomimetic synthesis. Few of these studies have used radical methodology. The major studies using radical synthesis have been reported by Curran and co-workers who have synthesised camptothecin and analogues[4–6] and mappicine[7] *via* bimolecular radical additions of radicals derived from 6-iodo-1*H*-pyridin-2-ones onto aryl-isonitriles. A synthesis of camptothecin using cyclisation of 2-quinolinyl radicals onto pyridones has also been reported.[8] Synthetic studies towards mappicine using radical cyclisation onto enamides have also been reported.[9]

Another group of alkaloids containing the 2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoline ring system are the recently discovered pyrroloquinazolinoquinoline alkaloids, luotonins A **4**, B **5** and E **6** and other congeners.[10] Although the compounds were only isolated four years ago[10] there are already several syntheses of luotonin A, which has proved a popular synthetic target.[11] None of the syntheses have used radical protocols. The luotonins are used in traditional Chinese medicine and are reported to exhibit activity against a range of ailments including rheumatism, inflammation, influenza, hepatitis and luekemia.[10,11] More recently, luotonin A has shown great promise as an antitumour compound and is a poison for human DNA topoisomerase I.[10*b*]

In our studies of radical reactions of nitriles we showed that the cyclisation onto the nitrile group could be used in synthesis with understanding of the reactivity and rates of reactions.[12] The rates of cyclisation onto nitriles are slow, and faster, competing reactions need to be avoided in the design of syntheses. For example, the rate cyclisation of 4-cyanobutyl radicals [$^{\bullet}CH_2(CH_2)_3CN$] is slow ($4 \times 10^3$ $s^{-1}$ at 25 °C).[13] We showed that 5-*exo* cyclisation of reactive aryl and vinyl radicals was faster than alkyl radicals thus providing more suitable reactions for synthesis and that cyclisation onto nitriles to generate intermediate iminyl radicals could be used for further tandem cyclisations onto alkenes.[12] We have developed these studies to a new protocol for the synthesis of the 2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinoline ring system **7** which depends on several radical reactions in a cascade sequence (Scheme 1).[14]




**Scheme 1**

In this synthetic protocol, the first of the radical cyclisations in the cascade sequence is 5-*exo* cyclisation of vinyl radicals onto nitriles, *i.e.* **9** to **8**. Vinyl[6,14,15] and imidoyl[16] radical cyclisations onto nitriles have been reported in a few examples. In the second

† Electronic supplementary information (ESI) available: preparation and analytical details for heteroarene compounds. See http://www.rsc.org/suppdata/ob/b5/b501509j/

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step of the cascade process (**8** to **7**), the newly formed iminyl radical intermediate **8** undergoes 6-*endo* (or 5-*exo* cyclisation followed by neophyl rearrangement) cyclisation onto the arene. The cyclisation reactions of the iminyl radical have been extensively studied by Zard and co-workers.[17] The final step is formally an aromatic homolytic substitution in which the iminyl radical substitutes for a hydrogen radical (H•). Aromatic homolytic substitution is a much under-used and maligned synthetic reaction but importantly is usefully regioselective when intramolecular.[18] In recent years many of the aromatic homolytic substitutions have been facilitated using tributyltin hydride to excellent synthetic application.[19] While these reactions can be formally described as aromatic homolytic substitution, the exact mechanism is unclear.[19]

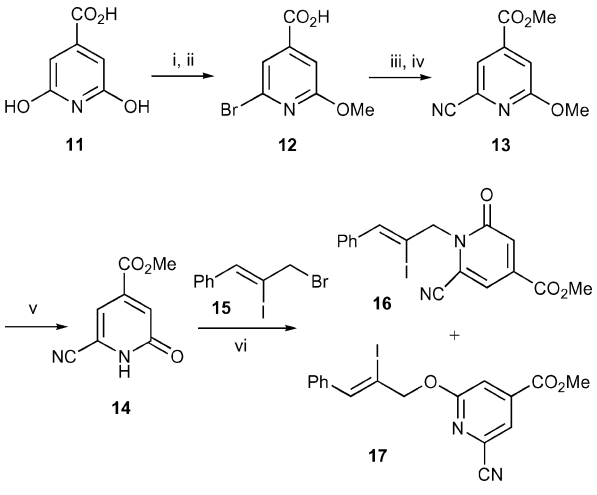
With the dual aim of further studying cyclisation onto nitriles and investigating its use in synthesis, we report the application of the methodology to the synthesis of mappicine (**2**) and mappicine ketone (nothapodytine B; **3**) and luotonin A (**4**).

## Results and discussion

### Mappicine 2 and nothapodytine B 3

Our first investigation was the synthesis of mappicine **2** and mappicine ketone **3**. We sought to synthesise the simplest relay **21** which has been used in the synthesis of mappicine, thereby constituting a formal synthesis.[2e,20] The use of the electron-withdrawing substituent also provides an interesting test for the chemistry. The interconversion between the ketone of nothapodytine B and the alcohol of mappicine are facile so both present a formal synthesis of each other.

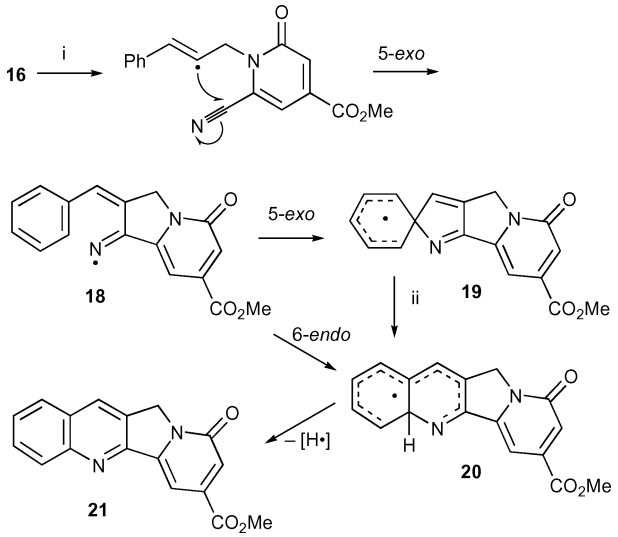
The radical precursor **16** was synthesised as shown in Scheme 2 using a similar procedure to our earlier study.[14] 2,6-Dibromopyridine-4-carboxylic acid was synthesised from the commercially available citrazinic acid **11** in an 80% yield.[21] $S_NAr$ substitution with methoxide yielded 2-bromo-6-methoxypyridine-4-carboxylic acid **12** in a 96% yield.[14,22] The usual procedure[14] for the introduction of the nitrile group using CuCN and decomposition of the resultant copper complex to liberate the aryl nitrile proved problematic and black tars were observed. Therefore, the copper(I)-catalysed cyanation was carried out on the methyl ester, methyl 2-bromo-6-methoxypyridine-4-carboxylate, instead of the free carboxylic acid. Various alternative procedures were attempted but the yield of 40% could not be further maximised, indicating that the ester group hinders the reaction. The product **13** was only obtained when methanol was used in place of water in the decomposition of the copper complex. The low yield is likely




**Scheme 2** *Reagents and conditions*: i, $POBr_3$, 180 °C, 80%; ii, NaOMe, MeOH, 60 °C, 96% (**12**); iii, MeOH, conc. $H_2SO_4$, 87%; iv, CuCN, DMF, reflux, 48 h, 40% (**13**); v, TMSCl, NaI, MeCN, 63% (**14**); vi, **15**, NaH, LiCl, DME, DMF, 32% (**16**), 30% (**17**).

to be due to some hydrolysis to 2-cyano-6-methoxypyridine-4-carboxylic acid which binds to the copper in the reaction. Conversion of **13** to the cyanopyridone **14** was carried out using a literature procedure.[5,14] The cyanopyridone **14** was alkylated with the α-iodocinnamyl bromide[14] **15** using conditions that normally favour *N*-alkylation of pyridones.[14,23] The radical precursor **16** was obtained in only a 32% yield. The low yield was due to *O*-alkylation (**17**, 30%) and the formation of small amounts of methyl 6-cyano-1,2-dihydro-1-methyl-2-oxo-4-pyridine-carboxylate. The reasons for the low *N*-selectivity are not obvious.

The radical precursor **16** was reacted under similar conditions to those reported in our earlier paper,[14] *i.e.* hexamethylditin (7.5 equiv.) in *tert*-butylbenzene with sun lamp irradiation (Scheme 3). Hexamethylditin was used in order to prevent trapping of intermediate radicals with a reagent such as tributyltin hydride. Irradiation and heating at 150 °C gave considerable decomposition with an isolated yield of methyl 9-oxo-9,11-dihydroindolizino[1,2-*b*]quinoline-7-carboxylate **21** of only 15%. Reaction at a lower temperature of 85 °C with a smaller amount of hexamethylditin (2 equiv.) gave a better yield of **21** (50% crude, 21% purified). These lower yields were disappointing compared with yields of up to 80% in earlier studies but indicate that the ester group makes the substrate **16** more reactive.[14] The use of di-*tert*-butyl peroxide as an initator[14] largely resulted in decomposition with only a trace of **21**. This may be related to the presence of the methoxy functional group, as decomposition under these conditions was also observed in the synthesis of the tetracyclic rings A–D of nothapodytine A which contains a 1-methoxy substituent.[14] Hydrogen-abstraction from methoxy groups is unfortunately common due to the formation of a stable radical.



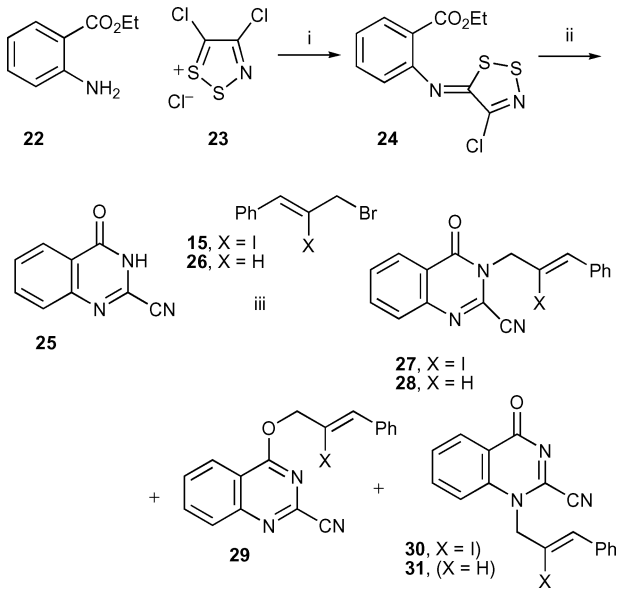

**Scheme 3** *Reagents and conditions*: i, $(Me_3Sn)_2$, *tert*-BuPh, *hv*, 85 °C, 24 h, 21% (**21**).

Scheme 3 shows the putative mechanism of the cascade reaction.[14] Abstraction of iodine by the trimethyltin radical ($Me_3Sn^•$) yields the vinyl radical which undergoes 5-*exo* cyclisation onto the nitrile group to yield an intermediate iminyl radical **18**. The rate of bromine abstraction by $Bu_3Sn^•$ radicals of bromine from vinyl bromides is fast ($10^6$–$10^7$ $M^{-1}$ $s^{-1}$),[24] and therefore, abstraction of iodine by $Me_3Sn^•$ will be faster and is unlikely to be rate determining in the reaction sequence. Both the 5-*exo* cyclisation onto the nitrile to yield **18** and cyclisation of the iminyl radical intermediate onto the phenyl ring (5-*exo* to **19** or 6-*endo* to **20**) are slow. The abstraction of the hydrogen from **20** is the second step of the aromatic homolytic substitution. The mechanism of this step is not clear but we have proposed that the abstracting species are methyl radicals from the breakdown of

trimethyltin radicals.[14] Blank reactions without hexamethylditin gave traces of **21** indicating iodine-homolysis or Diels–Alder cyclisation as possible minor mechanisms.

### Luotonin A (4)

Our initial aim for the synthesis of luotonin A **4** was to use the same methodology, *i.e.* to alkylate a suitable α-cyano NH-heteroarene (Scheme 4) and carry out the [4 + 2] cascade radical cyclisation as exemplified in Scheme 3 for the synthesis of mappicine and our earlier studies.[14] To this end we decided to use 4-oxo-3,4-dihydroquinazoline-2-carbonitrile **25** (Scheme 4). This model would allow study of the quinazoline ring system in the radical cascade protocol.

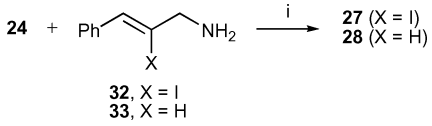



**Scheme 4** *Reagents and conditions*: i, pyridine, DCM, rt, 24 h, 92% (**24**); ii, $NH_3$, dioxane, rt, 5 d, 98% (**25**); iii, NaH, LiCl, DME, DMF, rt, 5 h: **15** gave 16% (**27**), 0% (**29**, X = I), 6% (**30**) and **26** gave 45% (**28**), 9% (**29**, X = H), <1% (**31**); NaH, DMF, 60 °C, 20 h, **26** gave 44% (**28**), trace (**29**, X = H), 0% (**31**).

4-Oxo-3,4-dihydroquinazoline-2-carbonitrile **25** was synthesised in high yield (98%) from ethyl 2-[(4-chloro-5*H*-1,2,3-dithiazol-5-yliden)amino]benzene-1-carboxylate **24** and ammonia. This represents a new route to quinazoline-2-carbonitriles. This unusual reaction between amines and the (4-chloro-5*H*-1,2,3-dithiazol-5-yliden)amino ring system, developed by Rees and co-workers,[25] proved useful in our studies. A similar application has been reported by Kim and Mohanta for the 2-cyanoquinazoline system.[26] The protocol relies on the reaction between Appel's salt[27] **23** and anthranilate esters (*e.g.* **22**) to yield **24**.[25]

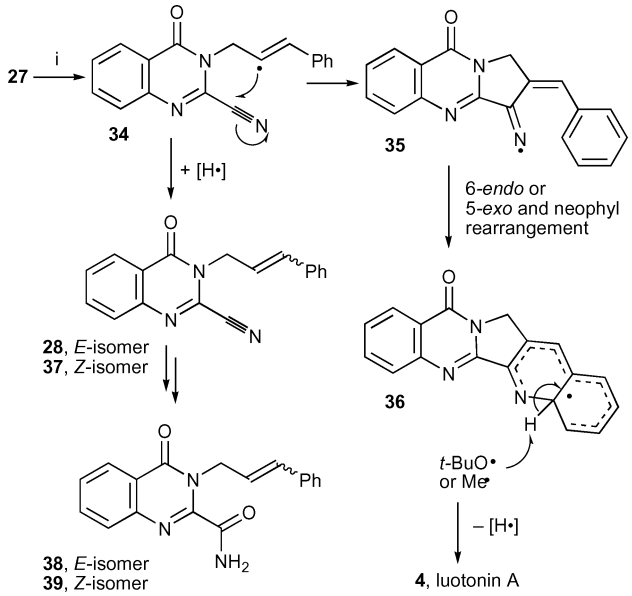
The procedure for regioselective *N*-alkylation over *O*-alkylation which has been successfully applied to 6-cyanopyridones[14] and to 6-iodopyridones[23] again gave only small amounts of *O*-alkylation (Scheme 4). In contrast, *O*-alkylation can be selectively facilitated over *N*-alkylation by using the Mitsunobu reaction with alcohols instead of halides for quinazolines and isoquinolines based on low (hard) polarisability factors.[28] We have observed the same *O*-selectivity with the Mitsunobu reaction when attempting alkylation of 6-oxo-1,6-dihydro-pyridine-2-carbonitrile with 1-[(*Z*)-3-bromo-2-iodoprop-1-enyl]benzene **15** and DEAD.[29] However, in this study the protocol was largely *N*-selective but it was not completely selective between alkylation at the 1-*N* and 3-*N* and the isomers were difficult to separate. At ambient temperatures, alkylation of **25** with cinnamyl bromide **26** gave a moderate yield of the required 3-*N* alkylated product **28**. When the temperature was raised, *O*-alkylation (to **29**, X = H) and 1-*N* alkylation (to **31**) were largely eliminated. Unfortunately, the yields for alkylation with 1-[(*Z*)-3-bromo-2-iodoprop-1-enyl]benzene[14] **15** were poor and the two regio-isomers could not be separated even after extensive chromatography.

We therefore developed a protocol which would be regioselective to the required 3-*N* product. Ethyl 2-[(4-chloro-5*H*-1,2,3-dithiazol-5-yliden)amino]benzene-1-carboxylate **24** was reacted with the required cinnamylamines **32** and **33** (Scheme 5). The cinnamylamines were prepared by standard methodology. Both cinnamylamines gave moderate yields of the required products **27** and **28**. The quinazoline **28** was synthesised as a possible product of unsuccessful cascade cyclisation for comparison and identification purposes. The yields could not be optimised but are similar to reported reactions of similar compounds in the literature.[25,26] An excess (1.5 equiv.) of Appel's salt was used to ensure complete conversion of ethyl 2-aminobenzoate **22** because it co-elutes with the product **24** creating yet further separation problems. The advantage of the Rees method in the synthesis of the radical precursor is that it avoids the possibility of alkylation at oxygen and 1-*N*. The *Z*-stereochemistry of the alkene **27** and the *E*-stereochemistry of **28** were determined by NOE difference NMR spectroscopy.




**Scheme 5** *Reagents and conditions*: i, THF, rt, 48 h, **32** gave 42% (**27**); **33** gave 40% (**28**).

The radical precursor **27** was reacted under the general reaction conditions[14] using hexamethylditin (14 equiv.) in *tert*-butylbenzene with sun lamp irradiation at 150 °C for 46 h (Scheme 6). Luotonin A **4** was formed as predicted in 21% yield along with other products (30%, an *E*/*Z* isomeric mixture). We initially assumed that the other product was the reduced uncyclised compound **28**. However, after independent syntheses of potential products, we realised that the unknown products were an *E*/*Z* isomeric mixture of the primary amides **38** and **39**. No unaltered starting material or other products were observed in the radical reactions except for large amounts of a polymeric organotin compound.[14]




**Scheme 6** *Reagents and conditions*: i, $(Me_3Sn)_2$, *tert*-BuPh, *hv*.

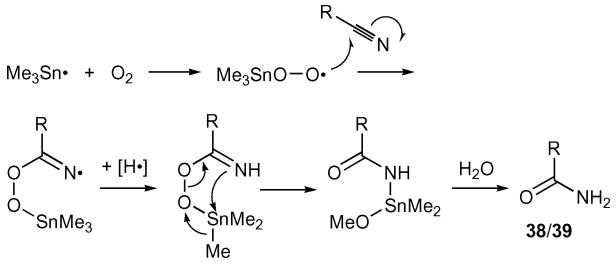
In order to improve the yield of luotonin A, milder conditions using di-*tert*-butyl peroxide were studied.[14] *tert*-Butoxyl radicals

are formed by thermal or photochemical homolysis at lower temperatures and react rapidly with hexamethylditin to yield trimethyltin radicals. The use of *tert*-butylperoxyl radicals also has the advantage of providing a reactive and efficient H-abstractor for the final rearomatisation step (Scheme 6, **36** to **4**). The reaction was carried out with **27** ($6.33 \times 10^{-2}$ M) and fewer equivalents of hexamethylditin (3.8 equiv.) and di-*tert*-butyl peroxide (2.0 equiv.) in a sealed tube at 120 °C and for a shorter reaction time (24 h) and yielded luotonin A (30%) and **38/39** (16%). The reaction was repeated at lower dilution ($1.47 \times 10^{-2}$ M) to encourage cyclisation over potential bimolecular reactions. None of the unwanted products **38/39** were observed but the yield of luotonin A dropped to 22%. This result indicates a bimolecular reaction in the formation of **38** and **39**. However, it was not clear whether formation of **38** and **39** had been prevented or whether there were subtle differences in the conditions of the reaction, *e.g.* traces of oxygen. All the starting material was consumed in these reactions, therefore, it may be possible to improve the yield under milder conditions and shorter reaction times.

The proposed mechanism of the cascade cyclisation is shown in Scheme 6. 5-*exo*-Cyclisation of the vinyl radical **34** onto the nitrile yields the iminyl intermediate **35** which undergoes cyclisation onto the phenyl ring (5-*exo* followed by a neophyl rearrangement, or 6-*endo*, to **36**). In this case both 5-*exo* and 6-*endo* routes yield the same product. We have provided evidence in previous examples of cyclisation proceeding *via* initial 5-*exo* cyclisation to a spirodienyl intermediate.[14] The abstraction of the hydrogen from the π-radical intermediate **36** to yield luotonin A **4** is formally the second step of the aromatic homolytic substitution. The mechanism of this step is not clear but we have proposed that the abstracting species are methyl radicals from the breakdown of trimethyltin radicals or *tert*-butoxyl radicals when di-*tert*-butyl peroxide was used.[14] The synthesis provides a further example, albeit in moderate yield, of our cascade methodology indicating that cyanoquinazolines can also be used and furthermore represents the first synthesis of luotonin A using radical methodology.

In order to gain further mechanistic understanding of the radical reactions of **27**, blank reactions were carried out with the radical precursor **27** and also the equivalent non-iodo 3-alkylated compound **28** in which the hexamethylditin (and di-*tert*-butyl peroxide) were omitted. Both reactions gave near quantitative recovery of unaltered starting materials with only traces of luotonin A (<1%). These blank reactions served several purposes. Firstly, the reaction with **27** proved that the radical reagents were required and hence that the reaction was radical mediated. A putative mechanism initiated by iodine-homolysis is also eliminated by the lack of reaction under these conditions. Secondly, a mechanism involving a purely thermal Diels–Alder reaction followed by loss of hydroiodic acid for the synthesis of luotonin A **4** could be envisaged for **27** but is ruled out by the blank reaction. There is literature precedence for an intramolecular Diels–Alder reaction in which a nitrile functional group behaves as the 2π component, the product in this case was also luotonin A.[11a]

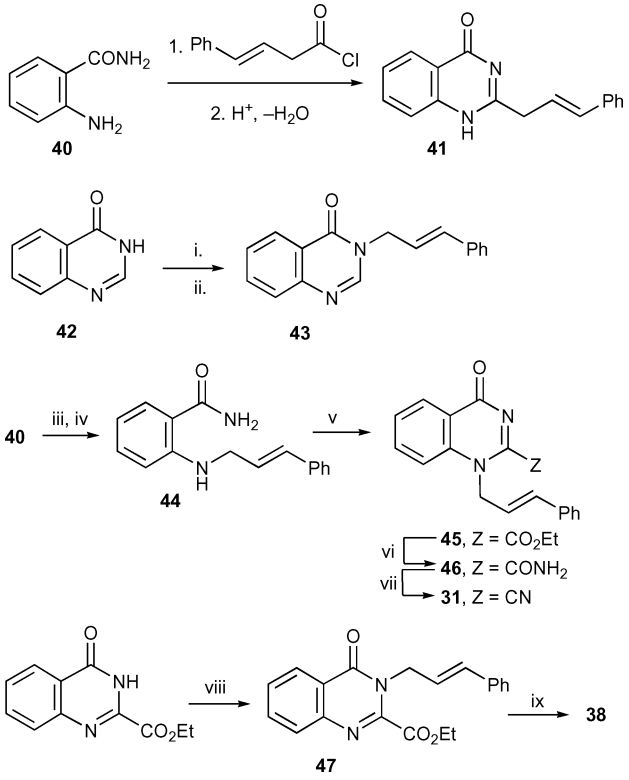
The mechanism of formation of the primary amide by-products **38** and **39** is difficult to explain. The products are clearly formed by a radical mechanism because they are not formed in the blank reaction. The most likely scenario is a competing reaction whereby the initial intermediate radical **34** can either undergo cyclisation onto the nitrile or H-abstraction to yield **28** and **37** (Scheme 6). The isomerism to an *E*/*Z* mixture can be explained by the radical intermediate **34**. We have previously observed the formation of primary amides from reactions between nitriles and hexamethylditin under radical conditions. The mechanism is not obvious but we propose that the most likely explanation is that traces of oxygen react with the trimethylstannyl radicals as shown in Scheme 7.[30] Even with careful freeze–thaw techniques traces of oxygen are difficult to eliminate completely. The nucleophilic peroxyl




**Scheme 7** RCN = **38/37**.

radicals add to the electrophilic nitrile. The resulting iminyl radicals undergo 1,5-hydrogen abstraction or H-abstraction from π-radical intermediates to yield unstable intermediates which rearrange under the high temperature conditions. The rearranged products rapidly hydrolyse on work-up to yield the primary amides. A precedent has been reported for an analogous compound which has an acyl group in place in the iminyl group.[31]

The characterisation of the unknown products **38/39** isolated from the radical reactions was ambiguous and the purification was hindered by two geometrical isomers which co-eluted on chromatography. In order to be certain of the assignment of the structures, possible products were synthesised by unoptimised but unambiguous routes (Scheme 8).




**Scheme 8** *Reagents and conditions*: i, NaH, DMF, DME, LiBr; ii, cinnamyl bromide, 2 h; iii, cinnamaldehyde, EtOH, reflux, 15 min (46%); iv, $NaBH_4$, MeOH, 30 min, 94% (**44**); v, methyl oxalyl chloride, $Et_3N$ followed by $H^+$, 83% (**45**); vi, $NH_4OH$, EtOH, 64% (**46**); vii, EDCI, HOAT (1-hydroxy-7-azabenzotriazole) (catalytic), DCM, reflux, 3 d, 36% (**31**); viii, NaH, DMF; cinnamyl bromide, 50% (**47**); ix, $NH_3$, EtOH, 69% (**38**).

The absence of a nitrile absorption in the IR spectrum and the absence of a molecular ion including the nitrile in the mass spectrum suggested a product without a nitrile group. 2-[(*E*)-3-Phenylprop-2-enyl]-3*H*-quinazolin-4-one **41** was synthesised from anthranilamide **40** and the acid chloride of cinnamic acid using a protocol adapted from the literature.[32,33] Radical abstraction of iodine and the nitrile group presents another possibility to yield 3-[(*E*)-3-phenylprop-2-enyl]-3*H*-quinazolin-4-one **43**. The 3-cinnamyl derivative **43** was prepared by

alkylation of 3*H*-quinazolin-4-one **42**. The data for **41** and **43** were similar to the unknown **38** but clearly different, thereby ruling out these structures.

Although unlikely, we considered that a radical rearrangement to the 1-*N*-substituted 4-oxo-1-[(*E*)-3-phenylprop-2-enyl]-3,4-dihyroquinazoline-2-carbonitrile **31** may be possible. The nitrile **31** was prepared by an adapted literature procedure for the synthesis of 1-*N*-substituted 2-cyano-3*H*-quinazolin-4-ones (Scheme 8).[33,34] The conversion of the primary amide to the nitrile proved troublesome. The use of phosphorus oxychloride for dehydrating the primary amide to the nitrile led to removal of the cinnamyl group by $S_N2$ substitution by chloride on the cinnamyl methylene group. An alternative method of dehydration using EDCI [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide] proved satisfactory for converting **46** to **31**.[35] Again, the data for **46** and **31** were similar to **38** but not identical. Finally, we synthesised the unexpected primary amide **38** as shown in Scheme 8. The synthesised primary amide **38** was identical to the *E*-isomer of the isomeric mixture of unknown compounds isolated from the radical reactions.

Our studies report novel cascade radical reactions and have indicated that the methodology shown in Scheme 1 can be applied to a range of radical precursors. Further studies are underway to apply the general protocol to a wider range of syntheses.

## Experimental

Commercial dry solvents were used in all reactions except for light petroleum and ethyl acetate which were distilled from $CaCl_2$ and dichloromethane (DCM) which was distilled over phosphorus pentoxide. Light petroleum refers to the bp 40–60 °C fraction. Sodium hydride was obtained as a 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. $^1$H (250 MHz) and $^{13}$C (62.5 MHz) NMR spectra were recorded on a Bruker AC-250 spectrometer as solutions of $CDCl_3$ with tetramethylsilane (TMS) as the internal standard for $^1$H NMR spectra and deuteriochloroform the standard for $^{13}$C NMR spectra unless otherwise specified. 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. GC–MS was carried out on a Fisons 8000 series GC–MS using a 15 m × 0.25 mm DB-5 column and an electron impact low resolution mass spectrometer. TLC using silica gel as adsorbent was carried out with aluminium-backed plates coated with silica gel (Merck Kieselgel 60 F254). Silica gel (Merck Kieselgel 60 H silica) was used for column chromatography unless otherwise specified.

### Methyl 6-cyano-2-oxo-1,2-dihydropyridine-4-carboxylate 14

Chlorotrimethysilane (0.560 g, 5.16 mmol) was added slowly to a mixture of methyl 2-cyano-6-methoxypyridine-4-carboxylate **13** (0.323 g, 1.681 mmol) and sodium iodide (0.773 g, 5.16 mmol) in acetonitrile (2.5 cm$^3$) and the mixture stirred at 80 °C for 6 h. The solution was cooled to room temperature, evaporated under reduced pressure and water was added (2 cm$^3$). This suspension was purified by column chromatography using DCM/light petroleum as eluent to yield methyl 2-cyano-6-methoxypyridine-4-carboxylate **13** (0.12 g, 37%). Elution with a gradient mixture of DCM/EtOAc gave the product methyl 6-cyano-2-oxo-1,2-dihydropyridine-4-carboxylate **14** (0.189 g, 63%), mp 201–203 °C (Found: C, 53.8; H, 3.35; N, 15.51. $C_8H_6N_2O_3$ requires C, 53.94; H, 3.39; N, 15.73%); $\nu_{max}$ (Nujol)/cm$^{-1}$ 3100–2400 (broad NH); 2245 (CN), 1721, 1658 (C=O, pyridone), 1615, 1573, 1343, 1283, 1243, 1198, 1024, 993, 947, 909, 884, 775 and 759; $\delta_H$ ($d_7$-DMF) 3.91 (3 H, s, OMe), 7.31 (1 H, s, 5-H), 7.74 (1 H, s, 3-H) and 12.38 (1 H, br s, NH); $\delta_C$ ($d_6$-DMSO) 51.45 (OMe), 163.14 and 161.83 (C=O ester and 2-C), 139.70 (4-C), 128.05 (6-C), 117.49 (3-C), 114.77 (5-C) and 114.27 (CN); *m*/*z* (EI) 178 (M$^+$, 93%, Found: 178.0381. $C_8H_6N_2O_3$ requires 178.0378), 147 (75), 119 (100), 110 (15), 91 (45), 76 (10) and 64 (18).

### Methyl 6-cyano-1-[(*Z*)-2-iodo-3-phenylprop-2-enyl]-2-oxo-1,2-dihydropyridine-4-carboxylate 16

60% NaH (0.445 g, 11.13 mmol) was added portion-wise to a solution of methyl 6-cyano-2-oxo-1,2-dihydropyridine-4-carboxylate **14** (1.894 g, 10.64 mmol) in 1,2-dimethoxyethane (monoglyme) (21 cm$^3$) and dimethylformamide after 10 min. The mixture was stirred for 15 min at room temperature, 1-[(*Z*)-3-bromo-2-iodoprop-1-enyl]benzene[14] **15** (1.6 g, 4.97 mmol) added, and the reaction heated at 65 °C for 20 h. The mixture was cooled to room temperature and poured into brine (50 cm$^3$), extracted with EtOAc and dried. The solution was evaporated under reduced pressure to give an orange solid which was purified by column chromatography using EtOAc/DCM as eluent to give methyl 6-cyano-1-[(*Z*)-2-iodo-3-phenylprop-2-enyl]-2-oxo-1,2-dihydro-pyridine-4-carboxylate **16** (1.398 g, 31%), mp 122–123 °C (DCM/light petroleum) (Found: M$^+$, 419.9971. $C_{17}H_{13}IN_2O_3$ requires 419.9971); $\nu_{max}$ (DCM)/cm$^{-1}$ 2230 (CN), 1736, 1674 (C=O, pyridone), 1605, 1543, 1219, 1080, 988, 864, 772 and 694; $\delta_H$ 3.95 (3 H, s, $CO_2Me$), 5.22 (2 H, d, *J* = 1.2Hz, $CH_2N$), 7.07 (1 H, s, vinylic 3-H), 7.27 (3 H, d, *J* 2.0, pyridone 5-H), 7.32–7.38 (3 H, m, phenyl 3,4-H) and 7.48–7.50 (3 H, m, phenyl 2,6-H and pyridone 3-H); $\delta_C$ 53.41 (OMe), 58.20 ($CH_2N$), 95.70 (vinylic 2-C), 163.13, 160.34 (ester C=O, pyridone C=O), 139.33, 136.63 (pyridone 4-C, phenyl 1-C), 139.18 (vinylic 3-C), 128.96 (phenyl 4-C), 128.61 (phenyl 3-C), 128.59 (pyridone 3-C), 128.19 (phenyl 2-C), 121.67 (pyridone 6-C), 114.40 (pyridone 5-C) and 112.32 (CN); *m*/*z* 420 (M$^+$, 77%), 388 (3), 328 (7), 293 (13), 281 (4) 268 (30), 192 (7), 181 (6), 133 (9), 115 (14), 91 (100), and 65 (5). Methyl 2-cyano-6-{[(*Z*)-2-iodo-3-phenylprop-2-enyl]oxy}pyridine-4-carboxylate **17** was also eluted (1.37 g, 30%), Found: M$^+$, 419.9973. $C_{17}H_{13}IN_2O_3$ requires 419.9971; $\delta_H$ 3.97 (3 H, s, $CO_2Me$), 5.25 (2 H, d, *J* = 1.1 Hz, $CH_2O$), 7.21 (1 H, s, vinylic 3-H), 7.33–7.37 (3 H, m, phenyl 4- and 3-H), 7.54–7.56 (2 H, m, phenyl 2-H), 7.64 (1 H, d, *J* 1.1, 5-H) and 7.85 (1 H, d, *J* 1.1, 3-H); $\delta_C$ 53.23 (ester OMe), 75.71 ($CH_2O$), 97.48 (vinylic 2-C), 116.51 (CN), 116.67 (5-C), 121.78 (pyridine 3-C), 128.17 (phenyl CH), 128.52 (phenyl CH), 128.62 (phenyl CH), 131.01 and 136.55 (2-C, phenyl 1-C), 137.74 (vinylic 3-C), 141.55 (4-C) and 163.43 and 163.69 (ester C=O, 6-C). Methyl 6-cyano-1,2-dihydro-1-methyl-2-oxo-4-pyridine-carboxylate was eluted (0.2133 g), mp 144–145 °C (DCM/light petroleum) (lit.,[36] 143–144 °C) (Found: M$^+$, 192.0536. $C_9H_8N_2O_3$ requires 192.0535); $\nu_{max}$ (DCM)/cm$^{-1}$ 2233, 1737 (C=O, ester), 1675 (C=O, pyridone), 1603, 1543, 1220, 1128, 1081, 1000, 992, 964, 909 and 856; $\delta_H$ 3.73 and 3.95 (3 H each, s, $CO_2Me$, N–Me), 7.22 (1 H, d, *J* = 2.0 Hz, 5-H), 7.43 (1 H, d, *J* 2.0, 3-H); $\delta_C$ 34.83 (NMe), 53.36 (ester OMe), 112.27 (6-C), 113.63 (5-C), 122.08 (CN), 128.31 (3-C), 139.12 (4-C), 163.29, 161.00 (ester C=O, pyridine C=O); *m*/*z* 192 (M$^+$, 63%), 153 (8), 136 (8), 133 (100), 115 (16), 105 (18), 91 (10), 89 (14), 77 (36), 67 (25), 63 (9), 59 (19), 51 (18) and 43 (17).

### Methyl 9-oxo-9,11-dihydroindolizino[1,2-*b*]quinoline-7-carboxylate 21 using a 300 W sun lamp

A solution of methyl 6-cyano-1-[(*Z*)-2-iodo-3-phenylprop-2-enyl]-2-oxo-1,2-dihydropyridine-4-carboxylate **16** (0.10 g, 0.24 mmol) in *tert*-butylbenzene (6.5 cm$^3$) in a flat-bottomed, two-necked flask (Pyrex, 5 × 1 × 20 cm$^3$, wall thickness 1 mm) was purged with nitrogen for 20 min. Hexamethylditin (0.156 g, 0.48 mmol) was added by syringe and the resultant solution purged with nitrogen for a further 30 min. The mixture was

irradiated with two 150 W sun lamps at 85 °C for 24 h. The reaction was cooled to room temperature, diluted with methanol and evaporated under reduced pressure. Analysis by LCMS and $^1$H NMR spectroscopy showed **21** (50%) along with a number of unidentified products. The residue was purified using column chromatography with an eluent gradient of DCM/EtOAc/MeOH and gave methyl 9-oxo-9,11-dihydroindolizino[1,2-*b*]quinoline-7-carboxylate **21** (14.6 mg, 21%), mp 184–186 °C (lit.,[37] 185–187 °C) (Found: M$^+$, 292.0848. $C_{17}H_{12}N_2O_3$ requires 292.0848); $\delta_H$ 3.99 (3 H, s, $CO_2Me$), 5.30 (2 H, s, 11-H), 7.37 (1 H, s, 6-H), 7.66 (1 H, ddd, $J$ = 7.5, 7.8, 1.0 Hz, 2-H), 7.81 (1 H, s, 8-H), 7.83 (1 H, ddd, $J$ 7.5, 7.8, 1.2, 3-H), 7.93 (1 H, dd, $J$ 7.8, 1.0, 1-H), 8.24 (1 H, dd, $J$ 7.8, 1.2, 4-H), 8.39 (1 H, s, 12-H); $\delta_C$ 50.59 (11-C), 53.39 (OMe), 100.09 (6-C), 122.45 (8-C), 128.37, 128.53 (1-C, 2-C), 128.59, 129.01 (12a-C, 11a-C), 130.24, 130.97, 131.46 (12-C, 4-C, 3-C), 142.36 (7-C), 147.13, 149.37 (4a-C, 5b-C), 152.93 (5a-C), 161.58 (9-C) and 165.50 (ester C=O); *m/z* 292 (M$^+$, 100%), 277 (8), 263 (6), 249 (2), 233 (12), 205 (27), 177 (6), 140 (8), 121 (6), 115 (14), 105 (7), 95 (11), 84 (30), 77 (14), 69 (29), 57 (23) and 49 (31).

The reaction was carried out under similar conditions at 150 °C with a larger excess of hexamethyditin (3.66 mmol) and **16** (0.048 mmol) in *tert*-butylbenzene (6.5 cm$^3$) which yielded **21** (15%). The reaction was also repeated with the addition of di-*tert*-butyl peroxide in a sealed tube and heated which yielded **21** in less than 5%.

### 4-Oxo-3,4-dihydroquinazoline-2-carbonitrile 25

Ethyl 2-[(4-chloro-5*H*-1,2,3-dithiazol-5-yliden)amino]benzene-1-carboxylate **24** (4.453 g, 14.84 mmol) was added to an ammonia solution (0.5 M) in 1,4-dioxane (100 cm$^3$, 0.05 mol). The solution was sealed under nitrogen and stirred at room temperature for 5 d. The brown precipitate was filtered and washed with light petroleum to give 4-oxo-3,4-dihydroquinazoline-2-carbonitrile **25** (2.48 g, 98%). (Found: [M + $NH_4$]$^+$ 189.0772, $C_9H_5N_3O$+$NH_4$ requires 189.0776; Found: M$^+$, 171.0432. $C_9H_5N_3O$ requires 171.0433); $\nu_{max}$ (Nujol)/cm$^{-1}$ 3134 (NH), 2236 (CN), 1698 (C=O), 1608, 1574, 1521, 1408, 1367, 1346, 1112, 998 and 776; $\delta_H$ (DMSO-$d_6$) 7.34–7.37 (1 H, m, 6-H), 7.50–7.52 (1 H, m, 8-H), 7.59–7.61 (1 H, m, 7-H) and 7.99–8.00 (1 H, m, 5-H); $\delta_C$ 118.08 (CN), 123.75 (4a-C), 126.49 (5-C), 126.03 (6-C, 8-C, overlap), 132.35 (7-C), 143.62 (8a-C), 150.73 (2-C) and 171.21 (C=O); *m/z* [CI+($NH_3$)] 189 [(M + $NH_4$)$^+$, 50%], 172 (92), 161 (30) and 147 (100); GC–MS shows one peak, (EI) 171 (M$^+$, 100%), 143 (50), 116 (25), 90 (25), 76 (10), 63 (30), and 53 (25).

### 4-Oxo-3-[(*E*)-3-phenylprop-2-enyl]-3,4-dihyroquinazoline-2-carbonitrile 28: procedure for the alkylation of 4-oxo-3,4-dihydroquinazoline-2-carbonitrile 25

NaH (93.9 mg, 2.35 mmol) was added slowly with stirring to a solution of 4-oxo-3,4-dihydroquinazoline-2-carbonitrile **25** (0.402 g, 2.35 mmol) in anhydrous dimethyl sulfoxide (4.7 cm$^3$) under an atmosphere of nitrogen. Cinnamyl bromide (0.4631 g, 2.35 mmol) was added after 1 h and the solution stirred at room temperature under nitrogen for 5 h. Water was added and the mixture extracted with DCM. The organic fractions were evaporated under reduced pressure and the residue purified by column chromatography using DCM/light petroleum as eluent to give an inseparable mixture of 4-oxo-3-[(*E*)-3-phenylprop-2-enyl]-3,4-dihyroquinazoline-2-carbonitrile **28** (0.302 g, 45%) and 4-{[(*E*)-3-phenylprop-2-enyl]oxy}quinazoline-2-carbonitrile **29** (X = H) (59 mg, 9%). Further elution gave 4-oxo-1-[(*E*)-3-phenylprop-2-enyl]-1,4-dihydroquinazoline-2-carbonitrile **31** (<1%).

**28**: mp 147–148 °C (from DCM/light petroleum) (Found: C, 75.4; H, 4.4; N, 14.4. $C_{18}H_{13}N_3O$ requires C, 75.25; H, 4.56; N, 14.63%); $\nu_{max}$ (Nujol)/cm$^{-1}$ 2207 (CN), 1693 (C=O), 1590, 1558, 776 and 692; $\delta_H$ 5.02 (2 H, d, $J$ = 6.7 Hz, $CH_2$), 6.33 (1 H, dt, $J$ 6.7, 15.8, propenyl 2-H), 6.81 (1 H, d, $J$ 15.8, propenyl 3-H), 7.24–7.31 (3 H, m, phenyl 3,4,5-H), 7.36–7.38 (2 H, m, phenyl 2,6-H), 7.63 (1 H, dd, $J$ 7.9, 7.9, 6-H), 7.78–7.83 (2 H, m, 7- and 8-H) and 8.32 (1 H, d, $J$ 7.9, 5-H); values were assigned using NOE difference spectroscopy; important NOEs were observed between the methylene protons and the propenyl 2-H (2.6%) and propenyl 3-H (3.6%) indicating the *E*-stereochemistry but not with 8-H indicating the 3-*N* isomer; $\delta_C$ 48.11 ($CH_2$), 111.64 (CN), 120.91 (propenyl 2-C), 122.79 (4a-C), 126.75 (phenyl 2,6-C), 127.11 (8-C), 128.45 and 128.49 (propenyl 3-C, phenyl 4-C), 128.63 (phenyl 3,5-C), 130.02 (6-C), 131.32 (phenyl 1-C), 135.09 (5-C), 135.58 (8a-C), 136.13 (7-C), 146.37 (2-C), and 159.72 (C=O); *m/z* 287 (M$^+$, 37%, Found: M$^+$, 287.1058. $C_{18}H_{13}N_3O$ requires 287.1058), 258 (2), 196 (43), 117 (100), 102 (4), 91 (14), 77 (5) and 76 (4).

**29** (X = H) (Found: M$^+$, 287.1058. $C_{18}H_{13}N_3O$ requires 287.1059); $\delta_H$ 5.25 (2 H, d, $J$ = 6.2 Hz, $OCH_2$), 6.6.4–6.61 (1 H, dt, $J$ 6.2, 15.9, propenyl 2-H), 6.83 (1 H, d, $J$ 15.9, propenyl 3-H), 7.24–7.31 (3 H, m, phenyl 3, 4, 5-H), 7.41–7.43 (2 H, m, phenyl 2, 6-H), 7.68 (1 H, dd, $J$ 7.9, 7.9, 6-H), 7.85 (1 H, dd, $J$ 7.9, 7.9, 7-H), 7.98 (1 H, d, $J$ 7.9, 8-H) and 8.21 (1 H, d, $J$ 7.9, 5-H); $\delta_C$ 68.83 ($OCH_2$), 116.27 and 116.94 (CN, 4a-C), 122.08 (propenyl 2-C), 139.60 (2-C), 123.71, 129.68, 135.03 and 135.55 (5,6,7,8-C), 150.50 (8a-C), 166.90 (4-C), the remaining resonances overlap with those of **28**; *m/z* 244 (31%), 230 (9), 171 (4), 153 (4), 131 (49) and 84 (18). **31** was not fully characterised but exhibited a similar mass spectrum using GC–MS.

The alkylation was repeated with **25** (0.275 g) using only NaH and DMF with heating at 65 °C for 20 h after the addition of cinnamyl bromide. **28** (0.203 g, 44%) was obtained with only a trace of the *O*-alkyl **29** and none of the *N*-1 alkylated product was observed.

### 3-[(*Z*)-2-Iodo-3-phenylprop-2-enyl]-4-oxo-3,4-dihydroquinazoline-2-carbonitrile 27 using amine 32

(*Z*)-2-Iodo-3-phenylprop-2-en-1-amine **32** (0.7856 g, 3.03 mmol) was added to a solution of ethyl 2-[(4-chloro-5*H*-1,2,3-dithiazol-5-yliden)amino]benzene-1-carboxylate **24** (0.2275 g, 0.76 mmol) in anhydrous tetrahydrofuran (20 cm$^3$). The mixture was stirred for 2 d at room temperature under an atmosphere of nitrogen. The reaction mixture was evaporated under reduced pressure and the residue purified by column chromatography using DCM/light petroleum as eluent to yield **27** (0.128 g, 42%), mp 152–152.5 °C (DCM/light petroleum). (Found: C, 52.4; H, 2.7; N, 9.8. $C_{18}H_{12}IN_3O$ requires C, 52.32; H, 2.93; N, 10.17%); $\nu_{max}$ (DCM)/cm$^{-1}$ 2234 (CN), 1698 (C=O), 1605 (C=N), 1586, 1561, 1471 and 1383; $\delta_H$ 5.32 (2 H, s, $CH_2$, NOE enhancement from propenyl 3-H, 6%), 7.17 (1 H, s, propenyl 3-H, NOE enhancement from $CH_2$, 6%), 7.32–7.34 (3 H, m, phenyl 3,4,5-H), 7.52–7.49 (2 H, m, phenyl 2,6-H); 7.67–7.62 (1 H, m, 6-H), 7.81–7.85 (2 H, m, 7,8-H), 8.32–8.34 (1 H, m, 5-H); $\delta_C$ 56.94 ($CH_2$), 96.14 (propenyl 2-C), 111.59 and 122.61 (CN, 4a-C), 127.36 (CH), 128.16 (CH) and 128.59 (CH) with two overlapping CH peaks, 130.20 (CH), 131.25 (phenyl 1-C), 135.31 (7-C), 136.48 (8a-C), 139.26 (propenyl 3-C), 146.13 (2-C), and 159.51 (4-C); *m/z* (FAB), 414 [(M + H)$^+$, 12%, Found: 414.0101. $C_{18}H_{12}IN_3O$ + H requires 414.0105], 286 (100), 259 (41), 254 (35), 243 (45), 219 (15), 208 (25), 165 (29), 116 (70) and 105 (40); *m/z* (EI) 354 (6%), 286 (92), 262 (4), 146 (7), 125 (7), 115 (100), 97 (18), 83 (20), 69 (22), 63 (10), 57 (37) and 43 (33).

### 11,13-Dihydroquino[2′,3′:3,4]pyrrolo[2,1-*b*]quinazolin-11-one (luotonin A) 4 and 4-oxo-3-(3-phenylprop-2-enyl)-3,4-dihydroquinazoline-2-carboxylic acid amide 38/39 (*E*/*Z* mixture 2 : 1)

**Sun lamp irradiation at 150 °C.** A solution of 3-[(*Z*)-2-iodo-3-phenylprop-2-enyl]-4-oxo-3,4-dihydroquinazoline-2-carbonitrile **27** (107.0 mg, 0.26 mmol), hexamethylditin (1.20 g,

3.66 mmol, 14 equiv.) and *tert*-butylbenzene (6.5 $cm^3$), in a flat-bottomed, two-necked Pyrex flask (5 × 1 cm and 25 cm high, wall thickness = 1 mm), was purged with nitrogen for 30 min. The mixture was irradiated with a combined 300 W sun lamp at 150 °C for 46 h. The reaction was cooled to room temperature, diluted with MeOH and evaporated under reduced pressure to a small volume. The residue was purified using column chromatography with light petroleum as eluent to remove the *tert*-butylbenzene. Further elution with DCM/diethyl ether gave luotonin A **4** as a white solid (15.4 mg, 21%) and 4-oxo-3-[(*E*)-3-phenylprop-2-enyl]-3,4-dihydroquinazoline-2-carboxylic acid amide **38/39** (*E*/*Z* mixture = 2.8 : 1) (22.3 mg, 30%) as a mixture. Separation was achieved using preparative silica gel plates and DCM as eluent. Data for **4**: mp 277–279 °C (DCM/light petroleum ether) (lit.,[10] 281–283 °C) (Found $M^+$, 285.0904. $C_{18}H_{11}N_3O$ requires 285.0902); $\nu_{max}$ (DCM)/$cm^{-1}$ 1674, 1628, 1605, 1465, 1352, 1320, 1234, 1189, 1134, 1026, 768 and 686; $\delta_H$ 5.36 (2 H, s, 13-H), 7.57–7.61 (1 H, dd, *J* = 8.0, 8.0 Hz, 9-H), 7.69–7.73 (1 H, ddd, *J* 0.8, 8.0, 8.0, 2-H), 7.86 and 7.87 (2 H, dd and dd, *J* 8.0, 8.0, 3-H and 8-H, overlap), 7.97 (1 H, d, *J* 7.6, 1-H), 8.13 (1 H, d, *J* 8.0, 7-H), 8.44 (1 H, dd, *J* 0.8, 8.0, 4-H H-4), 8.47 (1 H, s, 14-H) and 8.49 (1 H, d, *J* 8.0, 4-H), values were assigned using NOESY and COSY correlation spectra; $\delta_C$ 47.33 (13-C), 121.38 (10a-C), 126.49 (10-C), 127.49 (9-C), 128.00 (1-C), 128.59 (2-C), 128.79 (7-C), 128.85 (14a-C), 129.45 (13a-C), 130.71 and 130.75 (3-C and 4-C), 131.56 (14-C), 134.60 (8-C), 149.40 and 149.47 (6a-C, 4a-C), 151.22 (5a-C), 152.58 (5b-C) and 160.68 (11-C); *m*/*z*(FAB) 286 [$(M + H)^+$, 100%, Found 286.0984. $C_{18}H_{11}N_3O$ + H requires 286.0980], 249 (45), 190 (30), 167 (12), 127 (14), 115 (45) and 105 (25); *m*/*z* (EI) 285 ($M^+$, 100%), 257 (10), 229 (8), 189 (3), 149 (8), 128 (5), 115 (11), 84 (28), 77 (9), 71 (18), 57 (29) and 43 (14).

Data for **38/39** [(mixture of *E*/*Z*-isomers (2.8 : 1)]: [Found $(M - CONH_2)^+$ 261.1027. $C_{18}H_{13}N_3O - CONH_2$ requires 261.1027]; $\nu_{max}$ (DCM)/$cm^{-1}$ 1682, 1587, 1265 and 727; $\delta_H$ (400 MHz) 5.40 (2 H, dd, *J* = 1.2, 6.6 Hz, $CH_2$, *E*-isomer), 5.50 (2 H, dd, *J* 2.0, 6.0, $CH_2$, *Z*-isomer), 5.67 (1 H, dt, *J* 6.0, 11.8, propenyl 2-H, *Z*), 5.77 (1 H, brs, NH, *E*), 6.39 (1 H, dt, *J* 6.6, 15.8, propenyl 2-H, *E*), 6.61 (1 H, dd, *J* 2.0, 11.8, propenyl 3-H, *Z*; NOE with *Z*-propenyl 2-H of 8.4% but none with the methylene indicating *Z*-stereochemistry), 6.73 [1 H, br d, *J* 1.2, 15.8, propenyl 3-H, *E*; NOE with *Z*-propenyl 2-H (1.7%) and the methylene (3.8%) indicating *E*-stereochemistry], 7.21 (1 H, ddd, *J* 8.0, 1.6, 1.6, phenyl *o*-H, *Z*), 7.22 (1 H, ddd, *J* 8.0, 8.0, 1.6, phenyl *p*-H, *E*), 7.25–7.31 (2 H each, m, phenyl-H, *E*,*Z* overlap), 7.35–7.37 (2 H each, m, phenyl-H, *E*,*Z* overlap), 7.47 (1 H, brs, NH), 7.56 (1 H, ddd, *J* 1.3, 7.9, 7.9, 6-H, *Z*), 7.58 (1 H, ddd, *J* 1.3. 7.9, 7.9, 6-H, *E*), 7.69 (1 H, ddd, *J* 0.6, 1.3, 7.9, 8-H, *Z*), 7.70 (1 H, ddd, *J* 0.6, 1.3, 7.9, 8-H, *E*), 7.75 and 7.77 (1 H each, ddd, *J* 1.3, 7.9, 7.9, 7-H, *E*,*Z* overlap), 8.30 (1 H, ddd, *J* 0.6, 1.3, 7.9, aryl 5-H, *Z*) and 8.34 (1 H, ddd, *J* 0.6, 1.3, 7.9, 5-H, *E*); values were assigned using COSY correlation; *m*/*z* (GC–MS, EI) GC–MS showed two peaks with similar retention times and mass spectra; major isomer: 287 (25%), 279 (5), 258 (2), 196 (50), 167 (10), 117 (100), 91 (34), 76 (13), 63 (12) and 51 (8). The structure of **38** was confirmed by unambiguous synthesis (TLC, IR and $^1H$ NMR spectra).

**With di-*tert*-butyl peroxide.** A solution of 3-[(*Z*)-2-iodo-3-phenylprop-2-enyl]-4-oxo-3,4-dihydroquinazoline-2-carbonitrile **27** (90.6 mg, 0.219 mmol), hexamethylditin (274.2 mg, 0.837 mmol, 3.8 equiv.) and di-*tert*-butyl peroxide (98%, 64.9 mg, 0.423 mmol, 2.0 equiv.) in *tert*-butylbenzene (3.5 $cm^3$) in a Schlenk tube was subjected to the freeze–thaw method (six times). The sealed tube was immersed in an oil bath at 120 °C for 24 h surrounded by a safety shield in a fumehood. The reaction mixture was cooled to room temperature and placed directly on a silica gel column. Elution with light petroleum removed the *tert*-butylbenzene. Further elution with DCM/diethyl ether gave luotonin A **4** as a white solid (18.8 mg, 30%) and **38/39** (*E*/*Z* mixture 3.5 : 1) (10 mg, 16%) as a mixture. All data agreed with authentic materials.

The reaction was repeated except that a higher dilution was used [*tert*-butylbenzene (15 $cm^3$)]. The reaction gave only luotonin A **4** as a white solid (13.8 mg, 22%).

### 4-Oxo-3-[(*E*)-3-phenylprop-2-enyl]-3,4-dihydroquinazoline-2-carboxylic acid ethyl ester 47

To a pre-dried flask was added 4-oxo-3,4-dihydroquinazoline-2-carboxylic acid ester (1.00 g, 4.61 mmol), anhydrous DMF (30 $cm^3$) and sodium hydride (60% mineral oil suspension, 0.28 g, 6.92 mmol) and the reaction stirred for 10 min. Cinnamyl bromide (0.61 g, 3.09 mmol) was added and the mixture stirred for 1.5 h. The DMF was removed under reduced pressure and the residue washed with saturated brine and extracted into ethyl acetate. The product was purified by flash silica column chromatography to yield **47** as a pale yellow semi-solid (0.52 g, 50%) (Found $M^+$ 334.1319. $C_{20}H_{18}N_2O_3$ requires: 334.1317); $\nu_{max}$ (thin film)/$cm^{-1}$ 2359, 1734, 1683, 1596, 1464, 1301, 1262, 1153 and 1033; $\delta_H$ (400 MHz) 1.03 (3 H, t, *J* = 7.1 Hz, $CH_3$), 4.14 (2 H, q, *J* 7.1, $CH_2O$), 4.75 (2 H, dd, *J* 6.4, 1.4, $CH_2N$), 5.97 (1 H, dt, *J* 15.9, 6.4, propenyl-2-H), 6.35 (1 H, dd, *J* 15.9, 1.4, propenyl-3-H), 6.91–7.08 (5 H, m, phenyl-H), 7.23–7.30 (1 H, m, 8-H), 7.48–7.50 (2 H, m, 6-H and 7-H) and 8.04 (1 H, ddd, *J* 1.2, 1.2, 8.1, 5-H); $\delta_C$ (100 MHz) 161.6 (qC), 160.8 (qC), 146.7 (qC), 146.2 (qC), 135.8 (qC), 134.7 (CH), 134.6 (CH), 128.6 (CH), 128.4 (CH), 128.1 (CH), 128.0 (CH), 127.0 (CH), 126.5 (CH), 122.9 (CH), 121.9 (qC), 63.3 ($CH_2$), 45.9 ($CH_2$) and 13.8 ($CH_3$); *m*/*z* (EI) 334 ($M^+$, 8%), 261 (100), 145 (5), 115 (30) and 91(16).

### 4-Oxo-3-[(*E*)-3-phenylprop-2-enyl]-3,4-dihydroquinazoline-2-carboxylic acid amide 38

4-Oxo-3-[(*E*)-3-phenylprop-2-enyl]-3,4-dihydroquinazoline-2-carboxylic acid ethyl ester **47** (0.50 g, 1.5 mmol) was dissolved in a absolute ethanol (10 $cm^3$) to which was added concentrated aqueous ammonia (100 $cm^3$). The reaction was stirred for 30 min and the resultant precipitate filtered off. The precipitate was washed with water and dried to yield the title compound **38** as a white solid (0.315 g, 69%) (Found 306.1237. $C_{18}H_{15}N_3O_2$ + H requires 306.1237); $\nu_{max}$ (thin film)/$cm^{-1}$ 1675, 1653, 1585, 1559, 1457 and 1436; $\delta_H$ (400 MHz, $d_6$-DMSO) 4.93 (1 H, *J* = 6.8 Hz, $CH_2N$), 6.36 (1 H, *J* 6.8, 16.1, propenyl-2-H), 6.55 (1 H, *J* 16.1, propenyl-3-H), 7.23 (1 H, t, *J* 7.6, Ph *p*-H), 7.31 (2 H, t, *J* 7.6, 7.6, Ph *m*-H), 7.40 (2 H, t, *J* 7.6, 7.6, Ph *o*-H), 7.62 (1 H, ddd, *J* 1.2, 7.9, 7.9, 6-H), 7.74 (1 H, ddd, *J* 0.5, 1.2, 7.9, 8-H), 7.90 (1 H, ddd, *J* 1.2, 7.9. 7.9, 7-H), 8.19 (1 H, ddd, *J* 0.5, 1.2, 7.9, 5-H), 8.15 (1 H, brs, NH) and 8.45 (1 H, brs, NH); $\delta_C$ (100 MHz, $d_6$-DMSO) 50.8 ($CH_2$), 126.3 (qC), 129.3 (propenyl-2-C), 131.5 (Ph *o*-C), 131.6 (5-C), 132.6 (8-C), 133.0 (6-C), 133.1 (Ph *p*-C), 133.8 (Ph *m*-C), 137.8 (propenyl-3-C), 140.0 (7-C), 141.2 (qC), 151.5 (qC), 155.5 (qC), 165.5 (qC), and 168.8 (qC). The assignments were confirmed with COSY, HMQC and NOESY techniques; *m*/*z* (EI) no $M^+$; (CI) 306 ($[M + H]^+$, 90%), 263, (100) and 190 (28). The $^1H$ NMR spectra in $CDCl_3$ and TLC were identical to those in the mixture from the radical reaction to synthesise luotonin A. All peaks in the IR spectrum taken in DCM were identified in the IR spectrum of the mixture.

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