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Annulation of indole via indole radicals: addition of the 2-indolyl radical to aromatic rings

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Abstract

The reactions of the radicals derived from indoles **4** are described leading to a short synthesis of fused [1,2-*a*]indoles via radical addition to the benzene ring followed by rearomatisation whilst one example undergoes an unusual radical translocation/addition reaction.

We have recently described the cyclisation of the indolyl-2-radical onto alkenes and alkynes to give fused [1,2-*a*]indoles.[1] Subsequently, we have investigated the intermolecular addition of the same radical to electron-deficient alkenes.[2] During this latter work we found that in aromatic solvents, addition of the indole radical to the solvent was significant, a result that caused us to change to the catalytic method of Stork using *t*-butanol as solvent.[3] The addition of carbon-centred radicals to aromatic rings followed by rearomatisation of the aromatic ring under apparently reductive conditions is well known. This has been reported in the case of radical additions to benzene rings[4] and has been utilised by Murphy,[5] Bowman[6] and Moody[7] in the addition of alkyl radicals to heterocycles. The apparent ease with which the indole radical added to aromatic solvents in our studies of its intermolecular reactions caused us to investigate this process in an intramolecular sense for the annulation of indoles. There has been considerable interest in tetracycles of this type as they possess a range of biological activities.[8]

The radical precursors **4a**–**d** were prepared as shown in Scheme 1. The reaction of oxindole **2** with PBr_3/DMF has been reported to give **3** in 28% yield.[9] In our hands, we were able to isolate **3** in 47% yield using a different work-up. However, the most convenient method involved the preparation of 2-bromoindole from indole **1**[1] followed by formylation with PBr_3/DMF. Use of $POCl_3$ in this latter reaction led to the 2-chloroindole instead. *N*-Alkylation was achieved by two methods. Reaction of **3** under Mitsunobu conditions[10] with the appropriate alcohol led to **4a** and **4b** in good yields whilst reaction of **3** with base and the appropriate alkyl bromide gave **4c** and **4d** in excellent yields. The radical reactions of indoles **4** revealed some rather unexpected aspects of this system. In order to avoid competitive addition to the solvent, we initially used cyclohexane as the solvent and syringe pump conditions. Treatment of

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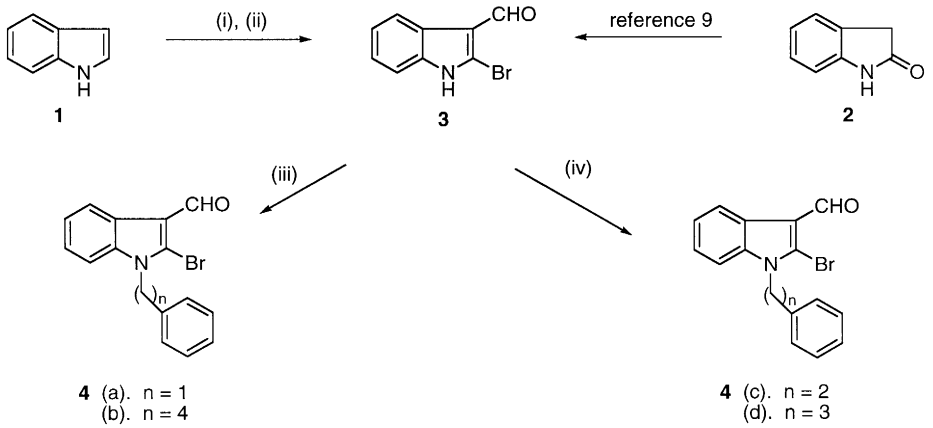
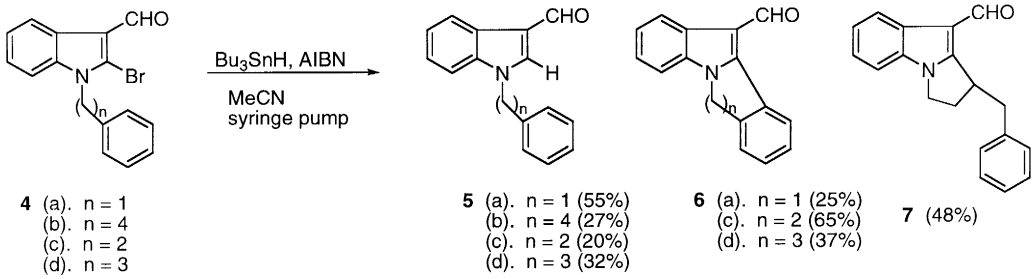
4a with tributyltin hydride (TBTH) and AIBN under these conditions gave only **5a**, the product of direct reduction, in 78% yield. Using acetonitrile as solvent, a 25% yield of the tetracyclic product **6a** was isolated along with 55% of reduction product **5a**. Similar reaction of **4c** gave the cyclised indolo[2,1-*a*]isoquinoline **6c** in 65% yield along with some 20% of reduction product **5c**. Presumably the flexibility imparted by the longer chain favours cyclisation over bimolecular reduction in this case. In the case of **4d**, we fully expected hydrogen atom abstraction from the benzylic position to dominate leading to reduced product. Much to our surprise, we isolated 37% of the seven-membered ring cyclisation product **6d** along with 32% of reduction product **5d** (Scheme 2).



Scheme 1. Reagents and conditions: (i) *n*-BuLi, THF, −78°C; CO_2, *t*-BuLi, CCl_2BrCCl_2Br (96%); (ii) PBr_3, DMF (70%); (iii) Ph_3P, DEAD, THF, $Ph(CH_2)_nOH$ (*n*=1, 75%; *n*=4, 80%); (iv) K_2CO_3, acetone, $Ph(CH_2)_nBr$ (*n*=2, 91%; *n*=3, 94%)



Scheme 2.

The most unexpected result arose from the reaction of **4b**. The major product, isolated in 48% yield, proved to be the tricyclic compound **7** which must arise from a [1,5]-hydrogen atom abstraction by the initial indole radical followed by cyclisation of the resulting alkyl radical onto the indole with subsequent rearomatisation. The cyclisation of alkyl radicals onto indoles with rearomatisation has been reported[7] although the translocation step is unknown and is under further investigation.[11] This reaction also gave 27% of reduced product **5b**.

In summary, the indolyl-2-radical shows some interesting features in its intramolecular reactions with aromatic rings. The geometric constraints imposed by the indole skeleton led to considerable reduction although the seven-membered ring product **6d** is formed in moderate yield.[12] An unusual translocation–cyclisation reaction has been uncovered which shows considerable promise for the rapid synthesis of pyrrolo[1,2-*a*]indoles.

Acknowledgements

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