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

Tomoshige KOBAYASHI,* Hidetaka KAKIUCHI, and Hiroshi KATO*
Department of Chemistry, Faculty of Science, Shinshu University, Matsumoto 390
(Received October 1, 1990)

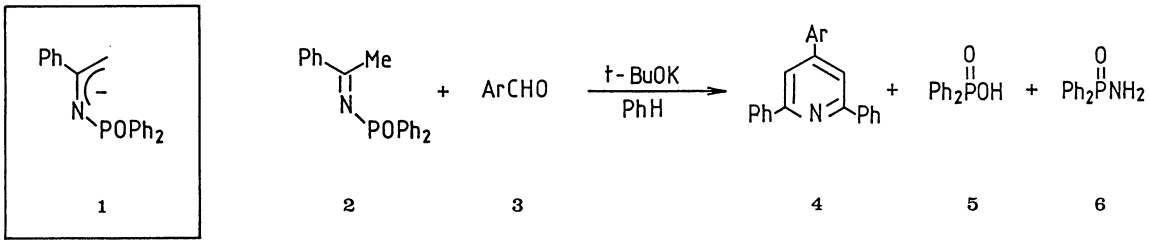
*N*-(Diphenylphosphinyl)-2-phenyl-1-azaallyl anion (**1**), generated from *N*-(diphenylphosphinyl)-1-phenylethanimine, reacted with aromatic aldehydes in a 2 : 1 molar ratio to give 4-aryl-2,6-diphenylpyridines in moderate yields. The intervention of *N*-phosphinyl-1-azadiene intermediates is proposed 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.[1] 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.[2] The primary vinylamines[2] and their synthetic equivalents such as an *N*, *N*-bis(trimethylsilyl) enamine,[3] 1-amino-2-hydroxyalkylsilanes,[4] and *N*-vinyliminophosphoranes[5] 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

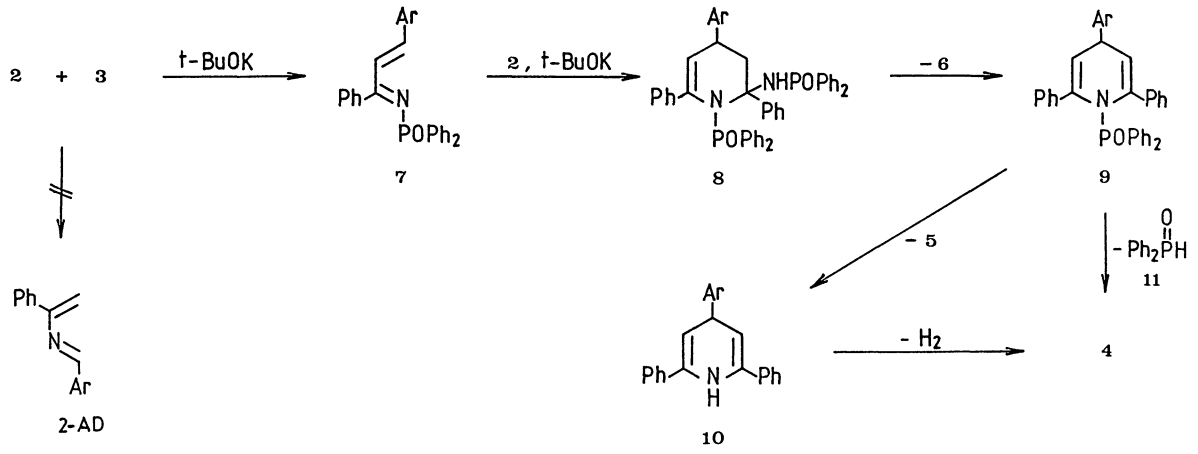
In a preliminary study, *N*-(diphenylphosphinyl)-1-phenylethanimine (**2**)[1,6] was treated with an equimolar amount of benzaldehyde **3a** in the presence of potassium *t*-butoxide to afford 2,4,6-triphenylpyridine **4a** in 8% yield, instead of the presumed 2-azadiene (**2-AD**, Scheme 2). Since the 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-azaally 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**

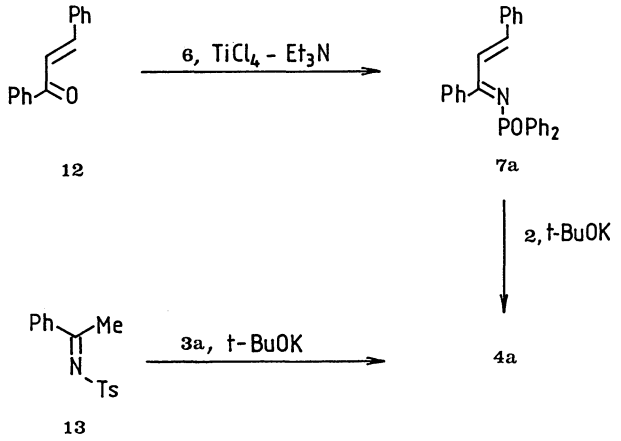



**a**: Ar=$C_6H_5$, **b**: Ar=*p*-$MeC_6H_4$, **c**: Ar=*p*-$ClC_6H_4$, **d**: Ar=*p*-$O_2NC_6H_4$, **e**: Ar=*p*-$MeOC_6H_4$, **f**: Ar=*p*-$Me_2NC_6H_4$, **g**: Ar=*o*-$MeC_6H_4$, **h**: Ar=*o*-$ClC_6H_4$, **i**: Ar=2-Thienyl

Scheme 1.




Scheme 2.




Scheme 3.

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.[7] 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.[8] 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 group seems to be essential for the present transformation, because a similar reaction of benzaldehyde **3a** with *N*-(*p*-tolylsulfonyl)-1-phenylethanimine (**13**)[9] 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.[2-5] Although the yields of the pyridines are modest, the present reaction has shown a novel reactivity of the azaallyl anion **1**.

## Experimental[10]

**General Procedure for the Reaction of N-(Diphenylphosphinyl)phenylethanimine (2) and Aromatic Aldehydes (3) (2 : 1 molar ratio).** To a solution of the imine **2**[1,6] (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 $Na_2SO_4$, 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.[1] 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,[11] mp 137 °C).

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

and mixed mp 124.5—125 °C (methanol) (lit,[12] mp 118—119 °C.

**4-(*p*-Chlorophenyl)-2,6-diphenylpyridine (4c):** 41%; mp and mixed mp 129—130 °C (methanol) (lit,[13] mp 129—130 °C).

**4-(*p*-Nitrophenyl)-2,6-diphenylpyridine (4d):** 37%; mp 202—203 °C (benzene-hexane=1 : 1) (lit,[14] mp 188 °C); IR ($CHCl_3$) 1590, 1540, 1380, 1350, 1100 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=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 ($M^+$, 100), 322 (14), 306 (37). Found: C, 77.95; H, 4.46; N, 7.63%. Calcd for $C_{23}H_{16}N_2O_2$: 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,[12] mp 99—100 °C).

**4-[*p*-(Dimethylamino)phenyl]-2,6-diphenylpyridine(4f):** 28%; mp 142—143 °C (methanol) (lit,[14] mp 138 °C); IR ($CHCl_3$) 1590, 1520, 1360, 1180, 1120 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=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 ($M^+$, 100), 333 (5), 306 (6).

**4-(*o*-Methylphenyl)-2,6-diphenylpyridine (4g):** 7%; mp and mixed mp 122—123 °C (methanol) (lit,[15] mp 116-117 °C); IR (KBr) 1610, 1580, 1536, 1490, 1400 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=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 ($M^+$, 75), 320 (100). Found: C, 89.39; H, 5.95; N, 4.44%. Calcd for $C_{24}H_{19}N$: 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,[12] mp 112—113 °C); IR (KBr) 1600, 1551, 1478, 1405 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=7.20—7.64 (10H, m), 7.76 (2H, s), 8.08—8.28 (4H, m); MS $m/z$ (rel intensity) 343 ($M^+$+2, 31), 341 ($M^+$, 100), 306 (51). Found: C, 80.48; H, 4.75; N, 3.81%. Calcd for $C_{23}H_{16}NCl$: 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 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=7.00—7.62 (9H, m), 7.83 (2H, s), 8.02—8.25 (4H, m); MS $m/z$ (rel intensity) 313 ($M^+$ 100); HR-MS Found: 313.0928. Calcd for $C_{21}H_{15}NS$: 313.0925. Found: C, 80.38; H, 4.75; N, 4.32%. Calcd for $C_{21}H_{15}NS$: C, 80.48; H, 4.82; N, 4.47%.

**Diphenyphosphinic Acid (5):** Mp and mixed mp 196—198 °C (lit,[16] mp 190—192 °C); IR (KBr) 3450, 1421, 1180, 1138 $cm^{-1}$.

**Diphenylphosphinic Amide (6):** Mp and mixed mp 170—171 °C (lit,[17] mp 168 °C); IR (KBr) 3250, 1440, 1190, 1126 $cm^{-1}$.

**Independent Synthesis of the Pyridine 4g.**[18] A mixture of 3-(*o*-methylphenyl)-1-phenyl-2-propen-1-one[19] (2.123 g, 9.5 mmol), acetophenone (0.916 g, 7.6 mmol), and $BF_3 \cdot OEt_2$ (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 $C_{24}H_{19}OBF_4$: 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 $NH_3$ (5 ml) and stirring was continued for 24 h at ambient temperature. The product was extracted with dichloromethane prior to drying over $Na_2SO_4$. 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.**[18] By a similar procedure for **4g**, a mixture of 3-(*o*-chlorophenyl)-1-phenyl-2-propen-1-one[19] (3.191 g, 13.1 mmol), acetophenone (1.221 g, 10 mmol), and $BF_3 \cdot OEt_2$ (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 $C_{23}H_{16}OClBF_4$: 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.**[20] 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 $NaHCO_3$, and the aqueous phase was acidified with hydrochloric acid. The product was extracted with dichloromethane prior to drying over $MgSO_4$. 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 $TiCl_4$ (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 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=6.99 (1H, d, $J$=16.4 Hz), 7.21—8.11 (20H, m), 8.28 (1H, dd, $J$=16.4, 1.4 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$=124.2—146.4, 180.3 ($J_{P-C}$=8.5 Hz, C=N); $^{31}P$ NMR ($CDCl_3$) $\delta$=19.0; MS $m/z$ (rel intensity) 407 ($M^+$, 60), 206 (86), 77 (100); HR-MS Found: 407.1426. Calcd for $C_{27}H_{22}NOP$: 407.1439. Found: C, 79.74; H, 5.51; N, 3.33%. Calcd for $C_{27}H_{22}NOP$: C, 79.59; H, 5.44; N, 3.44%.

**Reaction of the Ethanimine 2 and the Propenimine 7a.** A mixture of the ethanimine **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 $NaHCO_3$ and water, then dried over $Na_2SO_4$. 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-phenylethanimine (13).**[9] 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*-toluenesulfinyl chloride[21] (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 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$=2.42 (3H, s), 2.96 (3H, s), 7.12—7.58 (5H, m), 7.80—8.00 (4H, m); $^{13}C$ NMR ($CDCl_3$) $\delta$=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 ($M^+$, 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**[9] (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.

Financial support for T. K. by Grant-in-Aid for Encouragement of Young Scientist (No. 01740303, 1989—1990) from the Ministry of Education, Science and Culture is acknowledged.

## References

1) T. Kobayashi, H. Kawate, H. Kakiuchi, and H. Kato, *Bull. Chem. Soc. Jpn.*, **63**, 1937 (1990).

2) J. L. Ripoll, H. Lebrun, and A. Thuillier, *Tetrahedron*, **36**, 2497 (1980).

3) R. J. P. Corriu, V. Huynh, J. J. E. Moreau, and M. Pataud-Sat, *Tetrahedron Lett.*, **23**, 3257 (1982); R. J. P. Corriu, J. J. E. Moreau, and M. Pataud-Sat, *J. Org. Chem.*, **55**, 2878 (1990).

4) S. Tomoda, Y. Matsumoto, Y. Takeuchi, and Y. Nomura, *Chem. Lett.*, **1986**, 1193.

5) J. Barluenga, M. Ferrero, and F. Palacios, *Tetrahedron Lett.*, **29**, 4863 (1988); *idem.*, *J. Chem. Soc., Perkin Trans. 1*, **1990**, 2193.

6) B. Krzyzanowska and W. J. Stec, *Synthesis*, **1982**, 270.

7) The Diels-Alder reaction of an *N*-phosphinyl-1-azadiene with vinyl ethers under high pressure conditions has been reported: D. L. Boger and A. M. Kasper, *J. Am. Chem. Soc.*, **111**, 1517 (1989).

8) W. B. Jennings and C. J. Lovely, *Tetrahedron Lett.*, **29**, 3725 (1988).

9) C. Brown, R. F. Hudson, and K. A. F. Record, *J. Chem. Soc., Perkin Trans. 2*, **1978**, 822.

10) Instruments used in this work and general conditions are described in Ref. 1.

11) A. R. Katritzky, D. E. Leaby, A. Maguestiau, and R. Hamming, *J. Chem. Soc., Perkin Trans. 1*, **1983**, 45.

12) R. Lombard and J.-P. Stephan, *Bull. Soc. Chim. Fr.*, **1958**, 1458.

13) R. L. Frank and R. P. Seven, *J. Am. Chem. Soc.*, **71**, 2629 (1949).

14) G. N. Dorofeenko and S. V. Krivum, *Zh. Obshch. Khim.*, **34**, 105 (1964).

15) N. S. Prostakov, G. A. Vasilev, V. P. Zvolinskü, A. V. Vorlanov, A. A. Savina, O. I. Sorolin, and N. D. Lopatina, *Khim. Geterotsikl. Soedin.*, **1975**, 1112.

16) W. A. Higgins, P. W. Vogel, and W. G. Craig, *J. Am. Chem. Soc.*, **77**, 1864 (1955).

17) N. Kreutzkamp and H. Schindler, *Arch. Pharm. (Weinheim)*, **293**, 296 (1960).

18) A. R. Katritzky, A. M. El-Mowafy, G. Musumarra, K. Sakizadeh, C. Sana-Ullah, S. M. M. El-Shafie, and S. S. Thind, *J. Org. Chem.*, **46**, 3823 (1981).

19) K. T. Potts and R. Robinson, *J. Chem. Soc.*, **1955**, 2466.

20) For the preparation of the phosphine oxide **11** and its conversion to the phosphinic acid **5** under basic conditions, see: R. C. Miller, *J. Org. Chem.*, **24**, 2013 (1959).

21) F. Kurzer, *Org. Synth.*, Coll. Vol. IV, 937 (1963).