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Preparation of *trans*-2-Allyl-6-alkyl(aryl)-1,2,3,6-tetrahydropyridines by Reductive *trans*-2,6-Dialkylation of Pyridine. Synthesis of (±)-Epidihydropinidine.

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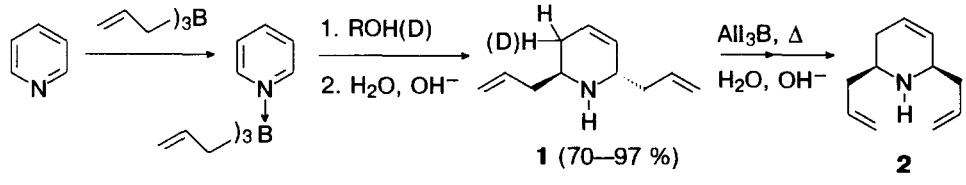
Abstract: A convenient method for the preparation of the title compounds involving the sequential treatment of pyridine with RLi (R = Alk, Ar), triallylborane and methanol is developed.

Organoboron compounds have been attracting attention currently because of their importance as synthetic intermediates.[1] Recently we have found that pyridines undergo reductive *trans*-2,6-diallylation on treatment with triallylborane and alcohols (1:1:4) to give the corresponding 1,2,3,6-tetrahydropyridines in 70—97 % yields,[2—5] e.g.



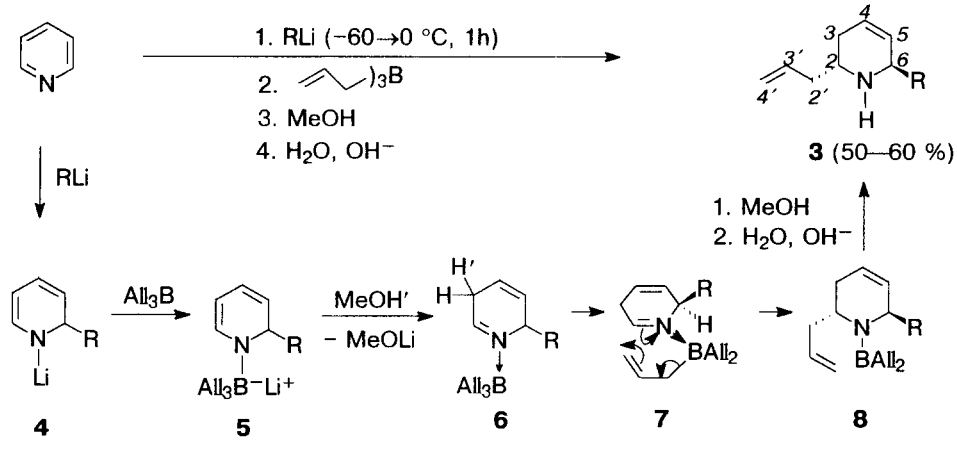
1 (70—97 %) **2**

Furthermore, the *trans*-isomer **1** and related compounds are cleanly converted into the corresponding *cis*-isomers (e.g. **2**) on heating with triallylborane at 130 °C followed by deboronation (H_2O, OH^-).[2,4,5] By hydrogenation of **1** and **2**, *trans*- and *cis*-dipropylpiperidines were obtained in isomerically pure form.[2,3] Consequently, it is now possible to synthesize each of the two isomers of 2,6-diallyl-Δ^3-piperideine and 2,6-dipropylpiperidine starting from the corresponding pyridine and triallylborane. These elegant reactions open new perspectives in heterocyclic chemistry leading to the compounds of type **1** and **2** containing several functional group: double bonds and the NH group.

However only symmetrical 2,6-disubstituted Δ^3-piperideines and piperidines can be prepared with the use of the above reactions. At the same time a number of the piperidine alkaloids contain two different substituents at C-2 and C-6, e.g. solenopsin A (*trans*-2-methyl-6-undecylpiperidine), dihydropinidine (*cis*-2-methyl-6-propylpiperidine), and epidihydropinidine (*trans*-2-methyl-6-propylpiperidine).

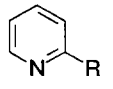
Taking this into account we worked out a convenient general way to unsymmetrical *trans*-2-allyl-6-alkyl(aryl)-1,2,3,6-tetrahydropyridines **3** based on the combination of the well known 1,2-addition reaction of RLi to pyridine[6] and allylboration of intermediate imine formed on treatment of the adduct with methanol.

Synthesis of **3** is performed in a one-pot procedure. Pyridine is first added to a solution of RLi at 0 °C (R = Me, Ph) or at – 60 °C (R = Bu) and the mixture is stirred for 1 h. Triallylborane and methanol are then successively added below – 15 °C (conditions are presented in the Table). Final deboronation is carried out by treating the reaction mixture with a solution of NaOH (10—20 %), upon which all the organoboron and lithium compounds formed pass into the aqueous layer. Reagents should be used in a ratio Py:RLi:All_3B:MeOH:NaOH = 1:1:1:3:1.2.



3a, R = Me
3b, R = *n*-Bu
3c, R = Ph

Possible pathway to **3** is presented in the Scheme. Reaction of lithium derivative **4** with triallylborane seems to produce enamine ate-complex **5**, alcoholysis of which (cleavage of B—N bond) proceeds with the migration of the double bond[2—4] to give imine complex **6** (proton of MeOH adds to C-3 of the ring). Allylboration of the C=N double bond in the latter *proceeds trans-stereoselectively (7) with respect to the substituent in the ring (Alk, Ph) and this step is responsible for the trans-stereochemistry in the final product* **3**. Subsequent alcoholysis of **8** (the cleavage of B—N bond by methanol used in excess) affords amine **3**.



9b, R = Bu
9c, R = Ph

Yields of **3** reached 90—94 % (g.l.c. and NMR) and the isolated yields were 50—60 % (see below). Thus the crude product from the reaction of BuLi contains **3b** (90 %), 2-butylpyridine **9b** (9 %) and, probably, 2-butyl-1,2,5,6-tetrahydropyridine (1 %). When reaction of BuLi with pyridine is carried out at 0 °C, the content of **9b** in the crude product increases to 40 %.

In the crude product from the reaction with PhLi, compounds **3c** (94 %) and

2-phenylpyridine **9c** (6 %) were detected by g.l.c.

Secondary amines **3** are stronger bases ($pK_a \approx 10$) than 2-R-pyridines ($pK_a \approx 6$)[7] and the differences in their basity make it possible to develop a convenient procedure for the isolation of **3b,c** in pure state (separation of **9b,c**). Thus, a mixture of **3c** (94 %) and **9c** (6 %) obtained from PhLi is treated with 2 N HCl (0.95 equiv., based on content of **3c**). The hydrochloride **3c•HCl** thus formed passes into the aqueous layer. The organic layer containing **9c** and some **3c** is separated and the water layer is extracted twice with ether. Amine **3c** was isolated in a 53 % yield by treating the aqueous layer with NaOH and then extracting it with ether, drying (K_2CO_3) and distilling (Table). Amine **3b** was prepared similarly in a 60 % isolated yield.

Product **3a** was isolated by distillation.

Table. Synthesis and Physical Properties of Compounds **3**.

3[a]	Yield (%)[b]	B.p. °C (Torr)	n_D^{19}	M.p. °C of 3·HCl	Conditions of reaction RLi + Py	+ AlI_3B + MeOH
3a	52(92)	55–56(6)	1.4777	125.5–126	0→20 °C, 1 h, ether–THF (2:3)	–15 °C → (10 °C, 1 h)
3b	56(90)	100–101(6)	1.4751	150.5–151.5	–60 °C, 1 h, hexane–ether (1:5)	–60 °C → (10 °C, 1 h)
3c	53(94)	101–103(1)	1.5510	145–147	0 °C, 1 h, ether	–30 °C → 10 °C

[a]Satisfactory elemental analyses were obtained. [b]Isolated yields of purified products (g.c.yield).

The structures of the compounds **3a—c** were in a complete accordance with the data of IR, MS, ^1H, and ^{13}C NMR.[8] The assignment of signals in ^1H NMR spectra was confirmed by $^1H—^1H$ COSY spectra. The *trans*-configuration of amines **3a—b** was established by 2D NOESY experiments (see Fig.).

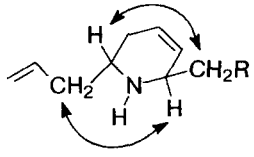
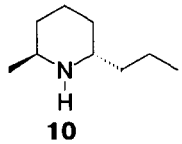


Fig. NOE's observed, in a phase-sensitive 2D NOESY experiment, indicative of the *trans*-configuration of compound **3a** (R = H) and **3b** (R = Pr).

Trans-configuration **3c•HCl** was confirmed by X-ray analysis.[9]



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Hydrogenation of **3a** over Raney Ni in acetic acid (100 atm H_2, 100—105 °C) led (70 %) to alkaloid (±)-epidihydropinidine (*trans*-2-methyl-6-propylpiperidine), an alkaloid isolated from several *Picea* (spruce) species,[10] b.p. 53—54 °C/7 Torr, n_D^{20} 1.4480; **10•HCl**, m.p. 136.5—137.5 °C; ^1H and ^{13}C NMR spectra of **10** and **10•HCl** are in accordance with spectra described previously.[10a]

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8. **3a:** IR (neat, cm^{-1}) 3260 (br), 3070, 3010, 2960, 2910, 2820, 1640, 1430, 1365, 1320, 1200, 1125, 1060, 995, 915, 715. ^1H NMR (400 MHz, $CDCl_3$): δ 1.15 (d, 3H, CH_3, J = 7 Hz), 1.48 (br. s, 1H, NH), 1.80 (dddt, 1H, H-3a, ^2J = 17.3 Hz, ^3J = 8.2, 2.7 Hz, ^4J = 2.6 Hz), 2.07 (dddt, 1H, H-3b, ^3J = 2×5.8 Hz, ^4J = 1.3 Hz), 2.19 (m, 2H, H-2′), 2.98 (m, 1H, H-2), 3.54 (m, 1H, H-6), 5.07 (dm, 1H, H-4′a, ^3J = 10.1 Hz), 5.11 (dm, 1H, H-4′b, ^3J = 16.2 Hz), 5.64 (dm, 1H, H-5, ^3J = 10.0 Hz), 5.70 (dm, 1H, H-4), 5.80 (ddt, 1H, H-3′, ^3J = 7.6 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.24 (CH_3), 30.90 (C-3), 39.88 (C-2′), 46.34 and 47.23 (C-2 and C-6), 116.79 (C-4′), 123.69 (C-4), 131.09 (C-5), 135.20 (C-3′). EIMS: 96 $[M-C_3H_5]^+$. Anal. calc. for $C_9H_{15}N$: C 78.77, H 11.02, N 10.21. Found: C 78.81, H 11.42, N 10.57.

   3a•HCl: M.p. 125.5—126 °C (from ethyl acetate). ^1H NMR (200 MHz, $CDCl_3$): δ 1.60 (d, 3H, CH_3), 2.20—2.75 (m, 3H, H-3a and H-2′), 2.82—3.08 (m, 1H, H-3b), 3.35—3.55 (m, 1H, H-2), 3.90—4.15 (m, 1H, H-6), 5.05—5.33 (m, 2H, H-4′), 5.52—5.96 (m, 3H, —CH=), 9.75 (br. s, 2H, NH_2^+). ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.91 (CH_3), 26.14 (C-3), 35.56 (C-2′), 47.13 and 48.07 (C-2 and C-6), 119.21 (C-4′), 123.64 (C-4), 125.36 (C-5), 131.61 (C-3′).

   3b: IR (neat, cm^{-1}) 3250 (br), 3035, 3010, 2960, 2920, 2860, 1640, 1460, 1435, 1000, 915, 710. ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 3H, CH_3, J = 7 Hz), 1.30 (m, 4H, 2 CH_2 in Bu), 1.40 (m, 2H, CH_2 in Bu), 1.61 (s, 1H, NH), 1.80 (ddd, 1H, H-3a, ^2J = 17.3 Hz, ^3J = 10.5, 2.3 Hz), 2.05 (dt, 1H, H-3b, ^3J = 2×3.7 Hz), 2.16 (m, 2H, H-2′), 2.92 (m, 1H, H-2), 3.29 (td, 1H, H-6, ^3J = 7.2, 1.9 Hz), 5.07 (dm, 1H, H-4′a, ^3J = 10.0 Hz), 5.10 (dm, 1H, H-4′b, ^3J = 15.4 Hz), 5,67 (m, 2H, close AB system of H-4 and H-5), 5.79 (ddt, 1H, H-3′, ^3J = 7.7 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.72 (CH_3), 22.40 (C-1 in Bu), 28.34 (C-2 in Bu), 31.32 (C-3), 34.85 (C-3 in Bu), 39.97 (C-2′), 46.51 and 51.84 (C-2 and C-6), 116.81 (C-4′), 123.94 (C-4), 130.08 (C-5), 135.29 (C-3′). EIMS: 138 $[M-C_3H_5]^+$, 122 $[M-C_4H_9]^+$, 80 $[M-(C_4H_9 + CH_2=CH-CH_3)]^+$. Anal. calc. for $C_{12}H_{21}N$: C 80.38, H 11.81, N 7.81. Found: C 80.65, H 11.95, N 7.58.

   3b•HCl: M.p. 150.5—151.5 °C (from hexane:chloroform). ^1H NMR (200 MHz, $CDCl_3$): δ 0.66—1.13 (m, 3H, CH_3), 1.15—3.15 (m, 10H, CH_2), 3.26—3.61 (m, 1H, H-2), 3.61—4.0 (m, 1H, H-6), 4.98—5.38 (m, 2H, H-4′), 5.56—6.15 (m, 3H, —CH=), 9.71 (br. s, 2H, NH_2^+). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.78 (CH_3), 22.31 (C-1 in Bu), 26.4 (C-2 in Bu), 27.51 (C-3), 32.52 (C-3 in Bu), 35.75 (C-2′), 40.01 and 51.18 (C-2 and C-6), 119.39 (C-4′), 123.84 (C-4), 124.62 (C-5), 132.01 (C-3′).

   3c: IR (neat, cm^{-1}) 3320 (br), 3060, 3030, 2910, 1640, 1490, 1450, 1110, 1000, 920, 900, 760, 740, 705. ^1H NMR (200 MHz, $CDCl_3$): δ 1.87—2.35 (m, 5H, CH_2—C= and NH), 2.85—3.08 (m, 1H, H-2), 4.6 (s, 1H, H-6), 4.95—5.20 (m, 2H, H-4′), 5.55—6.15 (m, 3H, =CH—), 7.20—7.55 (m, 5H, Ph). ^{13}C NMR (50 MHz, $CDCl_3$): δ 31.31 (C-3), 40.27 (C-2′), 45.90 (C-2), 56.27 (C-6), 117.16 (C-4′), 126.23 (C-4), 126.90 (C_p), 127.48 (C-5), 127.54 and 128.20 (C_o and C_m), 134.96 (C-3′), 143.46 (C_i). EIMS: 199 $[M]^+$, 158 $[M-C_3H_5]^+$, 91 $[C_7H_7]^+$. Anal. calc. for $C_{14}H_{17}N$: C 84.37, H 8.60, N 7.03. Found: C 84.39, H 8.65, N 6.75.

   3c•HCl: M.p. 145—147 °C (from ether:methanol). ^1H NMR (200 MHz, $CDCl_3$): δ 2.32—2.70 (m, 3H, H-2′ and H-3a), 2.75—2.95 (m, 1H, H-3b), 3.20—3.48 (m, 1H, H-2), 4.85 (s, 1H, H-6), 5.05—5.25 (m, 1H, H-4′), 5.55—5.90 (m, 2H, H-3′ and H-4), 6.05—6.25 (m, 1H, H-5), 7.30—7.70 (m, 5H, Ph), 9.55 (br. s, 1H, NH), 10.55 (br. s, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.79 (C-3), 35.86 (C-2′), 48.32 (C-2), 54.57 (C-6), 119.38 (C-4′), 122.55 (C_p), 126.67 (C-4), 128.81 (Ph), 129.61 (C-5), 130.25 (Ph), 131.87 (C-3′), 133.72 (C_i).
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