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A CONVENIENT SYNTHESIS OF 4-SUBSTITUTED 1,2,3,4-TETRAHYDROISOQUINOLIN-4-OLS BY A NOVEL INTRAMOLECULAR BARBIER REACTION AND BY AN INSERTION REACTION: REACTION SCOPE AND LIMITATIONS

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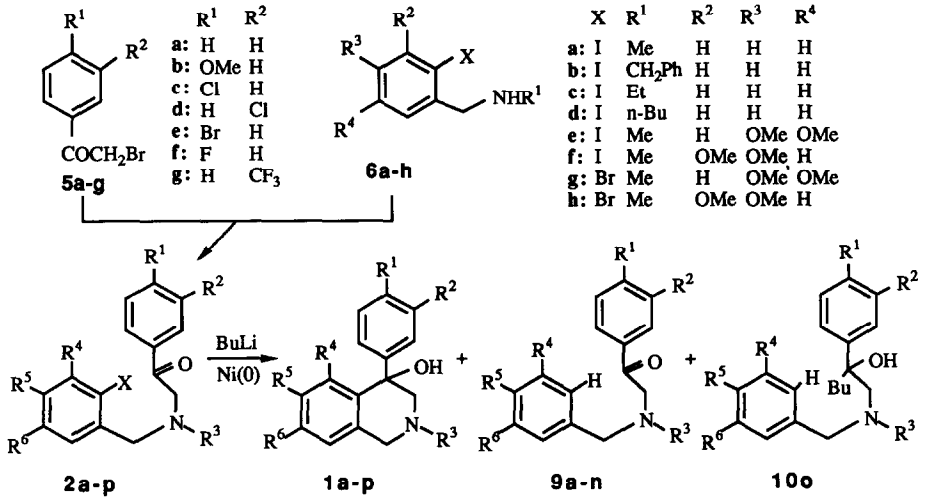
Key Words: tetrahydroisoquinolin-4-ol; intramolecular Barbier reaction; butyllithium; zerovalent nickel; scope and limitation

Abstracts: 4-Substituted 1,2,3,4-tetrahydroisoquinolin-4-ols were prepared from N-(2-iodobenzyl)phenacylamines by an intramolecular Barbier reaction with butyllithium and by an insertion reaction with zerovalent nickel. The scope and limitations of these reactions were discussed.

4-Aryl-1,2,3,4-tetrahydroisoquinolines have been attractive because of their biological activities[1] and of their skeletons constructing basic natural products.[2] We have reported the synthesis of 4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol(**1a**) by a novel insertion reaction of an N-benzylphenacylamine with zerovalent nickel even though in a low yield.[3] The isoquinolinol(**1a**) was found to have a potent and selective noradrenaline uptake inhibiting property.[4] There are several studies[5] on the intramolecular cyclization reactions of alkyl halides containing a carbonyl group with metals such as Mg, Li, or with BuLi. On the basis of these findings, we carried out the improved and convenient synthesis[6] of **1a** by the intramolecular Barbier reaction of **2a** with BuLi. This paper describes the details of the first intramolecular Barbier reaction of aryl halides, N-benzylphenacylamines(**2**) and alkyl aminomethyl ketones(**3**), for the preparation of 4-phenylisoquinolinols(**1**) and the related compounds(**4**). In addition, intramolecular insertion reactions of **2** and **3** with zerovalent nickel were performed in order to clarify the scope and limitations of these reactions.

A variety of N-alkyl-N-(2-halogenobenzyl)phenacylamines(**2a-p**) as starting materials were prepared from the corresponding phenacyl bromides(**5a-g**) and 2-halo-N-alkylbenzyl-

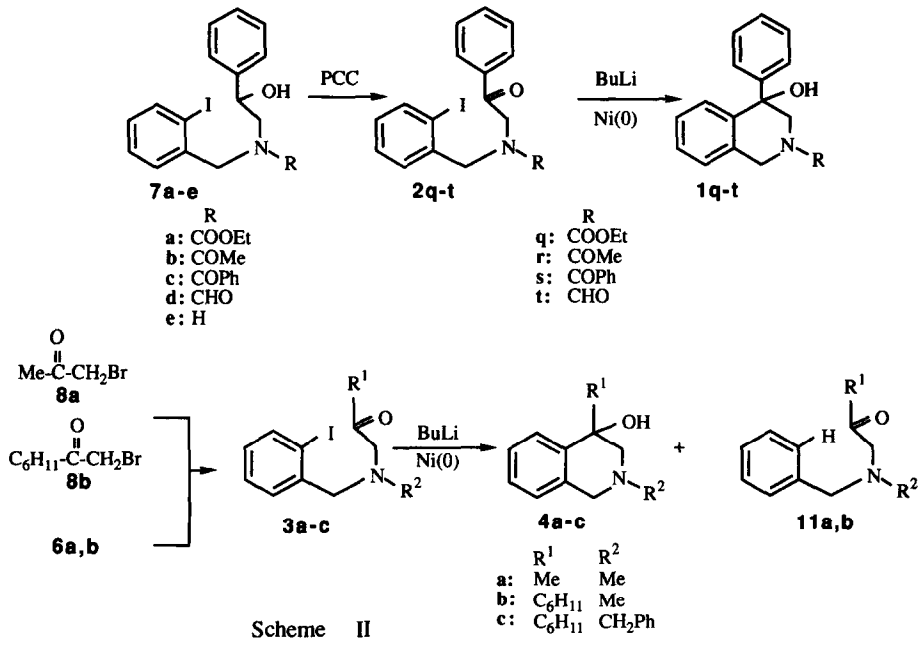


	X	R^1	R^2	R^3	R^4	R^5	R^6
a:	I	H	H	Me	H	H	H
b:	I	OMe	H	Me	H	H	H
c:	I	OMe	H	Me	H	OMe	OMe
d:	I	OMe	H	Me	OMe	OMe	H
e:	I	Cl	H	Me	H	H	H
f:	I	H	Cl	Me	H	H	H
g:	I	Br	H	Me	H	H	H
h:	I	F	H	Me	H	H	H
i:	I	H	H	CH_2Ph	H	H	H
j:	I	OMe	H	CH_2Ph	H	H	H
k:	I	H	CF_3	Me	H	H	H
l:	I	H	H	Et	H	H	H
m:	I	H	H	n-Bu	H	H	H
n:	I	Et	H	Me	H	H	H
o:	Br	OMe	H	Me	H	OMe	OMe
p:	Br	OMe	H	Me	OMe	OMe	H

Scheme I

amines(**6a-h**) in good yields (Scheme I). The benzylamines(**6b-h**) were obtained by reductive amination[3,7] of the corresponding benzaldehydes. On the other hand, the N-acylphenacylamines(**2q-t**) were prepared in good yields by N-acylation of a β-phenylethanolamine(**7e**), followed by PCC oxidation of the products(**7a-d**). The methyl aminomethyl ketones(**3a-c**) were prepared from bromomethyl ketones(**8a,b**) and the benzylamines(**6a,b**) (Scheme II).

In the preliminary experiments of an intramolecular Barbier reaction of **2a**, the best result was obtained by using 1.3 equivalent of BuLi in THF at -78°C as shown in Table I. Under these conditions the phenacylamines(**2b-t**) and the alkyl ketones(**3a-c**) obtained as above were treated with BuLi. The intramolecular insertion reactions of **2c,2e-t** and **3a,b** with zerovalent nickel were also performed by the method developed by us.[3] Table II shows the results for both reactions of **2a-t** and **3a-c**. The results are summerized and the scope and limitations of these reactions are shown as follows: 1) in general the N-alkylisoquinolin-4-ols(**1a-n**) were obtained from phenacylamines(**2a-n**) in higher yields with



Scheme II

BuLi than with zerovalent nickel, although the reaction with BuLi gave deiodinated products(**9a-n**) as by-products. 2) The insertion reaction of N-acylphenacylamines(**2q-t**) with zerovalent nickel gave the isoquinolinols(**1q-t**) in moderate yields, but the reactions of **2q-t** with BuLi gave unsatisfactory results except for **2q**. The difference between the reactivities of **2q-t** for the Barbier reaction seems to be due to the resonance effect in the amide groups. 3) From the results of the reactions of **2c,d** and **2o,p**, the reactivity of the bromine atoms on the benzyl benzene ring of **2o,p** for the insertion reaction is similar to that of the corresponding iodine atom of **2c**. However, the bromine atoms of **2o,p** are less active for the intramolecular cyclization with BuLi and thus the reaction of **2o,p** gave an alcohol(**10o**) produced by nucleophilic attack of BuLi to the carbonyl groups. 4) The Barbier reaction gave good results for the compounds (**2e-h**) having halogen atoms(F, Cl, Br) on the phenacyl benzene ring, contrary to the insertion reaction of **2e-g** which gave the dehalogenated product(**1a**)[8] as a by-product along with **1e-g**. 5) 4-Alkylisoquinolinols(**4a-c**) could also be prepared by the Barbier reaction of **3a-c** in good yields, while the reaction of **3a,b** with zerovalent nickel gave low yields of **4a,b**.

Synthesis of **1** reported so far needed multi-step reactions via 1,2-dihydro-3H-4-isoquinolones.[9] Therefore, this intramolecular Barbier reaction of **2** and **3** which were easily obtained offers the most convenient and simple method for the preparation of 4-substituted 1,2,3,4-tetrahydroisoquinolin-4-ols (**1**) and (**4**).

These isoquinolin-4-ols are easily converted to pharmacologically active 4-aryl-

Table I. Reaction of Phenacylamine 2a with BuLi

run	BuLi(eq.)	Solvent	Condition	Yield (%) of Product 1a	9a	2a
1	1.0	THF	-78℃, 10 min. to RT[a]	64	17	11
2	1.3	THF	-78°C, 10 min. to RT	69	18	----
3	1.5	THF	-78°C, 10 min.	62	24	----
4	1.3	ether	-78°C, 10 min.	54	15	----

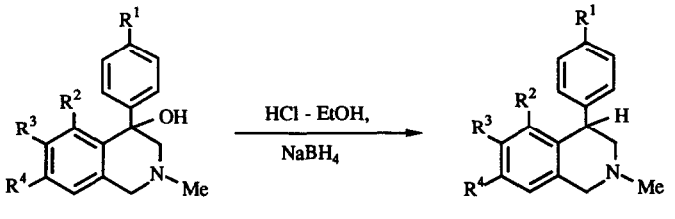
a. Room temperature.

Table II. Yields of Isoquinolinols(1a-n,1q-t and 4a-c) from N-Benzylphenacylamines(2a-t) and Alkyl Aminomethyl Ketones(3a-c) with BuLi and Zerovalent Nickel

Starting material	Yield (%) of Product: With BuLi — Isoquinolinol		By-Product		With Ni(0) — Isoquinolinol	
2a	1a	69	9a	18	1a	45[a]
2b	1b	50	9b	21	1b	21[b]
2c	1c	77	9c	3	1c	30
2d	1d	64	9c	15		
2e	1e	62	9e	8	1e	12(12)[b,c]
2f	1f	54	9f	6	1f	11(11)[c]
2g	1g	67	9g	12	1g	19(13)[c]
2h	1h	59	9h	9	1h	35
2i	1i	86	-------		1i	59
2j	1j	76	9j	8	1j	61
2k	1k	73	9k	11	1k	41[b]
2l	1l	93	9l	5	1l	64
2m	1m	89	9m	3	1m	63
2n	1n	64	9n	15	1n	27
2o	1c	0	9c	17	1c	29
			10o	31		
2p	1d	9	9c	25	1d	27
			10o	26		
2q	1q	61	-------		1q	45
2r	1r	0	-------		1r	40
2s	1s	24	2s	37	1s	56
2t	1t	0	-------		1t	33
3a	4a	72	11a	15	4a	27
3b	4b	56	11b	12	4b	15
3c	4c	43	-------			

a. Ref. 4b. b. Ref. 3b. c. A numerical value in parenthesis is a yield of 1a.

1,2,3,4-tetrahydroisoquinolines.[10] Amaryllidaceae alkaloids, (±)-O,O-dimethylcherylline (12c),[11] (±)-O,O-dimethyllatifine (12d),[2c,d] and 4-phenyltetrahydroisoquinoline(12a)[12] were prepared by dehydration and reduction of 1c,d and 1a in good yields, respectively (Scheme III).



1a,c,d 12a,c,d

	R^1	R^2	R^3	R^4
a:	H	H	H	H
c:	OMe	H	OMe	OMe
d:	OMe	OMe	OMe	H

Scheme III

EXPERIMENTAL

All melting points are given as uncorrected values. Infrared(IR) spectra were taken with a Perkin-Elmer 1720 infrared fourier transform spectrometer and are given in cm^{-1}. High-resolution mass(MS) spectra were recorded on a JEOL JMS-D 300 spectrometer. Proton nuclear magnetic resonance(^{1}H-NMR) spectra were recorded on a JEOL JNM-FX 200 spectrometer in $CDCl_3$ with tetramethylsilane as a standard and are given in δ values.

4-Fluorophenacyl Bromide(5f) A solution of benzyltrimethylammonium tribromide[13](5.25 g, 13.46 mmol) in CH_2Cl_2-MeOH(5:2) (50 ml) was added to a solution of 4'-fluoroacetophenone(1.69 g, 12.23 mmol) in CH_2Cl_2- MeOH(5:2) (20 ml) and was stirred for 4.5 h at room temperature. The mixture was evaporated in vacuo and H_2O(50 ml) was added to the residue. The mixture was extracted with ether(50 ml x 3). The extract was washed with H_2O, dried over $MgSO_4$ and evaporated to give 5f as a colorless oil(2.56 g, 96%). ^{1}H-NMR: 7.93(2H,dd,J=8.5 and 5.5Hz), 7.07(2H,dd,J=8.5 and 8.5Hz), 4.37(2H,s). IR(KBr):1697(C=O). MS(m/z)(M^+):Calcd for C_8H_6BrFO:215.9586. Found:215.9596.

Phenacyl bromide(5d) and cyclohexyl bromomethyl ketone(8b) were prepared in the same way as 5f. Phenacyl bromides(5a-c and 5e) were commercially available.

3-Chlorophenacyl Bromide(5d) Colorless oil(97%). ^{1}H-NMR: 7.89(1H,dd,J=1.5 and 1.5Hz), 7.79(1H,ddd,J=8,1.5 and 1.5Hz), 7.51(1H,ddd,J=8,1.5 and 1.5Hz), 7.37(1H,dd,J=8 and 8Hz), 4.35(2H,s). IR(KBr): 1685(C=O). MS(m/z)(M+2): Calcd for C_8H_6BrClO: 233.9271. Found: 233.9294.

Cyclohexyl Bromomethyl Ketone(8b) Pale yellow oil(66%). MS(m/z)(M^+): Calcd for $C_8H_{13}BrO$:206.0130. Found:206.0100. IR(KBr):1709(C=O). ^{1}H-NMR: 3.97(2H,s), 2.70(1H,m).

N-Benzyl-2-iodobenzylamine(6b) 2-Iodobenzaldehyde(9.41 g, 40.6 mmol) and 5N HCl-

MeOH(17 ml) were added to a solution of benzylamine(26.1 g, 243.6 mmol) in absolute MeOH(50 ml) and $NaBH_3CN$(1.7 g, 27.1 mmol) was added. The mixture was stirred for 72 h at room temperature. The precipitates formed were filtered and the filtrate was acidified with conc.HCl and evaporated. H_2O(200 ml) was added to the residue and the mixture was washed with ether, basified with KOH and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated to give a crude product(10.84 g). This was purified by flash chromatography on SiO_2 with $CHCl_3$-MeOH(10:1) to give a pale yellow oil(10.09 g), which was converted to the hydrochloride of **6b** as colorless cubes(10.6 g, 72.6%)(from acetone), mp 144-145°C. ^{1}H-NMR(free base): 7.83(1H,dd,J=8 and 1Hz), 6.95(1H,ddd,J=8, 7 and 2Hz), 3.84 and 3.95(each 2H,s), 1.75(1H,br s). Anal.Calcd for $C_{14}H_{14}IN \cdot HCl$:C,46.76;H,4.20; N,3.89. Found:C,47.03;H,4.18;N,3.65.

The benzylamines(**6c-h**) were prepared in the same way as **6b**.

N-Ethyl-2-iodobenzylamine(**6c**) Colorless needles(60.8%)(from acetone) as a hydrochloride, mp 194-196°C. ^{1}H-NMR: 7.82(1H,dd,J=8 and 1Hz), 7.38(1H,dd,J=7.5 and 2Hz), 7.31(1H,ddd,J=7.5, 7 and 1Hz), 6.94(1H,ddd,J=8, 7 and 2Hz), 3.81(2H,s), 2.68(2H,q,J=7Hz), 1.55(1H,br s), 1.15(3H,t,J=7Hz). Anal.Calcd for $C_9H_{12}IN \cdot HCl$:C,36.33;H,4.40;N,4.71. Found:C,36.46;H,4.47;N,4.60.

N-n-Butyl-2-iodobenzylamine(**6d**) Colorless leaflets(54.0 %)(from acetone-ether) as a hydrochloride, mp 108-113°C. ^{1}H-NMR(free base): 7.82(1H,dd,J=8 and 1Hz), 7.38(1H,dd, J=7.5 and 2Hz), 7.31(1H,ddd,J=7.5, 7 and 1Hz), 6.95(1H,ddd,J=8, 7 and 2Hz), 3.80(2H,s), 2.63(2H,t,J=7Hz), 0.92(3H,t,J=7Hz). Anal.Calcd for $C_{11}H_{16}IN \cdot HCl$:C,40.58;H,5.26;N,4.30. Found:C,40.46;H,5.39;N,4.19.

4,5-Dimethoxy-2-iodo-N-methylbenzylamine(**6e**) Colorless needles(53%) (from acetone) as a hydrochloride, mp 198.5-200.5°C. ^{1}H-NMR(CD_3OD): 7.28(1H,s), 7.40(1H,s), 3.95 and 3.87 (each 3H,s), 4.35(2H,s), 2.78(3H,s). Anal.Calcd for $C_{10}H_{14}INO_2 \cdot HCl$:C,34.96;H,4.40; N,4.08. Found:C,34.61;H,4.38;N,4.02.

3,4-Dimethoxy-2-iodo-N-methylbenzylamine(**6f**) Pale yellow plates(27%) (from MeOH-acetone) as a hydrochloride, mp 198-202°C(dec.). ^{1}H-NMR(free base): 7.07 and 6.86(each 1H,d,J=8.5Hz), 3.86 and 3.84(each 3H,s), 3.76(2H,s), 2.44(3H,s). Anal.Calcd for $C_{10}H_{14}INO_2 \cdot HCl$:C,34.96;H,4.40;N,4.08. Found:C,34.89;H,4.46;N,4.07.

2-Bromo-4,5-dimethoxy-N-methylbenzylamine(**6g**) Colorless plates(43%) (from MeOH-acetone) as a hydrochloride, mp 182-184°C. ^{1}H-NMR(free base): 7.01(1H,s), 6.93(1H,s), 3.88 and 3.86(each 3H,s), 3.75(2H,s), 2.46(3H,s), 1.66(1H,br s). Anal.Calcd for $C_{10}H_{14}BrNO_2 \cdot HCl$: C,40.50;H,5.10;N,4.72. Found:C,40.47;H,5.21;N,4.71.

2-Bromo-3,4-dimethoxy-N-methylbenzylamine(**6h**) Colorless needles(59%) (from acetone) as a hydrochloride, mp 85-89°C. ^{1}H-NMR(free base): 7.07 and 6.84(each 1H,d,J=8Hz),3.86 and 3.85(each 3H,s), 3.78(2H,s), 2.43(3H,s). Anal.Calcd for $C_{10}H_{14}BrNO_2 \cdot HCl$:C,40.50;H,5.10; N,4.72. Found:C,40.34;H,5.08;N,4.48.

N-(2-Iodobenzyl)-β-phenylethanolamine(**7e**) 2-Iodobenzaldehyde(3.0 g, 12.9 mmol) and 9N HCl-MeOH(3 ml) were added to a solution of β-phenylethanolamine(5.31 g, 38.9 mmol) in absolute MeOH(20 ml) and $NaBH_3CN$(0.6 g, 9.5 mmol) was added. The mixture was stirred for

9 days at room temperature. Work-up in the same way as **6b** gave a crude product(3.4 g). This was purified by flash chromatography on SiO_2 with $CHCl_3$-MeOH(10:1) and converted to the hydrochloride of **7e** as colorless plates(3.28 g, 64%) (from MeOH), mp 160-163°C. ^{1}H-NMR(free base): 7.82(1H,d,J=8Hz), 6.96(1H,m), 4.75(1H,dd,J=9 and 4Hz), 3.85(2H,s), 2.90(1H,dd,J=12 and 4Hz), 2.74(1H,dd,J=12 and 9Hz). Anal.Calcd for $C_{15}H_{16}INO \cdot HCl$: C,46.24;H,4.40;N,3.59. Found:C,46.10;H,4.44;N,3.58.

N-Ethoxycarbonyl-N-(2-iodobenzyl)-β-phenylethanolamine(**7a**) A solution of the hydrochloride(779 mg, 2.0 mmol) of **7e** in pyridine(10 ml) was added to a solution of ethyl chloroformate(434 mg, 4.0 mmol) in pyridine(10 ml) under ice-cooling. The mixture was stirred for 3 h at room temperature. H_2O(100 ml) was added and the mixture was extracted with ether. The extract was washed with 2% HCl, dried and evaporated to give an oil. This crude product was purified by flash chromatography on SiO_2 with $CHCl_3$-ethyl acetate(15:1) to give **7a** as an oil(675 mg, 82%). ^{1}H-NMR:7.83(1H,dd,J=8 and 1Hz), 6.97(1H,ddd,J=8, 8 and 2Hz), 4.96(1H,m), 4.50(2H,m), 4.22(2H,q,J=7Hz), 1.12(3H,t,J=7Hz). IR(KBr):1681(C=O). MS(m/z)(M-H_2O): Calcd for $C_{18}H_{18}INO_2$:407.0381. Found:407.0370.

N-Acetyl-N-(2-iodobenzyl)-β-phenylethanolamine(**7b**) The hydrochloride(799 mg, 2.05 mmol) of **7e** was dissolved in pyridine(10 ml) and acetic anhydride(10 ml) and stirred for 50 h at room temperature. Ether(50 ml) was added and the mixture was washed with 2% HCl (50 ml x 3) and then with 5% KOH. The organic layer was dried over $MgSO_4$ and evaporated to give an oil(806 mg). This was dissolved in EtOH(10 ml) and 0.5M KOH(10 ml) was added. The mixture was stirred for 10 h at room temperature and evaporated in vacuo. The residue was extracted with ether(30 ml x 3). The extract was washed with 2% HCl, dried over $MgSO_4$ and evaporated to give **7b** as an oil(601 mg, 85%). ^{1}H-NMR: 7.88(1H,d,J=8Hz), 4.98(1H,dd, J=8.5 and 7.5Hz), 4.60(1H,m), 2.12 and 2.23(3H,each s). IR(KBr): 1630(C=O). MS(m/z)(M-H_2O): Calcd for $C_{17}H_{16}INO$:377.0275. Found:377.0255.

N-Benzoyl-N-(2-iodobenzyl)-β-phenylethanolamine(**7c**) 25% KOH(10 ml) was added to a suspension of the hydrochloride(708 mg, 1.82 mmol) of **7e** in benzene(20 ml). The mixture was stirred for 10 min. A solution of benzoyl chloride(383 mg, 2.70 mmol) in benzene(5 ml) was added. The mixture was stirred for 1 h at room temperature. Work-up in the usual way gave a crude product, which was purified by flash chromatography on SiO_2 with $CHCl_3$-ethyl acetate(15:1) to give **7c** as an oil(607 mg, 73%). ^{1}H-NMR: 7.82(1H,d,J=8Hz), 7.01 (1H,dd,J=8 and 8Hz), 5.03(1H,m), 4.43 and 4.34(each 1H,d,J=13Hz), 3.82(1H,dd,J=17 and 5.5Hz), 3.56 (1H,d,J=17Hz). IR(KBr): 1616 (C=O). MS(m/z) (M-H_2O): Calcd for $C_{22}H_{18}INO$: 439.0411. Found: 439.0438.

N-Formyl-N-(2-iodobenzyl)-β-phenylethanolamine(**7d**) A mixture of the hydrochloride(779 mg, 2.0 mmol) of **7e**, K_2CO_3(8 g), 3A molecular sieves(8 g), and HCOOEt-EtOH(1:1)(80 ml) was refluxed under N_2 for 5 h. The mixture was filtered and the filtrate was concentrated. H_2O(50 ml) was added and the mixture was extracted with ether(50 ml x 4). The extract was washed with 10% HCl(50 ml x 3), dried over $MgSO_4$ and evaporated to give a crude oil(706 mg). This was purified by flash chromatography on SiO_2 with $CHCl_3$-ethyl acetate(5:1) to give **7d** as an oil(675 mg, 89%). ^{1}H-NMR: 8.36 and 8.20(1H,each s), 7.86

Table III. Yields, MS and ^{1}H-NMR Spectral Data[a] for **2c**, **2d**, **2f-j**, **2l-t** and **3a-c**

No	Yield (%)	Formula	MS (m/z)(M^+) Calcd(Found)	^{1}H-NMR ($CDCl_3$) δ
2c	78	$C_{19}H_{22}INO_4$	454.0518 (454.0518)	7.97, 6.90(each 2H,d,J=9Hz),7.21,7.03(each 1H,s), 3.79,3.67(each 2H,s),3.86,3.85,3.81(each 3H,s)
2d	76	$C_{19}H_{22}INO_4$	454.0515 (454.0500)	7.98, 6.89(each 2H,d,J=9Hz),3.79, 3.72(each 2H,s), 3.83(3H,s),3.86(6H,s),2.39(3H,s)
2f	68	$C_{16}H_{15}ClINO$	398.9886 (398.9864)	7.92(1H,dd,J=1.5,1.5Hz),3.76,3.83(each 2H,s),2.42 (3H,s)
2g	88	$C_{16}H_{15}BrINO$	442.9399 (442.9349)	7.83(2H,d,J=8.5Hz),7.55(2H,d,J=8.5Hz),3.80,3.73 (each 2H,s),2.40(3H,s)
2h	69	$C_{16}H_{15}FINO$	383.0177 (383.0182)	8.00(2H,dd,J=8.5,5.5Hz),7.85(1H,dd,J=8,1Hz),7.08 (2H,dd,J=8.5,8.5Hz),3.82,3.74(each 2H,s),2.41(3H,s)
2i	97	$C_{22}H_{20}INO$	441.0590 (441.0560)	7.80(3H,m),6.93(1H,ddd,J=8,7,2Hz),3.92(4H,s),3.87 (2H,s)
2j	62	$C_{23}H_{22}INO_2$	471.0695 (471.0685)	7.80 and 6.81(each 2H,d,J=9Hz),3.89(2H,s),3.85(4H, s),3.84(3H,s)
2l	84	$C_{17}H_{18}INO$	378.0357 (378.0368)	7.93(2H,dd,J=8,1.5Hz),7.81(1H,dd,J=8,1Hz),3.81 and 3.94(each 2H,s),2.78(2H,q,J=7Hz),1.11(3H,t,J=7Hz)
2m	78	$C_{19}H_{22}INO$	407.0747 (407.0707)[b]	7.91(2H,dd,J=8,1.5Hz),7.81(1H,dd,J=8,1Hz),3.83 and 3.95(each 2H,s),2.70(2H,t,J=7Hz),0.85(3H,t,J=7Hz)
2n	79	$C_{18}H_{20}INO$	392.0468[b] (392.0510)	7.90,7.25(each 2H,d,J=8.3Hz),3.87,3.75(each 2H,s), 2.69(2H,q,J=7.6Hz),2.42(3H,s),1.25(3H,t,J=7.6Hz)
2o	74	$C_{19}H_{22}BrNO_4$	409.0711[c] (409.0681)	7.97,6.89(each 2H,d,J=9Hz),6.99(1H,s),3.80,3.71 (each 2H,s),3.85(3H,s),3.81(6H,s),2.41(3H,s)
2p	87	$C_{19}H_{22}BrNO_4$	407.0737 (407.0698)	7.99,6.89(each 2H,d,J=9Hz),7.19,6.89(each 1H,J=8.5 Hz),3.80,3.75(each 2H,s),3.86(6H,s),3.85(3H,s)
2q	94	$C_{18}H_{18}INO_3$	423.0330 (423.0290)[b]	7.88(3H,m),4.68,4.63,4.62(4H,each s),4.23,4.17 (2H,each q,J=7Hz),1.28,1.19(3H,each t,J=7Hz)
2r	70	$C_{15}H_{13}INO_2$	350.0044[d] (350.0084)	7.87(3H,m),7.02(1H,m),4.80,4.76,4.69,4.61(4H,each s),2.23,2.07(3H,each s)
2s	82	$C_{22}H_{19}INO_2$	456.0460[e] (456.0429)	7.96(2H,d,J=8Hz),7.82(2H,d,J=7.5Hz),4.94,4.87,4.63, 4.57(4H,each s)
2t	69	$C_{16}H_{14}INO_2$	379.0069 (379.0044)	8.51,8.18(1H,each s),7.84(3H,m),4.75,4.66,4.63,4.59 (4H,each s)
3a	77	$C_{11}H_{14}INO$	303.0120 (303.0103)	3.63,3.23(each 2H,s),2.34(3H,s),2.15(3H,s)
3b	88	$C_{16}H_{22}INO$	371.0748 (371.0708)	3.63,3.29(each 2H,s),2.60(1H,m),2.33(3H,s)
3c	42	$C_{22}H_{26}INO$	447.1061 (447.1056)	3.81,3.78,3.30(each 2H,s),2.66(1H,m)

a. Ref. 3a for **2a** and Ref. 3b for **2b,e** and **2k**. b. M-I. c. M+2. d. M-COMe. e. M+1.

and 7.84 (1H,each dd,J=8 and 1Hz), 4.89 (1H,m), 4.60 and 3.39 (each 2H,m). IR (KBr): 1675 (C=O). MS(m/z)(M-H_2O):Calcd for $C_{16}H_{14}INO$:363.0119. Found:363.0104.

General Procedure for the Preparation of N-Alkyl-N-(2-halogenobenzyl)phenacylamines

This is exemplified by the preparation of **2l**. A solution of the benzylamine(**6c**)(685 mg, 2.62 mmol) in dioxane(10 ml) was added to a solution of phenacyl bromide(**5a**)(261 mg, 1.31 mmol) in dioxane(10 ml). The mixture was stirred for 4 h at room temperature. The white precipitates(338 mg) of the hydrobromide of **6c** formed were filtered and the filtrate was evaporated to give a crude oil(578 mg). This was purified by flash chromatography on SiO_2 with $CHCl_3$-benzene(5:1) to give **2l** as an oil(418 mg, 84%). The spectral data for **2l** thus obtained are shown in Table III.

Other N-alkylphenacylamines(**2c**, **2d**, **2f-j** and **2m-p**), and alkyl aminomethyl ketones

(3a-c) were prepared in the same way as 21(Table III).

General Procedure for the Preparation of N-Acyl-N-(2-iodobenzyl)phenacylamines This is exemplified by the preparation of 2t. Pyridinium chlorochromate(547 mg, 2.54 mmol) was added to a solution of N-formylethanolamine(7d)(645 mg, 1.69 mmol) in CH_2Cl_2(10 ml) and the mixture was stirred for 1 h. H_2O was added and the mixture was extracted with CH_2Cl_2 (50 ml x 3). The extract was washed with 10% HCl(50 ml x 3), dried over $MgSO_4$ and evaporated to a crude oil(511 mg). This was purified by flash chromatography on SiO_2 with $CHCl_3$-ethyl acetate(5:1) to give 2t as an oil(440 mg, 69%). The spectral data for 2t are shown in Table III.

Other N-acylphenacylamines(2q-s) were prepared in the same way as 2t (Table III).

General Procedure for Reaction of N-Substituted N-(2-Halogenobenzyl)phenacylamines with BuLi This is exemplified by the reaction of 21 with BuLi. BuLi(1.6 M sol. in hexane, 0.48 ml, 0.77 mmol) was added to a solution of the phenacylamine(21)(222 mg, 0.59 mmol) in dry THF (5 ml) by a syringe at -78°C under N_2 and the mixture was stirred for 10 min. at -78°C. H_2O(20 ml) was added and the mixture was extracted with ether(20 ml x 3). The extract was dried over $MgSO_4$ and evaporated to give an oil(180 mg). This was subjected to preparative TLC on SiO_2 with $CHCl_3$-ethyl acetate(3:1). The fraction of Rf 0.22-0.47 gave 11 as colorless cubes(138 mg, 93%), mp 72-73°C. A part of this free base was converted to the hydrochloride as colorless needles(from EtOH), mp 178-180°C(dec.). The physical and spectral data for 11 are shown in Table IV. The fraction of Rf 0.71-0.80 gave deiodinated product(91) as an oil(8 mg, 5%). The MS and ^{1}H-NMR spectral data are listed on Table V.

Reactions of other phenacylamines(2a-k, and 2m-t) and alkyl aminomethyl ketones (3a-c) with BuLi were carried out in the same way as 21. The physical and spectral data for the products are summerized in Tables IV and V.

General Procedure for Reaction of N-Substituted N-(2-Halogenobenzyl)phenacylamines with Zerovalent Nickel This is exemplified by the reaction of 21 with zerovalent nickel.[3] Ph_3P(2.057 g, 7.84 mmol), $NiCl_2$(508 mg, 3.92 mmol), and Zn(256 mg, 3.92 mmol) were placed in a two-necked flask. The flask was evacuated and filled with N_2. Dry oxygen-free DMF(30 ml) was added through a syringe. The mixture was stirred at 55°C for 5 min. A solution of 21(729 mg, 1.92 mmol) in dry oxygen-free DMF(3 ml) was added and the mixture was stirred for 4.5 h. Then, the mixture was acidified with 2% HCl and washed with ether. The aqueous layer was basified with NH_4OH and extracted with $CHCl_3$(50 ml x 5). The extract was dried over $MgSO_4$ and evaporated to give a crude product(423 mg). This was subjected to preparative TLC on Al_2O_3 with benzene-$CHCl_3$(10:1) to give the isoquinolinol(11) as a colorless cubes(414 mg, 64%), which was converted to the hydrochloride as colorless needles(from EtOH), mp 179-182°C(dec.). This was identical with 11 prepared with BuLi as described above by comparison of their ^{1}H-NMR spectra and a mixed melting point test of their hydrochlorides.

Reactions of other phenacylamines(2c, 2f-j, and 2m-t) and alkyl aminomethyl ketones (3a,b) with zerovalent nickel were carried out in the same way as 21.

Table IV. Physical and ^{1}H-NMR Spectral Data[a] for **1c**, **1d**, **1f-j**, **1l-n**, **1q-t** and **4a-c**

No	mp (°C)	Formula	Elemental analysis Calcd(Found) C	H	N	^{1}H-NMR ($CDCl_3$) δ
1c	129-130	$C_{19}H_{23}NO_4 \cdot 1/2H_2O$	67.44 (67.69)	7.15 (7.03)	4.14 (4.07)	7.35,6.86(each,2H,d,J=9Hz),3.87,3.82,3.64 (each 3H,s),3.76,3.37(each 1H,d,J=14.5Hz), 2.88,2.57(each 1H,d,J=11.5Hz),2.44(3H,s)
1d	189-191 (dec.)	$C_{19}H_{23}NO_4 \cdot HCl \cdot 1/3H_2O$	61.37 (61.54)	6.69 (7.00)	3.77 (3.54)	7.30,6.82(each 2H,d,J=9Hz),3.80,3.77,3.10 (each 3H,s),3.64,3.49(each 1H,d,J=14Hz), 2.80,2.65(each 1H,d,J=11.5Hz),2.33(3H,s)
1f	203-204 (dec.)	$C_{16}H_{16}ClNO \cdot HCl \cdot 1/5H_2O$	61.24 (61.51)	5.59 (5.53)	4.46 (4.48)	7.52(1H,br s),3.50,3.34(each 1H,d,J=15Hz), 2.92,2.60(each 1H,d,J=12Hz),2.38(3H,s)
1g	199-202 (dec.)	$C_{16}H_{16}BrNO \cdot HCl$	54.18 (54.49)	4.83 (4.85)	3.95 (3.89)	7.45,7.32(each 2H,d,J=9Hz),3.79,3.40(each 1H,d,J=15Hz),2.91,2.62(each 1H,d,J=12Hz)
1h	216-219 (dec.)	$C_{16}H_{16}FNO \cdot HCl$	65.42 (65.76)	5.83 (5.85)	4.77 (4.87)	7.41(2H,m),3.66,3.39(each 1H,d,J=15Hz), 2.92,2.62(each 1H,d,J=12Hz),2.42(3H,s)
1i	181-185 (dec.)	$C_{22}H_{21}NO \cdot HCl$	75.10 (75.14)	6.30 (6.25)	3.98 (3.96)	3.94 and 3.56(each 1H,d,J=15Hz),3.04 and 2.79(each 1H,d,J=12Hz),3.74(2H,s)
1j	196-200 (dec.)	$C_{23}H_{23}NO_2 \cdot HCl$	72.34 (72.10)	6.33 (6.55)	3.67 (3.68)	6.85(2H,d,J=9Hz),3.95,3.54(each,1H,d,J=15 Hz),3.80(3H,s),3.73(2H,s),3.00,2.75(each 1H,d,J=12Hz)
1l	178-180 (dec.)	$C_{17}H_{19}NO \cdot HCl$	70.46 (70.62)	6.96 (7.00)	4.83 (4.60)	4.03 and 3.55(each 1H,d,J=15Hz),3.05 and 2.71(each 1H,d,J=12Hz),1.19(3H,t,J=7Hz)
1m	177-180 (dec.)	$C_{19}H_{23}NO \cdot HCl$	71.80 (71.46)	7.61 (7.77)	4.41 (4.28)	3.98 and 3.51(each 1H,d,J=15Hz),2.99 and 2.69(each 1H,d,J=12Hz),0.93(3H,t,J=7Hz)
1n	180-183 (dec.)	$C_{18}H_{21}NO \cdot HCl \cdot 1/2H_2O$	69.11 (69.00)	7.41 (7.59)	4.48 (4.32)	7.34,6.99(each 2H,d,J=8Hz),3.38,3.21(each 1H,d,J=15Hz),2.94,2.88(each 1H,d,J=11.5Hz) 2.32(3H,s),1.23(3H,t,J=7.5Hz)
1q	oil	$C_{18}H_{19}NO_3$	297.1364(M^+) (297.1359)			4.82,4.54(each 1H,d,J=17Hz),3.99(2H,q,J=7 Hz),3.93,3.71(each 1H,d,J=14Hz),1.12(3H,t, J=7Hz)
1r	161.5-163	$C_{17}H_{17}NO_2$	76.38 (76.46)	6.41 (6.48)	5.24 (5.20)	5.14,4.60(each 1H,d,J=17.5Hz),3.87,3.74 (each 1H,d,J=14Hz),1.93,1.65(3H,each s)
1s	oil	$C_{22}H_{19}NO_2$	329.1416(M^+) (329.1418)			5.15,4.76(each 1H,d,J=18Hz),4.12,3.71 (each 1H,d,J=14Hz)
1t	oil	$C_{16}H_{15}NO_2$	253.1103(M^+) (253.1126)			8.05,7.79(1H,each s),5.05,4.43(2H,d,J=17 Hz),4.29,3.67,3.61,3.48(2H,each d.J=14Hz)
4a	182-185 (dec.)	$C_{11}H_{15}NO \cdot HCl \cdot 1/5H_2O$	60.80 (61.17)	7.61 (7.78)	6.45 (6.59)	3.68,3.33(each 1H,d,J=15Hz),2.80,2.45 (each 1H,d,J=12Hz),2.43(3H,s),1.55(3H,s)
4b	207-211 (dec.)	$C_{16}H_{23}NO \cdot HCl \cdot 1/3H_2O$	66.77 (67.00)	8.64 (8.72)	4.87 (4.77)	3.62,3.21(each 1H,d,J=15Hz),2.83,2.43 (each 1H,d,J=12Hz),2.41(3H,s)
4c	190-195 (dec.)	$C_{22}H_{27}NO \cdot HCl$	73.83 (73.61)	7.89 (8.13)	3.91 (3.89)	3.79,3.64(each 1H,d,J=13Hz),3.74,3.34 (each 1H,d,J=15Hz),2.94,2.62(each 1H,d, J=12Hz)

a. Ref. 3b for **1a,b,e** and **1k**.

(±)-O,O-Dimethylcherylline(12c) A solution of **1c**(60 mg, 0.18 mmol) in 35% HCl-EtOH(4 ml) was refluxed for 3 h. The mixture was concentrated. $NaBH_4$(70 mg, 1.85 mmol) was added to a solution of the residue in MeOH(3 ml) during 5 min. The mixture was stirred for 2 h. H_2O(10 ml) was added and the mixture was extracted with $CHCl_3$. The extract was washed with H_2O, dried over $MgSO_4$ and evaporated to give a crude product(70 mg). This was purified by preparative TLC on Al_2O_3 with $CHCl_3$-ethyl acetate(5:1) to afford **12c** as colorless plates(from MeOH)(40 mg, 70%), mp 96-97°C (lit. mp 87-89°C[2b], mp 82-83°C[11]). ^{1}H-NMR:7.10 and 6.83(each 2H,d,J=9Hz), 6.56 and 6.35(each 1H,s), 4.15(1H,dd,J=8.5 and 5.5Hz), 3.86, 3.79 and 3.65(each 3H,s), 3.66 and 3.53(each 1H,d,J=14.5Hz), 2.97(1H,dd, J=11.5 and 5.5Hz), 2.48(1H,dd,J=11.5 and 8.5Hz), 2.41(3H,s). Anal.Calcd for $C_{19}H_{23}NO_3$:

Table V. MS and ^{1}H-NMR Data for **9a-c, 9e-h, 9j-n, 10o and 11a,b**

No	Formula	MS(m/z)(M^+) Calcd(Found)	^{1}H-NMR ($CDCl_3$) δ
9a	$C_{16}H_{17}NO$	239.1310 (239.1292)	7.90(2H,dd,J=8,2Hz),3.74,3.83(each 2H,s),2.41(3H,s)
9b	$C_{17}H_{19}NO_2$	269.1416 (269.1424)	7.86,6.82(each 2H,d,J=9Hz),3.86(3H,s),3.73,3.63(each 2H, s),2.34(3H,s)
9c	$C_{19}H_{23}NO_4$	329.1624 (329.1617)	7.97,6.90(each 2H,d,J=8Hz),3.86,3.85,3.84(each 3H,s), 3.72,3.61(each 2H,s),2.38(3H,s)
9e	$C_{16}H_{16}ClNO$	272.0841[a] (272.0841)	7.90,7.39(each 2H,d,J=9Hz),3.74,3.67(each 2H,s),2.36(3H, s)
9f	$C_{16}H_{16}ClNO$	273.0921 (273.0922)	7.95(1H,dd,J=1.5,1.5Hz),7.67,7.52(each 1H,ddd,J=8,1.5,1.5 Hz),3.73,3.67(each 2H,s),2.36(3H,s)
9g	$C_{16}H_{16}BrNO$	317.0240 (317.0149)	7.82,7.56(2H,d,J=9Hz),3.74,3.68(each 2H,s),2.36(3H,s)
9h	$C_{16}H_{16}FNO$	257.1213 (257.1175)	8.00(2H,dd,J=9,5.5Hz),7.09(2H,dd,J=9,9Hz),3.74,3.57(each 2H,s),2.36(3H,s)
9j	$C_{23}H_{23}NO_2$	345.1726 (345.1688)	7.84,6.85(each 2H,d,J=9Hz),3.85(4H,s),3.77(2H,s),3.75 (3H,s)
9k	$C_{17}H_{16}F_3NO$	307.1182 (307.1156)	8.29(1H,s),3.74,3.66(each 2H,s),2.35(3H,s)
9l	$C_{17}H_{19}NO$	253.1466 (253.1471)	7.94(2H,m),3.87,3.76(each 2H,s),2.71(2H,q,J=7Hz),1.11 (3H,t,J=7Hz)
9m	$C_{19}H_{23}NO$	281.1777 (281.1769)	7.92(2H,d,J=8Hz),3.86,3.76(each 2H,s),2.63(2H,t,J=7Hz), 0.85(3H,t,J=7Hz)
9n	$C_{18}H_{21}NO$	267.1623 (267.1629)	7.88(2H,d,J=8Hz),3.80,3.70(each 2H,s),2.74(2H,q,J=7.5Hz), 2.38(3Hs),1.25(3H,t,J=7.5Hz)
10o	$C_{23}H_{33}NO_4$	386.2329[a] (386.2283)	7.35,6.85(each 2H,d,J=9Hz),3.87,3.85,3.78(each 3H,s), 3.37,3.26,2.87,2.76(each 1H,d,J=13Hz),1.99(3H,s),0.80 (3H,t,J=7Hz)
11a	$C_{11}H_{15}NO$	177.1151 (177.1133)	7.32(5H,s),3.61,3.58(each 2H,s),2.30,2.14(each 3H,s)
11b	$C_{16}H_{23}NO$	245.1781 (245.1785)	7.32(5H,s),3.59,3.24(each 2H,s),3.15(1H,m),2.29(3H,s), 1.75(4H,m),1.26(6H,m)

a. M-1.

C,72.82;H,7.40;N,4.47. Found: C,72.85;H,7.57; N,4.47. The ^{1}H-NMR spectrum of **12c** was identical with that of a natural **12c**.[11]

Compounds (**12d**) and (**12a**) were prepared in the same way as **12c**.

(±)-O,O-Dimethyllatifine(**12d**) Colorless needles(from MeOH)(73%), mp 89-90°C(lit.[14] mp 85-89°C). ^{1}H-NMR: 7.12 and 6.78(each 2H,d,J=9Hz), 6.80(2H,s), 4.15(1H,t,J=4.5Hz), 3.79, 3.75 and 3.20(each 3H,s), 3.80 and 3.32(each 1H,d,J=14.5Hz), 2.70(2H,d,J=4.5Hz), 2.32 (3H,s). Anal.Calcd for $C_{19}H_{23}NO_3$:C,72.82;H,7.40;N,4.47. Found:C,72.48;H,7.50;N,4.50. The ^{1}H-NMR spectrum of **12b** was identical with that of a natural **12b**.[2d]

2-Methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline(**12a**) Colorless needles (from acetone) (80%) as a hydrochloride, mp 164-167°C(lit.[15] mp 178-179°C). ^{1}H-NMR(free base): 4.29 (1H,dd,J=8.5 and 5.5Hz), 3.77 and 3.61(each 1H,d,J=15Hz), 3.04(1H,dd,J=11.5 and 5.5Hz), 2.57(1H,dd,J=11.5 and 8.5Hz), 2.43(3H,s). Anal.Calcd for $C_{16}H_{17}N\cdot HCl\cdot 1/5H_2O$: C,72.96; H,7.04;N, 5.32. Found:C,73.13;H,7.14;N,5.12.

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