STUDIES ON THE SELECTIVE INTRAMOLECULAR BIARYL COUPLING REACTION OF 2-TRIFLYLOXY-6-HALOBENZANILIDES USING A PALLADIUM REAGENT†

Takashi Harayama,* Hiroko Toko, Kyoko Kubota, Hiromi Nishioka, Hitoshi Abe, and Yasuo Takeuchi
Faculty of Pharmaceutical Sciences, Okayama University, Tsushima-naka 1-1-1, Okayama 700-8530, Japan
E-mail: harayama@pharm.okayama-u.ac.jp

Abstract-The aryl-aryl coupling reaction of 2-triflyloxy-6-halobenzanilides using a palladium reagent under several reaction conditions was examined. The 6-iodo compound gave triflyloxyphenanthridone selectively in excellent yield under the conditions for the ordinary Heck reaction.

Palladium-assisted aryl-aryl coupling reactions, such as the Heck and Suzuki-Miyaura reactions, have been used to synthesize condensed aromatic compounds.1 Recently, we found that intramolecular coupling reaction between aromatic halides and arenes using palladium reagents was a very versatile way to synthesize condensed aromatic compounds.2,3 Moreover, we reported that a novel palladium reagent prepared from Pd(OAc)$_2$, 1,3-diphenylphosphinepropane (DPPP), and Bu$_3$P was suitable for coupling reactions not only between aryl triflates and arenes, but also between aryl halides and arenes.4 In order to examine the ability of triflyoxy and halogen groups to be the leaving group in biaryl coupling reactions using this palladium reagent, we investigated the coupling reactions of benzanilides (1) possessing both groups on the benzoyl moiety. If each leaving group on 1 can be arbitrarily differentiated under certain reaction conditions, triflyoxyphenanthridone (A=4) or halophenanthridone (B) can be synthesized selectively. Here, we describe the results of biaryl coupling reactions of 1 in the presence of the palladium reagent under different conditions.

The starting materials, 2-trifluoromethanesulfonyloxy-6-iodo-$N$-methylbenzanilide (1a) and 2-bromo-6-trifluoromethanesulfonyloxy-$N$-methylbenzanilide (1b), were prepared as shown in Scheme 1. The reaction of 2-hydroxy-6-iodobenzaldehyde (2a)$^5$ with Tf$_2$O, followed by oxidation gave iodobenzoic acid (3a) in 70% yield. Subsequent treatment of 3a with oxalyl chloride and $N$-methylaniline afforded 1a in 98% yield. Benzanilide (1b) was synthesized from 2-bromo-6-hydroxybenzaldehyde (2b)$^6$ via the same reaction sequence in 72% total yield. The biaryl coupling reaction of 1 was examined using the palladium

† Dedicated to Professor A. I. Meyers for the celebration of his 70th birthday.
Scheme 1

Table 1. Results of coupling reactions of 2-trifluoromethanesulfonyloxy-6-halo-N-methylbenzanilides (1) to phenanthridones in DMF.

<table>
<thead>
<tr>
<th>run</th>
<th>Pd(OAc)$_2$ (eq.)</th>
<th>phosphine (P/Pd) $^a$</th>
<th>base $^b$</th>
<th>temp.</th>
<th>time</th>
<th>yield (%) $^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>1a</td>
<td>0.2</td>
<td>PPh$_3$ (2)</td>
<td>Ag$_2$CO$_3$</td>
<td>reflux</td>
<td>30 min</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>0.2</td>
<td>PPh$_3$ (2)</td>
<td>Ag$_2$CO$_3$</td>
<td>rt</td>
<td>26 h</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>n-Bu$_3$P (1), DPPP (1)</td>
<td>i-Pr$_2$NEt</td>
<td>reflux</td>
<td>30 min</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>n-Bu$_3$P (1), DPPP (1)</td>
<td>i-Pr$_2$NEt</td>
<td>rt</td>
<td>26 h</td>
<td>57</td>
</tr>
<tr>
<td>5d</td>
<td>0.1</td>
<td>-</td>
<td>AcOK</td>
<td>100°C</td>
<td>30 min</td>
<td>-</td>
</tr>
<tr>
<td>6d</td>
<td>0.1</td>
<td>-</td>
<td>NaOCOCMe$_3$</td>
<td>100°C</td>
<td>30 min</td>
<td>-</td>
</tr>
<tr>
<td>1b</td>
<td>0.2</td>
<td>PPh$_3$ (2)</td>
<td>Ag$_2$CO$_3$</td>
<td>reflux</td>
<td>2 h</td>
<td>33</td>
</tr>
<tr>
<td>8</td>
<td>1.0</td>
<td>PPh$_3$ (2)</td>
<td>Ag$_2$CO$_3$</td>
<td>reflux</td>
<td>45 min</td>
<td>53</td>
</tr>
<tr>
<td>9f</td>
<td>0.2</td>
<td>P(o-Tol)$_3$(2)</td>
<td>Ag$_2$CO$_3$</td>
<td>reflux</td>
<td>1 h</td>
<td>30</td>
</tr>
<tr>
<td>10</td>
<td>1.0</td>
<td>P(o-Tol)$_3$(2)</td>
<td>Ag$_2$CO$_3$</td>
<td>reflux</td>
<td>2 h</td>
<td>72</td>
</tr>
<tr>
<td>11</td>
<td>1.0</td>
<td>n-Bu$_3$P (1), DPPP (1)</td>
<td>i-Pr$_2$NEt</td>
<td>reflux</td>
<td>45 min</td>
<td>-</td>
</tr>
<tr>
<td>12g</td>
<td>1.0</td>
<td>n-Bu$_3$P (1), DPPP (1)</td>
<td>i-Pr$_2$NEt</td>
<td>rt</td>
<td>48 h</td>
<td>-</td>
</tr>
<tr>
<td>13d</td>
<td>0.1</td>
<td>-</td>
<td>AcOK</td>
<td>100°C</td>
<td>30 min</td>
<td>-</td>
</tr>
<tr>
<td>14d</td>
<td>0.1</td>
<td>-</td>
<td>NaOCOCMe$_3$</td>
<td>100°C</td>
<td>30 min</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$ Molar ratio between phosphine and Pd.  
$^b$ 2 Eq. of base was added unless otherwise noted.  
$^c$ Isolated yield.  
$d$) 2 Eq. of n-Bu$_4$NCl and 5.5 eq. of base were added.  
$e$) 1b was recovered in yield of 53%.  
$f$) 1b was recovered in yield of 37%.  
$g$) 1b was recovered in yield of 80%.  
$h$) 9 was obtained in yield of 42%.
Reagent under several reaction conditions. The results are summarized in Table 1. Reaction of 1a using the palladium reagent under the ordinary Heck reaction conditions mainly gave the coupling product (4) possessing the OTf group, indicating that the iodo group is more reactive than the triflyloxy group (see runs 1, 2 and 4). Using the palladium reagent prepared from Pd(OAc)₂, DPPP, and Bu₃P, a deoxygenated coupling product (6) was obtained in 76% yield (see run 3). The reaction of 1a under phosphine-free reaction conditions (see runs 5 and 6) gave products (7 or 8) with the OTf group replaced by the RCOO group together with 5. The reaction of 4 under the same reaction conditions gave the hydrolyzed product (5) in 70% yield and no substituted product (7). These facts indicate that the nucleophilic substitution reaction of the triflyloxy group occurred before the biaryl coupling reaction. The reaction of 1b with an equimolar amount of Pd(OAc)₂ and monodentate phosphine ligand gave mainly the coupling product (4) (see runs 8 and 10).

In conclusion, the biaryl coupling reaction of 2-triflyloxy-6-halobenzenilides (1) using palladium reagent mainly produced 4 possessing the OTf group; especially, 1a gave 4 exclusively. However, each leaving group on 1 cannot be differentiated arbitrarily.

**EXPERIMENTAL**

Melting points were measured on a micro melting point hot-stage apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded on a JASCO A-102 or JASCO FT/IR 350 spectro-photometer and ¹H-NMR spectra in deuteriochloroform on a Hitachi R-1500 (60 MHz) or a Varian VXR-500 (500 MHz) spectrometer unless otherwise stated. NMR data are reported in ppm downfield from tetramethylsilane as an internal standard (δ 0.0) and coupling constants are given in Hertz. MS spectra were obtained on a VG-70SE spectrometer. Column chromatography was carried out on silica gel (Wako gel C-200 or Merck, silica gel 60, No. 9385). All experiments were carried out in an argon atmosphere and the extract was washed with brine, dried over anhydrous MgSO₄, then filtered, and the filtrate was evaporated to dryness under reduced pressure, unless otherwise noted. Pd(OAc)₂ was treated with boiling benzene and the mixture was filtered while hot. The hot filtrate was then concentrated to dryness to give purified Pd(OAc)₂.

**2-Trifluoromethanesulfonxyloxy-6-iodobenzoic acid (3a)**

To a mixture of 2-hydroxy-6-iodobenzaldehyde (2a) (1.6 g, 6.45 mmol) and dry NEt₃ (1.8 mL, 12.9 mmol) in dry CH₂Cl₂ (30 mL) at 0°C was added triflic anhydride (1.7 mL, 10.1 mmol) in CH₂Cl₂ (10 mL). The whole was stirred for 5 min at the same temperature. The mixture was diluted with CH₂Cl₂ and washed with 1 N HCl, aqueous sat. NaHCO₃ and brine. The residue dissolved in CHCl₃-hexane (1 : 1) was subjected to column chromatography on silica gel. Elution with CHCl₃-hexane (1 : 1) gave 2-trifluoromethanesulfonyloxy-6-iodobenzoic acid (1.7 g, 71%) as colorless plates (from hexane) mp 59-60.5°C. IR (KBr) cm⁻¹: 1710, 1420, 1140. ¹H-NMR (60 MHz) δ : 7.29-8.14 (3H, m. aromatic protons), 10.07 (1H, s, CHO).


A solution of sodium chlorite (80%; 715 g, 7.91 mmol) in water (5 mL) was added to a stirred mixture of triflate-benzaldehyde (1.0 g, 2.63 mmol) prepared above, sodium phosphate monobasic dihydrate (100 mg, 0.64 mmol), and 31% hydrogen peroxide (0.87 mL, 7.92 mmol) in MeCN (20 mL) and water (3 mL) and
then the whole was stirred at 10°C for 15 h. After the decomposition of excess hydrogen peroxide with 10% aqueous sodium sulfite solution, the mixture was made to acidic with 1 N hydrochloric acid and extracted with ether. The residue was recrystallized from hexane to give 3a (1.03 g, 99%) as colorless needles, mp 105.5-107°C. IR (KBr) cm⁻¹: 2900, 1720, 1410, 1140. ¹H-NMR (60 MHz) δ : 7.10-7.54 (2H, m, aromatic protons), 7.95 (1H, dd, J=7, 2 Hz), 8.33 (1H, s, COOH). Anal. Calcd for C₆H₄O₂F₃I₂S : C, 24.26; H, 1.02. Found : C, 24.20; H, 1.20.

2-Trifluoromethanesulfonyloxy-6-iodo-N-methylbenzanilide (1a)
A few drops of dry DMF and oxalyl chloride (0.3 mL, 3.1 mmol) were added to a solution of 3a (1.0 g, 2.52 mmol) in dry CH₂Cl₂ (20 mL) under ice-cooling and the mixture was refluxed for 2 h. Then the reaction mixture was concentrated to dryness under reduced pressure. To this residue was added a solution of N-methylaniline (0.7 mL, 6.46 mmol) in dry CH₂Cl₂ (10 mL) and dry NEt₃ (0.45 mL, 3.23 mmol) and the whole was stirred for 1 h at rt. The reaction mixture was concentrated to dryness and diluted with CH₂Cl₂, then washed with 10% HCl, aqueous sat. NaHCO₃ solution and brine. The residue dissolved in AcOEt-benzene was subjected to column chromatography on silica gel. Elution with AcOEt-hexane (1 : 2) gave 1a (1.20 g, 98%) as colorless prisms (from ether-hexane) mp 60.5-62.5°C. IR (KBr) cm⁻¹ : 1650, 1420, 1140. ¹H-NMR (60 MHz, rotamer) δ : 3.25 (2/7x3H, s, NCH₃), 3.50 (5/7x3H, s, NCH₃), 6.79-8.00 (8H, m, aromatic protons). Anal. Calcd for C₁₅H₁₁NO₄F₃I₂S : C, 37.10; H, 2.29; N, 2.89. Found : C, 36.94; H, 2.46; N, 2.79.

2-Bromo-6-trifluoromethanesulfonyloxybenzoic acid (3b)
To a mixture of 2-bromo-6-hydroxybenzaldehyde (2b)⁶ (2.0 g, 9.95 mmol) and dry NEt₃ (2.8 mL, 20.0 mmol) in dry CH₂Cl₂ (20 mL) at 0°C was added triflic anhydride (4.2 g, 14.9 mmol) in CH₂Cl₂ (10 mL). The whole was stirred for 30 min at the same temperature. The mixture was diluted with CH₂Cl₂ and washed with 1 N HCl, aqueous sat. NaHCO₃ and brine. The organic layer was dried over anhydrous MgSO₄. The residue dissolved in CHCl₃-hexane (1 : 2) was subjected to column chromatography on silica gel. Elution with CHCl₃-hexane (1 : 2) gave 2-bromo-6-trifluoromethanesulfonyloxybenzaldehyde (2.83 g, 86%) as colorless plates (from hexane) mp 54-55°C. IR (KBr) cm⁻¹ : 1710, 1425, 1135. ¹H-NMR (60 MHz) δ : 7.27-7.85 (3H, m, aromatic protons), 10.36 (1H, s, CHO). Anal. Calcd for C₈H₄O₄BrF₃O : C, 28.85; H, 1.16. Found : C, 28.97; H, 1.45.

A solution of sodium chlorite (80%; 2.03 g, 18.0 mmol) in water (20 mL) was added to a stirred mixture of triflate-benzaldehyde (2.0 g, 6.0 mmol) prepared above, sodium phosphate monobasic dihydrate (234 mg, 1.5 mmol), and 31% hydrogen peroxide (1.8 mL, 18.0 mmol) in MeCN (50 mL) and water (5 mL) and then the whole was stirred at 10°C for 15 h. After the decomposition of excess hydrogen peroxide with 10% aqueous sodium sulfite solution, the mixture was made to acidic with 1 N hydrochloric acid and extracted with ether. The residue was recrystallized from hexane to give 3b (1.93 g, 92%) as colorless needles, mp 94-95.5°C. IR (KBr) cm⁻¹ : 2900, 1715, 1135. ¹H-NMR (60 MHz) δ : 7.37-7.78 (3H, m, aromatic protons), 8.20 (1H, s, COOH). Anal. Calcd for C₈H₄BrF₃O₅S : C, 27.53; H, 1.16. Found : C, 27.80; H, 1.45.
2-Bromo-6-trifluoromethanesulfonyloxy-N-methylbenzanilide (1b)
A few drops of dry DMF and oxalyl chloride (1.5 mL, 17.2 mmol) were added to a solution of 3b (3.0 g, 8.59 mmol) in dry CH₂Cl₂ (300 mL) under ice-cooling and the mixture was stirred for 1 h at 10°C. Then the reaction mixture was concentrated to dryness under reduced pressure. To this residue was added a solution of N-methylaniline (1.1 mL, 10.3 mmol) in dry CH₂Cl₂ (30 mL) and dry NEt₃ (1.6 mL, 11.2 mmol) and the whole was stirred for 5 h at rt. The reaction mixture was concentrated to dryness and diluted with CH₂Cl₂, then washed with 10% HCl, aqueous sat. NaHCO₃ solution and brine. The residue dissolved in AcOEt-hexane (1 : 8) was subjected to column chromatography on silica gel. Elution with AcOEt-hexane (1 : 8) gave 1b (3.45 g, 91%) as colorless plates (from pet. ether) mp 73.5-75°C. IR (KBr) cm⁻¹ : 1665, 1425, 1140. ¹H-NMR (60 MHz, rotamer) δ : 3.25 (1/9H, s, NCH₃), 3.50 (8/9H, s, NCH₃), 7.06-7.52 (8H, m, aromatic protons).

General Procedure for the Coupling Reaction of Benzanilides (1) (runs 1~4 and 7~10 in Table 1)
The reaction of 1 (0.3 mmol) with Pd(OAc)₂, a phosphine ligand, and a base in dry DMF (8 mL) was carried out using Pd(OAc)₂ and the phosphine ligand in the ratios indicated in Table 1, and 2 mol equivalents of base for the times and temperatures indicated in Table 1. The reaction mixture was diluted with ether and the precipitates were removed by filtration. The filtrate was washed with brine. The residue dissolved in hexane-AcOEt (4 : 1) was subjected to column chromatography on silica gel. Elution with hexane-AcOEt (4 : 1) gave 7-hydroxy-5-methylphenanthridin-6(5H)-one (5) and successive elution with the same solvent gave 5-methylphenanthridin-6(5H)-one (6) and then 7-trifluoromethanesulfonyloxy-5-methylphenanthridin-6(5H)-one (4).

7-Hydroxy-5-methylphenanthridin-6(5H)-one (5) : mp 125-127°C (from ether) as colorless needles. IR (CHCl₃) cm⁻¹ : 3020, 1635. ¹H-NMR (500 MHz, CDCl₃) δ : 3.75 (3H, s, NCH₃), 7.01 (1H, dd, J=8.1, 0.9 Hz, C₈-H), 7.34 (1H, t, J=8.1 Hz, C₂-H), 7.40 (1H, br. d, J=8.5 Hz, C₄-H), 7.54 (1H, ddd, J=8.5, 6.7, 1.3 Hz, C₅-H), 7.60 (1H, td, J=8.1, 1.3 Hz, C₃-H), 7.78 (1H, t, J=8.2 Hz, C₉-H), 8.24 (1H, dd, J=8.2, 0.8 Hz, C₁₀-H), 8.34 (1H, br. d, J=8.1 Hz, C₁-H). FAB-MS (positive ion mode) m/z: 226 [M+1]+. Anal. Calcd for C₁₄H₁₁NO₂: C, 74.06; H, 4.97; N, 6.17. Found : C, 73.86; H, 5.14; N, 5.97.

5-Methylphenanthridin-6(5H)-one (6) : mp 109-110.5°C (from hexane) as colorless needles. The synthetic sample was identified with the authentic sample.

General Procedure for the Coupling Reaction of Benzanilides (1) in the Presence of...
Palladium under Phosphine-free Conditions (runs 5, 6, 11, and 12 in Table 1)

The reaction of 1 (0.3 mmol) with 0.1 equivalent of Pd(OAc)$_2$, 2 equivalents of $n$-Bu$_4$NCl, and 5.5 equivalents of base in dry DMF (8 mL) was carried out for the times indicated in Table 1 at 100°C. The reaction mixture was diluted with ether and the precipitates were removed by filtration. The filtrate was washed with brine. The residue dissolved in CHCl$_3$ was subjected to column chromatography on a silica gel. Elution with hexane-AcOEt (4 : 1) gave 7-hydroxy-5-methylphenanthridin-6(5H)-one (5) and successive elution with the same solvent gave 7-acetoxy-5-methylphenanthridin-6(5H)-one (7) or 5-methyl-7-pivaloyloxyphenanthridin-6(5H)-one (8). In the cases of 1b using sodium pivalate as base, elution with hexane-AcOEt (4 : 1) gave 5 and successive elution gave 2-bromo-$N$-methyl-6-pivaloyloxybenzanilide (9).

7-Acetoxy-5-methylphenanthridin-6(5H)-one (7) : mp 140.5-142°C, colorless needles (from ether). IR (CHCl$_3$) cm$^{-1}$ : 1760, 1635. $^1$H-NMR (500 MHz) $d$ : 2.49 (3H, s, OCOCH$_3$), 3.72 (3H, s, NCH$_3$), 7.20 (1H, dd, $J$=8.0, 1.2 Hz, C$_8$-H), 7.30 (1H, ddd, $J$=8.3, 7.0, 0.8 Hz, C$_2$-H), 7.36 (1H, br d, $J$=8.5 Hz, C$_4$-H), 7.54 (1H, dd, $J$=8.5, 7.0, 1.5 Hz, C$_5$-H), 7.73 (1H, t, $J$=8.0 Hz, C$_6$-H), 8.20 (1H, dd, $J$=8.0, 1.2 Hz, C$_{10}$-H), 8.24 (1H, dd, $J$=8.3, 1.5 Hz, C$_1$-H). Anal. Calcd for C$_{16}$H$_{13}$NO$_3$: C, 71.90; H, 4.90; N, 5.24. Found : C, 71.77; H, 5.19; N, 5.19.

5-Methyl-7-pivaloyloxyphenanthridin-6(5H)-one (8) : 129.5-131°C, colorless prisms (from ether). IR (KBr) cm$^{-1}$ : 1740, 1650. $^1$H-NMR (500 MHz) $d$ : 1.49 (9H, s, C(CH$_3$)$_3$), 3.70 (3H, s, NCH$_3$), 7.13 (1H, dd, $J$=7.9, 0.8 Hz, C$_8$-H), 7.28 (1H, dd, $J$=8.5, 6.7, 1.3 Hz, C$_2$-H), 7.34 (1H, br d, $J$=8.5 Hz, C$_4$-H), 7.53 (1H, dd, $J$=8.5, 6.7, 1.3 Hz, C$_3$-H), 7.71 (1H, t, $J$=7.9 Hz, C$_6$-H), 8.19 (1H, br d, $J$=7.9 Hz, C$_{10}$-H), 8.24 (1H, dd, $J$=8.5, 1.3 Hz, C$_1$-H). Anal. Calcd for C$_{19}$H$_{19}$NO$_3$: C, 73.77; H, 6.19; N, 4.53. Found : C, 73.73; H, 6.30; N, 4.50.

2-Bromo-6-pivaloyloxy-$N$-methylbenzanilide (9) : mp 124-125.5°C, colorless needles (from ether-hexane). IR (CHCl$_3$) cm$^{-1}$ : 1750, 1640. $^1$H-NMR (500 MHz, rotamer) $d$ : 1.35 and 1.39 (total 9H, s, C(CH$_3$)$_3$), 3.21 and 3.47 (total 3H, s, NCH$_3$), 6.99-7.51 (total 8H, m, aromatic protons). Anal. Calcd for C$_{19}$H$_{20}$NO$_3$Br : C, 58.47; H, 5.17; N, 3.59. Found : C, 58.61; H, 5.35; N, 3.48.

Treatment of Triflyloxyphenanthridone (4) with Palladium under Phosphine-free Conditions

A mixture of 4 (100 mg, 1.4 mmol), Pd(OAc)$_2$ (10 mg, 0.03 mmol), $n$-Bu$_4$NCl (170 mg, 0.6 mmol), and AcOK (160 mg, 1.65 mmol) in dry DMF (10 mL) was heated for 2 h at 100°C. The reaction mixture was diluted with ether and the precipitates were removed by filtration. The filtrate was washed with brine. The residue dissolved in CHCl$_3$ was subjected to column chromatography on a silica gel. Elution with hexane-AcOEt (4:1) gave 5 (44 mg, 70%) and successive elution with the same solvent gave the starting material (4) (28 mg, 28%). These samples were identified using the respective authentic samples.

ACKNOWLEDGEMENT

This research was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education,
REFERENCES AND NOTE


8  Treatment of 1a with AcOK in the presence of n-Bu₄NCl in dry DMF for 30 min at 100°C afforded 2-acetoxy-6-iodo-N-methylbenzanilide and 2-hydroxy-6-iodo-N-methylbenzanilide in yields of 44% and 44%, respectively.