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Synthetic applications of aryl radical building blocks for cyclisation onto azoles

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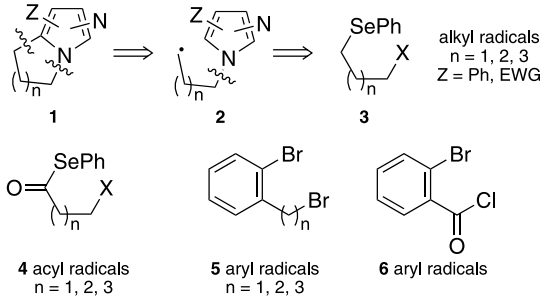
Abstract—2-(2-Bromophenyl)ethyl groups have been used as building blocks in radical cyclisation reactions onto azoles to synthesise tri- and tetra-cyclic heterocycles. 2-(2-Bromophenyl)ethyl methanesulfonate was used to alkylate azoles (imidazoles, pyrroles, indoles and pyrazoles) for the synthesis of the radical precursors. Cyclisations of the intermediate aryl radicals yield new 6-membered rings attached to the azoles. The aryl radicals undergo intramolecular homolytic aromatic substitution onto the azole rings. Tributylgermanium hydride has been used with success to replace the toxic and troublesome tributyltin hydride. Initial studies show that the protocol can be used on solid phase resins. The molecular and crystal structures of methyl 5,6-dihydroimidazo[5,1-*a*]iso-quinoline-1-carboxylate and methyl 5,6-dihydroimidazo[2,1-*a*]isoquinoline-3-carboxylate were determined by X-ray crystallography.

1. Introduction

The use of radical cyclisations for the synthesis of heterocyclic compounds has become commonplace.[1] One of the advances, that has proved most useful, is the cyclisation of radicals onto heteroarenes to yield bi- and tri-cyclic heterocycles. In these reactions, which are mediated by Bu_3SnH and related hydrides, the heteroarene undergoes rearomatisation in the radical cyclisation. With the use of *NH*-heteroarenes, *N*-alkylation provides a facile route for the addition of 'radical' building blocks. These units can then be used for cyclisation onto a range of different *NH*-heteroarenes and also in other radical cyclisations.

Our earlier studies have reported the application of *N*-(ω-phenylselanyl)alkyl **3** and *N*-(ω-bromo)alkyl building blocks for the cyclisation of *N*-(ω-alkyl)-radicals onto pyrroles,[2] imidazoles[2] and pyrazoles[3] with electron withdrawing groups or radical stabilising groups such as phenyl. The protocol is illustrated in Scheme 1; a bicyclic heterocycle (**1**) is synthesised via cyclisation of an intermediate alkyl radical (**2**). The moiety (**3**) is added by *N*-alkylation. Similar methodologies using alkyl radicals



Scheme 1. Radical building blocks.

have been used in the cyclisation onto other heteroarenes which include indoles[4,5,6] pyrroles,[4] pyridinium salts,[7] 1,2,3-triazoles,[8] and quinolones.[9] More recently, we have shown that acyl radical building blocks (**4**) can be used for cyclisation onto electron deficient pyrroles (pyrroles with electron withdrawing groups).[10]

The analogous use of these protocols to yield intermediate aryl radicals instead of alkyl radicals can also be envisaged. In this paper we report our studies of the development of the use of components derived from 2-(2-bromophenyl)ethyl groups (Scheme 2, e.g. (**8**)). The cyclisation of the intermediate aryl radicals (**9**) yield new 6-membered rings attached to the azoles (**11**). One of the aims of our study was to develop building blocks to facilitate diversity for use in

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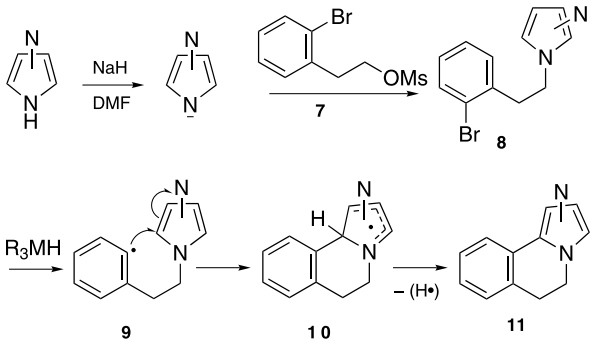


Scheme 2. General protocol for use of 2-(2-bromophenyl)ethyl building blocks for the synthesis of tricyclic heterocycles.

solid phase synthesis and combinatorial chemistry. We also report our further studies of the use of tributylgermanium hydride (Bu_3GeH) as the radical generating reagent in place of the toxic and troublesome tributyltin hydride (Bu_3SnH).[11] Bu_3GeH has a number of advantages over Bu_3SnH which include lower toxicity, better shelf life, ease of work-up and slower rates of H-abstraction by intermediate radicals which helps to facilitate cyclisation over reduction.

Building blocks which yield intermediate aryl radicals for cyclisation onto heteroarenes and other functional groups have been reported. For example, aryl radicals generated from precursors synthesised from 2-bromobenzoyl chloride (**6**) have been used in a number of reactions.[12] The most commonly used aryl radical entity has been pendant *N*-(2-bromophenyl)methyl moieties synthesised using (2-bromo-phenyl)methyl bromide (**5**), $n=1$. Examples of cyclisation using this unit include cyclisation onto indoles,[13,14] pyrroles,[4] pyridones[15] and 5-amino- and 5-hydroxyuracils.[16]

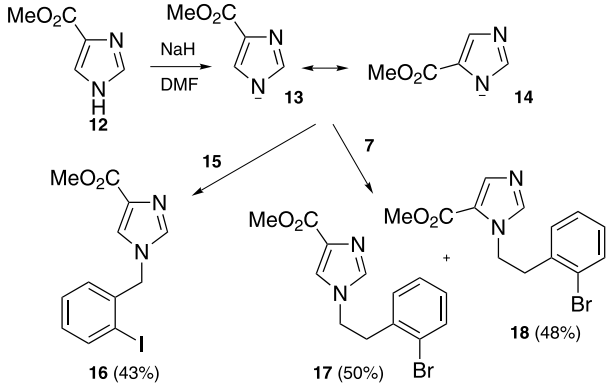
The analogous 2-(2-bromophenyl)ethyl components, which generate new six-membered rings by cyclisation of aryl radicals, have been less commonly used. These units have been attached by *N*-alkylation with 2-(2-bromophenyl)ethyl bromide (**5**), $n=2$. Cyclisation onto indoles,[13] pyridones[15] and 2-quinolones[17] has given high yields. In contrast, the 5-membered ring cyclisations of aryl radicals onto azoles have proven less successful. Cyclisation onto 5-membered ring azoles is less favoured due to the strain of formation of products with two 5-membered rings, one of which is a heteroarene.[2] In our studies on the alkyl radical cyclisation onto imidazoles, 6-membered ring cyclisation gave better yields than 5-membered ring cyclisation, in which reduced uncyclised products were also obtained. We showed using X-ray crystallography that the structure of 6,7-dihydro-5*H*-pyrrolo-[1,2-*c*]imidazole-1-carb-aldehyde is completely planar indicating considerable strain in the new five-membered ring.[2]

Cyclisation onto heteroarenes of aryl radicals generated from pendant 2-(2-bromophenyl)ethyl moieties, attached at atoms other than the nitrogen, have also been reported. Good yields have been reported for cyclisations onto indoles,[13] quinolines[18] and pyridines[19] showing that the 6-membered ring cyclisation is particularly favourable.

2. Discussion

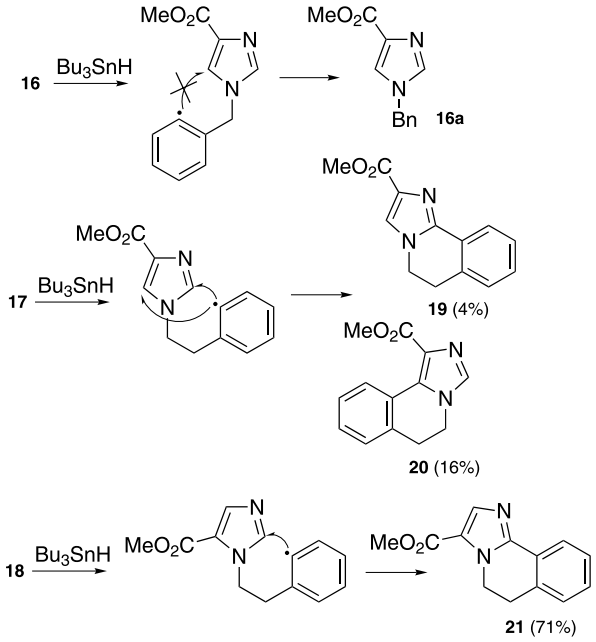
We chose four different representative azole esters for testing the 'building block' protocol. The esters were used in each case to provide a handle for solid phase studies and to facilitate lower electron density on the azole rings. Aryl radicals are nucleophilic and therefore lower electron density on the azole rings would help with cyclisation. We have previously shown that electron withdrawing and/or radical stabilising groups improve cyclisation.[2,3]

The alkylations were carried out by standard procedures using sodium hydride (NaH) in DMF to deprotonate the azoles followed by addition of 2-(2-bromophenyl)ethyl methane-sulfonate (**7**) as shown in Scheme 2. In the alkylation using 1*H*-imidazole-4-carboxylic acid methyl ester (**12**) two products are possible due to the ambident nature of the anion (Scheme 3). Alkylation with 1-iodo-2-(iodomethyl)benzene (**15**) gave only the 4-ester product in moderate yield. This regioselectivity was as expected from studies of alkylation of other imidazoles with electron withdrawing groups (e.g. aldehyde and nitro groups) in the 4/5-position.[2] The nitrogen anion furthest from the ester (as represented by the canonical form (**13**)) is more nucleophilic than the nitrogen anion nearest to the ester (as represented by the canonical form (**14**)) and normally facilitates selective alkylation to yield the product with the substituent in the 4-position (Scheme 3). Steric hindrance may also be a factor in the regioselectivity. Surprisingly, alkylation with 2-(2-bromo-phenyl)ethyl methane-sulfonate (**7**) gave both isomers (**17**) and (**18**). In the alkylation of 3-trifluoromethyl-1*H*-pyrazole-4-carboxylic acid ethyl ester which could yield two isomers, only the required isomer was obtained.



Scheme 3. Alkylation of 1*H*-imidazole-4-carboxylic acid methyl ester (**12**).

The radical cyclisations using Bu_3SnH were carried using syringe pump addition in order to maximise the chance of cyclisation. Because of the slower H-abstraction from Bu_3GeH, the reagent was added in one portion at the beginning of the reaction.[11] Initially we compared the cyclisation via a 5-membered ring versus cyclisation via a 6-membered ring in the imidazole system (Scheme 4). The radical reaction between methyl 1-[(2-iodophenyl)methyl]-1*H*-imidazol-4-carboxylate (**16**) and Bu_3SnH or Bu_3GeH gave only the reduced uncyclised methyl 1-benzyl-1*H*-imidazole-4-carboxylate. This is surprising for the Bu_3GeH reaction because the rate of H-abstraction from Bu_3GeH is



Scheme 4. Radical cyclisation onto imidazoles.

ca. 20 times slower than for Bu_3SnH and therefore should favour cyclisation over reduction.

In contrast, reaction of 1-[2-(2-bromophenyl)ethyl]-1*H*-imidazole-4-carboxylate (**17**) gave a mixture of methyl 5,6-dihydro-imidazo[2,1-*a*]isoquinoline-2-carboxylate (**19**)

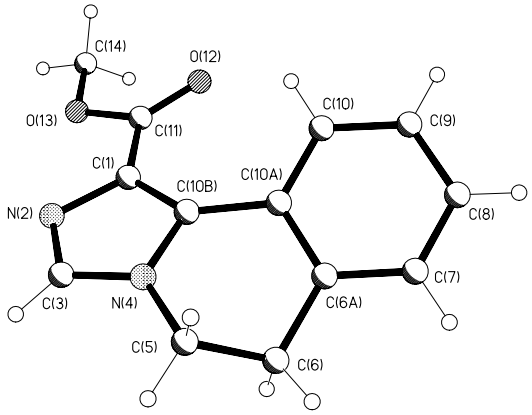


Figure 1. X-ray structure of methyl 5,6-dihydroimidazo[5,1-*a*]isoquinoline-1-carboxylate (**20**) with atom labelling.

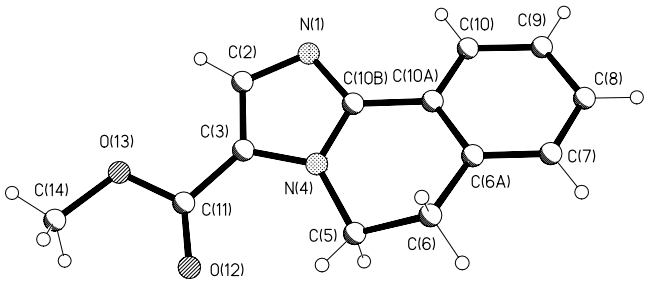


Figure 2. X-ray structure of methyl 5,6-dihydroimidazo[2,1-*a*]isoquinoline-3-carboxylate (**21**) with atom labelling.

(4%) and methyl 5,6-dihydro-imidazo[5,1-*a*]isoquinoline-1-carboxylate (**20**) (16%) with no uncyclised reduced material. These results further illustrate the strain involved in 5-membered ring cyclisation on 5-membered ring azoles. The use of Bu_3GeH and tris-(trimethylsilyl)silane (TTMSS) gave improved yields ((**19**) (19%), (**20**) (38%)] and [(**19**) (30%), (**20**) (30%)), respectively. The latter results illustrate the advantage of both Bu_3GeH and TTMSS over Bu_3SnH in facilitating easier work-up and higher yields. The use of Bu_3GeH along with phenylthiol in a polarity reversal catalysis (PRC)[20] experiment gave only (**20**) in 44% yield. The electrophilic phenylthiyl radical should intercept the nucleophilic aryl radical intermediate at a faster rate than the Bu_3GeH and this may have a bearing on the selectivity.

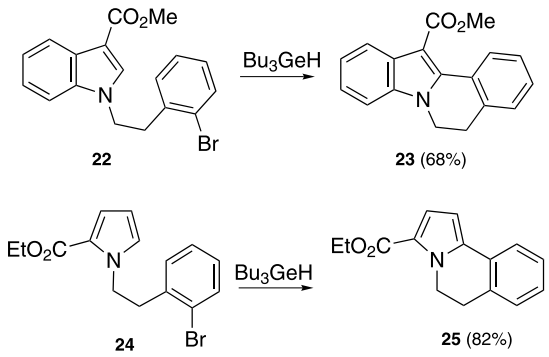
The structures of (**19**) and (**20**) could not be positively distinguished by normal analysis so the structure of (**20**) was confirmed by X-ray crystallography (Fig. 1).

Cyclisation of methyl 1-[2-(2-bromophenyl)ethyl]-1*H*-imidazole-5-carboxylate (**18**) yielded methyl 5,6-dihydroimidazo-[2,1-*a*]isoquinoline-3-carboxylate (**21**) [Bu_3SnH (71%) and Bu_3GeH (54%)] (Scheme 4). The structure of (**21**) was also confirmed using X-ray crystallography (Fig. 2). The cyclisation of the intermediate aryl radicals derived from (**17**) at both 2-C and 5-C, and from (**18**) at 2-C, is in contrast to the cyclisation of alkyl radicals which only give cyclisation at 5-C.[2] The considerably higher reactivity of aryl radical as compared to alkyl radicals is likely to be the dominant factor in the difference.

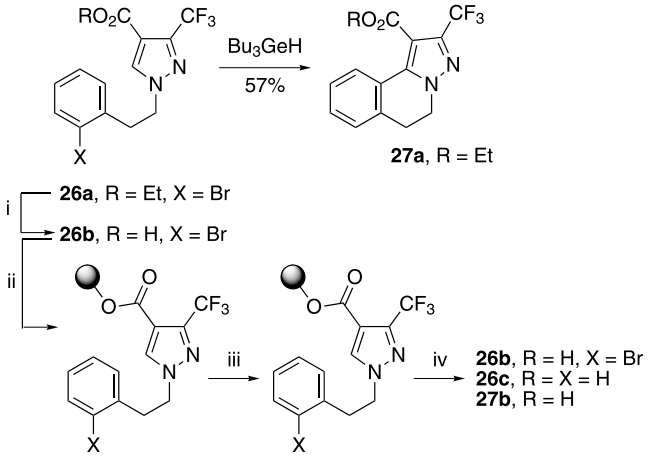
In the radical reactions of the other azoles, the indole (**22**) and the pyrrole (**24**) radical precursors were cyclised in good yields using Bu_3GeH to give methyl 5,6-dihydro-indolo[2,1-*a*]isoquinoline-12-carboxylate (**23**) (68%) and ethyl 5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (**25**) (82%), respectively (Scheme 5). The pyrazole precursor (**26a**) was also cyclised in good yield using Bu_3GeH to give ethyl 2-(trifluoromethyl)-5,6-dihydro-pyrazolo-[5,1-*a*]isoquinoline-1-carboxylate (**27a**) with no other products (57%) (Scheme 6).

The overall mechanism of the radical cyclisations is shown in Scheme 2. Formally the mechanisms of these radical reactions are intramolecular aromatic homolytic substitutions, i.e. hydrogen (H·) substituted by the cyclising aryl radicals (**9**) via intermediate aromatic π-radicals (**10**). Related Bu_3SnH and AIBN mediated 'oxidative' cyclisations have also been reported for cyclisations onto arenes by alkyl, vinyl and aryl and heteroaryl radicals. While previous studies have centred on the use of Bu_3SnH as the radical generating reagent, we suggest that similar mechanisms apply for the cyclisations using Bu_3GeH or TTMSS. The mechanism has been an area of debate and we refer readers to our recent publication[21] and a recent review[22] which have extensive discussion. Both publications contain full lists of relevant references.

The pyrazole radical precursor (**26a**) was also used for initial solid phase studies. The ester (**26a**) was hydrolysed to the corresponding carboxylic acid (**26b**) and attached by standard procedures to Wang resin. Cyclisation using standard radical conditions but over a longer time, followed



Scheme 5.



Scheme 6. (i) NaOH, EtOH, reflux, 8 h, 97% (**26b**); (ii) Wang resin (swollen in DCM), DMF, DMAP. DIC, 48 h; (iii) Bu_3GeH or TTMSS, AIBN, toluene, reflux, 30 h; (iv) TFA, DCM (9:1).

by cleavage from the resin with TFA, yielded a mixture of products. The use of Bu_3GeH gave (**27b**) (20%) and unreacted starting acid (**26b**) (70%).

The use of TTMSS gave a better yield of cyclised pyrazole (**27b**) (53%) but also yielded reduced uncyclised (**26c**) (27%). Although the results were disappointing as compared to the solution phase reaction, the results do give further indication that radical chemistry can be used for solid phase synthesis.[23]

3. Experimental

3.1. General

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. Melting points were determined on an Electrothermal 9100 melting point apparatus and are uncorrected. Elemental analyses were determined on a Perkin Elmer 2400 CHN Elemental Analyser in conjunction with a Perkin Elmer AD-4 Autobalance. IR spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer on NaCl plates. ^1H (250 MHz) and ^{13}C (62.5 MHz) NMR spectra were recorded on a Bruker AC-250 spectrometer as solutions in $CDCl_3$ 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). 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.

Tributylgermanium hydride was prepared using literature procedures.[11,24]

3.1.1. 2-(2-Bromophenyl)ethyl methanesulfonate (7). Methanesulfonyl chloride (0.43 mL, 5.6 mmol) was added to a solution of 2-(bromophenyl)ethyl alcohol (0.5 mL, 3.7 mmol) and triethylamine (1.54 mL, 11.1 mmol) in toluene (30 mL) which was cooled to 0 °C. The reaction mixture was stirred at room temperature for 18 h and then extracted into water and DCM. The DCM layers were combined and dried and evaporated under reduced pressure to afford (**7**) as a pale yellow oil (1.0 g, 3.7 mmol, 99%); ν_{max}(neat) 3057, 3024, 2939, 1594, 1568, 1473, 1442, 1353, 1173, 1038, 1022, 958, 905, 858, 805, 755, 657 cm^{-1}; δ_H 2.88 (3H, s, CH_3), 3.21 (2H, t, $J=6.8$ Hz, CH_2), 4.45 (2H, t, $J=6.8$ Hz, OCH_2), 7.11–7.15 (1H, m, ArH), 7.28–7.29 (2H, m, ArH), 7.55 (1H, d, $J=8.1$ Hz, Ar-3-H); δ_C 35.86 (2-CH_2), 37.2 (CH_3), 68.5 (OCH_2), 124.4 (Ar-2-C), 127.7, 128.9, 131.5 and 132.9 (Ar-3,4,5,6-C), 135.6 (Ar-1-C); *m/z* 278 (M^+, 3), 220 (26), 182 (68), 169 (100), 103 (38), 90 (40), 77 (34%); HRMS: M^+, found: M^+, 277.9611. $C_9H_{11}BrO_3S$ requires 277.9612.

3.1.2. 1-Iodo-2-(iodomethyl)benzene (15). A solution of 1-iodo-2-(chloromethyl)benzene (10.0 g, 39.6 mmol) and sodium iodide (30.0 g, 0.20 mol) in dry acetonitrile (250 mL) was heated under reflux for 18 h. The precipitated sodium chloride was removed by filtration on a Celite® bed and the solution was evaporated under reduced pressure. The residue was triturated with diethyl ether and the solution filtered a second time. The ether solution was evaporated under reduced pressure to afford (**15**) as a dark brown oil (13.48 g, 39.2 mmol, 99%). Found: M^+, 343.8552. $C_7H_6I_2$ requires 343.8559); ν_{max}(neat) 2360, 2342, 1580, 1560, 1464, 1433, 1424, 1273, 1212, 1152, 1012, 827, 757, 644 cm^{-1}; δ_H 4.54 (2H, s, CH_2), 6.92 (1H, dd, $J=7.6$, 7.6 Hz, 5-H), 7.28 (1H, dd, $J=7.6$, 7.6 Hz, 4-H), 7.47 (1H, d, $J=7.6$ Hz, 3-H), 7.80 (1H, d, $J=7.6$ Hz, 6-H); δ_C 12.2 (CH_2), 99.7 (1-C), 129.3, 129.6 and 129.8 (3,4,5-C), 140.23 (6-C), 141.4 (2-C); *m/z* 344 (MH^+, 5), 254 (12), 217 (100), 90 (47%).

3.2. General procedure for alkylation

The azole was added slowly to a suspension of NaH (1.5 equiv) in dry DMF (40 mL). The mixture was stirred and heated at 80 °C for 1 h. A solution of the alkylating

agent (1.5 equiv) in DMF (10 mL) was added drop wise to the reaction mixture which was heated at 80 °C for a further 12 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.

3.2.1. Methyl 1[(2-iodophenyl)methyl]-1*H*-imidazole-4-carboxylate (16). Colourless oil (43%); ν_{max}(neat)/cm^{-1} 2947, 1718, 1545, 1437, 1380, 1224, 1204, 1119, 1014, 765, 742, 660; δ_H 3.88 (3H, s, CH_3), 5.20 (2H, s, CH_2), 7.02 (1H, dd, J=7.6, 1.2 Hz, Ar-6-H), 7.07 (1H, ddd, J=7.6, 7.6, 1.2 Hz, Ar-4-H), 7.36 (1H, ddd, J=7.6, 7.6, 1.2 Hz, Ar-5-H), 7.59 (1H, s, 2- or 5-H), 7.60 (1H, s, 2- or 5-H), 7.89 (1H, dd, J=7.6, 1.2 Hz, Ar-3-H); δ_C 51.7 (CH_3), 55.86 (CH_2), 98.6 (Ar-2-C), 125.4, 129.1, 129.2 and 130.5 (5-C and Ar-4,5,6-C), 134.1 (4-C), 137.4 (Ar-1-C), 138.4 and 140.2 (2-C and Ar-3-C), 163.2 (C=O); *m/z* 342 (M^+, 27), 311 (12), 284 (13), 217 (100), 183 (46), 121 (15), 90 (43%); HRMS: found: M^+, 341.9860. $C_{12}H_{11}IN_2O_2$ requires 341.9865).

3.2.2. Methyl 1-[2-(2-bromophenyl)ethyl]-1*H*-imidazole-4-carboxylate (17) and methyl 1-[2-(2-bromophenyl)-ethyl]-1*H*-imidazole-5 carboxylate (18). (**17**), pale yellow oil (50%), ν_{max}(neat) 2948, 1724, 1547, 1472, 1439, 1382, 1225, 1197, 1120, 1029, 997, 757, 660 cm^{-1}; δ_H 3.10 (2H, t, J=7.2 Hz, CH_2), 3.79 (3H, s, OCH_3), 4.16 (2H, t, J=7.2 Hz, NCH_2), 6.88 (1H, dd, J=7.2, 1.6 Hz, Ar-6-H), 7.04 (1H, ddd, J=7.6, 7.6, 1.6 Hz, Ar-4- or 5-H), 7.11 (1H, ddd, J=7.6, 7.6, 1.6 Hz, Ar-4- or 5-H), 7.24 (1H, s, 5-H), 7.47–7.50 (2H, m, imidazole 2-H and Ar-3-H); δ_C 37.04 (CH_2), 45.95 (NCH_2), 50.61 (OCH_3), 123.16 (Ar-2-C), 124.11, 126.98, 128.14, 129.97 and 132.18 (5-C and Ar-3,4,5,6-C), 132.84 and 134.93 (4-C and Ar-1-C), 136.89 (imidazole 2-C), 162.19 (C=O); *m/z* 309 (MH^+, 1), 229 (34), 197 (95), 169 (52), 115 (53), 108 (100), 89 (68), 77 (69), 53 (77%). HRMS: found: M^+, 308.0157. $C_{13}H_{13}BrN_2O_2$ requires 308.0160. Further elution yielded the other regioisomer (**18**) as a colourless crystalline powder (48%), mp 92.0–95.9 °C. (Found: C, 50.29; H, 4.05; N, 9.25. $C_{13}H_{13}BrN_2O_2$ requires C, 50.50; H, 4.24; N, 9.06%); ν_{max}(KBr) 3079, 1715, 1539, 1475, 1437, 1362, 1236, 1162, 1108, 1025, 947, 867, 761, 660 cm^{-1}; δ_H 3.22 (2H, t, J=7.0 Hz, CH_2), 3.89 (3H, s, OCH_3), 4.55 (2H, t, J=7.0 Hz, NCH_2), 6.98 (1H, d, J=7.4 Hz, Ar 6-H), 7.10 (1H, ddd, J=7.4, 7.4, 1.9 Hz, Ar-4- or 5-H), 7.17 (1H, ddd, J=7.4, 7.4, 1.9 Hz, Ar-4- or 5-H), 7.28 (1H, s, 4-H), 7.56 (1H, d, J=7.4 Hz, Ar-3-H), 7.73 (1H, s, 2-H); δ_C 37.7 (CH_2), 46.4 (NCH_2), 51.5 (OCH_3), 122.1 (5-C), 124.4 (Ar-2-C), 127.8, 128.7, 131.1 and 133.0 (Ar-3,4,5,6-C), 136.8 (Ar-1-C), 138.0 (4-C), 142.1 (2-C), 160.7 (C=O); *m/z* 309 (MH^+, 1), 277 (2), 229 (100), 197 (15), 182 (8), 169 (25), 103 (18), 89 (13), 77 (29%); HRMS: found: MH^+, 309.0239. $C_{13}H_{13}BrN_2O_2$ requires 309.0238).

3.2.3. Methyl 1-[2-(2-bromophenyl)ethyl]-1*H*-indole-3-carboxylate (22). Colourless crystals (40%), mp 111.7–112.8 °C. (Found: C, 60.84; H, 4.27; N, 3.80. requires C, 60.35; H, 4.50; N, 3.91%); ν_{max}(KBr) 2946, 1696, 1534, 1470, 1442, 1267, 1224, 1162, 1116, 1093, 1026, 747 cm^{-1}; δ_H 3.27 (2H, t, J=7.6 Hz, CH_2), 3.90 (3H, s, OCH_3), 4.40 (2H, t, J=7.6 Hz, NCH_2), 6.93 (1H, dd, J=7.2, 2.0 Hz, 7-H or Ar-6-H), 7.08–7.16 (1H, m), 7.25–7.30 (1H, m), 7.40–7.42 (1H, m), 7.57 (1H, dd, J=7.2, 2.0 Hz, Ar-3-H), 7.70 (1H, s, 2-H), 8.15–8.19 (1H, m, indole 4-H); δ_C 37.1 (CH_2), 46.6 (NCH_2), 51.0 (OCH_3), 107.2 (3-C), 109.9 (7-C), 121.8, 121.9 and 122.8 (4,5,6-C), 124.2 (Ar-2-C), 126.6 (3a-C), 127.8, 128.9, 131.1, 133.1 and 134.2 (2-C and Ar-3,4,5,6-C), 136.4 and 136.8 (7a-C and Ar 1-C), 165.5 (C=O); *m/z* 357 (M^+, 14), 278 (8), 138 (100), 129 (10), 77 (8%); HRMS: found: M^+, 357.0371. $C_{18}H_{16}BrNO_2$ requires 357.0364.

3.2.4. Ethyl 1-[2-(2-bromophenyl)ethyl]-1*H*-pyrrole-2-carboxylate (24). Pale yellow oil (97%); ν_{max}(neat) 3109, 3056, 2979, 2869, 1694, 1567, 1531, 1470, 1415, 1325, 1241, 1171, 1101, 1077, 1027, 917, 738, 657 cm^{-1}; δ_H 1.36 (3H, t, J=7.2 Hz, CH_3), 3.20 (2H, t, J=7.2 Hz, CH_2), 4.30 (2H, q, J=7.2 Hz, OCH_2), 4.52 (2H, t, J=7.2 Hz, NCH_2), 6.02 (1H, dd, J=3.9, 2.5 Hz, 4-H), 6.59 (1H, dd, J=2.5, 1.9 Hz, 3- or 5-H), 6.95 (1H, dd, J=3.9, 1.9 Hz, 3- or 5-H), 7.02–7.16 (3H, m, Ar-4, 5,6-H), 7.53 (1H, dd, J=7.9, 1.2 Hz, Ar-3-H); δ_C 14.5 (CH_3), 37.2 (CH_2), 48.7 (NCH_2), 59.8 (OCH_2), 107.8 (3-C), 118.2 (4-C) 124.4 (Ar-2-C), 128.3 (pyrrole 5-C), 121.6, 126.7, 127.5, 131.3 and 132.7 (2-C, Ar-3,4,5,6-C), 137.7 (Ar-1-C), 161.1 (C=O); *m/z* 321 (M^+, 2), 276 (11), 242 (100), 169 (98), 152 (22), 124 (100), 103 (24), 94 (46), 77 (25%); HRMS: found: M^+, 321.0367. $C_{15}H_{16}BrNO_2$ requires 321.0364.

3.2.5. Ethyl 1-[2-(2-bromophenyl)ethyl]-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (26a). Pale yellow oil (85%); ν_{max}(neat) 3135, 3070, 2984, 1732, 1543, 1474, 1443, 1368, 1303, 1223, 1143, 1054, 847, 776, 752 cm^{-1}; δ_H 1.33 (3H, t, J=7.2 Hz, CH_3), 3.32 (2H, t, J=7.2 Hz, CH_2), 4.30 (2H, q, J=7.2 Hz, OCH_2), 4.42 (2H, t, J=7.2 Hz, NCH_2), 6.99 (1H, dd, J=7.4, 1.8 Hz, Ar-6-H), 7.12 (1H, ddd, J=7.5, 7.5, 1.2 Hz, Ar-4- or 5-H), 7.20 (1H, ddd, J=7.5, 7.5, 1.6 Hz, Ar-4- or 5-H), 7.58 (1H, dd, J=7.5, 1.2 Hz, Ar-3-H), 7.74 (1H, s, pyrazole 5-H); δ_C 14.1 (CH_3), 36.8 (CH_2), 52.4 (NCH_2), 60.9 (OCH_2), 113.0 (CF_3), 119.1, 121.7 and 124.3 (3-C, 4-C, Ar-2-C), 127.9, 129.1, 131.1, 133.2 and 135.8 (5-C, Ar-3.4.5.6-C), 136.1 (Ar-1-C), 160.8 (C=O); *m/z* 391 (M^+, 1), 345 (10), 311 (100), 283 (29), 265 (18), 182(100), 169 (48), 103 (78), 77 (51%); HRMS: found: MH^+, 391.0269. $C_{15}H_{14}BrF_3N_2O_2$ requires 391.0269.

3.3. General procedure for radical reactions

Bu_3SnH. A deoxygenated solution of Bu_3SnH (2.2 equiv) in toluene was added drop wise using a syringe pump to a solution of the radical precursor (0.25–1.0 mmol) in anhydrous toluene under reflux under an atmosphere of nitrogen. The radical initiator (AIBN) was added, followed by heating under reflux for the time indicated for each reaction. AIBN (1.2 equiv) was added portion-wise every 45 min. The solution was refluxed for a further set time. The basic products were extracted from the cooled reaction mixture with dilute hydrochloric acid and the acidic extracts washed with light petroleum to remove Bu_3Sn-residues. The acidic aqueous layer was basified with sodium carbonate and aqueous sodium hydroxide (few drops) to pH 14 and extracted with DCM. The organic extracts were dried and evaporated under reduced pressure. The residues were analysed by ^1H NMR spectroscopy and TLC. The crude residues were purified by column chromatography.

Bu_3GeH. The procedure was the same as the procedure for Bu_3SnH radical reactions except that the Bu_3GeH (1.5 equiv) was added in one portion at the beginning of the reaction instead of addition using a syringe pump.

3.3.1. Methyl 1-benzyl-1*H*-imidazole-4-carboxylate (16a). *Bu_3SnH*. Reflux 7 h, methyl 1-benzyl-1*H*-imidazole-4-carboxylate as a colourless oil (**16a**) (33%); ν_{max}(neat) 2363, 1720, 1545, 1440, 1380, 1224, 1119, 997, 713 cm^{-1}; δ_H 3.88 (3H, s, OCH_3), 5.14 (2H, s, CH_2), 7.17–7.20 (2H, m, Ar-H), 7.25–7.26 (1H, m, Ar-H), 7.37–7.41 (2H, m, Ar-H), 7.56 (1H, s, 2- or 5-H), 7.60 (1H, m, 2- or 5-H); δ_C 51.4 (CH_2), 51.73 (OCH_3), 118.6 (4-C), 125.4, 127.6, 128.8 and 129.2 (5-C and Ph-2,3,4-C), 138.1 (2-C), 142.9 (Ph-1-C), 163.2 (C=O); *m/z* 216 (M^+, 10), 185 (5), 158 (8), 128 (4), 91 (100), 77 (8), 65 (18%); HRMS: found: MH^+, 217.0976. $C_{12}H_{12}N_2O_2$ requires 217.0977.

Bu_3GeH. 10 h reflux, methyl 1-benzyl-1*H*-imidazole-4-carboxylate (56%). The TLC and ^1H NMR and IR spectra were identical to an authentic sample.

3.3.2. Methyl 5,6-dihydroimidazo[5,1-*a*]isoquinoline-1-carboxylate (20) and methyl 5,6-dihydroimidazo[2,1-*a*]-isoquinoline-2-carboxylate (19). *Bu_3SnH*. Reflux (5 h addition, 5 h further reflux), (**20**) as crystalline colourless needles (16%), mp 179.0–182.9 °C; ν_{max}(KBr) 3118, 2951, 2368, 1689, 1546, 1469, 1432, 1347, 1217, 1182, 1164, 1107, 939, 769, 655 cm^{-1}; δ_H 3.10 (2H, t, J=6.5 Hz, 6-CH_2), 3.96 (3H, s, OCH_3), 4.17 (2H, t, J=6.5 Hz, NCH_2), 7.27 (1H, dd, J=8.0, 1.0 Hz, 7-H), 7.32 (1H, ddd, J=8.0, 8.0, 1.0 Hz, 8- or 9-H), 7.38 (1H, ddd, J=8.0, 8.0, 1.0 Hz, 8- or 9-H), 7.54 (1H, s, 3-H), 8.74 (1H, dd, J=8.0, 1.0 Hz, 10-H); δ_C 29.6 (5-C), 42.5 (6-C), 51.9 (OCH_3), 125.9 (1-C), 127.6, 127.8, 128.4 and 129.1 (7,8,9,10-C), 128.2, 133.0 and 133.8 (6a,10a,10b-C), 135.5 (3-C), 164.2 (C=O); *m/z* 228 (M^+, 74), 197 (100), 170 (54), 140 (13), 115 (25%); HRMS: found: M^+, 228.0900. $C_{13}H_{12}N_2O_2$ requires 228.0900. The structure was confirmed by X-ray crystallography.

Further elution yielded (**19**) as a pale yellow oil (4%); ν_{max}(neat) 3134, 2953, 2925, 2359, 1723, 1542, 1461, 1437, 1349, 1326, 1258, 1225, 1199, 1181, 1124, 1103, 1006, 808, 777, 737, 718 cm^{-1}; δ_H 3.11 (2H, t, J=7.2 Hz, 6-CH_2), 3.84 (3H, s, OCH_3), 4.15 (2H, t, J=7.2 Hz, NCH_2), 7.17 (1H, dd, J=6.8, 2.0 Hz, 7-H), 7.23–7.30 (2H, m, 8,9-H), 7.58 (1H, s, 3-H), 8.10 (1H, dd, J=7.6, 2.0 Hz, 10-H); δ_C 27.2 (6-C), 42.7 (5-C), 50.8 (OCH_3), 123.5, 124.4, 126.7, 126.8 and 128.3 (3.7,8,9,10-C), (C), 125.1 (2-C), 127.3 and 131.7 (6a,10a-C), 144.0 (10b-C), 162.5 (C=O); *m/z* 228 (M^+, 100), 197 (92), 170 (75), 140 (12), 115 (28), 77 (10%); HRMS: found: M^+, 228.0900. $C_{13}H_{12}N_2O_2$ requires 228.0900. A considerable amount of the two products was also obtained as a mixture after chromatography and was not further separated.

Bu_3GeH. Reflux (10 h), (**20**) (38%), (**19**) (19%).

Bu_3GeH and phenylthiol. Benzenethiol (10 mol%) was added at the beginning of the reaction. Reflux (10 h), (**20**) (44%). ^1H NMR spectroscopic analysis of the crude reaction product showed the presence of starting material and traces of other unidentifiable materials. The yield of unaltered starting material was not recorded.

Tris(trimethylsilyl)silane (TTMSS). The general procedure for Bu_3SnH reactions was used except that TTMSS was used in place of Bu_3SnH. Reflux (5 h addition, 5 h further reflux), (**20**) (30%), (**19**) (30%).

3.3.3. Methyl 5,6-dihydroimidazo[2,1-*a*]isoquinoline-3-carboxylate (21). *Bu_3SnH*. Reflux (5 h addition, 7 h further reflux), colourless crystals (71%), mp 122.0–124.9 °C; ν_{max}(KBr) 2372, 1710, 1509, 1441, 1387, 1337, 1252, 1184, 1108, 1072, 980 cm^{-1}; δ_H 3.17 (2H, t, J=7.2 Hz, 6-CH_2), 3.88 (3H, s, OCH_3), 4.62 (2H, t, J=7.2 Hz, NCH_2), 7.26–7.28 (1H, m), 7.33–7.39 (2H, m), 7.83 (1H, s, 2-H), 8.07 (1H, m, 10-H); δ_C 28.1 (6-C), 42.2 (5-C), 51.5 (OCH_3), 122.1 (3-C), 126.2 (10a-C), 124.7, 127.6, 127.7 and 129.8 (7,8,9,10-C), 133.2 (6a-C), 137.9 (imidazole 2-C), 148.3 (10b-C), 161.0 (C=O); *m/z* 228 (M^+, 100), 213 (8), 197 (42), 183 (7), 169 (17), 140 (13), 128 (17), 115 (35), 84 (29%); HRMS: found: MH^+, 229.0981. ($C_{13}H_{12}N_2O_2$+H) requires 229.0977. The structure was confirmed using X-ray crystallography.

Bu_3GeH. Reflux (10 h), (54%) starting material (**18**) (20%).

3.3.4. Methyl 5,6-dihydroindolo[2,1-*a*]isoquinoline-12-carboxylate (23). *Bu_3GeH*. Clear oil (68%); ν_{max}(neat) 2947, 1698, 1530, 1468, 1455, 1404, 1282, 1224, 1188, 1154, 1110, 1022, 768, 747 cm^{-1}; δ_H 3.15 (2H, t, J=6.5 Hz, 5-CH_2), 3.99 (3H, s, OCH_3), 4.24 (2H, t, J=6.5 Hz, NCH_2), 7.25–7.40 (6H, m), 8.19 (1H, m, 11-H) and 8.53 (1H, dd, J=7.2, 1.8 Hz, 1-H); δ_C 29.7 (5-C), 40.4 (6-C), 51.1 (OCH_3), 103.0 (12-C), 109.1 (8-C), 122.0, 122.4, 122.9, 126.7, 127.7, 129.3 and 129.7 (1, 2, 3, 4, 9, 10, 11-C), 133.2, 134.8, 135.3, 138.0 and 134.0 (4a, 7a, 11a, 12a, 12b-C), 166.4 (C=O); *m/z* 277 (M^+, 100), 246 (92), 217 (38), 188 (30), 108 (14), 77 (9%); HRMS: found: M^+, 277.1104. $C_{18}H_{15}NO_2$ requires 277.1103.

3.3.5. Ethyl 5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (25). *Bu_3GeH*. Clear oil (82%); ν_{max}(neat) 2928, 1694, 1489, 1446, 1260, 1224, 1150, 1105, 1068, 749 cm^{-1}; δ_H 1.37 (3H, t, J=7.1 Hz, CH_3), 3.08 (2H, t, J=6.8 Hz, CH_2), 4.31 (2H, q, J=7.1 Hz, OCH_2), 4.64 (2H, t, J=6.8 Hz, NCH_2), 6.52 (1H, d, J=4.0 Hz, 1-H), 7.02 (1H, d, J=4.0 Hz, 2-H), 7.20–7.28 (3H, m, 7,8,9-H), 7.56 (1H, d, J=7.6 Hz, Ar 10-H); δ_C 14.5 (CH_3), 28.9 (6-CH_2), 42.2 (NCH_2), 59.8 (OCH_2), 104.4 (1-C), 118.2 (2-C), 113.7 and 122.1 (3,10b-C), 123.6, 127.1, 127.4 and 128.4 (7,8,9,10-C), 131.7 (10a-C), 136.0 (6a-C), 161.4 (C=O); *m/z* 241 (M^+, 100), 213 (39), 196 (28), 168 (32), 139 (11), 115 (11), 77 (3%); HRMS: found: M^+, 241.1103. $C_{15}H_{15}NO_2$ requires 241.1103.

3.3.6. Ethyl 2-(trifluoromethyl)-5,6-dihydropyrazolo[5,1-*a*]isoquinoline-1-carboxylate (27a). *Bu_3GeH*. Colourless oil (57%); ν_{max}(neat) 2928, 2369, 1717, 1473, 1199, 1142, 1042 cm^{-1}; δ_H 1.39 (3H, t, J=7.2 Hz, CH_3), 3.19 (2H, t, J=6.8 Hz, 6-CH_2), 4.36–4.42 (4H, m, 5-CH_2 and OCH_2), 7.30–7.40 (3H, m, ArH), 8.30–8.32 (1H, m, 10-H); δ_C 13.8 (CH_3), 29.3 (6-CH_2), 47.1 (5-CH_2), 61.4 (OCH_2), 109.0 (1-C), 119.5 (CF_3), 122.1 (2-C), 125.0 and

133.3 (2,6a,10a-C), 127.6, 127.8, 128.1 and 130.2 (7,8,9,10-C), 141.5 (10b-C), 162.6 (C=O); *m/z* 310 (M^+, 43), 282 (10), 265 (100), 238 (14), 140 (5), 104(38), 91 (10), 77 (6%); HRMS: found: M^+, 310.0926. $C_{15}H_{13}F_3N_2O_2$ requires 310.0929.

3.4. Solid phase studies

3.4.1. 1-[2-(2-bromophenyl)ethyl]-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid (26b). Ethyl 1-[2-(2-bromophenyl)ethyl]-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (**26a**) (1.20 g, 3.1 mmol) was dissolved in ethanol (10 mL) followed by addition of aqueous sodium hydroxide (2 M, 15 mL). The reaction mixture was heated under reflux for 8 h and the progress monitored by TLC. The reaction mixture was cooled and washed with ethyl acetate. The aqueous layer was acidified to pH 3 with hydrochloric acid and extracted with DCM. The organic layers were washed with water, dried and evaporated under reduced pressure to afford (**26b**) as light yellow crystals (1.10 g, 3.0 mmol, 97%); ν_{max}(KBr) 3300, 2953, 2683, 2600, 1697, 1547, 1499, 1438, 1309, 1236, 1191, 1145, 1048, 945, 754 cm^{-1}; δ_H 3.34 (2H, t, J=7.2 Hz, 6-CH_2), 4.45 (2H, t, J=7.2 Hz, NCH_2), 6.97 (1H, dd, J=7.6, 1.6 Hz, Ar 6-H), 7.15 (1H, ddd, J=7.6, 7.6, 1.6 Hz, Ar 4- or 5-H), 7.20 (1H, ddd, J=7.6, 7.6, 1.6 Hz, Ar 4- or 5-H), 7.58 (1H, dd, J=7.6, 1.6 Hz, Ar 3-H), 7.75 (1H, s, pyrazole 5-H); δ_C 36.7 (CH_2), 52.7 (NCH_2), 111.6 (CF_3), 118.8 (pyrazole 4-C), 121.5 (pyrazole 3-C), 124.2 (Ar-2-C), 127.9, 129.2, 131.1, 133.2 and 136.8 (5-C, Ar-3,4,5,6-C), 135.9 (Ar 1-C),165.6 (C=O); *m/z* 283 (95), 182 (100), 169 (60), 103 (62), 90 (52), 77 (45), 69 (32%); HRMS: found: MH^+, 362.9956. $C_{13}H_{10}BrF_3N_2O_2$ requires 362.9961.

3.4.2. Synthesis of solid-supported 1-[2-(2-bromophenyl)-ethyl]-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (28). DCM (8.0 mL) was added to a portion of Wang resin (0.40 g, 0.7 mmol). The resin was allowed to swell for 30 min under an atmosphere of nitrogen. (**26b**) (0.62 g, 1.7 mmol) in DMF (8.0 mL), DMAP (0.25 g, 2.1 mmol) and diisopropylcarbodiimide (DIC) (0.64 mL, 4.1 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 mL each). The resin was dried at 40 °C under vacuum for 24 h. The coupling reaction was repeated with equimolar reagents. ν_{max}(KBr) 3458, 3026, 2922, 2370, 1723, 1602, 1508, 1370, 1290, 1211, 1138, 1037, 815, 747, 693 cm^{-1}.

3.4.3. Radical cyclisations of solid-supported 1-[2-(2-bromo-phenyl)ethyl]-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (28). *Use of Bu_3GeH.* Bu_3GeH (0.55 mL, 2.1 mmol) was added to the solid supported pyrazole (**28**) (140 mg, 0.11 mmol) in toluene (10 mL) under reflux. AIBN (0.25 g, 1.5 mmol) was added to the refluxing reaction mixture at equal intervals of 1 h. The reaction mixture was heated under reflux for 30 h. The reaction mixture was cooled to room temperature, filtered and washed with toluene, DCM and MeOH. The resin was dried at 40 °C under vacuum for 24 h. The products were cleaved from the resin using TFA/DCM (9:1) and a crystalline material was recovered (44 mg). LC-MS analysis of the cleaved sample from the resin showed a mixture of the cyclised adduct 2-(trifluoromethyl)-5,6-dihydropyrazolo[5,1-*a*]isoquinoline-1-carboxylic acid (**27b**) and the starting material (**26b**). The ^1H NMR spectrum of the cleaved sample showed a mixture the cyclised product (**27b**) (20%) and the unreacted starting material (**26b**) (70%). The separation of these products by column chromatography was unsuccessful due to co-elution and therefore products were not fully characterised.

Use of TTMSS. The above procedure was used with TTMSS (1.3 mL, 4.2 mmol), AIBN (0.20 g, 1.2 mmol) and resin-bound pyrazole moiety (**27b**) (111 mg, 0.09 mmol). Cleavage from the resin yielded a brown oil (30 mg) which LC-MS analysis confirmed a mixture of the cyclised adduct (**27b**) and the reduced product (**26c**). ^1H NMR spectral analysis showed a mixture of (**27b**) (53%) and the reduced product (**26c**) (27%) with no other products.

(**27b**): δ_H 3.20 (2H, t, J=6.8 Hz, 6-CH_2), 4.40 (2H, t, J=6.8 Hz, 5-CH_2), 7.16–7.34 (3H, m, ArH), 8.33–8.35 (1H, m, 10-H); δ_C 29.35 (6-CH_2), 47.25 (5-CH_2), 108.0 (1-C), 119.2 (CF_3), 121.9, 124.7 and 133.7 (2,6a,10a-C), 127.7, 128.1, 128.4 and 130.5 (7,8,9,10-C), 142.7 (pyrazole 10b-C), 166.9 (C=O).

(**26c**): δ_H 3.20 (2H, t, J=6.8 Hz, CH_2), 4.40 (2H, m, NCH_2), 7.08 (1H, d, J=7.6 Hz, ArH), 7.16–7.34 (1H, m, ArH), 7.39–7.42 (3H, m, ArH), 7.75 (1H, s, 5-H); δ_C 36.2 (CH_2), 54.8 (NCH_2), 111.7 (CF_3), 118.9 (4-C), 121.6 (3-C), 127.3 (PhCH), 128.6 (PhCH), 128.9 (PhCH), 133.6 (Ph-1-C), 136.7 (5-C), 165.4 (C=O).

3.5. X-ray crystallography

Both sets of data for methyl 5,6-dihydroimidazo[5,1-*a*]-isoquinoline-1-carboxylate (**20**) and methyl 5,6-dihydroimidazo[2,1-*a*]isoquinoline-3-carboxylate (**21**) were collected on a Bruker SMART 1000 diffractometer at 150(2) K using Mo Kα radiation. The structures were solved by direct methods and refined by full-matrix least-squares on F^2 using all the data. All non-hydrogen atoms were refined with anisotropic atomic displacement parameters and hydrogen atoms were included at calculated positions using a riding model. Data collection and

Table 1. Crystal data for heterocycles **20** and **21**

Identification code	**20**	**21**
Empirical formula	$C_{13}H_{12}N_2O_2$	$C_{13}H_{12}N_2O_2$
Formula weight	228.25	228.25
Crystal system	Triclinic	Monoclinic
a (Å)	7.077(3)	11.9248(13)
b (Å)	7.830(3)	11.9615(13)
c (Å)	9.856(4)	7.6375(8)
α (°)	100.317(6)	90
β (°)	92.468(6)	98.895(2)
γ (°)	93.062(6)	90
U (Å^3)	535.7(3)	1076.3(2)
Z	2	4
Space group	$P\bar{1}$	$P2_1/c$
μ (mm^{-1})	0.098	0.097
Refl. collected	4162	5967
Unique refl. (R_{int})	2332 (0.0314)	1861 (0.0292)
$R1$, $wR2$ [$I>2\sigma(I)$]	0.0701, 0.2164	0.0363, 0.0924
$R1$, $wR2$ (all data)	0.0829, 0.2253	0.0475, 0.0985

refinement parameters are summarized in Table 1. All programs used in structure solution and refinement are included in the SHELXTL package.[25] Crystallographic data (excluding structure factors) for the structures in this paper have been deposited at the Cambridge Crystallographic Data Centre supplementary publication numbers, (**20**) (CCDC 244723) and (**21**) (CCDC 244724).

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