Pergamon

Tetrahedron Letters, Vol. 36, No. 49, pp. 9051-9052, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01909-X

Synthesis of 1,2-Fused Indoles by Radical Cyclisation

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Abstract: Treatment of the 1-(ω-iodoalkyl)indole-3-carboxaldehydes **8-13** with tributyltin hydride and AIBN results in radical cyclisation with oxidation to give the 1,2-fused indoles **14-19**.

Free radical cyclisations now constitute a major tactic in the synthesis of mono-, bi-, and polycyclic ring systems.[1] Among such reactions, the intramolecular addition of radicals to an aromatic ring, often under oxidative conditions, has considerable synthetic potential,[2] although it has not been widely used with heteroaromatic rings.[3,4]

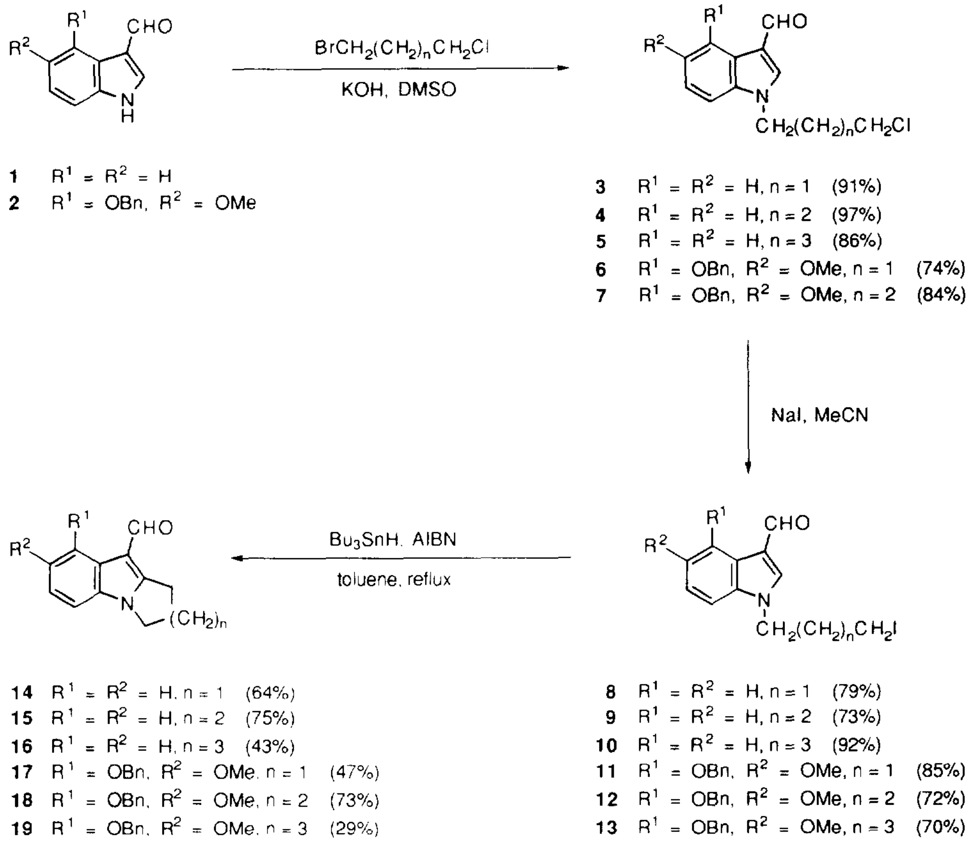
In view of our work on the synthesis of 1,2-fused indoles,[5] we were interested in the recent reports, most notably by Ziegler and by Caddick, of intramolecular radical cyclisations onto the indole 2-position.[2,6-8] Thus Ziegler and co-workers have shown that alkyl, vinyl, oxiranyl and aziridinyl radicals cyclise under photochemical or reductive conditions to give mainly 1,2-fused 2,3-dihydroindoles (or their dimers);[6] in contrast, Caddick's work involves radical *ipso*-substitution of a SPh, SOPh or SO_2Ar group from the indole 2-position, and results in the formation of 1,2-fused indoles.[7] We now report some new results in this area, which complement those referred to above.

The substrates for the radical cyclisation were the 1-(ω-iodoalkyl)indole-3-carboxaldehydes **8-13**; these were prepared from the corresponding indole-3-carboxaldehydes **1** and **2**[9] as shown in Scheme 1.[10] Thus alkylation of the indole with the appropriate 1-bromo-ω-chloroalkane using KOH in DMSO gave the corresponding 1-(ω-chloroalkyl)indoles **3-7** in good yield (74-97%). Reaction of the chlorides **3-7** with sodium iodide in acetonitrile gave the corresponding iodides **8-12** again in good yield (72-92%); the iodide **13** was prepared directly from aldehyde **2** by alkylation with 1,5-diiodopentane.

The cyclisation reactions were carried out by slow addition of tributyltin hydride (excess) and azobisisobutyronitrile (AIBN) (1 equiv) to the iodoalkylindoles in boiling toluene. This resulted in formation of the desired 1,2-fused indoles **14-19** (Scheme 1). Interestingly, the cyclisation of the iodides **8** and **9** has been carried out previously under oxidative [H_2O_2, Fe(II), DMSO] conditions and gave the same cyclised products **14** and **15**, albeit in slightly poorer yield (60 and 45% respectively).[2] For comparison, we also used these oxidative conditions for the cyclisation of **12** to **18**, although in this case the yield was worse (33%).

The formation of the *aromatic* indoles **14-19** in good yield under reductive conditions is in direct contrast to Ziegler's results on similar substrates which resulted in formation of 1,2-dihydroindoles (or their dimers), with only trace amounts of the indoles themselves.[6a] Oxidations during reductive cyclisations using tributyltin hydride are becoming increasingly common,[11,12] and although we cannot rule out disproportionation, or oxidation of an intermediate radical by AIBN as proposed by Curran,[13] we prefer the 'pseudo' $S_{RN}1$ mechanism proposed by Bowman.[11] In this, the key step is the acid-base reaction of the radical, formed by cyclisation of the initially formed radical, with tributyltin hydride to give a highly delocalised radical anion, which undergoes single electron transfer with the (iodoalkyl)indole, to regenerate, after loss of iodide, the initial radical to continue the chain process.

Acknowledgements We thank the Cancer Research Campaign for their generous support of our research and Dr Russ Bowman for invaluable discussions and helpful advice.



1 $R^1 = R^2 = H$
2 R^1 = OBn, R^2 = OMe

3 $R^1 = R^2 = H, n = 1$ (91%)
4 $R^1 = R^2 = H, n = 2$ (97%)
5 $R^1 = R^2 = H, n = 3$ (86%)
6 R^1 = OBn, R^2 = OMe, n = 1 (74%)
7 R^1 = OBn, R^2 = OMe, n = 2 (84%)

8 $R^1 = R^2 = H, n = 1$ (79%)
9 $R^1 = R^2 = H, n = 2$ (73%)
10 $R^1 = R^2 = H, n = 3$ (92%)
11 R^1 = OBn, R^2 = OMe, n = 1 (85%)
12 R^1 = OBn, R^2 = OMe, n = 2 (72%)
13 R^1 = OBn, R^2 = OMe, n = 3 (70%)

14 $R^1 = R^2 = H, n = 1$ (64%)
15 $R^1 = R^2 = H, n = 2$ (75%)
16 $R^1 = R^2 = H, n = 3$ (43%)
17 R^1 = OBn, R^2 = OMe, n = 1 (47%)
18 R^1 = OBn, R^2 = OMe, n = 2 (73%)
19 R^1 = OBn, R^2 = OMe, n = 3 (29%)

References and Notes

1. Giese, B. *Radicals in Organic Synthesis: Formation of Carbon Carbon Bonds,* Pergamon, Oxford, 1986; Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis,* Academic Press, London, 1992.
2. Artis, D. R.; Cho, I.-S.; Jaime-Figueroa, S.; Muchowski, J. M. *J. Org. Chem.* **1994**, *59*, 2456-2466, and references therein.
3. For example, intramolecular radical additions to: pyridiniums, Murphy, J. A.; Sherburn, M. S. *Tetrahedron Lett.* **1990**, *31*, 1625-1628; **1990**, *31*, 3495-3496; pyrroles, Antonio, Y.; de la Cruz, M. E.; Galeazzi, E.; Guzman, A.; Bray, B. L.; Greenhouse, R.; Kurz, L. J.; Lustig, D. A.; Maddox, M. L.; Muchowski, J. M. *Can J. Chem.* **1994**, *72*, 15-22 and references therein.
4. For examples of *inter*molecular radical additions to heteroaromatics, see Baciocchi, E.; Muraglia, E.; Sleiter, G. *J. Org. Chem.* **1992**, *57*, 6817-6820; Caddick, S.; Joshi, S. *Synlett* **1992**, 805-806.
5. Cotterill, A. S.; Hartopp, P.; Jones, G. B.; Moody, C. J.; Norton, C. L.; O'Sullivan, N.; Swann, E. *Tetrahedron* **1994**, *50*, 7657-7674.
6. (a) Ziegler, F. E.; Jeroncic, L. O. *J. Org. Chem.* **1991**, *56*, 3479-3486; (b) Ziegler, F. E.; Harran, P. G.; *J. Org. Chem.* **1993**, *58*, 2768-2773; (c) Ziegler, F. E.; Harran, P. G.; *Tetrahedron Lett.* **1993**, *34*, 4505-4508; (d) Ziegler, F. E.; Belema, M. *J. Org. Chem.* **1994**, *59*, 7962-7967.
7. Caddick, S.; Aboutayab, K.; West, R. *Synlett* **1993**, 231-232; *J. Chem. Soc., Chem. Commun.* **1995**, 1353-1354.
8. Kraus, G. A.; Kim, H. *Synth. Commun.* **1993**, *23*, 55-64.
9. Moody, C. J.; Swann, E. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2561-2565.
10. All new compounds gave satisfactory spectroscopic data.
11. Bowman, W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron* **1991**, *47*, 10119-10128, and references therein.
12. For a recent example, see Beckwith, A. L. J.; Storey, J. M. D. *J. Chem. Soc., Chem. Commun.* **1995**, 977-978.
13. Curran, D. P.; Yu, H.; Liu, H. *Tetrahedron* **1994**, *50*, 7343-7366.

(*Received in UK* 31 *August* 1995; *revised* 29 *September* 1995; *accepted* 6 *October* 1995)