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Radical Cyclisation onto Imidazoles and Benzimidazoles

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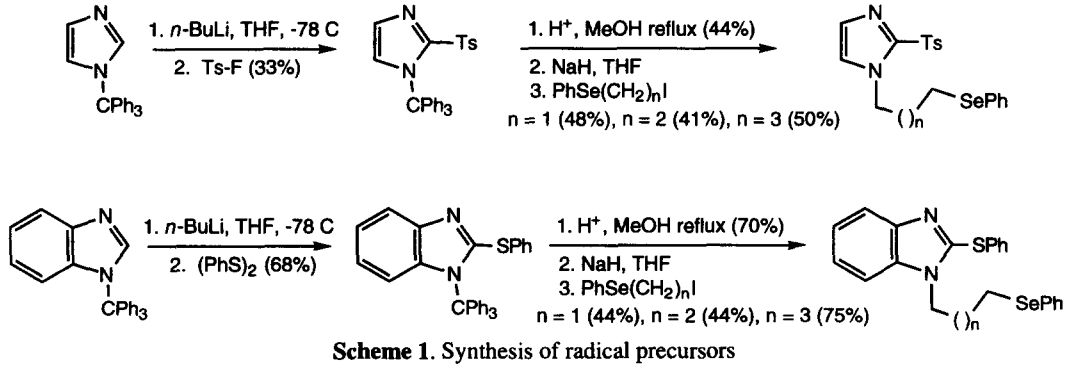
Abstract: *A new protocol for the synthesis of [1, 2-a]-fused benzimidazoles and imidazoles has been developed using intramolecular homolytic aromatic substitution via ω–alkyl radicals generated from 1-(ω–benzeneselenylalkyl)- 2-(benzenesulfenyl)-benzimidazoles and -2-(p-toluenesulfonyl)imidazoles.*

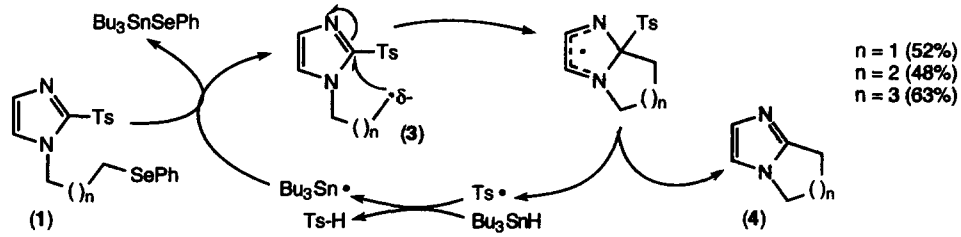
Radical cyclisation has become a major route for the synthesis of heterocyclic comounds.[1] However, intramolecular addition of radicals onto heteroaromatic rings is less common. Recent examples include radical cyclisations with oxidative rearomatisation onto the 2-position of indoles[2,3] pyrroles,[2] and pyridinium salts.[4] Caddick *et al*[5] have reported an innovative protocol for the synthesis of [1,2-*a*]indoles using intramolecular homolytic aromatic substitution with radical *ipso*-substitution of SPh, SOPh or SO_2Ar groups on the indole-2-position. In our synthetic studies of target [1,2-*a*]-benzimidazoles and imidazoles with potential biological activity we have developed a new synthetic methodology based on this protocol.[5] In this paper we describe the first examples of radical cyclisations onto imidazoles and benzimidazoles. Non-radical syntheses have been reported for [1,2-*a*]-fused benzimidazoles which have antitumor activity[6] and [1,2-*a*]-fused imidazoles which have antiulcer, antidepressant and antimicrobial activity.[7]

The radical precursors were prepared as shown in Scheme 1. Caddick *et al*[5] used 1-[ω-bromo(or iodo)-alkyl]indole radical precursors. However, we found the analogous benzimidazole and imidazole precursors troublesome to prepare because of the basic nitrogen in diazoles which caused diakylation and other side reactions. This problem was circumvented by using benzeneselenyl groups[8] in place of iodine or bromine. Benzeneselenyl groups are excellent radical precursors, but are poor leaving groups in S_N2 reactions.[8]



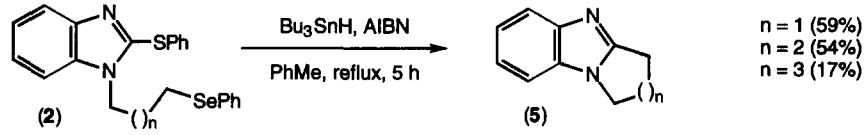
Scheme 1. Synthesis of radical precursors

Treatment of the imidazole precursors **1** with Bu_3SnH under standard radical conditions[9] gave the cyclisation products **4** in reasonable yields (48-63%) without the formation of any uncyclised reduced products (1-alkyl-2-tosylimidazoles) (Scheme 2). We propose the cyclisation mechanism as shown in Scheme 2. If the addition of Bu_3SnH was not slow a mixture of cyclised and uncyclised products were obtained. Of interest is the ready formation of the seven membered ring in the cyclisation of **1** (n = 3). Cyclisation of **1** (n = 1, with $PhSO_2$ in



Scheme 2. Cyclisation of 1-(ω-benzeneselenylalkyl)-2-tosylimidazoles

place of Ts) gave a similar yield (51%). Cyclisation of **1** (n = 1, with PhS in place of tosyl) gave a mixture of **4** (n = 1) (16%) and uncyclised 1-propyl-2-(benzenesulfenyl)imidazole (18%). The rate of cyclisation of nucleophilic alkyl radical onto the electrophilic 2-position **3**, *i.e.* the rate determining step, is enhanced by a strongly electron withdrawing tosyl group as compared to a sulfide. Cyclisation of **3** competes less favourably with reduction by Bu_3SnH when a PhS is present at C-2.



The benzimidazole precursors also gave reasonable yields of cyclised products **5** (17-59%) when treated with Bu_3SnH under standard radical conditions.[9] The imidazole ring in benzimidazole is much less aromatic than in imidazole and the intermediate radical is also more stabilised. Therefore, cyclisation takes place with a 2-benzenesulfenyl substituent and does not require the more strongly electron withdrawing tosyl group.

We have shown that benzeneselenides are valuable radical precursors in diazole cyclisations and are easily accessible. Although our reactions require optimisation, our protocol provides a novel route for the synthesis of fused [1,2-*a*]-benzimidazoles and -imidazoles and compares favourably with other procedures.[6,7]

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9. Bu_3SnH (1.33 equiv.) and AIBN (0.33 equiv.) in toluene were added to the toluene solution of the precursor in refluxing toluene using a syringe pump under an atmosphere of nitrogen over 5 h. Products were separated from tin residues by extraction into dil. hydrochloric acid. All products were characterised by IR, ^1H and ^{13}C NMR, and mass spectra, and combustion analysis or accurate mass. Yields are of pure isolated material and were not optimised.

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