Photochemical intramolecular aromatic substitutions of the imidazol-2-yl radical are superior to those mediated by Bu_3SnH

Mairéad A. Clyne and Fawaz Aldabbagh*

Received 12th September 2005, Accepted 10th November 2005
First published as an Advance Article on the web 5th December 2005
DOI: 10.1039/b512729g

Six-membered photochemical cyclisations of 2-iodo-*N*-(2-arylethyl)imidazoles proceeded regioselectively in higher yields than the equivalent tin hydride-mediated reactions. The decrease in yield of cyclisation products, 5,6-dihydroimidazo[2,1-*a*]isoquinolines containing strongly deactivating substituents on the aryl ring confirmed the electrophilic nature of the σ-imidazol-2-yl radicals. The seven-membered cyclisation was only successful under photochemical conditions, as radical reduction occurred with tin hydride. Nitration of 5,6-dihydroimidazo[2,1-*a*]isoquinoline with nitric/sulfuric acid occurred at the 2- and 8-positions.

Introduction

The use of tributyltin hydride (Bu_3SnH) and azobisisobutyronitrile (AIBN) has become commonplace in the synthesis of fused aromatics by intramolecular aromatic substitution of aryl and heteroaryl radicals.[1–9] Less toxic and more expensive silanes and germanes have been used as substitutes for Bu_3SnH.[7–10] The reactions have attracted mechanistic interest, because an "oxidative" re-aromatisation occurs in the presence of the "reductant" metal hydride.[11–12] It is now perceived that upon radical addition, the generated intermediate π-cyclohexadienyl radical surrenders a hydrogen atom due to abstraction by the azo-initiator and/or derived radical to give the aromatic product. A non-chain reaction requiring more than stoichiometric amounts and sometimes large excesses of azo-initiator in order to form adequate yields of rearomatised product may be the outcome.[11] The AIBN derived 2-cyano-2-propyl radical can also be trapped by the relatively long-lived π-cyclohexadienyl radical.[2a,11–12] Further, there are serious toxicity concerns associated with using Bu_3SnH, as well as problems of separation of tin residues from organic products,[13] disposal of the wastes and reduction of the intermediate carbon-centered radicals by Bu_3SnH. These many disadvantages associated with the metal hydride/azo-initiator mediated reactions make the search for alternative methodologies synthetically important. Recent alternatives were reported by Harrowven and co-workers including intramolecular aryl radical cyclisations onto pyridine mediated by sodium cobalt(I) salophen[5] and samarium(II) iodide (SmI_2)–HMPA in THF.[7] Tanaka and co-workers showed that in the absence of *i*-PrOH, rearomatised products were obtained from intramolecular arylations mediated by SmI_2–HMPA in THF rather than spirocycles and/or reduced *cine*-cyclised products.[14]

Nevertheless, the simplest and most environmentally friendly protocol has to be the simple generation of the σ-aryl or heteroaryl radical by UV-induced homolytic cleavage of an aryl halide with subsequent intramolecular substitution onto a nearby aromatic ring. Metal hydride–AIBN seems to have superseded the photochemical reaction, although there are mostly older reports of preparative examples of the latter.[6,15–19] In recent times, Park and co-workers have extensively studied photocyclisations of aryl and pyridyl radicals onto aromatics, and reported several synthetically useful examples.[18–19] As part of our studies towards new bioreductive polycyclic diazoles,[20] we were interested in cyclising the imidazol-2-yl radicals **2** onto the aromatic ring of *N*-(ω-arylalkyl) substituents to give tricyclic [2,1-*a*] fused heterocycles **3** (Scheme 1). The following paper demonstrates that for the present aromatic substitutions, UV-mediated radical cyclisations give higher yields and allow for simpler work up procedures than the Bu_3SnH method. Some reports add tin radical sources to photochemical substitutions,[1b,7] however in our case this was not necessary. Generation of the radical at the imidazole-2-position was chosen, because cyclisation of aryl radicals is non-regioselective, as substitution can occur onto either the 2- or 5-position of the imidazole ring.[8] We thus report the first examples of intramolecular homolytic aromatic substitutions of imidazole radicals, although there are two examples of intermolecular reactions.[11,21] In the photolysis, as well as Bu_3SnH–AIBN-mediated reactions, σ-imidazol-2-yl radicals **2** and π-cyclohexadienyl radicals can be assumed to be the reaction intermediates, as laser flash photolysis has been used to detect and characterize analogous intermediates in photocyclisations onto aromatics of 2-halopyridinium salts and 2-halo-*N*-pyridinylbenzamides.[19]

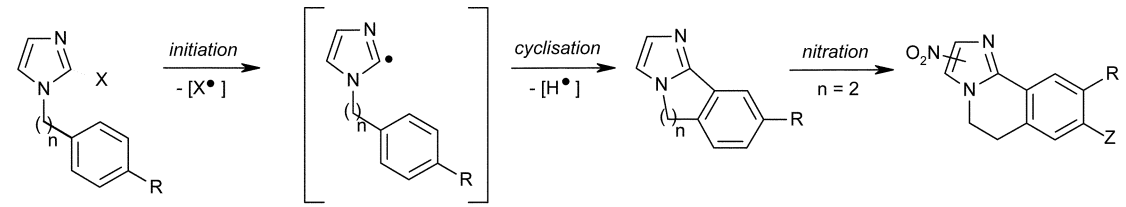
The 2- and 5-nitroimidazoles (free imidazole numbering) are well known bioreductive compounds that are used to selectively target anaerobic diseases, and hypoxic tumours.[22] However, alicyclic fused nitroimidazoles are less known cytotoxins with only limited patent information available on such compounds.[23a] Therefore, attempts at nitrating tricyclic diazoles **3b**, **3d**–**f** (Scheme 1) with the aim of forming bioreductive compounds, 2 or 3-nitro-5,6-dihydroimidazo[2,1-*a*]isoquinolines **4** are also described.

Results and discussion

Radical cyclisations of the imidazole-2-yl radicals 2a–g

Bu_3SnH–AIBN-mediated reactions. The conditions for the Bu_3SnH–AIBN procedure were optimised for the six-membered radical cyclisation of the imidazol-2-yl radical **2b** generated

Department of Chemistry, National University of Ireland, Galway, Ireland. E-mail: Fawaz.Aldabbagh@nuigalway.ie; Fax: 353 (0)91 525700



1a X = Br, R = H, n = 1
1b X = Br, R = H, n = 2
1c X = Br, R = H, n = 3
1d X = Br, R = F, n = 2
1e X = Br, R = Cl, n = 2
1f X = I, R = H, n = 1
1g X = I, R = H, n = 2
1h X = I, R = H, n = 3
1i X = I, R = Cl, n = 2
1j X = I, R = CF_3, n = 2
1k X = Cl, R = H, n = 1
1l X = I R = NO_2, n = 2

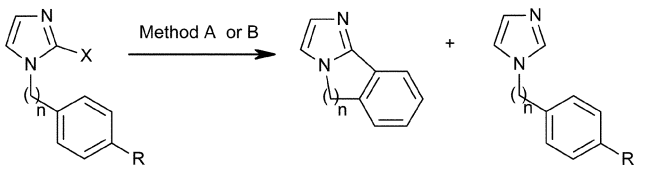
2a R = H, n = 1
2b R = H, n = 2
2c R = H, n = 3
2d R = F, n = 2
2e R = Cl, n = 2
2f R = CF_3, n = 2
2g R = NO_2, n = 2

3a R = H, n = 1
3b R = H, n = 2
3c R = H, n = 3
3d R = F, n = 2
3e R = Cl, n = 2
3f R = CF_3, n = 2
3g R = NO_2, n = 2

4a R = H, Z = NO_2
4b R = F, Z = NO_2
4c R = Cl, Z = NO_2
4d R = CF_3, Z = H
4e R = NO_2, Z = H

Scheme 1

from bromide **1b** in acetonitrile. As with previous homolytic aromatic substitutions using Bu_3SnH–AIBN,[11,12] an excess of AIBN (3.0 equivalents) was required giving cyclised product, 5,6-dihydroimidazo[2,1-*a*]isoquinoline **3b** in 35% yield with the product of Bu_3SnH reduction of **2b**, 1-(2-phenylethyl)-1*H*-imidazole **5b** obtained in 26% yield (Scheme 2, method A in Table 1). The poor mass balance in Bu_3SnH–AIBN reactions can be primarily attributed to the cumbersome work up procedure, which required up to 20 washes with hexane of the acidic imidazolium salts solution in order to eliminate tin halide residues. During the course of our studies, Harrowven and Guy reported an improved procedure for removal of tin residues using KF–silica as the stationary chromatographic phase,[13] which has improved isolation of diazoles in other Bu_3SnH-mediated reactions performed in our group (radical cyclisations using benzimidazole substrates to be published). However, for the present work, we wanted to completely avoid the use of metal hydride radical sources, and this was achieved using the photochemical initiated cyclisations discussed in the next section.



1a-l **3a-g**

5a R = H, n = 1
5b R = H, n = 2
5c R = H, n = 3
5d R = F, n = 2
5e R = Cl, n = 2
5f R = CF_3, n = 2

Scheme 2

Table 1 Reactions of halides **1a**–**l**

Starting material (SM)	Method[a]	Products (% yields)[b]		
		Cyclised	Reduced	Recovered SM
1b	A	**3b** (35)	**5b** (26)	**1b** (0)
1a	A	**3a** (0)	**5a** (45)	**1a** (0)
1c	A	**3c** (0)	**5c** (65)	**1c** (0)
1d	A	**3d** (32)	**5d** (19)	**1d** (0)
1e	A	**3e** (20)	**5e** (31)	**1e** (0)
1j	A	**3f** (21)	**5f** (51)	**1j** (0)
1b	B	**3b** (10)	**5b** (0)	**1b** (60)
1g	B	**3b** (70)	**5b** (0)	**1g** (7)
1g	C	**3b** (0)	**5b** (0)	**1g** (100)
5b	B	**3b** (0)	—	**5b** (100)
1g	D	**3b** (61)	**5b** (0)	**1g** (14)
1g	E	**3b** (0)	**5b** (0)	**1g** (97)
1f	B	**3a** (0)	**5a** (45)	**1f** (5)
1k	B	**3a** (0)	**5a** (0)	**1k** (100)
1h	B	**3c** (48)	**5c** (0)	**1h** (10)
1i	B	**3e** (66)	**5e** (0)	**1i** (13)
1j	B	**3f** (53)	**5f** (0)	**1j** (15)
1l	B	**3g** (32)	—	**1l** (36)

[a] The methods used were as follows: A. Bu_3SnH (1.2 equiv., 51 mM) and AIBN (3.0 equiv.) in acetonitrile were added over 8 h to SM (17 mM) in acetonitrile under reflux and heated under reflux for a further 1 h. B. SM (20 mM) in acetonitrile (purged with N_2) was irradiated at 254 nm for 4–10 h (refer to the Experimental section). C. SM (20 mM) in acetonitrile (purged with N_2) was irradiated at 366 nm for 15 h. D. SM (20 mM) in acetonitrile (purged with O_2) was irradiated at 254 nm for 4 h. E. SM (20 mM) and benzophenone (5.3 equiv.) in acetonitrile (purged with N_2) were irradiated at 254 nm for 10 h. [b] Yields quoted are of the pure isolated compounds after column chromatography.

Using the same conditions as for Bu_3SnH-mediated cyclisation of **1b**, attempted 5-membered and 7-membered cyclisations of bromides **1a** and **1c** gave only reduction products **5a** and **5c** in 45 and 65% isolated yield, respectively.

Six-membered cyclisations of substrates containing electron-withdrawing substituents were attempted, in order to deactivate the fused aryl ring towards the subsequent nitration. 4-Fluoro **1d**, 4-chloro **1e** and 4-trifluoromethyl (–CF_3) **1j** substituted precursors gave tricyclic products **3d** (32%), **3e** (20%) and **3f** (21%), respectively in lower yield than the radical precursor containing no aryl substituent **1b**. Significant amounts of the respective reduced products **5d** (19%), **5e** (31%) and **5f** (51%) were also given (Scheme 2). This procedure should now be compared with the equivalent photochemical reaction (method B).

Photochemical initiated reactions

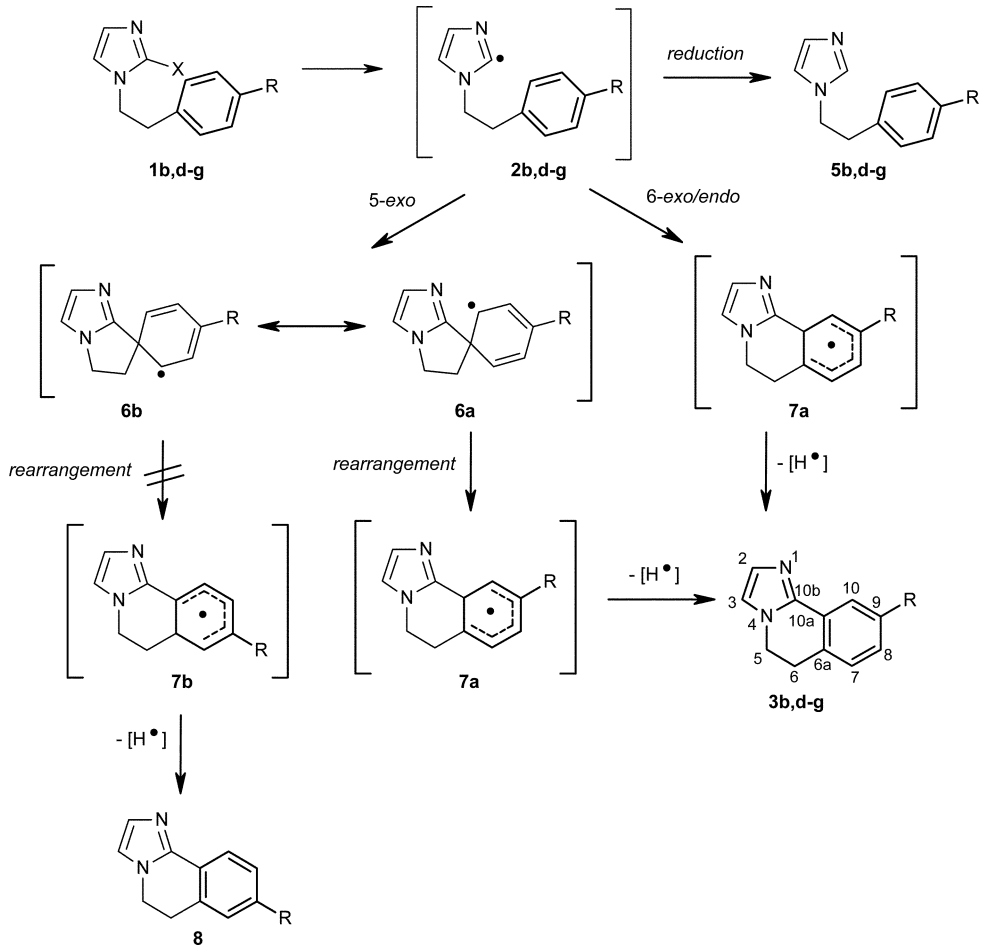
In pursuit of higher yields of the six-membered cyclisation product **3b** and simpler work up procedures, we irradiated **1b** in acetonitrile for 10 h at 254 nm generated from mercury lamps using a Rayonet photochemical reactor. This resulted in the isolation of **3b** in 10% yield with 60% unaltered **1b** recovered. It seemed that the C–Br bond is too strong for rapid photochemical generation of σ-radical **2b**, however we were encouraged by the lack of reduced product. The photochemical reaction was repeated using iodide precursor **1g** resulting in isolation of **3b** in 70% yield after only 4 h of irradiation with 7% recovery of unaltered **1g** (method B in Table 1). This represented a vast improvement on the Bu_3SnH–AIBN-mediated reaction for the following reasons; (i) elimination and disposal of toxic tin residues was completely avoided, (ii) there was no need for hazardous azo-initiators, (iii) syringe pump addition of initiators was no longer required and thus shorter reaction times were achieved, (iv) a simpler work up procedure allowing good recovery of cyclised product (improved mass-balance) and (v) no competitive reduction of **2b** occurred.

Iodide precursors for photochemical reactions were generally prepared in good and comparable yields to bromide precursors for the Bu_3SnH–AIBN reactions by alkylation of 2-iodo-1*H*-imidazole rather than 2-bromo-1*H*-imidazole (refer to the Experimental section). Although, there was no competitive reduction in our six- and seven-membered photochemical cyclisations, slow degradation of **3b**–**c** and **3e**–**g** to unidentified products was observed with prolonged irradiation at 254 nm (monitored by thin-layer chromatography, TLC) and the probable reversal of the homolytic scission by combination of the imidazol-2-yl radicals with released $I^{\bullet}$ led to recovery of starting material (5–36%). Reaction solutions turned brown after irradiation, and crude product solutions appeared purple upon elution on column chromatography indicating the presence of molecular iodine. However, optimisation of yields by dilution of the reaction solution was not carried out, as this would lessen the amount of recovered product. The photolysis of **1g** and **5b** at the longer wavelengths of 366 nm (method C) and 254 nm, respectively, gave no reaction after 15 h of irradiation.

Irradiation of an oxygenated solution of **1g** at 254 nm led to a decrease in yield of **3b** to 61% (method D) and the cyclisation of **1g** could not be sensitised by benzophenone (method E). D'Auria and co-workers observed that intermolecular photoarylations of halogenothiophenes and 4(5)-nitro-2-iodoimidazoles also could not be sensitised, and concluded that higher energy excited triplet states may be involved in the rupture of the C–I bond.[21] We cannot rule out subtle mechanistic differences in our various photochemical annulations, however most evidence supports the formation of radical intermediates. Further, the presence of residual oxygen may be advantageous, as it may be involved in the rearomatisation of π-cyclohexadienyl radical intermediates **7** (Scheme 3). However, dehydrogenation of radicals **7** by the former imidazole halogen atom substituent to give HI or HBr and tricyclic aromatic products is the major source of rearomatisation in UV-initiated reactions.[17,19]

Attempts at the 5-membered cyclisation of radical **2a** generated from iodide **1f** under photochemical conditions (method B) resulted in only radical reduction to 1-benzyl-1*H*-imidazole **5a**. The formation of reduction product **5a** is further evidence for intermediate **2a**, and a radical-mediated mechanism in the photochemical initiated reactions. The result may be explained in terms of strain, as proposed by Bowman and co-workers for the lack of an anticipated 5-*exo*-trig cyclisation of a phenyl radical onto the 5-position of imidazole-4-methylcarboxylate using either Bu_3SnH or tributylgermanium hydride (Bu_3GeH) as initiators.[8] However, Park and co-workers have reported the formation of the same ring system, 5*H*-imidazo[5,1-*a*]isoindole in 40% yield from the photochemical cyclisation of *N*-(*o*-chlorobenzyl)imidazole.[18] Thus it is likely that any strain arguments only apply to the formation of imidazo[2,1-*a*]isoindole **3a**, and not 5-membered cyclisations onto the imidazole-5-position. Failed 5-membered cyclisations may also indicate that such processes are more akin to proceed *via* 5-*endo*-trig rather than 5-*exo*-trig.[7] However, the low mass balance from the 5-membered photochemical reaction (50%) is probably due to degradation of substrate and/or products to unidentified intractable material. There are several successful literature 5-membered photochemical cyclisations using aromatic chloride radical precursors.[16a,17b–19a] 1-Benzyl-2-chloroimidazole **1k** was thus irradiated at 254 nm in acetonitrile and 2 M hydrochloric acid solution.[18] It was anticipated that in the photo-excited state the C–Cl bond may be weakened through co-ordination of the electrophilic chlorine atom with the phenyl ring or by Grimshaw's proposed homolysis assisted by radical complexation.[17] The 2-chloro substituent may be held in closer proximity to the tethered phenyl ring in **1k** containing methylene rather than for 2-halo substituents in precursors containing ethylene connectors.[19] However, only unaltered **1k** was recovered from both attempted reactions.

The superiority of the photochemical method was however demonstrated with the seven-membered cyclisation[16b] to give 6,7-dihydro-5*H*-imidazo[2,1-*a*][2]benzazepine **3c** in 48% yield *via* irradiation of iodide **1h** (10% recovered) at 254 nm for 6 h. Bu_3SnH–AIBN reaction of bromide **1c** gave only the reduced compound 1-(3-phenylpropyl)-1*H*-imidazole **5c** (Table 1). The absence of **5c** as a product from the photochemical reaction confirmed that a 1,5-hydrogen atom abstraction from the benzylic position was not occurring, and that the cause of the reduction in the Bu_3SnH-mediated reaction was the slower cyclisation of **2c** in comparison to the intermolecular reduction by Bu_3SnH. Jones and Fiumana found that the indol-2-yl radical will undergo a similar seven-membered cyclisation onto a phenyl ring, but as Bu_3SnH was used, significant reduction also occurred.[3d] Higher isolated yields of **3c** were not obtained because of degradation of **3c** to



Scheme 3

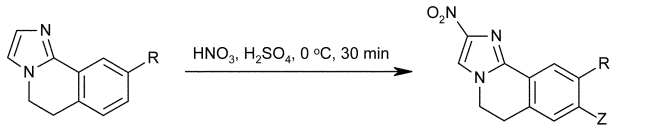
unidentifiable products with prolonged exposure to UV-light at 254 nm (as indicated by TLC).

Mechanism of the six-membered cyclisation

The six-membered cyclisation was further investigated using 4-aryl substituents on the 2-halo-1-(2-arylethyl)-1*H*-imidazole substrates. The formation of **3b** may conceivably occur *via* an initial 5-*exo*-trig followed by a rearrangement to the six-membered ring or 6-*exo*/*endo*-trig of the imidazol-2-yl radical **2b** (Scheme 3). The yield of 9-chloro-5–6-dihydroimidazo[2, 1-*a*]isoquinoline **3e** was much improved using method B in comparison to the Bu_3SnH–AIBN procedure (method A) giving **3e** in 66% yield with 13% unaltered **1i**. In order to deactivate the aryl ring towards nitration, and allow for selective nitration at the diazole-2 or 3-positions (see nitration discussion), iodide **1j** containing a 4-trifluoromethyl substituent on the aryl ring was irradiated at 254 nm giving cyclised product **3f** in 53% yield. Thus, iodide **1j** gave the lowest yield of cyclised product of all the aryl halide-containing substrates. This is in line with the electrophilic character of the imidazol-2-yl radical due to the inductive electron-withdrawing effect of the adjacent nitrogen atoms[11] creating a slower cyclisation for **2f** compared to **2b** and **2d**–**e**, since the CF_3 substituent is more strongly deactivating (inductively electron-withdrawing) than the 4-fluoro and chloro substituents. The photolysis of iodide **1l** yielded least cyclised product (**3g** given in 32% yield), which is indicative of the strong electron-withdrawing nature of the nitro group (NO_2). For the photochemical reactions, this provides further support for a homolysis mechanism, and the formation of σ-imidazole radicals **2**.

Therefore, all Bu_3SnH–AIBN and photochemical mediated cyclisations were selective giving only the 9-aryl substituted isomeric products **3d**–**g**, and no 8-substituted tricyclic products **8**. The location of the aryl substituent at the 9- rather than the 8-position of **3d**–**g** was ascertained by careful NMR analysis (refer to the Experimental section). For example the location of the 10-H of **3f** was obtained from its down field location, as a singlet at 8.31 ppm in the ^1H NMR spectrum. This signal did not give any NOE enhancement. The HMQC, ^1H-^{13}C NMR 2D spectra allowed us to assign the 10-CH at 121–124 ppm for **3b**, **3e**–**f**. The 10-CH appeared relatively up field in **3d** at 110.2–110.5 ppm, and the magnitude of C–F couplings allowed us to assign all aromatic signals. The preparation of **3g** and nitration to **4e** (see nitration discussion, Scheme 4) allowed us to confirm that the aryl-NO_2 substituent in **3g** and **4e** is at the 9-position, since **4e** is the isomer of **4a**.

The 5-*exo*-trig cyclisations give spirocycles **6a** and **6b**, which would rearrange to tricyclic cyclohexadienyl radicals **7a** and **7b** respectively. Oxidative rearomatisation of **7a** would give tricyclic products **3b**, **3d**–**g**, while oxidation of **7b** would give the isomeric products **8** (Scheme 3). The rearrangements of **6a** to **7a** and **6b** to **7b**



3b R = H
3d R = F
3e R = Cl
3f R = CF_3
3g R = NO_2

4a R = H, Z = NO_2, (50%)
4b R = F, Z = NO_2, (70%)
4c R = Cl, Z = NO_2, (70%)
4d R = CF_3, Z = H, (68%)
4e R = NO_2, Z = H, (50%)

Scheme 4

would involve 1,2-aryl (neophyl rearrangement) and 1,4-aryl shifts respectively,[24] and such rearrangements are thermodynamically favoured since more stable ring-enlarged conjugated tertiary cyclohexadienyl radicals **7a** and **7b** are formed. The absence of isomeric products **8** from all our six-membered cyclisations would support 5-*exo*- and 6-*exo*/*endo* pathways *via* intermediates **7a** and not **7b**. However, we believe that the latter direct six-membered cyclisation is more likely since rearrangement pathways *via* **6a**–**b** are most favoured at low tin hydride concentrations (*i.e.* the photochemical reaction), and such spirocyclic intermediates were not observed in flash photolysis studies of six-membered radical cyclisations of σ-pyridyl and aryl radicals onto aromatic rings.[19] Further support for the 6-*exo*/*endo* pathway is provided by the lack of a five-membered cyclisation for imidazol-2-yl radical **2a**.

Nitration of tricyclic diazoles 3b, 3d–g

1-Methylimidazoles usually give a mixture of 4 and 5-nitro isomers upon nitration under electrophilic aromatic substitution conditions with the 4-isomer predominating.[25] However, it was not clear from the literature, where the substitution of the nitro group would occur upon treatment of tricyclic diazoles **3b**, **3d**–**g** with mixtures of concentrated nitric and sulfuric acid. The resultant 2 or 3-nitro-5,6-dihydroimidazo[2,1-*a*]isoquinolines would be of interest, because of their conjugated ring system possibly leading to lower reductive potentials than commercially available 1-alkyl-2(5)-nitroimidazole antibiotics (more stable radical anion would be formed upon single-electron reductive activation). Reductive potentials are known to influence the cytotoxicity and selectivity of bioreductive compounds.[20,22]

All nitration reactions gave only one product with the 2-position of the diazole ring found to be the most easily nitrated (Scheme 4). However nitration occurred at the 8-position as well as the 2-position for **3b**, **3d** and **3e** giving 2,8-dinitro compounds **4a** (50%), **4b** (70%) and **4c** (70%), respectively. Thus activation of the 8-position through π-conjugation of the adjacent 9-fluoro- and chloro-substituents is significant. Deactivation of the aryl ring was achieved with CF_3 and NO_2 substituents leading to selective nitration at the 2-position of **3f** and **3g** giving 2-nitro and 2,9-dinitro compounds **4d** (68%) and **4e** (50%) respectively. Compound **4e** is an isomer of **4a**, and was required to confirm that the nitration of **3b** had resulted in the NO_2 substituent being located at the 8- rather than the 9-position of **4a**.

The location of the NO_2 substituent at the 2-position rather than the 3-position was ascertained using literature chemical shifts for 4- and 5-nitro-1-alkylimidazoles.[26] ^{13}C NMR spectra of compounds **4a**–**e** all contained CH at 123–125 ppm assigned to the 3-CH, which is of similar chemical shift magnitude to the 5-CH of 1-alkyl-4-nitroimidazoles, since the equivalent 5-nitro isomer has 4-CH at 132–133 ppm. Confirmation of assignments was obtained using NOE irradiation at 8.62 ppm for the 3-CH of **4b**, which gave the required enhancement at 4.36–4.39 ppm for the NCH_2 of the fused six-membered ring.

Conclusions

Six-membered cyclisations of 2-iodo-*N*-(2-arylethyl)imidazoles **1g**, **1i**–**j** at 254 nm gave higher yields of 5,6-dihydroimidazo[2,1-*a*]isoquinolines **3b**, **3e**–**f** than the equivalent radical cyclisations using 2-bromo(iodo)-*N*-(2-arylethyl)imidazoles **1b**, **1e** and **1j** under Bu_3SnH–AIBN-mediated conditions. All Bu_3SnH–AIBN reactions gave a considerable amount of radical reduction products **5b**, **5d**–**f**, and the ratio of reduced/cyclised products increased for substrates containing inductively electron withdrawing substituents at the 4-position of the aryl ring (*e.g.* Cl and CF_3). Yields of cyclised product were also considerably less in photochemical reactions of substrates containing 4-aryl deactivating substituents **1j** and **1l** (CF_3 and NO_2, respectively) leading to the recovery of increasing amounts of unaltered starting material. This is rationalised in terms of slow cyclisation of an electrophilic σ-imidazol-2-yl radical onto a deactivated aromatic ring. The formation of 9-substituted tricyclic imidazoles from the six-membered cyclisations inferred that a 6-*exo*/*endo* cyclisation is the most likely route for formation of tricyclic products.

A rare example of a seven-membered photochemical homolytic aromatic substitution is provided by the conversion of 2-iodo-1-(3-phenylpropyl)imidazole **1h** into 6,7-dihydro-5*H*-imidazo[2,1-*a*][2]benzazepine **3c**. The equivalent Bu_3SnH–AIBN-mediated reaction gave only reduced product **5c**. Attempted five-membered cyclisations of 1-benzyl-2-halo-1*H*-imidazoles **1a**, **1f** and **1k** under both photochemical and Bu_3SnH–AIBN-mediated conditions gave only radical reduction product **5a** or recovery of starting material for the irradiation of the 2-chloro substrate **1k** at 254 nm.

Although yields for the photochemical reactions could not be improved, because of decomposition of products over prolonged irradiation times, yields were always substantially greater than the equivalent Bu_3SnH method. The photochemical method circumvents the use of toxic and hazardous initiators and allowed a simpler work-up procedure. Thus, it is possible that this method may be applicable to other intramolecular aromatic substitution reactions of σ-aryl and heteroaryl radicals previously carried out using Bu_3SnH–AIBN.

Nitration of unsubstituted **3b** and 9-fluoro **3d** and chloro **3e** substituted tricyclic diazoles occurred at 2 and 8-positions. Deactivation of the fused aryl moiety in **3f** and **3g** by 9-trifluoromethyl and nitro substituents allowed selective nitration at the 2-position. Future work in our group will attempt preparations of 3-nitro-5,6-dihydroimidazo[2,1-*a*]isoquinolines in order to compare reductive and cytotoxicity properties with the 2-nitroisomers prepared in this paper.

Experimental

General

Materials. All chemicals were obtained from Aldrich, except AIBN, which was obtained from DuPont Chemical Solution

Enterprise, and was re-crystallized using methanol before use. Monitoring of reactions by thin later chromatography (TLC) was performed using aluminium backed plates coated with silica gel (Merck Kieselgel 60 F_{254}). Column chromatography using silica gel was carried out using Merck Kiesel 60 H silica.

Measurements. Melting points were measured on a Stuart Scientific melting point apparatus SMP3. Elemental analysis was carried out on a Perkin-Elmer 2400 Series II analyser. IR spectra were acquired using a Perkin-Elmer Spec 1 with ATR attached.

All ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz respectively using a Jeol GXFT 400 MHz instrument equipped with a DEC AXP 300 computer work station. Chemical shifts are given in parts per million (ppm) and J values are in Hz. NMR assignments were supported by NOE difference spectra (400 MHz) and heteronuclear multiple-quantum correlation (HMQC) ^{1}H–^{13}C 2D spectra for compounds **3b**, **3f**, **3g** and **4b**. HMQC ^{1}H–^{13}C 2D spectra were also carried out on compounds **1l**, **3c**, **3d**, **4c**, **4d** and **5f**.

Low and high resolution electron impact (EI) and chemical ionisation (CI) mass spectra were obtained on a Micro Mass GTC spectrometer. EPSRC National Mass Spectrometry Service carried out low resolution EI on the Micromass Quattro II triple quadrupole instrument and high-resolution mass spectrometry on the Finnigan MAT 900 XLT in CI mode for compounds **1l**, **3g** and **4a**–**d**.

Synthesis of radical precursors. 2-Bromo-1*H*-imidazole, 2-chloro-1*H*-imidazole and 2-iodo-1*H*-imidazole were prepared using literature procedures.[27] Radical precursors **1a**–**k** were prepared in mostly good to excellent yields of 59–93% (apart from **1j** prepared in 27% yield) by appropriate alkylation of the 2-halo-1*H*-imidazoles with ω-arylalkyl bromide using the procedure given for **1a** as a representative example. Radical precursor **1l** was prepared differently, because 1-(2-bromoethyl)-4-nitrobenzene was found to readily eliminate in the presence of sodium hydride to give 1-nitro-4-vinylbenzene.

1-Benzyl-2-bromo-1*H*-imidazole (1a). 2-Bromo-1*H*-imidazole (0.20 g, 1.36 mmol), sodium hydride (0.04 g, 1.63 mmol) in THF (15 ml) were stirred at reflux for 1 h under a nitrogen atmosphere. Benzyl bromide (0.26 ml, 2.18 mmol) was added and stirred at reflux for a further 3 h. The solution was filtered and evaporated to dryness to yield a residue, which was purified by column chromatography using silica as absorbent with gradient elution of hexane–ethyl acetate–methanol to yield the title compound **1a** (0.27 g, 84%) as a colourless oil. Spectroscopic data were consistent with the literature.[28]

2-Bromo-1-(2-phenylethyl)-1*H*-imidazole (1b). 2-Bromo-1*H*-imidazole (0.50 g, 3.40 mmol), sodium hydride (0.10 g, 4.08 mmol) and (2-bromoethyl)benzene (0.74 ml, 5.44 mmol) in THF (40 ml) gave the title compound **1b** (0.53 g, 62%) as a cream solid; R_f 0.56 (1 : 1 hexane–ethyl acetate), mp 99–101 °C; (found: C, 52.3; H, 4.6; N, 11.1. $C_{11}H_{11}N_2Br$ requires C, 52.6; H, 4.4; N, 11.1%); ν_{max}/cm^{-1} 3099, 1603, 1497, 1460, 1276, 1167, 1113, 913; δ_H ($CDCl_3$) 3.00–3.03 (2 H, t, J 7.3, CH_2Ph), 4.11–4.15 (2 H, t, J 7.3, NCH_2), 6.78 (1 H, s, Im-5-H), 6.94 (1 H, s, Im-4-H), 7.24–7.31 (5 H, m, Ph–H); δ_C ($CDCl_3$) 36.8 (CH_2Ph), 49.1 (NCH_2), 119.1 (Im-2-C), 121.9 (Im-5-CH), 126.9 (CH), 128.7–129.6 (CH), 136.9 (Ph-1-C); m/z (EI) 250 (M^+, 3%), 171 (100), 105 (52), 91 (85).

2-Bromo-1-(3-phenylpropyl)-1*H*-imidazole (1c). 2-Bromo-1*H*-imidazole (0.16 g, 1.09 mmol), sodium hydride (0.03 g, 1.33 mmol) and 3-(bromopropyl)benzene (0.26 ml, 1.74 mmol) in THF (15 ml) gave title compound **1c** (0.27 g, 93%) as a colourless oil; R_f 0.54 (1 : 1 hexane–ethyl acetate), (found: C, 54.0; H, 4.8; N, 10.6. $C_{12}H_{13}N_2Br$ requires C, 54.4; H, 4.9; N, 10.6%); ν_{max}/cm^{-1}1603, 1468, 1434, 1348, 1265, 1101, 908; δ_H ($CDCl_3$) 2.04–2.13 (2 H, m, 2′-CH_2), 2.62–2.66 (2 H, t, J 7.6, CH_2Ph), 3.89–3.93 (2 H, t, J 7.1, NCH_2), 6.95 (1 H, s, Im-5-H), 7.01 (1 H, s, Im-4-H), 7.16–7.32 (5 H, m, Ph–H); δ_C ($CDCl_3$) 31.6 (2′-CH_2Ph), 32.4 (CH_2Ph), 47.0 (NCH_2), 119.4 (Im-2-C), 121.8 (Im-5-CH), 126.2 (CH), 128.2 (CH), 128.6 (CH), 129.9 (CH), 140.1 (Ph-1-C); m/z (EI) 266 (2), 264 (M^+, 3%), 186 (17), 185 (100), 162 (30), 160 (31), 157 (14), 117 (29), 91 (50), 81 (28), 77 (15)

2-Bromo-1-[2-(4-fluorophenyl)ethyl]-1*H*-imidazole (1d). 2-Bromo-1*H*-imidazole (0.50 g, 3.40 mmol), sodium hydride (0.10 g, 4.08 mmol) and 1-(2-bromoethyl)-4-fluorobenzene (1.10 g, 5.44 mmol) in THF (40 ml) gave title compound **1d** (0.78 g, 86%) as a cream solid; R_f 0.46 (1 : 1 hexane–ethyl acetate), mp 80–82 °C; ν_{max}/cm^{-1} 3099, 1601, 1509, 1464, 1279, 1220, 914; δ_H ($CDCl_3$) 2.99–3.02 (2 H, t, J 7.1, CH_2Ar), 4.10–4.14 (2 H, t, J 7.1, NCH_2), 6.76–6.77 (1 H, d, J 1.5, Im-5-H), 6.96–7.05 (5 H, m, Ar–H); δ_C ($CDCl_3$) 36.0 (CH_2Ar), 49.1 (NCH_2), 115.5–115.7 (d, J_{C-F} 21.1, Ar-3,5-CH), 119.2 (Im-2-C), 121.9 (Im-5-CH), 129.8 (Im-4-CH), 130.2–130.3 (d, J_{C-F} 9.0, Ar-2,6-CH), 132.6 (Ar-1-C), 160.7–163.7 (d, J_{C-F} 243.9, Ar-4-C); m/z (EI) 268.0016 (5%, M^+, $C_{11}H_{10}N_2BrF$ requires M^+ 268.0011), 189 (100), 109 (98).

2-Bromo-1-[2-(4-chlorophenyl)ethyl]-1*H*-imidazole (1e). 2-Bromo-1*H*-imidazole (0.38 g, 2.59 mmol), sodium hydride (0.07 g, 2.90 mmol) and 1-(2-bromoethyl)-4-chlorobenzene (0.57 g, 4.13 mmol) in THF (30 ml) gave title compound **1e** (0.52 g, 71%) as a yellow oil; R_f 0.66 (1 : 1 hexane–ethyl acetate); ν_{max}/cm^{-1} 1598, 1492, 1467, 1434, 1267, 1092, 1015, 908; δ_H ($CDCl_3$) 2.98–3.02 (2 H, t, J 7.3, CH_2Ar), 4.11–4.14 (2 H, t, J 7.3 Hz, NCH_2), 6.77 (1 H, s, Im-5-H), 6.96 (1 H, s, Im-4-H), 6.99–7.01 (2 H, d, J 8.3, Ar–H), 7.25–7.27 (2 H, d, J 8.3, Ar–H); δ_C ($CDCl_3$) 36.2 (CH_2Ar), 48.9 (NCH_2), 119.1 (Im-2-C), 122.0 (Im-5-CH), 128.9 (CH), 129.8 (CH), 130.1 (CH), 132.7 (C), 135.3 (C); m/z 283.9714 (2%, M^+, $C_{11}H_{10}N_2BrCl$ requires M^+ 283.9716), 286 (22), 284 (14), 205 (100), 160 (6), 158 (8), 139 (3), 138 (2), 127 (5), 125 (92), 103 (2).

1-Benzyl-2-iodo-1*H*-imidazole (1f). 2-Iodo-1*H*-imidazole (0.35 g, 1.81 mmol), sodium hydride (0.05 g, 2.08 mmol) and benzyl bromide (0.26 ml, 2.17 mmol) in THF (25 ml) gave title compound **1f** (0.30 g, 59%) as a cream solid; R_f 0.44 (1 : 1 hexane–ethyl acetate), mp 99–100 °C (lit.,[29] 99–101 °C), (found: C, 42.4; H, 3.4; N, 9.8. $C_{10}H_9N_2I$ requires C, 42.4; H, 3.2; N, 9.9%). Spectroscopic data were consistent with the literature.[29]

2-Iodo-1-(2-phenylethyl)-1*H*-imidazole (1g). 2-Iodo-1*H*-imidazole (0.40 g, 2.06 mmol), sodium hydride (0.06 g, 2.47 mmol) and (2-bromoethyl)benzene (0.45 ml, 3.30 mmol) in THF (25 ml) gave title compound **1g** (0.51 g, 83%) as a cream solid; R_f 0.66 (ethyl acetate), mp 99–101 °C, (found: C, 44.1; H, 3.5; N, 9.0. $C_{11}H_{11}N_2I$ requires C, 44.3; H, 3.7; N, 9.4%); ν_{max}/cm^{-1} 1587, 1490, 1450, 1420, 1263, 1090, 1057, 933, 910; δ_H ($CDCl_3$) 3.00–3.04 (2 H, t, J 7.3, CH_2Ph), 4.10–4.14 (2 H, t, J 7.3, NCH_2), 6.87 (1 H, s, Im-5-H), 7.04 (1 H, s, Im-4-H), 7.09–7.10 (2 H, d, J 6.8, Ph–H), 7.25–7.32

(3 H, m, Ph–H); δ_C ($CDCl_3$) 37.2 (CH_2Ph), 50.9 (NCH_2), 89.7 (Im-2-C), 123.0 (Im-5-CH), 127.0 (CH), 128.7 (CH), 132.4 (CH), 136.9 (Ph-1-C); *m/z* (EI) 297.9962 (14%, M^+, $C_{11}H_{11}N_2I$ requires M^+ 297.9967), 207 (63), 172 (100), 171 (78), 170 (49), 156 (72), 126 (77), 105 (56), 104 (29), 103 (26), 91 (78).

2-Iodo-1-(3-phenylpropyl)-1*H*-imidazole (1h). 2-Iodo-1*H*-imidazole (0.38 g, 1.96 mmol), sodium hydride (0.06 g, 2.45 mmol) and 3-(bromopropyl)benzene (0.51 ml, 3.33 mmol) in THF (25 ml) gave title compound **1h** (0.51 g, 83%) as a cream solid; R_f 0.53 (ethyl acetate), mp 97–99 °C, (found: C, 46.4; H, 4.3; N, 9.0. $C_{12}H_{13}N_2I$ requires C, 46.2; H, 4.2; N, 9.0%); ν_{max}/cm^{-1} 1603, 1453, 1423, 1264, 1096, 908; δ_H ($CDCl_3$) 2.06–2.14 (2 H, m, 2′-CH_2Ph), 2.63–2.67 (2 H, t, *J* 7.8, CH_2Ph), 3.88–3.92 (2 H, t, *J* 7.3, NCH_2), 7.01 (1 H, s, Im-5-H), 7.09 (1 H, s, Im-4-H), 7.17–7.32 (5 H, m, Ph–H); δ_C ($CDCl_3$) 31.9 (2′-CH_2Ph), 32.5 (CH_2Ph), 48.9 (NCH_2), 90.0 (Im-2-C), 122.8 (Im-5-CH), 126.3 (CH), 128.3 (CH), 128.6 (CH), 132.60 (CH), 140.2 (Ph-1-C); *m/z* (EI) 312 (8%), 208 (69), 185 (100), 127 (95), 117 (79), 91 (97).

1-[2-(4-Chlorophenyl)ethyl]-2-iodo-1*H*-imidazole (1i). 2-Iodo-1*H*-imidazole (0.50 g, 2.57 mmol), sodium hydride (0.07 g, 3.08 mmol) and 1-(2-bromoethyl)-4-chlorobenzene (0.85 g, 3.87 mmol) in THF (35 cm^3) gave title compound **1i** (0.53 g, 62%) as a yellow oil; R_f 0.72 (ethyl acetate); ν_{max}/cm^{-1} 1597, 1491, 1458, 1423, 1265, 1090, 1015, 907; δ_H ($CDCl_3$) 2.96–3.00 (2 H, t, *J* 7.1, CH_2Ar), 4.06–4.10 (2 H, t, *J* 7.1, NCH_2), 6.83 (1 H, s, Im-5-H), 7.00–7.03 (2 H, d, *J* 8.2, Ar–H), 7.03 (1H, s, Im-4-H), 7.24–7.25 (2 H, d, *J* 8.2, Ar–H); δ_C ($CDCl_3$) 36.6 (CH_2Ar), 50.8 (NCH_2), 89.9 (Im-2-C), 123.1 (Im-5-CH), 129.0 (CH), 130.0 (CH), 132.7 (CH), 133.0 (C), 135.3 (C); *m/z* (EI) 331.9576 (24%, M^+, $C_{11}H_{10}N_2ClI$ requires M^+ 331.9577), 207 (60), 206 (10), 205 (100), 204 (15), 170 (24), 169 (13), 127 (24), 125 (82), 103 (20).

2-Iodo-1-{2-[4-(trifluoromethyl)phenyl]ethyl}-1*H*-imidazole (1j). 2-Iodo-1*H*-imidazole (0.37 g, 1.91 mmol), sodium hydride (0.06 g, 2.29 mmol) and 1-(2-bromoethyl)-4-(trifluoromethyl)benzene (0.72 g, 2.86 mmol) in THF (35 ml) gave title compound **1j** (0.19 g, 27%) as a yellow oil; R_f 0.50 (ethyl acetate); ν_{max}/cm^{-1} 1619, 1459, 1424, 1323, 1162, 1009, 1065, 1018; δ_H ($CDCl_3$) 3.07–3.11 (2 H, *J* 7.3, CH_2Ar), 4.13–4.16 (2 H, t, *J* 7.3, NCH_2), 6.87 (1 H, s, Im-5-H), 7.05 (1 H, s, Im-4-H), 7.19–7.21 (2 H, d, *J* 8.3, Ar-2,6-H), 7.54–7.56 (2 H, d, *J* 8.3, Ar-3,5-H); δ_C ($CDCl_3$) 36.9 (CH_2Ar), 50.3 (NCH_2), 89.8 (Im-2-C), 122.9 (Im-5-CH), 125.6 (CH), 129.1 (CH), 132.6 (CH), 140.9 (C); *m/z* (CI) 366.9912 (100%, M + H^+, $C_{12}H_{11}N_2F_3I$ requires M + H^+ 366.9919), 346 (14).

1-Benzyl-2-chloro-1*H*-imidazole (1k). 2-Chloro-1*H*-imidazole (0.14 g, 1.37 mmol), sodium hydride (0.04 g, 1.50 mmol) and benzyl bromide (0.16 ml, 1.37 mmol) in THF (20 ml) gave title compound **1k** (0.22 g, 84%) as a colourless oil; R_f 0.61 (1 : 1 hexane–ethyl acetate); ν_{max}/cm^{-1} 1471, 1454, 1437, 1388, 1362, 1272, 1105, 910; δ_H ($CDCl_3$) 5.07 (2 H, s, CH_2), 6.87 (1 H, s, Im-5-H), 6.95 (1H, s, Im-4-H), 7.13–7.15 (2 H, m, Ph–H), 7.30–7.35 (3 H, m, Ph–H); δ_C ($CDCl_3$) 50.3 (CH_2), 121.2 (Im-5-CH), 127.4 (Im-4-CH), 128.4 (CH), 128.6 (CH), 129.1 (CH), 132.3 (C), 135.5 (C); *m/z* (EI) 194 (30), 192.0449 (88%, M^+, $C_{10}H_9N_2Cl$ requires M^+ 192.0454) 92 (100), 91 (92), 65 (31).

2-Iodo-1-[2-(4-nitrophenyl)ethyl]-1*H*-imidazole (1l). 2-Iodo-1*H*-imidazole (0.67 g, 3.45 mmol) and potassium carbonate (0.48 g, 3.45 mmol) in DMF (80 ml) were stirred at reflux for 30 min. 1-(2-Bromoethyl)-4-nitrobenzene (0.42 g, 6.90 mmol) was added and stirred at reflux for a further 2 h. The solution was filtered and evaporated to dryness to yield a residue, which was purified by column chromatography using silica as absorbent with gradient elution of hexane–ethyl acetate–methanol to yield title compound **1l** (0.46 g, 39%) as a yellow oil; R_f 0.44 (ethyl acetate); ν_{max}/cm^{-1} 1600, 1513 (NO_2), 1424, 1343 (NO_2), 1264, 1095; δ_H ($CDCl_3$) 3.12–3.16 (2 H, t, *J* 7.1, CH_2Ar), 4.15–4.19 (2 H, t, *J* 7.1, NCH_2), 6.84 (1 H, s, Im-5-H), 7.04 (1 H, s, Im-4-H), 7.23–7.25 (2 H, d, *J* 8.5, Ar-2,6-H), 8.13–8.15 (2 H, d, *J* 8.5, Ar-3,5-H); δ_C ($CDCl_3$) 37.1 (CH_2Ar), 50.1 (NCH_2), 90.0 (Im-2-C), 123.0 (Im-5-CH), 124.1 (Ar-3,5-CH), 129.9 (Ar-2,6-CH), 133.0 (Im-4-CH), 144.6 (C), 147.3 (C); *m/z* (CI) 343.9895 (66%, M + H^+, $C_{11}H_{11}N_3O_2I$ requires M + H^+ 343.9890), 314 (16), 216 (16), 188 (33), 186 (18), 91 (100).

General procedure for Bu_3SnH-mediated radical cyclisations (method A)

Attempted synthesis of 5*H*-imidazo[2,1-*a*]isoindole (3a)[23b] using method A. Bu_3SnH (0.67 ml, 2.53 mmol) and AIBN (1.04 g, 6.33 mmol) in acetonitrile (50 ml) was added over 8 h *via* syringe pump to **1a** (0.50 g, 2.11 mmol) in acetonitrile (125 ml) at reflux under a nitrogen atmosphere. The solution was stirred at reflux for a further 1 h, cooled to ambient temperature and evaporated to dryness. Hydrochloric acid (4 M, 30 ml) was added, and the acidic solution washed with hexane (20 × 30 ml). The aqueous solution was basified with saturated sodium carbonate solution (40 ml), extracted with dichloromethane (3 × 70 ml) and dried ($MgSO_4$). The organic extracts were evaporated to dryness to yield a brown residue, which was purified by column chromatography using silica gel as absorbent with gradient elution of hexane and ethyl acetate as eluent to yield 1-benzyl-1*H*-imidazole **5a** (0.15 g, 45%) as white needles; mp 70–72 °C (mp[30] 70–72 °C), (found: C, 75.9; H, 6.3; N, 17.5. $C_{10}H_{10}N_2$ requires C, 75.9; H, 6.3; N, 17.7%); spectroscopic data were consistent with the literature.[30]

5,6-Dihydroimidazo[2,1-*a*]isoquinoline (3b)[23c] using method A. Bu_3SnH (0.32 ml, 1.20 mmol), AIBN (0.49 g, 2.99 mmol) in acetonitrile (24 ml) and **1b** (0.25 g, 1.00 mmol) in acetonitrile (60 ml) gave title compound **3b** (0.06 g, 35%) and 1-(2-phenylethyl)-1*H*-imidazole (0.04 g, 26%) in order of elution after column chromatography.

3b, yellow oil; R_f 0.30 (ethyl acetate); ν_{max}/cm^{-1} 1499, 1471, 1452, 1327, 1282, 1099; δ_H ($CDCl_3$) 3.14–3.17 (2 H, t, *J* 6.8, CH_2Ar), 4.15–4.19 (2 H, t, *J* 6.8, NCH_2), 6.94 (1 H, s, 3-H), 7.15 (1 H, s, 2-H), 7.22–7.36 (3 H, m, Ar–H), 8.03 (1 H, d, *J* 7.8, 10-H); NOE irradiation at δ_H 8.03 led to enhancement at δ_H 7.22–7.36; δ_C ($CDCl_3$) 28.5 (CH_2Ar), 43.4 (NCH_2), 119.3 (3-CH), 123.5 (10-CH), 126.6 (6a-C), 127.6 (CH), 127.8 (CH), 128.4 (CH), 128.6 (CH), 132.5 (10a-C), 144.0 (10b-C); *m/z* (EI) 170.0846 (100%, M^+, $C_{11}H_{10}N_2$ requires M^+ 170.0844), 169 (60), 168 (57), 128 (16).

*1-(2-Phenylethyl)-1H-imidazole (**5b**).* yellow oil, R_f 0.50 (1 : 4 methanol–ethyl acetate); spectroscopic data were consistent with the literature.[31]

Attempted synthesis of 6,7-dihydro-5*H*-imidazo[2,1-*a*][2]benzazepine (3c)[23c] using method A. Bu_3SnH (0.54 ml, 2.04 mmol), AIBN (0.84 g, 5.09 mmol) in acetonitrile (40 ml) and **1c** (0.45 g,

1.70 mmol) in acetonitrile (102 ml) gave 1-(3-phenylpropyl)-1*H*-imidazole **5c** (0.19 g, 65%) as a yellow oil; R_f 0.50 (1 : 4 methanol–ethyl acetate); spectroscopic data were consistent with the literature.[31]

9-Fluoro-5,6-dihydroimidazo[2,1-*a*]isoquinoline (3d) using method A. Bu_3SnH (0.77 ml, 2.90 mmol), AIBN (1.20 g, 7.26 mmol) in acetonitrile (57 ml) and **1d** (0.65 g, 2.42 mmol) in acetonitrile (145 ml) gave title compound **3d** (0.15 g, 32%) and 1-[2-(4-fluorophenyl)ethyl]-1*H*-imidazole (0.09 g, 19%) in order of elution after column chromatography.

3d, yellow oil; R_f 0.44 (ethyl acetate); ν_{max}/cm^{-1} 1615, 1504, 1467, 1449, 1282, 1210, 1168, 872; δ_H ($CDCl_3$) 3.10–3.13 (2 H, t, *J* 6.8, CH_2Ar), 4.14–4.18 (2 H, t, *J* 6.8, NCH_2), 6.93–6.97 (2 H, m, Ar–H), 7.15–7.20 (2 H, m, Ar–H), 8.03 (1 H, m, 10-H); δ_C ($CDCl_3$) 27.9 (CH_2Ar), 43.4 (NCH_2), 110.2–110.5 (d, J_{C-F} 25.1, 10-CH), 114.9–115.2 (d, J_{C-F} 22.0, 8-CH), 119.5 (3-CH), 127.9 (6a-C), 128.8–128.9 (d, J_{C-F} 10.0, 10a-C), 129.3 (2-CH), 129.3–129.4 (d, *J* 7.0, 7-CH), 143.4 (10b-C), 161.1–163.5 (d, J_{C-F} 244.8, C–F); *m/z* (EI) 188.0750 (72%, M^+, $C_{11}H_9N_2F$ requires M^+ 188.0750), 187 (100), 146 (2).

*1-[2-(4-Fluorophenyl)ethyl]-1H-imidazole (**5d**).* yellow oil; R_f 0.45 (1 : 4 methanol–ethyl acetate); spectroscopic data were consistent with the literature.[31]

9-Chloro-5,6-dihydroimidazo[2,1-*a*]isoquinoline (3e) using method A. Bu_3SnH (0.53 ml, 2.02 mmol) and AIBN (0.83 g, 5.04 mmol) in acetonitrile (40 ml) and **1e** (0.48 g, 1.68 mmol) in acetonitrile (100 ml) gave the title compound **3e** (0.07 g, 20%) and 1-[2-(4-chlorophenyl)ethyl]-1*H*-imidazole (0.11 g, 31%) in order of elution after column chromatography.

3e, white solid; R_f 0.50 (ethyl acetate), mp 63–66 °C; ν_{max}/cm^{-1} 1601, 1498, 1456 1426, 1281, 1088; δ_H ($CDCl_3$) 3.11–3.14 (2 H, t, *J* 6.8, CH_2Ar), 4.15–4.18 (2 H, t, *J* 6.8, NCH_2), 6.95 (1 H, s, 3-H), 7.05–7.26 (3 H, m, Ar–H), 8.02 (1 H, *J* 1.5 Hz, 10-H); δ_C ($CDCl_3$) 28.1 (CH_2Ar), 43.2 (NCH_2), 119.5 (3-CH), 123.6 (10-CH), 128.2 (CH), 128.7 (C), 129.1 (CH), 129.5 (CH), 130.5 (C), 133.6 (C), 143.1 (10b-C); *m/z* (EI) 206 (9), 205 (3), 204.0449 (100%, M^+, $C_{11}H_9N_2Cl$ requires M^+ 204.0454), 203 (33).

*1-[2-(4-chlorophenyl)ethyl]-1H-imidazole (**5e**).* colourless oil; R_f 0.52 (1 : 4 methanol–ethyl acetate); spectroscopic data were consistent with the literature.[31]

9-(Trifluoromethyl)-5,6-dihydroimidazo[2,1-*a*]isoquinoline (3f) using method A. Bu_3SnH (0.11 ml, 0.42 mmol) and AIBN (0.18 g, 1.06 mmol) in acetonitrile (8 ml) and **1j** (0.13 g, 0.35 mmol) in acetonitrile (21 ml) gave the title compound **3f** (0.02 g, 21%) and 1-{2-[4-(trifluoromethyl)phenyl]ethyl}-1*H*-imidazole (0.04 g, 51%) in order of elution after column chromatography, **3f**, white solid, R_f 0.45 (ethyl acetate); mp 130–132 °C; ν_{max}/cm^{-1} 1630, 1461, 1324, 1264, 1162, 1103, 1067, 902; δ_H ($CDCl_3$) 3.20–3.24 (2 H, t, *J* 6.8, CH_2Ar), 4.19–4.23 (2 H, t, *J* 6.8, NCH_2), 6.98 (1 H, s, 3-H), 7.18 (1 H, s, 2-H), 7.34–7.36 (1 H, d, *J* 7.8, 7-H), 7.50–7.51 (1 H, d, *J* 7.8, 8-H), 8.31 (1 H, s, 10-H); NOE irradiation at δ_H 3.20–3.24 led to enhancement at δ_H 4.19–4.23 and δ_H 7.34–7.36. Irradiation at δ_H 4.19–4.23 led to enhancement at δ_H 3.20–3.24 and δ_H 6.98. Irradiation at δ_H 7.34–7.36 led to an enhancement at δ_H 3.20–3.24 and δ_H 7.50–7.51. Irradiation at δ_H 8.31 gave no observed enhancement; δ_C ($CDCl_3$) 28.5 (CH_2Ar), 43.0 (NCH_2), 119.6 (3-CH), 120.6 (10-CH), 124.8 (8-CH), 127.8 (6a-C), 128.3 (7-CH), 129.7 (2-CH), 135.9 (10a-C) 143.2 (10b-C), 149.7 (9-C); *m/z* (EI) 238.0723 (100%, M^+, $C_{12}H_9N_2F_3$ requires M^+ 238.0718), 203 (32), 168 (12).

*1-{2-[4-(Trifluoromethyl)phenyl]ethyl}-1H-imidazole (**5f**).* colourless oil; R_f 0.50 (1 : 4 methanol–ethyl acetate); ν_{max}/cm^{-1} 1619, 1506, 1300, 1162, 1106, 1065, 1019, 906; δ_H ($CDCl_3$) 3.09–3.13 (2 H, t, *J* 6.8, CH_2Ar), 4.18–4.21 (2 H, t, *J* 6.8, NCH_2), 6.83 (1 H, s, Im-5-H), 7.05 (1 H, s, Im-4-H), 7.14–7.16 (2 H, d, *J* 7.8, Ar-2,6-H), 7.30 (1 H, s, Im-2-H), 7.53–7.55 (2 H, d, *J* 7.8, Ar-3,5-H); δ_C ($CDCl_3$) 37.6 (CH_2Ar), 48.0 (NCH_2), 118.6 (Im-5-CH), 125.6 (Ar-3,5-CH), 128.9 (Ar-2,6-CH), 129.7 (Im-4-CH), 137.0 (Im-2-CH), 141.4 (Ar-1-C); *m/z* (EI) 240.0874 (100%, M^+, $C_{12}H_{11}N_2F_3$ requires M^+ 240.0874), 203 (32), 168 (12).

Information on the photochemical reactor

The photochemical reactions were carried out at 254 and 366 nm using Rayonet photochemical reactors, RPR-100, encompassing sixteen mercury lamps.

General procedure for photochemical radical cyclisations (method B)

5,6-Dihydroimidazo[2,1-*a*]isoquinoline (3b) using photochemical reactor. A solution of **1g** (0.41 g, 1.37 mmol) in acetonitrile (70 ml) was degassed with N_2 for 20 min in a cylindrical quartz tube, and irradiated at 254 nm. The reaction was monitored by TLC, and removed when the starting iodide **1g** appeared to be consumed, in this case after 4 h. The solution was evaporated to dryness, and 30% sodium carbonate solution (30 ml) added, and extracted with dichloromethane (2 × 30 ml). The combined organic extracts dried ($MgSO_4$) and evaporated to dryness to yield a brown residue, which was purified by column chromatography using silica gel as absorbent with gradient elution of hexane and ethyl acetate as eluent to yield the title compound **3b** (0.16 g, 70%), and recovered starting material **1g** (0.03 g, 7%).

Method C. The procedure for method B was repeated using **1g** (0.20 g, 0.67 mmol) in acetonitrile (34 ml) degassed with N_2 for 20 min in a cylindrical Pyrex tube, and irradiated at 366 nm for 15 h giving recovered starting material **1g** (0.20 g, 100%).

Method D. The procedure for method B was repeated using **1g** (0.20 g, 0.67 mmol) in acetonitrile (34 ml) purged with O_2 for 20 min in a cylindrical quartz tube, and irradiated at 254 nm for 4 h giving **3b** (0.07 g, 61%), and recovered starting material **1g** (0.03 g, 14%) after column chromatography.

Method E. The procedure for method B was repeated using **1g** (0.20 g, 0.67 mmol) and benzophenone (0.61 g, 3.56 mmol) in acetonitrile (34 ml) degassed with N_2 for 20 min in a cylindrical quartz tube, and irradiated at 254 nm for 10 h giving recovered starting material **1g** (0.19 g, 97%) after column chromatography.

Attempted synthesis of 5*H*-imidazo[2,1-*a*]isoindole (3a) using method B. A solution of **1f** (0.20 g, 0.70 mmol) in acetonitrile (35 ml) was irradiated at 254 nm for 10 h giving 1-benzyl-1*H*-imidazole **5a** (0.05 g, 45%) and recovered starting material (0.01g, 5%) after column chromatography.

A solution of **1k** (0.20 g, 1.03 mmol) in acetonitrile (50 ml) was irradiated at 254 nm for 10 h, but only unaltered starting material **1k** (0.02 g, 100%) was recovered. The reaction gave identical results when carried out in 2 M hydrochloric acid

solution under analogous conditions. Except to isolate **1k** from the acidic solution, the solution was basified with saturated sodium carbonate solution. Extracted with dichloromethane (3 × 70 ml), dried ($MgSO_4$), and evaporated to dryness.

6,7-Dihydro-5H-imidazo[2,1-a][2]benzazepine (3c) using method B. A solution of **1h** (0.32 g, 1.02 mmol) in acetonitrile (50 ml) was irradiated for 6 h giving the title compound **3c** (0.09 g, 48%) as a yellow oil; R_f 0.41 (ethyl acetate); ν_{max}/cm^{-1} 2937, 1528, 1493, 1467, 1451, 1265, 1107, 1022, 915; δ_H ($CDCl_3$) 2.28–2.31 (2 H, m, 6-CH_2), 2.68–2.71 (2 H, t, *J* 7.1, CH_2Ar), 3.87–3.90 (2 H, t, *J* 6.9, NCH_2), 6.99 (1 H, s, 3-H), 7.11 (1 H, s, 2-H), 7.23–7.31 (3 H, m, Ar–H), 8.31 (1 H, d, *J* 7.3, 11-H); δ_C ($CDCl_3$) 30.9 (6-CH_2), 31.4 (CH_2Ar), 44.6 (NCH_2), 120.8 (3-CH), 127.2 (CH), 128.2 (CH), 128.6 (CH), 129.1 (CH), 129.3 (CH), 131.3 (7a-C), 138.1 (11a-C), 148.3 (11b-C); *m/z* (EI) 184.1000 (100%, M^+, $C_{12}H_{12}N_2$ requires M^+ 184.1000), 183 (82), 169 (16), 156 (8), 128 (4), and recovered starting material **1h** (0.03 g, 10%) after column chromatography.

9-Chloro-5,6-dihydroimidazo[2,1-a]isoquinoline (3e) using method B. A solution of **1i** (0.32 g, 0.96 mmol) in acetonitrile (48 ml) was irradiated at 254 nm for 5 h giving the title compound **3e** (0.13 g, 66%), and recovered starting material **1i** (0.04 g, 13%) after column chromatography.

9-(Trifluoromethyl)-5,6-dihydroimidazo[2,1-a]isoquinoline (3f) using method B. A solution of **1j** (0.27 g, 0.74 mmol) in acetonitrile (35 ml) was irradiated at 254 nm for 5 h giving the title compound **3f** (0.09 g, 53%), and recovered starting material **1j** (0.04 g, 15%) after column chromatography.

9-Nitro-5,6-dihydroimidazo[2,1-a]isoquinoline (3g) using method B. A solution of **1l** (0.40 g, 1.17 mmol) in acetonitrile (55 ml) was irradiated at 254 nm for 5 h giving the title compound **3g** (0.08 g, 32%), as a yellow solid; mp 218–220 °C; R_f 0.32 (ethyl acetate); ν_{max}/cm^{-1} 1590, 1514 (NO_2), 1499, 1337 (NO_2), 1283, 1099, 1050; δ_H ($CDCl_3$) 3.23–3.27 (2 H, t, *J* 6.9, CH_2Ar), 4.21–4.25 (2 H, t, *J* 6.9, NCH_2), 6.99 (1 H, s, 3-H), 7.18 (1 H, s, 2-H), 7.37–7.39 (1 H, d, *J* 8.4, 7-H), 8.06–8.08 (1 H, dd, *J* 8.4, *J* 2.0, 8-H), 8.82–8.83 (1 H, d, *J* 2.0, 10-H); NOE irradiation at δ_H 3.23–3.27 led to enhancement at δ_H 4.21–4.25 and δ_H 7.37–7.39. Irradiation at δ_H 8.06–8.08 led to enhancement at δ_H 7.37–7.39. Irradiation of δ_H 8.83 gave no observed enhancement; δ_C ($CDCl_3$) 28.6 (CH_2Ar), 42.7 (NCH_2), 118.4 (10-CH), 119.9 (Im-3-CH), 122.6 (8-CH), 128.4 (6a-C), 128.8 (7-CH), 130.0 (2-CH), 138.8 (10a-C), 142.3 (10b-C), 147.9 (9-C); *m/z* (CI) 216.0768 (100%, M + H^+, $C_{11}H_{10}N_3O_2$ requires M + H^+ 216.0768), 186 (74), and recovered starting material **1l** (0.14 g, 36%) after column chromatography.

General procedure for nitration

2,8-Dinitro-5,6-dihydroimidazo[2,1-*a*]isoquinoline (4a). Nitric acid (0.15 ml, 65%) was added drop-wise to a stirred solution of **3b** (0.04 g, 0.23 mmol) in concentrated sulfuric acid (0.75 ml) at 0 °C. The mixture was stirred at room temperature for 30 min, poured onto ice-water (2.50 ml) and neutralised with ammonium hydroxide (1.50 ml, 15 M). The title compound **4a** was precipitated (0.03 g, 50%) as a red solid, mp 230–232 °C (from ethanol); ν_{max}/cm^{-1} 3164, 1528 (NO_2), 1336 (NO_2), 1307, 1121, 828, 795; δ_H {$(CD_3)_2SO$} *ca.* 3.31–3.33 (covered by water in DMSO, 2 H, CH_2Ar), 4.34–4.37 (2 H, t, *J* 7.1, NCH_2), 8.06–8.09 (1 H, d, *J* 8.7, 10-H), 8.19–8.22 (1 H, d, *J* 8.7, 9-H), 8.30 (1 H, s, 7-H), 8.57 (1 H, s, 3-H); δ_C {$(CD_3)_2SO$} 29.0 (CH_2Ar), 42.3 (NCH_2), 125.2 (CH), 125.3 (CH), 125.9 (CH), 127.1 (CH), 133.0 (C), 138.4 (C), 143.1 (C), 149.5 (C), 150.1 (C); *m/z* (CI) 261.0618 (31%, M + H^+, $C_{11}H_9N_4O_4$ requires M + H^+ 261.0622), 163 (62), 102 (33), 52 (100).

9-Fluoro-2,8-dinitro-5,6-dihydroimidazo[2,1-*a*]isoquinoline (4b). Nitric acid (0.40 ml, 65%), concentrated sulfuric acid (2.20 ml) and **3d** (0.125 g, 0.67 mmol) gave the title compound **4b** (0.13 g, 70%) as an orange solid, mp 253–256 °C (from ethanol); ν_{max}/cm^{-1} 3121, 1531 (NO_2), 1498, 1471, 1358 (NO_2), 1338, 1330, 912; δ_H {$(CD_3)_2SO$} *ca.* 3.31–3.33 (covered by water in DMSO, 2 H, CH_2Ar), 4.36–4.39 (2 H, t, *J* 6.8, NCH_2), 7.93–7.95 (1 H, d, *J* 11.7, 10-H), 8.27–8.29 (1 H, d, *J* 7.8, 7-H), 8.62 (1 H, s, 3-H); NOE irradiation at δ_H 4.36–4.39 led to enhancement at δ_H 8.62. Irradiation at δ_H 8.62 led to enhancement at δ_H 4.36–4.39; δ_C {$(CD_3)_2SO$} 25.9 (CH_2Ar), 43.2 (NCH_2), 112.7–112.9 (d, J_{C-F} 23.1 10-CH), 123.2 (3-CH), 126.4 (7-CH), 131.2 (C), 131.6 (C), 136.8 (C), 139.8 (C), 147.1 (10b-C), 152.7–155-3 (d, J_{C-F} 261.0, C–F); *m/z* (CI) 296.0791 (100%, M + NH_4^+, $C_{11}H_{11}N_5O_4$ requires M + NH_4^+ 296.0790), *m/z* (EI) 278 (M^+, 65%), 248 (23), 193 (50), 158 (65), 147 (75), 132 (72), 120 (52).

9-Chloro-2,8-dinitro-5,6-dihydroimidazo[2,1-*a*]isoquinoline (4c). Nitric acid (0.1 ml, 65%), concentrated sulfuric acid (0.6 ml) and **3e** (0.04 g, 0.19 mmol) gave the title compound **4c** (0.04 g, 70%) as a orange solid, mp 245–247 °C (from ethanol); ν_{max}/cm^{-1} 3125, 1531 (NO_2), 1351 (NO_2), 1121, 1335, 1315, 943, 913; δ_H {$(CD_3)_2SO$} *ca.* 3.31–3.33 (covered by water in DMSO, 2 H, CH_2Ar), 4.34–4.37 (2 H, t, *J* 6.8, NCH_2), 8.09 (1 H, s, 10-H), 8.21 (1 H, s, 7-H), 8.61 (1 H, s, 3-H); δ_C {$(CD_3)_2SO$} 26.2 (CH_2Ar), 43.1 (NCH_2), 123.7 (3-CH), 124.8 (C), 126.2 (10-CH), 126.5 (7-CH), 130.3 (C), 135.5 (C), 140.2 (10b-C), 147.6 (C), 147.8 (C); *m/z* (CI) 295.0230 (100%, M + H^+, $C_{11}H_8N_4O_4Cl$ requires M + H^+ 295.0229), *m/z* (EI): 296 (9), 294 (M^+, 3), 264 (5), 209 (6), 140 (11), 128 (10), 46 (100).

2-Nitro-9-(trifluoromethyl)-5,6-dihydroimidazo[2,1-*a*]isoquinoline (4d). Nitric acid (0.25 ml, 65%), concentrated sulfuric acid (1.2 ml) and **3f** (90 mg, 0.37 mmol) gave the title compound **4d** (0.07 g, 68%) as a orange solid, mp 186–188 °C (from ethanol); ν_{max}/cm^{-1} 3141, 1530 (NO_2), 1326 (NO_2), 1301, 1165, 1113, 1067, 819, 737; δ_H {$(CD_3)_2SO$} *ca.* 3.31–3.33 (covered by water in DMSO, 2 H, CH_2Ar), 4.31–4.35 (2 H, t, *J* 6.8, NCH_2), 7.62–7.64 (1 H, d, *J* 8.7, 7-H), 7.76–7.78 (1 H, d, *J* 8.7, 8-H), 8.05 (1 H, s, 10-H), 8.53 (1 H, s, 3-H); δ_C {$(CD_3)_2SO$} 27.4 (CH_2Ar), 43.2 (NCH_2), 120.2 (10-CH), 123.1 (3-CH), 126.3 (C), 126.9 (8-CH), 128.8 (C), 129.1 (C), 130.4 (7-CH), 139.5 (C), 141.7 (C), 147.4 (C); *m/z* (CI) 301 (22%, M + NH_4^+), 284.0642 (67%, M + H^+, $C_{12}H_9N_3O_2F_3$ requires M + H^+ 284.0641), 254 (100), 239 (25), 233 (36).

2,9-Dinitro-5,6-dihydroimidazo[2,1-*a*]isoquinoline (4e). Nitric acid (0.1 ml, 65%), concentrated sulfuric acid (0.6 ml) and **3g** (0.04 g, 0.19 mmol) gave the title compound **4e** (0.03 g, 50%) as a red solid, mp 204–206 °C. ν_{max}/cm^{-1} 1517 (NO_2), 1342 (NO_2), 1299, 1055, 1051; δ_H {$(CD_3)_2SO$} *ca.* 3.31–3.33 (covered by water in DMSO, 2 H, CH_2Ar), 4.34–4.37 (2 H, t, *J* 6.5, NCH_2), 7.67–7.69 (1 H, d, *J* 8.2, 7-H), 8.22–8.24 (1 H, d, *J* 8.2, 8-H), 8.50 (1 H, s, 3(10)-H), 8.54 (1 H, s, 3(10)-H); δ_C {$(CD_3)_2SO$} 27.6 (CH_2Ar),

43.2 (NCH_2), 118.4 (10-CH), 123.1 (8-CH), 124.9 (3-CH), 126.5 (C), 128.3 (C), 130.8 (7-CH), 141.1 (C), 142.3 (C), 147.5 (C).

Acknowledgements

The authors would like to thank Dr Niall W. A. Geraghty (National University of Ireland, Galway) for use of the Rayonet photochemical reactors. Mr Ger Fahy (National University of Ireland, Galway), and EPSRC National Mass Spectrometry Service, University of Wales, Swansea for mass spectra of compounds. This work was funded by Enterprise Ireland Basic Research Grant.

References

1 (*a*) D. L. Comins, H. Hong and G. Jianhua, *Tetrahedron Lett.*, 1994, **35**, 5331; (*b*) Y. Antonio, E. De la Cruz, E. Galeazzi, A. Guzman, B. L. Bray, R. Greenhouse, L. J. Kurz, D. A. Lustig, M. L. Maddox and J. M. Muchowski, *Can. J. Chem.*, 1994, **72**, 15; (*c*) J. C. Estévez, M. C. Villaverde, R. J. Estévez and L. Castedo, *Tetrahedron*, 1995, **51**, 4075; (*d*) A. M. Rosa, A. M. Lobo, P. S. Branco, S. Prabhakar and A. M. D. L. Pereira, *Tetrahedron*, 1997, **53**, 269; (*e*) A. M. Rosa, A. M. Lobo, P. S. Branco and S. Prabhakar, *Tetrahedron*, 1997, **53**, 285; (*f*) L. Giraud, E. Lacôte and P. Renaud, *Helv. Chim. Acta*, 1997, **80**, 2148; (*g*) O. Tsuge, T. Hatta and H. Tsuchiyama, *Chem. Lett.*, 1998, 155; (*h*) B. Alcaide and A. Rodríguez-Vicente, *Tetrahedron Lett.*, 1998, **39**, 6589; (*i*) A. Nadin and T. Harrison, *Tetrahedron Lett.*, 1999, **40**, 4073; (*j*) K. Orito, Y. Satoh, H. Nishizawa, R. Harada and M. Tokuda, *Org. Lett.*, 2000, **2**, 2535; (*k*) W. R. Bowman, E. Mann and J. Parr, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2991; (*l*) A. K. Ganguly, C. H. Wang, M. David, P. Bartner and T. M. Chan, *Tetrahedron Lett.*, 2002, **43**, 6865.

2 (*a*) M. L. E. N. da Mata, W. B. Motherwell and F. Ujjainwalla, *Tetrahedron Lett.*, 1997, **38**, 137; (*b*) M. L. E. N. da Mata, W. B. Motherwell and F. Ujjainwalla, *Tetrahedron Lett.*, 1997, **38**, 141.

3 (*a*) A. P. Dobbs, K. Jones and K. T. Veal, *Tetrahedron Lett.*, 1997, **38**, 5379; (*b*) A. P. Dobbs, K. Jones and K. T. Veal, *Tetrahedron Lett.*, 1997, **38**, 5383; (*c*) T. C. T. Ho and K. Jones, *Tetrahedron*, 1997, **53**, 8287; (*d*) A. Fiumana and K. Jones, *Tetrahedron Lett.*, 2000, **41**, 4209; (*e*) C. Escolano and K. Jones, *Tetrahedron Lett.*, 2000, **41**, 8951.

4 (*a*) D. C. Harrowven, M. I. T. Nunn, N. A. Newman and D. R. Fenwick, *Tetrahedron Lett.*, 2001, **42**, 961; (*b*) D. C. Harrowven, B. J. Sutton and S. Coulton, *Tetrahedron Lett.*, 2001, **42**, 9061; (*c*) D. C. Harrowven, B. J. Sutton and S. Coulton, *Tetrahedron*, 2002, **58**, 3387.

5 D. C. Harrowven, M. I. T. Nunn, N. J. Blumire and D. R. Fenwick, *Tetrahedron Lett.*, 2000, **41**, 6681.

6 S. Donnelly, J. Grimshaw and J. Trocha-Grimshaw, *Acta Chem. Scand.*, 1999, **53**, 913.

7 D. C. Harrowven, B. J. Sutton and S. Coulton, *Org. Biomol. Chem.*, 2003, **1**, 4047.

8 S. M. Allin, W. R. Bowman, M. R. J. Elsegood, V. McKee, R. Karim and S. S. Rahman, *Tetrahedron*, 2005, **61**, 2689.

9 A. Ryokawa and H. Togo, *Tetrahedron*, 2001, **57**, 5915.

10 (*a*) A. Nunez, A. García de Viedma, V. Martínez-Barrasa, C. Burgos and J. Alvarez-Builla, *Synlett*, 2002, 1093; (*b*) W. Zhang and G. Pugh, *Tetrahedron*, 2003, **59**, 3009.

11 P. T. F. McLoughlin, M. A. Clyne and F. Aldabbagh, *Tetrahedron*, 2004, **60**, 8065.

12 A. L. J. Beckwith, V. W. Bowry, W. R. Bowman, E. Mann, J. Parr and J. M. D. Storey, *Angew. Chem., Int. Ed.*, 2004, **43**, 95.

13 D. C. Harrowven and I. L. Guy, *Chem. Commun.*, 2004, 1968.

14 H. Ohno, H. Iwasaki, T. Eguchi and T. Tanaka, *Chem. Commun.*, 2004, 2228.

15 (*a*) A. Fozard and C. K. Bradsher, *J. Org. Chem.*, 1967, **32**, 2966; (*b*) M. P. Cava, M. J. Mitchell, S. C. Havlicek, A. Lindert and R. J. Spangler, *J. Org. Chem.*, 1970, **35**, 175.

16 (*a*) D. E. Portlock, M. J. Kane, J. A. Bristol and R. E. Lyle, *J. Org. Chem.*, 1973, **38**, 2351; (*b*) P. W. Jeffs, J. F. Hansen and G. A. Brine, *J. Org. Chem.*, 1975, **40**, 2883.

17 (*a*) J. Grimshaw and A. P. De Silva, *Can J. Chem.*, 1980, **58**, 1880; (*b*) J. Grimshaw and A. P. de Silva, *J. Chem. Soc. Perkin Trans. 2*, 1982, 857.

18 Y.-S. Byun, C.-H. Jung and Y. –T Park, *J. Heterocycl. Chem.*, 1995, **32**, 1835.

19 (*a*) Y.-T. Park, N. W. Song, C.-G. Hwang, K.-W. Kim and D. Kim, *J. Am. Chem. Soc.*, 1997, **119**, 10677; (*b*) Y.-T. Park, C.-H. Jung, M.-S. Kim, K.-W. Kim, N. W. Song and D. Kim, *J. Org. Chem.*, 2001, **66**, 2197 and references therein.

20 (*a*) J. O'Shaughnessy, D. Cunningham, P. Kavanagh, D. Leech, P. McArdle and F. Aldabbagh, *Synlett*, 2004, 2382; (*b*) J. O'Shaughnessy and F. Aldabbagh, *Synthesis*, 2005, 1069.

21 M. D'Auria, E. De Luca, G. Mauriello and R. Racioppi, *J. Chem. Soc., Perkin Trans. 1*, 1998, 271.

22 (*a*) R. J. Hodgkiss, *Anti-Cancer Drug Des.*, 1998, **13**, 687; (*b*) M. Vidakovic, C. R. Crossnoe, C. Neidre, K. Kim, K. L. Krause and J. P. Germanas, *Antimicrob. Agents Chemother.*, 2003, **47**, 302.

23 (*a*) L. Sarett, D. R. Hoff and D. W. Henry, *US Pat.* 1964, 19640310; CAN 63:98375; AN 1965:498375; (*b*) V. A. Kovtunenko, A. M. Demchenko, A. K. Tyltin and F. S. Babichev, *U.S.S.R. Pat.*, 1985, SU 1150250 A1 19850415 CAN 104:129902 AN 1986:129902; (*c*) M. W. Gittos, J. W. James and J. P. Verge, *Ger. Offen.*, 1969, DE 1911519 19691009 CAN 72:12601 AN 1970:12601.

24 A. Studer and M. Bossart, *Tetrahedron*, 2001, **57**, 9649.

25 A. R. Katritzky, E. F. V. Scriven, S. Majumder, R. G. Akhmedova, N. G. Akhmedov and A. V. Vakulenko, *Arkivoc*, 2005, 179.

26 A. McKillop, D. E. Wright, M. L. Podmore and R. K. Chambers, *Tetrahedron*, 1983, **39**, 3797.

27 K. L. Kirk, *J. Org. Chem.*, 1978, **43**, 4381.

28 P. B. W. McCallum, R. T. Weavers, M. R. Grimmett and A. G. Blackman, *Aust. J. Chem.*, 1999, **52**, 159.

29 M. Moreno-Manas, J. Bassa, N. Lladó and R. Pleixats, *J. Heterocycl. Chem.*, 1990, **27**, 673.

30 E. Díez-Barra, A. de la Hoz, A. Sánchez-Migallón and J. Tejeda, *Synth. Commun.*, 1993, **23**, 1783.

31 S. Ahmed, J. H. Smith, P. J. Nicholls, R. Whomsley and P. Cariuk, *Drug Des. Discovery*, 1995, **13**, 27.