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# Radical dearomatising spirocyclisations onto the C-2 position of benzofuran and indole

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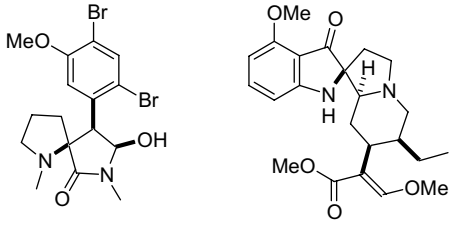
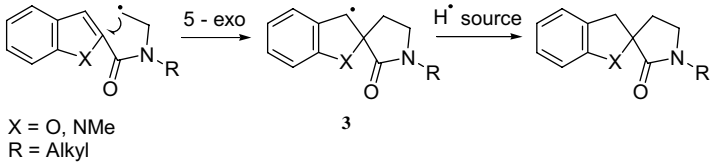
**Abstract**—Spirolactams were obtained via an intramolecular radical *ipso*-type spirocyclisation in benzofuran and indole systems. Alkyl, vinyl and aryl radicals, tethered at the C-2 position of the heterocycle underwent radical cyclisation to produce novel tricyclic partially dearomatised heterocycles in moderate yields. Fragmentation of the furan ring was observed subsequent to spirocyclisation of a vinyl radical onto a benzofuran.


A spirocyclic fragment consisting of two fused five-membered saturated heterocycles appears in many naturally occurring compounds. Marine amathaspiramides[1] **1** and pseudoindoxyl alkaloids[2] **2** of plant origin are potent antiviral agents that display promising anticancer properties. Due to their biological activity and complex structure, spirocycles represent challenging synthetic targets thus prompting development of better ways for such quaternary centre generation. In this context we decided to explore radical dearomatising spirocyclisations onto benzofuran and indole nuclei as outlined in Scheme 1.

Radical *ipso*-type substitution onto aryl rings is well precedented and usually proceeds with rearomatisation.[3] One of the first examples of a radical spirocyclisation, which resulted in a dearomatised spirocycle was reported by Zard and co-workers.[4] Parsons et al.[5] have




Amathaspiramide A **1** Mytraginine pseudoindoxyl **2**




**Scheme 1.**

*Keywords*: Alkyl radical; Vinyl radical; Aryl radical; Spirocyclisation; Benzofuran; Indole; Spirocycle.
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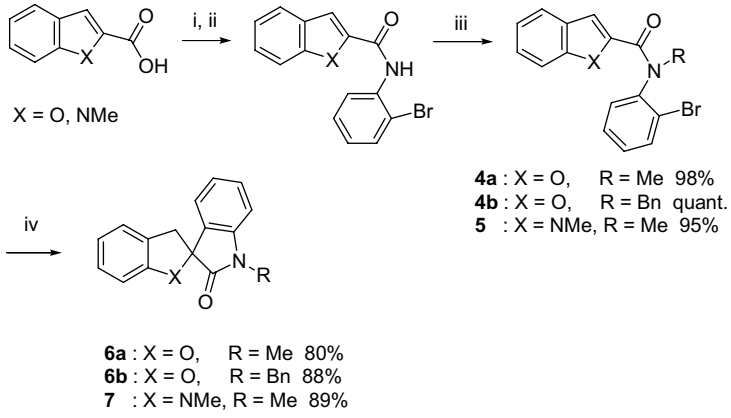
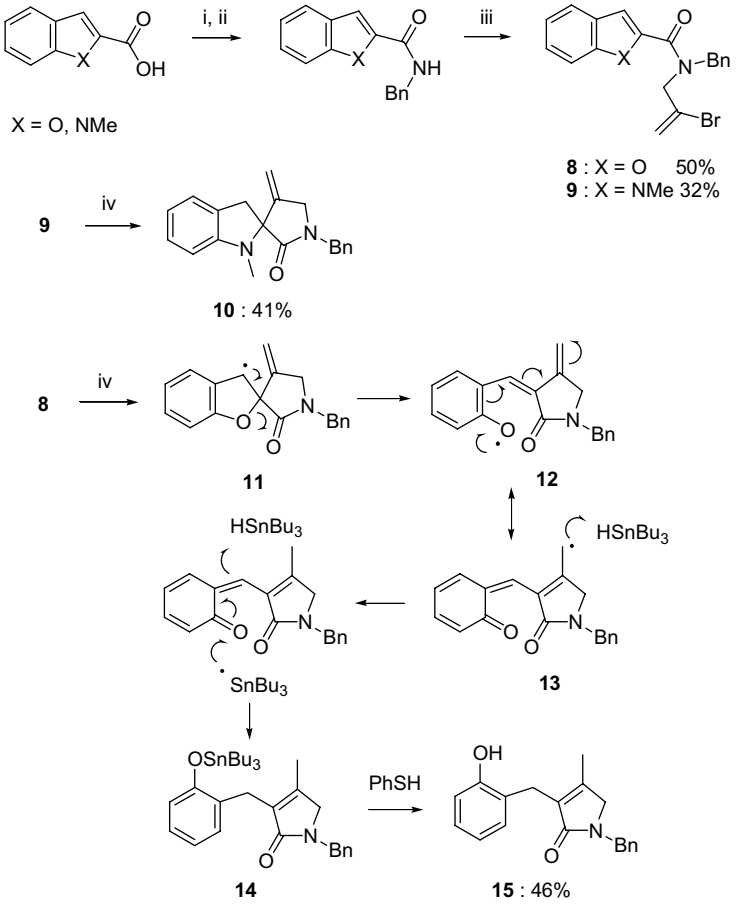
demonstrated vinyl radical *ipso*-type substitutions on furan, which proceeded with subsequent fragmentation of the dearomatised heterocycle, and this strategy was applied in synthesis by Pattenden.[6] Jones et al. have studied aryl radical spirocyclisations onto pyrroles[7] and the C-3 position of indoles,[8] which produced spirocycles in moderate to good yields. However no systematic study of the radical *ipso*-type spirocyclisation on heterocycles generating novel partially or fully dearomatised spirocycles has been presented to date. It is our aim to establish the scope and limitation of such a process and the initial findings on additions of aryl, vinyl and alkyl radicals onto the C-2 position of benzofuran and indole are presented in this letter.

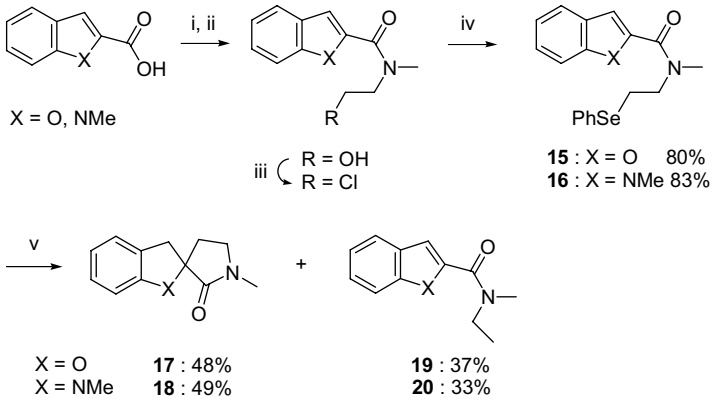
Our choice of the models for the initial investigation was based on the prediction that the intermediate radical **3** (Scheme 1) will receive extra stabilisation via




**Scheme 2.** Reagents: (i) $(COCl)_2$, DCM; (ii) 2-bromoaniline, $Et_3N$, DCM 92–98% for two steps; (iii) NaH, DMF, then MeI or BnBr; (iv) $Bu_3SnH$, AIBN, benzene, reflux, then PhSH.




**Scheme 3.** Reagents: (i) $(COCl)_2$, DCM; (ii) benzylamine, $Et_3N$, DCM, quant. for two steps; (iii) NaH, DMF, then 2,3-dibromo-1-propene; (iv) $Bu_3SnH$, AIBN, benzene, reflux, then PhSH.




**Scheme 4.** Reagents: (i) $(COCl)_2$, DCM; (ii) 2-(methylamino)ethanol, $Et_3N$, DCM, quant. for two steps; (iii) MsCl, $Et_3N$, DCM, 80–85%; (iv) $(PhSe)_2$, $NaBH_4$, EtOH, reflux (see Ref. 11); (v) $Bu_3SnH$, AIBN, benzene, reflux.

conjugation with the adjacent aryl ring and will not undergo unwanted fragmentation prior to the hydrogen transfer step.

At first we investigated the cyclisations of the higher energy aryl radicals. Radical cyclisation precursors **4a**,**b** and **5** were prepared as shown in Scheme 2. To our delight, when these were subjected to standard radical cyclisation conditions,[9] the spirocycles **6a**,**b** and **7** were formed in excellent yields with only traces of reduced materials detectable by the $^1H$ NMR of the crude reaction mixture (Scheme 2).

Next, we set out to investigate vinyl radical additions and the cyclisation precursors **8** and **9** were prepared via alkylation of secondary benzyl amides with 2,3-dibromo-1-propene as indicated in Scheme 3.

Under the radical cyclisation conditions, the indole derivative **9** was converted into the spirocycle **10** while the benzofuran derivative **8** underwent spirocyclisation followed by a reductive fragmentation to **15**. Our mechanistic proposal for the rearrangement is outlined in Scheme 3. The spirocyclic radical **11** undergoes fragmentation with formation of a more stable phenoxy radical **12**. Reduction of the quinone resonance form **13** by tributyltin hydride results in the oxystannane **14**, which is hydrolysed to the phenol **15** on work up. The different outcome of the two reactions is mostly attributed to the greater stabilisation of the intermediate spirocyclic radical by the lone pair of nitrogen in the indole case.

The yields of isolated radical cyclisation products were lower in this case compared to the aryl radical additions, however no reduced starting materials were observed in the crude NMR spectra.

Finally, we moved on to investigate the alkyl radical additions. Selenides **15** and **16** proved to be the best models as the iodides and bromides were highly unstable due to the presence of a nucleophilic amide. The cyclisation precursors were prepared via the sequence shown in Scheme 4. When subjected to the radical conditions both selenides underwent spirocyclisation forming spirocycles **17** and **18**, respectively. The yields of isolated spirocycles[10] were similar to the vinyl radical addition cases but significant amounts of reduced starting materials **19** and **20** were isolated in this case.

In summary, we have investigated alkyl, vinyl and aryl radical dearomatising spirocyclisations onto the C-2 position of benzofuran and indole. Additions of tethered aryl radicals proceeded in near quantitative yields while vinyl and alkyl radical cyclisations provided novel spirocycles in moderate yields. Addition of a vinyl radical to benzofuran proceeded with fragmentation due to instability of the intermediate radical.

## Acknowledgements

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9. The typical radical cyclisation conditions as in the experimental procedure for spirocycle (**6a**). To a stirred solution of aryl bromide (**4a**) (200 mg, 0.6 mmol) and AIBN (12 mg, 0.07 mmol) in degassed benzene (25 mL) at reflux was added a solution of tributyltin hydride (178 μL, 0.66 mmol) and AIBN (6 mg, 0.04 mmol) in degassed benzene (10 mL) over a period of 4 h via a syringe pump. After 9 h of further reflux the solvent was removed in vacuo, thiophenol (62 μL, 0.66 mmol) was added and the resulting mixture was purified by column chromatography (P.E.30-40:EtOAc;2:1) to give the product (121 mg, 80%) as a pale yellow oil. $\lambda_{max}$ (film) $cm^{-1}$ 1653; $\delta_H$ (500 MHz, $CDCl_3$) 7.42 (1H, t, *J* 7.5), 7.34 (1H, d, *J* 7.0), 7.31 (1H, d, *J* 7.5), 7.24 (1H, d, *J* 7.0), 7.11 (1H, t, *J* 7.0), 7.01 (1H, dd, *J* 7.5, 7.0), 6.92 (2H, m), 3.78 (1H, d, *J* 15.5), 3.50 (1H, d, *J* 15.5), 3.30 (3H, s); $\delta_C$ (100 MHz, $CDCl_3$) 174.9, 158.9, 143.5, 133.9, 130.6, 129.9, 129.6, 128.9, 126.6, 124.9, 123.7, 122.3, 109.9, 85.1, 39.1, 26.4; *m/z* ($CI^+$) 252 ($MH^+$, 59%), 234 (12), 224 (8); HRMS found 252.1031 ($MH^+$); $C_{16}H_{14}NO_2$ requires 252.1025.
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