A FACILE SYNTHESIS OF 4-ARYL-1,2,3,4-TETRAHYDROISOQUINOLINES: A TOTAL SYNTHESIS OF (±)-CHERYLLINE

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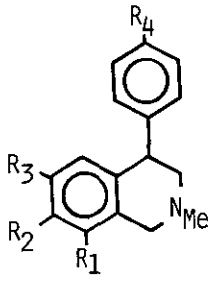
Abstract --- Reaction of benzylamines (3a-d) and styrene oxide at 140°C gave quantitatively β-hydroxyphenethylamine (2a-d), acid treatment of which afforded 4-aryl-1,2,3,4-tetrahydroisoquinolines (8a-d) in high yields. On the other hand, the styrene oxide (10 or 15) was treated with BF_3-Et_2O in MeOH yielding regioselectively a β-methoxyphenethyl alcohol (12 or 16), the mesylate of which reacted with the benzylamine (3e) in the presence of Hünig's base to give the N-benzyl-β-methoxyphenethylamine (2f or 2g). Acid treatment of 2f or 2g afforded (±)-cherylline (1) or (±)-4'-O-methylcherylline (14) in 85 or 67% overall yield from O-benzylisovanillin.

Synthetic studies on aryl-1,2,3,4-tetrahydroisoquinolines have attracted much attention owing to the potential biological activities.[1,2] Among others, the basic skeleton of a natural alkaloid, (-)-cherylline (1) being 4-aryl-1,2,3,4-tetrahydroisoquinoline, its synthesis has long been a fascinating target for many organic chemist.[2]

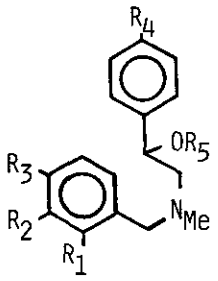
We considered that the key intermediate, N-benzyl-β-hydroxyphenethylamine derivatives (2), chosen by both Schwartz[2c] and Kametani[2d] was also suitable for our synthesis and decided to improve the preparation.

Here we wish to report a new methodology for the formation of 2 using a S_N2 reaction of amines (3)[3] with styrene oxides and an efficient synthesis of (±)-cherylline (1).

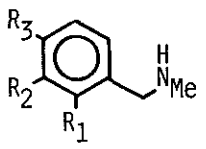
Heating the styrene oxide (4) and benzylmethylamines (3a-d) at 140°C gave regiosel-



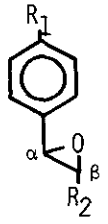
	R_1	R_2	R_3	R_4
1	H	OH	OMe	OH
8a	H	OH	OMe	H
8b	H	OCH_2O		H
8c	OH	OMe	H	H
8d	H	OMe	OH	H
14	H	OH	OMe	OMe



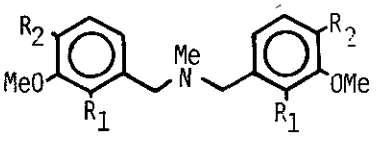
	R_1	R_2	R_3	R_4	R_5
2a	H	OH	OMe	H	H
2b	H	OCH_2O		H	H
2c	OBz	OMe	H	H	H
2d	H	OMe	OBz	H	H
2e	H	OH	OMe	OBz	H
2f	H	OBz	OMe	OBz	Me
2g	H	OBz	OMe	OMe	Me



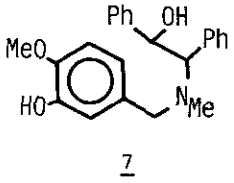
	R_1	R_2	R_3
3a	H	OH	OMe
3b	H	OCH_2O	
3c	OBz	OMe	H
3d	H	OMe	OBz
3e	H	OBz	OMe
3f	OH	OMe	H
3g	H	OMe	OH



	R_1	R_2
4	H	H
10	OBz	H
15	OMe	H
17	H	Ph



	R_1	R_2
5	OH	H
6	H	OH



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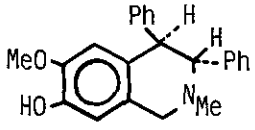

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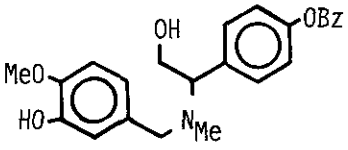

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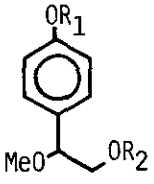

	R_1	R_2
12	OBz	H
13	OBz	Ms
16	OMe	H
18	OMe	Ms

Bz = CH_2Ph

ectively the desired N-benzyl-β-hydroxyphenethylamines (2a-d) in excellent yields, respectively (Table II). However, o-vanillyl-(3f) or vanillyl-methylamine (3g) was easily transformed to the dibenzylamine (5 or 6) at the reaction temperature, undoubtedly via o- or p-quinone methide. In such cases, the phenolic hydroxyl group was protected before use. Structures of products (2a-d) were determined on the basis of proton NMR spectra, i.e. double doublets of one proton around δ 4.73 were reasonably assigned to the phenyl carbinol methine proton (see Table II).[4] The reaction of 3a and stilbene oxide also afforded an amino alcohol (7), quantitatively. Without purification, 2a and 7 were cyclized into 4-phenyl-1,2,3,4-tetrahydroisoquinolines (8a and 9) by acid treatment, respectively. The cyclization proceeded smoothly at room temperature and 80% (w/w) sulfuric acid was the choice of acid. However, treatment of 2c or 2d with 80% H_2SO_4 gave rise to an intractable mixture of products probably as a result of the rearrangement of the benzyl group. In such cases, debenzylation procedure by refluxing for 1 h with conc. HCl-benzene was necessary prior to cyclization. Since the methylenedioxy group was sensitive to 80% H_2SO_4, reaction conditions were checked thoroughly as shown in Table III. Thus, 75% H_2SO_4 was found to be the best.

Structure of products (8a-d) was clearly determined by proton NMR spectra. Namely, in all compounds signals of two aromatic protons except phenyl protons and of C-4 proton (around δ 4.16) were appeared. The latter signal showed typical pattern of C-4 axial proton coupled with C-3 methylene protons. On the other hand, 3,4-diphenyl groups of 9 were trans oriented as shown by the coupling constant (J= 9 Hz) between a pair of protons at C-3 and C-4 positions.

Next, we decided to apply the above method in order to synthesize (±)-cherylline (1). p-Benzyloxystyrene oxide (10) was quantitatively prepared from p-benzyloxybenzaldehyde by use of Kutsuma's method.[5] The reaction between 3a and 10 was attempted to give non-regioselectively a mixture of the p-benzyloxyphenethylamine (2e) and the dibenzylamine (11) in a ratio of 1:1. The fission between the α-carbon and the oxygen atoms was facilitated by an electron donating group at the para position.

To overcome the difficulty a by-pass was seeked. Thus, treatment of the epoxide (10) with BF_3-Et_2O in MeOH at room temperature afforded solely the β-methoxyphenethyl alcohol (12) in an excellent yield.[6] Usual mesylation of 12 quantitatively gave the mesylate (13). The reaction of the benzylmethylamine (3e) with 13 proceeded nicely. Namely, heating of 3e and 13 together with Hünig's base in a seal-

Table I. Mp and Yield of Benzylmethylamines

	Mp(°C) and Recrystallizing solvent	Yield (%)
3a	142-144° (benzene), lit.[2e] 142-143°	86
3b	191-193°* (iso-PrOH), lit.[8] 194°	97
3c	145.5-146.5°* (iso-PrOH)	100
3d	172-173°* (iso-PrOH-ether)	94
3e	210-212°* (MeOH), lit.[9] 209-211°	97
3f	92-94° (benzene-n-hexane)	97
3g	113-114° (benzene)	33

*Melting point of HCl salt.

Table II. Preparation of N-Benzyl-β-hydroxyphenethylamine derivatives

Starting material	Amine	Product	Yield (%)	NMR data of ArCH(OR)-	Reaction time (hr)
4	3a	2a	96	δ 4.69 (dd, J=5, 8 Hz)	1
4	3b	2b	94	δ 4.64 (dd, J=6, 8 Hz)	1
4	3c	2c	100	δ 4.58 (dd, J=6, 7 Hz)	1
4	3d	2d	100	δ 4.87 (dd, J=6, 7 Hz)	1
17	3a	7	100	δ 5.27 (d, J=6 Hz)	1
13	3e	2f	100	δ 4.18 (dd, J=6, 7 Hz)	24
18	3e	2g	100	δ 4.17 (dd, J=5, 7 Hz)	24

Table III. Preparation of 4-Aryl-1,2,3,4-tetrahydroisoquinolines

Starting material	Reaction condition*	Product	Mp(°C)	Yield (%)	NMR data of C-4 proton
2a	A	8a	161-162° (benzene)	89	δ 4.18 (dd, J=6, 8 Hz)
7	A	9	138-139° (iso-PrOH)	93	δ 3.33[§] (d, J=9 Hz)
2c	B	8c	147-149° (iso-PrOH)	90	δ 4.19 (dd, J=6, 9 Hz)
2d	B	8d	183.5-184.5° (EtOH)	87	δ 4.13 (dd, J=6, 9 Hz)
2b	A	8b	237-239° (HCl salt)	15	
2b	C	8b		13	δ 4.13 (dd, J=6, 8 Hz)
2b	D	8b	(iso-PrOH)	44	
2b	E	8b		61	
2f	F	1	208-211°	85	δ 4.01[¶] (dd, J=6, 8 Hz)
2g	G	14	131-133°	67	δ 4.12 (dd, J=5, 7 Hz)

*A : 80% H_2SO_4, r.t., 1 h; B : i) conc.HCl-benzene, reflux, 1 h, ii) 80% H_2SO_4, r.t., 1 h; C : 70% H_2SO_4, r.t., 1 h; D : 75% H_2SO_4, r.t., 1 h; E : 75% H_2SO_4, r.t., 3 h; F : conc.HCl-benzene, reflux, 5 h; G : conc.HCl-benzene, reflux, 3 h.
[§]C-3 proton; [¶]In d_6-acetone

ed tube at 120°C for 24 h gave the expected β-methoxyphenethylamine (2f), mp 85-87°C (lit.[2d] 90-91°C), quantitatively. Finally, refluxing of 2f with conc. HCl-benzene for 5 h gave (±)-cherylline (1),[7] mp 208-211°C (lit.[2e] 209-211°C), in 85% yield. The overall yield from benzylisovanillin was 82%. Similarly, 4'-O-methylcherylline (14), mp 131-133°C (lit.[2e] 129-130°C), was prepared through the same route as above from p-methoxystyrene oxide (15) and the benzylmethylamine (3e) in a high yield.

Conclusively, we could establish a facile and general synthesis of 4-aryl-1,2,3,4-tetrahydroisoquinolines by employment of styrene oxide as a crucial synthon.

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3. Benzylmethylamines (3a-g) were prepared from the corresponding aryl aldehydes in high yields, according to Evans's procedure[2e] (Table I).
4. NMR spectra were taken with a JEOL model JNR-FX 100 or a Hitachi model R-24B in $CDCl_3$ by using Me_4Si as internal standard.
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7. NMR spectrum of (±)-1 was superimposable on that of an authentic (±)-cheryllline[2i] supplied by Prof. Takayama.
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