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Aromatic homolytic substitution using solid phase synthesis

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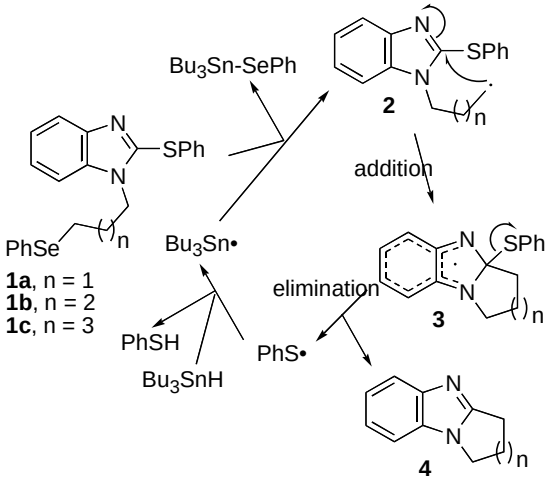
Abstract—Solid phase synthesis has been used to carry out intramolecular aromatic homolytic substitution with benzoimidazole precursors. The protocol attaches the radical precursors to the resins via the radical leaving groups (in the aromatic homolytic substitution). When the radical reactions are complete, the leaving group, unaltered starting material and reduced uncylised products remain attached to the resin, which facilitates easy separation of the cyclised products. Novel use of focussed microwave irradiation in solid phase radical reactions drastically shortens the reactions times. Tributylgermanium hydride has been used to replace the toxic and troublesome tributyltin hydride in the radical reactions.

1. Introduction

Solid phase synthesis has become a central tool in organic synthesis. However, there have been surprisingly few applications to radical chemistry. The small amount of literature has been recently reviewed[1] and more recent references continue to show the untapped potential.[2] Solid phase radical reagents have also been developed and show promise. For example, we have recently demonstrated that solid phase triorganogermanium hydride gives good results for a wide range of radical reactions and compares very well with the corresponding solution-phase use of tributyltin or tributylgermanium hydride.[3] Other references to solid phase radical reagents are included in our recent publications.[3,4] We sought to further investigate the potential of radical reactions on solid phase with a view to applications in combinatorial chemistry.

Solid phase synthesis and combinatorial chemistry have centred on the synthesis of heterocycles because of the importance of these compounds to the pharmaceutical industry as likely lead compounds.[5] The use of radical cyclisation for the synthesis of prospective biologically active heterocyclic compounds has also continued to grow in interest.[6] Therefore, in this study we chose radical cyclisation onto benzoimidazoles as a suitable methodology for investigation. We have previously shown that alkyl radical substitution of phenylthiyl radicals at 2-C gave good results and used this in our initial study (Scheme 1).[7]



Scheme 1. Homolytic aromatic substitution.

This procedure of intramolecular aromatic homolytic substitution was first developed by Caddick et al. as a novel regioselective methodology for the synthesis of [1,2-*a*]indoles in which SPh, SOPh or SO_2Ar groups on the indole-2-position act as radical leaving groups.[8] Whereas bimolecular homolytic aromatic substitution is relatively unselective and therefore of limited synthetic application, these substitutions are regioselective, controlled by stereo-electronic effects and the good radical leaving groups. Homolytic aromatic substitution has been recently reviewed.[9]

Keywords: Aryl radicals; Radical cyclisation; Solid phase synthesis; Microwave; Benzoimidazoles.
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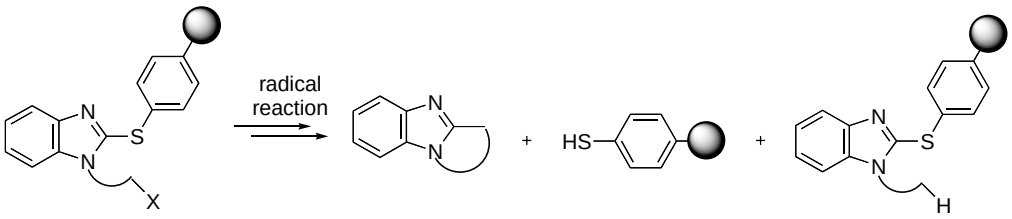


Scheme 2. Solid phase radical cyclisation protocol.

In our earlier synthetic studies, [1,2-*a*]fused-benzoimidazoles and -imidazoles were synthesised using new methodology.[7] In this procedure, ω-phenylselanyl-alkyl side chains were used in place of ω-bromoalkyl side chains to avoid reaction between the basic benzoimidazole nitrogen atom reacting with alkyl halides. The aromatic homolytic substitution mechanism is shown in Scheme 1. The tributyltin radical ($Bu_3Sn^{\bullet}$) abstracts the phenylselanyl group from the precursor **1** to yield an intermediate radical **2** by an S_H2 mechanism. Cyclisation gives a stabilised σ-complex **3** with the unpaired electron delocalised over the aromatic system. The eliminated phenylsulfanyl radical ($PhS^{\bullet}$) is electrophilic and reacts extremely rapidly with the nucleophilic tributyltin hydride (Bu_3SnH) to complete the chain cycle. This latter process has been termed polarity reversal catalysis (PRC).[10,11]

We sought to use 'building blocks', which could be adapted to combinatorial chemistry. The use of N-alkylation of NH-heteroarenes provides a route for the addition of 'radical' building blocks. The application of *N*-(ω-phenylselanyl)-alkyl 'building blocks' is illustrated in Scheme 1. *N*-(ω-Phenylselanyl)alkyl and *N*-(ω-bromo)alkyl 'building blocks' have also been applied to cyclisation of *N*-(ω-alkyl)-radicals onto pyrroles,[12] imidazoles[12] and pyrazoles[13] with electron withdrawing groups or radical stabilising groups. We have recently shown that 2-(2-bromophenyl)ethyl and 2-(2-bromophenyl)methyl 'building blocks' can be used via aryl radical cyclisation.[11] We sought in the study to use these two groups of building blocks, *N*-(ω-phenylselanyl)alkyl and 2-(2-bromophenyl)alkyl, to explore the use of radicals on solid phase.

The radical reactions were first carried out in solution-phase to determine the best conditions and also to provide an accurate comparison with the equivalent solid phase reactions. The use of the three possible triorgano-metal hydrides, Bu_3SnH, tris-(trimethylsilyl)silane (TTMSS) and tributylgermanium hydride (Bu_3GeH) were investigated. The latter two reagents have the advantage of low toxicity as compared to Bu_3SnH.

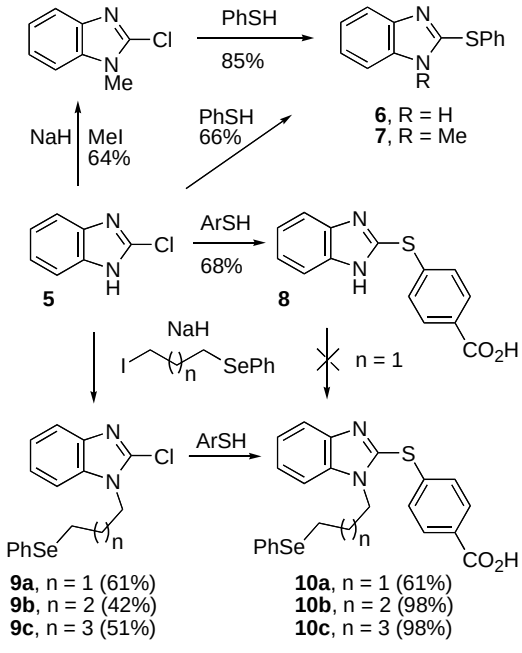
Our studies used the protocol shown in Scheme 2, that is, the radical precursors are attached to the solid phase resin via the arylsulfanyl radical leaving group. The advantage of this protocol is that after the radical reaction, only the cyclised product is released from the resin. Reduced uncyclised products and unaltered starting materials remain attached to the resin and hence do not need to be separated from the desired product. The cyclised benzoimidazoles were separated from the radical reagents by extraction into dilute hydrochloric acid, thereby facilitating a very clean separation.

2. Discussion

2.1. Solution-phase studies with alkyl radicals

Initially, we repeated earlier studies[7] on the cyclisation of the selanides **1a** and **1b** (see Scheme 1) in order to test the conditions for solution-phase homolytic aromatic substitution for comparison with solid phase studies. The five-membered ring cyclisation of **1a** gave low yields (**4a**, 25% as opposed to 49% in earlier studies[7]). Use of hexamethyldiditin did not improve yields of **4a** (26%). The six-membered ring cyclisation of **1b** to **4b** gave much better yields. The best yield (61%) was obtained using acetonitrile as solvent (54% in the earlier study[7]) whereas toluene (**4b**, 25%) and cyclohexane (**4b**, 23%) gave lower yields. Six-membered ring cyclisations onto heteroarene rings are less strained than the five-membered ring cyclisations and hence give higher yields.[7,11–13]

Initially, we synthesised the 2-(phenylsulfanyl)benzoimidazole by lithiation of the 1-trityl protected bezimidazole followed by reaction with diphenyl disulfide. The yields were variable and not suited for the preparation of precursors for solid phase studies. We therefore investigated S_NAr substitution by thiolate of chloride at the 2-C position. 2-Chlorobenzoimidazole **5** is commercially available and cheap. Test reactions showed that chloride was easily replaced from 2-chlorobenzoimidazole or 1-methyl-2-chlorobenzoimidazole (Scheme 3). Potassium hydroxide

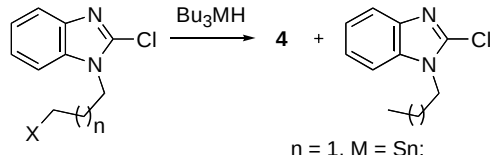


Scheme 3. Synthesis of precursors, ArSH=4-(SH)-$C_6H_4CO_2H$.

(KOH) in ethanol proved best whereas potassium carbonate/acetone, triethylamine/DCM and NaH/DMF gave poor yields. Attempted S_NAr substitution of 1-trityl-2-chlorobenzoimidazole failed, probably due to steric hindrance.

Our original aim was to prepare the benzoimidazole with the linker attached thereby allowing the possibility of alkylation and radical cyclisation on the solid phase resin. S_NAr substitution with the unprotected 2-chlorobenzoimidazole 5 using the solid phase linker, 4-mercaptobenzoic acid, proceeded in a good unoptimised yield (68%) but subsequent alkylations failed (Scheme 3). Alkylation may have been more favourable with the resin acting as protection for the carboxyl group but difficulties were encountered with selectively attaching the 4-mercaptobenzoic acid via the carboxylate to Wang resin. Selective thiol protection followed by attachment also encountered problems. Selective *S*-trityl and *S*-acyl protection of 4-mercaptobenzoic acid gave ca. quantitative yields but trityl removal failed and acyl migration problems were encountered. At this point, we successfully alkylated 2-chlorobenimidazole **5** to afford **9a–c** and carried out the S_NAr substitutions to give **10a–c** in good yields, that is, alkylations were carried out prior to loading on the resins (Scheme 3).

We have also shown that chlorine is a good leaving group and can replace phenylthiyl and phenylsulfonyl groups in intramolecular aromatic homolytic substitutions (Scheme 4). We tested two 2-chlorobenzoimidazoles **9a** and **12** under standard radical cyclisation conditions. The five-membered ring cyclisation again gave a poor yield of cyclisation (10%) with a large amount of uncyclised reduced material **13a** (51%) whereas the six-membered ring cyclisation gave a reasonable yield (54%) with no uncyclised reduced material **13b**. The use of Bu_3GeH allows more time for intermediate radicals to cyclise and syringe pump addition is not required.[3] We suggest that the mechanism is as shown in Scheme 1 (with SPh = Cl).

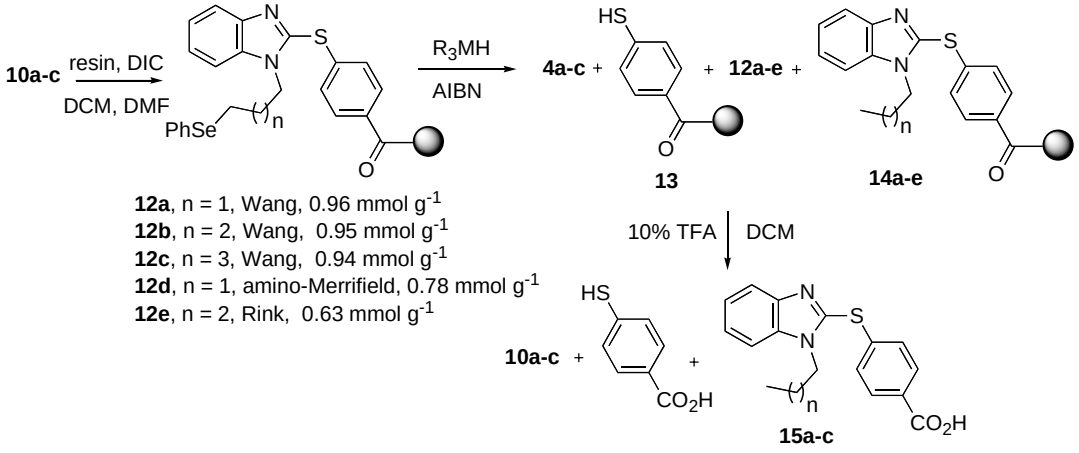


Scheme 4.

2.2. Solid phase studies with alkyl radicals

The alkyl radical precursors (with linker attached) **10a–c** were successfully attached to three resins, Wang, amino-Merrifield and Rink, by standard procedures (Scheme 5). Each loading was assessed by FTIR and MAS (magic angle) ^1H NMR spectroscopy. The FTIR showed formation of an ester linkage for Wang resin attachments. The level of loading was determined by cleavage of the loaded precursor from a portion of each resin. The radical reactions were carried out using a variety of conditions and the results are shown in Table 1. The cyclised products **4a–c** were isolated by filtration of the resin whereas reduced uncyclised products **15a–c** (if formed) and unaltered precursors were cleaved from the resin by TFA hydrolysis and analysed by LCMS and/or isolation. The five-membered ring cyclisation on Wang resin **12a** gave poor yields (maximum 11% yield) as observed for the solution-phase reactions. Slow addition of Bu_3SnH by syringe pump and repeat addition appeared to give better yields. One attempt with the amino-Merrifield precursor **12d** gave very poor yields and was not further investigated.

The six-membered ring cyclisations, as for solution-phase reactions, gave much better yields with the optimised maximum yield of 60%, that is, very similar yields to solution-phase reactions. A more useful comparison would be the solution-phase cyclisation of the carboxylic acids **10a–c** or their respective esters. However, these comparisons were not carried out. Extended addition and reflux times gave much lower yields. The use of TTMSS and Bu_3GeH gave lower yields than Bu_3SnH but further optimisation is needed to determine the relative utility of the three reagents in these reactions. The use of Rink resin in place of Wang resin gave a similar yield of cyclised product **4b** (44%). As for the solution-phase reactions, the seven-membered ring cyclisation also gave very low yields (**4c**, 4%) with largely the reduced uncyclised product (**14c** to **15c**, 72%) being formed.



Scheme 5. Radical reactions on solid phase ($R_3MH = Bu_3SnH$, Bu_3GeH, TTMSS).

Table 1. Radical cyclisation of resin-bound 1-[ω-(phenylselanyl)alkyl]benzoimidazoles **12a–e**

Precursor	Reaction conditions	Yields
12a	Bu_3SnH, syringe pump addition over 26 min, repeat addition after 3 h, AIBN, toluene, reflux, 5 h	**4a** (11%), **10a** and **15a**[a]
12a	Bu_3SnH, syringe pump addition over 2 h, AIBN, benzene, reflux, 5 h	**4a** (5%), **15a**[a]
12a	Bu_3SnH, syringe pump addition over 5 h, repeat addition over 5 h, AIBN, benzene, reflux, 10 h	**4a** (5%), **15a**[a]
12a	Bu_3SnH, syringe pump addition over 7 h, AIBN, benzene, reflux, 10 h	**4a** (3%), **10a** (41%), **15a** (10%)
12a	Bu_3SnH, AIBN, benzene, reflux, 24 or 48 h	**4a** (trace), **15a**[a]
12d	Bu_3SnH, AIBN, benzene, reflux, 18 h	**4a** (trace)
12b	Bu_3SnH, syringe pump addition over 7 h, AIBN, benzene, reflux, 7 h	**4b** (60%), **15b**[a]
12b	Bu_3SnH, syringe pump addition over 2 h, repeat addition after 3 h, AIBN, benzene, reflux, 6.5 h	**4b** (58%, 49%), **15b**[a]
12b	Bu_3SnH, syringe pump addition over 7 h, AIBN, benzene, reflux, 8 h	**4b** (57%), **15b**[a]
12b	Bu_3SnH, syringe pump addition over 7 h, AIBN, benzene, reflux, 7 h	**4b** (49%)
12b	Bu_3SnH, syringe pump addition over 12 h, AIBN, benzene, reflux, 12 h	**4b** (14%), **10b** and**15b**[a]
12b	Bu_3SnH, syringe pump addition over 12 h, AIBN, benzene, reflux, 24 h	**4b** (trace), **10b** and**15b**[a]
12b	Bu_3SnH, AIBN, benzene, reflux, 48 h	**4b** (3%), **10b** and**15b**[a]
12b	Bu_3GeH, AIBN, toluene, reflux, 8 h	**4b** (22%), **10b**[a]
12b	TTMSS, AIBN, benzene, reflux, 10 h	**4b** (20%), **15b**[a]
12b	TTMSS, syringe pump addition over 5 h, AIBN, benzene, reflux, 8 h	**4b** (16%), **15b**[a]
12e	Bu_3SnH, syringe pump addition over 6 h, AIBN, benzene, reflux, 7 h	**4b** (44%), **10b** and **15b**[a]
12c	Bu_3SnH, syringe pump addition over 2.5 h, AIBN, *tert*-butylbenzene, heating at 130 °C, 9 h	**4c** (4%), **15c** (72%)
12c	Bu_3SnH, syringe pump addition over 5 h, AIBN, *tert*-butylbenzene, heating at 130 °C, 10 h	**4c** (2%), **15c**[a]

[a] Qualitative analysis by HPLC.

2.3. Solid phase radical cyclisation using microwave irradiation

We used focussed microwave irradiation to cut down the reactions times of the reactions from hours to minutes (Table 2). Typically, non-radical solid phase reactions using this technique take place in 1–5 min. Although the radical reactions required the longer time of 10–20 min the time is still considerably shorter than the non-irradiated reactions (see Table 1). The technique gave comparable results to the non-irradiated reactions with the highest yield (52%) achieved using a mixture of propan-1-ol and benzene. Propan-1-ol was found to be the most favourable solvent. Polar solvents tend to give the best results with this technique. Propan-1-ol is a reasonably good H-donor, which may account for the formation of the reduced uncyclised (**14b**, and **15b** after cleavage from the resin). However, use of *tert*-butanol, which is not a good H-donor did not improve the yields.

Table 2. Radical cyclisation with Wang resin-bound precursor **12b** using focussed microwave irradiation

Reaction conditions[a]	Yield[b]
10 min, 10 min,[c] 100 °C, PrOH/PhH (1 cm^3 each)	**4b** (52%)[d]
10 min, 10 min,[c] 135 °C, PrOH/PhH (1.25 cm^3 each)	**4b** (44%)[d]
10 min, 135 °C, PrOH/PhH (1.25 cm^3 each)	**4b** (44%)[d]
20 min, 135 °C, PrOH/PhH (1.25 cm^3 each)	**4b** (38%)[d]
10 min, 10 min,[c] 100 °C, *tert*-BuOH/PhH (1.25 cm^3 each)	**4b** (44%)[d]
10 min, 130 °C, PrOH (2.5 cm^3)	**4b** (20%)[d]
10 min, 10 min,[c] 100 °C, MeCN/PhH (1.25 cm^3 each)	**4b** (17%)[d]
10 min, 10 min,[c] 100 °C, DMF/PhH (1.25 cm^3 each)	**4b** (14%)[d]

[a] Bu_3SnH, AMBN [azobismethylisobutyronitrile or by IUPAC nomenclature, 2-(1-cyano-1-methyl-propylazo)-2-methyl-butyronitrile], focussed microwave irradiation.
[b] The % yield of **4b** was measured using ^1H NMR spectroscopy with an internal standard.
[c] Second addition of reagents and further irradiation.
[d] Reduced uncyclised **15b** was observed by LCMS analysis of products cleaved from the resin.

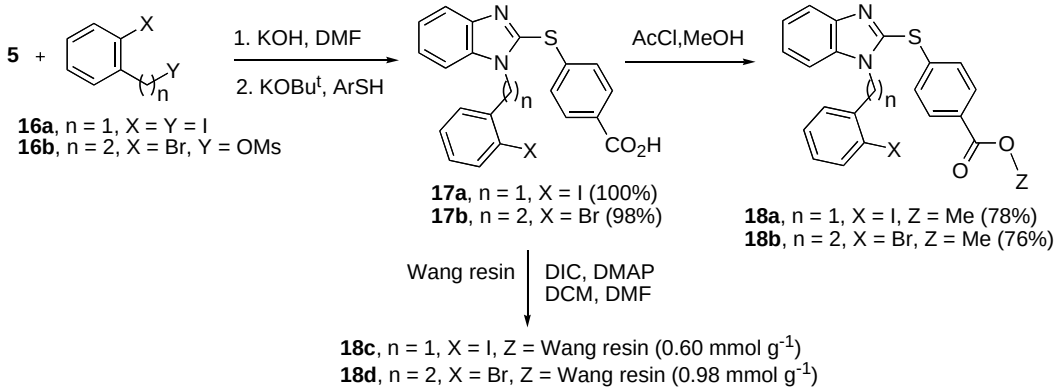
At the time of our study focussed microwave irradiation had not been used for radical reactions on solid phase, but recently an example has been published for the synthesis of oxindoles by 5-*exo* cyclisation of aryl radicals onto α,β-unsaturated amides.[14] We believe that our studies indicate potential for the use of microwave irradiation to shorten reaction times of solid phase radical reactions. Further study should improve yields and determine the most suitable reaction conditions.

The technique was also applied to the five-membered ring cyclisation of the amino-Merrifield bound **12d**. Again, poor results were obtained [**4a** (3%), 20 min, propan-1-ol/benzene, 135 °C] showing no real improvement over the non-irradiated reaction. The cyclisation of the equivalent non-solid phase precursor **10b** under similar condition using microwave irradiation gave inferior yields suggesting that the solid phase reaction may be more efficient [10 min, PrOH/PhH, 1.25 cm^3, Bu_3SnH: (a) AIBN, 135 °C, **4b** (11%), (b) AMBN, 100 °C, **4b** (14%)].

2.4. Solution- and solid phase studies with aryl radicals

With the success of the alkyl radical cyclisation we sought to show that aryl radicals could also be used in solid phase synthesis. 2-(2-Bromophenyl)ethyl and 2-(2-bromophenyl)methyl 'building blocks' have been suceessfully used to generate aryl radicals for cyclisation onto heteroarenes.[11] The same methodology was applied as for the alkyl radicals. The synthesis of aryl radical precursors and attachement to the solid phase is shown in Scheme 6. The methyl esters were prepared for prior testing of the reactions in solution-phase in order to determine the best conditions and to provide an accurate comparison with the equivalent solid phase reactions.

2-Chloro-1*H*-benzoimidazole **5** was alkylated with suitable aryl radical building blocks (**16a** and **16b**) followed by the



Scheme 6. Synthesis of aryl precursors, ArSH=4-(SH)-$C_6H_4CO_2H$.

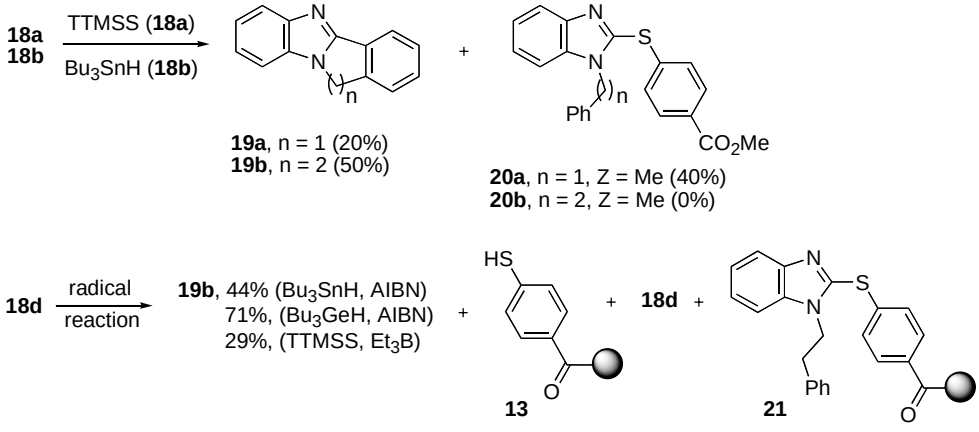
S_NAr protocol using 4-mercaptobenzoic acid to yield **17a** and **17b** in near quantitative yield (Scheme 6). The benzoimidazoles **17a** and **17b** were methylated to provide precursors for the solution studies and attached to Wang resin using carbodiimide-mediated coupling. Good loadings were easily achieved and quantified by cleavage from the resin (TFA/DCM, 9:1) and measurement of the radical precursors. The IR spectrum of the solid supported precursors showed the formation of the ester linkages at 1713 cm^{-1} and MAS ^1H NMR spectra showed complete immobilisation (Scheme 7).

The solution-phase studies were similar to those observed for alkyl radicals. Attempted five-membered cyclisation with the radical precursor **18a** using Bu_3SnH gave only reduced uncyclised material **20a** (60%), even with the use of a syringe pump. However, use of TTMSS, which is a poorer H-donor than Bu_3SnH gave a low yield of the cyclised product **19a** (20%) with **20a** (40%) as the major product. As expected the six-membered cyclisation gave a good yield of cyclised material **19b** (50%) with no traces of the reduced uncyclised product **20b**. The results show that homolytic aromatic substitution by aryl radicals at 2-C of benzoimidazoles is a useful synthetic protocol.

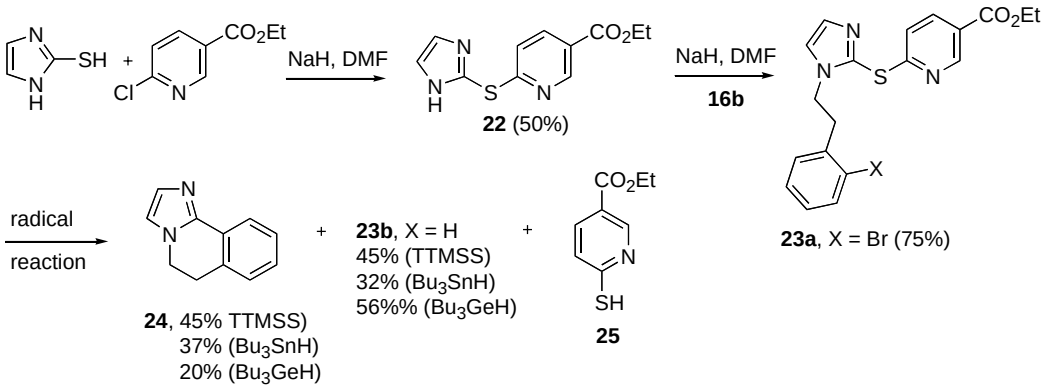
The better yielding six-membered ring cyclisation was chosen for study on solid phase using Wang resin. Syringe pump addition of Bu_3SnH gave the tetracycle **19b** in a reasonable yield (44%). The use of Bu_3GeH proved much more satisafactory with a high yield of **19b** (71%) but TTMSS with Et_3B as initiator at room temperature gave a lower yield (29%). Further optimisation would be likely to give improved yields. The result again illustrates the potential of the non-toxic Bu_3GeH to replace the toxic Bu_3SnH. The by-products were cleaved from the resin and analysed by GC–MS, which showed small amounts of the reduced uncyclised product resulting from **21** and **17b** resulting from unreacted starting material **18d**.

2.5. Homolytic aromatic substitution on imidazole

We had earlier shown that cyclisation via homolytic aromatic substitution onto 2-(phenylsulfanyl)imidazoles gave good yields.[7] We sought to extend the use of the solid phase protocol for the synthesis of bi-and tri-cyclic imidazoles. 2-Chloroimidazole is not readily available so we developed an alternative procedure to widen the scope of our protocol using the cheap and available 2-mercaptoimidazole as shown in Scheme 8. The S_NAr substitution, which is reversed from the previous protocol gave a reasonable yield of **22** (50%), which can be used for a variety of alkylations on the imidazole-NH. The pyridine moiety has a suitable ester handle for attaching to a solid phase resin as required. Alkylation with the 2-(2-bromophenyl)ethyl building block **16b** gave a good yield of a radical precursor for testing the solution-phase cyclisation. Hydrolysis of the ester to the carboxylic acid would facilitate coupling to solid phase resins using carbodiimide coupling.



Scheme 7. Cyclisation of aryl precursors on solid phase.



Scheme 8. Cyclisation of imidazole precursors.

The cyclisation was studied with the precursor **23a** using three radical-mediators of which TTMSS gave the best yield of 5,6-dihydroimidazo[2,1-*a*]isoquinoline **24**. The results show that the pyridine thiol **25** is an equally good radical leaving group in aromatic nucleophilic subsitution to that of the earlier solid phase leaving group **13** or 4-mercaptobenzoic acid methyl ester. TTMSS and Bu_3SnH were added by syringe pump to keep their concentration low to facilitate cyclisation over reduction. The poor result with Bu_3GeH indicates that syringe pump addition is required. Further studies are required to optimise the cyclisation and apply to solid phase synthesis.

3. Conclusions

The solid phase reactions gave very similar yields to equivalent solution-phase reactions indicating the potential use of radical reactions using solid phase synthesis. There does not appear to be any side reactions in the solid phase reactions of the radical intermediates reacting with the resin. We believe that our results give further evidence[1–3] that solid phase synthesis should be fully considered as a useful technique in radical synthesis.

4. Experimental

Commercial dry solvents were used in all reactions except for light petroleum and ethyl acetate, which were distilled from $CaCl_2$ and dichloromethane (DCM) was distilled over phosphorus pentoxide. Light petroleum refers to the bp 40–60 °C fraction. Sodium hydride was obtained as 60% dispersion in oil and was washed with light petroleum. Mps were determined on an Electrothermal 9100 melting point apparatus and are un-corrected. Elemental analyses were determined on a Perkin Elmer 2400 CHN Elemental Analyser in conjunction with a Perkin Elmer AD-4 Autobalance. IR spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer on NaCl plates. ^1H (250 MHz) and ^{13}C (62.5 MHz) NMR spectra were recorded on a Bruker AC-250 spectrometer as solutions of $CDCl_3$ with tetramethylsilane (TMS) as the internal standard for ^1H NMR spectra and deuteriochloroform the standard for ^{13}C NMR spectra unless otherwise specified. Chemical shifts are given in parts per million (ppm) and *J* values in hertz (Hz). MAS Magic angle NMR spectroscopy was carried by GlaxoSmithKline. MAS spectra of the resins were recorded, and again once the radical precursor was loaded. Mass spectra were recorded on a JEOL SX102 mass spectrometer or carried out by the EPSRC Mass Spectrometry Service at University of Wales, Swansea. All mass spectra are electron impact spectra (EI) unless otherwise stated. TLC using silica gel as absorbent was carried out with aluminium backed plates coated with silica gel (Merck Kieselgel 60 F254). Column chromatography was carried out using neutral alumina unless otherwise specified.

1-Iodo-3-(phenylselanyl)propane **11a**,[7] 1-iodo-4-(phenylselanyl)butane **11b**,[7] 1-iodo-5-(phenylselanyl)pentane **11c**,[7] 1*H*-benzo[*d*]imidazol-2-yl phenyl sulfide **6**,[7] 1-[3-(phenylselanyl)propyl]-2-(phenylsulfanyl)-1*H*-benzo[*d*]imidazole **1a**,[7] 1-[4-(phenylselanyl)butyl]-2-(phenylsulfanyl)-1*H*-benzo[*d*]imidazole **1b**,[7] 1-iodo-2-(iodomethyl)benzene **16a**,[11] 2-(2-bromophenyl)ethyl methanesulfonate **16b**[11] and tributylgermanium hydride[4] were prepared by literature procedures.

4.1. General procedure for radical cyclisations. 2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole 4a

4.1.1. Tributyltin hydride. A solution of tributyltin hydride (0.83 cm^3, 3.1 mmol) in toluene (50 cm^3) was added to 1-[3-(phenylselanyl)propyl]-2-(phenylsulfanyl)-1*H*-benzo[*d*]-imidazole **1a** (0.60 g, 1.4 mmol) in toluene (150 cm^3) at reflux over 5 h using a syringe pump. AIBN (0.16 g, 1.4 mmol) was added to the refluxing reaction mixture at equal intervals. The solution was stirred and heated under reflux for a further 1 h. Dil, hydrochloric acid was added to the cooled reaction mixture to extract the protonated benzoimidazole compounds into the aqueous layer and washed with light petroleum to remove Bu_3Sn-residues. The acidic aqueous layer was basified with sodium carbonate followed by aqueous sodium hydroxide (few drops) to pH 14. The basic solution was extracted with DCM, and evaporated under reduced pressure to give a pale yellow oil crude product. The residue was purified by column chromatography using silica gel as absorbent with light petroleum and ethyl acetate as eluents to give 2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole **4a** as white crystals (57 mg, 0.36 mmol, 25%), mp 105–107 °C (lit.[7] mp 114–115 °C); δ_H 2.70 (2H, quintet, $J=7.4$ Hz, 2-H), 3.05 (2H, t, $J=7.6$ Hz, 3-C), 4.1 (2H, t, $J=7.2$ Hz, 1-C), 7.25–7.40 (3H, m, ArH) and 7.67–7.73 (1H, m, ArH).

The spectroscopic data were identical to those reported in the literature.[7]

4.1.2. Hexamethylditin. The reaction mixture of 1-[3-(phenylselanyl)propyl]-2-(phenylsulfanyl)-1*H*-benzo[*d*]-imidazole **1a** (89 mg, 0.21 mmol) and hexamethylditin (114 mg, 0.35 mmol) in *tert*-butylbenzene (10.0 cm^3) was irradiated with a sun lamp at 85 °C for 30 h. The work-up was carried out as in the previous experiment to give 2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole **4a** (26%).

4.1.3. 1,2,3,4-Tetrahydrobenzo[4,5]imidazo[1,2-*a*]-pyridine 4b. 1-[4-(Phenylselanyl)butyl]-2-(phenylsulfanyl)-1*H*-benzo[*d*]imidazole **1b** was reacted using the general procedure for radical cyclisations except that acetonitrile was used in place of toluene to yield 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyridine **4b** as colourless crystals (61%), mp 96–100 °C (lit.[7] mp 99.8–100.1 °C). The spectroscopic data were identical to the reported data.[7]

4.2. General procedure for alkylation

The azole was added slowly to a suspension of NaH (1.15 equiv) in dry THF (240 cm^3). The mixture was stirred and heated at 80 °C for 1 h. A solution of the alkylating agent (1.5 equiv) in THF (10 cm^3) was added dropwise to the reaction mixture, which was heated under reflux for a further 2 h. The salts were removed by filtration on a Celite bed and the solution evaporated under reduced pressure to yield the crude product. The crude product was purified by column chromatography using light petroleum–ethyl acetate (1/4) as the eluent.

4.2.1. 2-Chloro-1-[(3-phenylselanyl)propyl]-1*H*-benzo-[*d*]imidazole 9a. 2-Chlorobenzoimidazole (2.00 g, 13.1 mmol) and 1-iodo-3-(phenylselanyl)propane **11a** gave 2-chloro-1-[(3-phenylselanyl)propyl]-1*H*-benzo[*d*]-imidazole **9a** as a pale yellow oil (2.79 g, 8.0 mmol, 61%) (Found: C, 55.38; H, 4.40; N, 7.94 requires C, 54.95; H, 4.32; N, 8.01%); ν_{max} (neat)/cm^{-1} 2930, 1615, 1578, 1469, 1450, 1375, 1329, 1247, 1154, 1022, 761, 740 and 691; δ_H 2.12–2.33 (2H, m, CH_2), 2.88 (2H, t, J=6.9 Hz, CH_2Se), 4.28 (2H, t, J=7.1 Hz, CH_2N), 7.20–7.23 (6H, m, ArH), 7.43–7.45 (2H, m, ArH) and 7.65–7.68 (1H, m, ArH); δ_C 24.1 (CH_2), 29.3 (CH_2Se), 43.8 (CH_2N), 109.4 and 119.5 (4- and 7-C), 122.7 and 123.2 (5- and 6-C), 127.3 (PhCH), 129.1 (Ph 1-C), 129.2 (PhCH), 133.0 (PhCH), 135.0, 140.3 and 141.7 (2-3a, 7a-C); *m*/*z* EI 350 (M^+, 43%) (Found: M^+, 350.0091. $C_{16}H_{15}ClN_2Se$ requires 350.0089), 315 (55), 165 (62), 91 (100) and 77 (29).

4.3. General procedure for S_NAr substitution at 2-C

4.3.1. 1-Methyl-1*H*-benzo[*d*]imidazol-2-yl phenyl sulfide 7. Benzenethiol (0.31 cm^3, 3.0 mmol) was dissolved in a solution of KOH (0.17 g, 3.0 mmol) in EtOH (30 cm^3) and the mixture was stirred for 5 min. 2-Chloro-1-methyl-1*H*-benzoimidazole (0.50 g, 3.0 mmol) was added to the reaction mixture and the reaction mixture heated under reflux for 18 h. The reaction mixture was filtered and evaporated under reduced pressure to give 1-methyl-1*H*-benzo[*d*]imidazol-2-yl phenyl sulfide **7** as colourless crystals (0.62 g, 2.6 mmol, 85%), mp 66–69 °C (Found: M^+, 240.0726. $C_{14}H_{12}N_2S$ requires 240.0721); ν_{max} (KBr)/cm^{-1} 2373, 1577, 1441, 1409, 1324, 1276, 1078 and 739; δ_H 3.69 (3H, m, CH_3), 7.20–7.29 (6H, m), 7.34 (2H, dd, J=8.2, 1.1 Hz) and 7.75–7.77 (1H, m); δ_C 30.7 (CH_3), 109.4 and 119.8 (4- and 7-C), 122.4 and 123.2 (5- and 6-C), 127.6 (ArCH), 129.4 (ArCH), 130.2 (ArCH), 132.1 and 136.5 (3a- and 7a-C), 143.1 (Ph 1-C) and 147.6 (2-C); *m*/*z* EI 239 (M^+, 100%), 224 (11), 207 (14), 91 (14) and 77 (15).

4.3.2. 4-[(1*H*-Benzo[*d*]imidazol-2-yl)sulfanyl]benzoic acid 8. 4-Mercaptobenzoic acid and 2-chlorobenzoimidazole **5** gave **8** as colourless crystals (68%), mp 270–275 °C (Found: MH^+, 271.0541. $C_{14}H_{10}N_2O_2S$ requires 271.0544); ν_{max} (DCM)/cm^{-1} 3500, 3054, 2987, 1690, 1593, 1567, 1506, 1423 and 1265; δ_H (DMSO-d_6) 7.23–7.26 (2H, m, benzoimidazole 5-H and 6-H), 7.51 (2H, d, J=8.2 Hz, 3- and 5-H), 7.50–7.70 (2H, m, benzoimidazole 4- and 7-H) and 7.94 (2H, d, J=8.3 Hz, 2- and 6-H); δ_C (DMSO-d_6) 122.0 (benzoimidazole 4- and 7-C), 126.5 (benzoimidazole 5- and 6-C), 129.5 (3- and 5-C), 130.1 (1-C), 130.6 (2- and 6-C), 138.6 (4-C), 144.79 (benzoimidazole 2-C) and 167.1 (C=O); *m*/*z* EI 270 (M^+, 72%), 269 (100), 225 (15), 150 (16), 77 (18) and 44 (91).

4.3.3. Radical cyclisation of 1-(4-bromobutyl)-2-chloro-1*H*-benzo-[*d*]imidazole 12b. Tributylgermanium hydride (0.56 cm^3, 2.16 mmol) was added to 1-(4-bromobutyl)-2-chloro-1*H*-benzo[*d*]imidazole **12b** (0.31 g, 1.1 mmol) in toluene (100 cm^3) followed by portion wise addition of AIBN (0.35 g, 2.2 mmol) to the refluxing reaction mixture at equal intervals. The solution was stirred and heated under reflux for 12 h. The reaction mixture was evaporated under reduced pressure to yield a crude product, which was purified by column chromatography with light petroleum and ethyl acetate as eluents to give 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyridine **4b** as colourless crystals (0.10 g, 0.58 mmol, 54%); ν_{max} (KBr)/cm^{-1} 1610, 1505, 1425, 1397, 1328, 1278 and 745; δ_H 1.98–2.09 (2H, m, 3-H), 2.10–2.13 (2H, m, 2-H), 3.09 (2H, t, J=7.0 Hz, 4-H), 4.06 (2H, t, J=7.0 Hz, 1-H), 7.21–7.30 (3H, m, ArH) and 7.66–7.69 (1H, m, ArH). The data was identical to data reported in the literature.[7]

4.4. Loading of alkyl radical precursors onto resins

4.4.1. General procedure. Wang resin-bound benzoimidazole 12a. DCM (20 cm^3) was added to a portion of Wang resin (1.0 g, 1.7 mmol) and the resin was left to swell for 1 h under an atmosphere of nitrogen. 4-({1-[3-Phenylselanyl)-propyl]-1*H*-benzo[*d*]imidazol-2-yl}sulfanyl)benzoic acid **10a** (0.55 g, 1.2 mmol), DMAP (0.36 g, 2.9 mmol) and DIC (1.0 cm^3, 5.8 mmol) were added sequentially. The suspension was shaken for 48 h at room temperature. The reaction mixture was filtered and washed with DCM, MeOH, DMF, MeOH and DCM (20 cm^3 each). The resin was dried at 40 °C under vacuum for 24 h. The coupling reaction was repeated. The (MAS) magic angle ^1H NMR spectrum showed complete immobilisation of **10a** onto the Wang resin. FTIR ν_{max} (KBr)/cm^{-1} 3025, 2920, 1713, 1591, 1511, 1447, 1265, 1173, 1097, 1010, 822, 738 and 693.

4.4.2. Wang resin-bound benzoimidazole 12b. The (MAS) magic angle ^{1}H NMR spectrum showed complete immobilisation of the compound onto the Wang resin. FTIR ν_{max} (KBr)/cm^{-1} 3026, 2921, 2363, 1713, 1591, 1512, 1447, 1356, 1265, 1173, 1097, 1011, 822, 739 and 694.

4.4.3. Wang resin-bound benzoimidazole 12c. The (MAS) magic angle ^{1}H NMR spectrum showed complete immobilisation of the compound onto the Wang resin. FTIR ν_{max} (KBr)/cm^{-1} 3024, 2921, 2851, 1943, 1717, 1592, 1511, 1451, 1421, 1374, 1353, 1266, 1238, 1173, 1098, 1013, 824, 758, 738 and 697.

4.4.4. Amino-Merrifield resin-bound benzoimidazole 12d. FTIR ν_{max} (KBr)/cm^{-1} 3424, 3024, 2923, 1655, 1594, 1511, 1478, 1422, 1245, 1014, 838, 736 and 691.

4.4.5. Rink resin-bound benzoimidazole 12e. DCM (15 cm^3) was added to a portion of Rink resin (0.62 g, 0.5 mmol). The resin was left to swell for 1 h under an atmosphere of nitrogen. 4-({1-[4-Phenylselanyl)butyl]-1*H*-benzo[*d*]imidazol-2-yl}sulfanyl)benzoic acid **10b** (0.3 g, 0.6 mmol), HOAT (0.25 g, 1.8 mmol) and DIC (0.5 cm^3, 3.15 mmol) were added sequentially. The suspension was shaken for 48 h at room temperature. The reaction mixture was filtered and washed with DCM, MeOH, DMF, MeOH and DCM (20 cm^3 each). The resin was dried at 40 °C under vacuum for 24 h. The coupling reaction was repeated with equimolar reagents. The (MAS) magic angle ^{1}H NMR spectrum showed immobilisation of the compound onto the Rink resin. FTIR ν_{max} (KBr)/cm^{-1} 3413, 2921, 1659, 1503, 1349, 1207, 1026, 827, 742 and 695.

4.5. Radical cyclisations of resin-bound 1-[ω-(phenylselanyl)]benzoimidazoles

4.5.1. General procedure. Radical cyclisation of Wang resin-bound 12a. A solution of Bu_3SnH (0.10 cm^3, 0.4 mmol) and AIBN (26 mg, 0.16 mmol) in toluene (2.0 cm^3) was added to refluxing suspension of resin-bound benzoimidazole **12a** (170 mg, 0.16 mmol) in toluene (4.0 cm^3) over 26 min using a syringe pump. The reaction was stirred at reflux for 3 h and then a further portion of Bu_3SnH and AIBN in toluene (1 cm^3) was added over 5 min and the reaction mixture was heated under reflux for a further 1.5 h. The reaction mixture was filtered and the resin washed with toluene, DCM and MeOH (20 cm^3 each). The resin was dried at 40 °C under vacuum for 24 h. The LCMS analysis of the filtrate showed cyclised product **4a** (3 mg, 0.018 mmol, 11%). The remaining products were cleaved from the resin using 10% TFA in DCM. The LCMS analysis of the cleaved sample from the resin showed the reduced product **15a**. **4a** was isolated and characterised. All data were identical to aunthentic material.

The reaction was repeated under different conditions. The conditions and yields are reported in Table 1.

4.5.2. Radical cyclisations of resin-bound 12b. The general procedure was used with Wang and Rink resins. The different conditions and yields are reported in Table 1. 1,2,3,4-Tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyridine **4b** was isolated by HPLC and characterised in each case. The data were identical to authentic material. In several reactions the reduced uncyclised 4-[(1-butyl-1*H*-benzo[*d*]-imidazol-2-yl)sulfanyl]benzoic acid **15b** was isolated using HPLC and characterised. (Found: MH$^+$, 327.1170. $C_{18}H_{18}N_2O_2S$ requires 327.1167); ν_{max} (KBr)/cm^{-1} 3490, 2934, 2363, 1700, 1594, 1420, 1364, 1258, 1199, 1179, 1122 and 1017; δ_H (DMSO-d_6) 0.78 (3H, t, J=7.4 Hz, CH_3), 1.16–1.25 (2H, m, CH_2), 1.56–1.63 (2H, m, CH_2), 4.27 (2H, t, J=7.3 Hz, NCH_2), 7.23–7.31 (2H, m, ArH), 7.43 (2H, d, J=6.6 Hz, 3-H and 5-H), 7.62–7.65 (2H, m, ArH) and 7.88 (2H, d, J=6.4 Hz, 2-H and 6-H); δ_C (DMSO-d_6) 13.4 (Me), 19.3 (CH_2), 31.3 (CH_2), 44.0 (NCH_2), 110.9 and 119.0 (benzoimidazole 4- and 7-C), 122.4 and 123.3 (benzoimidazole 5- and 6-C), 128.9 (ArCH), 129.7 (1-C), 130.3 (ArCH), 135.6 (benzoimidazole 7a-C), 138.1 (4-C), 142.5 (benzoimidazole 3a-C), 145.1 (benzoimidazole 2-C) and 166.6 (C=O); *m/z* (FAB) 327 (MH$^+$, 100%), 271 (12), 176 (12), 154 (33) and 136 (31).

4.5.3. Radical cyclisations of Wang resin-bound benzoimidazole 12c. The general procedure for radical reactions of resin-bound precursors was used and the conditions and results are reported in Table 1. 7,8,9,10-Tetrahydro-6*H*-benzo[4,5]imidazo[1,2-*a*]-azepine **4c** was analysed by ^{1}H NMR spectroscopy using an internal standard. The data were indentical to those reported in the literature.[7] 4-[(1-Pentyl-1*H*-benzo[*d*]imidazol-2-yl)sulfanyl]benzoic acid **15c** was isolated and characterised. (Found: M$^+$, 340.1242. $C_{19}H_{20}N_2O_2S$ requires 340.1246); ν_{max} (KBr)/cm^{-1} 3056, 2928, 2477, 1910, 1689, 1596, 1463, 1385, 1272, 1115, 1007, 836 and 742; δ_H (DMSO-d_6) 0.76 (3H, t, J=6.9 Hz, CH_3), 1.15–1.24 (4H, m, CH_2CH_2), 1.62–1.68 (2H, m, CH_2), 4.28 (2H, t, J=7.3 Hz, NCH_2), 7.26 (1H, t, J=8.1 Hz, ArH), 7.31 (1H, t, J=7.9 Hz, ArH), 7.44 (2H, d, J=7.7 Hz, 3-H and 5-H), 7.64 (1H, d, J=8.0 Hz, benzoimidazole 7-H), 7.67 (1H, d, J=7.9 Hz, benzoimidazole 4-H) and 7.91 (2H, d, J=6.7 Hz, 2-H and 6-H); δ_C (DMSO-d_6) 13.6 (CH_3), 21.6 (CH_2), 28.1 (CH_2), 28.8 (CH_2), 44.1 (NCH_2), 110.8 and 119.1 (benzoimidazole 4- and 7-C), 122.2 and 123.2 (benzoimidazole 5- and 6-C), 128.7 (ArCH), 130.0 (1-C), 130.2 (ArCH), 135.6 and 138.2 (benzoimidazole 3a- and 7a-C), 142.7 (4-C), 144.9 (benzoimidazole 2-C) and 166.5 (C=O); *m/z* 339 (M$^+$, 100%), 307 (14), 297 (34), 269 (86), 225 (26), 187 (28), 150 (30), 131 (24) and 73 (28).

4.5.4. Radical cyclisation of Wang resin-bound 12b using microwave irradiation. General method. A suspension of the Wang resin-bound **12b** (22 mg, 0.021 mmol) was prepared in propan-1-ol/benzene (1.25 cm^3 of each) was prepared in a microwave pyrex tube. Bu_3SnH (3.57 equiv) and AIBN (3.57 equiv) were added and the pyrex tube sealed and placed in an automated microwave apparatus (Smiths Personnel Chemistry Synthesiser). This synthesiser has an integrated liquid handler, which facilitates automated microwave reactions for up to 96 separate reaction vessels. The sample was irradiated for 10 min at 100 °C. A second addition of reagents the sample was carried out and the reaction irradiated for another 10 min. After 20 min the reaction vessel was removed from the microwave apparatus, cooled to room temperature and unsealed. The reaction mixture was filtered and washed with toluene, DCM and MeOH (20 cm^3 each). LCMS analysis of the filtrate showed

only the presence of the cyclised product 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyridine **4b** (52%) and tributyltin residues. The yield was determined by ^{1}H NMR spectroscopy using the internal standard.

The reaction was repeated under various conditions to optimise the yield and minimise the time. Conditions and yields of reactions are reported in Table 2 and the discussion.

4.6. Alkylations of 2-chloro-1*H*-benzo[*d*]imidazole

4.6.1. 2-Chloro-1-[(2-iodophenyl)methyl]-1*H*-benzo[*d*]-imidazole. (3.00 g, 19.7 mmol) was added to a vigorously stirred suspension of ground potassium hydroxide (3.30 g, 59.0 mmol) in dry DMF (80 cm^3) and stirred for 30 min. 1-Iodo-2-(iodomethyl)benzene **16a** (13.53 g, 39.3 mmol) was added in one portion. The reaction was stirred for 24 h, partitioned between ethyl acetate and water and the organic layer was removed. The organic extract was washed with water followed by brine, dried and evaporated under reduced pressure. The residue was purified by column chromatography using neutral alumina as absorbent and light petroleum–ethyl acetate (4/1) as eluents to afford 2-chloro-1-[(2-iodophenyl)methyl]-1*H*-benzo[*d*]imidazole as cream coloured crystals (6.87 g, 18.7 mmol, 95%), mp 106.2–109.3 °C (Found: M$^+$, 367.9573. $C_{14}H_{10}ClIN_2$ requires 367.9577); ν_{max} (KBr)/cm^{-1} 3059, 2920, 1700, 1615, 1455, 1428, 1329, 1282, 1240, 1198, 1013, 986, 749 and 650; δ_H 5.38 (2H, s, CH_2), 6.48 (1H, d, J=8.0 Hz), 7.00 (1H, dd, J=8.0, 8.0 Hz), 7.08–7.34 (4H, m), 7.75 (1H, d, J=8.0 Hz) and 7.91 (1H, d, J=8.0 Hz); δ_C 52.9 (CH_2), 96.7 (Ar 2-C), 109.9 (CH), 119.7 (CH), 123.1 (CH), 123.6 (CH), 126.6 (CH), 128.9 (CH), 130.1 (CH), 135.0 (3a-C), 136.8 (7a-C), 139.7 (CH), 141.0 (2-C) and 141.8 (Ar 1-C); *m*/*z* (EI) 368 (M$^+$, 62%), 241 (35), 217 (100), 205 (13), 152 (19) and 90 (47).

4.6.2. 1-[2-(2-Bromophenyl)ethyl]-2-chloro-1*H*-benzo-[*d*]imidazole. The general procedure for alkylation was used with 2-chlorobenzoimidazole and 2-(2-bromophenyl)-ethyl methanesulfonate **16b** to afford 1-[2-(2-bromophenyl) ethyl]-2-chloro-1*H*-benzo[*d*]imidazole as cream coloured crystals (98%), mp 73.5–75.4 °C (Found: M$^+$, 333.9871. $C_{15}H_{12}BrClN_2$ requires 333.9872); ν_{max} (KBr)/cm^{-1} 3042, 2932, 1614, 1473, 1452, 1378, 1357, 1329, 1329, 1263, 1170, 1032, 1004, 758, 746, 729 and 655; δ_H 3.20 (2H, t, J=7.3 Hz, CH_2), 4.40 (2H, t, J=7.3 Hz, NCH_2), 6.89 (1H, t, J=6.5 Hz), 7.05–7.10 (2H, m), 7.22–7.23 (3H, m), 7.51–7.54 (1H, t, J=8.0 Hz) and 7.64–7.68 (1H, m); δ_C 35.9 (CH_2), 43.8 (NCH_2), 109.3 (CH), 119.4 (CH), 122.6 (CH), 123.1 (CH), 124.4 (C), 127.8 (CH), 128.9 (CH), 131.1 (CH), 133.0 (CH), 134.9 (C), 136.4 (C), 140.4 (C) and 141.6 (C); *m*/*z* (EI) 334 (M$^+$, 22%), 255 (11), 182 (45), 165 (100), 129 (27), 90 (34) and 70 (32).

4.7. S_NAr substitutions with 4-mercaptobenzoic acid

4.7.1. 4-({1-[(2-Iodophenyl)methyl]-1*H*-benzo[*d*]imidazol-2-yl}sulfanyl)benzene-1-carboxylic acid 17a. 4-Mercaptobenzoic acid (1.54 g, 10.0 mmol) was dissolved in EtOH (60 cm^3) followed by potassium *tert*-butoxide (1.70 g, 15.2 mmol) and the mixture was stirred for 5 min. 2-Chloro-1-[(2-iodophenyl)methyl]-1*H*-benzo[*d*]imidazole (3.74 g, 10.1 mmol) was added to the reaction mixture and heated under reflux overnight. The reaction mixture was filtered and evaporated to dryness to give the crude product, which was purified by column chromatography using silica gel as absorbent and light petroleum–ethyl acetate (1/1) as eluents to afford the benzoimidazole **17a** as pale yellow crystals (4.88 g, 10.0 mmol, 99%), mp 98.2–103.5 °C (Found: M$^+$, 485.9915. $C_{21}H_{15}IN_2O_2S$ requires 485.9905); ν_{max} (KBr)/cm^{-1} 3382, 3056, 2964, 1924, 1695, 1591, 1544, 1434, 1385, 1271, 1185, 838 and 734; δ_H 5.49 (2H, s, CH_2), 6.31 (1H, dd, J=7.6, 1.4 Hz, CH), 7.02 (1H, ddd, J=7.6, 7.6, 1.4 Hz, CH), 7.19 (1H, ddd, J=7.6, 7.6, 1.4 Hz, CH), 7.25–7.28 (2H, m, CH), 7.34 (2H, dd, J=6.6, 1.7 Hz, 3-H and 5-H), 7.40–7.44 (1H, m, CH), 7.69–7.73 (1H, m, CH), 7.81 (2H, dd, J=6.6, 1.7 Hz, 2-H and 6-H), and 7.91 (1H, dd, J=7.6, 1.0 Hz, CH); δ_C 52.8 (CH_2), 98.0 (C–I), 111.1 (CH), 119.5 (CH), 122.8 (CH), 123.8 (CH), 126.8 (CH), 129.0 (CH), 129.9 (CH), 129.9 (CH), 130.4 (CH), 133.0 (C), 136.3 (C), 137.8 (C), 138.3 (C), 139.7 (CH), 143.2 (C), 147.9 (C) and 167.9 (C=O); *m*/*z* (EI) 486 (M$^+$, 4%), 465 (48), 431 (8), 378 (7), 262 (22), 217 (100), 178 (20), 154 (50), 90 (61) and 73 (58).

4.8. Methylation of aryl radical precursors

4.8.1. Methyl 4-({1-[(2-iodophenyl)methyl]-1*H*-benzo-[*d*]imidazol-2-yl}sulfanyl)benzene-1-carboxylate 18a. Acetyl chloride (2.0 cm^3, 28.0 mmol) was added dropwise over 10 min to MeOH (25 cm^3) cooled in an ice bath. The solution was stirred for 5 min and 4-({1-[(2-iodophenyl)-methyl]-1*H*-benzo[*d*]imidazol-2-yl}sulfanyl)benzene-1-carboxylic acid (0.62 g, 1.3 mmol) was added in one portion and the solution heated under reflux for 18 h. The solution was cooled and evaporated under reduced pressure to give the crude methyl ester hydrochloride. Water was added to the crude and the aqueous layer was basified to pH 14 with sodium carbonate and aqueous sodium hydroxide solution. The basic solution was extracted with DCM. The organic extracts were dried and evaporated under reduced pressure. The residue was purified by column chromatography using neutral alumina as absorbent and light petroleum–ethyl acetate (1/1) as eluents to afford methyl ester **18a** as colourless crystals (0.5 g, 1.0 mmol, 78%), mp 179.1–181.2 °C (Found: MH$^+$, 501.0131. $C_{22}H_{17}IN_2O_2S$ requires 501.0134); ν_{max} (KBr)/cm^{-1} 2940, 1713, 1589, 1544, 1428, 1351, 1277, 1107, 1012, 841, 824, 748 and 689; δ_H 3.79 (3H, s, CH_3), 5.33 (2H, s, CH_2), 6.19 (1H, d, J=7.2 Hz), 6.81 (1H, dd, J=7.6, 1.0 Hz), 6.94 (1H, dd, J=7.6, 1.0 Hz), 7.07 (1H, d, J=7.6 Hz), 7.17–7.27 (2H, m), 7.30 (2H, d, J=8.6 Hz, 3-H and 5-H), 7.72–7.74 (2H, m) and 7.76 (2H, d, J=8.6 Hz, 2-H and 6-H); δ_C 51.2 (CH_3), 52.3 (CH_2), 95.8 (C-I), 109.2 (CH), 119.3 (CH), 122.1 (CH), 123.1 (CH), 125.6 (CH), 127.6 (CH), 128.1 (1-C), 128.3 (6-C), 128.4 (CH), 129.3 (CH), 134.8 (CH), 136.2 (3a-C), 137.0 (7a-C), 138.5 (CH), 142.3 (benzoimidazole 2-C), 145.5 (1-C) and 165.2 (C=O); *m*/*z* (FAB) 501 (MH$^+$, 32%), 327 (19), 281 (22), 217 (40), 147 (54) and 136 (100).

4.9. Radical cyclisations of methyl esters 18a and 18b

4.9.1. 5,6-Dihydrobenzo[4,5]imidazo[2,1-*a*]isoquinoline 19b. The general procedure for radical cyclisations was carried out with the methyl ester **18b** with Bu_3SnH added at

reflux over 5 h using a syringe pump. The solution was stirred and heated under reflux for a further 3 h. Colourless crystals (50%), mp 125.0–130.0 °C (Found: M^+, 220.1000. $C_{15}H_{12}N_2$ requires 220.1001); ν_{max} (KBr)/cm^{-1} 2922, 2370, 2344, 1480, 1458, 1406, 1325, 1171 and 736; δ_H 3.30 (2H, t, J=6.9 Hz, 5-H), 4.35 (2H, t, J=6.9 Hz, 6-H), 7.26–7.43 (6H, m, ArH), 7.81–7.85 (1H, m, ArH) and 8.29–8.32 (1H, m, ArH); δ_C 28.3 (5-C), 40.4 (6-C), 109.0 (CH), 119.8 (CH), 122.5 (CH), 122.7 (CH), 125.7 (CH), 126.6 (12b-C), 127.8 (CH), 128.1 (CH), 130.2 (CH), 134.3 (C), 134.6 (C), 143.9 (C) and 149.1 (C); *m/z* (EI) 220 (M^+, 100%), 109 (9), 86 (10) and 77 (9).

4.9.2. 11*H*-Benzo[4,5]imidazo[1,2-*a*]isoindole 19a. The general procedure for radical cyclisations was carried out with the methyl ester **18a** with TTMSS instead of Bu_3SnH to afford the tetracycle **19a** as colourless crystals (20%), mp 144.0–149.0 °C (Found: M^+, 206.0841. $C_{14}H_{10}N_2$ requires 206.0844); ν_{max} (KBr)/cm^{-1} 2927, 2367, 1657, 1433, 1399, 1269 and 740; δ_H 5.27 (2H, s, CH_2), 7.26–7.42 (7H, m, ArH) and 7.70–7.72 (1H, m, ArH); δ_C 46.2 (CH_2), 108.3 (CH), 118.9 (CH), 122.1 (CH), 122.6 (CH), 123.4 (C), 127.1 (CH), 127.5 (CH), 127.8 (CH), 128.8 (CH), 129.1 (C), 134.7 (C), 134.7 (C) and 143.9 (C); *m/z* (EI) 206 (M^+, 46%), 149 (17), 119 (8), 91 (16) and 77 (18). The reduced uncyclised 4-[(1-benzyl-1*H*-benzo[*d*]imidazole-2-yl)sulfanyl]benzene-1-carboxylate **20a** was also isolated as a pale yellow oil (40%) (Found: M^+, 375.1167. $C_{22}H_{18}N_2O_2S$ requires 375.1167); ν_{max} (KBr)/cm^{-1} 2950, 1721, 1594, 1434, 1350, 1276, 1181, 1108, 1016, 824 and 760; δ_H 3.89 (3H, s, CH_3), 5.45 (2H, s, CH_2), 7.06–7.08 (2H, m, ArH), 7.23–7.34 (8H, m, ArH), 7.88 (1H, d, J=7.6 Hz, ArH) and 7.90 (2H, d, J=7.9 Hz, 2-H and 6-H); δ_C 48.3 (CH_3), 52.2 (CH_2), 110.4 (CH), 120.3 (CH), 122.9 (CH), 123.9 (CH), 126.7 (CH), 128.0 (CH), 128.7 (CH), 128.9 (CH), 130.4 (CH), 128.9 (C), 135.5 (C), 136.0 (C), 138.8 (C), 143.5 (C), 146.0 (C) and 166.4 (C=O); *m/z* (FAB) 375 (M^+, 74%), 322 (20), 243 (43), 167 (87), 154 (100) and 136 (74).

4.10. Loading of aryl-radical precursors 17a and 17b onto resins

4.10.1. Wang solid supported benzoimidazole 18d. The general procedure for loading precursors to Wang resin was carried out with the acid **17b**. The loading on the resin (0.98 mmol/g) was determined by cleaving a known amount of resin using TFA–DCM (9/1). FTIR ν_{max} (KBr)/cm^{-1} 3023, 2919, 1713, 1590, 1441, 1263, 1170, 1095, 1090, 1010, 821, 742 and 694. The (MAS) magic angle ^{1}H NMR spectrum showed complete immobilisation of the compound onto the Wang resin.

4.10.2. Wang solid supported benzoimidazole 18c. The loading on the resin (0.60 mmol/g) was determined. FTIR ν_{max} (KBr)/cm^{-1} 3424, 3058, 3024, 2919, 2365, 1944, 1717, 1596, 1510, 1492, 1445, 1371, 1266, 1239, 1173, 1099, 1011, 822, 743 and 696. The (MAS) magic angle ^{1}H NMR spectrum showed complete immobilisation of the compound onto the Wang resin.

4.11. Radical cyclisations of resin-bound benzoimidazole 18d

4.11.1. Bu_3SnH. The general procedure for radical cyclisation of Wang bound precursors with **18d** (100 mg, 0.10 mmol) gave 5,6-dihydrobenzo[4,5]imidazo[2,1-*a*]isoquinoline **19b** as colourless crystals (44%). The data were indentical to authentic material.

4.11.2. Bu_3GeH. The general procedure for radical cyclisation of Wang bound precursors with **18d** (140 mg, 0.14 mmol) using Bu_3GeH added in one portion at the beginning and heated for 8 h gave **19b** (71%).

4.11.3. TTMSS. TTMSS (0.06 cm^3, 0.19 mmol) and Et_3B (1.0 M in cyclohexane, 0.2 mmol) were added dropwise to a suspension of the resin-bound benzoimidazole **18d** (111 mg, 0.11 mmol) in toluene (15 cm^3), The flask was fitted with a rubber septum and air was introduced through a needle during stirring at room temperature for 5 h. Further addition of TTMSS (0.12 mL, 0.38 mmol) and Et_3B (1.0 M in hexane, 0.3 mmol) was carried out and the reaction mixture was stirred for another 10 h. Standard work-up gave **19b** (29%).

4.12. Ethyl 6-({1-[2-(2-bromophenyl)ethyl]-1*H*-imidazol-2-yl}sulfanyl)pyridine-3-carboxylate 23a

4.12.1. Ethyl 6-[(1*H*-imidazol-2-yl)sulfanyl]pyridine-3-carboxylate 22. 2-Mercaptoimidazole (2.00 g, 20.0 mmol) was added slowly to a suspension of NaH (0.58 g, 24.2 mmol) in dry DMF (40 cm^3). The mixture was stirred and heated at 80 °C for 1 h, followed by addition of ethyl 6-chloronicotinate (3.71 g, 20.0 mmol) in DMF (10 cm^3) and the reaction mixture was heated at 80 °C for 12 h. The reaction mixture was evaporated under reduced pressure and the residue purified by column chromatography using silica gel as absorbent and light petroleum–ethyl acetate (1/1) as eluents to afford **22** as colourless crystals (2.49 g, 50%), mp 145.7–146.9 °C (Found: M^+, 249.0573. $C_{11}H_{11}N_3O_2S$ requires 249.0572); ν_{max} (KBr)/cm^{-1} 3079, 2986, 2745, 2502, 1866, 1715, 1574, 1444, 1275, 1113, 1011, 965, 851 and 767; δ_H 1.39 (3H, t, J=7.2 Hz, CH_3), 4.39 (2H, q, J=7.2 Hz, OCH_2), 7.12 (1H, dd, J=8.6, 0.4 Hz, 5-H), 7.23–7.26 (2H, br s, imidazole 4,5-H), 8.10 (1H, dd, J=8.6, 2.4 Hz, 4-H) and 8.98 (1H, dd, J=2.4, 0.4 Hz, 2-H), NH was not observed; δ_C 14.2 (CH_3), 61.5 (OCH_2), 121.3 (5-C), 123.3 (imidazole 4,5-C), 133.2 and 135.1 (3-C and imidazole 2-C), 137.6 (4-C), 150.5 (2-C) and 163.2 and 164.8 (6-C and C=O); *m/z* (EI) 250 (MH^+, 100%), 232 (33), 221 (7), 163 (11), 130 (12), 103 (21), 91 (10) and 77 (11).

4.12.2. Ethyl 6-({1-[2-(2-bromophenyl)ethyl]-1*H*-imidazol-2-yl}sulfanyl)pyridine-3-carboxylate 23a. The standard procedure for alkylation was used with the imidazole **22** and 2-(2-bromophenyl)ethyl methanesulfonate **16b** to afford **23a** as a pale yellow oil (75%) (Found: M^+, 431.0312. $C_{19}H_{18}BrN_3O_2S$ requires 431.0303); ν_{max} (neat)/cm^{-1} 3105, 3056, 2981, 1716, 1584, 1472, 1456, 1429, 1366, 1283, 1269, 1173, 1128, 1025, 854 and 766; δ_H 1.38 (3H, t, J=7.2 Hz, CH_3), 3.13 (2H, t, J=7.2 Hz, CH_2), 4.32 (4H, t, J=7.2 Hz, NCH_2), 4.38 (4H, q, J=7.2 Hz,

OCH_2), 6.88 (1H, dd, J=8.4, 0.4 Hz, 5-H), 6.96 (1H, dd, J=7.5, 1.4 Hz, CH), 7.08 (1H, ddd, J=7.5, 7.5, 1.4 Hz, CH), 7.10 and 7.27 (2H, 2×s, imidazole 4,5-H), 7.16 (1H, ddd, J=7.5, 7.5, 1.4 Hz, CH), 7.49 (1H, dd, J=7.5, 1.4 Hz, CH), 8.04 (1H, dd, J=8.4, 2.0 Hz, 4-H) and 8.96 (1H, dd, 2.0, 0.4, 2-H); δ_C 14.2 (CH_3), 37.9 (CH_2), 46.7 (NCH_2), 61.4 (OCH_2), 120.4 (5-C), 123.1 (Ar 2-C), 123.4 (imidazole 4-C), 124.4 (3-C), 127.7 (imidazole 5-C), 128.9 (CH), 131.0 (CH), 131.2 (CH), 133.0 (CH), 134.4 and 136.3 (Ar 1-C and imidazole 2-C), 137.7 (4-C), 150.9 (2-C), 164.4 and 164.9 (6-C and C=O); m/z (EI) 431 (M^+, 4%), 352 (11), 249 (46), 181 (100), 153 (64), 84 (45) and 49 (39).

4.12.3. 5,6-Dihydroimidazo[2,1-*a*]isoquinoline 24. *Bu_3SnH*. The standard procedure for radical cyclisations was carried out using the imidazole **23a** (150 mg) to afford 5,6-dihydroimidazo[2,1-*a*]isoquinoline **24** as a clear oil (37%) (Found: M^+, 170.0847. $C_{11}H_{10}N_2$ requires 170.0844); ν_{max} (neat)/cm^{-1} 3171, 2923, 1708, 1499, 1466, 1329, 1250, 1195, 1099, 911, 772, 738 and 714; δ_H 3.16 (2H, t, J=6.8 Hz, CH_2), 4.17 (2H, t, J=6.8 Hz, NCH_2), 6.94 (1H, d, J=1.0 Hz, 2/3-H), 7.15 (1H, d, J=1.0 Hz, 2/3-H), 7.26–7.27 (3H, m, ArH) and 8.02 (1H, d, J=8.0 Hz, 10-H); δ_C 28.6 (6-C), 43.3 (5-C), 119.1 (CH), 123.6 (CH), 127.6 (CH), 127.8 (CH), 128.3 (CH), 129.1 (CH), 129.6 (C), 132.3 (C) and 142.9 (C); m/z EI 170 (M^+, 4%), 149 (5), 128 (16), 115 (16), 77 (21) and 57 (23).

TTMSS. **24** (45%). Bu_3GeH. Bu_3GeH was added in one portion at the beginning of the reaction. **24** (20%).

Yields of isolated unreacted starting material **23a** and reduced uncyclised **23b** are reported in Scheme 8.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.02.071. Supplementary data includes syntheses of compounds in which the general method and a representative example has been included in the paper.

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