



Pyridine Radicals in Synthesis: a Formal Total Synthesis of (\pm)-Oxerine

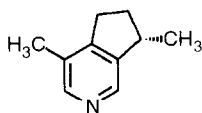
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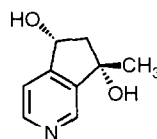
Abstract: The cyclisation of pyridine radicals derived from 3-bromo-4-substituted pyridines carrying both alkene and alkyne groups in the 4-substituent to give is described. The cyclopentano[c]pyridine skeleton formed by cyclisation is found in many monoterpene alkaloids and a short synthesis of a late intermediate in the previous synthesis of (\pm)-oxerine is presented.

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Although the use of aryl radicals derived from iodo- and bromo-substituted benzenes has achieved popularity in synthesis, the use of radicals derived from heteroaromatic systems is rare.² We have recently published some cyclisation reactions of the radical derived from 2-bromoindole³ and Sundberg has utilised the radical derived from 3-iodoindole.⁴ In the pyridine system, there are only three reports⁵ which briefly mention cyclisations involving radicals generated from 2- and 4-bromopyridines. We are interested in synthetic routes to the monoterpene alkaloids⁶ such as (-)-actinidine **1** and (-)-oxerine **2**⁷ and it is apparent that an approach involving the cyclisation of a 3-pyridyl radical onto a suitable unsaturated function at the 4-position would provide a rapid entry to the core cyclopentano[c]pyridine ring system. We now wish to describe our preliminary results and present a short synthesis of a late intermediate in the only previous synthesis of (\pm)-oxerine.⁸



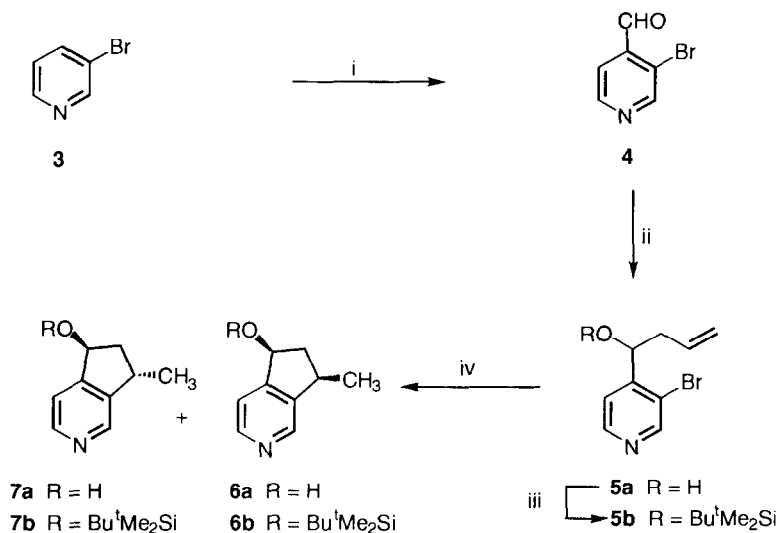
1



2

Ortholithiation and formylation of 3-bromopyridine **3** to give 3-bromo-4-formylpyridine **4** has been reported⁹ to proceed in 73% yield although in our hands the best yield we could obtain was 60% (Scheme 1). The temperature control and the purity of the DMF used in this reaction are crucial for success. Allylation of **4** to introduce the unsaturated functionality for cyclisation was explored using a variety of reagents. Reaction at room temperature with allylmagnesium bromide in diethyl ether gave the desired alcohol **5a**¹⁰ but in only 35% yield. The reaction of aldehyde **4** with allyltrimethylsilane using freshly-distilled titanium (IV) chloride as catalyst in dichloromethane at room temperature¹¹ gave **5a** in only 19% yield. Changing to allyltributylstannane and boron trifluoride at -78°C¹² gave **5a** in 60% yield but the best conditions were found

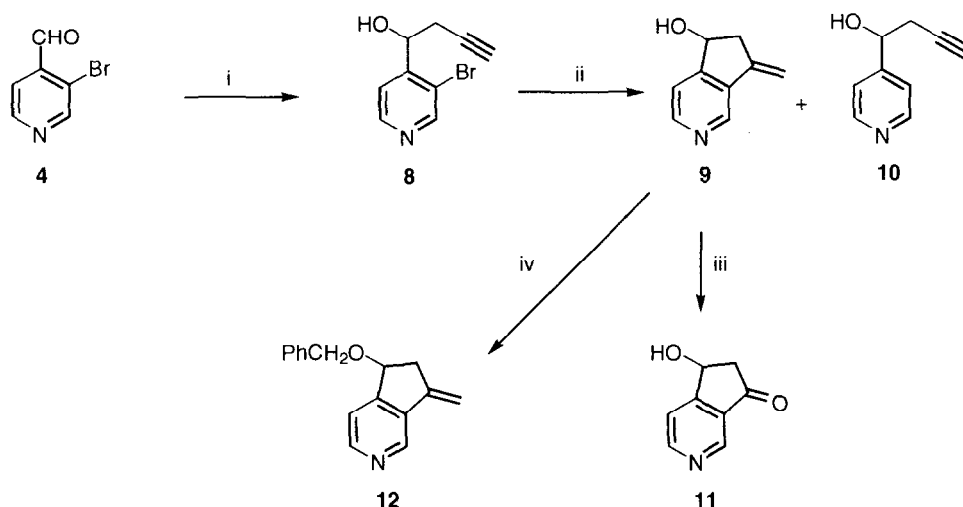
to be the Barbier conditions¹³ using activated zinc powder and allyl bromide in THF at room temperature which gave **5a** in 73% yield. With one cyclisation substrate in hand, we protected the hydroxyl group with *tert*-butyldimethylsilyl chloride (TBDMSCl) to give silyl ether **5b**.¹⁰ Reaction of alcohol **5a** with tributyltin hydride under the usual conditions (0.02M) gave the cyclopentano[c]pyridine in 86% yield as an inseparable 7:3 mixture of *cis*- and *trans*- isomers **6a**¹⁰ and **7a**.¹⁰ The structures and stereochemistries of the two isomers were deduced from ¹H nmr experiments, in particular the minor isomer showed a clear nOe between the benzylic proton attached to the alcohol centre and the methyl group which leads us to assign this the *trans*-stereochemistry. Cyclisation of **5b** under identical conditions gave the corresponding silyl ethers **6b**¹⁰ and **7b**¹⁰ in quantitative yield as a 3:1 mixture of *cis*- and *trans*-isomers. These assignments were confirmed by deprotection to give the alcohols **6a** and **7a** in 88% yield. The predominance of the *cis*-isomer in these cyclisations is in accord with the Beckwith model¹⁴ although it is interesting to note that the bulky silyl group has only a small effect on the isomer ratio. These cyclisations show that pyridine radicals behave in a similar manner to aryl radicals giving exclusively 5-exo cyclisation in these simple cases and with little or no direct reduction product formed. Although lacking an aromatic methyl group and carrying a superfluous hydroxyl group, these cyclisations indicate that the radical approach is a viable route to (±)-actinidine.



Scheme 1 Reagents and conditions: i, LDA in THF at -78°C for 10 min then DMF, 1 hr at -78°C then to room temp. over 1 hr; ii, allyl bromide, Zn powder in THF, room temp. for 2 hr; iii, Bu^tMe₂SiCl, imidazole, DMF, room temp. 4 days; iv, Bu₃SnH, AIBN, toluene, 110°C, 3 hr;

Radical cyclisations onto alkynes are well known^{5a} but present two problems compared to cyclisations onto alkenes. Firstly, sterically-comparable cyclisations are about an order of magnitude slower¹⁵ and secondly, hydrostannation of the triple bond is a competing reaction.¹⁶ This latter problem can be overcome by adding a bulky group to the end of the alkyne.³ Starting with 3-bromo-4-formylpyridine **4** reaction with zinc powder and propargyl bromide proceeded smoothly to give alcohol **8**¹⁰ in 82% yield as a colourless solid (Scheme 2). Without protection of either the hydroxyl group or the terminal alkyne, reaction as before with tributyltin hydride gave a 10:1 mixture of cyclised product **9**¹⁰ and directly reduced product **10**¹⁰ in a combined yield of

84%. The desired product **9** could conveniently be isolated in a pure form by recrystallisation of the mixture. It was pleasing to note that neither hydrostannation nor 6-endo cyclisation were observed. The small amount of reduction product **10** could presumably be eliminated by slow addition of tributyltin hydride. In order to complete the synthesis of (\pm)-oxerine **2**, alkene **9** was reacted with mercury (II) acetate followed by reaction with sodium borohydride but with no success. Even the use of the more reactive mercury (II) trifluoroacetate¹⁷ failed. Similarly, attempts to epoxidise the double bond to allow the synthesis of the tertiary alcohol failed. Ozonolysis of the double bond was successful and gave the aldol **11**¹⁰ in 70% yield. However, it proved impossible to add a methyl group to the ketone using an excess of Grignard reagent (5 equivalents of MeMgBr in THF) and only starting material was recovered. As the benzyl ether **12** corresponding to alcohol **9** had previously been prepared in 8 steps from 3-bromopyridine and converted into (\pm)-oxerine **2** in 3 steps, we simply reacted **11** with benzyl bromide and potassium hydride in THF to give **12** in 80% yield. The analytical and spectral data¹⁸ of **12** matched that reported in the literature⁸ and thus we have completed a formal synthesis of (\pm)-**2**.



Scheme 2 *Reagents and conditions:* i, propargyl bromide, Zn powder in THF, room temp., 12 hr; ii, Bu₃SnH, AIBN, toluene, 110°C, 2 hr; iii, O₃, -78°C, 5:1 dichloromethane:methanol, 4 hr then Me₂S; iv, KH in THF at 0°C for 1 hr then benzyl bromide at 0°C for 2 hr.

In summary, we have shown that the 3-pyridyl radical can be generated under the usual tin hydride conditions and undergoes cyclisation onto both alkenes and alkynes. This chemistry provides a short entry to the cyclopentano[c]pyridine alkaloids.

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References and Notes

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18. There is a typographical error in the ^1H nmr spectrum reported for **12** in reference 8. The ^1H nmr spectrum at 360MHz in CDCl_3 is: δ H 8.83 (1H, s, C2-H), 8.50 (1H, d, J 5 Hz, C6-H), 7.39-7.28 (6H, m, C5-H and phenyl-H), 5.64 (1H, t, J 2 Hz, $\text{C}=\text{CH}_2$), 5.20 (1H, t, J 2 Hz, $\text{C}=\text{CH}_2$), 5.07 (1H, dd, J 7 and 4 Hz, HOCH), 4.68, 4.62 (2H, ABq, J 12 Hz, PhCH_2), 3.10 (1H, ddt, J 16, 7 and 2 Hz, CH_2C), 2.82 (1H, ddt, J 16, 4 and 2 Hz, CH_2C).

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