Photostimulated synthesis of 2-(diphenylphosphino)benzoic acid by the $S_{RN}1$ reaction

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Abstract

2-(Diphenylphosphino)benzoic acid, isolated as the ester, was obtained by the photostimulated reaction of 2-chlorobenzoate ion with Ph_2P^- ions in good yield in liquid ammonia. The reaction did not occur in the dark; it was inhibited by *m*-dinitrobenzene and partially inhibited by a radical trap such as TEMPO. The results were consistent with the $S_{RN}1$ mechanism. No evidences for aromatic nucleophilic substitution (S_NAr) or benzyne mechanisms were found.

Keywords: Photostimulated reaction, electron transfer, $S_{RN}1$, triarylphosphines, ligands

Introduction

Tertiary phosphines constitute the group of ligands most widely used in transition metal-catalyzed reactions, mainly due to their electron-donating capacity and versatile tuning abilities via steric and electronic properties.[1] Accordingly, the development of new synthetic approaches to obtain organophosphines is increasingly recognized as central in the synthesis of new ligands. A variety of methods for the formation of C-P bond have been established, including direct construction via transition metal-catalyzed cross-coupling reactions,[2] or less common radical protocols.[3]

Functionalized phosphines containing hydrophilic substituent, such as diphenylphosphino benzoic acid (DPPBA) derivatives, represent a versatile family of water-soluble ligands.[2c, 4] Moreover, DPPBA has found applications as an important phosphine building block for the design of *C2*-symmetric Trost ligands,[5] a class of ligands widely applied for asymmetric Pd-catalyzed allylic substitution.[6] DPPBA has also been established as a ligand in allylic substitution.[7] Additionally, DPPBA has been used as the base for a variety of phosphine-based ligands applied to different metal-catalyzed reactions,[8] as well as a mediator in Staudinger reactions.[9]

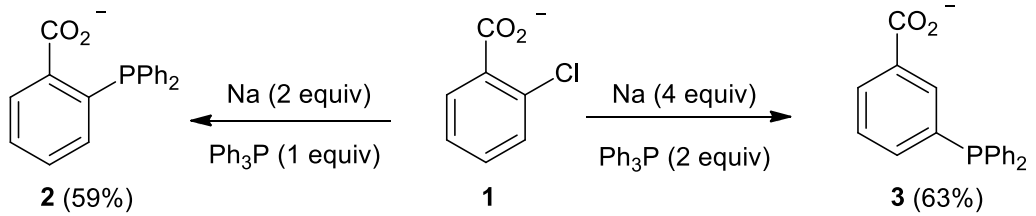
Several procedures to obtain DPPBA derivatives have been reported. One of them is the Pd-catalyzed P-C coupling reaction of ArX with Ph_2PH.[10] This process generally requires several hours or days of reaction at high temperatures. Recently, the synthesis of DPPBA by microwave heating using Pd-catalyzed cross-coupling reactions was described.[11] However, only 26% yield of the product was achieved. We reported the synthesis of DPPBA by the Pd-catalyzed phosphination with stannane *n*-Bu_3SnPPh_2 and 2-iodobenzoic acid to provide the tertiary phosphine oxide in 69% isolated yield.[12] DPPBA can also be prepared by the Ni-catalyzed cross-coupling of methyl 2-(trifluoromethyl-sulfonyloxy)benzoate with Ph_2PCl.[13] Additionally, the synthesis of DPPBA was accomplished by the nucleophilic reaction of 2-fluorobenzoate salt with Ph_2PK.[14] The DPPBA was also obtained by metal-halogen exchange in 2-bromobenzoate salt, followed by phosphorylation of the resulting 2-lithiated benzoate salt with Ph_2PCl.[15]

Normally, most of the procedures involve several steps, high temperatures, many hours of reaction and generally low overall yields. Thus, a simple, efficient and general method of synthesizing triarylphosphines would be particularly interesting. The $S_{RN}1$ reaction is an attractive synthetic alternative to obtain triarylphosphines.

The $S_{RN}1$ reaction is a process in which radicals and radical anions are intermediates, through which an aromatic nucleophilic substitution could be achieved.[16] The scope of this process has increased considerably and nowadays it serves as an important synthetic strategy. It is compatible with many substituents, and several nucleophiles, such as carbanions and heteroatom anions react to give new C-C or C-heteroatom bonds in good yields.[16]

The reactions of Ph_2P^- ions with methyl and methoxy phenyl halide derivatives,[17] naphthyl and quinolyl halides,[17b] and also diarylsulfides, sulfones, and sulfoxides[18] have been reported to afford aryldiphenylphosphines in good yields by the $S_{RN}1$ mechanism. Although these synthetic strategies are known, so far there has been no instance of the reaction of the phosphorus nucleophiles with an aromatic acid with an appropriate leaving group. In the present study, we report the $S_{RN}1$ reaction to obtain triarylphosphines with 2-chlorobenzoic acid as starting substrates.

Recently**,** the synthesis of 2- (**2**) and 3-(diphenyl-phosphino)benzoate (**3**) salts by the reaction of 2-chlorobenzoate ion (**1**) with Ph_2P^- ions in ammonia (-78 ºC) was reported. A change in the stoichiometry of Ph_2P^- ions allowed the synthesis of **2** or **3** (Scheme 1).[19]



Scheme 1. Synthesis of 2- (**2**) and 3-(diphenyl-phosphino)benzoate (**3**) salts.

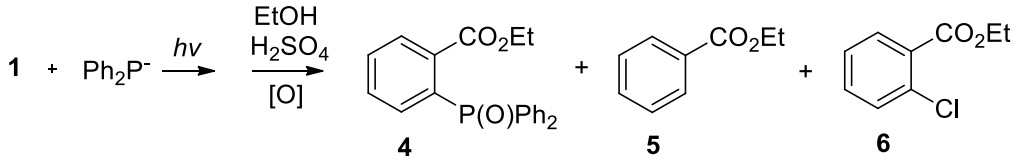
Substrate **1** was proposed to react with Ph_2P^- ions in excess through a benzyne mechanism to

achieve the *cine* substitution product **3**. On the other hand, the reaction of **1** with one equivalent of Ph_2P^- ions gave the substitution product **2** through a S_NAr type of mechanism (Scheme 1). However, mechanistic studies were not conducted.

Here we report our results on the synthesis of 2-(diphenylphosphino)benzoic acid by the photostimulated $S_{RN}1$ substitution reaction using **1** and Ph_2P^- ions as starting substrates. Our work focused on the development of a new strategy to synthesize triarylphosphines and explore the mechanism that takes place.

Results and Discussion

The Ph_2P^- ions were easily prepared in liquid ammonia (-33 ºC) by the reaction of Ph_3P with Na metal (2 equiv). The H_2N^- ions generated in the formation of Ph_2P^- ions were neutralized with *t*-BuOH.[17c] The photostimulated reaction (120 min) of **1** with the Ph_2P^- ions (1.1 equiv) was quenched with NH_4NO_3. The liquid ammonia was allowed to evaporate. The residue was treated with EtOH-H_2SO_4 to form the ester to facilitate product quantification and isolation (Equation 1).



(**1**)

Ethyl 2-(diphenylphosphoryl)benzoate (**4**) was thus obtained in 59% yield together with the reduced product ethyl benzoate (**5**, 29%) and the substrate recovered as ethyl 2-chlorobenzoate (**6**, 13%) (entry 1, Table 1). Similar results were found with 90 min and even with 120 min of irradiation, **4** was achieved in 51% yield (entries 2 and 3, Table 1). Complete conversion of **1** was accomplished when the concentrations of Ph_2P^- ions were increased to 2 equiv, and the yield of **4** was improved up to 75% (entry 4, Table 1).

In dark conditions (90 min), the reaction did not proceed and the substrate remained unaltered (entry 5, Table 1). These results excluded an aromatic nucleophilic substitution (S_NAr) or benzyne mechanisms. The fact that Ph_2P^- ions react only under photostimulation with **1** suggest that there was an electron transfer (ET) from Ph_2P^- ions to **1** under irradiation to initiate the reaction. This is highly probable because Ph_2P^- ions absorb strongly in the visible region ($\lambda >$ 350 nm),[16] being the best candidates for absorption in the common reaction conditions used.

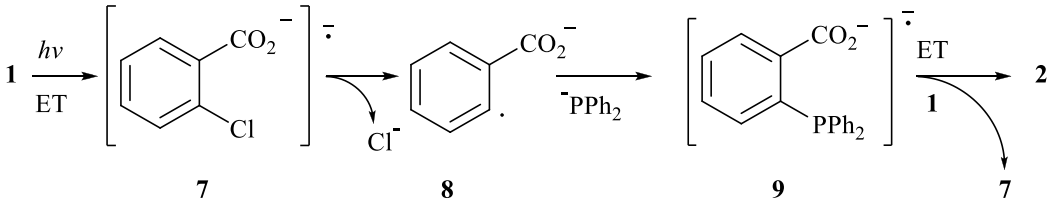
A complete inhibition of the reaction was observed when **1** was irradiated in the presence of *m*-dinitrobenzene (*m*-DNB), a good electron acceptor[16] (entry 6, Table 1). This could be attributed to electron transfer events that are being inhibited, which would indicate the occurrence of a chain mechanism. The photostimulated reaction of **1** was partially inhibited by 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (entry 7, Table 1), a free radical traps. All these results suggest that this reaction proceeds through the $S_{RN}1$ mechanism.

Table 1. Reactions of **1** with Ph_2P^- ions by $S_{RN}1$ mechanism.[a]

Entry	Conditions[a]	Cl^- (%)[b]	**4** (%)[c]	**5** (%)[c]	**6** (%)[c]
1	NH_3, hv, 60 min	nc[d]	59	29	13
2	NH_3, hv, 90 min	87	46	38	11
3	NH_3, hv, 120 min	89	51	29	12
4[e]	NH_3, hv, 120 min	102	75	26	>5
5	NH_3, dark, 90 min	>4	--	--	100
6	NH_3, hv, 90 min 30 mol % of *m*-DNB	7	>5	--	89
7	NH_3, hv, 90 min 30 mol % of TEMPO	67	37	28	28

[a] Reactions carried out under N_2 in 150 mL of liquid ammonia (-33 ºC), with 1.0 equiv of **1**, 1.1 equiv of Ph_2P^- ions, 1.1 equiv of *t*-BuOH. Irradiation was conducted in a photochemical reactor equipped with two 400 W lamps refrigerated with water unless otherwise indicated.
[b] Determined potentiometrically.
[c] Yields were determined by GC (internal standard method).
[d] Not quantified.
[e] Reaction carried out under N_2 in 150 mL of liquid ammonia, with 1 equiv of **1**, 2 equiv of Ph_2P^- ions, 2 equiv of *t*-BuOH.

We propose that **1** receives an electron from Ph_2P^- ions under irradiation to yield the radical dianion **7** (Scheme 2). Fragmentation of the C-Cl bond of **7** gives the distonic radical anion **8** and Cl^- anion. The intermediate **8** reacts with Ph_2P^- ions to afford the radical dianion **9**. An ET from **9** to **1** forms the substitution product **2** and the radical dianion **7**, propagating the reaction chain.



Scheme 2. The possible mechanism of 2-(diphenyl-phosphino)benzoate (**2**) salts formation from 2-chlorobenzoate ion (**1**).

The reaction of **1** with Ph_2P^- ions in liquid ammonia to obtain **2**, under diferent conditions of temperature, concentration, photostimulation and without adding *t*-BuOH, was reported to occur by the S_NAr mechanism.[19] However, our studies lead us to propose that the reaction occurs by the $S_{RN}1$ mechanism. To provide further evidence to support our mechanism, we conducted the experiments under the same experimental conditions as those previously reported (Table 2).

Under the same reaction conditions described, **1** was allowed to react with Ph_2P^- ions in liquid ammonia at -78 ºC under ambient light conditions.[19] The residue was treated with EtOH-H_2SO_4 to achieve the corresponding esters to facilitate the product quantification and isolation. The product **4** was obtained in 46%, together with the reduced product **5** and the unreacted substrate as **6** (compared entry 1 with entry 2, Table 2). The reaction was totally inhibited in the presence of 20 mol % *m*-DNB and partially inhibited by 20 mol % TEMPO (entries 3 and 4, Table 2). Moreover, the reaction was slower in dark conditions (compared entry 1 with entry 5, Table 2). Thus, this reaction occurs in dark conditions (thermal initiation) but is faster under the photostimulation of ambient light.[17a]

Table 2. Reactions of **1** with Ph_2P^- ions under the experimental conditions reported in ref 19

Entry	Conditions[a]	Cl^- (%)[b]	**4** (%)[c]	**5** (%)[c]	**6** (%)[c]
1	NH_3, -78 ºC, ambient light to evaporation	61	46	18	31
2[d]	NH_3, -78 ºC, ambient light to evaporation	-	59	-	-
3	NH_3, -78 ºC, ambient light to evaporation, 20 mol% of *m*-DNB	>4	-	-	ca 100
4	NH_3, -78 ºC, ambient light to evaporation, 20 mol% of TEMPO	27	7	14	56
5[e]	NH_3, -78 ºC, dark to evaporation	59	30	16	45

[a]Reactions carried out under N_2 in 10-15 mL of liquid ammonia at -78 ºC, with 1 equiv. (4.44 mmoles) of **1,** 1 equiv. (4.44 mmoles) of Ph_2P^- ions and 2.5 h of stirring before adding **1** and 0.5 h of stirring before adding of THF (6 mL).
[b]Determined potentiometrically.
[c]Yields were determined by GC (internal standard method).
[d]Reported results, see Ref. 19.
[e]2-Chlorobenzoic acid was added in one portion.

In summary, we found that the reaction was stimulated by light and that in the presence of low amounts of a good electron acceptor or TEMPO, the reaction was considerably inhibited. Accordingly, these results suggest that in these experimental conditions the reaction occurs by the $S_{RN}1$ mechanism with both thermal and photochemical initiation steps.[20] However, with an excess of amide ions, the product **3** is formed by the benzyne mechanism, as reported.[19]

Experimental Section

General. Gas chromatographic analyses were performed on a Hewlett Packard 5890 series II with a flame ionization detector and equipped with the following column: HP1 column (0.53 mm x 5 m). Quantification by GC was performed by the internal standard method. Gas Chromatographic-Mass Spectrometer analyses were carried out on a Shimadzu QP-5050 spectrometer equipped with a quadrupole detector and a VF-5 ms column (30 m x 0.25 mm x 0.25 μm). ^{1}H NMR (400.16 MHz), ^{31}P NMR (162 MHz) and ^{13}C NMR (100.62 MHz) spectra were recorded on a High Resolution Spectrometer Bruker Advance 400 in $CDCl_3$ as solvent and against internal TMS (^{1}H) and external 85% phosphoric acid (^{31}P). Coupling constants (*J*) are given in Hz units. Irradiation was conducted in a reactor equipped with two 400-W lamps of metal iodide refrigerated (Philips, Model HPI-T) with water. An Orion 420A pHmeter with Ag/Ag^+ electrode was used for the potentiometric titration of halide ions in the aqueous phases.
$PhCO_2H$, $2\text{-}ClC_6H_4CO_2H$, Na metal, Ph_3P, *t*-BuOH, NH_4NO_3, EtOH and H_2SO_4 were commercially available and used as received. THF was dried over Na metal and benzophenone, and distilled under atmosphere of N_2. All solvents were analytical grade and used as received from the supplier. Silica gel (0.063-0.200 mm Macherey-Nagel) was used in column chromatography. **5** and **6** were prepared according to the literature procedure.[21]

Ethyl 2-(diphenylphosphoryl)benzoate (4)[22]: Representative procedure for photostimulated reactions of 1 with Ph_2P^- ions in liquid ammonia

Ammonia (150 mL), previously dried with Na metal under N_2, was condensed into a 250 mL three-necked, round-bottomed flask equipped with a coldfinger condenser charged with ethanol, a nitrogen inlet, and a magnetic stirrer. PPh_3 (0.144 g, 0.55 mmol) was then added, and Na metal was introduced in small pieces; addition was continued until the solution kept its dark brown color for at least 15 min. After its color turned red, *t*-BuOH (0.5 mL, 0.55 mmol) was added to eliminate the H_2N^- anions formed. An orange solution of Ph_2P^- ions was obtained. 2-Chlorobenzoic acid was added to the solution to form **1** (0.078 g, 0.50 mmol), and the mixture was irradiated for 120 min with two metal iodide lamps of 400 W refrigerated with water. The reaction was quenched with an excess of NH_4NO_3 and the ammonia was allowed to evaporate. Water (50 mL) was added to the residue and SO_4H_2 was afterwards added until the aqueous phase reached pH 1-2. The aqueous phase was extrated with ethyl acetate (3 x 30 mL) and the combined organic layers were washed with H_2O (20 mL) and dried over anhydrous $MgSO_4$; the solvent was evaporated under vacuum. The chloride ions in the aqueous solution were determined by potentiometry.
The crude products were mixed with EtOH (1.8 mL, 30.8 mmol) and concentrate H_2SO_4 (0.05 mL, 0.94 mmol) in a 10 mL tube sealed and equipped with a magnetic stirrer. The mixture was heated to 80 °C for 4 days. The excess of EtOH was eliminated on a rotary evaporator and allowed cooling. The residue was dissolved with water (50 mL) and $NaHCO_3$ was then added until reaching pH 8-9.

The aqueous phase was extracted with ethyl acetate (3 x 30 mL) and the combined organic layers were washed with H_2O (20 mL), dried over anhydrous $MgSO_4$ and then quantified by GC using the internal standard method.

Alternatively, the solvent was removed under reduced pressure and the product was purified by column chromatography on silica gel eluting with a dichloromethane/etanol gradient (100:0 → 95:5) as a colourless liquid. ^{1}H NMR (400.16 MHz, $CDCl_3$): δ_H 7.92-7.89 (1H_{aro}, m, 1CH), 7.69-7.43 (13 H_{aro}, m, 13CH), 3.97 (2H, q, J_{HH} = 7.2 Hz, CH_2CH_3), 1.00 (3H, t, J_{HH} = 7.2 Hz, CH_2CH_3). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ_C 167.26 (d, *J* = 3 Hz), 136.45 (d, *J* = 6 Hz), 134.76 (d, *J* = 10 Hz), 133.48 (d, *J* = 108 Hz), 132.12 (d, *J* = 99 Hz), 131.85 (d, *J* = 10 Hz), 131.57 (d, *J* = 3 Hz), 130.77 (d, *J* = 12 Hz), 130.39 (d, *J* = 8 Hz), 128.31 (d, *J* = 13 Hz), 61.61 (s, CH_2CH_3), 13.53 (s, CH_2CH_3). ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 31.16. MS, *m/z* (%) = 350 (M^+, 2), 349 (4), 322 (30), 321 (88), 305 (21), 303 (25), 278 (11), 277 (35), 274 (20), 273 (100), 257 (16), 246 (17), 245 (87), 229 (25), 228 (13), 227 (31), 201 (15), 200 (16), 199 (35), 183 (12), 168 (11), 167 (22), 153 (17), 152 (51), 105 (12), 77 (56), 51(20). ESI-HRMS Anal. Calcd for $C_{21}H_{19}O_3PNa^+$ (M+ Na^+) 373.0964, found 373.0993.

Conclusions

The experimental results showed the efficient synthesis with good yields of 2-(diphenylphosphino)benzoic acid in ammonia by the $S_{RN}1$ mechanism. No evidence for aromatic nucleophilic substitution (S_NAr) or benzyne mechanisms was found. Considering the availability and simplicity of the starting materials, the short reaction times, as well as the mild conditions of the procedure, we have demonstrated that the $S_{RN}1$ reaction could be useful to prepare different triarylphosphines in good yields.

As mentioned, DPPBA has found applications as an important building block for a variety of phosphine-based ligands. So we believe that aryl-phosphorus bond formation by the $S_{RN}1$ reaction offers important opportunities for the synthesis of DPPBA with a wide range of substituents, for example with electron-donating groups in different positions of the aromatic acid. It should be noted the diference with the S_NAr, where aromatic substrates having electron-withdrawing group are accepted.

Supplementary material

See Supplementary material for experimental procedures and full spectroscopic data for all compounds.

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