

# On the Reaction of *N*-(Diphenylphosphinyl)-1-phenylethanamine with Aromatic Aldehydes Giving 4-Aryl-2,6-diphenylpyridine Derivatives

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*N*-(Diphenylphosphinyl)-2-phenyl-1-azaallyl anion (**1**), generated from *N*-(diphenylphosphinyl)-1-phenylethanamine, reacted with aromatic aldehydes in a 2 : 1 molar ratio to give 4-aryl-2,6-diphenylpyridines in moderate yields. The intervention of *N*-phosphinyl-1-azadiene intermediates is proposed on the basis of the independent synthesis of an *N*-phosphinyl-1-azadiene and its conversion into a pyridine by the reaction with **1**.

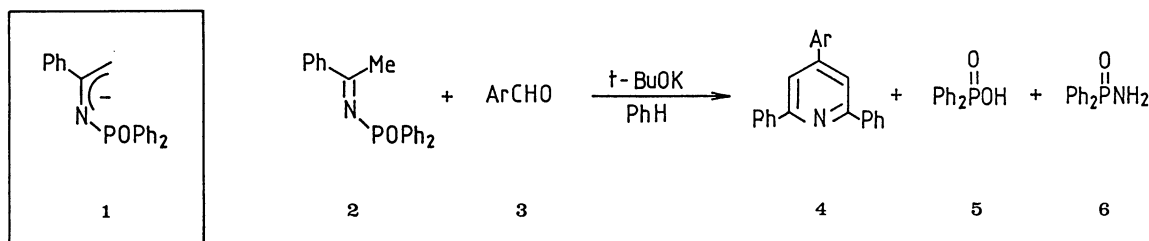
In the previous paper, we described a novel route to phenyl-substituted pyridines by the reaction of  $\alpha,\beta$ -unsaturated carbonyl compounds with *N*-phosphinyl-1-azaallyl anions, which are easily generated from the corresponding *N*-phosphinylimine and enamine.<sup>1)</sup> The *N*-phosphinyl-1-azaallyl anions have shown bidentate reactivity at the  $\beta$ -carbon and the nitrogen atoms to behave as a synthetic equivalent of primary vinylamines, which are labile even at low temperature.<sup>2)</sup> The primary vinylamines<sup>2)</sup> and their synthetic equivalents such as an *N*, *N*-bis(trimethylsilyl) enamine,<sup>3)</sup> 1-amino-2-hydroxyalkylsilanes,<sup>4)</sup> and *N*-vinyliminophosphoranes<sup>5)</sup> have been reported to provide 2-azadienes upon treatment with aldehydes. Our attention, therefore, turned to the reaction of the *N*-phosphinyl-1-azaallyl anion **1** with aromatic aldehydes **3** to investigate the chemo-selectivity of **1** towards simple carbonyl compounds with the result that the unexpected formations of 4-aryl-2,6-diphenylpyridines was observed.

## Results and Discussion

In a preliminary study, *N*-(diphenylphosphinyl)-1-phenylethanamine (**2**)<sup>1,6)</sup> was treated with an equimolar amount of benzaldehyde **3a** in the presence of potassium *t*-butoxide to afford 2,4,6-triphenylpyridine **4a** in 8% yield, instead of the presumed 2-azadiene (**2-AD**, Scheme 2). Since the two phenyl groups at the 2- and 6-positions of **4a** seemed to arise from two molecules of **2**, the reaction of **2** and **3a** in a 2 : 1 molar

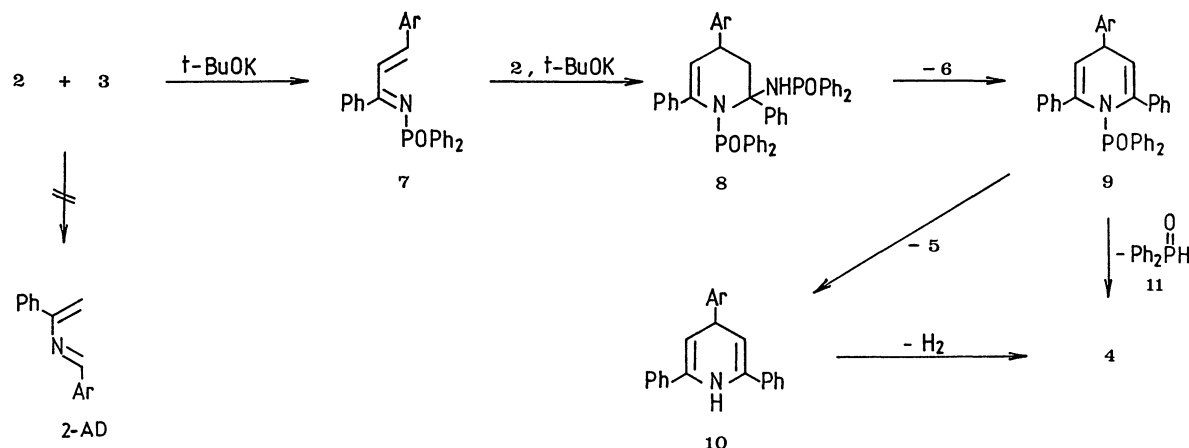
ratio in the presence of potassium *t*-butoxide at ambient temperature was investigated to give the pyridine **4a** in 52% yield along with diphenylphosphinic acid (**5**) and diphenylphosphinic amide (**6**) in 58 and 18% yield, respectively. Similarly, the reactions of the imine **2** with substituted benzaldehydes **3b–h** as well as 2-thiophenecarbaldehyde **3i** also resulted in the regioselective formation of pyridine derivatives **4b–i** in which the aryl groups derived from the aldehydes are located exclusively at the 4-position of the pyridine ring. The use of ortho-substituted benzaldehydes **3g** and **3h** obviously decreases the yields of the pyridines **4g** and **4h**. All the pyridines except **4i** have been reported. Pyridines **4a–f** were characterized by comparison of their spectral data and melting points with those described in the literatures for **4a–f**, and **4g** and **4h** were identified by independent syntheses.

The present reaction can be best explained as shown in Scheme 2. Upon treatment with an aromatic aldehyde **3**, the 1-azaallyl anion **1** undergoes the condensation reaction on the  $\beta$ -carbon atom to give *N*-phosphinyl-1-azadiene **7**. The 1-azadiene **7** further reacts with **1** to lead to a dihydropyridine **9** via elimination of the phosphinic amide **6** from **8**. Since the phosphinic acid **5** was isolated from the reaction of **2** and **3a**, a route involving release of the phosphinic acid **5** from **9**, followed by dehydrogenation is likely for the formation of the pyridine **4**. However, an alternative route through direct elimination of diphenylphosphine oxide (**11**) from **9** can not be excluded, as **11** was easily converted to the phosphinic acid **5**

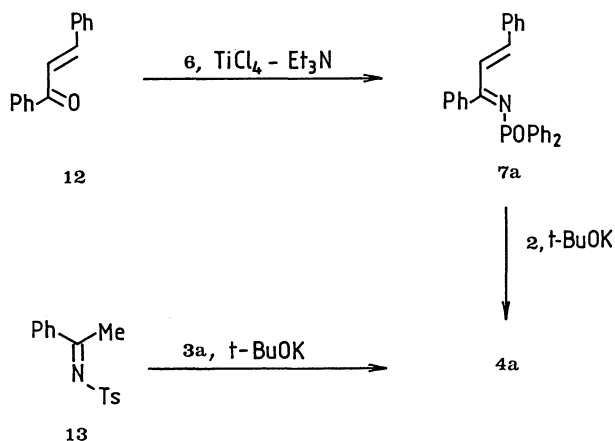


a: Ar=C<sub>6</sub>H<sub>5</sub>, b: Ar=*p*-MeC<sub>6</sub>H<sub>4</sub>, c: Ar=*p*-ClC<sub>6</sub>H<sub>4</sub>, d: Ar=*p*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, e: Ar=*p*-MeOC<sub>6</sub>H<sub>4</sub>,  
f: Ar=*p*-Me<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, g: Ar=*o*-MeC<sub>6</sub>H<sub>4</sub>, h: Ar=*o*-ClC<sub>6</sub>H<sub>4</sub>, i: Ar=2-Thienyl

Scheme 1.



Scheme 2.



Scheme 3.

group seems to be essential for the present transformation, because a similar reaction of benzaldehyde **3a** with *N*-(*p*-tolylsulfonyl)-1-phenylethanamine (**13**)<sup>9</sup> gave only a trace amount of the pyridine **4a**.

In conclusion, the reaction of *N*-phosphinyl-2-phenyl-1-azaallyl anion **1** with aromatic aldehydes has been found to give 4-aryl-2,6-diphenylpyridines probably via *N*-phosphinyl-1-azadiene intermediate. It is surprising to observe nucleophilic attack exclusively by the anionic carbon of the 1-azaallyl anion **1**. This result sharply contrasts with the behavior of primary vinylamines and their synthetic equivalents known so far.<sup>2-5</sup> Although the yields of the pyridines are modest, the present reaction has shown a novel reactivity of the azaallyl anion **1**.

### Experimental<sup>10</sup>

**General Procedure for the Reaction of *N*-(Diphenylphosphinyl)phenylethanamine (**2**) and Aromatic Aldehydes (**3**) (2:1 molar ratio).** To a solution of the imine **2**<sup>1,6</sup> (160 mg, 0.5 mmol) in anhydrous benzene (5 ml) was added potassium *t*-butoxide (56 mg, 0.5 mmol). The mixture was stirred at ambient temperature for 10 min, and a solution of aromatic aldehyde **3** (0.25 mmol) in anhydrous benzene (3 ml) was added to the mixture. Stirring was continued for 2 h at the same temperature. The mixture was washed with water, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. The residue was purified on TLC (silica gel, benzene) to give the pyridine **4**. In the reaction of **2** and **3a**, the base line portion on the TLC plate was developed again with benzene-methanol (3:1) to yield diphenylphosphinic amide **6** in 18% yield, and acidification of the aqueous phase with hydrochloric acid provided diphenylphosphinic acid **5** in 58% yield. The yields of the pyridine derivatives **4** are based on the amount of aromatic aldehydes. The spectra of the pyridines **4a**, **4b**, **4c**, and **4e** were previously described.<sup>11</sup> The reactions of the imine **2** and benzaldehyde **3a** in molar ratios of 1:1 and 1:2 were carried out in similar manners.

**2,4,6-Triphenylpyridine (4a):** 52%; mp and mixed mp 134–135 °C (methanol) (lit,<sup>11</sup> mp 137 °C).

**4-(*p*-Methylphenyl)-2,6-diphenylpyridine (4b):** 57%; mp

under the reaction conditions (see Experimental).

Some efforts were devoted to the isolation and capture of the *N*-phosphinyl-1-azadiene intermediate **7**. The azadiene **7a** could not be formed among the products of the reaction of the imine **2** with two fold excess amount of benzaldehyde **3a**, while the reaction gave the pyridine **4a** in 7% yield. Further, the reaction of **2** and **3a** in the presence of 1-(1-pyrrolidinyl)-1-cyclohexene, 1-trimethylsiloxy-1-cyclohexene, or ethyl vinyl ether did not afford the expected adducts.<sup>7</sup> Thus, an independent synthesis of the azadiene **7a** was performed in 78% yield by treatment of 1,3-diphenyl-2-propen-1-one (**12**) with the phosphinic amide **6** in the presence of titanium tetrachloride and triethylamine in refluxing toluene.<sup>8</sup> Upon treatment with **2** and potassium *t*-butoxide in benzene at ambient temperature, the propenimine **7a** provided the pyridine **4a** in 52% yield, and this outcome agrees with the mechanism shown in Scheme 2 including both an intervention of the 1-azadiene intermediate **7** and its sequential reaction with **1**.

Finally, it should be noted that the phosphinyl

and mixed mp 124.5–125 °C (methanol) (lit.<sup>12</sup>) mp 118–119 °C.

**4-(*p*-Chlorophenyl)-2,6-diphenylpyridine (4c):** 41%; mp and mixed mp 129–130 °C (methanol) (lit.<sup>13</sup>) mp 129–130 °C.

**4-(*p*-Nitrophenyl)-2,6-diphenylpyridine (4d):** 37%; mp 202–203 °C (benzene–hexane=1:1) (lit.<sup>14</sup>) mp 188 °C; IR (CHCl<sub>3</sub>) 1590, 1540, 1380, 1350, 1100 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ=7.20–7.66 (6H, m), 7.85 (2H, s), 7.87 (2H, d, *J*=9.0 Hz), 8.08–8.25 (4H, m), 8.36 (2H, d, *J*=9.0 Hz); MS *m/z* (rel intensity) 352 (M<sup>+</sup>, 100), 322 (14), 306 (37). Found: C, 77.95; H, 4.46; N, 7.63%. Calcd for C<sub>23</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>: C, 78.34; H, 4.58; N, 7.95%.

**4-(*p*-Methoxyphenyl)-2,6-diphenylpyridine (4e):** 34%; mp and mixed mp 99–100 °C (methanol) (lit.<sup>12</sup>) mp 99–100 °C.

**4-[*p*-(Dimethylamino)phenyl]-2,6-diphenylpyridine(4f):** 28%; mp 142–143 °C (methanol) (lit.<sup>14</sup>) mp 138 °C; IR (CHCl<sub>3</sub>) 1590, 1520, 1360, 1180, 1120 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ=2.99 (6H, s), 6.80 (2H, d, *J*=8.7 Hz), 7.20–7.60 (6H, m), 7.66 (2H, d, *J*=8.7 Hz), 7.84 (2H, s), 8.14–8.24 (4H, m); MS *m/z* (rel intensity) 350 (M<sup>+</sup>, 100), 333 (5), 306 (6).

**4-(*o*-Methylphenyl)-2,6-diphenylpyridine (4g):** 7%; mp and mixed mp 122–123 °C (methanol) (lit.<sup>15</sup>) mp 116–117 °C; IR (KBr) 1610, 1580, 1536, 1490, 1400 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ=2.36 (3H, s), 7.20–7.60 (10H, m), 7.66 (2H, s), 8.12–8.28 (4H, m); MS *m/z* (rel intensity) 321 (M<sup>+</sup>, 75), 320 (100). Found: C, 89.39; H, 5.95; N, 4.44%. Calcd for C<sub>24</sub>H<sub>19</sub>N: C, 89.68; H, 5.96; N, 4.36%.

**4-(*o*-Chlorophenyl)-2,6-diphenylpyridine (4h):** 11%; mp and mixed mp 114–115 °C (methanol) (lit.<sup>12</sup>) mp 112–113 °C; IR (KBr) 1600, 1551, 1478, 1405 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ=7.20–7.64 (10H, m), 7.76 (2H, s), 8.08–8.28 (4H, m); MS *m/z* (rel intensity) 343 (M<sup>+</sup>+2, 31), 341 (M<sup>+</sup>, 100), 306 (51). Found: C, 80.48; H, 4.75; N, 3.81%. Calcd for C<sub>23</sub>H<sub>16</sub>NCl: C, 80.81; H, 4.72; N, 4.10%.

**2,6-Diphenyl-4-(2-thienyl)pyridine (4i):** 31%; mp 165–166 °C (methanol); IR (KBr) 1600, 1580, 1560, 1500, 1410, 1250, 1080, 1040 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ=7.00–7.62 (9H, m), 7.83 (2H, s), 8.02–8.25 (4H, m); MS *m/z* (rel intensity) 313 (M<sup>+</sup>, 100); HR-MS Found: 313.0928. Calcd for C<sub>21</sub>H<sub>15</sub>NS: 313.0925. Found: C, 80.38; H, 4.75; N, 4.32%. Calcd for C<sub>21</sub>H<sub>15</sub>NS: C, 80.48; H, 4.82; N, 4.47%.

**Diphenylphosphinic Acid (5):** Mp and mixed mp 196–198 °C (lit.<sup>16</sup>) mp 190–192 °C; IR (KBr) 3450, 1421, 1180, 1138 cm<sup>-1</sup>.

**Diphenylphosphinic Amide (6):** Mp and mixed mp 170–171 °C (lit.<sup>17</sup>) mp 168 °C; IR (KBr) 3250, 1440, 1190, 1126 cm<sup>-1</sup>.

**Independent Synthesis of the Pyridine 4g.<sup>18</sup>** A mixture of 3-(*o*-methylphenyl)-1-phenyl-2-propen-1-one<sup>19</sup> (2.123 g, 9.5 mmol), acetophenone (0.916 g, 7.6 mmol), and BF<sub>3</sub>·OEt<sub>2</sub> (3.336 g, 22.8 mmol) was heated at 115 °C for 7 h. The solution was cooled to room temperature, and the product was crystallized from benzene to give 4-(*o*-methylphenyl)-2,6-diphenylpyrylium tetrafluoroborate (1.142 g, 37%) as yellow powders: Mp 113–115 °C (decomp). Found: C, 70.58; H, 4.78%. Calcd for C<sub>24</sub>H<sub>19</sub>OBF<sub>4</sub>: C, 70.27; H, 4.67%.

To a suspension of the pyrylium salt (1.076 g, 2.6 mmol) in ethanol (3 ml) was added 25% aq NH<sub>3</sub> (5 ml) and stirring was continued for 24 h at ambient temperature. The product was extracted with dichloromethane prior to drying over Na<sub>2</sub>SO<sub>4</sub>. After removal of the solvent, recrystallization of the resulting solid from methanol gave the pyridine **4g**

(515 mg, 62%).

**Independent Synthesis of the Pyridine 4h.<sup>18</sup>** By a similar procedure for **4g**, a mixture of 3-(*o*-chlorophenyl)-1-phenyl-2-propen-1-one<sup>19</sup> (3.191 g, 13.1 mmol), acetophenone (1.221 g, 10 mmol), and BF<sub>3</sub>·OEt<sub>2</sub> (4.346 g, 30 mmol) was heated at 115 °C for 7 h to afford 4-(*o*-chlorophenyl)-2,6-diphenylpyrylium tetrafluoroborate (1.102 g, 26%) as yellow powders: Mp 114–116 °C (decomp). Found: C, 64.15; H, 3.74%. Calcd for C<sub>23</sub>H<sub>16</sub>OCIBF<sub>4</sub>: C, 63.63; H, 3.75%. The pyrylium salt was used without further purification.

A similar treatment of the pyrylium salt (1.028 g, 2.4 mmol) gave the pyridine **4h** (610 mg, 67%).

**Reaction of Diphenylphosphine Oxide (11) under Basic Conditions.<sup>20</sup>** A mixture of the phosphine oxide **11** (89 mg, 0.44 mmol) and potassium *t*-butoxide (62 mg, 0.55 mmol) in benzene was stirred for 3 h at ambient temperature under nitrogen atmosphere. The organic phase was washed with aq NaHCO<sub>3</sub>, and the aqueous phase was acidified with hydrochloric acid. The product was extracted with dichloromethane prior to drying over MgSO<sub>4</sub>. Removal of the solvent gave the phosphinic acid **5** (57 mg, 59%).

**Independent Synthesis of (2*E*)-*N*-(Diphenylphosphinyl)-1,3-diphenyl-2-propenimine (7a).** A mixture of the propenone **12** (2.083 g, 10 mmol), the phosphinic amide **6** (2.384 g, 11 mmol), and triethylamine (3.03 g, 30 mmol) in toluene (20 ml) was heated at 70 °C. To this mixture was slowly added TiCl<sub>4</sub> (0.60 ml, 5.5 mmol), and the mixture was heated under reflux for 6 h. Insoluble material was removed by filtration and the filtrate was concentrated. The residue was chromatographed on silica gel using benzene–ethyl acetate (1:1) as an eluent to give an oily product, which was crystallized from ether to give **7a** (3.17 g, 78%) as colorless powders: Mp 120–121 °C; IR (KBr) 3090, 1610, 1590, 1560, 1430, 1300, 1180, 1120, 1100, 1020, 990, 980, 910 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ=6.99 (1H, d, *J*=16.4 Hz), 7.21–8.11 (20H, m), 8.28 (1H, dd, *J*=16.4, 1.4 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ=124.2–146.4, 180.3 (*J*<sub>P-C</sub>=8.5 Hz, C=N); <sup>31</sup>P NMR (CDCl<sub>3</sub>) δ=19.0; MS *m/z* (rel intensity) 407 (M<sup>+</sup>, 60), 206 (86), 77 (100); HR-MS Found: 407.1426. Calcd for C<sub>27</sub>H<sub>22</sub>NOP: 407.1439. Found: C, 79.74; H, 5.51; N, 3.33%. Calcd for C<sub>27</sub>H<sub>22</sub>NOP: C, 79.59; H, 5.44; N, 3.44%.

**Reaction of the Ethanamine 2 and the Propenimine 7a.** A mixture of the ethanamine **2** (191 mg, 0.6 mmol), the propenimine **7a** (204 mg, 0.5 mmol), and potassium *t*-butoxide (67 mg, 0.6 mmol) in benzene (5 ml) was stirred for 4 h at ambient temperature. The mixture was washed with aq NaHCO<sub>3</sub> and water, then dried over Na<sub>2</sub>SO<sub>4</sub>. Purification on TLC (silica gel, benzene) gave 2,4,6-triphenylpyridine **4a** (80 mg, 52%): Mp and mixed mp 139–140 °C.

**Synthesis of *N*-(*p*-Tolylsulfonyl)-1-phenylethanamine (13).<sup>9)</sup>** To a cooled solution (–35 °C) of acetophenone oxime (16.23 g, 0.12 mol) and triethylamine (12.14 g, 0.12 mol) in petroleum ether–dichloromethane (160 ml, 1:1) was added *p*-toluenesulfonyl chloride<sup>21</sup> (20.96 g, 0.12 mol). The mixture was warmed up to room temperature and stirring was continued for 1 h. Insoluble material was filtered and the filtrate was concentrated. The residue was crystallized from ether to give **13** (4.048 g, 12%): Mp 71.5–73.5 °C; IR (KBr) 1605, 1600, 1570, 1313, 1301, 1280 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ=2.42 (3H, s), 2.96 (3H, s), 7.12–7.58 (5H, m), 7.80–8.00 (4H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ=21.1 (q), 21.5 (q), 127.1, 128.2, 128.6, 129.4, 133.1, 137.5, 138.8, 143.5, 179.8 (s); MS *m/z* (rel intensity) 273 (M<sup>+</sup>, 26), 209 (24), 155 (95), 91

(100). HR-MS Found: 273.0809. Calcd for  $C_{15}H_{15}O_2S$ : 273.0823.

**Reaction of the *N*-Sulfonylimine (13) with Benzaldehyde (3a).** A solution of the *N*-sulfonylimine **13**<sup>9)</sup> (547 mg, 2 mmol) and potassium *t*-butoxide (226 mg, 2 mmol) in benzene (5 ml) was stirred at ambient temperature for 10 min. To the mixture was added benzaldehyde **3a** (106 mg, 1 mmol) and stirring was continued for 24 h. The mixture was washed with aq  $NaHCO_3$  and dried over  $MgSO_4$ . Separation on TLC (silica gel, benzene) afforded only a trace amount of the pyridine **4a**, which was detectable only by the  $^1H$  NMR spectrum.

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