Pergamon

Tetrahedron Letters, Vol. 37, No. 44, pp. 8049-8052, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01822-9

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

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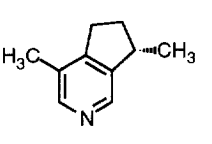
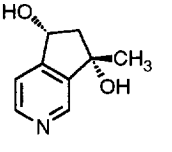
Abstract: *The cyclisation of pyridine radicals derived from 3-bromo-4-substituted pyridines carrying both alkene and alkyne groups in the 4-substituent to give is described. The cyclopentano[c]pyridine skeleton formed by cyclisation is found in many monoterpene alkaloids and a short synthesis of a late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

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-bromoindole[3] and Sundberg has utilised the radical derived from 3-iodoindole.[4] In the pyridine system, there are only three reports[5] which briefly mention cyclisations involving radicals generated from 2- and 4-bromopyridines. We are interested in synthetic routes to the monoterpene alkaloids[6] 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 (±)-oxerine.[8]



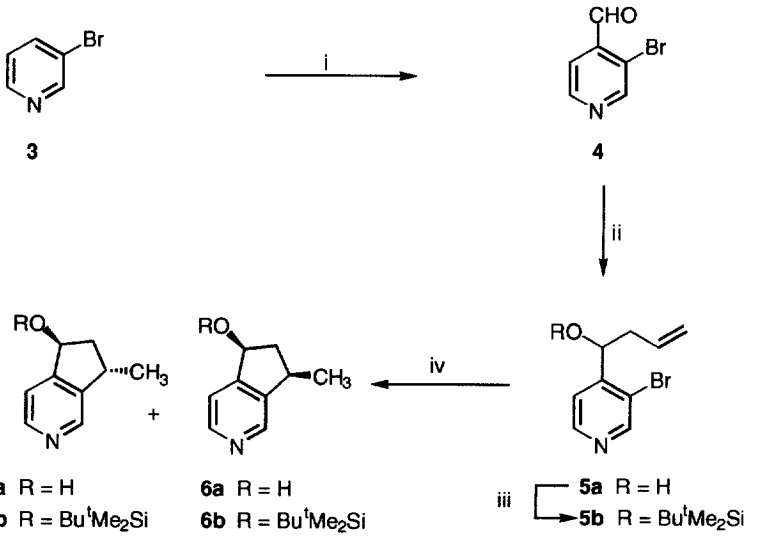
1



2

Ortholithiation and formylation of 3-bromopyridine **3** to give 3-bromo-4-formylpyridine **4** has been reported[9] 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 temperature[11] gave **5a** in only 19% yield. Changing to allyltributylstannane and boron trifluoride at -78°C[12] gave **5a** in 60% yield but the best conditions were found

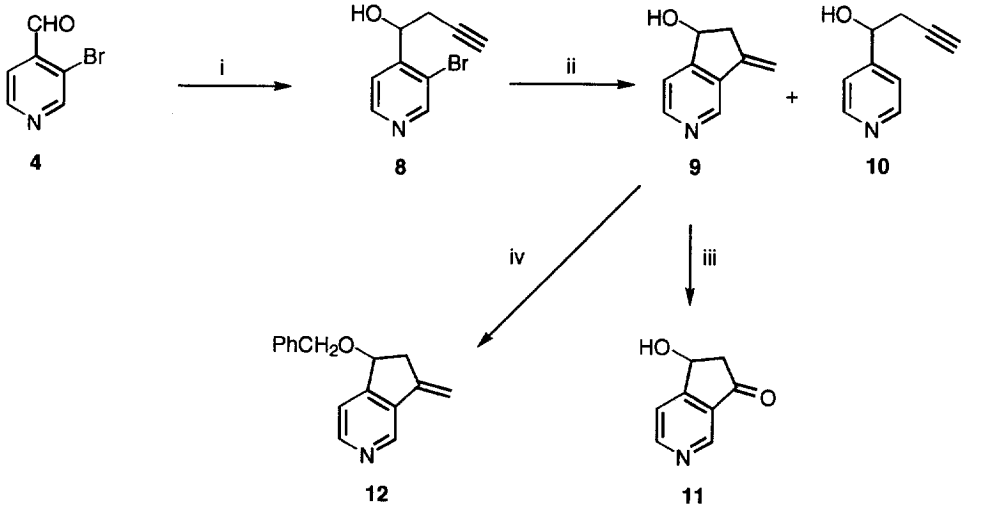
to be the Barbier conditions[13] using activated zinc powder and allyl bromide in THF at room temperature which gave **5a** in 73% yield. With one cyclisation substrate in hand, we protected the hydroxyl group with *tert*-butyldimethylsilyl chloride (TBDMSCl) to give silyl ether **5b**.[10] Reaction 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 ^{1}H 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 model[14] 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^{t}Me$_2$SiCl, imidazole, DMF, room temp. 4 days; *iv*, Bu_3SnH, 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 magitude slower[15] 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 (±)-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) trifluoroacetate[17] 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 (±)-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 data[18] of **12** matched that reported in the literature[8] and thus we have completed a formal synthesis of (±)-**2**.



Scheme 2 *Reagents and conditions*: *i*, propargyl bromide, Zn powder in THF, room temp., 12 hr; *ii*, Bu_3SnH, AIBN, toluene, 110°C, 2 hr; *iii*, O_3, -78°C, 5:1 dichloromethane:methanol, 4 hr then Me_2S; *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.

Acknowledgements. We thank the E.C. for an Erasmus fellowship (AF) and Drs A. Dobbs (King's College London) and C. McCarthy (Rhône-Poulenc Rorer) for invaluable discussions.

References and Notes

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18. There is a typographical error in the ^{1}H nmr spectrum reported for **12** in reference 8. The ^{1}H nmr spectrum at 360MHz in $CDCl_3$ is: δH 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, C=CH_2), 5.20 (1H, t, *J* 2 Hz, C=CH_2), 5.07 (1H, dd, *J* 7 and 4 Hz, HOC<u>H</u>), 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).

(*Received in UK* 22 *August* 1996; *accepted* 13 *September* 1996)