New Entry of Coupling Reaction of Phenacylamine Derivatives with Silylstannane

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The new coupling reaction of phenacylamines with silylstannane and lithium diisopropylamide (LDA) is reported. The treatment of a phenacylamine iodide 1 with (trimethylsilyl)tributylstannane ($Me_3SiSnBu_3$) and cesium fluoride (CsF) gave a dimerization product 2 having no iodine atom. Reaction of 1 with LDA afforded a dimerization product 3 with an iodine atom. The products 2 and 3 were separated to the *meso* and racemic isomers, respectively.

Key words coupling reaction; enolate; silylstannane; phenacylamine

Controlled generation of carbon–carbon bonds forms the core of organic synthesis. Coupling reaction of electron-rich intermediates is an effective methodology for achieving such transformation. Known examples include a variety of enolates[1] and dianions[2] dimerization. We now report the new coupling reactions of *N*-(2-iodobenzyl)-*N*-methylphenacylamine (**1**) with (trimethylsilyl)tributylstannane ($Me_3SiSnBu_3$) and cesium fluoride (CsF), and lithium diisopropylamide (LDA) to the dimeric compounds **2** and **3**, and the separation of **2** and **3** to the *meso* and racemic isomers (Chart 1).

We have reported the synthesis[3] of 2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol (PI-OH) (**4**) having noradrenaline (NA) potentiating activity due to NA reuptake inhibition as a candidate of antidepressants[4] by intramolecular Barbier reaction of the phenacylamine **1** with *n*-BuLi. Optical resolution of racemic **4** to *R*-(+)-**4** and *S*-(−)-**4** was carried out by using HPLC on a chiral stationary phase. The NA potentiating activity was found to reside exclusively in *R*-(+)-**4**.[5]

This high enantioselectivity of **4** for the NA potentiating activity prompted us to perform the asymmetric synthesis of *R*-(+)-**4** by intramolecular cyclization of optically active chromium complex[6] of the phenacylamine **1** with $Me_3SiSnBu_3$ and CsF, which are used as a mild and effective reagent[7] for intramolecular carbon–carbon bond formation of ketones possessing halogen atom. As a preliminary experiment, we tried to react **1** with $Me_3SiSnBu_3$ and CsF to examine to produce **4**. The product was found to be not an expected compound **4** but a coupling product **2** along with deiodinated phenacylamine **5** by the following spectral data. The ^{1}H-NMR spectrum of **2** showed the presence of two *N*-methyl protons (δ 2.18, 2.37), two methylene protons as AB-type doublets (δ 4.00, 3.79 and 3.79, 3.59), and two methine protons (δ 5.22, 5.27). The ^{13}C-NMR spectrum of **2** indicated the presence of two kinds of *N*-methyl (δ 37.0, 38.2), methylene (δ 59.4, 60.4), methine (δ 63.2, 63.8), and ketone (δ 197.8, 198.9) carbons. High resolution (HR)-FAB-MS of **2** showed the molecular formula of $C_{32}H_{32}N_2O_2$. These spectral data suggested that the product should be a dimer **2** without iodine atom formed by coupling at the active methylene carbon atom of **1** and also suggested the product **2** to be a mixture of *meso* and racemic isomers. Thus, **2** was separated by recrystallization from CH_2Cl_2 and *n*-hexane to give two compounds, **2A** (mp 140—141 °C) and **2B** (mp 139—139.5 °C). The structure of each compound **2A** and **2B** was confirmed by their IR, ^{1}H- and ^{13}C-NMR spectra, and HR-FAB-MS as described in Experimental. To elucidate their stereochemistry, the separated compounds **2A** and **2B** were analyzed by using HPLC on a chiral stationary phase. The HPLC diagrams showed a single peak (9.33 min retention time) for **2A** and two peaks (10.26, 10.87 min) for **2B**, respectively. From these results, the compounds **2A** and **2B** were concluded to be *meso* and racemic isomer, respectively. In addition, the integral values of *N*-methyl protons (δ 2.18, 2.37) in the ^{1}H-NMR spectrum of **2** showed a 1 : 2 *meso* : racemic product ratio.

In order to examine the appropriate substrate and reaction conditions, the bromide **6** and chloride **7** as well as **1** were treated with $Me_3SiSnBu_3$ and CsF in a variety of conditions. As shown in Table 1, the treatment of **6** at room temperature for 24 h gave the best result (39.1% yield of **2**, run 6), whereas the reaction of the chloride **7** gave only poor yield of **2** (run 10). This coupling reaction was found to proceed stoichiometrically from the results of runs 6, 8, and 9. The mechanism of this new reaction is not investigated in detail but may proceed by oxidative coupling of the cesium enolate **9** of **5**, which is formed from the phenyl anion **8** as depicted in Chart 2. The phenyl anion **8** should be formed by attacking the iodine atom of **1** with stannyl anion generated from $Me_3SiSnBu_3$ and CsF since the generation of aryl anion from aryl halide with such reagents is well investigated by Mori and co-workers.[7] This mechanism was supported by the fact that the deiodinated compound **5** was detected as a sole product on the reaction of **1** for *ca.* 10 min at room temperature by monitoring the TLC behavior of the reaction mixture. This mixture was successively stirred for 35 h to give the coupling product **2** without **5** (run 2). The fact that the reaction of **5** gave no good result (run 11) showed the difficulty of the direct enolate formation of **5** with $Me_3SiSnBu_3$ and CsF.

LDA is usually used as a base for the preparation of enolates. Compound **1** was treated with LDA (1.2 eq) at room temperature for 24 h to give the coupling product **3** without reducing the iodine atom of **1** even in low yield (29%). The ^{1}H-NMR spectrum of this product **3** is similar to that of **2** obtained from **1** with $Me_3SiSnBu_3$ and CsF except for the aromatic protons, and suggested **3** to be a mixture of meso and racemic isomers. Crystallization of **3** from CH_2Cl_2 and *n*-

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Table 1. Reaction of Phenacylamines **1**, **5**—**7** with $Me_3SiSnBu_3$ and CsF in DMF

Run	Compound	$Me_3SiSnBu_3$ (eq)	CsF (eq)	Temp.	Time	Yield (%)		
						2	**5**	Starting material
1	**1**	2.0	3.0	rt[a)]	70 min	6.9	26.1	—
2	**1**	2.0	3.0	rt	35 h	33.0	—	—
3	**6**	2.0	3.0	60 °C	2 h	14.5	44.4	—
4	**6**	2.0	3.0	0 °C	7 d	9.9	16.5	—
5	**6**	2.0	3.0	rt	7 h	30.4	27.5	—
6	**6**	2.0	3.0	rt	24 h	39.1	—	—
7	**6**	2.0	3.0	60 °C	24 h	21.4	—	—
8	**6**	0.1	0.16	rt	24 h	4.7	—	57.2
9	**6**	1.05	1.07	rt	24 h	35.1	15.1	3.6
10	**7**	2.0	3.0	rt	14 h	4.3	—	—
11	**5**	2.0	3.0	60 °C	7 h	1.9	8.8	—

a) rt, room temperature.

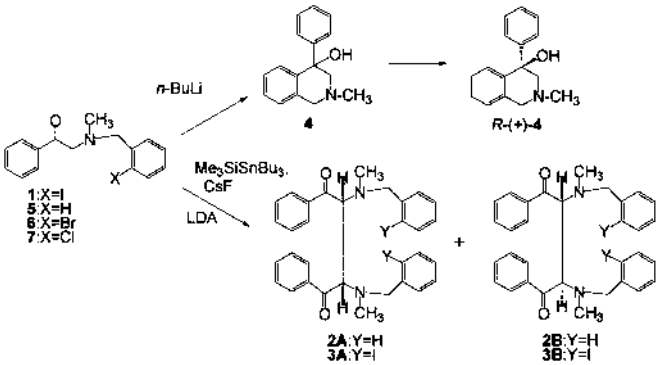

Chart 1

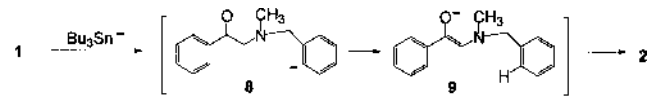

Chart 2

hexane gave two compounds **3A** (mp 137—137.5 °C) and **3B** (mp 130—131 °C). HPLC analysis of **3A** (single peak, 10.44 min retention time) and **3B** (two peaks, 17.92, 19.54 min) on chiral stationary phase showed their stereochemistry to be *meso* and racemic isomers, respectively. HR-FAB-MS of **3A** and **3B** indicated $C_{32}H_{30}I_2N_2O_2$ of their molecular formulae having iodine atoms. It is interesting to note that the 2 : 1 *meso* : racemic product ratio of **3** is different from that (1 : 2 *meso* : racemic ratio) of **2** obtained with $Me_3SiSnBu_3$ and CsF. The coupling reaction of phenacylamines with silylstannane and LDA reported in this study is a first example.

In conclusion, the treatment of phenacylamine **1** with *n*-BuLi gave a intramolecular cyclization product **4**, whereas the reaction of **1** with $Me_3SiSnBu_3$ and CsF, and with LDA afforded intermolecular coupling compounds **2** and **3**, which were separated to *meso* and racemic isomers.

Experimental

Melting points were measured on a Yanako micro melting point apparatus and uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL JNM-FX 200 spectrometer in $CDCl_3$ with tetramethylsilane as a standard. HR-FAB-MS and HR-EI-MS were recorded on a JEOL JMS SX-102A. HPLC was run on a Shimadzu LC-6A liquid chromatograph equipped with a chiral stationary phase column (Daicel Chiralcel OJ). IR spectra were recorded on a Perkin-Elmer 1720 infrared Fourier transform spectrometer.

***N*-Methyl-*N*-(2-bromobenzyl)phenacylamine (6)** To a mixture of 2-bromobenzaldehyde (6.12 g, 33.1 mmol) and 3A molecular sieves (5.60 g) in absolute MeOH (15 ml) was added CH_3NH_2 (12.8 ml of 40% solution in MeOH, 165 mmol) under N_2. The mixture was stirred for 24 h at room temperature. After cooling to 0 °C, $NaBH_4$ (1.375 g, 32.7 mmol) was added and the mixture was stirred for 15 min at the same temperature. Water (10 ml) was added and the mixture was filtered. The filtrate was evaporated *in vacuo.* Water (20 ml) was added to the residue. The mixture was extracted with ethyl acetate (30 ml×3). The extracts were washed with water, dried over $MgSO_4$, and evaporated *in vacuo* to give an oily product. This was subjected to flash chromatography on SiO_2 with *n*-hexane–ethyl acetate (9 : 1) to afford *N*-methyl-2-bromobenzylamine (6.62 g, 98.2%) as a pale yellow oil. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.55 (1H, dd, J=8.1, 1.2 Hz), 7.35 (1H, ddd, J=7.6, 6.8, 2.0 Hz), 7.26 (1H, dd, J=7.4, 1.3 Hz), 7.12 (1H, ddd, J=7.6, 7.6, 2.0 Hz), 3.83 (2H, s), 2.45 (3H, s). HR-EI-MS (*m/z*): Calcd for $C_8H_{10}BrN$ (M^+): 200.9976. Found: 200.9978. IR (NaCl) cm^{-1}: 3301, 3063, 2936, 2793, 1661, 1568, 1471.

A solution of *N*-methyl-2-bromobenzylamine (492 mg, 2.46 mmol) obtained as above, phenacyl bromide (467 mg, 2.35 mmol), and propylene oxide (1.6 ml, 22.8 mmol) in dry dioxane (2 ml) was stirred for 3 h at 50 °C. The mixture was evaporated *in vacuo* to give a crude product. This was subjected to flash chromatography on SiO_2 with *n*-hexane–ethyl acetate (20 : 1) to afford **6** as a pale yellow oil (716 mg, 95.9%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.29 (2H, dd, J=8.5, 1.7 Hz), 7.38 and 7.59 (5H, m), 7.23 (1H, ddd, J=7.3, 7.3, 1.5 Hz), 7.11 (1H, ddd, J=7.7, 7.6, 1.7 Hz), 3.90 (2H, s), 3.81 (2H, s), 2.42 (3H, s). HR-EI-MS (*m/z*): Calcd for $C_{16}H_{16}BrNO$ (M^+): 318.0318. Found: 318.0334. IR (NaCl) cm^{-1}: 3060, 2972, 1684, 1598, 1449.

Compounds **1** and **7** were prepared by the method reported in our previous papers.[8)]

General Procedure for the Reaction of Compound 1 with $Me_3SiSnBu_3$ and CsF This is exampled by the reaction of run 2 in Table 1. A solution of $Me_3SiSnBu_3$ (2.364 g, 6.31 mmol) in dry *N*,*N*-dimethylformamide (DMF, 5 ml) was added to a solution of **1** (1.151 g, 3.15 mmol) and CsF (90%) (1.570 g, 9.31 mmol) in dry DMF (5 ml). The mixture was stirred for 35 h at room temperature. Water (30 ml) was added and the mixture was basified with 10% KOH, and extracted with ether (30 ml×3). The extracts were washed with water, dried over $MgSO_4$, and evaporated *in vacuo* to give a crude product. This was subjected to column chromatography on SiO_2 with *n*-hexane–ethyl acetate (10 : 1) to afford **2** as a yellow solid (248 mg, 33.0%). This was recrystallized from CH_2Cl_2–*n*-hexane to give **2A** of yellow plates as a first crop (31.3 mg, mp 140—141 °C) and **2B** of yellow plates as a second crop (88.4 mg, mp 139—139.5 °C). Compounds **2A** and **2B** were submitted to HPLC with a *n*-hexane–2-propanol (100 : 1) mixture at a flow rate of 1 ml/min to show a single peak at 9.33 min retention time and two peaks at 10.26 and 10.87 min, respectively.

2A: ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 8.05 (4H, d, J=7.7 Hz), 7.47—7.64 (6H, m), 7.09—7.12 (6H, m), 6.96—6.98 (4H, m), 5.25 (2H, s), 3.79 and 3.59 (each 2H, d, J=13.9 Hz), 2.18 (6H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 197.79, 139.19, 138.77, 133.14, 128.84, 128.46, 128.33, 128.02, 126.79, 63.24, 59.34, 38.19. HR-FAB-MS (*m/z*): Calcd for $C_{32}H_{33}N_2O_2$ $(M+H)^+$: 477.2542. Found: 477.2527. IR ($CHCl_3$) cm^{-1}: 3020, 1668, 1449, 1287,

1212.

2B: ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 8.05 (4H, d, J=7.3 Hz), 7.43—7.61 (6H, m), 7.24 (10H, s), 5.25 (2H, s), 4.00 and 3.78 (each 2H, d, J=13.7 Hz), 2.37 (6H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 198.86, 139.38, 138.28, 132.90, 128.95, 128.67, 128.53, 128.24, 127.06, 63.84, 60.41, 36.98. HR-FAB-MS (*m/z*): Calcd for $C_{32}H_{33}N_2O_2$ $(M+H)^+$: 477.2542. Found: 477.2533. IR ($CHCl_3$) cm^{-1}: 3020, 1671, 1449, 1219.

The reaction of **5**—**7** with $Me_3SiSnBu_3$ and CsF was carried out in the same way as for **1** described above (Table 1).

Reaction of Compound 1 with LDA *n*-BuLi (5.2 ml of 1.54 M solution in *n*-hexane, 7.98 mmol) was added to a solution of diisopropylamine (1.18 ml, 9.04 mmol) in dry tetrahydrofuran (THF, 5 ml) at −78 °C under argon. The mixture was stirred for 1 h under ice-cooling. A solution of **1** (1.947 g, 5.32 mmol) in dry THF (8 ml) was added and the mixture was stirred for 24 h at room temperature. Water (30 ml) was added under ice-cooling and the mixture was extracted with ethyl acetate (30 ml×3). The extracts were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to give an oily product. This was subjected to column chromatography on SiO_2 with *n*-hexane–ethyl acetate (15 : 1) to afford **3** as a yellow oil (554 mg, 28.5%) and the starting material **1** (114 mg, 5.9%). Crystallization of **3** (205 mg) from CH_2Cl_2–*n*-hexane gave **3A** of yellow plates as a first crop (41 mg, mp 137—137.5 °C) and **3B** of yellow powder as a second crop (21 mg, mp 130—131 °C). Compounds **3A** and **3B** were submitted to HPLC with a *n*-hexane–2-propanol (4 : 1) mixture at a flow rate of 0.5 ml/min to show a single peak at 10.44 min retention time and two peaks at 17.92 and 19.54 min, respectively.

3A: ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.98 (4H, d, J=7.0 Hz), 7.66 (2H, d, J=7.8 Hz), 7.43—7.60 (6H, m), 7.01—7.10 (4H, m), 6.77—6.85 (2H, m), 5.19 (2H, s), 3.85 and 3.63 (each 2H, d, J=15.1 Hz), 2.28 (6H, s). HR-FAB-MS (*m/z*): Calcd for $C_{32}H_{31}I_2N_2O_2$ $(M+H)^+$: 729.0475. Found: 729.0476. IR (KBr) cm^{-1}: 2944, 1669, 1435, 1194.

3B: ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.99 (4H, d, J=6.8 Hz), 7.77 (2H, J=7.6 Hz), 7.23—7.57 (10H, m), 6.91—6.94 (2H, m), 5.21 (2H, s), 4.06 and 3.89 (each 2H, d, J=14.9 Hz), 2.42 (6H, s). HR-FAB-MS (*m/z*): Calcd for $C_{32}H_{31}I_2N_2O_2$ $(M+H)^+$: 729.0475. Found: 729.0491. IR (KBr) cm^{-1}: 2864, 1671, 1436, 1201.

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