The Synthesis of Bicyclic and Tricyclic Ring Systems by Radical Cyclisation Reactions of Oxime Ethers

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Vinyl and aryl bromides have been shown to undergo intramolecular radical cyclisation reactions onto oxime ether acceptors to give five-, six- and seven-membered rings.

Intramolecular radical cyclisation reactions are now widely used in organic synthesis for the construction of carbocyclic rings.[1] There have been relatively few examples involving intramolecular trapping of radicals by carbon–nitrogen double bonds. Corey and Pyne[2] first demonstrated that oxime ethers were good acceptors for alkyl radicals, and there have been more recent reports of similar reactions leading to five-[3,4] and six-membered[5] carbocyclic rings. A recent paper by Enholm *et al.*[6] which describes intramolecular cyclisation reactions of vinyl radicals onto oxime ether acceptors, prompts us to report our related studies of the reactions of aryl and vinyl radicals which form part of a strategy for the general synthesis of five-, six- and seven-membered carbocyclic and heterocyclic rings.

The oxime ethers **1a–c** could be cyclised by slow addition of a solution of azoisobutyronitrile (AIBN) in benzene to a solution containing Bu_3SnH in refluxing benzene over 18 h (method *A*) to give the cyclised products **2a–c** as clear, colourless oils in moderate to good yields.† Under similar conditions cyclisation of **1d–e** proceeded in only low yields (<35%), but addition of 1 mol. equiv. of AIBN to the initial

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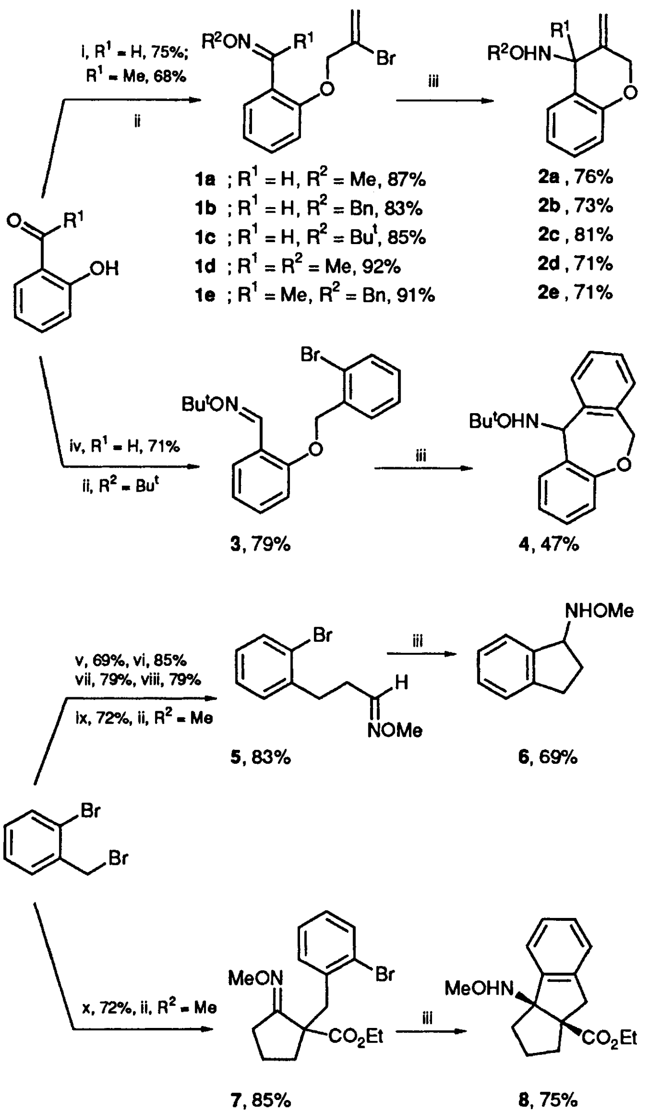
† All new compounds were fully characterised by ^1H and ^{13}C NMR spectroscopy and high-resolution mass spectrometry. The compounds **2a–e** were characterised as their hydrochloride salts for which satisfactory analytical data were obtained.



Scheme 1 *Reagents and conditions*: i, $BrCH_2C(Br)=CH_2$, K_2CO_3, Me_2CO, reflux 5 h; ii, $R^2ONH_2\cdot HCl$, pyridine, room temp., 4 h; iii, Bu_3SnH, AIBN, PhH, reflux; iv, 2-$BrC_6H_4CH_2Br$, K_2CO_3, Me_2CO, reflux 5 h; v, NaOEt, EtOH, $CH_2(CO_2Et)_2$, reflux 12 h; vi, NaOH, heat, then HCl, heat; vii, EtOH, cat. H_2SO_4, reflux; viii, $LiAlH_4$, Et_2O, reflux, 2 h; ix, $(COCl)_2$, Me_2SO, Et_3N; x, NaH, tetrahydrofuran, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, ethyl 2-oxocyclopentane carboxylate, reflux

reaction mixture (method *B*) gave the improved yields shown in Scheme 1 after only 4 h at reflux temperature. The cyclisation of **3** to **4** was accompanied by some reduction of the aryl bromide even when a mixture of Bu_3SnH and AIBN (cat.) was added dropwise over 8 h to a solution of **3** at reflux temperature in benzene. Under the conditions of method *B* the reduction product only was formed. When oxime **5** was treated under cyclisation method *A* the indane **6** was formed Cyclisation of **7** proceeded smoothly under the conditions of method *A* to give the product **8**, which was assigned the *cis* stereochemistry on the basis of general literature precedent[7] and similar radical cyclisations to bicyclo[3.3.0]octane derivatives which have been shown to have the expected *cis*-ring junctions.[8] This demonstrates the potential of these reactions for the simultaneous formation of bicyclic systems and a tertiary amino function. Several methods are available for the reduction of the N–O bond with the introduction of an amine,[9] and we hope to apply this new methodology to the synthesis of natural products related to the lycopodium alkaloids.

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