Pergamon

Tetrahedron Letters, Vol. 38, No. 45, pp. 7937-7940, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10052-1

Oxidative Radical Cyclisations onto Imidazoles and Pyrroles using Bu_3SnH

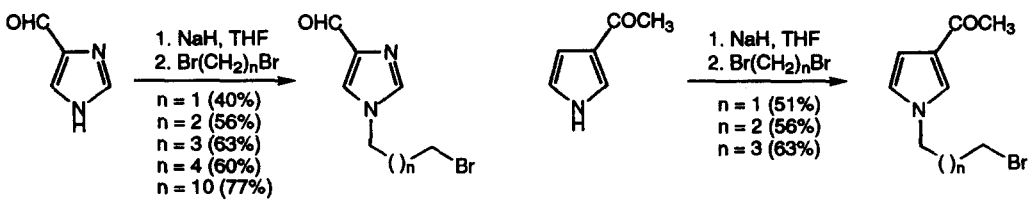
Fawaz Aldabbagh, W. Russell Bowman* and Emma Mann.

Department of Chemistry, Loughborough University, Leics. LE11 3TU, Great Britain

Abstract: *Oxidative radical cyclisation using Bu_3SnH has been used for the synthesis of [1,2-c]-fused imidazoles and [1,2-a]-fused pyrroles from imidazolecarbaldehydes and acylpyrroles respectively. The intermediate nucleophilic N-alkyl radicals cyclise onto imidazole and pyrrole rings followed by oxidative re-aromatisation.* © 1997 Elsevier Science Ltd.

The development of new free radical methodology for the synthesis of heterocyclic compounds is of increasing importance.[1] However, radical protocols involving heteroarenes have not been widely studied. In our studies of the synthesis of target biologically active bicyclic imidazoles we recently reported the first radical cyclisations onto imidazoles and benzimidazoles to form [1,2-*a*]-fused imidazoles and [1,2-*a*]-fused benzimidazoles using *ipso* substitution at the C-2 position.[2] In an earlier study we reported the synthesis of pyrrolo[1,2-*c*]-imidazoles *via* 5-*exo* cyclisation of *N*-alkenyl-imidazol-5-yl radicals.[3] In this paper we describe the first synthesis of [1,2-*c*]-fused imidazoles *via* oxidative cyclisation of *N*-alkyl radicals onto imidazoles. Oxidative radical cyclisations using Bu_3SnH are unusual but have now been reported for a variety of heterocyclic syntheses. These syntheses include heterocycles formed by the cyclising ring[4-10] and oxidative cyclisation onto the heteroarenes, *e.g.* indoles[11-13] pyrroles,[11] and pyridinium salts.[14]

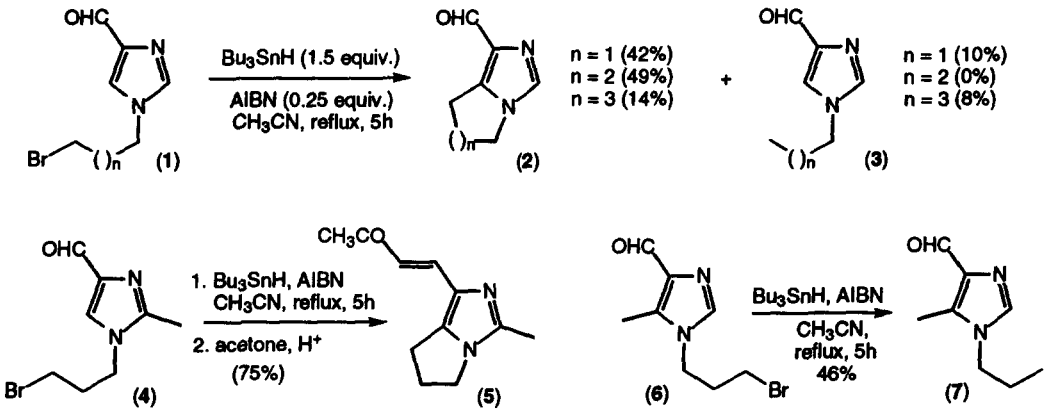
The target imidazoles require a hydroxymethyl group at C-4 and the success of oxidative cyclisation onto indole-3-carbaldehydes[13] suggested that imidazole-4-carbaldehydes would be good precursors. The analogous 3-acetylpyrroles were also synthesised for comparison purposes. 3-Acetylpyrrole was used instead of pyrrole-3-carbaldehyde because of a shorter synthesis. The synthesis of the required radical precursors was carried out by alkylation with a large excess of ω-dibromoalkanes as shown in Scheme 1. The ambident imidazole-4-carbaldehyde anion gave largely the 4-isomer but in each case small amounts of the 5-isomer was separated by chromatography.



Scheme 1. Synthesis of radical precursors

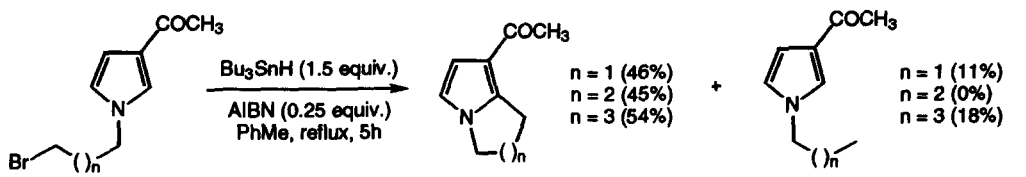
Treatment of the imidazole precursors **1** with Bu_3SnH under nitrogen using syringe pump addition gave reasonable yields of the predicted cyclised compounds **2**, and for the 5- and 7-membered ring cyclisations, a small amount of reduction to the imidazole **3** (Scheme 2). No other products were detected. Acetonitrile was used as solvent because of solubility problems with toluene. Only the 6-membered ring cyclisation was

selective, which suggests ring strain in the 5-membered ring cyclisation. The 7-membered ring cyclisation was encouraging but attempts at 8- and 14-ring cyclisations gave only reduction to the *N*-alkylimidazoles **3** (n = 4, 10). The intermediate alkyl radicals are nucleophilic thus facilitating attack at the electrophilic positions on the imidazole ring (C-2 or C-5). The regioselectivity of cyclisation onto the 5-position, [1,2-*c*]-fused, rather than the 2-position, [1,2-*a*]-fused, could not be verified using ^{1}H and ^{13}C NMR spectra of the products. The regioselectivity of cyclisation onto C-5 was confirmed by determination of the structure of **2** (n = 1) by X-ray crystallography. The regioselectivity was further illustrated by blocking the imidazole-2-position with a methyl group, *e.g.* **4** (Scheme 2). Radical cyclisation of the 2-methylimidazole-4-carbaldehyde **4** gave a high yield of cyclised aldehyde which was derivatised without purification as the α,β-unsaturated ketone **5** by an aldol condensation with acetone. In contrast, when the 5-position was blocked, *i.e.* **6**, the only product was the corresponding reduced compound **7** indicating that attack at the C-2 position is not favoured (Scheme 2). The regioselectivity appears to be determined by the nucleophilic alkyl radical undergoing addition to the electrophilic β-position of the α,β-unsaturated aldehyde moiety in a Michael type manner.



Scheme 2. Radical cyclisations of imidazole-4-carbaldehydes

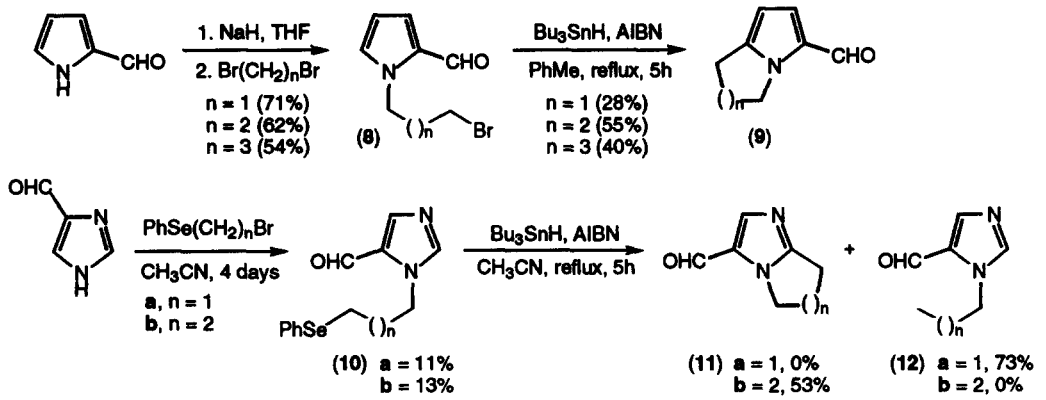
The regioselectivity of radical cyclisation exhibited by the corresponding 3-acetylpyrroles is similar to that for the imidazole-4-carbaldehydes (Scheme 3). As for the imidazole series, cyclisation at C-2 was completely selective for the 6-membered ring cyclisation and largely selective for 5- and 7-membered ring cyclisation. Again, the regioselectivity is determined by the nucleophilic radicals adding to the β-position of the α,β-unsaturated ketone moiety. Similar regioselectivity has been reported in related pyrrole cyclisations.[11]



Scheme 3. Cyclisation of 3-acetyl -*N*-(ω-bromoalkyl)pyrroles

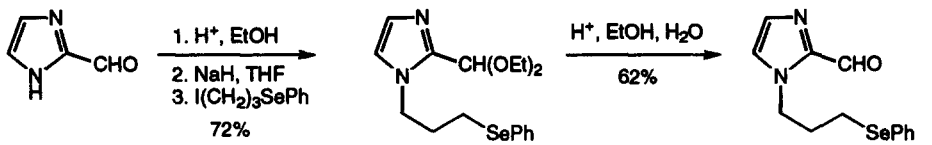
The effect on cyclisation of a carbaldehyde in the α-position of imidazole and pyrrole was also investigated. The required radical precursors were prepared and reacted with Bu_3SnH as shown in Scheme 4. The pyrrole precursors were readily alkylated using the anion of pyrrole-2-carbaldehyde but the imidazole alkylations had to be carried out in neutral solution to force alkylation onto the more basic 'imine' nitrogen. These alkylations were slow (3-5 days at reflux) and low yielding and ω-(benzeneselenyl)alkyl iodides[2] were used to avoid dialkylation problems. The pyrrole-2-carbaldehydes **8** gave selective 5-, 6-, and 7-membered

ring cyclisation onto C-5 to yield the pyrrolizidines **9** without any traces of the corresponding *N*-alkylpyrrole-2-carbaldehydes (Scheme 4). The lowish yields were due to problems of separating tributyltin residues from the products. In contrast, the imidazole analogues **10a** and **10b** gave a marked difference between 5- and 6-membered ring cyclisation. Imidazole **10a** yielded no 5-membered ring cyclisation and only gave reduction to 1-propylimidazole-5-carbaldehyde**12a** (73%). The imidazole **10b** gave selective 6-membered ring cyclisation to yield **11b** (53%) and no reduction to 1-butylimidazole-5-carbaldehyde **12b**, again indicating that the 5-membered ring cyclisation is disfavoured due to strain.



Scheme 4. Radical cyclisations onto pyrrole-3-carbaldehydes and imidazole-5-carbaldehydes

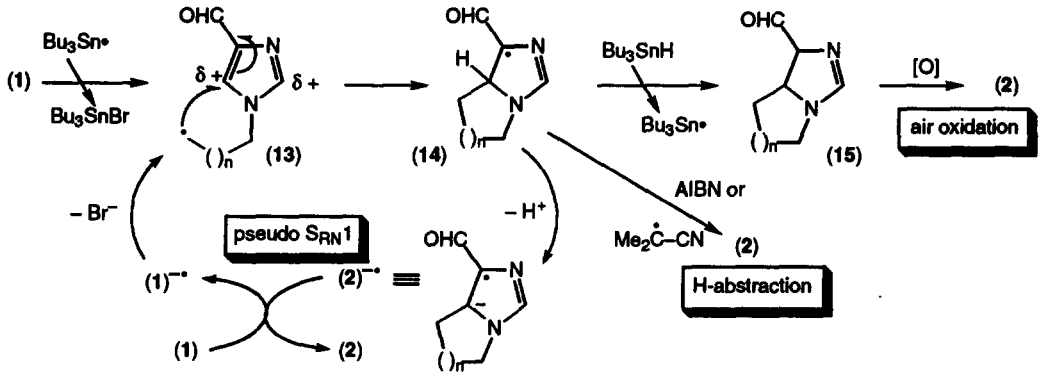
1-(3-Benzeneselenylpropyl)imidazole-2-carbaldehyde was synthesised as shown in Scheme 5 using alkylation of the corresponding acetal. Imidazole-2-carbaldehyde could not be directly alkylated and has been reported to be unstable to various organic and aqueous bases.[15] Reaction of the selenide with Bu_3SnH gave selective loss of the 2-aldehyde to yield 1-(3-benzeneselenylpropyl)imidazole and no cyclised products could be observed. The 2-aldehyde is also not stable under radical conditions and loss of the aldehyde is faster than S_H2 abstraction of the benzeneselenyl group.



Scheme 5. Synthesis of 1-(3-benzeneselenylpropyl)imidazole-2-carbaldehyde

There is no definitive mechanism for the oxidative radical cyclisations using Bu_3SnH.[4-9] All of the examples reported in the literature proceed to aromatic products which provides a strong driving force. Three putative mechanisms are illustrated for the cyclisation of the imidazoles **1** in Scheme 5. Abstraction of bromine by $Bu_3Sn^{\bullet}$ radicals and cyclisation of the radicals **13** to yield the intermediate radicals **14** are the most probable first steps. The question is how is the hydrogen at C-5 lost to yield the aromatic imidazole. The most obvious explanation is that a dihydro product, *e.g.* **15**, is produced by a normal chain reaction involving Bu_3SnH, followed by air oxidation. However, the reactions are carried under an inert atmosphere which is counter to this mechanism. A mechanism proceeding *via* H-abstraction by AIBN and/or 2-cyanoprop-2-yl radicals has been suggested.[7] AIBN has been shown to be able to abstract hydrogens in radical reactions.[16] Lobo, Prabhakar *et al*, in their recent studies[5] of the syntheses of phenanthridines which appear to proceed by the same oxidative cyclisation, have clearly shown that the 'hydrogen' which is lost in the oxidation is not abstracted by 2-cyanoprop-2-yl radicals. We have proposed a 'pseudo $S_{RN}1$' mechanism[4] for similar reactions

which would involve the loss of a proton from the intermediate radical **14** to form the aromatic radical anion ($2^{-\bullet}$) as the key step. The other steps are in common with the chain reactions observed for $S_{RN}1$ reactions.



Scheme 5. Putative mechanisms for the oxidative cyclisation of imidazole-4-carbaldehydes

In conclusion, although our reactions require optimisation, we have shown the utility of the oxidative protocol using Bu_3SnH to synthesise novel heterocyclic systems, and some of the limitations encountered. Further studies are being carried out to elucidate the mechanism of these oxidative cyclisations.

Acknowledgements

We thank Loughborough University for a Postgraduate Research Studentship (F.A.), the EPSRC for a 400 MHz NMR machine, and the EPSRC Mass Spectrometry Unit, University of Wales, Swansea, for mass spectra.

References

1. Aldabbagh, F.; Bowman, W.R. *Contemp. Org. Synth.*, **1997**, *4*, 261-280; Kappe, Th.; Kappe, C.O. in *Progress in Heterocyclic Chemistry*, eds., H. Suschitzky and G. Gribble, Elsevier Science, New York, **1996**, vol. 8.
2. Aldabbagh, F; Bowman, W.R. *Tetrahedron Lett.*, **1997**, *38*, 3793.
3. Bowman, W.R.; Taylor, P.F. *J. Chem. Soc., Perkin Trans. 1*, **1990**, 919-924.
4. Bowman, W.R.; Heaney, H.; Jordan, B.M. *Tetrahedron Lett.*, **1991**, *47*, 10119-10128.
5. Rosa, A. M.; Lobo, A.M.; Branco, P. S.; Prabhakar, S.; Pereira, A.M.D.L., *Tetrahedron* , **1997**, *53*, 269-284; Rosa, A. M.; Lobo, A.M.; Branco, P. S.; Prabhakar, S.; Sá-da-Costa, M. *Tetrahedron* , **1997**, *53*, 299-306, and references therein.
6. Beckwith, A.L.J; Storey, J.M.D, *J. Chem. Soc., Chem. Commun.*, **1995**, 997-998
7. Curran, D.P.; Yu, H.; Liu, H. *Tetrahedron*, **1994**, 7343-7366 and *J. Chem. Soc., Perkin Trans. 1.*, **1994**, 1383-1393.
8. Motherwell, W.B.; Pennell, A.M.K. *J. Chem. Soc., Chem. Commun.*, **1991**, 877-879.
9. Estévez, J.C.; Villaverde, M.C.; Estévez, R.J.; Castedo, L. *Tetrahedron* , **1995**, *51*, 4075-4082.
10. Lee, E.; Lee, C.; Tae, J.S.; Whang, H.O.; Li, K.S. *Tetrahedron Lett.*, **1993**, *34*, 2342-2346.
11. Antonio, Y.; De La Cruz, 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.
12. Ziegler, F.E.; Belema, M. *J. Org. Chem.*, **1994**, *59*, 7962-7967, and references therein.
13. Moody, C.J.; Norton, C.L. *Tetrahedron Lett.*, **1995**, *36*, 9051-9052 and *J. Chem. Soc., Perkin Trans. 1.*, **1997**, in print.
14. Murphy, J.A.; Sherburn, M.S. *Tetrahedron*, **1991**, *47*, 4077-4088; and references therein.
15. Kim, J-W; Abdelaal, S.M.; Bauer, L.; Heimer, N.E., *J. Heterocyclic Chem.*, **1995**, *32*, 611.
16. Engel, P.S.; Wy, W.-X. *J. Am. Chem. Soc.*, **1989**, *111*, 1830-1835.

(*Received in UK* 14 *August* 1997; *revised* 3 *September* 1997; *accepted* 5 *September* 1997)