65-66 °C; ^{1}H NMR ($CDCl_3$) δ 1.53 (d, 3H, *J*=6.3 Hz), 2.87 (dd, 1H, *J*=15.9, 7.2 Hz), 3.40 (dd, 1H, *J*=15.9, 8.4 Hz), 5.22 (m, 1H), 6.87 (dd, 1H, *J*=8.4, 7.2 Hz), 7.38 (dd, 1H, *J*=7.2, 1.2 Hz), 7.85 (dd, 1H, *J*=8.4, 1.2 Hz); Mass m/e (%) 77 (88), 103 (31), 117 (23), 132 (100), 162 (21), 179 (53, M^+).

The following compounds (**2b-2d** and **6**) were obtained using the above procedure.

2,2-Dimethyl-7-nitro-2,3-dihydrobenzo[*b*]furan (2b): yield 90%; mp 62-63 °C; ^{1}H NMR ($CDCl_3$) δ 1.55 (s, 6H), 3.07 (s, 2H), 6.85 (dd, 1H, *J*=8.4, 7.2 Hz), 7.36 (dd, 1H, *J*=7.2 Hz, 1.2 Hz), 7.86 (dd, 1H, *J*=8.4, 1.2 Hz); Mass m/e (%) 51 (82), 63 (30), 77 (58), 91 (32), 103 (29), 115 (43), 131 (100), 146 (72), 176 (69), 193 (48, M^+).

2,3-Dimethyl-7-nitro-2,3-dihydrobenzo[*b*]furan (2c): yield 95%; yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.35 (d, 3H, *J*=7.0 Hz), 1.56 (d, 3H, *J*=6.6 Hz), 3.12 (m, 1H), 4.63 (m, 1H), 6.92 (dd, 1H, *J*=8.4, 7.2 Hz), 7.43 (dd, 1H, *J*=7.2, 1.2 Hz), 7.90 (dd, 1H, *J*=8.4, 1.2 Hz); Mass m/e (%) 51 (62), 63 (36), 77 (49), 91 (45), 103 (27), 115 (20), 131 (100), 146 (43), 176 (27), 193 (57, M^+).

2-Ethyl-7-nitro-2,3-dihydrobenzo[*b*]furan (2d): yield 24%; yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.06 (t, 3H, *J*=7.4 Hz), 1.75-2.02 (m, 2H), 2.96 (dd, 1H, *J*=16.0, 7.4 Hz), 3.38 (dd, 1H, *J*=16.0, 9.2 Hz), 5.03 (m, 1H), 6.89 (dd, 1H, *J*=8.4, 7.2 Hz), 7.40 (dd, 1H, *J*=7.2, 1.2 Hz), 7.89 (dd, 1H, *J*=8.4, 1.2 Hz); Mass m/e (%) 131 (100), 146 (63), 176 (38), 193 (63, M^+).

2-Methyl-8-nitro-3,4-dihydro-2*H*-1-benzopyran (6): yield 60%; yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.46 (d, 3H, *J*=6.4 Hz), 1.82 (m, 1H), 2.10 (m, 1H), 2.84-2.92 (m, 2H), 4.30 (m, 1H), 6.86 (dd, 1H, *J*=8.0, 7.2 Hz), 7.25 (dd, 1H, *J*=7.2, 0.8 Hz), 7.63 (dd, 1H, *J*=8.0, 0.8 Hz); Mass m/e (%) 105 (35), 130 (40), 131 (77), 135 (21), 152 (100), 176 (31) 193 (68, M^+).

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Palladium-Catalyzed Phosphonation of Heterocyclic Compounds Containing Nitrogen and Sulfur

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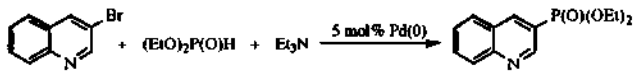
Although Arbuzov and Michaelis-Becker reactions are one of the most common methods for the formation of carbon-phosphorus bonds, they are not applicable to the formation of sp^2 hybridized carbon-phosphorus bonds.[1] Only a few methods to prepare arylphosphonates and vinylphosphonates have been reported.[2] Furthermore, these methods suffer from separation problems and the use of rather expensive reagents. T. Hirao reported the palladium-catalyzed sp^2 hybridized carbon-phosphorus bond formation.[3] However, the only one example of sp^2 hybridized carbon including heterocycles-phosphorus bond formation was repotred.[3] Recently we have studied the synthesis of heterocyclic aromatic phosphonate and their related derivatives in connection with our research program toward functionalization of heterocyclic aromatic compounds and studying the behavior of heterocyclic aromatic organophosphorus compounds with enzyme. Also, various phosphonates have been reported as having antagonistic and inhibitory effects.[1] In this paper, we wish to report palladium catalyzed phosphonation of heterocyclic aromatic compounds containing nitrogen and sulfur.

In order to access to the phosphonation, we began our stu-

Table 1. Palladium-Catalyzed Phosphonation of 3-Bromoquinoline



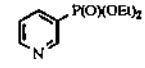
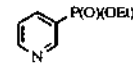
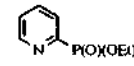
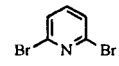
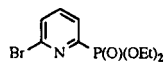
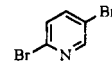
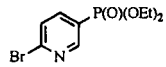
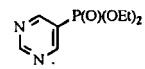
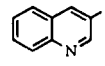
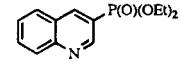
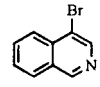
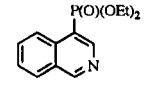
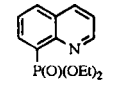
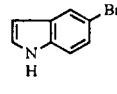
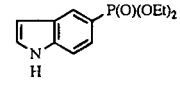
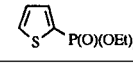
Pd(0)	Solvent	Temp (°C)	Time (h)	Isolated yield (%)[a]
$Pd_2dba_3CHCl_3/8PPh_3$	THF	25	32	5
	THF	65	4	85
	THF	65	32	37[b] (59)
	DMSO	25	24	5
	DMSO	80	3	80
	$PhCH_3$	80	3	85
$Pd_2dba_3CHCl_3/7(i\text{-}PrO)_3P$	THF	65	26	73
$Pd(OAc)_2/6(i\text{-}PrO)_3P$	THF	65	40	53
$Pd(OAc)_2/12(i\text{-}PrO)_3P$	THF	65	48	7(72)

[a] The numbers in parentheses indicate the recovered yield of starting material. [b] 1 mol% $Pd_2dba_3CHCl_3$ was used.

dies by mixing 3-bromoquinoline with diethyl phosphite and triethylamine in the presence of 5 mol% Pd(0) catalyst in THF at room temperature for 32 h. Although the reaction proceeded to some extent, the phosphonation product was obtained in less than 5% yield. When the same reaction was carried out in THF at 65 °C for 4 h, the desired compound was obtained in 85% yield. Also, DMSO and toluene were effective to yield the corresponding phosphorus compound in 80% and 85% yield, respectively, in 80 °C for 3 h. Use of triisopropyl phosphite was less effective than triphenylphosphine. Pd(0) catalyst derived from palladium acetate and triisopropyl phosphite gave the desired compound in 53% yield. The effect of solvent and Pd catalyst was shown in Table 1.

To determine the scope and limitations of the present method, the reaction was carried out with several structurally different N-containing heteroaryl bromide using diethyl phosphite and triethylamine in the presence of 5 mol% Pd(0) catalyst in THF at 65 °C and experimental results are shown in Table 2. When 3-bromopyridine (Table 2, entry 1) was treated with diethyl phosphite under the similar conditions, the desired product was isolated in 79% yield. However, when the same reaction was carried out with 3-chloropyridine (Table 2, entry 2), the reaction was not proceeded. It should be noted that 2,6-dibromopyridine (Table 2, entry 4) reacted with 1 equiv of diethyl phosphite to yield 2-bromo-6-diethoxyphosphorylpyridine in 51% yield whereas 2-bromopyridine (Table 2, entry 3) didn't react with diethyl phosphite. 2,5-Dibromopyridine (Table 2, entry 5) was treated with 1 equiv of diethyl phosphite to produce regioselectively 2-bromo-5-diethoxyphosphorylpyridine in 55% yield. This result means that bromide at 3-position of pyridine is more reactive than that at 2-position. In case of 5-bromopyrimidine (Table 2, entry 6), 5-diethoxyphosphorylpyrimidine was obtained in 70% yield. 4-Bromoisoquinoline (Table 2, entry 8) reacted with diethyl phosphite to produce the desired compound in 84% yield. Also, 8-bromoquinoline reacted with diethyl phosphite to produce 8-diethoxyphosphorylquinoline in 75% yield. The present method reaches a limit with 5-bromoindole (Table 2, entry 10). 2-Bromothiophene produced the desired compound in 59% yield (Table 2, entry 11). The results described here show the preparative method of heterocyclic aromatic phosphonates containing N and S from the corresponding bromide via palladium-catalyzed coupling with diethyl phosphite.

Table 2. Palladium-Catalyzed Phosphonation of Heterocyclic Compounds

Entry	Heterocyclic compound	Temp (°C)	Time (h)	Product	Isolated yield (%)[a]
1		65	5		79
2		65	5		0
3		65	5		0
4		85	8		51[b]
5		80	43		55[b]
6		65	4		70
7		65	4		85
8		65	45		84
9		85	9		75[b]
10		90	44		33(51)
11		85	5		59[b]

[a] The numbers in parentheses indicate the recovered yield of starting material. [b] Toluene was used.

Experimental

3-Diethoxyphosphorylquinoline[4]

To a solution of tris(dibenzylideneacetone)dipalladium(0) chloroform (20.7 mg, 0.02 mmol) and triphenylphosphine (42.0 mg, 0.16 mmol) in THF (2 mL) was added successively diethyl phosphite (58.0 mg, 0.42 mmol), triethylamine (52.5 mg, 0.42 mmol) and 3-bromoquinoline (83.2 mg, 0.4 mmol) under nitrogen atmosphere. The reaction mixture was stirred at 65 °C for 4h. After the addition of ether (10 mL), triethylamine hydrogen bromide was removed by filteration. The filterate was concentrated under reduced pressure and purified by column chromatography

using EtOAc/Hexane=1/5 as eluant on silica gel to give 3-diethoxyphosphorylquinoline 89.9 mg (85%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.12 (br s, 1H), 8.68 (d, *J*=14.89 Hz, 1H), 8.13 (d, *J*=8.56 Hz, 1H), 7.88 (d, *J*=8.21 Hz, 1H), 7.81 (t, *J* =8.07 Hz, 1H), 7.60 (t, *J*=8.00 Hz, 1H), 4.27-4.06 (m, 4H), 1.32 (t, *J*=7.10 Hz, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 150.8, 150.6, 149.4, 142.3, 142.1, 132.0, 129.5, 128.8, 127.7, 62.7, 62.6, 16.4, 16.2. IR (film) 1250 (P=O st), 1115 (P-O-C st) cm^{-1}. MS (m/e, %): 266 (M^++1, 27), 265 (M^+, 100).

4-Diethoxyphosphorylisoquinoline. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.38 (br s, 1H), 9.04 (d, *J*=9.31 Hz, 1H), 8.46 (d, *J*=8.68 Hz, 1H), 8.02 (d, *J*=8.21 Hz, 1H), 7.82 (t, *J* =7.73 Hz, 1H), 7.67 (t, *J*=7.45 Hz, 1H), 4.32-4.01 (m, 4H), 1.30 (t, *J*=7.07 Hz, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.7, 156.6, 148.6, 148.2, 131.3, 127.9, 127.3, 125.1, 125.0, 61.8, 61.7, 15.5, 15.4. IR (film) 1259 (P=O st), 1017 (P-O-C st) cm^{-1}. MS (m/e, %): 266 (M^++1, 27), 265 (M^+, 100).

8-Diethoxyphosphorylquinoline. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.06 (d, *J*=3.24 Hz, 1H), 8.38 (dd, *J*=15.82, 7.13 Hz, 1H), 8.18 (d, *J*=8.28 Hz, 1H), 7.99 (d, *J*=8.07 Hz, 1H), 7.59 (dt, *J*=3.52, 7.57 Hz, 1H), 7.45 (dd, *J*=8.28, 4.20 Hz, 1H), 4.40-4.20 (m, 4H), 1.34 (t, *J*=7.11 Hz, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 151.2, 136.9, 136.8, 136.4, 133.0, 132.9, 125.9, 125.6, 121.7, 62.6, 62.5, 16.5, 16.3. IR (film) 1240 (P=O st), 1013 (P-O-C st) cm^{-1}. MS (m/e, %): 265 (M^+, 2), 129 (100).

3-Diethoxyphosphorylpyridine. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.93 (d, *J*=6.34 Hz, 1H), 8.74-8.71 (m, 1H), 8.10 (dd, *J*=13.35, 7.76 Hz, 1H), 7.40-7.32 (m, 1H), 4.21-4.01 (m, 4H), 1.30 (t, *J*=7.07 Hz, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.1, 152.5, 152.2, 139.7, 139.5, 123.6, 123.4, 62.6, 62.5, 16.3, 16.2. IR (film) 1263 (P=O st), 1020 (P-O-C st) cm^{-1}. MS (m/e, %): 216 (M^++1, 14), 215 (40), 160 (100).

2-Bromo-6-diethoxyphosphorylpyridine. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.88 (dt, *J*=1.86, 6.58 Hz, 1H), 7.67 (d, *J*=8.00 Hz, 1H), 7.61-7.58 (m, 1H), 4.31-4.12 (m, 4H), 1.33 (t, *J*=7.00 Hz, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 143. 4, 142.9, 138.6, 138.3, 131.0, 130.9, 127.4, 126.9, 63.5, 63.4, 16.3, 16.2. IR (film) 1255 (P=O st), 1000 (P-O-C st) cm^{-1}. MS (m/e, %): 251 (M^+-EtO, 27), 249 (28).

2-Bromo-5-diethoxyphosphorylpyridine. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.81 (d, *J*=1.80 Hz, 1H), 7.96-7.78 (m, 2H), 4.28-4.08 (m, 4H), 1.30 (t, *J*=7.04 Hz, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 152.0, 151.5, 139.0, 138.7, 129.5, 129.0, 63.2, 63.0, 16.3, 16.2. IR (film) 1253 (P=O st), 1005 (P-O-C st) cm^{-1}. MS (m/e, %): 294 (M^++5).

5-Diethoxyphosphorylpyrimidine. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.33 (d, *J*=3.52 Hz, 1H), 9.04 (d, *J*=6.76 Hz, 1H), 4.31-4.04 (m, 4H), 1.33 (t, *J*=78.11 Hz, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.2, 159.8, 159.6, 63.0, 62.9, 16.3, 16.2. IR (film) 1258 (P=O st), 1002 (P-O-C st) cm^{-1}. MS (m/e, %): 217 (M^++1, 7), 216 (M^+, 19).

5-Diethoxyphosphorylindole. ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.30 (br s, 1H), 8.18 (d, *J*=14.35 Hz, 1H), 7.54-7.44 (m, 2H), 7.28 (t, *J*=2.86 Hz, 1H), 6.58 (s, 1H), 4.21-4.00 (m, 4H), 1.31 (t, *J*=7.07 Hz, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.5, 138.4, 127.9, 127.5, 126.4, 126.2, 126.0, 124.3, 124.1, 112.2, 111.8, 102.8, 62.1, 62.0, 16.4, 16.2. IR (film) 1238 (P=O st), 1020 (P-O-C st) cm^{-1}. MS (m/e, %): 254 (M^++1, 4), 253 (M^+, 27).

2-Diethoxyphosphorylthiophene. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.71-7.61 (m, 2H), 7.20-7.14 (m, 1H), 4.22-4.02 (m, 4H), 1.31 (t, *J*=7.03 Hz, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.0, 136.7, 133.6, 133.5, 128.4, 128.0, 62.7, 62.6, 16.3, 16.2. IR (film) 1259 (P=O st), 1008 (P-O-C st) cm^{-1}. MS (m/e, %): 221 (M^++1, 12), 220 (M^+, 77).

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4. Pd catalysts and heterocycles were purchased from Aldrich. Diethyl phosphite and triethylamine were obtained from commercial suppliers and used with purification.