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# Intermolecular reactions of indol-2-yl radicals: a new route to 2-substituted indoles

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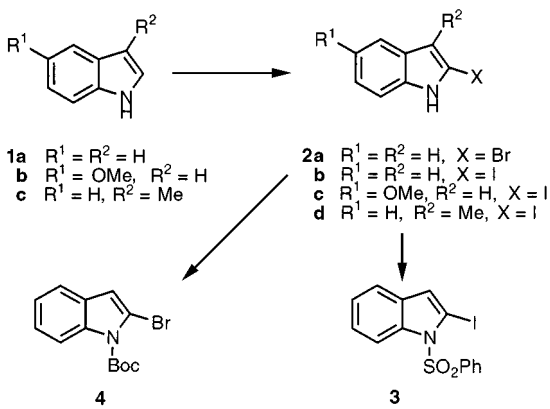
**The generation of indol-2-yl radicals and their addition to a variety of radical acceptors to prepare 2-substituted indoles is presented.**

The intermolecular reaction of alkyl radicals has been extensively studied and forms a useful method for the creation of new carbon–carbon bonds under mild conditions[1] and with the potential for stereocontrol.[2] Exploration of the more reactive aryl radicals has been centred almost exclusively on their intramolecular reactions and this has provided a powerful approach to a variety of polycyclic compounds.[3] Radicals derived from heteroaromatic systems have been much less extensively explored despite the fact that heteroaromatic rings form the basis of many natural products and synthetically-derived bioactive molecules.[4] However, the literature contains only vague reference to the intermolecular reactions of aryl radicals.[5] We now disclose the results of our studies on the intermolecular reactions of radicals derived from 2-haloindoles as a method for the regiospecific formation of carbon–carbon bonds to the 2-position of indoles.

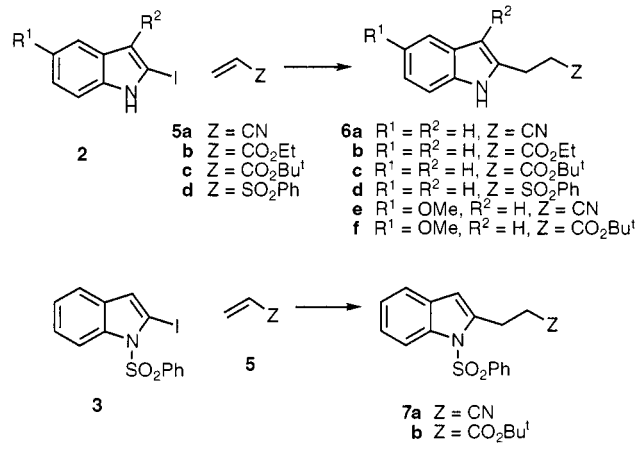
The generation of 2-lithioindoles using either an activating group attached to the indole nitrogen or the *in situ* activation of Bergman[6] and Katritzky[7] provides a method for reaction at C-2 but under extremely basic conditions. Alternatively, 2-haloindoles can be coupled with a variety of unsaturated carbon centres using palladium chemistry.[8] We have previously reported on the cyclisation reactions of radicals derived from 2-bromoindoles[9] and we wished to explore the possibility of trapping these radicals in an intermolecular sense. A range of 2-haloindole substrates were synthesised as shown in Scheme 1. Thus treatment of indole under Bergman conditions with either a brominating agent or iodinating agent gave 2-bromo- and 2-iodo-indole in 96 and 84% yields, respectively. Under similar conditions, 5-methoxyindole gave the 2-iodo derivative in 38% yield, whilst 3-methylindole gave 2-iodo-3-methylindole in 41% yield. Finally, 2-iodoindole was reacted with phenylsulfonyl chloride and base to give the *N*-phenylsulfonylindole in 95% yield, and 2-bromoindole was reacted with di-*tert*-butyl dicarbonate to give the *N*-Boc derivative in 98% yield.




**Scheme 1**

Initially, a range of these substrates were reacted under various conditions to explore the generation and intermolecular trapping of the indol-2-yl radical. Acrylonitrile, which is an excellent acceptor for nucelophilic alkyl radicals, was used as the trapping reagent. Reaction of either bromo- or iodo-indoles using tributyltin hydride (TBTH) at low concentration or delivered by syringe pump consistently gave reduced indole as product. The use of hexabutylditin instead of TBTH led to little or no reaction. Using a different strategy, the reaction of the 2-haloindoles with allyltributylstannane[10] was explored, but no 2-allylindoles could be detected. At this stage, the catalytic TBTH conditions developed by Stork and Sher were investigated.[11] The reaction of 2-iodoindole with tributyltin chloride and $NaCNBH_3$ in $Bu^tOH$ using AIBN as initiator and acrylonitrile as the radical trap gave 2-(2-cyanoethyl)indole in 30% yield. Having found suitable conditions, a range of 2-haloindoles and electron-deficient alkenes were reacted together and the results are presented in Scheme 2 and Table 1.†

With the exception of 2-iodo-3-methylindole, which gave only traces of the desired adducts by GC-MS, all 2-iodoindole substrates reacted under these conditions. Acrylonitrile proved in each case to be the best radical acceptor, with an acceptable yield of 37% for the reaction with *N*-phenylsulfonyl-2-iodoindole. Modest yields were obtained for the reactions with *N*-unsubstituted indoles, illustrating this important feature of radical reactions. Acrylate esters also proved to be reasonable radical acceptors, giving the appropriate 3-indole-substituted propionates in poor to modest yields. In the simplest case of 2-iodoindole, phenyl vinyl sulfone gave the desired adduct in 25% yield, although with other iodoindoles only reduction of the indole was observed. The effect of indole substituents is interesting. The *N*-phenylsulfonyl and the 5-methoxy group seem to have little effect on the reactions with acrylonitrile and acrylate esters, but the reaction with phenyl vinyl sulfone only works in the case of an unsubstituted indole. However, the 3-methyl group on the indole seems to shut down the intermolecular radical pathway almost completely. This is




**Scheme 2**

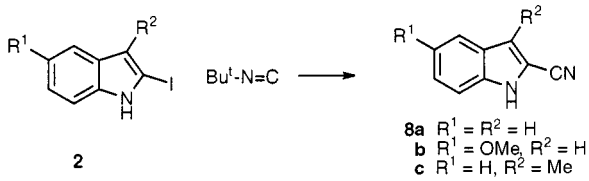
**Table 1** Reaction of 2-iodoindoles with electron-deficient alkenes

| Indole | Alkene | Product | Yield (%) |
|---|---|---|---|
| **2b** | **5a** | **6a** | 30 |
| **2b** | **5b** | **6b** | 25 |
| **2b** | **5c** | **6c** | 18 |
| **2b** | **5d** | **6d** | 25 |
| **3** | **5a** | **7a** | 37 |
| **3** | **5c** | **7b** | 28 |
| **3** | **5d** | | reduction[a] |
| **2c** | **5a** | **6e** | 25 |
| **2c** | **5c** | **6f** | 23 |
| **2c** | **5d** | | reduction[a] |
| **2d** | **5a** | | trace[b] |
| **2d** | **5b** | | trace[b] |
| **2d** | **5c** | | trace[b] |

[a] No addition product could be detected by GC-MS, only the de-iodinated product was isolated. [b] No addition product could be isolated, but it was detected in very low yield by GC-MS.

presumably caused by the increase in steric hinderance close to the radical centre and must reflect the sensitive nature of these reactions to the reaction conditions and the exact radical precursor and acceptor. The balance between intermolecular addition to the alkene, intermolecular reaction with TBTH (leading to reduction) and the radical chain breaking down (leading to starting material) is clearly delicate. The critical nature of the halogen abstracted to form the indolyl radical is demonstrated by the lack of any addition product using 2-bromoindoles as radical precursors.

Having achieved some success in the reaction of indol-2-yl radicals with electron-deficient alkenes, attention was turned to the reaction with *tert*-butyl isocyanide.[12] 2-Cyanoindoles have been shown to be useful in directing radical addition to indoles[13] but their synthesis generally requires multi-step sequences or an indole ring synthesis. Using the catalytic TBTH method and *tert*-butyl isocyanide the results shown in Scheme 3 and Table 2 were obtained. 2-Iodoindole and 2-iodo-5-methoxyindole gave 37 and 40% yields of cyanoindoles, respectively, whilst 2-iodo-3-methylindole again proved to be a significantly poorer substrate. Interestingly, *N*-phenylsulfonyl-2-iodoindole gave rise to mainly reduced product along with a small amount of the de-sulfonylated 2-cyanoindole. Investigation of the reaction




**Scheme 3**

**Table 2** Reaction of 2-iodoindoles with *tert*-butyl isocyanide

| Indole | Product | Yield (%) |
|---|---|---|
| **2b** | **8a** | 38 |
| **2c** | **8b** | 40 |
| **2d** | **8c** | 10 |
| **3** | *N*-Phenylsulfonylindole | 90 |
| | 2-Cyanoindole | trace |

mixture by GC-MS revealed the presence of *tert*-butyl phenyl sulfone, suggesting that the *tert*-butyl radical generated is able to cleave the N–S bond. This suggests a possible radical method for desulfonylation of *N*-sulfonyl indoles but a trial reaction using *tert*-butyl bromide as the source of *tert*-butyl radicals indicated that it is necessary to generate the *tert*-butyl radicals in the vicinity of the *N*-sulfonyl group to achieve the bond cleavage, providing some evidence for a cyclic mechanism (Fig. 1).

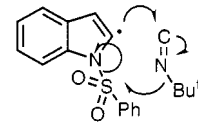



**Fig. 1**

In summary, we have demonstrated that, under appropriate conditions, indol-2-yl radicals can be generated from 2-iodoindoles, and they undergo addition to electron-deficient alkenes and addition of the cyano group from *tert*-butyl isocyanide in moderate yields. The fact that *N*-protection is not required for these reactions is a useful feature.

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## Notes and references

† *Typical procedure* for the radical additions: A mixture of 2-iodoindole (0.50 g, 2.06 mmol), $Bu_3SnCl$ (56 μl, 0.206 mmol), $NaCN{\cdot}BH_3$ (0.259 g, 4.12 mmol), ethyl acrylate (4.46 ml, 20.6 mmol) and AIBN (0.033 g, 0.2 mmol) in degassed Bu$^t$OH (40 ml) was prepared and immediately refluxed for 5 h under nitrogen. After cooling, the Bu$^t$OH was removed under reduced pressure. The residue was dissolved in $Et_2O$ (20 ml) and washed with 20% aq. $NH_3$ (3 × 20 ml), brine (3 × 20 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed (3:1 $CH_2Cl_2$–hexane; $R_f$ 0.45) to give a solid which was recrystallized from hexane–$Et_2O$ to give 3-(1*H*-indol-2-yl)propionic acid ethyl ester **6b** (0.125 g, 28%) as white needles, mp 83–85 °C (lit.,[14] 84–85 °C).

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