Site-Selective Cross-Coupling of Dichlorinated Benzo-Fused Nitrogen-Heterocycles with Grignard Reagents

Hideyuki Konishi, Tatsuya Itoh, and Kei Manabe*

School of Pharmaceutical Sciences, University of Shizuoka; 52–1 Yada, Suruga-ku, Shizuoka 422–8526, Japan.
Received May 11, 2010; accepted June 8, 2010; published online June 10, 2010

Site-selective cross-coupling of dihaloarenes constitutes a useful method for synthesis of multi-substituted arenes. In this paper, we report the site-selective cross-coupling of dichlorinated benzo-fused nitrogen-heterocycles having two chloro groups on the benzene ring. These dichlorinated heterocycles reacted with Grignard reagents in the presence of PdCl₂(PCy₃)₂ at the positions ortho to the nitrogen-based substituents with high selectivities. A mechanism in which interaction between Lewis acidic Mg and Cl of the ortho position facilitates C–Cl bond cleavage is proposed.

Key words catalysis; cross-coupling; palladium; site-selective; Grignard reagent; heterocycle

Site-selective cross-coupling of dihaloarenes constitutes a useful method for synthesis of multi-substituted arenes.¹⁻³) For dihalobenzenes having two substituents of the same halogen atom, however, site-selective cross-coupling involving selective conversion of one of the halogen atoms to another group still remains unestablished. Therefore, developing a new method of such cross-coupling is an important issue for synthesis of multi-substituted benzenes.

Recently, we developed a new site-selective cross-coupling in which chloro groups at a position ortho to a directing group such as OH, NH₂, CH₂OH, NHAc, or NHBoc reacted with Grignard reagents in the presence of a catalyst based on Pd and PCy₃ with high site-selectivities (Chart 1).⁴⁻⁶) This reaction system has several unique features: (1) although electron-donating groups typically retard the oxidative addition step in cross-coupling reactions, the presence of electron-donating groups such as OH and NH₂ is essential in the reactions for acceleration at the ortho-position; (2) substrates with protic substituents react faster than those with a non-protic substituent such as a methoxy group; (3) this type of high ortho-selectivity was not observed in Suzuki–Miyaura coupling with boronic acids.

To expand the utility of this catalytic system, we planned to apply it to benzo-fused heterocycles such as indole, indoline, and tetrahydroquinoline, which are frameworks ubiquitous in natural products and pharmaceuticals.⁷⁻¹¹) There are some examples of site-selective cross-coupling of dibrominated or dichlorinated benzo-fused heterocycles.¹²) For substrates having two halo groups on the benzene ring, however, no examples of highly selective cross-coupling have been reported. Therefore, development of site-selective cross-coupling of these benzo-fused heterocycles should be valuable. In addition, these benzo-fused heterocycles have a feature distinct from N-unsubstituted anilines that we previously used as substrates: rotation of the Cipso–N bonds is restricted for the benzo-fused heterocycles, while that of the anilines is not. We were interested in effects of the restricted conformation on site-selectivity. Herein we report the site-selective cross-coupling of dichlorinated benzo-fused nitrogen-heterocycles having two chloro groups on the benzene ring. The substrates reacted with Grignard reagents in the presence of PdCl₂(PCy₃)₂ at the positions ortho to the nitrogen-based substituents with high selectivities.

Substrates 1a—c, which were easily prepared according to literature procedures,¹²⁻¹⁵) were subjected to cross-coupling with 4-methoxyphenylmagnesium bromide in the presence of PdCl₂(PCy₃)₂ at 50—70 °C. We were pleased to find that highly site-selective reactions occurred to give products 2a—c (Table 1). Although the yields of 2a and 2b were modest

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Temperature (°C)</th>
<th>Yield (%) of 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>70</td>
<td>60 (2a)</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>50</td>
<td>41 (2b)</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>70</td>
<td>87 (2c)</td>
</tr>
</tbody>
</table>

Table 1. Site-Selective Cross-Coupling of Dichlorinated Benzo-Fused Nitrogen-Heterocycles

© 2010 Pharmaceutical Society of Japan
(entries 1, 2), neither isomers 3 nor doubly cross-coupled products 4 were obtained in any cases. In all cases, the homo-coupling product of the Grignard reagent was observed as the major by-product.

We next carried out reactions of 1c with various Grignard reagents. As shown in Table 2, the reactions proceeded to give the products with high site-selectivities. Not only aryl Grignard reagents but also heteroaryl and alkenyl Grignard reagents worked well. In all cases, the para Cl group of 1c did not react. When n-octylmagnesium bromide was used, the desired cross-coupled product was obtained only in a very small amount, and instead, a reduced compound in which the ortho-chloro group was converted to hydrogen was obtained.

The preference of the reaction at the ortho-position was also observed in a competitive reaction between two substrates. Thus, 7-chloroindole (6) preferentially reacted over 5-chloroindole (7) as shown in Eq. 1.

For substrates 1a—c, the proton on the nitrogen atom must be deprotonated with a Grignard reagent under the reaction conditions to generate the corresponding Mg amides. We assume that formation of the Mg amides is important for acceleration of the reactions at the position ortho to the Mg amido groups. To support this assumption, N-methylated compound 10, which cannot generate a Mg amide, was used as a substrate. As shown in Eq. 2, no cross-coupled products were obtained (homo-coupling of the Grignard reagent was observed). This result suggests that the formation of the Mg amides is the key for the acceleration at the ortho-positions in the cross-coupling of these benzo-fused nitrogen-heterocycles.

Although the origin of the site-selectivity remains unclear, we assume that the mechanism shown in Fig. 1 operates to facilitate C–Cl bond cleavage at the ortho-position. That is, interaction of the Lewis acidic Mg of the Mg amide with the Cl atom activates the ortho-C–Cl bond to accelerate the oxidative addition step,16–18) which is the selectivity-determining step and presumably the rate-determining step.

To support this proposed mechanism, we conducted a preliminary study using density functional theory (DFT) calculations (B3LYP/6-31G*) on Mg amides 11a—c derived from 1a—c (Fig. 2). One molecule of dimethyl ether, which is a simplified surrogate of THF, was included as a solvent coordinated to Mg. In the structures of 11a—c, the ortho-C–Cl bonds were found to be significantly longer than the para-C–Cl bonds; the differences between the ortho- and para-C–Cl bond lengths are 0.028 Å, 0.028 Å, and 0.038 Å for 11a—c, respectively. In the structures of the parent compounds (1a—c), the differences between the ortho- and para-C–Cl bond lengths are less than 0.008 Å. The elongation of the ortho-C–Cl bonds of Mg amides 11a—c is likely to result from an interaction between Cl and the Lewis acidic Mg. This interaction should activate the ortho-C–Cl bond for the oxidative addition step.

Although rotation of the C ipso–N bond is restricted for the benzo-fused heterocycles compared with anilines, high site-selectivity was still observed as in the cases of the aniline substrates. This suggests that the conformations shown in the calculated structures are plausible as the transition states.

Table 2. Site-Selective Cross-Coupling of 1c with Various Grignard Reagents

<table>
<thead>
<tr>
<th>Entry</th>
<th>RMgBr</th>
<th>Product 5</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BrMg</td>
<td>5a</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>BrMg</td>
<td>5b</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>BrMg</td>
<td>5c</td>
<td>77</td>
</tr>
<tr>
<td>4</td>
<td>BrMg</td>
<td>5d</td>
<td>53</td>
</tr>
</tbody>
</table>
The results shown in this paper strongly support the mechanism that the Mg–Cl interaction is the key for the acceleration of the cross-coupling at the position ortho to the nitrogen-based substituents, while further studies including those on transition states of the oxidative addition are necessary to clarify the precise mechanism for the site-selectivity.19—24)

In summary, we found that nitrogen-heterocycles fused with a dichlorobenzene ring underwent site-selective cross-coupling with Grignard reagents in the presence of a Pd catalyst. The reactions occurred at the position ortho to the nitro-group, while further studies including those on transition states of the oxidative addition are necessary to clarify the precise mechanism for the site-selectivity,19—24)

Experimental

General All reactions were performed in oven dried or flame dried glassware under argon atmosphere. Reactions were monitored by TLC on Merck silica gel 60 F254 plates visualized by UV lamp at 254 nm. Column chromatography was performed on MERCK Silica Gel 60 and preparative TLC was performed on Merck silica gel 60 F254 0.5 mm plates. NMR spectra were measured on a JEOL ECA-500 NMR spectrometer at 500 MHz for 1H spectra and 125 MHz for 13C spectra, and for 1H-NMR, tetramethylsilane (TMS) (δ=0) in CDCl3 served as an internal standard. For 13C-NMR, 77.00) served as an internal standard. Infrared spectra were measured on a SHIMADZU IR Prestige-21 spectrometer (ATR). High resolution-mass spectra (HR-MS) were measured on a BRUKER DALTONICS microTOF (electrospray ionization (ESI)). Melting point was measured using a SHIMADZU DSC-50 calorimeter under nitrogen atmosphere. Reactions were monitored by TLC on silica gel plates. Analytical purity of the compounds was determined by 1H-NMR analysis, and analytically pure compounds were obtained by further purification using preparative TLC. The structures of regioisomers were determined through conversion of the products to the corresponding dechlorinated compound (Pd/C, HCOONa) whose structures could be determined by NMR.

Materials

Tetrahydrofuran (THF) was distilled from Na/benzophenone and used immediately. PdCl2(PCy3)2, all Grignard reagents, 7-chloroindole (7) and 5-chloroindole (6) were purchased from Aldrich and used as received. Compounds 1a,12,13) 1b,14) and 1c15) were prepared according to previously reported procedures.

N-Methyl-6,8-dichloro-1,2,3,4-tetrahydroquinoline (10) N-Methyl-1,2,3,4-tetrahydroquinoline was obtained by methylation of 1,2,3,4-tetrahydroquinoline in the presence of formaldehyde and sodium cyanoborohydride in 75% yield.24) To a solution of N-methyl-1,2,3,4-tetrahydroquinoline (180 mg, 1.22 mmol) in CH2Cl2 (30 ml) was added N-chlorosuccinimide (360 mg, 2.69 mmol) at 0 °C and the resulting mixture was stirred at 0 °C for 1 h then at 40 °C for 42 h. The reaction mixture was diluted with CH2Cl2, successively washed with H2O and brine, and then dried over anhydrous Na2SO4. After filtration, all volatiles were evaporated and the crude mixture was purified by column chromatography (hexane : Et2O = 10:1) to give 10 as a yellow oil (215 mg, 82%).18

1H-NMR (CDCl3) δ: 8.93 (1H, d, J=8.5 Hz), 7.18 (1H, d, J=2.9 Hz), 7.45 (2H, m), 7.23 (1H, t, J=3.6 Hz), 7.15 (1H, d, J=1.2 Hz), 7.23 (1H, t, J=2.9 Hz), 7.53 (2H, m), 7.56 (1H, s), 7.37 (1H, d, J=8.5 Hz). 13C-NMR (CDCl3) δ: 128.0, 128.1, 127.5, 127.4, 127.3, 126.6, 126.0, 126.8, 125.7, 122.7, 117.0, 116.0, 111.1, 109.1, 51.8, 51.6, 47.6, 45.5. IR (ATR): 3429, 2926, 1499, 1411, 1356, 1261, 1135, 1107, 808 cm−1. HR-MS (ESI): Calcd for C16H16ClNO (M+H+)216.0341, Found 216.0329.

5-Chloro-7-(4-methoxyphenyl)indoline (2a) Solid white. mp 142—145 °C. 1H-NMR (CDCl3) δ: 8.93 (1H, s), 6.54—6.55 (1H, m), 7.05 (2H, d, J=8.5 Hz), 7.15 (1H, d, J=1.2 Hz), 7.23 (1H, t, J=2.9 Hz), 7.53 (2H, m), 7.56 (1H, s), 7.37 (1H, d, J=8.5 Hz). 13C-NMR (CDCl3) δ: 127.5, 127.4, 127.3, 126.6, 126.0, 126.8, 125.7, 122.7, 117.0, 116.0, 111.1, 109.1, 51.8, 51.6, 47.6, 45.5. IR (ATR): 3429, 2926, 1499, 1411, 1356, 1261, 1135, 1107, 808 cm−1. HR-MS (ESI): Calcd for C16H14ClNO (M+H+)256.0535, Found 256.0529.

5-Chloro-7-(4-methoxyphenyl)indoline (2b) The reaction was performed with 1b (94.0 mg, 0.500 mmol) at 50 °C. Purification by preparative TLC in hexane : AcOEt (5 : 1) afforded 2b (54.0 mg, 0.208 mmol, 41%) as a yellow-white solid. mp 118—122 °C. 1H-NMR (CDCl3) δ: 8.92 (1H, d, J=8.5 Hz), 7.33 (2H, t, J=8.2 Hz), 3.84 (3H, s), 3.98 (1H, br), 6.96 (2H, d, J=8.5 Hz), 7.02—7.02 (2H, m), 7.44 (2H, d, J=8.5 Hz). 13C-NMR (CDCl3) δ: 153.2, 147.7, 131.4, 123.2, 124.3, 125.3, 126.6, 129.0, 130.7, 131.4, 147.7, 158.8. IR (ATR): 3377, 2926, 1609, 1510, 1460, 1236, 1173 cm−1. HR-MS (ESI, negative mode): Calcd for C16H14ClNO (M−H−)255.0527, Found 255.0529.

6-Chloro-8-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinoline (2c) The reaction was performed with 1c (68.0 mg, 0.336 mmol, 50% purity) by preparative TLC (hexane : AcOEt=5 : 1) to give 2c (78.0 mg, 0.303 mmol, 61%) as a white solid. Note: in case that a biphenyl-type by-product which was obtained through homocoupling of the Grignard reagent was contaminated after preparative TLC separation, yields of the products were determined by H-NMR analysis, and analytically pure compounds were obtained by further purification using preparative TLC. The structures of regioisomers were determined through conversion of the products to the corresponding dechlorinated compound (Pd/C, H2O).
6-Chloro-8-(3-methoxyphenyl)-1,2,3,4-tetrahydronquinoline (5b) The reaction was performed with 1e (57.6 mg, 0.285 mmol) and a 1:1 solution of 3-methoxyphenylmagnesium bromide in THF (0.855 ml, 0.855 mmol). Purification by preparative TLC (hexane:AcOEt=9:1; developed twice) afforded 5b (59.6 mg, 0.218 mmol, 76%) as a yellow-white solid. mp 88—92 °C for 18 h. The reaction was quenched with a saturated NH4Cl aqueous solution at 0 °C. The resulting mixture was stirred at 0 °C for 30 min and then at room temperature for 24 h. The reaction was performed with 2-methylprop-1-en-1-ylmagnesium bromide in THF (1.63 ml, 4.07 mmol, 5 eq) and CuCl (78.7 mg, 0.674 mmol, 5 mol%) in THF (0.125 M) was slowly added 4-chloroindole (71.0 mg, 0.468 mmol), 5d (55.6 mg, 0.223 mmol, 77%) as a yellow oil. 1H-NMR (CDCl 3 ) δ: 1.91—1.96 (2H, m), 2.79 (2H, t, J =6.2 Hz), 3.29 (2H, t, J =6.2 Hz), 4.46 (1H, br), 6.93 (1H, d, J =2.3 Hz), 7.04 (1H, d, J =2.3 Hz), 7.10—7.11 (1H, m), 7.13—7.14 (1H, m), 7.35 (1H, dd, J =5.1, 1.1 Hz). 13C-NMR (CDCl 3 ) δ: 21.4, 27.4, 41.8, 55.3, 113.1, 114.6, 120.5, 121.4, 122.7, 127.3, 127.4, 128.2, 130.0, 131.5, 139.6, 141.0. IR (ATR): 3426, 2928, 2853, 1489, 1447, 1352, 1292, 1179, 1070, 880, 781, 702 cm⁻¹. HR-MS (ESI): Calcd for C 16H 16ClNO (M) + : 273.0913, Found 273.0912.

6-Chloro-8-(2-thienyl)-1,2,3,4-tetrahydronquinoline (5c) The reaction was performed with 1e (59.0 mg, 0.292 mmol) and a 1:1 solution of 2-thienylmagnesium bromide in THF (0.857 mg, 0.857 mmol). Purification by preparative TLC (hexane:AcOEt=5:1) afforded 5c (55.6 mg, 0.223 mmol, 77%) as a yellow oil. 1H-NMR (CDCl 3 ) δ: 1.91—1.96 (2H, m), 2.79 (2H, t, J =6.2 Hz), 3.29 (2H, t, J =6.2 Hz), 4.46 (1H, br), 6.93 (1H, d, J =2.3 Hz), 7.04 (1H, d, J =2.3 Hz), 7.10—7.11 (1H, m), 7.13—7.14 (1H, m), 7.35 (1H, dd, J =5.1, 1.1 Hz). 13C-NMR (CDCl 3 ) δ: 21.4, 27.4, 41.8, 55.3, 113.1, 114.6, 120.5, 121.4, 122.7, 127.3, 127.4, 128.2, 130.0, 131.5, 139.6, 141.0. IR (ATR): 3418, 2928, 2837, 1489, 1447, 1352, 1292, 1179, 1070, 880, 781, 702 cm⁻¹. HR-MS (ESI): Calcd for C 16H 16ClNS (M) + : 292.0838, Found 292.0832.

Acknowledgment We thank Takeda Science Foundation for financial support.

References