

# INTRAMOLECULAR CYCLIZATIONS OF HANTZSCH 1,4-DIHYDROPYRIDINES: SYNTHESIS OF DI- AND TETRAHYDROINDENO[2,1-c]PYRIDINES

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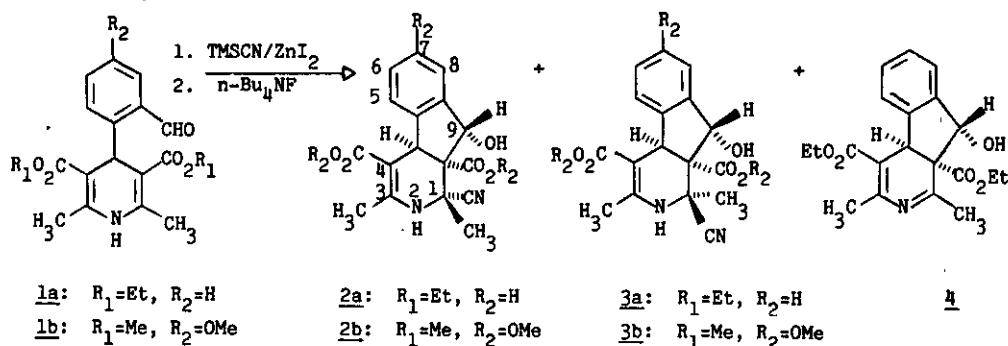
**Abstract** - Hantzsch 4-phenyl-1,4-dihydropyridines bearing electrophilic ortho substituents react with trimethylsilyl cyanide/zinc iodide or base resulting in an intramolecular cyclization reaction to give di- and tetrahydroindeno[2,1-c]pyridines in good yield.

The chemistry surrounding Hantzsch type 1,4-dihydropyridines<sup>1</sup>, stimulated in large part by the calcium channel blocking drugs exemplified by nifedipine, has seen a resurgence of interest.<sup>2</sup> Several novel and unexpected intramolecular cyclization reactions have been reported recently.<sup>3-8</sup> Further, intermolecular alkylations of Hantzsch 1,4-dihydropyridines have been disclosed.<sup>12</sup> This report prompts us to disclose our observation of useful intramolecular transformations in this class of molecules.

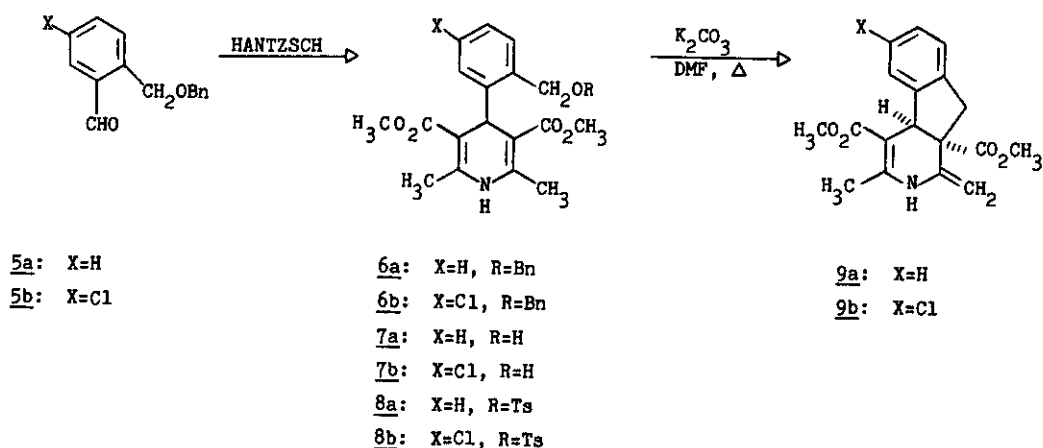
Hartman and coworkers<sup>6-9</sup> have reported that 4-aryl-1,4-dihydropyridines which bear olefinic substituents at the ortho position of the aryl ring undergo Lewis acid mediated cyclization between the olefin and the 2 and 5 positions of the dihydropyridine ring to produce bridged bicyclo structures. This result apparently arises in part from the nucleophilic nature of the C-3 carbon in a 3-carboxy substituted 1,4-dihydropyridine. Now we have observed nucleophilic behavior of the C-3 carbon in zinc iodide catalyzed and base catalyzed reactions of 4-aryl-1,4-dihydropyridines which bear nonolefinic electrophilic substituents at the ortho position of the aromatic ring.

Treatment of dihydropyridine carboxyaldehydes 1(a,b)<sup>5,6</sup> with three equivalents of trimethylsilyl cyanide and a catalytic amount of zinc iodide in methylene chloride at room temperature for 18 h followed by treatment of the crude product with tetrabutylammonium fluoride in tetrahydrofuran gave a 1:1 mixture of diastereomeric tetrahydroindeno[2,1-c]pyridines 2(a, mp:173-175°C; b, mp:118°C) and 3(a, mp:190-192°C; b, mp:120-121°C) along with a small amount of the dihydroindeno[2,1-c]pyridine 4(mp:150-152°C).<sup>10</sup> The diastereomers 2 and 3 along with compound 4 were readily separated by chromatography on silica gel (3:1 ether-hexane, 2a:  $R_f = 0.22$ , 3a:  $R_f = 0.28$ , 4:  $R_f = 0.38$ ). The relative stereochemistry of compounds 2(a,b) and 3(a,b) was assigned on the basis of observation of an nOe in 2(a,b) between the C-1 methyl group and the C-9 methine proton. An nOe between these resonances was not observed in isomer 3(a,b). The possibility that isomer 3(a,b) has the opposite configuration at C-9 relative to 2(a,b) cannot be ruled out entirely, however the expected change in chemical shift for the C-9 methine proton between the isomers is not observed. Compound 4

presumably arises by elimination of HCN from either of the tetrahydroindeno[2,1-c]pyridines. We feel that this must be the case as treatment of aldehyde 1 with a variety of Lewis acid catalysts alone does not lead to any cyclized products.



The base catalyzed mode of cyclization was observed when a 4-phenyl-1,4-dihydropyridine containing an ortho tosylmethyl group was treated with potassium carbonate in DMF. The requisite tosylates 8(a,b) were prepared from aldehydes 5(a,b)<sup>9</sup> by Hantzsch synthesis (2 eq. methyl acetoacetate, ammonium hydroxide, 2-propanol, reflux) to give dihydropyridines 6(a,b). The benzyl ethers 6(a,b) were selectively deprotected by hydrogenolysis over 5% palladium on carbon (methanol, 50 psi  $H_2$ ) and the resulting benzylic alcohols 7(a,b) were tosylated (1.1 eq.  $TsCl$ ,  $Et_3N$ ,  $CH_2Cl_2$ ,  $0^\circ C$ ) to give 8(a,b) in good yield. When a solution of tosylates 8(a,b) in dry DMF containing an excess of powdered potassium carbonate was heated at  $100^\circ C$  for 2.5h, tetrahydroindeno[2,1-c]pyridines 9(a, mp:186-187^\circ C; b, mp:205-208^\circ C)<sup>10</sup> were formed in 70 to 80% yield (after recrystallization from ethyl acetate).



The affinity of these conformationally restricted 1,4-dihydropyridine derivatives for the nitrendipine binding sites has provided further information on the topography of the regulatory sites in the calcium slow channel. The biological data acquired with these compounds will be reported elsewhere.

## ACKNOWLEDGEMENTS

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10. Aldehydes 5a and 5b were prepared from the corresponding o-bromobenzyl bromides using the general method described in ref. 6 by the following sequence of reactions: i) 1.5 eq.  $\text{BnONa}$ , DMF,  $90^\circ\text{C}$ , 18h, ii) 1.08 eq.  $n\text{-BuLi}$ , THF,  $-78^\circ\text{C}$ , 2h, iii) 1.0 eq. N-formylpiperidine,  $-78^\circ\text{C}$  to  $0^\circ\text{C}$ , 30 min.
11.  $^1\text{H}$  Nmr spectral data (360 MHz,  $\text{CDCl}_3$ ) 2a:  $\delta$ 1.23(t, J = 7.0, 3H), 1.34(t, J = 7.0, 3H), 1.82(s, 3H), 2.28(s, 3H), 4.2-4.4(m, 4H), 4.8(br s, 1H), 5.02(s, 1H), 5.39(s, 1H), 7.25-7.45(m, 4H). 2b:  $\delta$ 1.81(s, 3H), 2.28(s, 3H), 2.95(d, J = 4.1, 1H), 3.75(s, 3H), 3.79(s, 3H), 3.81(s, 3H), 4.20(s, 1H), 4.90(s, 1H), 5.39(d, J = 4.1, 1H), 6.85(dd, J = 2.5, 7.5, 1H), 6.91(d, J = 2.5, 1H), 7.13(d, J = 7.5, 1H). 3a:  $\delta$ 1.21(t, J = 7.0, 3H), 1.37(t, J = 7.0, 3H), 1.93(s, 3H), 2.20(s, 3H), 4.1-4.3(m, 4H), 4.80(s, 1H), 5.70(s, 1H), 7.15(m, 4H). 3b:  $\delta$ 1.95(s, 3H), 2.22(s, 3H), 3.65(d, J = 12.0, 1H), 3.75(s, 3H), 3.78(s, 3H), 3.80(s, 3H), 4.08(s, 1H), 4.75(s, 1H), 5.68(d, J = 12.0, 1H), 6.72(dd, J = 2.0, 8.0, 1H), 6.86(d, J = 2.0, 1H), 7.27(d, J = 8.0, 1H). 4:  $\delta$ 1.30(t, J = 7.0, 3H), 1.36(t, J = 7.0, 3H), 1.44(s, 3H), 2.25(s, 3H), 3.97(s, 1H), 4.26(q, J = 7.0, 2H), 4.92(s, 1H), 6.34(s, 1H), 7.15-7.45(m, 4H). 9a:  $\delta$ 2.30(s, 3H), 3.22(d, J = 15.0, 1H), 3.59(d, J = 15.0, 1H), 3.61(s, 3H), 3.70(s, 3H), 4.30(d, J = 1.5, 1H), 4.45(d, J = 1.5, 1H), 4.60(s, 1H), 6.00(br s, 1H), 6.90-7.20(m, 4H). 9b:  $\delta$ 2.31(s, 3H), 3.20(d, J = 15.0, 1H), 3.61(d, J = 15.0, 1H), 3.65(s, 3H), 3.70(s, 3H), 4.31(d, J = 1.5, 1H), 4.45(d, J = 1.5, 1H), 4.58(s, 1H), 6.08(br s, 1H), 6.85-7.10(m, 3H).
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