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Preparation of Chiral Hexahydroquinolizinones and Tetrahydroindolizinones by Regio- and Diastereoselective Sonochemical Cyclization of Chiral Dihydropyridines.

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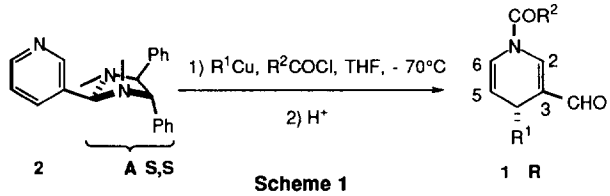
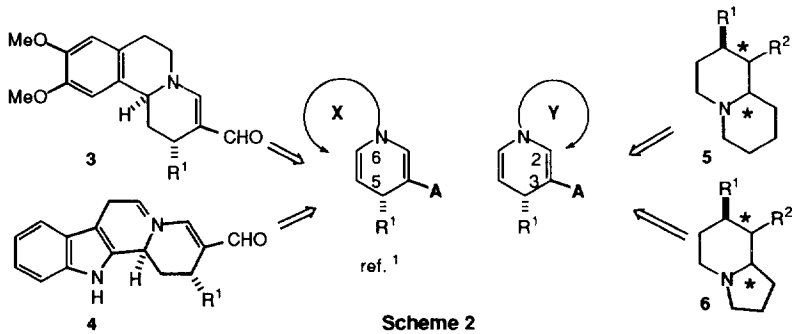
Abstract: *Chiral hexahydroquinolizinones* ***13*** *and tetrahydroindolizinones* ***17*** *were prepared from functionalized chiral dihydropyridines by regio- and diastereoselective sonochemical cyclization.*

We have recently described an efficient asymmetric synthesis of chiral 1,4-dihydropyridines **1** by the addition of organocopper reagents to chiral aminal **2** in the presence of various acyl chlorides (Scheme 1).[1]



Scheme 1

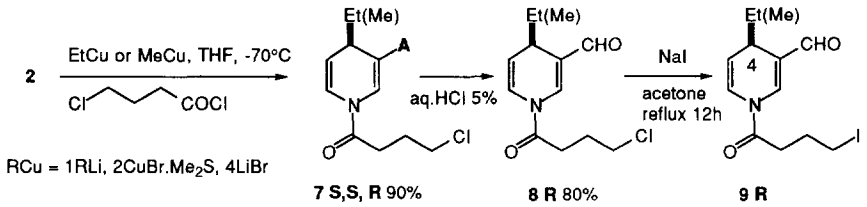
The possibility of utilizing functionalized acyl chlorides was exploited in short syntheses of chiral indolo and benzoquinolizines **3** and **4**, involving a cyclization on the C_5-C_6 double bond of the dihydropyridine ring (**X** in Scheme 2).[1]



Scheme 2

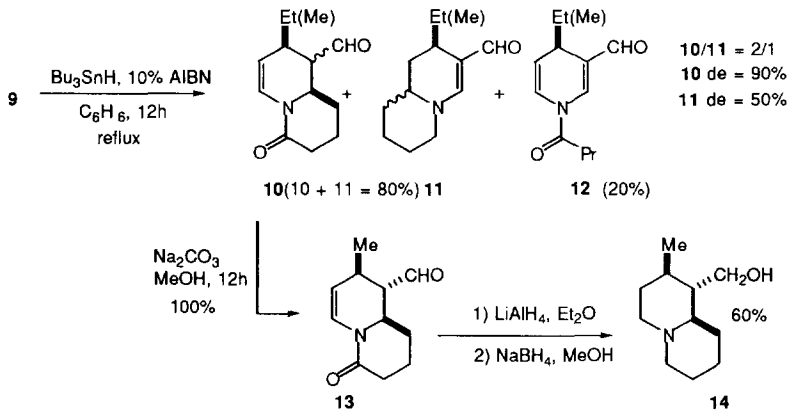
We now report that the use of chlorobutanoyl or chloropropanoyl chloride allows the preparation of functionalized 1,4-dihydropyridines which can be used for the synthesis of close precusors of chiral quinolizidines **5** and indolizidines **6**,[2] *via* a cyclization involving the C_2-C_3 double bond (**Y** in Scheme 2).

Addition of ethyl or methyl copper on aminal **2** (prepared with a diamine of S,S configuration) in the presence of 4-chlorobutanoyl chloride (Scheme 3) afforded aminals **7** in good yield (91%) as unique diastereomers, as shown by ^{1}H NMR. An acidic hydrolysis afforded the chlorodihydropyridines **8** (of R configuration[1]) which were then converted into iododihydropyridines **9.**



Scheme 3

By analogy with several reports on radical cyclizations of similar systems,[3] the pure crude iododihydropyridines **9** were treated with Bu_3SnH and AIBN in benzene under reflux to give, after isolation by flash chromatography (SiO_2, ether), **10** and **11** resulting from a cyclization on the C_2-C_3 or C_5-C_6 double bond (**10/11** = 2/1) and the reduction products **12** (Scheme 4).



Scheme 4

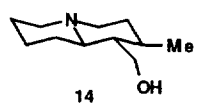
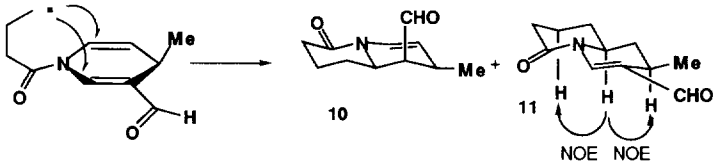


Fig. 1

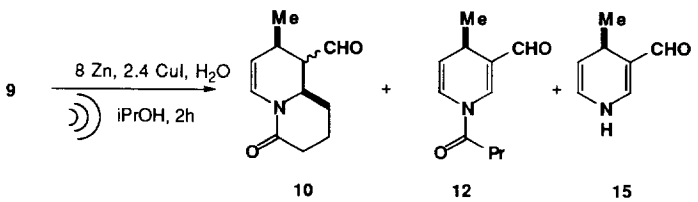
The bicycles **10** were obtained as a mixture of diastereomers (9/1) as shown by ^{1}H NMR. In the presence

of sodium carbonate in methanol, **10** (Me) afforded **13** [4] in a very good diastereomeric purity (de>95%). Reduction of **13**, according to Scheme 4, gave the quinolizidine **14** [5] as a crystalline compound. The relative configuration of the three stereogenic centers of **14** (fig.1), determined by X ray analysis, indicated that the radical obtained from **9** cyclized *cis* to the C_4 substituent. The two diastereomers **11** (de = 50%) were separated by preparative thin layer chromatograhy (SiO_2, ether, 2 migrations), and the relative configuration of the major diastereomer was determined by ^1H NMR (NOE effects, Scheme 5). These results indicated that again, the cyclization occured mainly *cis* to the C_4 substituent (Scheme 5).



Scheme 5

After several unsuccessful attempts to increase the regioselectivity of the cyclization, we have employed the Luche conditions: sonication of **9** in isopropanol in the presence of Zn and CuI (Scheme 6).[6] Under these conditions, a regioselective reaction was observed affording **10** (as a mixture of diastereomers) in 60% yield, the reduction product **12** (30%) and the "free" dihydropyridine **15** (10%).

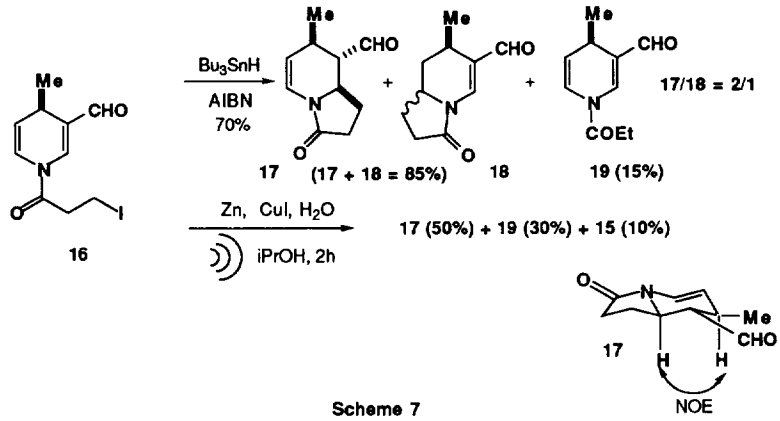


10 = 60%
12 = 30%
15 =10%

Scheme 6

As previously described in Scheme 4, the diastereomeric mixture **10** was quantitatively converted into the diastereomerically pure **13** under basic conditions. Therefore, the stereochemistry of the cyclization obtained under sonication is the same as the one observed with Bu_3SnH, AIBN.

A similar study was performed on the iododihydropyridine **16** prepared as for **9** (Scheme 3) using 3-chloropropanoylchloride. With Bu_3SnH / AIBN, two regioisomers **17** (de >95%), **18** (de = 50%) and the reduction product **19** were obtained (Scheme 7). The relative configuration of **17** was determined by ^1H NMR (NOE effects) suggesting as before that again the cyclization occurs *cis* to the C_4 substituent, but with epimerization of the aldehyde substituent *in situ*. Using Luche's conditions, only one regioisomer **17** [7] was obtained (50% yield, de >95%) with the by-products **19** (30%) and **15** (10%).



Scheme 7

In conclusion, we have described regio- and diastereoselective cyclizations of functionalized dihydropyridines affording bicyclic compounds which are possible precursors of benzo and indoloquinolizines. Applications of this methodology are in progress.

References and notes

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4 ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (d, J = 4.1 Hz, 1H), 7.24 (dd, J = 8.45 Hz, J = 2.4 Hz, 1H), 4.99 (dd, J = 8.45 Hz, J = 2.13 Hz, 1H), 3.72 (ddd, J = 10.5 Hz, J = 10.5 Hz, J = 3.8 Hz, 1H), 2.65 (m, 1H), 2.52 (m, 1H), 2.41 (m, 1H), 2.2 ((ddd, J = 10.5 Hz, J = 10.5 Hz, J = 4.1 Hz, 1H), 2.0 (m, 2H), 1.72 (m, 1H), 1.59 (m, 1H), 1.02 (d, J = 6.94 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 202.06, 167.26, 122.55, 113.72, 59.29, 54.36, 32.23, 29.09, 28.02, 19.42, 19.22; $[\alpha]^{20}_D$ = 154 (*c* = 1.2, $CHCl_3$)

5 ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (dd, J = 11.5 Hz, J = 2.2 Hz, 1H), 3.77, (dd, J = 11.5 Hz, J = 2.2 Hz, 1H), 2.83 (m, 2H), 2.20-1.10 (m, 14H), 0.99 (d, J = 6Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 62.96, 59.76, 57.26, 56.55, 50.50, 34.26, 30.95, 29.90, 25.63, 24.78, 20.11; $[\alpha]^{20}_D$ = -124 (*c* = 5, $CHCl_3$).

6 Dupuis, C., Petrier, C.; Sarandeses, L.A.; Luche, J.L. *Synth. comm.*, **1991**, *21*, 643-651.

7 ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (d, J = 2.5 Hz, 1H), 6.8 (dd, J= 8 Hz, J = 2.4 Hz, 1H), 4.93 (dd, J = 8 Hz, J = 2 Hz, 1H), 3.84 (ddd, J = 10.4 Hz, J = 10.4 Hz, J = 5.9 Hz, 1H), 2.69 (m, 1H), 2.42 (m, 3H), 2.19 (ddd, J = 10.4 Hz, J = 2.5 Hz, J = 2.5 Hz, 1H), 1.76 (m, 1H), 1.15 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 201.85, 171.08, 120.37, 114.23, 58.94, 55.0, 31.10, 30.42, 25.33, 19.50; $[\alpha]^{20}_D$ = +10 (*c* = 2.2, $CHCl_3$).

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