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Aryl radical cyclisation onto pyrroles: a divergent synthesis of spiropyrrolidinyloxindoles and pyrroloquinolines

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Abstract

The regiochemistry of cyclisation of an aryl radical on to a pyrrole is shown to depend on the *N*-substituent of the pyrrole. Changing this substituent allows the selective synthesis of either the spiropyrrolidinyloxindole or the pyrrolo[3,2-*c*]quinoline skeleton. © 2000 Elsevier Science Ltd. All rights reserved.

Aryl radical cyclisation reactions have become an important tool in the development of modern heterocyclic chemistry and the synthesis of natural products.[1] The addition of aryl radicals to multiple bonds is well documented in the literature.[2] The intramolecular addition of aryl radicals to benzene[3] and pyrrole[4] rings followed by re-aromatisation has also been reported. Our interest in the study of aryl radical cyclisations and their application to the synthesis of natural products prompted us to explore cyclisations of the radical precursors with the general structure shown in Scheme 1.

Depending on the position at which the aryl radical adds onto the pyrrole nucleus, alkaloids with the spiropyrrolidinyloxindole or pyrrolo[3,2-*c*]quinoline nucleus could be accessed. These ring systems are found in a wide range of biologically-active alkaloids such as spirotryprostatine A and B,[5] (+)-elacomine,[6] (−)-horsfiline,[7] potent gastric (H/K) ATPase inhibitors,[8] martinelline and martinellic acid[9] (Fig. 1).

In this letter, we present the results of our further studies[10] into the addition of aryl radicals to a pyrrole in which the linking chain is attached to the C-3 position. The difficulties found in the purification of some of the products described in our previous work and the interest in targets such as the natural products shown in Fig. 1, led us to develop our synthetic sequence with the methoxy-substituted aromatic system. Furthermore, substitution on the pyrrole nitrogen was explored in order to give substrates with differing electronic/steric properties. Our

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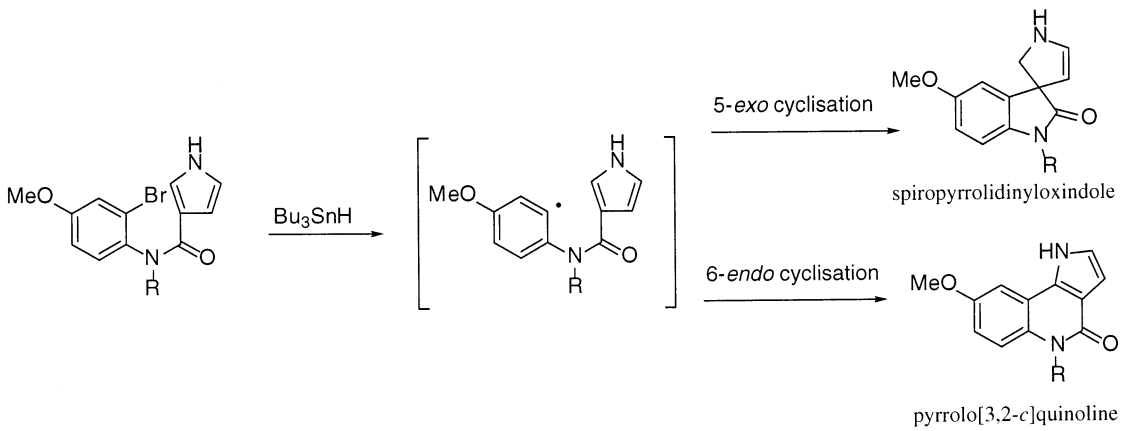


Scheme 1.

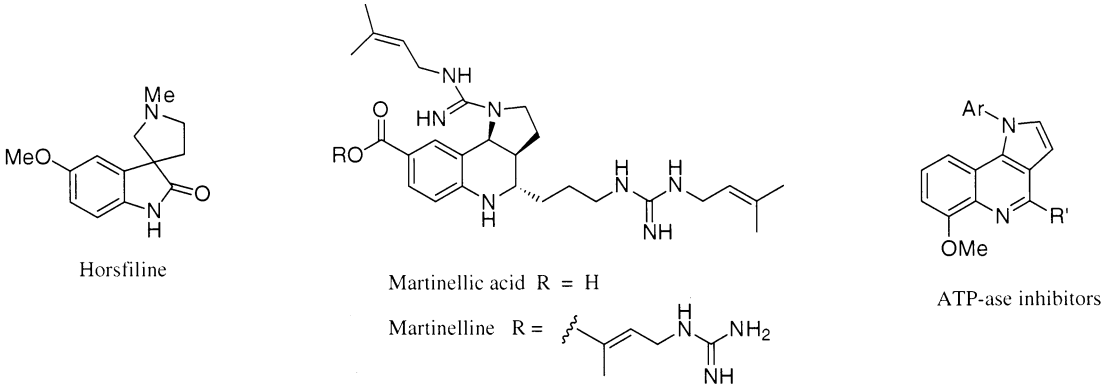
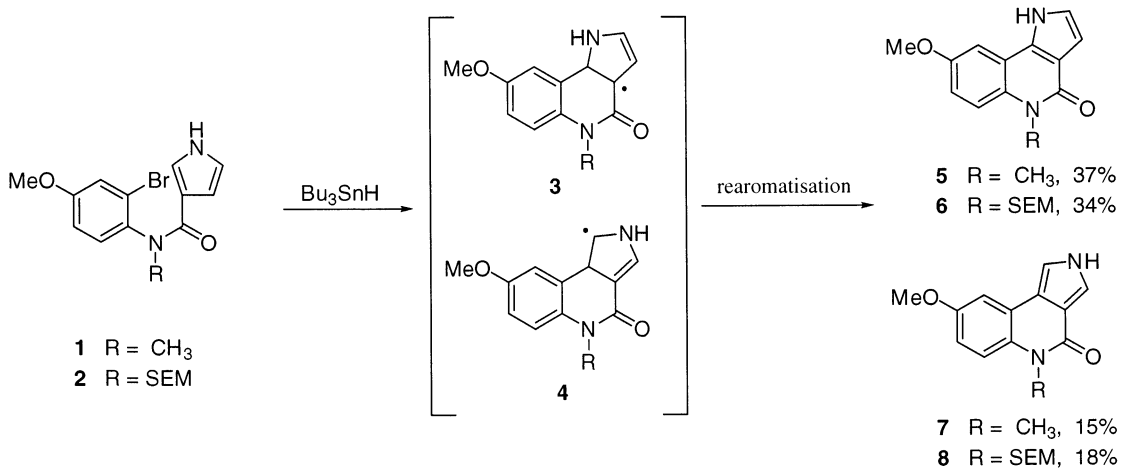


Figure 1.

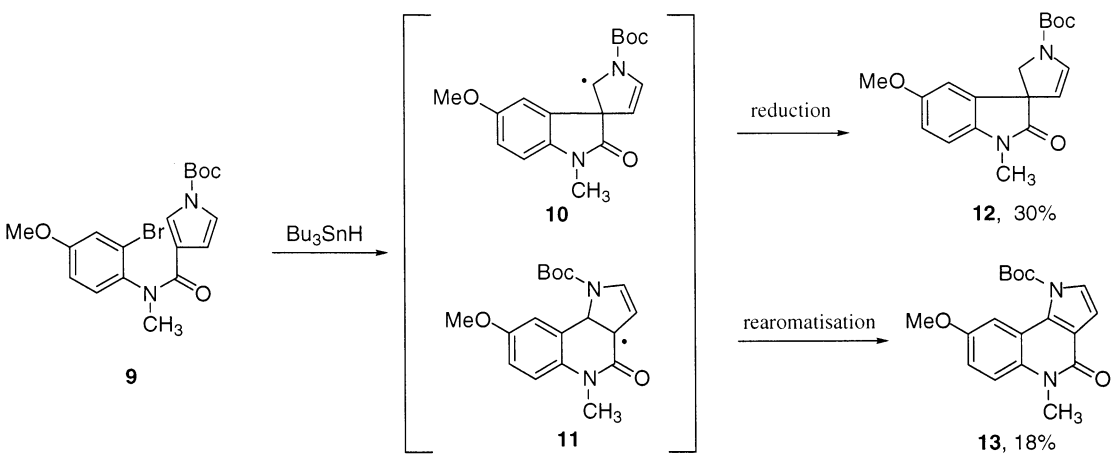
synthesis of the radical cyclisation precursors (**1**, **2**, **9**, **14** and **17**) will be presented in a full paper.[10b]

The radical cyclisation precursors were all treated with tri-*n*-butyltin hydride (0.02 M) using azobisisobutyronitrile (AIBN) as the initiator in refluxing toluene for 1 hour. Cyclisation of the *N*-unsubstituted pyrroles **1** and **2** (Scheme 2) gave a mixture (ca. 2:1) of regioisomeric pyrroloquinolines in 52% yield. The 6-*endo* products **5** and **6** were obtained as the major products in 37 and 34% yield, together with the 6-*exo* products **7** and **8** (15 and 18% yield). The structures of these isomeric pyrroloquinolones were determined by proton NMR chemical shifts and comparison with those for a previously synthesised pyrrolo[3,4-*c*]quinoline, prepared by an unambiguous route.[10b] Oxidation during Bu_3SnH mediated radical reactions has been well documented.[11] No products arising from 5-*exo* cyclisation were detected and in both examples it is interesting to note that the major product, the pyrrolo[3,2-*c*]quinoline skeleton, arises from the more stable radical intermediate **3**.



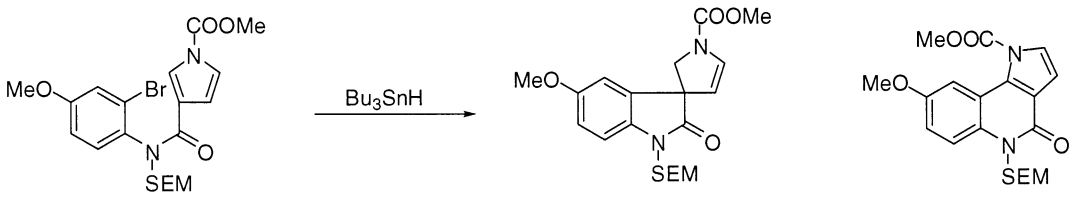
Scheme 2.

In contrast to this result, cyclisation of the *N*-*t*-BOC derivative **9** gave the spiropyrrolidinyloxindole **12** resulting from 5-*exo* cyclisation (via radical **10**) in 30% yield and the pyrrolo[3,2-*c*]quinoline **13** arising by 6-*endo* cyclisation in 18% yield (via radical **11**) (Scheme 3).



Scheme 3.

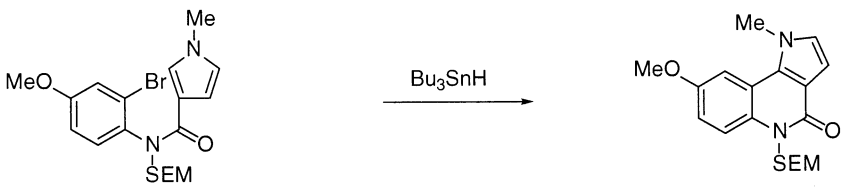
In order to investigate whether the regiochemistry of this radical cyclisation is caused by the steric effect of the bulky *N*-*t*-BOC group, we decided to prepare and cyclise a radical precursor in which the nitrogen was substituted with a methoxycarbonyl group. The cyclisation of **14** under the standard radical conditions gave, as before, two products, **15** (32% yield) and **16** (15% yield) with the spiropyrrolidinyloxindole again being the major product (Scheme 4). These results seem to indicate that the change in regiochemistry of cyclisation observed in these latter two examples is caused by electronic rather than steric factors and it is the electron-withdrawing effect of the carbamate group that is important.



14 **15**, 32% **16**, 15%

Scheme 4.

Finally, we examined the effect that an electron-donating group, on the pyrrole nitrogen, can have on the radical cyclisation reaction. From the crude reaction mixture of the reaction of *N*-methylpyrrole **17** with tri-*n*-butyltin hydride, only one product could be isolated in 43% yield (Scheme 5). This proved to be the pyrrolo[3,2-*c*]quinoline **18**.



17 **18**, 43%

Scheme 5.

In summary, we have shown that the regiochemistry of cyclisation of aryl radicals onto pyrroles attached through an amide at the 3-position is governed by the nature of the *N*-substituent on the pyrrole. Pyrroles substituted with an electron-donating group (methyl) on nitrogen give exclusively the pyrrolo[3,2-*c*]quinoline product arising from 6-*endo* cyclisation. On the other hand, pyrroles substituted on nitrogen with an electron-withdrawing group (carbamate), give rise to the spiropyrrolodinyloxindole as the major product via a 5-*exo* cyclisation. According to these observations, changing the substituent on the pyrrole will allow controlled formation of either the spiropyrrolidinyloxindole or pyrrolo[3,2-*c*]quinoline nucleus from a common intermediate.

Acknowledgements

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