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AN EFFICIENT SYNTHESIS OF (±)-PINIDINE

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Abstract. A total synthesis of (±)-pinidine I was accomplished starting from the readily available propargylic tosylate 1 and 5-bromo-2-pentanone 2.

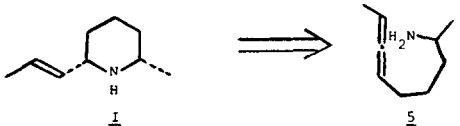
The most commonly employed ways of building up the 2,6-disubstituted piperidine skeleton are the hydrogenation of pyridines (1), cyclization of aminoketones (2), electrophile-initiated cyclization of alkenyl amine derivatives (3), rearrangements (4), and the elegant synthetic strategies using 2-cyano-Δ^3 piperidines and chiral 1,4 dihydropyridine equivalents which provide control of both diastereo-(5) and enantioselection (6) concerning the relative and absolute configuration of the alkyl substituents attached to the ring.

We have recently reported a new heterocyclization process on γ- and δ-allenic amines leading to 2-substituted pyrrolidines and piperidines, initiated either by mercuric chloride or silver nitrate (7). The synthetic usefulness of this methodology relies upon the possibility of facile substitution on the allenic linkage, on various substitution patterns possible for the aliphatic chain and nitrogen before and after preparation of the allenic precursor. In connection with this study, we describe in this paper a high yield process for the synthesis of the piperidine alkaloid pinidine I, isolated from Pinus Sabiniana Dougl. and related plant species (8).

The stereochemistry of pinidine was established by chemical and spectroscopic methods by Hill and coworkers (9), and its first synthesis has been achieved by Leete (10) starting from 2,6-lutidine.

From earlier observations on the intramolecular cyclization of δ-allenic alcohols (11), we expected a highly diastereoselective synthesis of the 2,6-disubstituted piperidine skeleton.

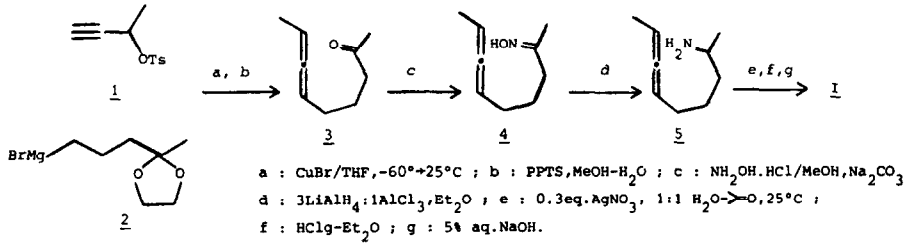
Our approach, which employs readily available precursors and can be carried out under mild conditions, is based on silver catalyzed C-N bond formation process which we are currently investigating.



I 5

Coupling of the Grignard reagent 2 (12) with propargylic tosylate 1 in the presence of CuBr provided the protected allenic ketone, which led, after deprotection (13), to the allenic ketone 3 in 85% overall yield. Oxime formation and

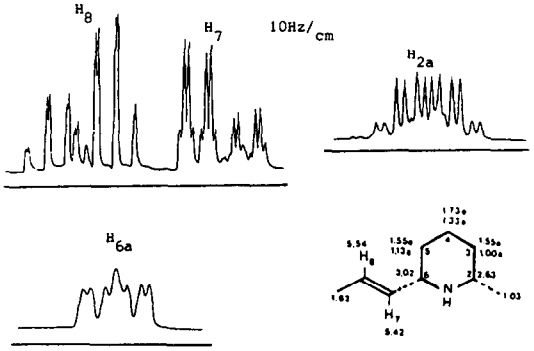
subsequent reduction (14) afforded the key intermediate 5 in quantitative yield. The cyclization procedure was simple to perform: the amine and the catalyst were stirred in 1:1 water-acetone at room temperature, until thin layer chromatography (100$CHCl_3$:20MeOH:1NH_4OH) or gas chromatography (fused silica capillary column OV101, 80 °C) indicated consumption of the starting material (~24 h). Workup was effected, after dilution with ether, by filtration of the catalyst, washing the organic layer with 5% aq. NaOH, brine and water drying over magnesium sulfate and concentrating at reduced pressure (15). The crude simply purified by Kugelrohr distillation, gave a mixture of two isomers (62/38) in quantitative yield (Scheme I).



Scheme I

The cis and trans-isomers of (±)-pinidine, thus obtained, were separated by fractional crystallization of the hydrochlorides from 1:20 CH_2Cl_2-Et_2O. The trans-isomer was the more soluble and the cis-isomer constituted more than 95% of the hydrochlorides, after one fractional crystallization.

Stereochemical assignment of I is based on the 360 MHz ^1H NMR spectrum which clearly establishes the (E)-double bond geometry (coupling constant of the vinylic protons: 15.4 Hz) and the position of substitution at C-2,C-6 (2,6-alkyl



Scheme II
360MHz ^1H-NMR ($CDCl_3$) spectrum of (±)-pinidine

substituents are equatorial, chemical shifts of C-2H:2.63 ppm; C-6H:3.02 ppm; axial-axial couplings for C-2H-3H, C-5H-6H:10 Hz). Physical data is identical in all respects with an authentic sample (16).

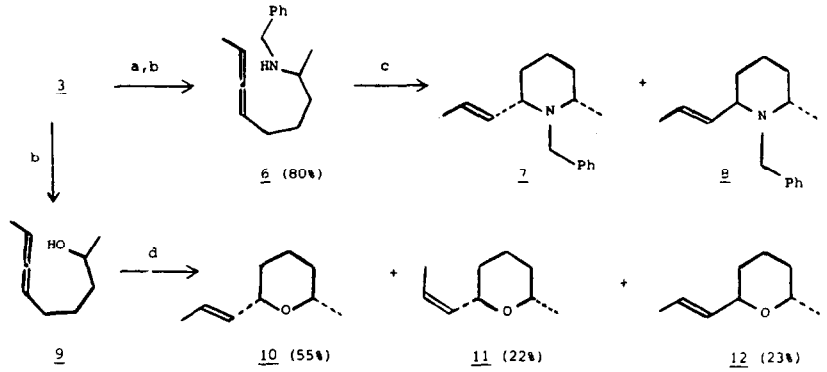
In an attempt to ascertain the factors controlling the diastereoselection in the cyclization reaction we examined the influence of experimental conditions

(such as solvent, temperature, time, metal stoichiometry) and substitution on nitrogen. While heating increased slightly the thermodynamically more stable cis-isomer (17) (cis/trans) ratio: 70/30 upon heating at 60 °C for 48 h), substitution on nitrogen exerted the opposite effect on product distribution. Thus, N-benzyl substituted allenic amine **6** which was synthesized as outlined in Scheme III, afforded an approximately 1:1 mixture of cis/trans-isomers upon treatment with 0.3 eq. of silver nitrate (48 h stirring at room temperature) in a quantitative yield (Scheme III).

The resulting N-benzylpinidines **7** and **8** were separated by silica gel column chromatography (eluant: 1:10 Et_2O-CH_2Cl_2), and their structures were assigned on the basis of well-defined spectral data (18).

Finally, for the purpose of comparison, we have also investigated diastereoselectivity in the oxygen analog **9**.

Treatment of **9** with 0.3 to 2.5 eq of $AgNO_3$ at room temperature failed to generate any cyclized product, and this provided evidence that allenic amines are considerably more reactive than their oxygen analogs where hydroxy group survive intact the catalytic cyclization process. Heating of **9** with 2.5 eq of $AgNO_3$ (24 h at 60 °C in 1:1 H_2O- >= 0) gave a mixture of three products **10-12**, characterized by their GC/MS - FFAP, 50 m, 60 °C - and 360 MHz ^1H NMR



a : $PhCH_2NH_2$,C_6H_6,reflux, Dean-Stark ; b : $LiAlH_4/Et_2O$,25°C ; c : 0.3eq.$AgNO_3$,1:1 H_2O->=0,25°C ; d : 2,5eq.$AgNO_3$, 1:1 H_2O- >=0,60°C.

Scheme III

spectra of the mixture. Unlike allenic amine **5**, alcohol **9** gave rise to the isomer **11** with (Z)-double bond geometry together with cis-2,6 **10** and trans-2,6 **12**.

The potential of this route to 2,6-disubstituted piperidines compares favorably with other reported methods by its use of non-toxic, readily available reagents, mild reaction conditions, and a minimum number of synthetic steps. We believe the current approach will be applicable to other piperidine and pyrroli-

dine alkaloids and will prove compatible with functionalized allenic amines.

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15. Care should be taken to avoid losses of volatile pinidine.

16. I: ^{13}C NMR ($CDCl_3$, 88 MHz, TMS δ = 0) 17.8(q); 23.0(q); 24.7(t); 32.3(t); 33.8(t); 52.2(d); 59.5(d); 125.0(d); 135.1(d). Pinidine. HCl m.p. 186-188 °C. Elemental composition substantiated by combustion analysis: $C_9H_{18}NCl$.MS m/z (relative intensity): 139 (M-HCl, 51); 124(100); 111(19); 98(27); 97(13).

17. In all cases investigated involving longer stirring periods, heating, excess of metal, varying solvent polarity, the 2,6-cis-isomer was the main isomer in the synthetic mixture. Shorter reaction times were obtained either by heating or adding a small excess of silver nitrate.

18. Our ^1H and ^{13}C NMR spectra--numerous decoupling experiments--are in complete agreement with those reported on the dihydropinidine series by M. BONIN, These de Docteur 3eme cycle, Universite Paris-Sud (Orsay), 1982.

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