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Radical Cyclisation Reactions of 7-Bromoindoles

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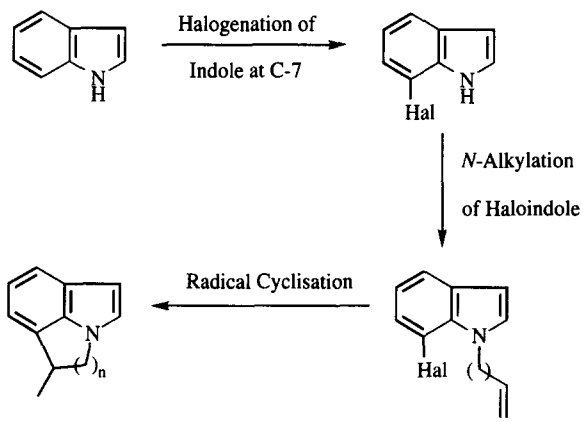
Abstract: The synthesis and radical cyclisation of 7-bromoindoles carrying an unsaturated *N*-alkyl group is described. © 1997 Elsevier Science Ltd.

As part of our continuing work on the generation of radicals in heteroaromatic systems, we have turned our attention to the generation and reactions of radicals at the *C*-7 position of indole. The chemical literature contains very few examples of radicals being generated in indole systems: by Sundberg, in his synthesis of Iboga alkaloids[1] where the radical is generated at the indole *C*-3 position; Srinivasan and Mohanakrishnan[2] have formed radicals at the *C*-3 position of indole and cyclised these onto a suitable radical acceptor on an alkyl chain from the *C*-2 position and we have performed radical cyclisations from the *C*-2 position on to a receptor on the indole nitrogen as a rapid route to mitosenes.[3] There are no examples of radicals being generated at the C-7 position. Black has however performed palladium-catalysed intramolecular cyclisation reactions of 7-halo-*N*-allylindoles.[4,5] This approach presents a whole new range of problems, since the chemistry of indole at the benzenoid *C*-7 position is very different from that of the C-2 position.

Our general approach is shown in Scheme 1.



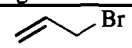
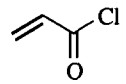
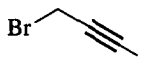
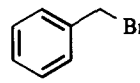
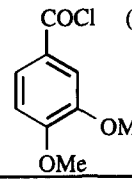
Scheme 1.

There are several methods for the synthesis of 7-bromoindole: Black *et al.* have synthesised a range of C-7 activated indoles from 4,6-dimethoxyindole, including 4,6-dimethoxy-7-bromoindole[5,6]; Black has also employed a Bischler indole synthesis as a potential route to these compounds[7]; a nitrene insertion reaction as a route to C-7 substituted indoles has been developed by Rees and Moody[8] and finally the

indoline/indole conversion has been used as a route to many substituted indoles.[9] All of these were unattractive to us either because of the number of steps involved or the requirement for extra substituents to direct a cyclisation step. Finally, the method developed by Bartoli proved to be the best method for the easy and rapid synthesis of 7-bromoindole. Reaction of three equivalents of vinylmagnesium bromide with 2-bromonitrobenzene gave 7-bromoindole in 65% yield.[10,11]

The next step was the *N*-alkylation or *N*-acylation of 7-bromoindole. This was achieved using the methods shown in Table 1.

Table 1. Results for N-alkylation and N-acylation of 7-bromoindole.

	Starting Material	Alkylating/acylating agent	Method	% yield
1	7-bromoindole		A B C	80 87 17
2	7-bromoindole		C	57
3	7-bromoindole		A B	47 85
4	7-bromoindole		B	67
5	7-bromoindole		B	60
6	7-bromoindole		B C D	42 60 31

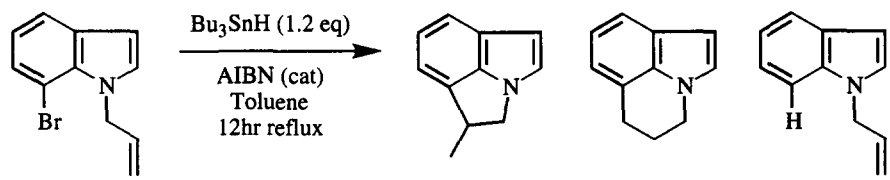
Method A: bromoalkene (4-5 eq.)/potassium carbonate (5 eq.)/acetone/reflux/24 hrs[3]

Method B: bromoalkene/acid chloride (1.5 eq.)/KOH/DMF/Room Temp./24 hrs.[12,13]

Method C: acid chloride (1.1 eq.)/NaH/DME or THF/0°C-room temp.

Method D: carboxylic acid (2-3 eq.)/boric acid/xylene/reflux/12 hours.[14]

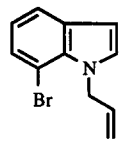
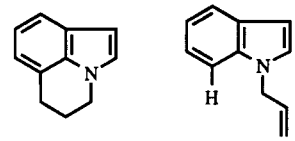
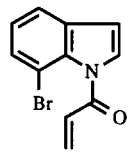
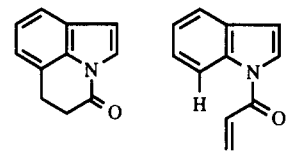
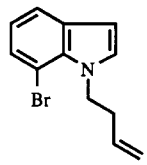
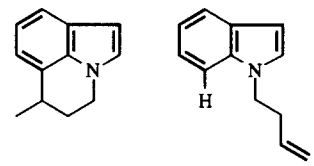
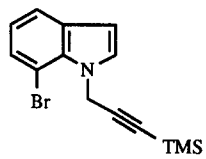
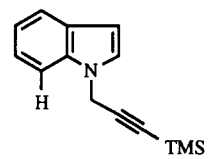
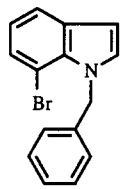
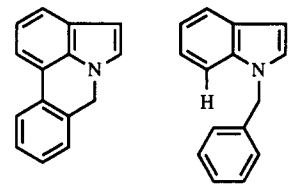
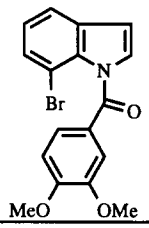
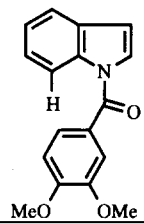
The radical cyclisation precursors were subjected to normal radical reaction conditions using tributyltin hydride (generally 1.2 equivalent, approximately 0.02 M) and AIBN as the radical initiator in refluxing toluene, with the reaction being followed by tlc (scheme 2).



Scheme 2.

The results of the cyclisations were rather different from those obtained for the *N*-C-2 radical cyclisations[3] and are shown in Table 2.

Table 2. Results of indole radical cyclisations.

Starting Material	Product (s)	Yield %
7 		84% 1:2
8 		74% 1:2.3
9 		64% 1:2.1
10 		18%
11 		66% 1:1.6
12 		53%

The first example, the cyclisation of *N*-allyl-7-bromoindole (entry 7), involved the potential 5-*exo*-trig cyclisation from the indole C-7 position on to an allyl chain. A mixture of products was obtained, comprising the 6-*endo* cyclisation product and the reduction product in the ratio 1:2; no 5-*exo* cyclisation product was obtained. The reason for this mixture is believed to be the constraints enforced on the system by the geometry of the indole ring. Although generally favoured under kinetic conditions, the 5-*exo* cyclisation is very difficult in this case as there is considerable strain and distortion in the five-membered ring product and hence presumably in the transition state. Thus a significant amount of direct reduction of the indolyl radical is observed Clearly, although the 6-*endo* reaction is usually much less favourable, the bond angles involved favour this pathway. We cannot however, rule out ring expansion via alkyl radical addition to the *ipso*-position to generate a cyclopropyl intermediate. Typically, the reduced and cyclised products proved to be

inseparable by chromatography and the determination of the relative ratios of products was performed by NMR integration.

A very similar result was observed using the corresponding acyl group, derived from acryloyl chloride (entry 8). The two products obtained were the 6-*endo* cyclisation product and the reduced product, in a similar ratio, with no 5-membered ring product. It is interesting to compare these results with those of Black[5] and Dankwardt.[15] Both groups have performed palladium-catalysed cyclisations on similar compounds; Black observed only six-membered ring formation in the cyclisation of various ring and chain substituted 7-halo-*N*-allylindoles and Dankwardt observed a preference for the 6-*endo*-trig cyclisation over the 5-*exo* one in the Heck reaction of *N*-acryloyl-7-bromoindolines.

On extending the chain length, *N*-(but-3'-ene)-7-bromoindole (entry 9) gave the expected mixture of 6-*exo* cyclisation product and reduced product. An attempt was made to employ an alkyne as the radical acceptor. A trimethylsilyl-protected alkyne was used in order to try and prevent any hydrostannylation reactions. The alkyne employed was derived from 3-bromo-1-(trimethylsilyl)-1-propyne (entry 10). After reaction, what little product that could be recovered was found to be the reduced product but only in low yield (18%). No other products could be isolated. The 7-indolyl radical was also shown to add to an aromatic nucleus (entry 11). *N*-Benzyl-7-bromoindole (derived from benzyl bromide and 7-bromoindole) reacted to give a mixture of cyclised and reduced products, but as shown in Table 2, with an increased amount of the cyclised product. This result seemed to be favourable for a potential synthesis of a range of pyrrolophenanthridone alkaloids.[16,17] The synthesis of one alkaloid of this family, pratosine,[18,19] was attempted (entry 12). However, none of the desired alkaloid product was obtained; only reduced product. Given the results of entries 8 and 11 this result is somewhat surprising but must be caused by the conformation of the amide bond in the cyclisation precursor. Attempting the cyclisation using the slow addition of tributyltin hydride or using a different radical chain carrier may prove to be more successful.

In summary, we have shown that radicals at the *C*-7 position of indole can be made and used in cyclisation reactions and we are extending this study to include the synthesis of indole-containing natural products.

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