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Intramolecular Addition of Free Radicals to Quaternised Heterocyclic Rings.

John A. Murphy* and Michael S. Sherburn, Department of Chemistry,
University of Nottingham, University Park, Nottingham NG7 2RD.

The intramolecular addition of free radicals to quaternary pyridinium salts gives good yields of tetrahydroquinolizinium salts.

The addition of carbon free radicals to protonated heterocyclic bases shown in figure 1 has been extensively explored by Minisci and coworkers[1] in elegant experiments over many years.These authors have shown that the heterocyclic ring needs to bear a positive charge for successful attack by nucleophilic carbon radicals. Barton and co-workers[2] have also explored this area. All of the examples in the literature[3], however, utilise **intermolecular** additions to **protonated** bases. Furthermore the methods of generating carbon radicals so far used by Minisci's group are all **oxidative**; this is quite logical since the mechanism by which the reactions proceed[4] requires an oxidative step to generate the aromaticity in the products. However, the development of free-radical strategies in synthetic organic chemistry has benefitted enormously from the availability of non-oxidative radicals e.g. trialkylstannyl radicals. Their reactions generally avoid the aggressive hydrogen-atom abstraction processes which feature so prominently in the chemistry of oxidative radicals. Our strategy was to see if carbon radicals generated using tributyltin hydride would lead to dihydropyridines , and by analogy with NADH to NAD^+ conversions, whether a subsequent mild oxidative step could complete the overall "substitution" process.

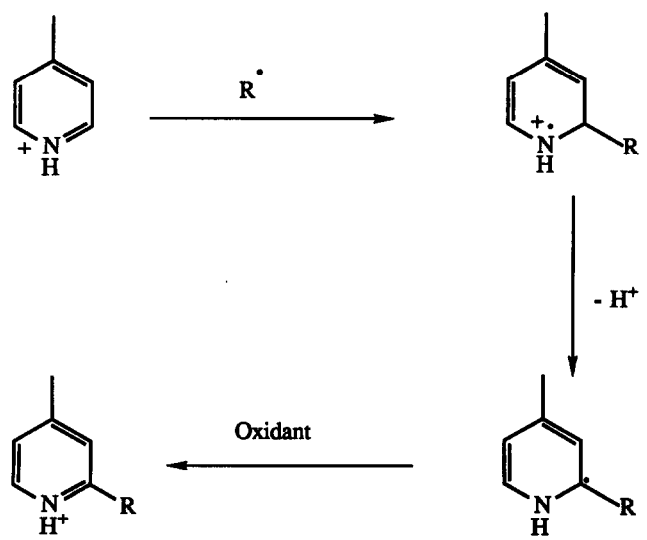


Figure 1

In this paper[5], we describe the first examples of **intramolecular** radical additions to **quaternized** pyridinium salts accomplished using the mild and **non-oxidative** chemistry of tributyltin hydride. There is no necessity to introduce a separate oxidative step; in fact it is not possible to isolate products other than the product of substitution.

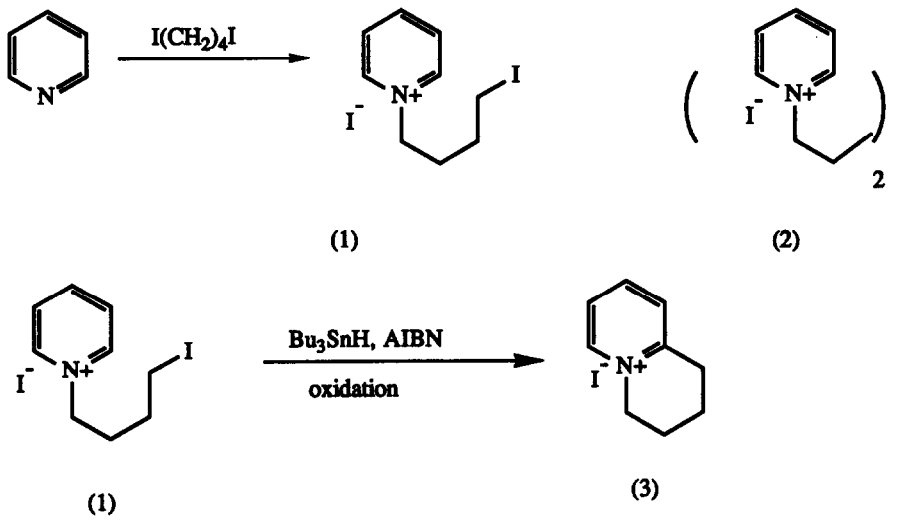


Figure 2

Pyridine was treated with diiodobutane to generate a mixture of the monopyridinium salt (1) and the dipyridinium salt (2). These were easily separated by column chromatography followed by recrystallisation. When the salt (1) (1 equivalent), was treated with tributyltin hydride (1.3 equivalents) under nitrogen and in the presence of azobisisobutyronitrile (1.2 equivalents) a clean cyclisation ensued as judged by n.m.r. The bicycle (3) , m.p. 178-182^0 C, was isolated in 60% yield simply by performing a petrol / acetonitrile partitioning of the crude reaction mixture, evaporating the acetonitrile and recrystallising from ethanol / ethyl acetate. The tin byproducts from tributyltin hydride reactions frequently cause purification problems, but because of the polarity of the pyridinium products, organotin compounds are very easily removed by the above procedure. Hence the use of tributyltin hydride is positively advantageous. The clean formation of (3) indicates that no polysubstitution is seen in the reaction; this contrasts with the intermolecular substitution reactions of pyridinium salts[4].

There are a number of mechanistic points which deserve consideration. A full equivalent of azobisisobutyronitrile was required in these reactions; to ensure that the isobutyronitrile radicals produced in the thermal decomposition of this substance were not responsible for direct attack on the iodo-compound, without involvement of the tributyltin hydride in the radical process, the reaction was performed in the absence of tributyltin hydride. This led solely to recovery of starting materials, showing that the tributyltin hydride was required for reaction. Another mechanistic possibility was that tributyltin hydride might be used in catalytic quantity in the reaction. This could occur if tributyltin iodide were reduced in situ by an intermediate dihydropyridine derivative. However we have demonstrated that this was not the case. In the presence of less

than one equivalent of tributyltin hydride, the reaction did not go to completion. Two possible pathways for the substitution reaction are suggested in Figure 3. Route A is the pathway suggested by Minisci for his substitutions. With tributyltin hydride as radical source, however, we cannot rule out the alternative possibility B. The nature of the oxidant required as part of this process is under investigation.

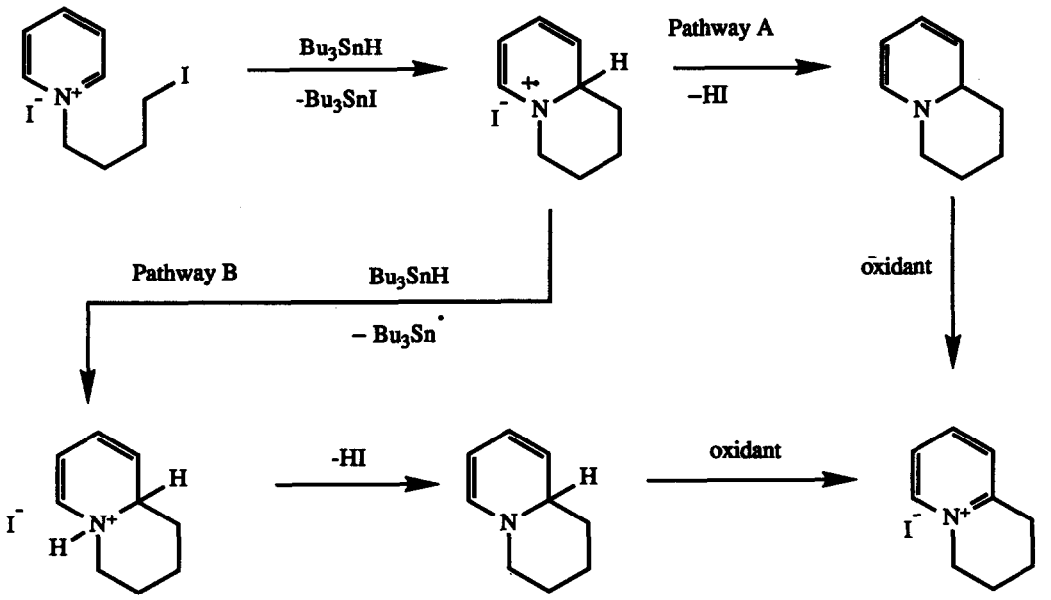
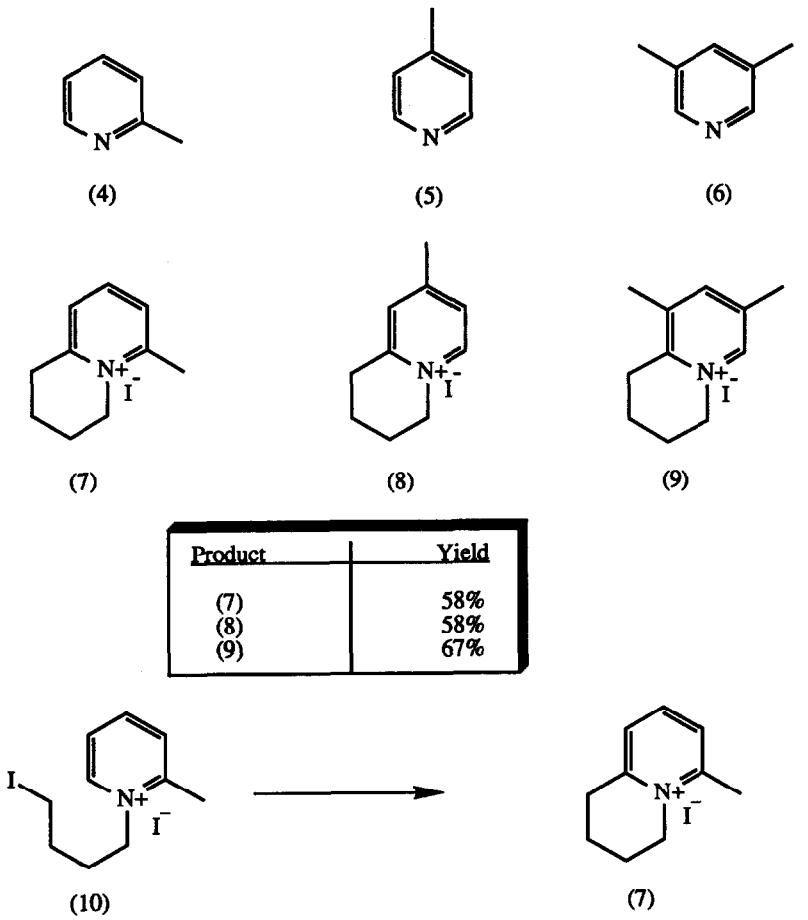


Figure 3

To test if substituted tetrahydroquinolizinium salts could also be synthesised in this manner 2-picoline (4), 4-picoline (5) and 3,5-lutidine (6) were converted to their corresponding iodobutyl quaternary salts. These were respectively transformed into bicyclic compounds (7) (8) and (9) on treatment with tributyltin hydride and AIBN. It is interesting to note that only one product arises from the N-iodobutyl-2-picolinium iodide (10). No product resulting from addition to the carbon bearing the methyl group is seen.We are currently exploiting this regioselectivity in the synthesis of more complex substitution products.

These reactions thus offer a valuable extension to known methods for the synthesis of heterocyclic molecules.The application of tributyltin hydride radical chemistry to the aromatic substitution reactions offers an interesting extension to the applications of this versatile reagent.



Product	Yield
(7)	58%
(8)	58%
(9)	67%

Figure 4

Acknowledgements. We thank the S.E.R.C. for the award of a Quota studentship.

References.
1. For a review see F. Minisci, E. Vismara, F. Fontana, *Heterocycles* **1989**, *28*, 489.
2.D. H. R. Barton, B. Garcia, H. Togo and S. Z. Zard,*Tetrahedron Letters*, **1986**, *27*, 1327
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5. These results were previously disclosed at the East Midlands Regional Meeting of the Royal Society of Chemistry, Nottingham, 1989.

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