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# The Generation and Cyclisation of Pyridinium Radicals as a Potential Route to Indolizidine Alkaloids

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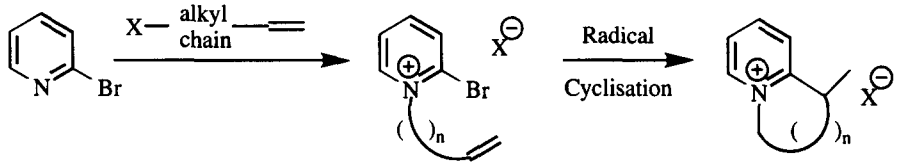
***Abstract***: The cyclisation of pyridine radicals derived from 2-bromo-N-alkyl pyridinium salts is described. The subsequent hydrogenation of the pyridinium salts is shown to give both the indolizidine and quinolizidine skeletons. © 1997 Elsevier Science Ltd.

As part of our on-going investigation into the generation and reactions of radicals formed from heteroaromatic compounds, our attention focused on bromopyridines as readily available starting materials which could serve as radical precursors. The literature contains few examples of pyridyl radicals. Both Snieckus[1,2] and Harrowven[3,4] have published papers which have included pyridyl radical cyclisations but as part of a much larger field and with little attention being drawn to the pyridyl radical. We recently described the use of radicals derived from 3-bromopyridine in the total synthesis of (±)-oxerine.[5] We now wish to report the extension of this chemistry to pyridinium radicals.

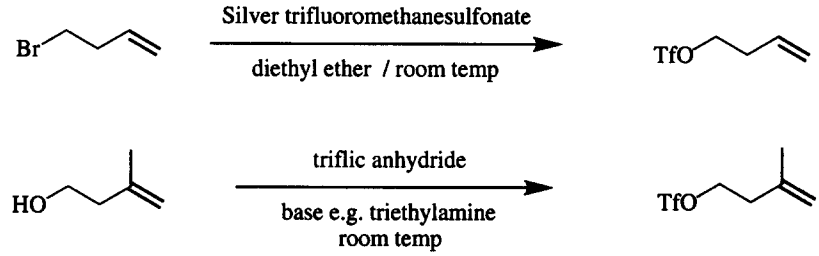
Scheme 1 outlines the general approach. 2-Bromopyridine is *N*-alkylated using a suitable alkyl chain bearing a radical receptor to form the *N*-alkenylpyridinium salt which is then cyclised under normal tin hydride conditions.




**Scheme 1.**

The chemical literature contains many examples of pyridines being substituted on the nitrogen to form pyridinium salts. There are very few examples of 2-bromopyridine being *N*-alkylated in this way. Our first attempt involved the normal type of alkyl halide approach which has been used to synthesise *N*-alkyl pyridines in other examples.[6] Thus 2-bromopyridine was reacted with 4-bromobut-1-ene in ether under reflux for considerable lengths of time but this gave only starting materials. It was decided to use a better leaving group than bromide in order to effect the coupling. Initially this simply involved exchanging the bromide for an iodide, in a straightforward Finkelstein reaction . The iodo-compound was much less stable than the bromo-derivative and so was reacted immediately with 2-bromopyridine. Nevertheless, despite its increased reactivity, this also failed to give any *N*-alkylated product, with starting material being recovered. Clearly, the 2-bromo-substituent reduces the nucleophilicity of the nitrogen considerably. In recent years, the use of alkanesulfonic esters has expanded to cover most areas in organic chemistry.[7-9] They have found particular use as reactive leaving groups; for example, the triflate group is known to be $10^6$ times better as a

leaving group than iodide.[7] So the next group to be tried was the tosylate group as there was considerable literature precedent for this, as pyridinium tosylates are well known compounds.[6,10,11] However they also failed to give any alkylated pyridinium compound. Hence a second group, the triflate group, was employed. Triflate derivatives were prepared in two ways, from alkyl halides by reaction with silver trifluoromethanesulfonate (yields 35-45%) or from alcohols by reaction with a base and trifluoromethanesulfonic anhydride (60-75%, Scheme 2). All the triflate derivatives prepared were both heat, air and moisture sensitive and needed to be further reacted immediately to avoid decomposition.



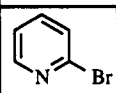
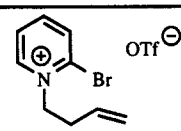
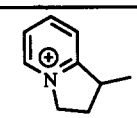
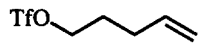
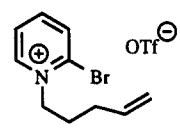
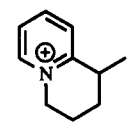
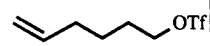
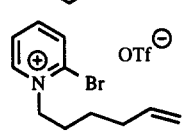
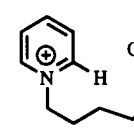
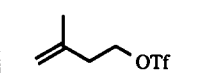
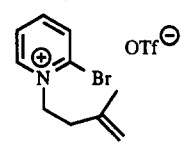
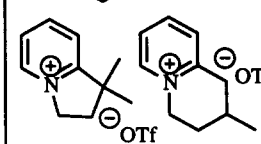
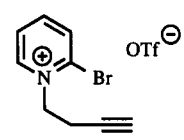
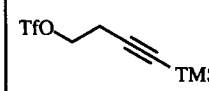
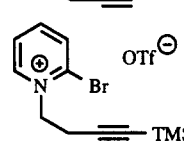
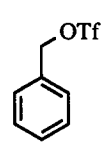
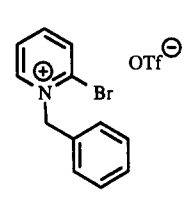
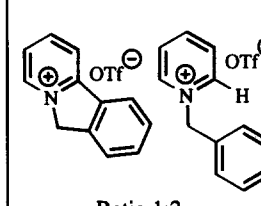

**Scheme 2.**

On reaction with 2-bromopyridine, excellent yields of *N*-alkylated pyridinium triflates were obtained (Table 1). These highly ionic salts were insoluble in organic solvents and very aqueous soluble; this however was a distinct advantage in their work-up and isolation.

The salts were initially reacted under standard radical cyclisation conditions of tri-*n*-butyltin hydride (1.2 eq., approximately 0.02 M) and AIBN in toluene under reflux for 12 hours and in general the cyclised products resulted (Table 1). In the simple 5-*exo*-trig reaction (entry 1), the *N*-but-3'-ene precursor gave the 5-membered ring product exclusively as expected.[12,13]. None of the 6-membered ring product potentially arising by addition of the cyclopentylmethyl radical to the pyridinium ring with subsequent ring opening to the cyclohexyl radical was observed. This example was then employed as the test case, in order to optimise the yields of cyclised product. Under these normal radical reaction conditions, the desired cyclised product was obtained in 65% yield. In an attempt to improve the yield of cyclised product, slow syringe pump addition of tributyltin hydride was carried out over 12 hours, but this gave very little improvement in yield (*ca.* 3-5% yield improvement). The fairly low yield was traced to the poor solubility of the highly ionic pyridinium salt in toluene. Dry acetonitrile was the next solvent to be tried and in general it gave a slight improvement in yield of cyclised product (*e.g.* up to 74% cyclised product for the *N*-but-3'-enylpyridinium triflate precursor). Although other solvents were explored (benzene, xylene and mesitylene) these gave no substantial improvements in yield and toluene and acetonitrile were the best two solvents for these reactions.

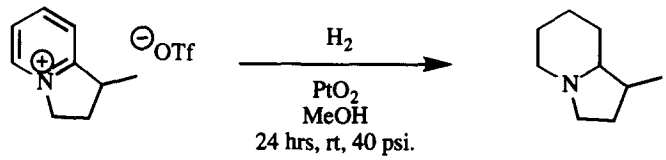
Increasing the steric hindrance at the proximal end of the double bond (entry 4) gave a mixture of 5-*exo*- and 6-*endo*-cyclisation with cyclohexane formation being favoured. When the chain length was extended to a *N*-pentenyl chain (entry 2), the 6-*exo* cyclisation product was obtained exclusively (55%); there was no evidence of either 7-*endo* or reduced products. However, when the chain length was increased further, *N*-4'-hexenyl-2-bromopyridinium triflate (entry 3) gave no cyclised material at all, only reduced product (47%). An alkyne derivative, 3-butyn-1-triflate was also employed as a potential radical acceptor. An unprotected triple bond failed to give any cyclised product (*c.f.* the reaction of the radical derived from 3-bromopyridine in the synthesis of (±)-oxerine[5]) and a complex mixture of inseparable aqueous soluble products was formed, including some hydrostannylated product. Unfortunately, a similar result was obtained when performing the cyclisation on the trimethylsilyl-protected alkyne. Although there was some evidence for the cyclised product, this again was formed as part of a complex mixture of products, all of which were aqueous soluble and inseparable. Finally, the pyridinium radical added in moderate yield onto another aromatic nucleus, to give the fused tricycle (entry 7), with rearomatisation of the aryl ring.

**Table 1.** Results for the formation of *N*-alkenylpyridinium triflates and their subsequent radical cyclisation.[14]

| | Starting Materials | Product | Yield (%) | Cyclisation Product | Yield (%) |
|---|---|---|---|---|---|
| 1 |  |  | 89 |  | 74 |
| 2 |  |  | 85 |  | 53 |
| 3 |  |  | 74 |  | 47 |
| 4 |  |  | 79 |  (11) (12) Ratio 1:3.5 | 76 |
| 5 |  |  | 77 | - | |
| 6 |  |  | 56 | - | |
| 7 |  |  | 62 |  Ratio 1:2 | 61 |

Having established that the cyclisation methodology worked, the synthetic potential of the highly ionic, insoluble products was explored. One possibility involved the hydrogenation of the pyridine ring, either selectively, to remove the quaternary nitrogen, or completely. Attempts to selectively reduce the pyridinium salt using reagents such as superhydride or sodium borohydride failed to give any reduced product. Attention instead was turned to the complete hydrogenation of the pyridine ring. This was first attempted using a palladium on carbon catalyst at normal pressure and only gave a trace of the desired hydrogenation product. Using high pressure and the same catalyst gave little improvement in yield (*ca.* 20%). Finally, using Adam's Catalyst ($PtO_2$) under high pressure and in a slightly acidic solution gave the best yields of the

completely hydrogenated product (52%, Scheme 3) as a single (undetermined) diastereoisomer. Not only did hydrogenation give a product that was much easier to handle, it also meant that the core skeleton of the indolizidine alkaloids had been obtained. Similarly, performing the hydrogenation on the [6,6] fused ring system from the corresponding pyridinium salt radical cyclisation gave the core skeleton of the quinolizidine alkaloids. Murphy has also performed hydrogenation reactions on his products in order to form indolizidine alkaloids.




**Scheme 3.**

In conclusion, it has been shown that it is possible to generate radicals at the C-2 position of pyridinium salts and to use these in cyclisation reactions. The products of these cyclisation reactions may then be hydrogenated to give a potentially rapid route to a range of interesting natural and unnatural indolizidine and quinolizidine alkaloids. Interestingly this approach can be seen as the reverse of the approach of Murphy[10,11] who carried out the intramolecular addition of alkyl radicals to the pyridinium ring (under reductive conditions) to obtain similar products and the extensive work of Minisci[15] involving the intermolecular addition of radicals to the C-2 position of pyridinium salts (under oxidative conditions). However, in our approach no re-aromatisation of the pyridinium ring is required.

***Acknowledgement:***

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