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5-Nitroisocoumarins from tandem Castro–Stephens coupling—6-*endo*-dig cyclisation of 2-iodo-3-nitrobenzoic acid and arylethynes and ring-closure of methyl 2-alkynyl-3-nitrobenzoates with electrophiles

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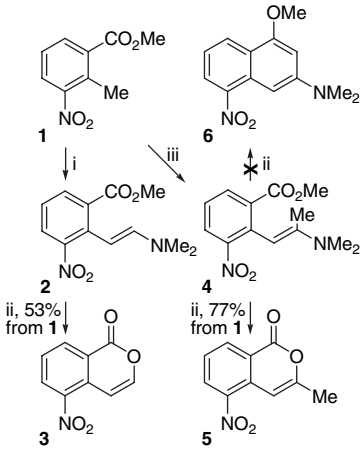
Abstract—Reaction of 2-iodo-3-nitrobenzoic acid with arylalkynyl copper(I) reagent gave 3-aryl-5-nitroisocoumarins. Castro–Stephens coupling was followed by in situ Cu-catalysed ring-closure. ^{1}H NMR and X-ray crystallography showed the cyclisations to be 6-*endo*, contrasting with reports of 5-*exo* cyclisation of analogous 2-iodobenzoate esters with alkynes. Sonogashira couplings of methyl 2-iodo-3-nitrobenzoate with phenylacetylene and with trimethylsilylacetylene gave the corresponding 2-alkynyl-3-nitrobenzoate esters. With $HgSO_4$, the phenylalkyne underwent 6-*endo* cyclisation to give 5-nitro-3-phenylisocoumarin. The disubstituted alkyne esters gave 4-phenylselenylisocoumarins with PhSeCl. 5-Nitro-3-phenyl-4-phenylselenylisocoumarin shows significant sterically-driven distortion of the isocoumarin ring. Reaction of methyl 3-nitro-2-phenylethynylbenzoate with ICl gave the 4-iodoisocoumarin. Thus the nitro group tends to direct these electrophile-driven cyclisations towards the 6-*endo* mode.

1. Introduction

As a part of our continuing research on the design and synthesis of heterocyclic compounds as enzyme inhibitors and potential drugs,[1–3] we required a series of 3-substituted-5-nitroisocoumarins. The synthesis of 5-nitroisocoumarin **3** (Scheme 1) is now well established,[4] through condensation of methyl 2-methyl-3-nitrobenzoate **1** with dimethylformamide dimethylacetal, followed by hydrolysis of the intermediate methyl *E*-2-(2-dimethylaminoethenyl)-3-nitrobenzoate **2** and cyclisation catalysed by wet silica. However, this synthesis cannot be extended to 3-methyl-5-nitroisocoumarin **5**, as the corresponding initial condensation with dimethylacetamide dimethylacetal takes an alternate course, giving a trisubstituted naphthalene **6**.[5] Compound **5** has been reported to be synthesised in moderate yield by an alternative route of Hurtley coupling of 2-bromo-3-nitrobenzoic acid with pentane-2,4-dione, followed by acyl cleavage and ring-closure with sodium chloride at very high temperature.[6] Although the corresponding condensations of **1** with dimethylacetals of Ar-substituted *N*,*N*-dimethylbenzamides would be expected to follow the isocoumarin-forming path, as they lack a reactive α-methylene or α-methyl, they are not easy to prepare and an alternative route was sought.



Scheme 1. Condensation of methyl 2-methyl-3-nitrobenzoate **1** with DMF–DMA (Ref. 4) and with DMA–DMA (Ref. 5), followed by different modes of cyclisation. Reagents: (i) $HC(OMe)_2NMe_2$, DMF, Δ; (ii) SiO_2, EtOAc and (iii) $MeC(OMe)_2NMe_2$, $AcNMe_2$, Δ.

Several groups have reported the cyclisation of 2-alkynylbenzoic acids and 2-alkynylbenzoate esters **7** under electrophilic conditions, although no examples have a substituent at

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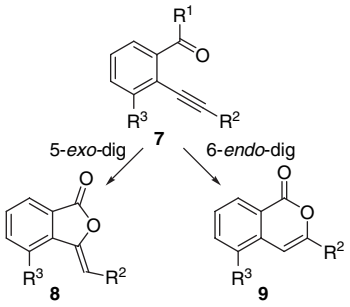
the 3-position of the benzoate (corresponding to the 5-position of the target isocoumarins). Moreover, there is debate about whether the reaction goes 5-*exo*-dig (giving ylidenephthalides **8**) or 6-*endo*-dig (giving isocoumarins **9**), as shown in Scheme 2 (R^3=H); both are favoured under Baldwin's Guidelines. For example, treatment of methyl 2-arylethynylbenzoates with $Hg^{(II)}$ under acidic conditions is reported to give intermediate mercurials from which 3-aryl-isocoumarins can be isolated by reduction with $NaBH_4$.[7,8] Similarly, reaction of the same starting materials with hydrogen iodide, electrophilic iodine reagents, bromine, sulfenyl chlorides and selenyl chlorides gave 3-arylisocoumarins and their 4-iodo, 4-bromo, 4-arylthio and 4-arylselenyl derivatives, respectively.[9–12] Dihydrofuroisocoumarins have also been synthesised by $Ag^{(I)}$-promoted 6-*endo*-dig cyclisation of the corresponding arylalkynylbenzoate esters.[13] In contrast, methyl 2-ethynylbenzoate undergoes 5-*exo*-dig cyclisation with iodine[12] and $Ag^{(I)}$-mediated cyclisation of 2-alkynylbenzoic acids affords the corresponding ylidenephthalides.[14] Under basic conditions (LiOH), methyl 2-(pent-1-ynyl)benzoate undergoes exclusive 6-*endo*-dig cyclisation whereas methyl 2-(3-hydroxypent-1-ynyl)benzoate gives a mixture of products from both cyclisation modes.[15] Regioisomeric mixtures are also formed during Pd-catalysed cyclisation of the former alkyne.[16] Cherry et al.[17] have shown very recently that treatment of 2-iodobenzoic acid with allenylstannanes under Pd-catalysed Stille conditions also gives isocoumarins through 6-*endo*-dig cyclisation of the intermediate 2-(3-substituted-allenyl)benzoic acids. 5-*exo*-Dig cyclisation is also evident at the lower (alcohol) oxidation level of the intramolecular nucleophilic oxygen under fluoride-ion catalysis.[18]



Scheme 2. Possible alternative cyclisation modes of 2-alkynylbenzoic acids **7** (R^1=OH) and 2-alkynylbenzoate esters (R^1=Oalkyl) via 5-*exo*-dig (giving **8**) and 6-*endo*-dig (giving **9**) routes. R^2=alkyl, aryl. R^3=H for previous examples; R^3=NO_2 in this paper.

While developing their synthesis of arylalkynes from iodoarenes and Cu^I-acetylides, Stephens and Castro[19] claimed that treatment of 2-iodobenzoic acid with Cu–C≡C–Ph gave 3-phenylisocoumarin **9** (R^2=Ph; R^3=H) by Cu-catalysed 6-*endo*-dig of the initial Castro–Stephens coupling product **7** (R^1=OH; R^2=Ph; R^3=H). However, this claim was later withdrawn[20] with correction of the characterisation of the product to be the benzylidine phthalide **8** (R^2=Ph; R^3=H), resulting from tandem Castro–Stephens coupling and 5-*exo*-dig cyclisation. Since then, an isocoumarin has been synthesised by this method[21] and mixtures of these isocoumarins and phthalides have been reported from analogous one-pot coupling–cyclisations of 2-iodobenzoic acid with terminal alkynes under Pd/Zn catalysis.[22]

2. Results and discussion

Given the dichotomy of reports for the outcome of the cyclisations, particularly in the Castro–Stephens tandem version, we initiated a short study on whether the mode of cyclisation would be influenced by the presence of the nitro group *ortho* to the alkyne. This strongly electron-withdrawing group should influence the electron distribution in the alkyne and was predicted to favour 6-*endo*-dig cyclisation by making the alkyne carbon further from the nitroarene more electrophilic (Fig. 1). Thus we investigated the tandem coupling–cyclisation of arylalkynes (as their Cu-acetylides) with 2-iodo-3-nitrobenzoic acid under Castro–Stephens conditions.

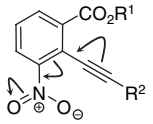
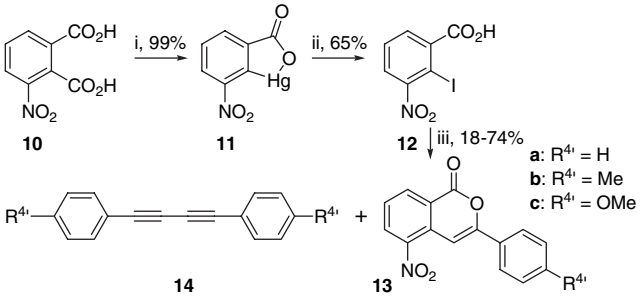


Figure 1. Proposed influence of the *ortho* nitro group on the electron-distribution in the alkyne in 2-alkynyl-3-nitrobenzoic acids and 2-alkynyl-3-nitrobenzoate esters. R^1=H or alkyl, R^2=H, silyl, alkyl and aryl.

The starting material, 2-iodo-3-nitrobenzoic acid **12**, was prepared in two steps from 3-nitrobenzene-1,2-dioic acid (**10**, 3-nitrophthalic acid). Decarboxylation/mercuration with mercury(II) acetate at high temperature in acetic acid gave the intermediate aryl-mercury **11**. Electrophilic replacement of the mercury with iodine, using crude **11**, gave **12** conveniently in excellent yield.

To test our hypothesis about the controlling effect of the nitro group, **12** was exposed to copper(I) phenylacetylide (prepared from phenylethyne and copper(I) iodide in aq ethanolic ammonia) under the classical conditions of boiling pyridine as solvent (Scheme 3). Conventional work-up gave a high yield of a single cyclisation product, along with a small amount of a highly non-polar by-product. The latter was readily identified as 1,4-diphenylbutadiyne **14a**,[23] derived from an unintended oxidative Glaser homo-coupling of the alkyne, despite carrying out the reaction under nitrogen. Careful examination of the ^{1}H NMR spectrum of the major (cyclisation) product suggested that it was the desired isocoumarin **13a**, rather than the alternative 5-*exo*-dig product **15a** (Fig. 2). Firstly, the chemical shift of the signal at δ 7.79 corresponds with the chemical shifts previously



Scheme 3. Synthesis of 2-iodo-3-nitrobenzoic acid **12** and tandem Castro–Stephens coupling and 6-*endo*-dig ring closure to give the 3-aryl-5-nitroisocoumarins **13**. Reagents: (i) $Hg(OAc)_2$, AcOH, reflux; (ii) I_2, KI, AcOH, H_2O, reflux and (iii) $R^{4'}$–C_6H_4C≡CCu, pyridine, reflux.

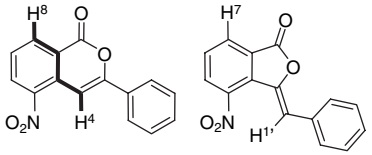


Figure 2. Structures of alternative 6-*endo*-dig (**13a**) and 5-*exo*-dig (**15a**) cyclisation products, showing the long-range ^{1}H–^{1}H NMR coupling path in **13a**.

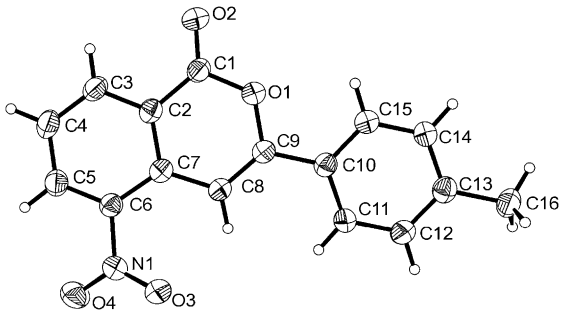
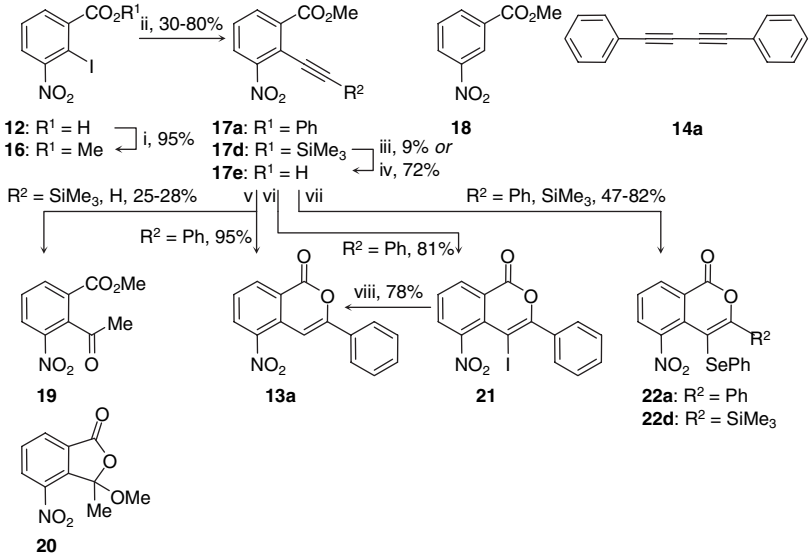


Figure 3. X-ray crystal structure of **13b**, with crystallographic numbering.

observed by us for the corresponding proton in 5-nitroisocoumarin (δ 7.39)[4] and for 3-phenylisocoumarin (δ 6.93)[24] better than it does with that observed for the alkene proton of 3-benzylidenephthalide (δ 6.40),[25] a close analogue of **15a**. Moreover, a small coupling (J 0.8 Hz) was observed for this proton signal. We have previously observed[4] a similar long-range coupling between H^4 and H^8 in 5-nitroisocoumarin and we propose that it arises from the extended-**W** ^{5}J H^4–H^8 coupling path shown for **13a** in Figure 2, rather than the alternative longer ^{6}J $H^{1'}$–H^7 path in **15a**. Moreover, the IR spectrum of **13a** showed an absorption band at 1739 cm^{-1}, which lies in the middle of the range 1730–1750 cm^{-1} for six-membered ring lactones but not in the corresponding range for five-membered ring lactones (1760–1780 cm^{-1}). These data point strongly towards the cyclisation having occurred in the 6-*endo*-dig mode. 2-Iodo-3-methylbenzoic acid was also treated with the Cu(I) acetylides of 4-methylphenylethyne and 4-methoxyphenylethyne under the same conditions. Unexpectedly, the yields of the cyclised products **13b**,**c** were lower, as were the yields of the Glaser coupling products **14b**,**c**. However, the NMR spectra of **13b**,**c** were similar to those of **13a**, with H^4 resonating at δ 7.80 and δ 7.66, respectively, indicating the same mode of cyclisation.

To confirm unequivocally that the products were indeed the isocoumarins, the structure of **13b** was established by X-ray crystallography. The structure and X-ray crystallographic numbering scheme are shown in Figure 3. In this structure, the isocoumarin bicycle is essentially planar. In particular, the protons and carbons of the extended-**W** $^{5}J_{H-H}$ NMR coupling path are shown to be coplanar, supporting the assignment of the observed long-range coupling. The 4-methylphenyl substituent in **13b** is only very slightly twisted out of the isocoumarin plane, with a dihedral angle of 4.8°; this closeness to coplanarity presumably reflects the presence of only one proton on the isocoumarin *ortho* to the 4-methylphenyl group. However, the nitro group is twisted some 22.4° out of the isocoumarin plane, owing to adverse steric interactions with the *peri*-hydrogen.

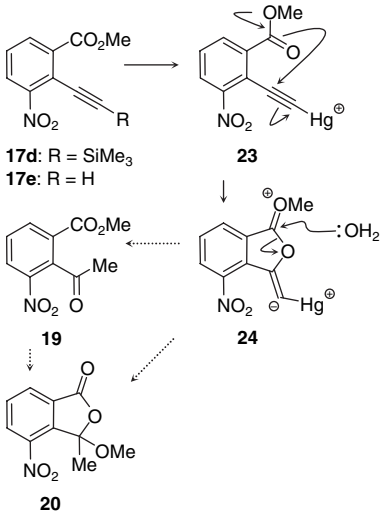
With the mode of Cu-catalysed cyclisation of the 2-(arylalkynyl)-3-nitrobenzoic acids firmly established as 6-*endo*-dig, attention was turned to study the mode(s) of cyclisation of representative methyl 2-(substituted)alkynyl-3-nitrobenzoates. To supply the starting material for this part of the study, 2-iodo-3-nitrobenzoic acid **12** was converted to its methyl ester **16** in the usual way (Scheme 4). Sonogashira coupling of this iodoarene with phenylethyne and with trimethylsilylethyne gave the disubstituted alkynes **17a**,**d**. The yield of **17a** was excellent but coupling of the more bulky alkyne with the sterically demanding *ortho*,*ortho*′-disubstituted iodoarene **16** gave a much lower yield (30%). In the latter case, the difficulty of the coupling was



Scheme 4. Sonogashira couplings of methyl 2-iodo-3-nitrobenzoate **16** and electrophile-driven cyclisations of methyl 2-alkynyl-3-nitrobenzoates **17a**,**d**,**e**. Reagents: (i) MeOH H_2SO_4; (ii) HC≡CPh or HC≡CSiMe$_3$, $(Ph_3P)_2PdCl_2$, Pr^i_2NH THF; (iii) Bu_4NF, THF; (iv) AgOTf, acetone, water, CH_2Cl_2; (v) $HgSO_4$, H_2SO_4, Me_2CO, Δ; (vi) ICl, CH_2Cl_2; (vii) PhSeCl, CH_2Cl_2 and (viii) HCO_2H, $Pd(OAc)_2$, Et_3N, DMF.

illustrated by the isolation of a 39% yield of the dehalogenated product **18**, arising from decomposition of the intermediate arylpalladium, which had failed to couple with the alkyne. Interestingly, despite the presence of copper(I) in the reaction mixture, no cyclised products were formed, although some runs with phenylethyne also gave 1,4-diphenylbutadiyne **14a**, the product of Glaser-like homodimerisation of the starting alkyne. Attempted desilylation of **17d** under a variety of basic conditions (e.g., potassium carbonate/methanol) caused extensive decomposition; indeed the classical fluoride ion-mediated desilylation gave only a maximum yield of 9% of **17e**. Removal of trimethylsilyl protection from alkynes with silver(I) nitrate is widely reported to be efficient if cyanide ion is added to break up the initially formed alkynylsilver(I).[26–28] However, Orsini et al.[29] have recently developed a selective desilylation of 1-trimethylsilyl-2-alkylalkynes with silver(I) triflate in a biphasic solvent system at room temperature, which obviates the use of large molar excesses of silver and of cyanide. Adapting this method to the current application, prolonged heating of **17d** with silver(I) triflate in a mixture of methanol, water and dichloromethane gave good yields (>70%) of the required alkyne **17e**. We attribute the need for the higher temperature and much longer reaction times (days, rather than hours) to the highly electron-deficient nature of the starting trimethylsilylalkyne.

Each of the three methyl 2-alkynyl-3-nitrobenzoates **17a**,**d**,**e** (carrying the diverse substituents Ph, $SiMe_3$ and H, respectively) was treated with three different electrophiles, to investigate whether or not cyclisation would occur and whether such cyclisation would be 5-*exo* or 6-*endo* (Scheme 4). Firstly, treatment of **17a** with mercury(II) sulfate under acidic conditions afforded an almost quantitative yield of a single product, the isocoumarin **13a**, which was identical to the material prepared by the Castro–Stephens one-pot method. 6-*endo* Cyclisation was relatively unsurprising in this case, in view of the exclusive formation of 3-phenylisocoumarin from methyl 2-phenylethynylbenzoate under the same conditions, as reported by Nagarajan and Balasubramanian.[7] Similar treatment of the analogous trimethylsilylalkyne **17d**, however, gave only methyl 2-acetyl-3-nitrobenzoate **19**, in modest yield after chromatography. The same ketone **19** was also isolated from the reaction of **17e** with mercury(II) sulfate and acid; the NMR spectrum also indicated the presence of a trace of the isomeric pseudoester **20**.[30] Formation of **19** from **17d** and **17e** clearly involves attack of an oxygen nucleophile on the alkyne carbon nearest to the benzene ring, in contrast to the formation of **13a** from **17a**, which must arise from 6-*endo* attack of the ester carbonyl oxygen on the carbon remote from the substituted ring. Thus the alkyne must be polarised in the opposite sense. Scheme 5 shows a mechanistic rationalisation for this change in reactivity. By analogy with the mechanism of the silver(I)-mediated desilylations,[29,31] we propose that transmetallation of **17d** occurs to form an alkynylmercury species, such as **23**. This intermediate could also be formed by direct metallation of **17e**. In intermediate **23**, it is likely that the polarisation of the alkyne caused by coordination to the mercury would over-ride the opposite polarisation induced by the two *ortho*-electron-withdrawing substituents (nitro, carbonyl) on the benzene ring. The ester carbonyl oxygen is then located oppositely for 5-*exo* nucleophilic attack, giving intermediate **24**. Hydrolysis would then afford the major product, the ketone **19**. It is not clear whether the minor side-product **20** is formed from **19** or directly from intermediate **24**.



Scheme 5. Proposed routes for the formation of **19** and **20** through 5-*exo* attack of the neighbouring ester carbonyl oxygen; the polarisation of the alkyne is driven by the mercury cation, rather than by the *ortho*-nitrophenyl group in this case.

The set of three alkynes **17a**,**d**,**e** was also treated with the electrophilic iodine reagent iodine monochloride at ambient temperature in dichloromethane. Only the phenylalkyne **17a** gave an identifiable product, affording 4-iodo-5-nitro-3-phenylisocoumarin **21** in high yield (Scheme 4). No isocoumarins or isobenzofuranones could be identified in the NMR spectra of the crude mixtures of products formed from the trimethylsilylalkyne **17d** or from the monosubstituted alkyne **17e**. The structure of **21** was confirmed as being the isocoumarin product of 6-*endo* cyclisation by two methods. Firstly, the IR spectrum showed an absorption at 1736 cm^{-1}, corresponding to a six-membered ring lactone of this type. Secondly, palladium-catalysed reductive deiodination of **21** with formic acid (by the general method of Rossi et al.[12]) gave an excellent yield of 5-nitro-3-phenylisocoumarin **13a**, identical to samples prepared by the one-pot Castro–Stephens method and the $Hg^{(II)}$-mediated cyclisation of **17a**.

Finally, the reactions of the electrophile phenylselenyl chloride with the alkynes **17a**,**d**,**e** were investigated (Scheme 4). As with the reaction with iodine monochloride, no isocoumarins or isobenzofuranones could be identified as products of the reaction with the monosubstituted alkyne **17e**. However, the disubstituted alkynes **17a**,**d** formed the corresponding 4-phenylselenylisocoumarins **22a**,**d** in moderate-to-good yields, through 6-*endo* cyclisation. Again, the IR spectra indicated 6-membered ring lactones, with bands at 1733 cm^{-1} for both isocoumarins. In view of the lack of suitable methods for reductive removal of the phenylselenyl group to provide material for comparison with **13a** synthesised previously by three independent routes, an X-ray crystal structure determination was carried out for 5-nitro-3-phenyl-4-phenylselenylisocoumarin **22a**. Large bright orange-red

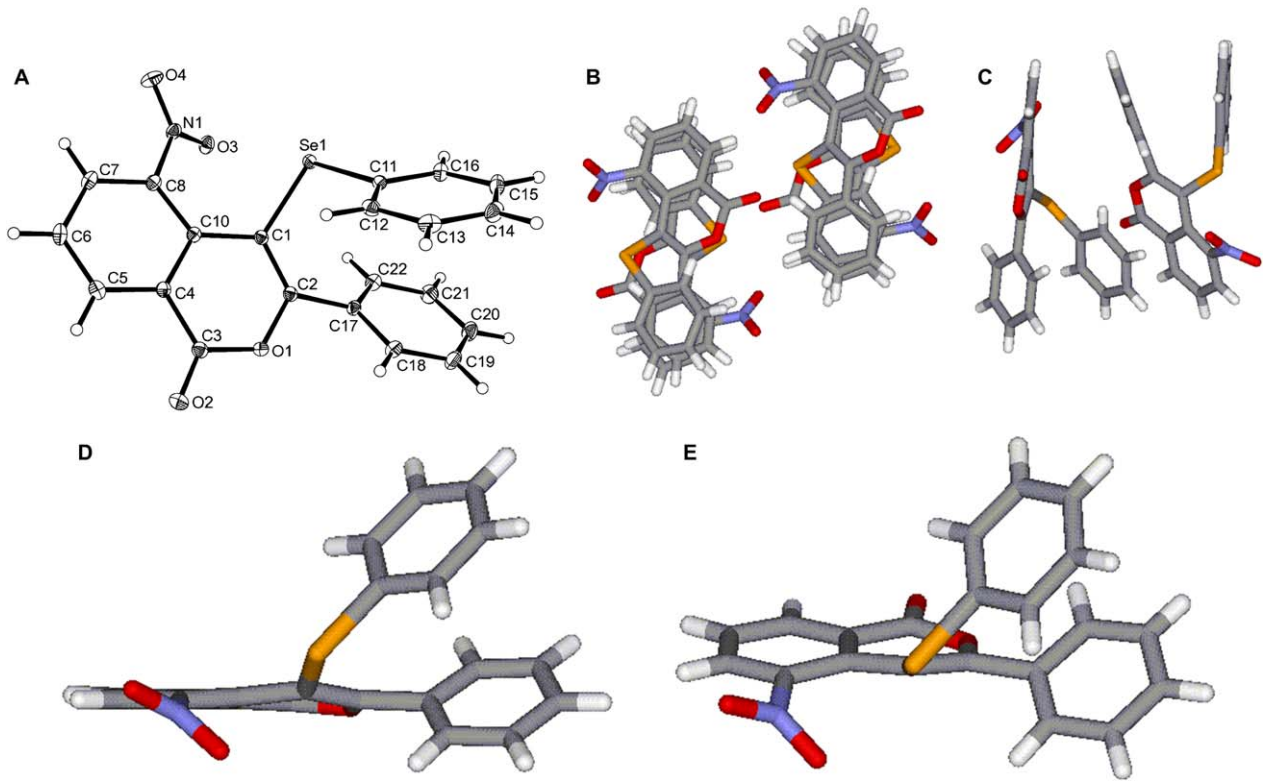


Figure 4. A. X-ray crystal structure of **22a**, with crystallographic numbering. B. Axial view of intermolecular and intramolecular π-stacking in the crystal of **22a**. C. Side view of intermolecular and intramolecular π-stacking of two molecules in the crystal of **22a**. D. View of single molecule of **22a** in the plane of the isocoumarin carbocyclic ring. E. View of single molecule of **22a** along the Se–C bond. Grey=C, white=H, blue=N, red=O and orange=Se.

crystals were formed from ethyl acetate. The structure and X-ray crystallographic numbering scheme are shown in Figure 4A. The most striking observation in this crystal structure is the intermolecular and intramolecular π-stacking of all three benzene rings in the molecule. Figure 4B shows four molecules in two parallel stacks, viewed from the axis of the stacking. The nature of the stacking is shown in the side view in Figure 4C, with the C–Ph and SePh rings stacked intramolecularly; these then stack intermolecularly with the carbocyclic ring of the isocoumarins. This isocoumarin also displays interesting conformational features within the molecule, as shown in Figure 4. The three adjacent substituents, phenyl, phenylselenyl and nitro, at the 3-, 4- and 5-positions, respectively, occupy very crowded regions of space. In particular, there is a severe *peri* interaction between the nitro and phenylselenyl groups. As for the structure of **13b**, the nitro group in **22a** is twisted out of the plane–plane subtended by atoms C2–C8 and C10 of the isocoumarin, by 36.9°. However, the severe steric crowding has a more profound effect, in that the pyranone ring of the isocoumarin of **22a** is forced out of the plane described; above, such that C-1 lies some 0.19 Å above same. This effect is demonstrated even more clearly by the position of the selenium atom at 0.93 Å above this mean plane, as depicted in Figure 4D (wherein the structure is viewed from the plane of the benzene ring) and in Figure 4E (in which the structure is viewed along the Se–C bond vector). Whereas the 3-aryl substituent was only twisted out of the isocoumarin plane in **13b** by <5°, the corresponding 3-phenyl in **22a** is twisted out of the isocoumarin mean plane by 36.5°. The presence of the adjacent bulky phenylselenyl is presumably responsible for this greater lack of coplanarity. The gross structure is dominated by interdigitating intra- and intermolecular stacking of the aromatic rings. The intermolecular centroid–centroid distance between the aromatic rings is 3.8 Å, while the comparable intermolecular aromatic–aromatic distances average 4.1 Å. This latter value reflects the fact that the π-stacking is offset in the intermolecular case.

3. Conclusions

In this paper, we have reported one-pot Castro–Stephens couplings of arylalkynes with 2-iodo-3-nitrobenzoic acid **12**, followed by Cu^{+}-catalysed cyclisation of the intermediate 2-arylalkynyl-3-nitrobenzoic acids in situ to give exclusively 3-aryl-5-nitroisocoumarins **13a–c**. These results contrast with the results reported by Stephens and Castro for the analogues lacking the nitro group, which cyclised in the 5-*exo* mode to give 5-benzylidene-isocoumarins.[20] We interpret this change in regiochemistry of cyclisation as being due to the nitro group inducing polarisation of the alkyne, making the remote sp-carbon more electrophilic as shown in Figure 1. Similarly, $Hg^{(II)}$-catalysed cyclisation of pre-formed methyl 2-phenylalkynyl-3-nitrobenzoate **17a** also proceeded in the 6-*endo* mode to give 2-nitro-3-phenylisocoumarin **13a**, again reflecting this polarisation of the alkyne. Cyclisations of methyl 3-nitro-2-phenylethynylbenzoate **17a** with iodine monochloride and with phenylselenyl chloride also followed the 6-*endo* route to give the isocoumarins **21** and **22a**, respectively, as did cyclisation of methyl 3-nitro-2-trimethylsilylethynylbenzoate **17d** with phenylselenyl chloride, affording the isocoumarins **22d**. Thus the regiochemistry of these cyclisations is also likely to be under

the control of the nitro group. In contrast, the formation of methyl 2-acetyl-3-nitrobenzoate **19** by treatment of **17d**,**e** with $Hg^{(II)}$ suggests that a 5-*exo* cyclisation may have been driven by the change in electron-distribution caused by the formation of an intermediate alkynylmercury complex. These studies extend the understanding of electrophile-driven cyclisations of 2-alkynylbenzoic acids and 2-alkynylbenzoate esters to the previously unreported cases where a powerful electron-withdrawing group is present, influencing the electron-distribution of the alkyne. This understanding will be useful in predicting modes of cyclisation in the synthesis of more complex isocoumarins.

4. Experimental

4.1. General

IR spectra were obtained as KBr discs and NMR spectra were obtained using solutions in $CDCl_3$, unless otherwise stated. Mass spectra were obtained using fast atom bombardment in the positive ion mode, unless otherwise stated. Solutions in organic solvents were dried with $MgSO_4$. Solvents were evaporated under reduced pressure. Mps were obtained using a Kofler–Galen hot stage microscope and are uncorrected.

4.1.1. 2-Hydroxymercuri-3-nitrobenzoic acid (11) and 2-iodo-3-nitrobenzoic acid (12). 3-Nitrobenzene-1,2-dicarboxylic acid **10** (21.1 g, 100 mmol) in hot aq NaOH (10%, 80 mL) was added to $Hg(OAc)_2$ (35.0 g, 110 mmol) in hot AcOH (5 mL) and water (70 mL). The mixture was boiled under reflux for 70 h, then filtered. The precipitate was washed (H_2O, then EtOH) and dried to give **11** (36.2 g, 99%) as a cream solid. Aq HCl (2 M, 12 mL) was added slowly to a boiling solution of **11** (36.2 g, 100 mmol) in aq NaOH (3.5%, 500 mL) and the mixture was allowed to cool to 25 °C. AcOH (3 mL) was then added, followed by KI (19.0 g, 114 mmol) and I_2 (29.0 g, 114 mmol) in water (30 mL). The mixture was boiled under reflux for 24 h, cooled and neutralised with aq NaOH, before being filtered and acidified with aq HCl (9 M). The precipitate was collected, dried and recrystallised (EtOH) to give **12** (19.1 g, 65%) as yellow crystals: mp 203–204 °C (lit.[32] mp 204–205.5 °C); IR ν_{max} 1375, 1542, 1712, 2800 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 7.66 (t, J=7.8 Hz, 1H, 5-H), 7.79 (dd, J=7.8, 1.7 Hz, 1H, 4-H), 7.92 (dd, J=7.8, 1.7 Hz, 1H, 6-H); MS m/z 293.9250 (M+H) ($C_7H_5INO_4$ requires 293.9263).

4.1.2. 5-Nitro-3-phenylisocoumarin (13a) and 1,4-diphenyl-1,3-butadiyne (14a). *Method A*. CuI (7.5 g, 39 mmol) in aq NH_3 (35%, 100 mL) was slowly added to phenylethyne (4.0 g, 39 mmol) in EtOH (200 mL). The mixture was stirred for 15 min. The precipitate was collected, washed with water (5×), EtOH (5×) and Et_2O (5×) and dried at 50 °C (20 torr) for 2 h to afford phenylethynylcopper(I) (4.7 g, 73%) as a bright canary-yellow solid. Compound **12** (3.0 g, 10 mmol) and phenylethynylcopper(I) (1.7 g, 10 mmol) were boiled under reflux in dry pyridine (100 mL) for 6 h under N_2. The mixture was poured into water (300 mL) and extracted with (Et_2O). The extract was washed (aq HCl (2 M), aq $NaHCO_3$ (5%), water). Evaporation and chromatography (hexane/EtOAc 12:1) yielded **14a** (105 mg, 5%) as a white solid: mp 85–86 °C (lit.[33] mp 88 °C); IR ν_{max} 2158 cm^{-1}; ^1H NMR δ 7.26–7.35 (6H, m, 2×3′,4′,5′-H_3), 7.45–7.50 (4H, m, 2×2′,6′-H_2); MS (EI) m/z 202.0784 (M) ($C_{16}H_{10}$ requires 202.0783). Further elution yielded **13a** (2.0 g, 74%) as yellow crystals: mp 142–143 °C; IR ν_{max} 1341, 1525, 1739 cm^{-1}; ^1H NMR δ 7.50–7.53 (3H, m, 3′,4′,5′-H_3), 7.62 (1H, t, J=7.8 Hz, 7-H), 7.79 (1H, d, J=0.8 Hz, 4-H), 7.93–7.97 (2H, m, 2′,6′-H_2), 8.51 (1H, dd, J=8.2, 1.2 Hz, 6-H), 8.65 (1H, ddd, J=8.2, 1.2, 0.8 Hz, 8-H); MS (EI) m/z 267.0532 (M) ($C_{15}H_9NO_4$ requires 267.0532), 237 (M−NO), 184, 150.

4.1.3. 5-Nitro-3-phenylisocoumarin (13a). *Method B*. Compound **17a** (2.5 g, 8.9 mmol) was boiled under reflux with $HgSO_4$ (3.0 g, 10 mmol) and concd H_2SO_4 (4 mL) in acetone (80 mL) for 48 h. The evaporation residue was extracted with $CHCl_3$. Evaporation and chromatography (hexane/Et_2O 9:1) gave **13a** (2.3 g, 95%) as yellow crystals, with data as above.

4.1.4. 5-Nitro-3-phenylisocoumarin (13a). *Method C*. HCO_2H (30 mg, 0.66 mmol) was added to a degassed mixture of **21** (130 mg, 0.33 mmol), Et_3N (100 mg, 1.0 mmol), $Pd(OAc)_2$ (6.6 mg, 7 μmol) and Ph_3P (13.2 mg, 13 μmol) in dry DMF (10 mL). The mixture was stirred at 60 °C for 4.5 h under Ar before being poured into water (50 mL). Extraction (EtOAc), drying, evaporation and chromatography (EtOAc/hexane 1:9) gave **13a** (69 mg, 78%) as pale yellow crystals, with data as above.

4.1.5. 3-(4-Methylphenyl)-5-nitroisocoumarin (13b) and 1,4-di(4-methylphenyl)-1,3-butadiyne (14b). Copper(I) 4-methylphenylacetylide was prepared and treated with **12**, as for the synthesis of **13a** (Method A), to give **14b** (0.4%) as pale yellow crystals: mp 180–181 °C (lit.[33] mp 183 °C); IR ν_{max} 2130 cm^{-1}; ^1H NMR δ 2.36 (6H, s, 2×Me), 7.14 (4H, d, J=8.1 Hz, 2×3′,5′-H_2), 7.41 (4H, d, J=8.1 Hz, 2×2′,6′-H_2); MS (EI) m/z 231.1141 (M+H) ($C_{18}H_{15}$ requires 231.1174). Further elution gave **13b** (18%) as yellow crystals: mp 161–162 °C; IR ν_{max} 1321, 1511, 1618, 1737 cm^{-1}; ^1H NMR δ 2.42 (3H, s, Me), 7.29 (2H, d, J=8.2 Hz, 3′,5′-H_2), 7.56 (1H, t, J=8.2 Hz, 7-H), 7.80 (1H, s, 4-H), 7.81 (2H, d, J=8.2 Hz, 2′,6′-H_2), 8.46 (1H, dd, J=8.2, 1.2 Hz, 6-H), 8.60 (1H, dt, J=8.2, 1.2 Hz, 8-H); MS (EI) m/z 282.0762 (M+H) ($C_{16}H_{11}NO_4$ requires 282.0766).

4.1.6. 3-(4-Methoxyphenyl)-5-nitroisocoumarin (13c) and 1,4-di(4-methoxyphenyl)-1,3-butadiyne (14c). Copper(I) 4-methoxyphenylacetylide was prepared and treated with **12**, for the synthesis of **13a** (Method A), to give **14c** (1%) as pale yellow crystals: mp 148–149 °C (lit.[34] mp 149 °C); IR ν_{max} 2145 cm^{-1}; ^1H NMR δ 3.82 (6H, s, 2×Me), 6.85 (4H, d, J=8.9 Hz, 2×3′,5′-H_2), 7.46 (4H, d, J=8.9 Hz, 2×2′,6′-H_2); MS (EI) m/z 262.0995 (M) ($C_{18}H_{14}O_2$ requires 262.0994), 247 (M−Me), 219 (M−Me−CO). Further elution gave **13c** (29%) as yellow crystals: mp 241–242 °C; IR ν_{max} 1346, 1511, 1620, 1738 cm^{-1}; ^1H NMR δ 3.88 (3H, s, Me), 6.99 (2H, d, J=9.0 Hz, 3′,5′-H_2), 7.54 (1H, t, J=8.2 Hz, 7-H), 7.76 (1H, s, 4-H), 7.88 (2H, d, J=9.0 Hz, 2′,6′-H_2), 8.46 (1H, dd, J=8.2, 1.2 Hz, 6-H), 8.59 (1H, dd, J=8.2, 1.2 Hz,

8-H); MS (EI) *m/z* 297.0639 (M) ($C_{16}H_{11}NO_5$ requires 297.0637), 277 (M−NO), 135.

4.1.7. Methyl 2-iodo-3-nitrobenzoate (16). Compound **12** (4.0 g, 14 mmol) was boiled under reflux with MeOH (120 mL) and concd H_2SO_4 (3 mL) for 48 h, then poured into ice-water. The precipitate was filtered, dried and recrystallised (MeOH) to give **16** (4.0 g, 95%) as yellow crystals: mp 65–66 °C (lit.[35] mp 62–64 °C); IR ν_{max} 1351, 1533, 1705 cm^{-1}; ^1H NMR δ 3.99 (3H, s, Me), 7.54 (1H, t, *J*=7.8 Hz, 5-H), 7.70 (1H, dd, *J*=7.8, 1.7 Hz, 4-H), 7.77 (1H, dd, *J*=7.8, 1.7 Hz, 6-H); MS (EI) *m/z* 306.9347 (M) ($C_8H_6INO_4$ requires 306.9342), 276 (M−OMe).

4.1.8. Methyl 3-nitro-2-(2-phenylethynyl)benzoate (17a) and methyl 3-nitrobenzoate (18). Compound **16** (3.0 g, 9.8 mmol) was stirred with $(Ph_3P)_2PdCl_2$ (300 mg, 0.4 mmol) and CuI (400 mg, 2.1 mmol) in dry THF (120 mL) and dry Pr^i_2NH (40 mL) at 45 °C for 30 min under Ar. Phenylethyne (1.5 g, 15 mmol) was added during 30 min and the mixture was stirred for 48 h. Filtration (Celite®), evaporation and chromatography (hexane/CH_2Cl_2 1:1) gave **17a** (2.2 g, 80%) as reddish-brown crystals: mp 59–60 °C; IR ν_{max} 1343, 1527, 1737, 2219 cm^{-1}; ^1H NMR δ 4.01 (3H, s, Me), 7.36–7.41 (3H, m, Ph 3,4,5-H_3), 7.49 (1H, t, *J*=7.8 Hz, 5-H), 7.57–7.62 (2H, m, Ph 2,6-H_2), 8.04 (1H, dd, *J*=7.8, 1.2 Hz, 4-H), 8.10 (1H, dd, *J*=7.8, 1.2 Hz, 6-H); ^{13}C NMR δ 52.81, 81.79, 102.61, 117.62, 122.06, 126.81, 127.63, 128.32, 129.44, 131.97, 133.56, 134.94, 151.87, 165.27; MS (EI) *m/z* 282.0757 (M+H) ($C_{16}H_{12}NO_4$ requires 282.0766), 266 (M−Me), 250 (M−OMe), 222 (M−CO_2Me). Further elution gave **18** (500 mg, 28%) as yellow crystals: mp 78–79 °C (lit.[36] mp 78 °C); ^1H NMR δ 3.99 (3H, s, Me), 7.66 (1H, t, *J*=7.8 Hz, 5-H), 8.37 (1H, ddd, *J*=7.8, 2.4, 1.2 Hz, 4-H), 8.42 (1H, ddd, *J*=7.8, 2.4, 1.2 Hz, 6-H), 8.87 (1H, t, *J*=2.4 Hz, 2-H). From some runs, 1,4-diphenylbutadiyne **14a** was also isolated.

4.1.9. Methyl 3-nitro-2-(2-trimethylsilylethynyl)benzoate (17d) and methyl 3-nitrobenzoate (18). Compound **16** (3.0 g, 9.8 mmol) in dry THF (120 mL) was added to $(Ph_3P)_2PdCl_2$ (300 mg, 0.4 mmol) and CuI (400 mg, 2.1 mmol) in dry Pr^i_2NH (40 mL) and the mixture was stirred at 45 °C for 30 min under Ar. Trimethylsilylethyne (1.1 g, 11 mmol) was added during 30 min. The mixture was stirred for 72 h at 45 °C. Filtration (Celite®), evaporation and chromatography (hexane/CH_2Cl_2 3:2) gave **17d** (810 mg, 30%) as a reddish-brown oil: IR (film) ν_{max} 1351, 1532, 1738, 2219 cm^{-1}; ^1H NMR δ 0.28 (9H, s, $SiMe_3$), 3.96 (3H, s, OMe), 7.49 (1H, t, *J*=7.8 Hz, 5-H), 7.96 (1H, dd, *J*=7.8, 1.6 Hz, 4-H), 8.01 (1H, dd, *J*=7.8, 1.6 Hz, 6-H); MS (EI) *m/z* 278.2361 (M+H) ($C_{13}H_{16}NO_4Si$ requires 278.2357). Further elution gave **18** (690 mg, 39%), with data as above.

4.1.10. Methyl 2-ethynyl-3-nitrobenzoate (17e). *Method A*. Bu_4NF (1.0 M in THF, 5.0 mL, 5.0 mmol) was added to **17d** (400 mg, 1.4 mmol) in THF (50 mL) and water (2.5 mL) at 0 °C and the mixture was stirred at 20 °C for 16 h. The mixture was diluted with Et_2O and washed with satd aq NH_4Cl and water. Evaporation and chromatography (hexane/EtOAc 7:3) gave **17e** (28 mg, 9%) as a pale yellow solid: mp 78–80 °C; IR (film) ν_{max} 1351, 1532, 1738, 2219 cm^{-1}; ^1H NMR δ 3.67 (1H, s, C≡CH), 3.90 (3H, s, Me), 7.48 (1H, t, *J*=7.8 Hz, 5-H), 7.91 (1 H, dd, *J*=7.8, 1.2 Hz, 4-H), 8.00 (1H, dd, *J*=7.8, 1.2 Hz, 6-H); MS (EI) *m/z* 205.0381 (M) ($C_{10}H_7NO_4$ requires 205.0375), 191 (M−CH_2), 175 (M−NO), 160 (M−NO−Me).

4.1.11. Methyl 2-ethynyl-3-nitrobenzoate (17e). *Method B*. Compound **17d** (250 mg, 0.9 mmol) was stirred with AgOTf (23 mg, 0.09 mmol) in a mixture of acetone (6.0 mL), water (1.5 mL) and CH_2Cl_2 (10.5 mL) for 7 d. Satd aq ammonium chloride (2 mL) was added and the mixture was extracted thrice with CH_2Cl_2. Evaporation and chromatography (EtOAc/hexane 1:6) gave **17e** (132 mg, 72%) with data as above.

4.1.12. Methyl 2-acetyl-3-nitrobenzoate (19). *Method A*. Compound **17d** (110 mg, 0.4 mmol) was boiled under reflux with $HgSO_4$ (148 mg) and concd H_2SO_4 (0.1 mL) in acetone (10 mL) for 48 h. The evaporation residue was extracted with $CHCl_3$. Evaporation and chromatography (toluene) gave **15** (25 mg, 28%) as a white solid: mp 81–82 °C (lit.[37] mp 81.5 °C); ^1H NMR δ 2.71 (3H, s, ArCOMe), 3.93 (3H, s, OMe), 7.65 (1H, t, *J*=8.2 Hz, 5-H), 8.33 (1H, dd, *J*=8.2, 1.2 Hz, 4-H or 6-H), 8.37 (1H, dd, *J*=8.2, 1.2 Hz, 6-H or 4-H); ^{13}C NMR δ 29.66, 53.09, 128.64, 129.47, 129.56, 136.20, 140.19, 146.04, 164.47, 200.03.

4.1.13. Methyl 2-acetyl-3-nitrobenzoate (19). *Method B*. Compound **17e** was treated with $HgSO_4$, as for Method A, to give **19** (25%) with properties as above. Also identified in trace amounts in the NMR spectrum was 3-methoxy-3-methyl-4-nitroisobenzofuran-1-one **20**:[30] ^1H NMR δ 2.05 (3H, s, CMe), 3.22 (3H, s, OMe), 7.43 (1H, m, 6-H), 8.22 (1H, dd, *J*=8.4, 0.9 Hz, 5-H or 7-H), 8.47 (1H, dd, *J*=8.8, 0.9 Hz, 7-H or 5-H).

4.1.14. 4-Iodo-5-nitro-3-phenylisocoumarin (21). Compound **17a** (114 mg, 0.37 mmol) was stirred with ICl (90 mg, 0.55 mmol) in CH_2Cl_2 (1.0 mL) for 2 h in the dark. The mixture was diluted with Et_2O (50 mL), washed with aq $Na_2S_2O_3$ and dried. Evaporation and chromatography (EtOAc/hexane 1:4) gave **21** (130 mg, 81%) as pale yellow crystals. A sample was recrystallised (EtOAc/hexane) to give a yellow powder: mp 154–156 °C; IR ν_{max} 1347, 1522, 1736 cm^{-1}; ^{13}H NMR δ 7.50 (3H, m, Ph 3,4,5-H_3), 7.66 (1H, t, *J*=7.8 Hz, 7-H), 7.75 (2H, m, Ph 2,6-H_2), 8.08 (1H, dd, *J*=7.8, 1.2 Hz, 6-H), 8.54 (1H, dd, *J*=7.8, 1.2 Hz, 8-H); ^{13}C NMR δ 61.58, 123.47, 128.35, 128.63, 130.46, 130.92, 131.21, 131.95, 133.25, 134.90, 150.06, 158.95, 159.55; MS (EI) *m/z* 392 (M−H), 265 (M−HI). Found: C, 46.1; H, 2.15; N, 3.69; $C_{15}H_8INO_4$ requires C, 45.83; H, 2.05; N, 3.56%.

4.1.15. 5-Nitro-3-phenyl-4-phenylselenylisocoumarin (22a). Compound **17a** (100 mg, 0.36 mmol) was stirred with PhSeCl (100 mg, 0.53 mmol) in CH_2Cl_2 (5.0 mL) under N_2 for 4 h. The mixture was washed (aq $NaHCO_3$) and dried. Evaporation and chromatography (EtOAc/hexane 1:7) gave **22a** (72 mg, 47%) as yellow crystals. A sample was recrystallised (EtOAc) to give orange-red crystals: mp 188–190 °C; IR ν_{max} 1354, 1533, 1733 cm^{-1}; ^1H NMR δ 6.77 (2H, ca. d, *J*=8.6 Hz, SePh 2,6-H_2), 6.95 (2H, ca. t, *J*=ca. 8 Hz, SePh 3,5-H_2), 7.07 (1H, tt, *J*=7.4, 1.2 Hz,

SePh 4-H), 7.32 (2H, ca. t, J=ca. 7.4 Hz, CPh 3,5-H_2), 7.39 (1H, tt, J=7.1, 1.5 Hz, CPh 4-H), 7.58 (2H, ca. d, J=ca. 7.5 Hz, CPh 2,6-H_2), 7.64 (1H, t, J=8.0 Hz, 7-H), 8.14 (1H, dd, J=8.0, 1.5 Hz, 6-H), 8.55 (1H, dd, J=8.0, 1.5 Hz, 8-H); ^{13}C NMR δ 102.24, 123.12, 127.61, 127.85, 128.04, 128.90, 130.34, 130.60, 131.05, 131.70, 132.18, 133.26, 133.68, 134.38, 137.27, 148.35, 159.90, 160.65; MS (EI) m/z 422 (M). Found: C, 59.8; H, 3.06; N, 3.32; $C_{21}H_{13}NO_4Se$ requires C, 59.73; H, 3.10; N, 3.32.

4.1.16. 5-Nitro-4-phenylselenyl-3-trimethylsilylisocoumarin (22d). Compound **17d** (110 mg, 0.4 mmol) was stirred with PhSeCl (114 mg, 0.6 mmol) in CH_2Cl_2 (3.0 mL) under N_2 for 24 h. The mixture was washed (aq $NaHCO_3$) and dried. Evaporation and chromatography (EtOAc/hexane 1:4) gave **22d** (136 mg, 82%) as a yellow solid. A sample was recrystallised (toluene) to give a yellow powder: mp 105–107 °C; IR ν_{max} 1733 cm^{-1}; ^{1}H NMR δ 0.34 (9H, s, $SiMe_3$), 7.00 (2H, m, Ph 2,6-H_2), 7.14 (3H, m, Ph 3,4,5-H_3), 7.38 (1H, t, J=7.8 Hz, 7-H), 7.80 (1H, dd, J=7.8, 1.4 Hz, 6-H), 8.50 (1H, dd, J=7.8, 1.4 Hz, 8-H); ^{13}C NMR δ 0.34, 110.26, 124.04, 126.67, 127.84, 128.30, 129.10, 129.36, 130.15, 130.33, 132.96, 133.73, 160.47, 175.22; MS (EI) m/z 419.0096 (M) ($C_{18}H_{17}NO^{80}Se^{28}Si$ requires 419.0092), 403 (M−CH_4). Found: C, 51.8; H, 4.15; N, 3.33; $C_{18}H_{17}NOSeSi$ requires C, 51.67; H, 4.10; N, 3.35.

4.1.17. X-ray crystallography. Compound 13b. *Crystal data*, $C_{16}H_{11}NO_4$, M=281.26, λ=0.71073 Å, monoclinic, space group $P2_1/n$, a=5.8870(2), b=12.0270(3), c=18.4880(7) Å, β=96.802(1)°, U=1299.79(7) Å^3, Z=4, D_c=1.437 mg m^{-3}, μ=0.105 mm^{-1}, F(000)=584, crystal size 0.40×0.13×0.08 mm, unique reflections=2964 [R_{int}=0.0686], observed $I>2\sigma(I)$=1523, data/restraints/parameters=2964/0/192, $R1$=0.0548 $wR2$=0.1228 (observed data), $R1$=0.1295 $wR2$=0.1617 (all data), max peak/hole 0.300 and −0.279 eÅ^{-3}, diffractometer=Nonius kappaCCD, software used, SHELXS,[38] SHELXL[39] and ORTEX.[40]

4.1.18. X-ray crystallography. Compound 22a. *Crystal data*, $C_{21}H_{13}NO_4Se$, M=422.28, λ=0.71073 Å, monoclinic, space group $P2_1/n$, a=11.8050(1), b=11.8550(1), c=13.3860(1) Å, β=113.969(1)°, U=1711.80(2) Å^3, Z=4, D_c=1.639 mg m^{-3}, μ=2.222 mm^{-1}, F(000)=848, crystal size 0.50×0.30×0.10 mm, unique reflections=3928 [R_{int}=0.0549], observed $I>2\sigma(I)$=3671, data/restraints/parameters=3928/0/245, $R1$=0.0248 $wR2$=0.0627 (observed data), $R1$=0.0275 $wR2$=0.0643 (all data), max peak/hole 0.380 and −0.568 eÅ^{-3}, software used, SHELXS,[38] SHELXL[39] and ORTEX.[40]

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CDCC-263103 and CDCC-288997. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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