SYNTHESIS OF 2-METHYL-4-PHENYL-1,2,3,4-TETRAHYDROISOQUINOLIN-4-OL DERIVATIVES BY A NOVEL INSERTION REACTION OF ARYL-NICKEL COMPLEXES

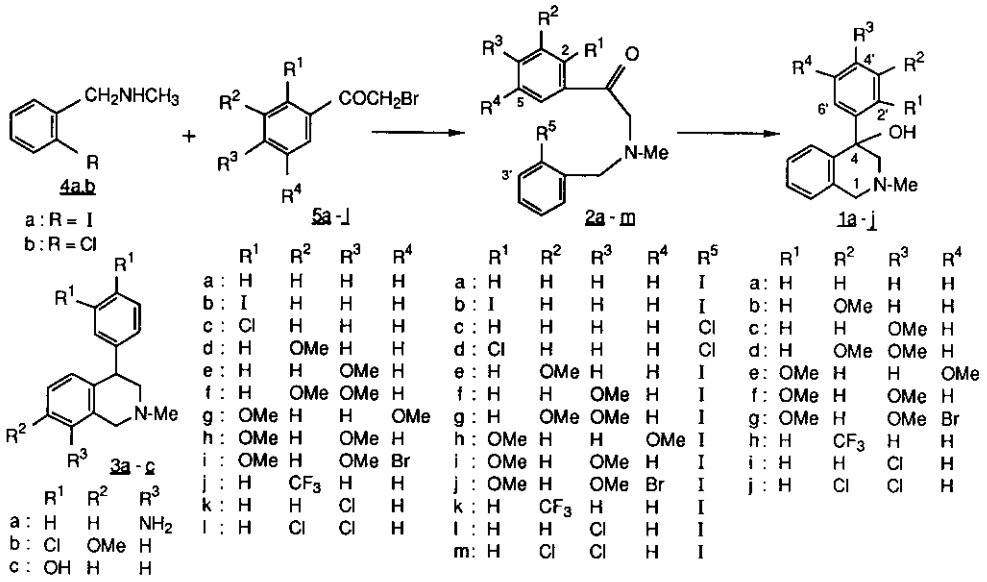
Masaru Kihara,* Akinori Nakanishi, and Shigeru Kobayashi
Faculty of Pharmaceutical Sciences, The University of Tokushima,
1-78, Sho-machi, Tokushima 770, Japan

Abstract - 2-Methyl-4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol derivatives (1a-j) as a new potentiator of noradrenaline were prepared by a novel intramolecular insertion of the aryl-nickel complexes of N-(2-halobenzyl)phenacylamines (2a-m).

The insertion of carbon monoxide into transition metal-carbon bonds has been extensively studied[1] from both a synthetic and a mechanistic point of view. However, there are only a few reports for the insertions of carbon dioxide[2] and formaldehyde,[2,3] and for the intramolecular insertion of a formyl group,[4] although of increasing interest.[5] Recently, we have reported[6] the novel synthesis of 2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol (1a) (PI-OH) by the intramolecular insertion reaction of N-(2-iodobenzyl)phenacylamines (2a,b) with zerovalent nickel. In addition, the isoquinolin-4-ol (1a) was found[7] to be an ideal potentiator of the response to noradrenaline and its activity was due to inhibition of noradrenaline uptake. Nomifensin (3a), diclofensin (3b) and the 3',4'-dihydroxyisoquinoline (3c), which are well known as antidepressants,[8] have a different type of substituents on the phenyl groups at C-4. From these findings, the preparation of the 4-phenyl-substituted derivatives of 1a is interesting in a synthetic and a pharmacological point of view.

This paper describes the improved synthesis of 1a and its 2'-, 3'-, 4'-, and/or 5'-substituted derivatives (1b-j) by an intramolecular insertion of the aryl-nickel complexes of N-(2-halobenzyl)phenacylamines (2a-m) (Chart 1).

Semmelhack and co-workers reported[9] the synthesis of biaryls from aryl iodides using zerovalent nickel in good yields. In our previous paper,[6] the isoquinolin-4-ol (1a) was synthesized in yields of 18.7 and 23.8% from 2a,b, respectively, by



	R^1	R^2	R^3	R^4
a :	H	H	H	H
b :	I	H	H	H
c :	Cl	H	H	H
d :	H	OMe	H	H
e :	H	H	OMe	H
f :	H	OMe	OMe	H
g :	OMe	H	H	OMe
h :	OMe	H	OMe	H
i :	OMe	H	OMe	Br
j :	H	CF_3	H	H
k :	H	H	Cl	H
l :	H	Cl	Cl	H

	R^1	R^2	R^3	R^4	R^5
a :	H	H	H	H	I
b :	I	H	H	H	I
c :	H	H	H	H	Cl
d :	Cl	H	H	H	Cl
e :	H	OMe	H	H	I
f :	H	H	OMe	H	I
g :	H	OMe	OMe	H	I
h :	OMe	H	H	OMe	I
i :	OMe	H	OMe	H	I
j :	OMe	H	OMe	Br	I
k :	H	CF_3	H	H	I
l :	H	H	Cl	H	I
m :	H	Cl	Cl	H	I

	R^1	R^2	R^3	R^4
a :	H	H	H	H
b :	H	OMe	H	H
c :	H	H	OMe	H
d :	H	OMe	OMe	H
e :	OMe	H	H	OMe
f :	OMe	H	OMe	H
g :	OMe	H	OMe	Br
h :	H	CF_3	H	H
i :	H	H	Cl	H
j :	H	Cl	Cl	H

	R^1	R^2	R^3
a :	H	H	NH_2
b :	Cl	OMe	H
c :	OH	H	H

Chart 1

Table 1 Synthesis of the isoquinolin-4-ol (1a) from the phenacylamines (2a-d)

Run	Starting material	$NiCl_2$	$(Ph_3P)_2NiCl_2$	Conditions temp.(°C)	time(h)	solvent	Yield of 1a (%)
1	2a	1 eq		55-60	10	DMF	28.5
2	2a	2 eq		55-60	10	DMF	40.1
3	2a	2 eq		55-60	40	DMF	35.8
4	2a		2 eq	55-60	10	DMF	18.7[a]
5	2a	2 eq		55-60	10	DMA	14.1
6	2a	2 eq		75-80	10	DMA	9.1
7	2b	2 eq		55-60	10	DMF	21.2
8	2b		2 eq	55-60	10	DMF	23.8[a]
9	2c	0.1 eq		55-60	10	DMF	b)
10	2c	1 eq		55-60	10	DMF	5.3
11	2c	2 eq		55-60	10	DMF	23.3
12	2c	2 eq		55-60	40	DMF	22.8
13	2c		2 eq	55-60	10	DMF	20.7
14	2d	2 eq		55-60	10	DMF	14.5
15	2d		2 eq	55-60	10	DMF	11.3

a) Ref. 6.
b) Only an ambiguous mixture was obtained.

the method[10] using zerovalent nickel generated in situ from $(Ph_3P)_2NiCl_2$, zinc and Ph_3P in dimethylformamide (DMF). Recently, Colon and Kelsey reported[11] the synthesis of biaryls from aryl chlorides using zerovalent nickel generated from $NiCl_2$, zinc and Ph_3P in good yields. Thus, to improve the yield of 1a, iodo- and chlorophenacylamines (2a,b) and (2c,d) prepared from benzylamines (4a,b) and phenacyl bromides (5a-c) were treated with $(Ph_3P)_2NiCl_2$ or $NiCl_2$ under the different conditions, as shown in Table 1. The best yield of 1a was obtained from monoiodophenacylamine (2a) using $NiCl_2$ (run 2) and was a twice of those[6] using $(Ph_3P)_2NiCl_2$ (runs 4 and 8). The longer reaction time (runs 3 and 12) and dimethylacetamide (DMA) as a solvent[11] (runs 5 and 6) did not improve the yield of 1a. The results of the reaction of 2c using $NiCl_2$ (runs 9-11) indicated that this insertion was a stoichiometric reaction. Apparently, this cyclization did not need a halogen atom in the phenacyl benzene ring (runs 1-6 and 10-13). These results suggest the reaction mechanism as shown in Chart 2.

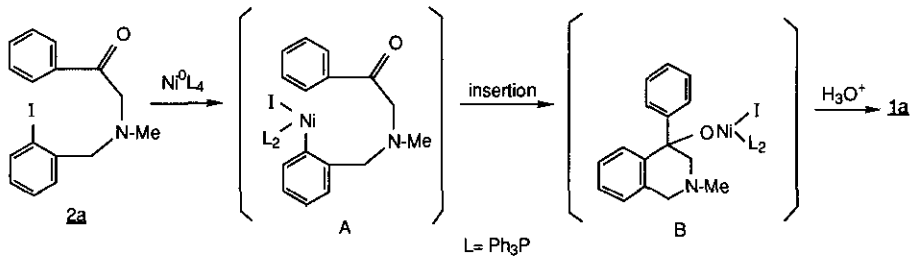


Chart 2

The phenacylamine (2a) is reacted with zerovalent nickel to form an aryl-nickel complex (A). Insertion of the carbonyl group[2] in A into the nickel-carbon bond gives an isoquinolinol complex (B), which is hydrolyzed[12] on treatment with 2% HCl to give 1a.

On the basis of these results, the monoiodophenacylamines (2e-m) as key intermediates for the synthesis of 1b-j were selected and prepared in good yields by condensation[13] of the benzylamine (4a) with phenacyl bromides (5d-l) (Table 4), of which 5d,e,g,k were commercially available. The phenacyl bromides (5c,f,h-j,l) were easily obtained by bromination[14] of the corresponding acetophenones with bromine and aluminium chloride as a catalyst. Bromination of 2',4'-dimethoxyacetophenone gave 5h (22.8%) and the aromatic substituted product (5i) (14.8%) of 5h. The phenacylamines

Table 2 Yields and physical data of the isoquinolin-4-ols (1b-j)

Starting material No	Product No	Yield (%)	mp (°C)	Formula	Elemental analysis Calcd (Found) C	H	N
2e	1b	37.0	198-199.5	$C_{17}H_{19}NO_2 \cdot HCl \cdot 1/3H_2O$	65.48 (65.24)	6.68 (6.56)	4.49 (4.37)
2f	1c	21.2	120.5-121.5	$C_{17}H_{19}NO_2$	75.92 (75.81)	7.11 (7.11)	4.95 (5.20)
2g	1d	23.8	oil	$C_{18}H_{21}NO_3$	Ms(m/z)(M^+): 299.1504 (299.1519)		
2h	1e	16.3	115.5-116.5	$C_{18}H_{21}NO_3$	72.22 (72.06)	7.07 (7.15)	4.68 (4.64)
2i	1f	13.2	103-104.5	$C_{18}H_{21}NO_3$	72.22 (71.95)	7.07 (7.06)	4.68 (4.51)
2j	1g	20.0	180-182.5	$C_{18}H_{20}BrNO_3 \cdot 1/2H_2O$	55.83 (55.96)	5.47 (5.19)	3.62 (3.42)
2k	1h	41.2	120-121	$C_{17}H_{16}F_3NO$	66.44 (66.44)	5.25 (5.30)	4.56 (4.54)
2l	1i	22.5	230.5-233.5	$C_{16}H_{16}ClNO \cdot HCl$	61.95 (61.66)	5.52 (5.56)	4.52 (4.37)
2m	1j	29.5	oil	$C_{16}H_{15}Cl_2NO$	Ms(m/z)(M^+): 307.0528 (307.0497)		

Table 3 ^{1}H-Nmr spectral data of 1b-j

No	^{1}H-Nmr ($CDCl_3$) δ
1b	3.80(3H,s), 3.39 and 3.23(each 1H,d,J=15Hz), 2.96 and 2.60(each 1H,d,J=12 Hz), 2.32(3H,s)
1c	7.35(2H,d,J=9Hz), 6.84(2H,d,J=9Hz), 3.81(3H,s), 3.55 and 3.31(each 1H,d,J= 15Hz), 2.94 and 2.58(each 1H,d,J=12Hz), 2.37(3H,s)
1d	7.13(1H,d,J=2Hz), 6.87(1H,dd,J=8 and 2Hz), 6.81(1H,d,J=8Hz), 3.89 and 3.86 (each 3H,s), 3.83 and 3.45(each 1H,d,J=15Hz), 2.92 and 2.66(each 1H,d,J=12 Hz), 2.47(3H,s)
1e	6.74(1H,s), 3.60(3H,s), 3.48 and 3.31(each 1H,d,J=15Hz), 3.28(3H,s), 3.06 and 2.79(each 1H,d,J=12Hz), 2.36(3H,s)
1f	7.62(1H,d,J=9Hz), 6.50(1H,dd,J=9 and 2Hz), 6.37(1H,d,J=2Hz), 3.80(3H,s), 3.65 and 3.41(each 1H,d,J=15Hz), 3.42(3H,s), 3.07 and 2.79(each 1H,d,J= 12Hz), 2.39(3H,s)
1g	8.04(1H,s), 6.38(1H,s), 3.88(3H,s), 3.57 and 3.32(each 1H,d,J=15Hz), 3.38 (3H,s), 2.99 and 2.74(each 1H,d,J=12Hz), 2.38(3H,s)
1h	7.83(1H,s), 7.54(1H,d,J=7Hz), 7.43(1H,d,J=7Hz), 3.59 and 3.38(each 1H,d, J=15Hz), 2.93 and 2.63(each 1H,d,J=12Hz), 2.41(3H,s)
1i	7.39(2H,d,J=9Hz), 7.29(2H,d,J=9Hz), 3.73 and 3.41(each 1H,d,J=15Hz), 2.90 and 2.62(each 1H,d,J=12Hz), 2.43(3H,s)
1j	7.63(1H,d,J=2Hz), 7.38(1H,d,J=8Hz), 3.64 and 3.39(each 1H,d,J=15Hz), 2.89 and 2.60(each 1H,d,J=12Hz), 2.41(3H,s)

(2e-m) thus obtained were treated with zerovalent nickel generated from $NiCl_2$-Zn-Ph_3P system in DMF for 10 h. The isoquinolin-4-ols (1b-j) were obtained in 20-40% yields (Table 2) together with an ambiguous material, but without the starting material. The structures of 1b-j were determined by their physical data, and mass and ^{1}H-nmr spectral data (Tables 2 and 3). The ^{1}H-nmr spectra of 1b-j showed the characteristic AB-type doublets (J=15 and 12Hz) of the methylene protons (δ3.30-3.84 and δ2.60-3.07) at C-1 and C-3, respectively.

As described above, our novel insertion reaction of the aryl-nickel complexes of N-(2-iodobenzyl)phenacylamines, although of a moderate yield, offers a more convenient method for the preparation of biologically active 4-phenyltetrahydroisoquinolin-4-ols than the other ones[15] reported to date.

EXPERIMENTAL

All melting points are given as uncorrected values. Infrared (ir) spectra were taken with a Perkin-Elmer 1720 infrared fourier transform spectrophotometer 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-PS 100 or a JEOL JNM-FX 200 spectrometer in $CDCl_3$ with tetramethylsilane as a standard and are given in δ values.

Bromination of 2',4'-dimethoxyacetophenone

To a solution of 2',4'-dimethoxyacetophenone (10.81 g, 64.3 mmol) in dry ether (20 ml) was added $AlCl_3$ (50 mg) and then bromine (9.60 g, 60.1 mmol) was added dropwise under ice-cooling with stirring during 16 min to give a pale yellow oil. The reaction mixture was extracted with $CHCl_3$ (50 ml) and the extract was washed with a saturated solution of $Na_2S_2O_3$ in H_2O, 2% Na_2CO_3 and brine, successively. The $CHCl_3$ solution was dried over $MgSO_4$ and evaporated to give crude crystals (10.65 g), which were subjected to flash chromatography on SiO_2 in $CHCl_3$-benzene (1:1). The first fraction gave pale violet needles (5.70 g) and the socond fraction afforded the starting material (1.21 g). The first fraction was further subjected to flash chromatography on SiO_2 in ethyl acetate-hexane (1:1) to give two fractions. The first fraction gave the monobromide (2h) as colorless needles (3.02g, 22.8%), mp 99-102°C (from ethyl acetate-hexane) (lit.[16] mp 102-104°C). Ir(KBr): 1665. ^{1}H-Nmr: 7.90(1H,d,J=9Hz), 6.57(1H,dd,J=9 and 2Hz), 6.47(1H,d,J=2Hz), 4.57(2H,s), 3.93 and 3.87(each 3H,s). Anal.Calcd for $C_{10}H_{11}BrO_3$: C,46.19; H,4.28. Found: C,46.36; H,4.22.

The socond fraction afforded the dibromide (5i) as colorless needles (1.97 g, 14.8%), mp 155-157.5°C (from ethyl acetate-hexane). Ir(KBr): 1665. ^{1}H-Nmr: 8.08(1H, s), 6.44(1H,d,J=2Hz), 4.52(2H,s), 3.99 and 3.98(each 3H,s). Anal.Calcd for $C_{10}H_{10}Br_2O_3$: C,35.54; H,2.98. Found: C,35.62; H,2.97.

3,4-Dichlorophenacyl Bromide (5l)

A solution of 3',4'-dichloroacetophenone (10.02g, 59.6 mmol) in ether-$CHCl_3$ (1:1) (40 ml) was treated with bromine (9.33 g, 58.4 mmol) and $AlCl_3$ (50 mg) in the same way as above. The crude oil (12.8 g) obtained was purified by flash chromatography on SiO_2 in benzene to afford 5l as pale yellow needles (10.13 g, 71.3%), mp 55-57°C (from benzene-hexane) (lit.[17] mp 54-56.5°C). Ir(KBr): 1695. ^{1}H-Nmr: 8.07(1H,d,J=2 Hz), 7.82(1H,dd,J=8 and 2Hz), 7.59(1H,d,J=8Hz), 4.38(2H,s). Anal.Calcd for $C_8H_5BrCl_2O$: C,35.86; H,1.88. Found: C,35.66; H,1.95.

The phenacyl bromides (5c,f,j) were prepared in the same way as 5l.

2-Chlorophenacyl bromide (5c)

Colorless oil (58.8%) (lit.[18] bp 97.5-98°C/1 mmHg). Ir(KBr): 1698. ^{1}H-Nmr: 7.57(1H, m), 7.47-7.32(3H,m), 4.52(2H,s). Ms(m/z)(M^+): Calcd for C_8H_6BrClO: 321.9335. Found: 321.9290.

3,4-Dimethoxyphenacyl bromide (5f)

Colorless needles (43.6%), mp 78.5-80°C (from benzene-hexane) (lit.[19] mp 81°C). Ir(KBr): 1671. ^{1}H-Nmr: 7.86(1H,dd,J=8 and 2Hz), 7.79(1H,s), 7.15(1H,d,J=8Hz), 4.71 (2H,s), 3.92 and 3.90(each 3H,s). Anal. Calcd for $C_{10}H_{11}BrO_3$: C,46.36; H,4.28. Found: C,46.54; H,4.25.

3-Trifluoromethylphenacyl bromide (5j)

Colorless oil (29.2%) (lit.[20] mp 22°C). Ir(KBr): 1703. ^{1}H-Nmr: 8.25(1H,s), 8.18 (1H,d,J=8Hz), 4.46(2H,s). Ms(m/z)(M^+): Calcd for C_9H_6BrFO: 265.9531. Found: 265.9552.

2-Chloro-N-methylbenzylamine (4b)

The benzylamine (4b) was prepared by the method reported by Borch and co-workers.[21] To a solution of 30% CH_3NH_2-MeOH (51.04 g, 493 mmol) and absolute MeOH (110 ml) was added 5N HCl-MeOH (32 ml), followed by 2-chlorobenzaldehyde (11.62 g, 82.7 mmol) and $NaBH_3CN$ (3.14 g, 50.0 mmol). The mixture was stirred at room temperature for 72 h and filtered. The filtrate was made acidic (pH 2) with conc. HCl (15 ml) and concentrated to the volume of one fifth. H_2O (20 ml) was added and the solution was washed with ether. The aqueous layer was made basic (pH 10) with solid KOH and extracted with ether. The extract was dried over $MgSO_4$ and evaporated to give 4b

Table 4 Yields, mass and ^{1}H-nmr spectral data of 2c-m[a)]

Compound	Yield (%)	Formula	Ms (m/z) (M^+) Calcd (Found)	^{1}H-Nmr ($CDCl_3$) δ
2c	59.4	$C_{16}H_{16}ClNO$	273.0918 (273.0902)	7.96(2H,dd,J=8 and 2Hz),3.88(2H,s),3.82(2H, s),2.40(3H,s)
2d	45.0	$C_{16}H_{15}Cl_2NO$	307.0528 (307.0501)	3.83(2H,s),3.81(2H,s),2.40(3H,s)
2e	71.6	$C_{17}H_{18}INO_2$	395.0381 (395.0361)	7.94(1H,ddd,J=8,3 and 1Hz),7.83(1H,dd,J=8 and 1Hz),7.33(1H,dd,J=8 and 8Hz),6.95(1H, ddd,J=8,2 and 1Hz),3.91(2H,s),3.84(3H,s), 3.77(2H,s),2.44(3H,s)
2f	61.1	$C_{17}H_{18}INO_2$	395.0384 (395.0400)	7.97(2H,d,J=9Hz),7.84(1H,dd,J=8 and 1Hz), 7.46(1H,dd,J=8 and 2Hz),7.31(1H,ddd,J=8,8, and 1Hz),6.90(2H,d,J=9Hz),3.86(3H,s),3.82 (2H,s),3.74(2H,s),2.40(3H,s)
2g	93.5	$C_{18}H_{20}INO_3$	425.0487 (425.0470)	7.90(1H,dd,J=8 and 2Hz),3.92(3H,s),3.90(3H, s),3.88(2H,s),3.78(2H,s),2.42(3H,s)
2h	66.6	$C_{18}H_{20}INO_3$	425.0490 (425.0500)	7.82(1H,dd,J=8 and 2Hz),7.44(1H,ddd,J=8,8, and 2Hz),3.99(2H,s),3.82(8H,s),2.47(3H,s)
2i	80.1	$C_{18}H_{20}INO_3$	425.0487 (425.0449)	7.84(1H,d,J=9Hz),7.81(1H,dd,J=8 and 1Hz), 7.49(1H,dd,J=8 and 1Hz),7.30(1H,ddd,J=8,8, and 1Hz),6.93(1H,ddd,J=8,8 and 1Hz),6.54 (1H,dd,J=9 and 2Hz),6.43(1H,d,J=2Hz),3.85 5H,s),3.83(5H,s),2.45(3H,s)
2j	73.1	$C_{18}H_{19}BrINO_3$	502.9615 (502.9605)	7.98(1H,s),7.81(1H,dd,J=8 and 1Hz),6.40(1H, s),3.96(2H,s),3.84(6H,s),3.80(2H,s),2.44 3H,s)
2k	67.2	$C_{17}H_{15}F_3INO$	414.0168 (414.0244)	8.30(1H,d,J=8Hz),8.22(1H,s),7.83(1H,dd,J= 8 and 1Hz),7.56(1H,dd,J=8 and 8Hz),7.42(1H, dd,J=8 and 2Hz),7.32(1H,ddd,J=8,8 and 2Hz), 6.96(1H,ddd,J=8,2 and 2Hz),3.85(2H,s),3.74 2H,s),2.41(3H,s)
2l	70.1	$C_{16}H_{15}ClINO$	398.9886 (398.9819)	7.91(2H,d,J=9Hz),7.85(1H,dd,J=8 and 1Hz), 7.39(2H,d,J=9Hz),7.30(1H,dd,J=8 and 1Hz), 6.97(1H,ddd,J=8,8 and 1Hz),3.81(3H,s),3.73 (2H,s),2.40(3H,s)
2m	74.0	$C_{16}H_{14}Cl_2INO$	432.9497 (432.9464)	8.04(1H,d,J=2Hz),7.85(1H,dd,J=8 and 2Hz), 7.78(1H,dd,J=8 and 1Hz),7.48(1H,d,J=8Hz), 3.75(2H,s),3.70(2H,s),2.38(3H,s)

a)Oily product.

as an oil (11.90 g). This was converted to the hydrochloride as colorless needles (5.20 g, 34.2%), mp 133-135°C (from MeOH-acetone). ^{1}H-Nmr (free base): 7.39-7.14 (4H,m), 3.84(2H,s), 2.45(3H,s). Anal. Calcd for $C_8H_{10}ClN\cdot HCl$: C,50.02; H,5.77; N,7.29. Found: C,50.21; H,5.87; N,7.20.

3,4-Dimethoxy-N-(2-iodobenzyl)-N-methylphenacylamine (2g)

A solution of 4a[6] (982 mg, 3.98 mmol) in dioxane (10 ml) was added to a solution of 5f (515 mg, 1.99 mmol) in dioxane (10 ml) and stirred at room temperature for 5 h. The precipitates formed were filtered and the filtrate was evaporated *in vacuo* to give a pale yellow oil. This crude product was purified by flash chromatography on SiO_2 in $CHCl_3$-benzene (1:1) to give 2g as a pale yellow oil (792 mg, 93.5%) (Table 4). The phenacylamines (2c-f and 2h-m) were prepared in the same way as 2g as shown in Table 4.

Reaction of the phenacylamine (2c) with $(Ph_3P)_2NiCl_2$-Zn-Ph_3P system

Ph_3P (904 mg, 3.4 mmol), $(Ph_3P)_2NiCl_2$ (1124 mg, 1.7 mmol), Zn (115 mg, 1.7 mmol) and KI (286 mg, 1.7 mmol) were placed in a two-necked flask. The flask was evacuated and filled with N_2. Dry oxygen-free DMF (15 ml) was added through a syringe. The mixture was stirred at 55°C for 5 min. A solution of 2c (314 mg, 0.86 mmol) in dry oxygen-free DMF (1.5 ml) was added, and the mixture was stirred at 55-60°C for 10 h. Then, 2% HCl (20 ml) was added and the aqueous layer was washed with ether. The aqueous layer was made basic with solid Na_2CO_3 and extracted with $CHCl_3$. The extract was washed with H_2O, dried over $MgSO_4$ and evaporated to give a crude product (226 mg). This was subjected to preparative tlc (PLC) on Al_2O_3 in benzene-ethyl acetate (1:1) to give 1a as colorless plates (54 mg, 20.7%), mp 105-106°C (from MeOH). This was identical with an authentic 1a[6] by comparison of the ^1H-nmr spectra and a mixed melting point test.

The phenacylamine (2d) was treated with $(Ph_3P)_2NiCl_2$-Zn-Ph_3P system in the same way as 2c (Table 1).

Reaction of the phenacylamine (2a) with $NiCl_2$-Zn-Ph_3P system

The phenacylamine (2a) (531 mg, 1.5 mmol) in dry oxygen-free DMF (3 ml) was treated with Ph_3P (1582 mg, 6.0 mmol), $NiCl_2$ (382 mg, 3.0 mmol) and Zn (197 mg, 3.3 mmol) in dry oxygen-free DMF (30 ml) in the same way as above to give a pale brown oil (217 mg). This crude product was purified by PLC on Al_2O_3 in benzene-ethyl acetate (1:1) and recrystallized from MeOH to give 1a as colorless plates (139 mg, 40.1%), mp 105.5-106°C. This was identical with the sample obtained above by comparison of the ^1H-nmr spectra and a mixed melting point test.

The phenacylamines (2e-m) were treated with $NiCl_2$-Zn-Ph_3P in the same way as above to give the isoquinolin-4-ols (1b-j). Yields, and physical and spectral data are summarized in Tables 2 and 3.

REFERENCES

1. C.P.Casey and L.M.Baltusis, J.Am.Chem.Soc., 1982, 104, 6347; J.Berke and R.Hoffmann, ibid., 1978, 100, 7224; M.Mori, Yakugaku Zasshi, 1981, 101, 383.
2. H.Carmona, P.Palma, M.Paneque, and M.L.Poveda, J.Am.Chem.Soc., 1986, 108, 6424.
3. W.R.Tikkanen and J.L.Petterson, Organometallics, 1984, 3, 1651; E.A.Maatta and T.J.Marks, J.Am.Chem.Soc., 1981, 103, 3576; P.Leoni and M.Pasquali, J.Organomet.Chem., 1983, 255, C31.
4. F.M.Semmelhack and E.S.C.Wu, J.Am.Chem.Soc., 1976, 98, 3384; F.M.Semmelhack and

S.J.Brickner, ibid., 1981, 103, 3945.

5. D.J.Darensbourg, P.K.Hankel, C.G.Bauch, M.Pala, D.Simmons, and J.N.White, J.Am.Chem.Soc., 1985, 107, 7463; D.J.Darensbourg and G.Grotsch, ibid., 1985, 107, 7473.
6. M.Kihara, Y.Ishida, and S.Kobayashi, J.Chem.Research(S), 1987, 236.
7. Y.Ishida, N.Koga, T.Nanbu, M.Kihara, and S.Kobayashi, Br.J.Pharmacol., 1988, 94, 19.
8. P.A.Dandridge, C,Kaiser, M.Brenner, D.Gaitanopoulos, L.D.Davis, R.L.Webb, J.J.Foley, and H.M.Sarau, J.Med.Chem., 1984, 27, 28; B.E.Maryanoff, D.F.MaComsey, M.J.Costanzo, P.E.Setler, J.F.Gardocki, R.P.Shank, and C.R.Schneider, ibid., 1984, 27, 946.
9. M.F.Semmelhack, P.M.Helquist, L.D.Jones, L.Keller, L.Mendelson, L.S.Lyono, J.G.Smith and R.D.Stauffer, J.Am.Chem.Soc., 1981, 103, 6460 and references cited theirin.
10. A.S.Kende, L.S.Liebeskind, and D.M.Braitsch, Tetrahedron Lett., 1975, 3375.
11. I.Colon and D.R.Kelsey, J.Org.Chem., 1986, 51, 2627.
12. M.Mori and Y.Ban, Tetrahedron Lett., 1976, 1807.
13. J.J.Barlow, B.G.Main, and H.M.Snow, J.Med.Chem., 1981, 24, 315.
14. R.M.Cowper and L.H.Davidson, "Organic Syntheses", Coll. Vol.II, ed. by A.H.Blatt, John Wiley and Sons, Inc., New York, 1943, p. 480.
15. I.G.Hinton and F.G.Mann, J.Chem.Soc., 1959, 599; D.V.Gardner, U.S. Pat. 4,113,869, 1978; B.Leseche, J.Gilbert and C.Viel, J.Heterocyclic Chem., 1981, 18, 143; G.Grethe, J.L.Lee, M.Uskokovic, and A.Brossi, J.Org.Chem., 1968, 33, 491 and 494; S.N.Quessy, L.R.Williams, and V.G.Baddeley, Synth.Commun., 1978, 8, 45.
16. A.Sonn, Chem.Ber., 1919, 52, 923.
17. R.Fuchs and L.A.VanderWerf, J.Am.Chem.Soc., 1956, 78, 5612.
18. R.E.Lutz, R.K.Allison, G.Ashburn, P.S.Bailey, M.T.Clark, J.F.Codington, A.J.Martin, and K.C.Nicodemus, J.Org.Chem., 1947, 12, 617.
19. J.N.Jacob, D.E.Nichols, J.D.Kholi, and D.Glock, J.Med.Chem., 1981, 24, 1013.
20. R.M.Laird and R.E.Parker, J.Am.Chem.Soc., 1961, 83, 4277.
21. R.E.Borch, M.D.Bernstein, and H.D.Durst, J.Am.Chem.Soc., 1971, 93, 2897.

Received, 18th January, 1989