Direct Phosphonylation of Mono- and Dihalogenoanilines

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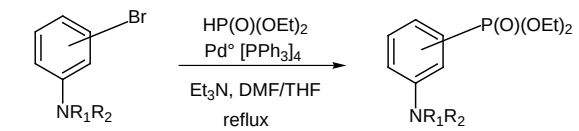
Abstract: The Pd(0)-catalyzed coupling reaction of diethyl phosphite to bromoaniline precursors or derivatives could not be realized at the *ortho*-position. On the other hand, the photoactivated substitution with diethyl phosphite anion was readily applied to unprotected mono- and dihalogenoanilines; the *ortho*-substitution was more rapid than the *para*, but side-products resulting from dehalogenation reactions were also formed. New fluorophosphonoanilines **8** and diphosphonoanilines **9** have been prepared.

Key words: photoactivated substitution, aromatic nucleophilic substitution, diethylphosphite anion, di[(diethyl)phosphono]anilines, fluoro(diethyl)phosphono-anilines

As part of a program in medicinal chemistry, we required several phosphonoaniline building blocks exemplified by the compounds **8a,b** and **9a,b** (Figure 2). According to the literature, phosphonylation of aromatic compounds can be realized under various experimental conditions, including: (i) the substitution of aryl halides with trialkyl phosphites (Arbuzov-type reaction) in the presence of nickel [1–3] or copper[4,5] catalysts; (ii) the coupling of aryl bromides or triflates with dialkyl phosphites in the presence of palladium catalyst (Heck-type reaction);[6,7] (iii) the reaction of diaryliodonium salts with trialkyl phosphites or dialkyl phosphite salts;[8,9] (iv) the quenching of aryllithium derivatives with diethyl chlorophosphate;[10] (v) the dediazoniation of aryldiazonium salts with phosphorus trichloride[11], alkyl phosphorodichloridites,[12] or trialkyl phosphites;[13] (vi) the anodic[14,15] or chemical oxidation[15,16] of a mixture of arenes and tri- or dialkyl phosphites; (vii) the rearrangement of aryl phosphoramidates,[17] aryl phosphates,[18] and aryl thiophosphates[19] into *ortho*-substituted aryl phosphonates; and (viii) the photostimulated condensation of aryl iodides with trialkyl phosphites,[20] or dialkyl phosphite salts.[21–25]

Among the listed methods, a few of them have been used for the phosphonylation of *N*,*N*-dialkyl or *N*-acylaniline derivatives.[1,5,6,15,17,25] More interesting, the photoactivated substitution of aryl iodides has been scarcely considered with phosphorus reagents in the case of unprotected anilines.[26–28]

We first examined the possibility to apply the Pd(0)-catalyzed coupling of diethyl phosphite to bromonitrobenzene (formal precursor of aniline) and *N*-protected bromoanilines (Scheme 1). Using the experimental conditions of Hirao,[6] and a THF/DMF mixture (5:1) as solvent, we could obtain diethyl *p*-nitrobenzenephosphonate in 80% yield by substitution of *p*-nitrobromobenzene (Lit.[6] 76%). However, in a similar way we were unable to isolate diethyl *o*-nitrobenzenephosphonate starting from *o*-nitrobromobenzene. The same disappointing observation was made with the *N*-protected *o*-bromoanilines. The *p*-substituted derivatives, *N*-(methyloxycarbonyl)- and *N*,*N*-(dibenzyl) bromoanilines, could be substituted with diethyl phosphite to furnish 4-(diethyl)phosphono-*N*-(methoxycarbonyl)aniline and 4-(diethyl)phosphono-*N*,*N*-(dibenzyl)aniline in 60 and 45% yield, respectively (Scheme 1). But the corresponding *o*-substituted derivatives could not be prepared by this method; only untractable mixtures were obtained. The reaction also failed with parent *o*- and *p*-bromoanilines. Our results in the *para*-series are consistent with the fact that the Pd(0)-catalyzed vinylic substitution reaction is generally activated by electron-withdrawing substituents and precluded by strongly electron-donating substituents.[29] The origin of the negative results we collected in the *ortho*-series has not been clarified. Therefore, we abandoned this method and turned to the photoactivated substitution which could be performed without protection of the aniline function.[26]



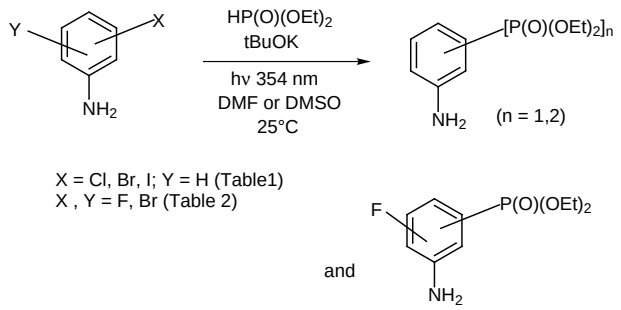
R^1, R^2 = O_2
R^1 = H; R^2 = CO_2Me
R^1 = R^2 = CH_2Ph

para : 80% - 45%
ortho : 0%

Scheme 1

We systematically re-examined the photoactivated substitution of *para*-[26] and *ortho*-[30] iodoanilines **1a** and **2a** with diethyl phosphite anions (Scheme 2 and Figure 1). In these former reports, the reactions were conducted in liquid ammonia, under irradiation with a high (or medium) pressure mercury vapor lamp.

Using THF, acetonitrile or DMF as solvent, we tried to substitute **1a** with sodium diethyl phosphite (prepared in situ from diethyl phosphite and sodium hydride), by acti-



Scheme 2

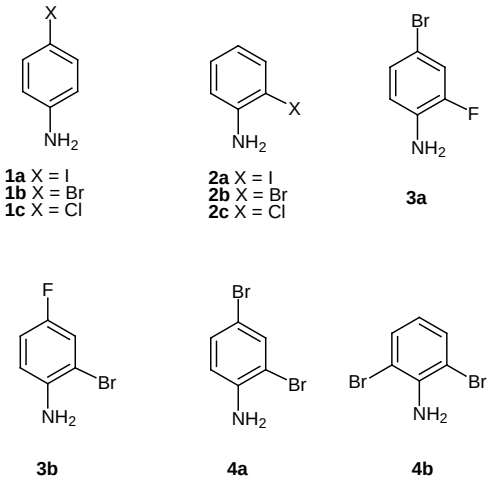


Figure 1 List of starting materials used in the coupling reaction

in DMSO allowed to significantly increase the yield of phosphonoaniline **5** (Table 1, Entry 3). The diminution of irradiation wattage increased the reaction time, but led to unchanged the ratios of substitution product **5** or **6** with respect to the dehalogenation product **7** (Table 1, Entries 2 and 4).

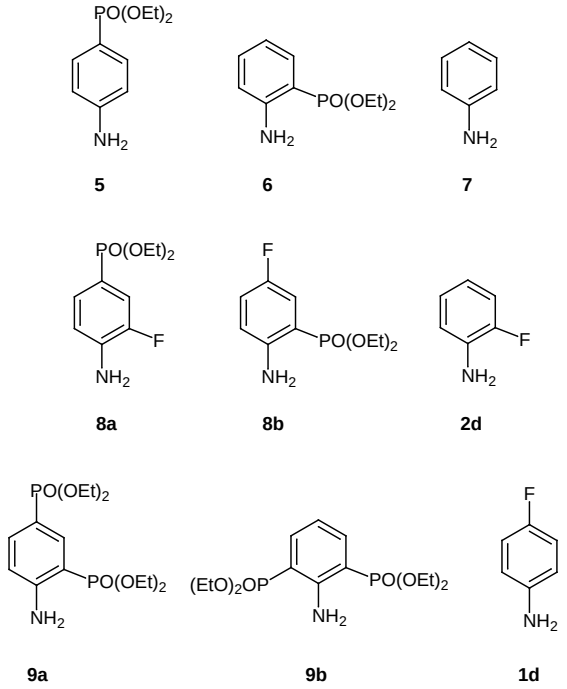


Figure 2 Substitution and dehalogenated products obtained from the coupling reaction

vation with a Heraeus TQ 150 lamp (150 W, λ = 360 nm). The reaction proceeded very slowly (several days), most probably because the medium was heterogeneous. Replacing the sodium counter-ion with potassium allowed to obtain a homogeneous mixture of reagents in DMF. The reaction of **1a** with potassium diethyl phosphite (prepared in situ from diethyl phosphite and potassium *tert*-butoxide in DMF) was complete within a few hours. However, problems of reproducibility appeared, mainly depending on the ageing of the mercury vapor lamp: significant variations in the reaction times and the occurrence of side-products were observed. Finally, we could obtain reproducible results using the Rayonet photochemical reactor. The standard conditions for the coupling reaction are exemplified in the case of 4-iodoaniline **(1a)**: a solution of 4-iodoaniline **(1a)** in DMF (final concentration of 0.6 M) was treated with a preformed mixture of diethyl phosphite (6 equiv) and potassium *tert*-butoxide (5 equiv) in DMF at 25°C under irradiation with 6 Rayonet lamps of 25 W at 354 nm. After 1.5 hours, two products were formed in 42:58 ratio, namely the 4-(diethyl)phosphonoaniline **(5)**[11] and aniline **(7)** (Table 1, Entry 1; Figure 2). Similar treatment of 2-iodoaniline **(2a)** gave, after 1 hour, 2-(diethyl)phosphonoaniline **(6)**[27] and aniline **(7)** in 75:25 ratio. (Table 1, Entry 6; Figure 2). The reaction of **1a** conducted

We also tested the reactivity of bromo- and chloroanilines under our standard conditions. *p*-Bromoaniline **(1b)** gave 30% of 4-aminophosphonate **5** after 20 hours of reaction (Table 1, Entry 5), while 2-bromoaniline **(2b)** furnished 63% of 2-aminophosphonate **6** after only 3 hours of reaction (Table 1, Entry 7). The chloroanilines **1c** and **2c** were found to be reluctant toward the photoactivated substitution: after one day of reaction, complex mixtures were recovered, containing traces of the expected products **5** and **6**. Our model study pointed out the possibility to consider bromoanilines as good precursors (often more easily accessible than the corresponding iodo derivatives) for the photoactivated substitution with phosphite anion, and the higher reactivity of the *ortho*-halogenoanilines over the *para*-regioisomers. Accordingly, we performed the substitution reaction with potassium diethyl phosphite starting from the commercially available disubstituted anilines **3** and **4** (Figure 1). Thus, the reaction of 4-bromo-2-fluoroaniline **(3a)** in DMF (standard conditions) gave 4-(diethyl)phosphono-2-fluoroaniline **(8a)** as the main product, and 2-fluoroaniline **(2d)** and 4-(diethyl)phosphonoaniline **(5)** as side-products (Table 2, Entry 1, Figure 2); a very similar ratio of products was obtained in DMSO (Table 2., Entry 2). The reaction of 2-bromo-4-fluoroaniline **(3b)** in DMF or DMSO afforded 2-(dieth-

Table 1 Reaction of Monosubstituted Anilines

Entry	Starting Material	Conditions[a]			Products (%)[b]		
		Solvent	hν[c]	Time	**5**	**6**	**7**
1	**1a**	DMF	6	1 h 30 min	42	–	58
2	**1a**	DMF	2	5 h	42	–	58
3	**1a**	DMSO	4	2 h 15 min	70	–	30
4	**1a**	DMSO	2	4 h	70	–	70
5	**1b**	DMF	6	20 h	30	–	70
6	**2a**	DMF	6	1 h	–	75	25
7	**2b**	DMF	6	3 h	–	63	37

[a] $(EtO)_2POH$ (6 equiv), *t*-BuOK (5 equiv), **1 2** (1 equiv).
[b] ^1H NMR analysis of the crude mixtures; % calculated from integration of aromatic protons (mean error ± 2%).
[c] Number of lamps of 25 W.

Table 2 Reaction of Disubstituted Anilines

Entry	Starting material	Reaction Conditions[a]			Products (%)[b]								
		Solvent	hν[c]	Time	**8a**	**8b**	**9a**	**9b**	**1d**	**2d**	**5**	**6**	Others
1	**3a**	DMF	8	3 h 15 min	52	–	–	–	–	39	9	–	–
2	**3a**	DMSO	8	8 h	60	–	–	–	–	27	13	–	–
3	**3b**	DMF	8	2 h	–	63	–	–	37	–	–	0	–
4	**3b**	DMSO	8	3 h 40 min	–	74	–	–	26	–	–	0	–
5	**4a**	DMF	6	5 h	–	–	43	–	–	–	11	30	16 (**4a**)
6	**4b**	DMF	6	1 h	–	–	–	32	–	–	–	55	13 (**7**)

[a–c] For footnotes a–c, see Table 1.

Table 3 ^1H NMR Data of **8a**,**b** and **9a**,**b** (500 MHz, $CDCl_3$/TMS) δ, *J* CHz)

Product	H-3	H-5	H-4 or H-6	NH_2	OCH_2	CH_3
8a	7.18 (m)	7.18 (m)	6.81 (ddd, $J_{H,H}$ = 8.6, $J_{H,F}$ = 8.6, $J_{H,P}$ = 5.1	5.90 (s)	3.91 (m)	1.18 (t, $J_{H,H}$ = 7.4)
8b	7.13 (ddd, $J_{H,H}$ = 3.1, $J_{H,F}$ = 8.2, $J_{H,P}$ = 15.1)	7.00 (ddd, $J_{H,H}$ = 3.1, 8.6, $J_{H,F}$ = 8.2)	6.60 (ddd, $J_{H,H}$ = 8.6, $J_{H,F}$ = 7.6, $J_{H,P}$ = 4.1)	4.67 (br)	4.06–4.14 (m)	1.32 (t, $J_{H,H}$ = 7.4)
9a	7.85 (dt, $J_{H,H}$ = 2.0, $J_{H,P}$ = 13.9)	7.60 (ddd, $J_{H,H}$ = 2.0, 8.7, $J_{H,P}$ = 13.9)	6.66 (ddd, $J_{H,H}$ = 8.7, $J_{H,P}$ = 3.5, 6.1)	5.69 (s)	4.06 (m)	1.30 (t, $J_{H,H}$ = 7.4)
9b	7.63 (dd, $J_{H,H}$ = 7.9, $J_{H,P}$ = 16.2)	–	6.66 (m)	6.73 (s)	4.05–4.14 (m)	1.32 (t, $J_{H,H}$ = 7.4)

yl)phosphono-4-fluoroaniline **(8b)** in about 70% yield; the only side-product was 4-fluoroaniline (**1d)** (Table 2, Entries 3 and 4).

Diphosphonoanilines **9** could also be prepared from dibromoanilines **4**. Thus the photosubstitution of the 2,4-dibromo precursor **4a** (Figure 1) led to the formation of 43% of 2,4-[di(diethyl)phosphono]aniline **(9a)** after 5 hours of reaction in DMF (standard conditions) together with 11 and 31% of the monophosphonoanilines **5** and **6**, respectively (Table 2, Entry 5, Figure 2). The 2,6-dibromo precursor **4b** reacted within 1 hour under similar conditions to furnish 32% of 2,6-[di(diethyl) phosphono]aniline **(9b)** together with 55% of 2-(diethyl)phosphonoaniline **(6)** and 13% of aniline **(7)**, resulting from competition with debromination reaction.

The new aniline derivatives **8a**, **8b**, **9a** and **9b** were isolated from the crude mixtures by flash chromatography and fully characterized by the usual spectroscopies. The NMR data are collected in Tables 3 and 4; the coupling constants were determined by selective decoupling experiments.

The photostimulated reaction of halogenobenzene derivatives with nucleophiles has been particularly well studied by Bunnett and coworkers.[22–25] The proposed mechanism

Table 4 ^{13}C NMR Data of **8a,b** and **9a,b** (125 MHz, $CDCl_3$/TMS), δ, *J* (Hz)

Product	C-1	C-2	C-3	C-4	C-5	C-6	OCH_2CH_3	OCH_2CH_3
8a	140.76 ($J_{C,F}$ = 12.8, $J_{C,P}$ = 2.4)	149.34 ($J_{C,F}$ = 239.3, $J_{C,P}$ = 21.3)	117.55 ($J_{C,F}$ = 18.9, $J_{C,P}$ = 10.9)	112.86 ($J_{C,F}$ = 4.3, $J_{C,P}$ = 198.3)	128.62 ($J_{C,F}$ = 2.4, $J_{C,P}$ = 10.7)	115.45 ($J_{C,F}$ = 4.2, $J_{C,P}$ = 17.1)	61.18	16.13
8b	147.38 ($J_{C,P}$ = 8.5)	108.91 ($J_{C,F}$ = 6.1, $J_{C,P}$ = 184.3)	118.21 ($J_{C,F}$ = 23.3, $J_{C,P}$ = 7.9)	154.45 ($J_{C,F}$ = 237.0, $J_{C,P}$ = 19.8)	121.25 ($J_{C,F}$ = 23.3, $J_{C,P}$ = 2.4)	117.57 ($J_{C,F}$ = 6.6, $J_{C,P}$ = 15.2)	62.18	16.13
9a	154.22 ($J_{C,P-2}$ = 7.2)	107.71 ($J_{C,P-2}$ = 184.9, $J_{C,P-4}$ = 14.4)	138.03 ($J_{C,P-2}$ = 12.7, $J_{C,P-4}$ = 9.0)	114.65 ($J_{C,P-2}$ = 14.4, $J_{C,P-4}$ = 119.3)	136.63 ($J_{C,P-4}$ = 9.0)	115.68 ($J_{C,P-2}$ = 12.6, $J_{C,P-4}$ = 14.4)	62.12–61.71	16.11
9c	154.33 ($J_{C,P-2}$ = 9.0	109.60 ($J_{C,P-2}$ = 184.9, $J_{C,P-2'}$ = 10.8)	138.62	115.04 ($J_{C,P-2}$ = 14.4)	–	–	62.11	16.11

of substitution is $S_{RN}1$, i.e. a radical chain mechanism involving electron transfer to the aryl halide, fragmentation of the resulting radical anion to an aryl radical which further reacts with the nucleophile;[24,31] the $S_{RN}2$ mechanism proposed by Denney,[32] i.e. direct reaction of the radical anion with the nucleophile, appears less plausible.[31] Our results are in good agreement with the usual pattern of the $S_{RN}1$ mechanism: (i) the order of reactivity is ArI>ArBr>>ArCl, while ArF is not substituted[23]; and (ii) the side-products result from dehalogenation reactions which could be photostimulated or not.[33–36] We have controlled that the phosphonoanilines are stable under the experimental conditions.

In the halogenoaniline series **1,2**, the *ortho*-halogen reacts faster than the *para*. This is also confirmed in the dihalogenoaniline series **3,4**, from the reaction times and the side-products distribution (%**6** > %**5**). Moreover, the presence of an electronegative substituent in *ortho*-position (F in **3a**; Br [or $PO(OEt)_2$] in **4a**), increases the reactivity of the *para*-bromine. In all cases, the substitution products are contaminated by dehalogenation products; the order of reactivity in these side reactions is ArI>ArBr>>ArF, with a particular activation of the *ortho*-position. This is clearly visible by the formation of about 10% of defluorination product **5** from the aniline precursor **3a** (Table 2; Entries 1 and 2), while the regioisomer **3b** does not produce defluorination product **6** (Table 2, Entries 3 and 4). The *ortho*-*ortho*'-dibromoaniline precursor **4b** leads mainly to debromination products **6** and **7** in 68% overal yield. Thus, from a synthetic point of view, the competition with dehalogenation reactions significantly limits the yields of phosphonylated anilines **8,9**, and requires careful chromatographic separations for the recovery of pure samples. Nevertheless, the direct photoactivated substitution of anilines **3,4** represents actually the best way to prepare our target molecules **8,9**.

Reagents and solvents were purchased from Aldrich. The IR spectra were taken with a Perkin-Elmer 1710 instrument and calibrated with polystyrene. The 1H and 13C NMR spectra were recorded on a Bruker AM-500 spectrometer in $CDCl_3$ solution. Chemical shifts are reported in ppm (δ) downfield from internal TMS. The mass spectra (FAB or EI modes) were obtained on a Finnigan MAT TSQ-70 instrument. The microanalysis were performed at the University College London (Dr. Alan Stones).

Photoactivated Substitution of Halogenoanilines 1–4 with Diethyl Phoshite; General Procedure

Into a pyrex tube (diameter: 1.5 cm; length: 18 cm) equipped with an addition funnel were successively introduced under argon atmosphere, a solution of KOBu-*t* (5 equiv) in anhyd DMF (1 mL/mmol) and diethyl phosphite (6 equiv). This mixture was stirred for 10 min at 20°C, then a solution of halogenoaniline (1 equiv) in anhyd DMF (4 mL/mmol) was added dropwise. After 15 min of degasing, the tube was closed with a septum and placed into a Rayonet photochemical reactor equipped with 6 or 8 lamps (25 W; λ = 354 nm). The reaction was followed by TLC. At the end, the reaction mixture was poured into brine (15 mL/mmol) and extracted with EtOAc (3 x 10 mL). After drying ($MgSO_4$) and concentration, the crude mixture was analyzed by NMR, and the phosphonoaniline purified by flash column chromatography on silica gel (10 g/mmol).

2-Fluoro-4-(diethyl)phosphonoaniline (8a)

Compound **8a** was prepared from **3a** (0.2 g, 1.042 mmol). Chromatography with hexane/EtOAc (40:60) gave 0.105 g of pure **8a** (30%) as a colourless oil; R_f (silica gel, hexane/EtOAc, 30:70) 0.41.

IR (film): ν = 3404, 3342, 3223, 2980, 1643, 1614, 1519, 1223, 1207, 1101, 1053, 1029 cm^{-1}.

MS(FAB^+): *m*/*z* = 248 (M^+ + 1).

Anal. calcd for $C_{10}H_{15}FNO_3P$: C, 48.59; H, 6.11; N, 5.66. Found C, 48.98; H, 6.27; N, 5.31.

4-Fluoro-2-(diethyl)phosphonoaniline (8b)

Compound **8b** was prepared from **3b** (0.3 g, 1.531 mmol). Chromatography with hexane/EtOAc (30:70) gave 0.173 g of pure **8b** (46%) as a colourless oil; R_f (silica gel, hexane/EtOAc, 30:70) 0.21; R_f (silica gel, EtOAc) 0.73.

IR (film): ν = 3436, 3341, 3232, 2983, 1635, 1419, 1229, 1021, 970 cm^{-1}.

MS(EI): *m*/*z* = 247 (M^+), 219, 191, 173, 151, 111, 83, 57.

Anal. calcd for $C_{10}H_{15}FNO_3P$: C, 48.59, H, 6.11; N, 5.66. Found C, 47.98; H, 6.15; N, 5.35.

2,4-Di[(diethyl)phosphono]aniline (9a)
Compound **9a** was prepared from **4a** (0.3 g, 1.195 mmol). Chromatography with hexane/EtOAc (from 70:30 to 30:70) gave 0.101 g of pure **9a** (23%) as a colourless oil; R_f (silica gel, hexane/EtOAc, 30:70) 0.20.

IR (film): ν = 3412, 3326, 3218, 2984, 1635, 1600, 1495, 1445, 1393, 1230, 1162, 1098, 1024, 965 cm^{-1}.

MS(FAB): *m*/*z* = 366 (M^+ + 1).

Anal. calcd for $C_{14}H_{25}NO_6P_2$: C, 46.03; H, 6.90; N, 3.83. Found C, 46.05; H, 6.78; N, 3.44.

2,6-Di[(diethyl)phosphono]aniline (9b)
Compound **9b** was prepared from **4b** (0.5 g, 1.933 mmol). Chromatography on basic alumina with hexane/EtOAc (from 70:30 to 0:100) gave a pure fraction of **9b** (0.105g, 15%) as a colourless oil; R_f (silica gel, EtOAc) 0.35.

IR (film): ν = 3421 (br), 2984, 1614, 1565, 1441, 1393, 1222, 1019, 967, 817 cm^{-1}.

MS(EI): *m*/*z* = 365 (M^+), 337, 309, 256, 228.

Anal. calcd for $C_{14}H_{25}NO_6P_2$: C, 46.03; H, 6.90; N, 3.83. Found C, 46.46; H, 6.93; N, 3.53.

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