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SYNTHESIS OF cis- AND trans-2,6-DIALKYLATED PIPERIDINES THROUGH HIGHLY REGIOSELECTIVE α-ALKYNYLATION OF PYRIDINIUM SALTS AND ITS APPLICATION TO SYNTHESIS OF (±)-SOLENOPSINE A

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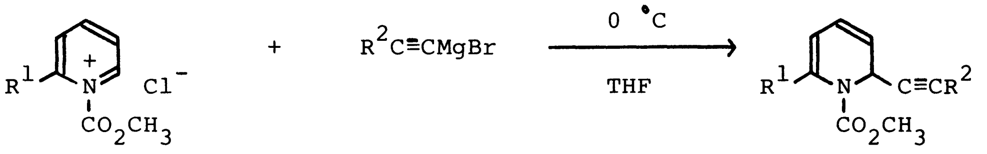
Reactions of N-methoxycarbonyl-2-alkylpyridinium salts with alkynyl Grignard reagents give exclusively 2,6-disubstituted 1,2-dihydropyridines, from which cis- and trans-2,6-dialkylated piperidines can be derived selectively. Consequently, (±)-solenopsine A is efficiently synthesized by this sequence.

2-Alkylated or 2,6-dialkylated piperidines constitute the principal structure of a number of piperidine alkaloids, which possess a variety of biological activity.1,2) We have recently reported the highly regioselective synthesis of 2-substituted 1,2-dihydropyridines by reaction of N-methoxycarbonylpyridinium chloride with a variety of alkenyl and alkynyl Grignard reagents.3) In this communication, we wish to report that the vesatile extention of this methodology to regioselective synthesis of 2,6-disubstituted 1,2-dihydropyridines4) as well as the first selective transformation of 2,6-disubstituted 1,2-dihydropyridines into cis- and trans-2,6-dialkylated piperidines. Furthermore, an application of the above sequence to synthesis of (±)-solenopsine A,5,6) a piperidine alkaloid isolated from the venom of the fire ant, is also described.

As mentioned before,3) a reaction of N-methoxycarbonyl-2-methylpyridinium chloride (**1a**), prepared in situ from 2-methylpyridine and methyl chloroformate, with trimethylsilylethynylmagnesium bromide gave exclusively N-methoxycarbonyl-6-methyl-2-trimethylsilylethynyl-1,2-dihydropyridine (**2a**). This high regioselectivity has now been observed in other combination of 2-alkylpyridine and alkynyl Grignard reagent as well (Table 1). 2-Ethylpyridine gave exclusively **2b** upon treatment of trimethylsilylethynylmagnesium bromide in the presence of methyl chloroformate (entry 2). The similar reactions of 2-methylpyridine with longer chain alkynyl Grignard reagents proceeded also in a highly regioselective manner to give exclusively 2,6-disubstituted-1,2-dihydropyridines (entries 3 and 4).



1a; R^1=CH_3
1b; R^1=C_2H_5

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Table 1. Reactions of N-Methoxycarbonyl-2-alkylpyridinium Chlorides with Alkynyl Grignard Reagents

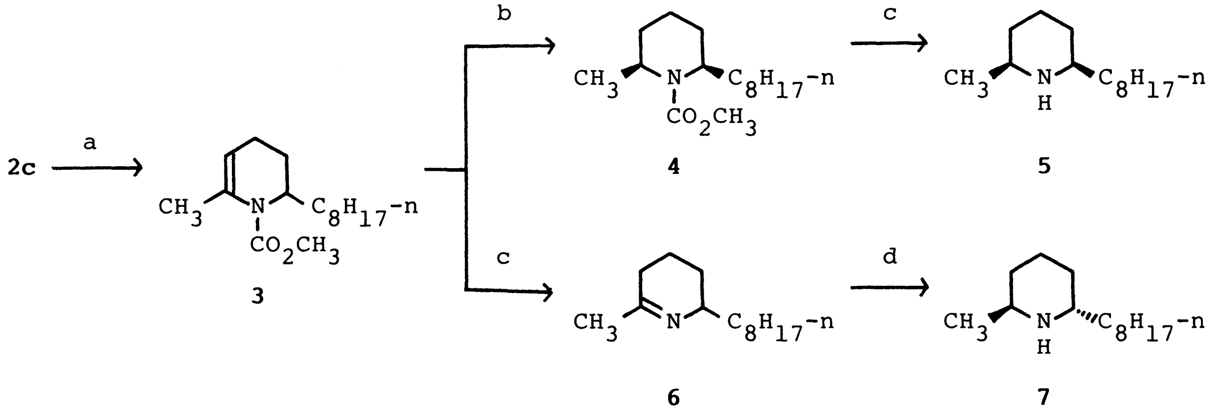
Entry	R^1	R^2	Product	Yield/%[a)]
1	CH_3	$(CH_3)_3Si$	**2a**	79
2	C_2H_5	$(CH_3)_3Si$	**2b**	66
3	CH_3	$n\text{-}C_6H_{13}$	**2c**	73
4	CH_3	$n\text{-}C_9H_{19}$	**2d**	74

a) Isolated yields.

With the desired 2,6-disubstituted N-methoxycarbonyl-1,2-dihydropyridines (**2**) in hand, we next turned our attention to their stereoselective transformation into cis- and trans-2,6-dialkylated piperidines. However, little has been known about the reductive transformation of 2,6-disubstituted 1,2-dihydropyridines into 2,6-disubstituted piperidines.[4,7)] We have found that careful hydrogenation of **2c** over 5% Pd-carbon in methanol gives a critical intermediate, 2,6-dialkylated 1,2,3,4-tetrahydropyridine (**3**) in 83% yield. Further hydrogenation of **3** over Pd-black in methanol afforded N-methoxycarbonyl-cis-2-methyl-6-octylpiperidine (**4**) in 62% yield. Demethoxycarbonylation of **4** with iodotrimethylsilane[8)] gave cis-2-methyl-6-octylpiperidine (**5**), which was identical with the authentic sample prepared by a different route.[9)]

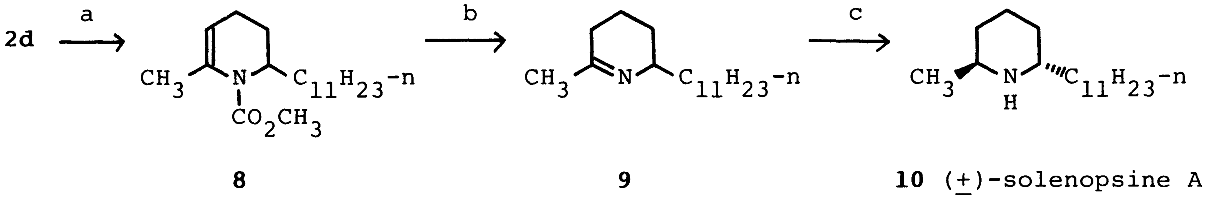
On the other hand, when the 1,2,3,4-tetrahydropyridine **3** was demethoxycarbonylated with iodotrimethylsilane, a cyclic imine (**6**) was obtained. The IR spectrum of **6** clearly showed a presence of C=N double bond (1655 cm^{-1}). Recently, Yamamoto et al. reported their elegant work on the stereoselective reduction of this type of cyclic imines prepared by organoaluminium-promoted Beckmann rearrangement-alkylation of the corresponding oxime sulfonate.[6a)] Thus, **6** was reduced by lithium tetrahydroaluminate in ether at -78 °C to afford trans-2-methyl-6-octylpiperidine (**7**) accompanied with a small amount of **5** (**7**:**5**=78:22) in

70% combined yield based on **3**. The resulting **7** was identical with the authentic sample prepared by a different route.[9)]



a) H_2, Pd/C, CH_3OH. b) H_2, Pd, CH_3OH. c) $(CH_3)_3SiI$, $CHCl_3$, 50-60 °C. d) $LiAlH_4$, $(C_2H_5)_2O$, -78 to 0 °C.

Consequently, (±)-solenopsine A (**10**) was synthesized by the similar sequence to the above. Careful hydrogenation of **2d** over 5% Pd-carbon in methanol gave the 1,2,3,4-tetrahydropyridine (**8**). Demethoxycarbonylation of **8** followed by reduction with lithium tetrahydroaluminate in the presence of trimethylaluminium[6a)] afforded (±)-solenopsine A (**10**)[10)] in 90% yield based on **8**, along with a small amount of its epimer.[11)] This synthetic route (40% overall yield in 4 steps from 2-methylpyridine) is more practical and efficient than another one which also starts from 2-methylpyridine (28% overall yield in 7 steps).[6b,12)]



a) H_2, Pd/C, CH_3OH. b) $(CH_3)_3SiI$, $CHCl_3$, 50-60 °C. c) $LiAlH_4$, $(CH_3)_3Al$, THF, -78 to 0 °C.

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2) V. Baliah, R. Jeyaraman, and L. Chandorasekaran, Chem. Rev., 83, 379 (1983).
3) R. Yamaguchi, Y. Nakazono, and M. Kawanisi, Tetrahedron Lett., 24, 1801

(1983).

4) There has been only one report on the alkylation of 2-alkylpyridinium salt, where alkyllithium reagents are used and the resulting 2,6-dialkylated 1,2-dihydropyridines have been subsequently converted to 2,6-dialkylated piperidines upon catalytic hydrogenation. However, the yields are low (20-30%) and some quantities (ca. 20%) of the 2,4-dialkylated isomers are contained as by-products: H. J. Bestmann and D. Ruppert, Chem.-Ztg., 96, 411 (1972).

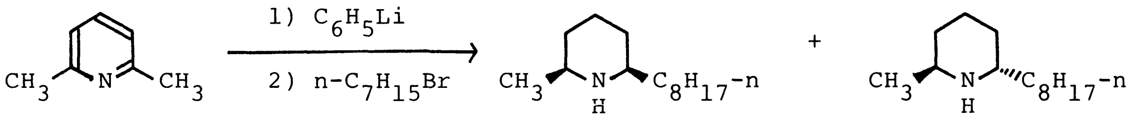
5) J. G. MacConnel, M. S. Blum, and H. M. Fales, Tetrahedron, 27, 1129 (1971).

6) Two stereoselective synthesis of solenopsine A have been reported so far; a) Y. Matsumura, K. Maruoka, and H. Yamamoto, Tetrahedron Lett., 23, 1929 (1982); J. Am. Chem. Soc., 105, 2831 (1983) and references cited therein; b) M. Bonin, J. R. Romero, D. S. Grierson, and H.-P. Husson, Tetrahedron Lett., 23, 3369 (1982) and references cited therein.

7) It should be noted that reductions of 2,6-dialkylated pyridines give exclusively or predominantly cis-2,6-dialkylated piperidines.[2,5]

8) M. E. Jung and M. A. Lyster, J. Chem. Soc., Chem. Commun., 1978, 315.

9) Authentic cis- and trans-2-methyl-6-octylpiperidines (**5** and **7**) were prepared by the similar method to the reported one,[5] as shown below.



5 (69 : 31) **7**

5: MS m/z (rel. intensity): 211 (M^+, 1), 98 (100); IR: 1320 (m) cm^{-1}; ^1H NMR $\delta(CDCl_3)$: 2.26-2.80 (m, 2H), 1.14-2.00 (m, 20H), 1.03 (d, 3H), 0.89 (t, 3H); ^{13}C NMR $\delta(CDCl_3)$: 57.4 (d), 52.7 (d), 37.7 (t), 34.8 (t), 32.6 (t), 32.0 (t), 30.0 (t), 29.7 (t), 29.4 (t), 26.1 (t), 25.1 (t), 23.2 (q), 22.7 (t), 14.1 (q). **7**: MS m/z (rel. intensity): 211 (M^+, 1), 98 (100); IR: 1320 (w) cm^{-1}; ^1H NMR $\delta(CDCl_3)$: 2.70-3.14 (m, 2H), 1.10-1.80 (m, 20H), 1.04 (d, 3H), 0.86 (t, 3H); ^{13}C NMR $\delta(CDCl_3)$: 51.1 (d), 46.1 (d), 34.4 (t), 33.3 (t), 32.0 (t), 31.1 (t), 29.9 (t), 29.7 (t), 29.4 (t), 26.6 (t), 22.7 (t), 21.3 (q), 19.8 (t), 14.1 (q). ^{13}C NMR seems useful to assign the stereochemistry of 2,6-dialkylated piperidines, since signals due to C-2 and C-6 of cis-isomer (**5**) appear in lower field (57.4 and 52.7 ppm) than those of trans-isomer (**7**) do (51.1 and 46.1 ppm).

10) **10**: IR: 1370 (w) cm^{-1}; ^1H NMR $\delta(CDCl_3)$: 2.70-3.13 (m, 2H), 1.13-1.87 (m, 26H), 1.05 (d, 3H), 0.87 (t, 3H); ^{13}C NMR $\delta(CDCl_3)$: 50.9 (d), 45.9 (d), 34.1 (t), 33.0 (t), 31.9 (t), 30.7 (t), 29.8 (t), 29.7 (t), 29.4 (t), 26.5 (t), 22.7 (t), 21.2 (q), 19.6 (t), 14.1 (q).

11) The stereoselectivity (90%) was slightly lower than the reported one (95%),[6a] since **8** was slightly contaminated by the perhydrogenated compound.

12) The Yamamoto's route is also efficient (38% overall yield in 5 steps from cyclopentanone).[6a]

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