

Mechanistic Study on Reaction of Dichlorophenylphosphine with Dicyclohexylamine

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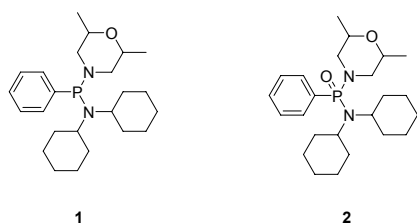
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Received August 21, 2010, Accepted October 7, 2010

Key Words: Phosphinamidic acid derivative, *N,N*-Dicyclohexyl-*P*-phenylphosphinic amide, *N,N*-Dicyclohexyl-*P*-phenylphosphonamidic chloride, *N,N*-Dicyclohexylchlorophenylphosphine amide, Reaction of dichlorophenylphosphine

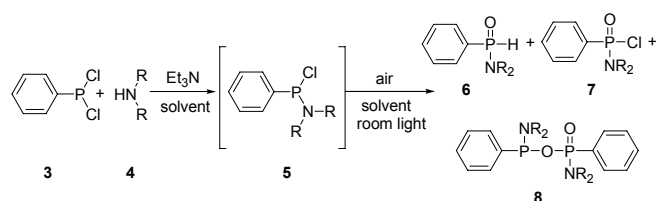
Organophosphorus compounds¹ continue to be popular targets due to their ubiquity in biological systems² and their potential to serve as novel pharmaceutical,³ agricultural,⁴ chemical agents⁵ and Pd-bound ligands.⁶ Especially, an electronically rich and sterically hindered phosphorus ligand needs in the Pd-catalyzed coupling reaction such as Suzuki-Miyaura coupling and Buchwald-Hartwig amination.^{7,8} Since the first general procedures for these coupling reactions were discovered,⁷ efforts have been made toward increasing the substrate scope and efficiency. An important area within this field is the development of more effective phosphorus/nitrogen (PN)-ligands involving two identical and/or different aliphatic amines.^{7,8} Recently, we reported *N,N*-dicyclohexyl-(2,6-dimethylmorpholino)-(phenyl)phosphinamine (**1**) and *N,N*-dicyclohexyl-*P*-(2,6-dimethylmorpholino)-*P*-phenylphosphinic amide (**2**) as novel PN₂ ligand for the Buchwald-Hartwig amination.⁹ The efficacy of phosphinic amide **2** is lower than one of phosphinamine derivative **1**. In connection with the development of more active PN₂ ligand, we attempted the synthesis of some other phosphonamidic acid derivatives containing two different amines using chloroalkylphenyl-phosphinamide as an intermediate. During the reaction of **1** with dicyclohexylamine and other amines, we detected commonly three unknown products instead of the required PN₂ ligands. Therefore, we studied on the formation process and the structures of these products in order to understand the reaction mechanism (Scheme 1). Herein, we report our results for the mechanistic study on reaction of dichlorophenylphosphine with dicyclohexylamine.



Firstly, the reaction of **3** with **4** (2 equiv.) in the presence of triethylamine in methylene chloride for 60 hours at room tem-

perature yielded **6** (22%), **7** (trace) and **8** (55%), but compound **5** was not isolated (Entry 7 in Table 1) (Scheme 1). We also found that the distribution of these products was dependent on the reaction conditions. The by-products were also detected after the formation of **5** on TLC. Therefore, we thought that the formation of by-products derived from **5** are due to the water and/or the oxygen in air and in solvents.

The distribution of products in the reaction of **3** with **4** under various conditions were investigated (Table 1) (Scheme 1). When the non-polar solvent such as *n*-hexane, toluene, and diethyl ether used, compound **6** was the main product (Entries 1, 2 and 4 in Table 1). Reaction **3** with **4** was carried out in benzene or methylene chloride under same condition to give three products **6-8** [benzene: **6** (41%), **7** (28%) and **8** (27%);



Scheme 1

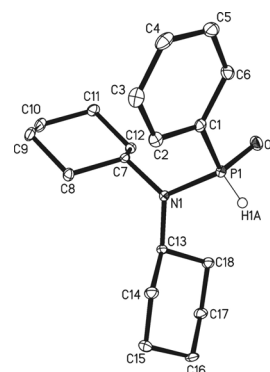


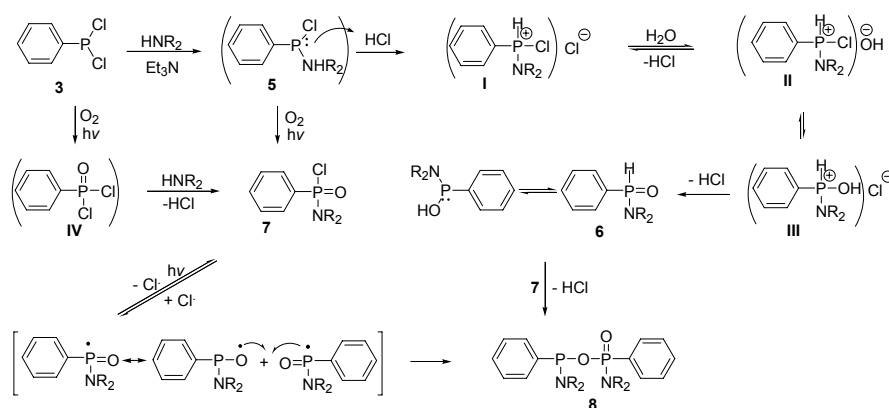
Figure 1. ORTEP plot for compound **6**.

methylene chloride: **6** (77%), **7** (7%) and **8** (2%)] (Entries 3 and 5 in Table 1).

In the polar solvents such as THF, chloroform, ethyl acetate, 1,4-dioxane, and acetonitrile, the reaction of **3** with **4** was yielded phosphonamidic acid anhydride **8** (main product) and phenylphosphinic amide **6** (minor product) (Entries 6-10 in Table 1). Phenylphosphonamidic chloride **7** as trace, however, was detected on TLC. On the other hand, when **3** was treated with **4** in the above polar solvent and methylene chloride under dark condition to give compound **6** (60 - 77%) and **8** (1 - 19%) (Entries 11-13 and 15 in Table 1). The formation of **8** was more favorable in polar solvents in light (Entries 6-10 in Table 1) than in dark (Entries 11-16 in Table 1). Also, we detected the compound

8 derived from **6** and/or **7** ever since formation of **7** in room light or UV light by TLC. In dry methylene chloride, **3** was treated with **4** under same condition to afford **6** (23%), **7** (2%) and **8** (57%) (Entry 17 in Table 1). According to TLC monitoring, we also detected compound **7** as the main product in initial step, and that compound **7** was then converted into **8** in the Entry 17. Therefore, the light may affect the formation of **7** and **8**. On the other hand, the reaction was carried out in dry THF in argon atmosphere in dark to give only **6** and **7** as trace (Entry 21 in Table 1).

According to our results, the product distributions in the reaction of **3** with **4** are affected by the oxygen and water in air and/or solvent, the solvent polarity, and the room light. The



Scheme 2. Plausible mechanism for formation of compound **6**, **7** and **8**

Table 1. Reaction of dichlorophenylphosphine (**3**) with dicyclohexylamine (**4**) in the presence of triethylamine under various conditions^a

| Entry | Conditions ^b | Solvent Polarity | Method | Time (h) | Product (Isolated Yield %) ^c | | |
|-------|---|------------------|--------|----------|---|----------|----------|
| | | | | | 6 | 7 | 8 |
| 1 | <i>n</i> -Hexane, rt, air, room light | 0 | A | 72 | 54 | 8 | trace |
| 2 | Toluene, rt, air, room light | 2.4 | A | 84 | 51 | trace | trace |
| 3 | Benzene, rt, air, room light | 2.7 | A | 144 | 41 | 28 | 27 |
| 4 | EtOEt, rt, air, room light | 2.8 | A | 95 | 77 | - | 3 |
| 5 | CH ₂ Cl ₂ , rt, air, room light | 3.1 | A | 6.5 | 77 | 7 | 2 |
| 6 | THF, rt, air, room light | 4.0 | A | 24 | 17 | - | 60 |
| 7 | CHCl ₃ , rt, air, room light | 4.1 | A | 60 | 22 | trace | 55 |
| 8 | EtOAc, rt, air, room light | 4.4 | A | 30 | 21 | trace | 59 |
| 9 | 1,4-Dioxane, rt, air, room light | 4.8 | A | 20 | 5 | trace | 58 |
| 10 | CH ₃ CN, rt, air, room light | 5.8 | A | 6 | 16 | trace | 63 |
| 11 | THF, rt, air, dark | 4.0 | B | 132 | 72 | - | 11 |
| 12 | CHCl ₃ , rt, air, dark | 4.1 | B | 20 | 70 | - | 9 |
| 13 | EtOAc, rt, air, dark | 4.4 | B | 166 | 60 | - | 19 |
| 14 | 1,4-Dioxane, rt, air, dark | 4.8 | B | 24 | 75 | - | trace |
| 15 | CH ₃ CN, rt, air, dark | 5.8 | B | 1.5 | 75 | - | 1 |
| 16 | CH ₂ Cl ₂ , rt, air, dark | 3.1 | D | 144 | 77 | - | - |
| 17 | CH ₂ Cl ₂ (dry), rt, O ₂ , UV | 3.1 | C | 81 | 23 | 2 | 57 |
| 18 | CH ₂ Cl ₂ , reflux, H ₂ O, air, room light | 3.1 | E | 8.5 | 75 | - | 4 |
| 19 | EtOEt, rt, O ₂ , room light | 2.8 | F | 18 | 19 | 64 | trace |
| 20 | CH ₂ Cl ₂ , rt, Argon, room light | 3.1 | G | 24 | 35 | - | trace |
| 21 | THF(dry), rt, Argon, dark | 4.0 | H | 90 | trace | trace | - |

^aThe mole ratio of the compound **3**, **4** and base is 1:2:2.5 equivalents. ^brt = room temperature. UV = 254 nm UV lamp for TLC. ^cIsolated yields after silica gel column chromatography.

formation of compound **8** is more favorable in the polar solvents in light, whereas the formation of **6** is more favorable in the non-polar solvents in dark. Interestingly, the reaction under excess oxygen in diethyl ether gave compound **7** as main product (Entry 19), whereas the reaction under ambient condition in diethyl ether afforded **6** as main product (Entry 4). Diethyl ether as solvent may be unfavorable the conversion of **6** and/or **7** to **8** in light under our system.

The plausible mechanism for the reaction show in Scheme 2. The structures of compounds **6-8** were established by IR, NMR, HRMS and also X-ray diffraction for **6**.

In conclusion, the product distribution in the reaction of dichlorophenylphosphine (**3**) with dicyclohexylamine depends on the solvent polarity, oxygen, water in air and solvent, and the light. The compound **6** may be formed *via* **3** → **5** → **I** → **II** → **III** → **6** process, whereas the compound **7** may be yield *via* the reaction of **3** and/or the intermediate **5** with molecular oxygen in light (Scheme 2). Compound **8** may be form *via* two routes such as **6** and/or **7** to **8**. The pathway of **7** to **8** is more favorable in light in polar solvent.

We believe that this may be a good guidance for the synthesis of the phenylphosphine ligands and phosphonamidic acid derivatives.

Experimental Section

General. Melting points were determined with a capillary apparatus and uncorrected. NMR spectra were recorded on a 300 MHz spectrometer for ^1H and ^{13}C NMR and a 500 MHz spectrometer for ^{31}P NMR with chemical shift values reported in δ units (ppm) relative to an internal standard (TMS for ^1H and ^{13}C NMR and phosphoric acid for ^{31}P NMR). IR spectra were obtained on a Mattson Genesis Series FT-IR spectrophotometer. Mass spectra were obtained on a GC Mate 2, JEOL. X-ray diffraction data were obtained with a Brüker SMART diffractometer equipped with a graphite monochromated Mo K α ($\lambda = 0.71073 \text{ \AA}$) radiation source and a CCD detector. The open-bed chromatography was carried out on silica gel (70 ~ 230 mesh, Merck) using gravity flow. The column was packed with slurries made from the elution solvent.

Reaction of compound **3** with **4**.

Method A: A mixture of **3** (8.4 mmol), **4** (16.8 mmol) and triethylamine (21 mmol) in solvent (30 mL) was stirred at room temperature until the **5** disappeared by TLC monitoring. The reaction mixture was filtered and washed with *n*-hexane. The combined filtrate was evaporated under reduced pressure. The resulting residue was purified by chromatography on silica gel using *n*-hexane:ethyl acetate (2:1, v/v) to afford the product.

Method B: A mixture of compound **3** (8.4 mmol), compound **4** (16.8 mmol) and triethylamine (21 mmol) in solvent (30 mL) was stirred at room temperature until the **5** was disappeared in the dark. The reaction mixture was filtered and washed with *n*-hexane. The combined filtrate was evaporated under reduced pressure. The resulting residue was purified by chromatography on silica gel using *n*-hexane:ethyl acetate (2:1, v/v) to afford the product.

Method C: A mixture of compound **3** (8.4 mmol), compound **4** (8.5 mmol) and triethylamine (10.5 mmol) in dry CH_2Cl_2 (30

mL) was refluxed 3 hours. After removing the air, the solution was stirred for 78 hours under oxygen atmosphere and UV (254 nm) light at room temperature. The reaction mixture was filtered and washed with *n*-hexane. The combined filtrate was evaporated under reduced pressure. The resulting residue was purified by chromatography on silica gel using *n*-hexane:ethyl acetate (2:1, v/v) to afford the product.

Method D: A mixture of compound **3** (8.4 mmol), compound **4** (16.8 mmol) and triethylamine (21 mmol) in CH_2Cl_2 (30 mL) was stirred at room temperature for 144 hours in the dark. The reaction mixture was filtered and washed with *n*-hexane. The combined filtrate was evaporated under reduced pressure. The resulting residue was purified by chromatography on silica gel using *n*-hexane:ethyl acetate (2:1, v/v) to afford the product.

Method E: A dichloromethane solution of compound **4** (33.6 mmol) and triethylamine (42 mmol) was slowly dropped to the compound **3** solution (compound **3**, 16.8 mol in 30 mL dichloromethane) with stirring at room temperature for 20 minutes and refluxed for 2.5 hours. After adding excess water, the mixture was refluxed for 6 hours. After cooling to the room temperature, the reaction mixture was filtered and washed with *n*-hexane. The combined filtrate was evaporated under reduced pressure. The resulting residue was purified by chromatography on silica gel using *n*-hexane:ethyl acetate (2:1, v/v) to afford the product.

Method F: A ether solution of compound **4** (8.5 mmol) and triethylamine (10.5 mmol) was slowly dropped to the compound **3** solution (compound **3**, 4.3 mmol in 40 mL ether) with stirring at room temperature for 10 minutes and then refluxed for 3 hours. And solution was then stirred for 15 hours under oxygen atmosphere at room temperature. The reaction mixture was filtered and washed with *n*-hexane. The combined filtrate was evaporated under reduced pressure. The resulting residue was purified by chromatography on silica gel using *n*-hexane:ethyl acetate (2:1, v/v) to afford the product.

Method G: A methylene chloride solution of compound **4** (8.5 mmol) and triethylamine (10.5 mmol) was slowly dropped to the compound **3** solution (compound **3**, 4.3 mmol in 10 mL methylene chloride) with stirring at room temperature for 10 minutes in argon atmosphere and then refluxed for 24 hours. After cooling to room temperature, the reaction mixture was filtered and washed with *n*-hexane. The combined filtrate was evaporated under reduced pressure. The resulting residue was purified by chromatography on silica gel using *n*-hexane:ethyl acetate (2:1, v/v) to afford the product.

Method H: A dry tetrahydrofuran solution of compound **4** (8.5 mmol) and triethylamine (10.5 mmol) was slowly dropped to the compound **3** solution (compound **3**, 4.3 mmol in 40 mL ether) with stirring at room temperature in argon atmosphere in dark for 90 hours. Only compounds **6** and **7** were detected as trace on TLC plate.

***N,N*-Dicyclohexyl-*P*-phenylphosphinic amide (**6**).** mp 105 - 106 °C. $R_f = 0.11$ (EtOAc:*n*-hexane = 1:2, v/v). IR (KBr) 3060, 2930, 2850, 2362 (P-H), 1738, 1500, 1343, 1254 (P=O), 1204, 1162, 1121, 1071, 990, 959, 891, 751, 706 cm^{-1} . ^1H NMR (CDCl_3) δ 0.99-2.02 (m, 22H), 2.88-3.02 (m, 2H), 7.55-7.44 (m, 3H), 7.68 (8.5352 + 6.8155/2) (d, PH, $J_{PH} = 510 \text{ Hz}$), 7.84-7.78 (m, 2H). ^{13}C NMR (CDCl_3) δ 25.35, 26.33, 26.35, 34.25, 34.29, 34.43, 34.48, 54.73, 54.78, 128.39 (d, $^2J_{CP} = 17.59 \text{ Hz}$, Ph-C_{ortho}),

131.78 (d, $^4J_{CP} = 3.76$ Hz, Ph-C_{para}), 131.82 (d, $^1J_{CP} = 172.9$ Hz, Ph-C_{ipso}), 132.07 (d, $^3J_{CP} = 14.37$ Hz, Ph-C_{meta}). ^{31}P NMR (85% phosphoric acid) δ 23.48; HRMS (ESI) m/z calcd for C₁₈H₂₈NPO M⁺: 305.1909; found: 305.1919.

Crystal data for 6: C₁₈H₂₈NOP, formula weight = 305.38, Crystal system = monoclinic, Space group = C2/c, Unit cell dimensions a = 27.156 (3) Å, b = 6.7537 (7) Å, c = 20.511 (3) Å, $\alpha = 90^\circ$, $\beta = 115.201 (4)^\circ$, $\gamma = 90^\circ$, Volume = 3403.7 (7) Å³, Z value = 8, Density (calculated) = 1.192 Mg/m³, Absorption coefficient = 0.161 mm⁻¹, F(000) = 1328, Crystal size = 0.40 × 0.21 × 0.10 mm³, Theta range for data collection = 1.66 to 28.30°, Index ranges = -35 ≤ h ≤ 34, -9 ≤ k ≤ 8, -26 ≤ l ≤ 26, Reflections collected = 14463, Independent reflections = 4023 [R(int) = 0.1013], Completeness to theta = 28.30° (95.5%), Absorption correction = None, Refinement method = Full-matrix least-squares on F², Data/restraints/parameters = 4023/0/190, Goodness-of-fit on F² = 1.025, Final R indices [I > 2 sigma(I)], R₁ = 0.0663, wR₂ = 0.1472, R indices (all data) = R₁ = 0.1278, wR₂ = 0.1743, Largest diff. peak and hole = 0.380 and -0.539 e.Å⁻³.

***N,N*-Dicyclohexyl-*P*-phenylphosphonamidic chloride (7).** mp 121 - 122 °C; R_f = 0.67 (EtOAc:*n*-hexane = 1:2, v/v); IR (KBr) 3059, 2929, 2855, 1447, 1408, 1341, 1260, 1232, 1165, 1109, 1060, 983, 894, 853, 753, 699, 630 cm⁻¹; ^1H NMR (CDCl₃) δ 0.97-1.26 (m, 6H), 1.54-2.03 (m, 14H), 2.79-2.95 (m, 2H), 7.44-7.56 (m, 3H), 7.87-7.94 (m, 2H); ^{13}C NMR (CDCl₃) δ 25.15, 26.36, 31.44, 32.43, 56.37, 56.42, 128.44 (d, $^2J_{CP} = 21.19$ Hz, Ph-C_{ortho}), 130.64 (d, $^3J_{CP} = 14.92$ Hz, Ph-C_{meta}), 132.35 (d, $^4J_{CP} = 4.51$ Hz, Ph-C_{para}), 134.20 (d, $^1J_{CP} = 220.99$ Hz, Ph-C_{ipso}). ^{31}P NMR (85% phosphoric acid) δ 40.37. HRMS (ESI) m/z calcd for C₁₈H₂₇NCIPO M⁺: 339.1519; found: 339.1518.

***(N,N)*-Dicyclohexyl-*P*-phenylphosphonamidic acid** (*N,N*-dicyclohexyl-*P*-phenylphosphonamidic acid) anhydride (8). mp 162 - 163 °C. R_f = 0.78 (EtOAc:*n*-hexane = 1:2, v/v). IR (KBr) 3053, 2930, 2851, 1447, 1402, 1340, 1255, 1229, 1165, 1119, 1068, 983, 889, 850, 751, 700, 666 cm⁻¹. ^1H NMR (CDCl₃) δ 1.01-1.11 (m, 4H), 1.45-1.75 (m, 16H), 2.79-2.88 (m, 2H), 7.23-7.35 (m, 3H), 7.51-7.56 (m, 2H). ^{13}C NMR (CDCl₃) δ 25.63, 25.70, 26.48, 26.60, 35.74, 53.42, 54.12, 54.41, 55.03, 127.53, 127.66, 127.72, 127.88, 128.01, 130.08, 130.34, 130.50, 142.96, 143.00. ^{31}P NMR (85% phosphoric acid) δ 22.46, 26.81. HRMS (ESI) m/z calcd for C₃₆H₅₄N₂P₂O₂ M⁺: 608.3661; found: 608.3665.

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