

Novel synthesis of bridgehead nitrogen heterocycles by ring-closure of α -ammonio radicals

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Ring-closure of 2,2-dialkyl-2-azoniahex-5-enyl radicals readily occurs and provides convenient access to heterocyclic compounds

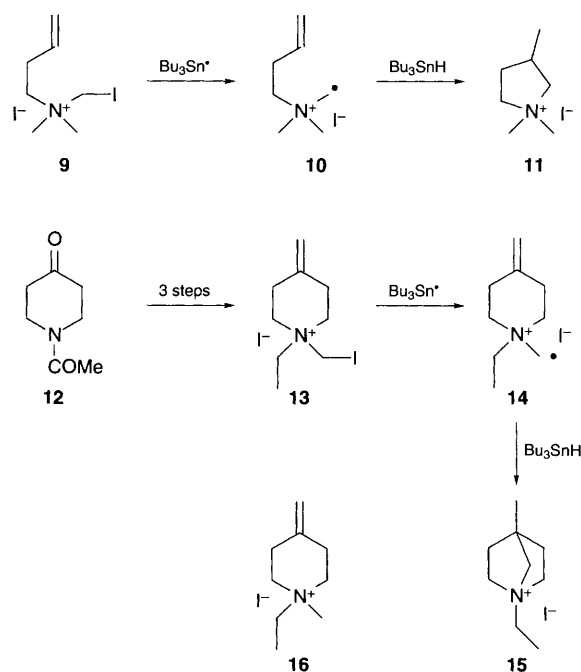
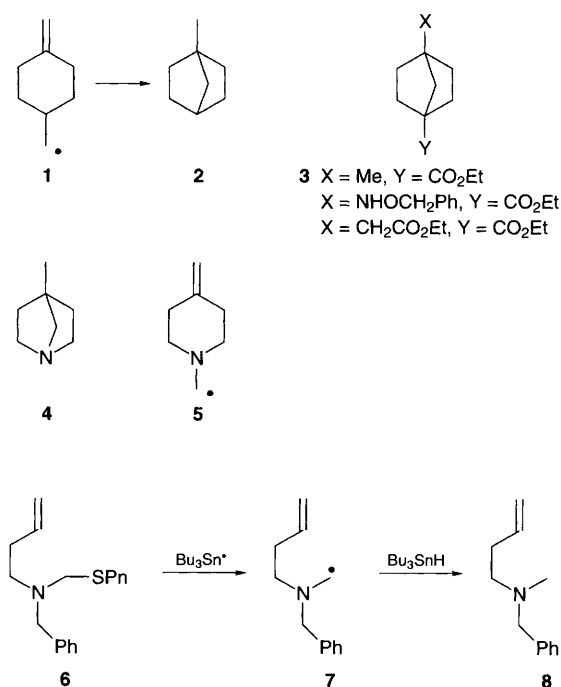
The modified hex-5-enyl radical **1** has recently been shown¹ to undergo ring-closure smoothly and irreversibly to give the isomeric species **2**. This transformation has been successfully exploited^{1,2} for the synthesis of various bridgehead-substituted bicyclo[2.2.1]heptanes **3** from readily-accessible derivatives of the 4-methylenecyclohexylmethyl radical **1**. We wished to take advantage of the rearrangement **1** \rightarrow **2** as a vehicle for the preparation of the 1-azabicyclo[2.2.1]heptyl system **4** via the corresponding intermediate radical **5**. Derivatives of the amine **4** have been shown to possess important physiological properties³ and, accordingly, we felt that the development of synthetic procedures that provide entry to this system is a worthwhile objective.

A predicament we faced from the outset, however, was the prediction from *ab initio* calculations conducted by Collidge and Borden⁴ some years ago that the presence of a nitrogen atom located alpha to a radical centre, as in the aminomethyl radical, confers enhanced thermodynamic stability on the species relative to its unsubstituted analogue. Thus, in contrast with the activation energy accompanying the rearrangement **1** \rightarrow **2**, a higher barrier to cyclisation of **5** is expected as a result of its lower ground state energy. In a practical demonstration of this phenomenon, Padwa and co-workers⁵ have observed that the 2-aza-2-benzylhex-5-enyl radical **7**, generated from the sulfide **6** by treatment with tributyltin hydride, affords the

reduction product **8** only; none of the cyclised isomer, 1-benzyl-3-methylpyrrolidine, was detected.

It occurred to us that the stabilising influence of the heteroatom on the adjacent electron-deficient centre in the 2-azahex-5-enyl radical could be removed effectively if the nitrogen lone pair was otherwise engaged through quaternisation. Indeed, this expectation is supported by *ab initio* calculations⁶ which predict the ammoniomethyl radical to have a considerably higher ground state energy than that of either the ethyl or the aminomethyl radical.⁴ Accordingly, in view of the anticipated decrease in the activation barrier to cyclisation, radicals such as **10** would be more inclined to undergo ring-closure compared with intermediates such as **7**.

To test these predictions we embarked upon an examination of the behaviour of the charged hex-5-enyl radical **10**. Synthesis of the selected precursor **9** in high yield was accomplished by stirring a mixture of *N,N*-dimethylbut-3-enylamine, prepared by treatment of but-4-enyl mesylate with ethanolic dimethylamine, with excess diiodomethane overnight. The reaction mixture was washed with diethyl ether to afford an almost quantitative yield of the salt **9**. A solution of tributyltin hydride (1.1 equiv.) and a catalytic quantity of AIBN in *tert*-amyl alcohol was added to a stirred solution (0.025 mol dm⁻³) of **9** in *tert*-amyl alcohol held at 80 °C and irradiated with a 300 W incandescent lamp. After 30 min the mixture was cooled, the solvent evaporated and the residue washed with ether to remove neutral material. The crude product thus obtained was shown by ¹H and ¹³C NMR analysis to consist of 1,1,3-trimethylpyrrolidinium iodide **11** in an essentially pure form (96% yield); neither the reduced product, trimethylbut-3-enylammonium iodide, nor any other com-



pounds were detected under the spectroscopic conditions employed. The identity of the cyclic salt **11** was established by its NMR spectral properties and by demethylation using DABCO®/DMF⁷ to give 1,3-dimethylpyrrolidine which proved to be identical with an authentic specimen.⁸ This result contrasts strongly with the observed⁵ reluctance of radical **7** towards ring-closure, and is in accord with the above predictions of the relative kinetic reactivity of the intermediate radical **10**.

In an attempt to extend this strategy to the synthesis of the 1-azabicyclo[2.2.1]heptyl system we prepared the corresponding precursor, 1-ethyl-1-iodomethyl-4-methylenepiperidinium iodide **13**, in a standard three-step sequence from commercially-available 1-acetylpiperidin-4-one **12**. Exposure of the salt **13** to Bu₃SnH added over 15 min at 100 °C, but otherwise under the conditions described above, afforded an excellent yield (92%) of 1-ethyl-4-methyl-1-azoniabicyclo[2.2.1]heptyl iodide **15** in a high state of purity. The identity of the product was established unambiguously by ¹H and ¹³C NMR spectral analysis, careful scrutiny of which confirmed that the salt **15** was obtained without contamination. In particular, signals associated with the product of reduction, *N*-ethyl-*N*-methyl-4-methylenepiperidinium iodide **16**, were not detected. An authentic specimen of **16** was prepared in order to facilitate analysis of the spectra.

These data demonstrate that the intermediate radical **14** does indeed undergo ring-closure readily with an activation barrier considerably lower than that expected for rearrangement of the parent radical **5**. The species **14** is also found to display a greater facility for cyclisation than the corresponding substituted analogues of the 4-methylenecyclohexylmethyl radical **1**.^{1,2}

In summary, the experimental observations described above illustrate that the ease of synthesis of the radical precursors **9**

and **13** and the rapidity of cyclisation of the derived α -ammonio-substituted radicals **10** and **14** provide a valuable entry into heterocyclic compounds in yields which are most impressive. We believe that ring-closure *via* this procedure has important implications in the synthesis of other bridgehead nitrogen bicyclic heterocycles, an aspect we hope to exploit and report upon favourably in the future.

We thank the Australian Research Council for financial support.

References

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Received, 25th April 1996; Com. 6/02914K