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Asymmetric Synthesis. XXXIV[1]. Synthesis of Spiro-Piperidine Derivatives via the CN(R,S) Method.

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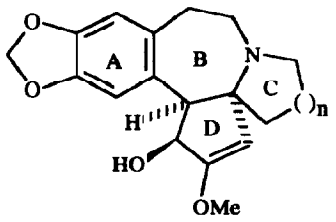
Key-words : Asymmetric synthesis; spiro-piperidine; 5-azaspiro-[3,5] nonane, 6-azaspiro-[4,5] decane.

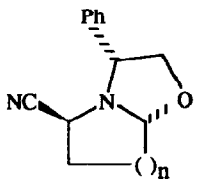
Abstract 5-Aza-spiro-[3,5] nonane and 6-aza-spiro-[4,5] decane derivatives **5** and **9** have been prepared from 2-cyano-6-phenyloxazolopiperidine synthon **2b** via alkylation followed by cyclisation of the resulting halogeno aminonitrile under dissolving metal conditions.

Cephalotaxine **1a**, the major alkaloid isolated from the *Cephalotaxus* species[2] has attracted considerable attention, because of the promising antitumor activity of certain derivatives and its unique structural features.[3,4] However no asymmetric synthesis of cephalotaxine has been yet reported.

In the course of the development of the CN(R,S) method toward the asymmetric synthesis of natural and non-natural biologicaly interesting compounds[5] we envisaged the synthesis of cephalotaxine **1a** and its piperidine homologue **1b** via a strategy based on the use of 2-cyano-phenyloxazolopyrrolidine and piperidine **2a** and **2b** respectively.[6]



1a : n=1
1b : n=2

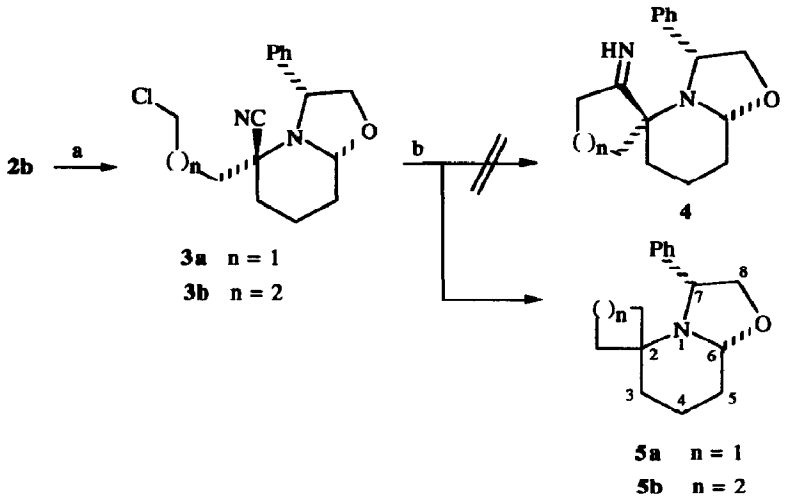


2a : n=1
2b : n=2

The key step of our synthesis was the closure of the spiro C/D ring system. For this purpose we decided to investigate the cyclization of the chiral halogenated cyano-piperidine **3a** obtained from **2b** by alkylation with 1-chloro-3-iodopropane (Scheme 1).

The 1-azaspiro [5,5]-undecan skeleton has recently been constructed by Grierson et coll.[7] by intramolecular reaction of an organolithium reagent, generated by reduction of a chloro substituent with lithium di-*tert*-butylbiphenyl (LiDTBB), on a cyano group. To our surprise, reaction of compounds **3a,b** under the same conditions led to a totally different result. No formation of imine **4** was observed. Instead compound **5a**[8] was obtained in 57% yield with traces of its C-6 epimer. The same reaction performed on compound **3b** furnished the spiro derivative **5b** in 53% yield.

This is the first report of the formation of 5-aza-spiro-[3,5] nonane skeleton. 5-Azaspiro-[3,4] octane has been isolated as a by-product during the oxidation of cyclopropylidene-cyclobutane,[9] and cyclobutyl spiro piperidines at position C-3[10] or C-4[11] are also known.

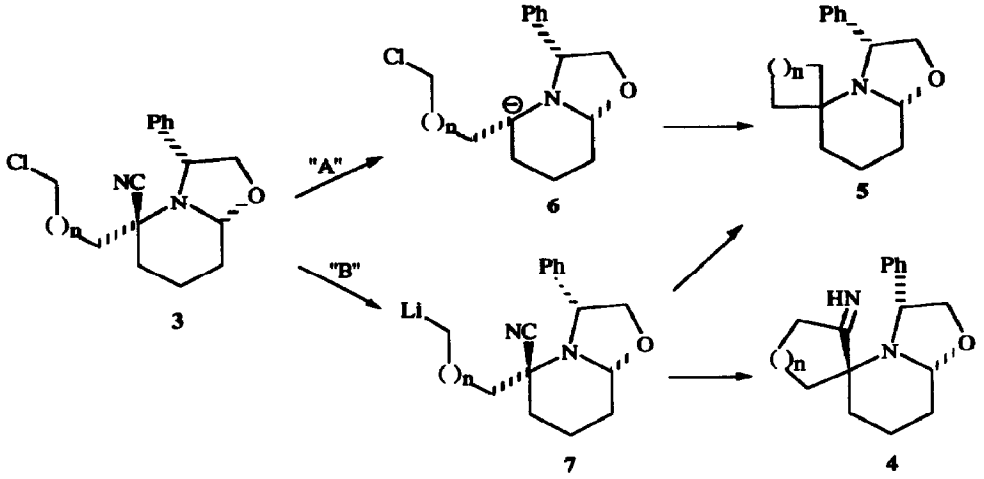


Scheme 1

Reagents and Conditions: a) LDA, THF/HMPA, -78°C then 1-chloro-3-iodopropane or 1-bromo-4-chlorobutane, b) LiDTBB, THF, -78°C, 15 min.

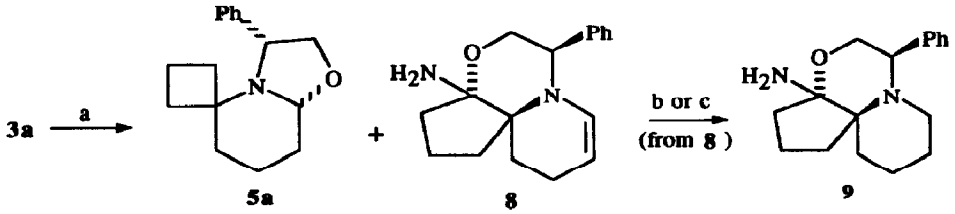
This result was surprising as it is known that alkyllithium compounds react generally with nitriles to give either imines[5b,7,12] or decyanation products[13]. To the best of our knowledge only one example of substitution of nitrile by a lithium reagent has been described: 3-cyanoindoloquinolizidine reacted with methyl or phenyl lithium leading to 3-substituted indoloquinolizidines.[14] Very recently, Yus[15] described the formation and the reactivity of organolithium reagents by reductive decyanation of nitriles under similar conditions (LiDTBB).

Two mechanisms can be considered to explain our result (Scheme 2). The first (pathway "A") involves the α-aminomethyl type carbanion **6** as an amino analogue of Yus' intermediate.[15] In the second one (pathway "B"), an organometallic species **7** could react with the aminonitrile in a substitution reaction leading to spiro derivative **5** instead of the expected imine **4**.



Scheme 2

In order to obtain more information as to the preferred mechanism, we investigated the reactivity of compound **3a** with lithium naphtalide, which is known to generate lithium reagents from alkyl halides.[16] However, depending of temperature, different results were obtained. At room temperature, only spiro derivative **5a** was isolated in 37% yield, but at -78°C we observed the formation of compound **8** (95% yield)[17] with a minor amount of **5a** (2%) (Scheme 3). Compound **8** resulted from cyclisation of the intermediate imine **4a**, after opening of the oxazolidine ring and iminium-enamine equilibrium. Structure **8** was confirmed through the study of the more stable reduction product **9**, obtained by catalytic hydrogenation or $NaBH_3CN$ treatment. Formation of such an enamine has already been observed when a substituted aminonitrile was treated with an organolithium reagent.[5b] Pathway "A" accounts only for the formation of **5**. However the other route "B" can explain the formation of both compounds **5** and **8**. We decided to study the formation of anion **6** in other conditions also described by Grierson,[7] but treatment of **3a** with K, THF, 18-crown-6 (20°C) led only to a complex mixture of products.[18]



Scheme 3

Reagents and conditions : a) Lithium naphtalide, THF, rt or -78°C; b) H_2, Pd/C, MeOH; c) $NaBH_3CN$, MeOH, citric acid.

The difference of reactivity between our series and previously reported tetrahydrooxazinopiperidine series[7] could be due to the presence of the phenyl ring α to the nitrogen. This aromatic ring could act as a Π electron acceptor, then an electron-transfer process might occur with the nitrile leading to anion **6**. It is known that such a process may take place between molecular entities which are separated by as much as 7-9 Å.[19] At -78°C this process would not be observed and the classical metallation of halide would be favoured.

In conclusion, in the course of this work it has been possible to synthetise new spiropiperidine systems which could be used for further transformation to cephalotaxine derivatives.

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References and Notes

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8. **5a** : oil; MS (CI), m/z: 244 (MH^+,100), 215 (4), 124 (6), 104 (8); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.8-2.2 (m, 12H), 3.45 (dd, J=4.9 Hz, J=7.4 Hz, 1H), 3.71 (dd, J=2.8 Hz, J=9.1 Hz, 1H), 3.92-4.04 (m, 2H), 7.1-7.5 (m, 5H); ^{13}C NMR ($CDCl_3$, 62.3MHz) δ (ppm): 14.6; 19.6; 23.3; 30.9; 32.8; 36.7; 60.5; 60.7; 74.5; 90.2; 126.9; 128.5; 145.6.
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17. **9** : Oil; MS (EI), m/z: 270, 253, 149, 148, 106; IR (neat): 1648 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.50 (dd, J=12.1 Hz, J= 4.0 Hz, H-7), 3.78 (t, J= 12.1 Hz, H-8ax), 4.20 (dd, J=12.1 Hz, J=4.0 Hz, H-8eq), 4.35 (m, H-5), 5.58 (dt, J= 8.2 Hz, J= 1.8 Hz, H-6); ^{13}C NMR (CDl_3, 62.3 MHz) d (ppm): 17.7, 20.3, 24.8, 29.2, 36.7, 58.4 (C-7), 64.1 (C-2), 65.8 (C-8), 91.9 (C-10), 99.3 (C-5), 128.1, 128.8, 134.5 (C-6), 138.9.
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