Synthesis of Diphenyl(nitroaryl)phosphine Oxides via Oxidative Nucleophilic Substitution of Hydrogen in Nitroarenes with Diphenylphosphine Anion

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Received 4 September 2008

Abstract: Potassium and sodium salts of diphenylphosphine add to nitroarenes in the position *ortho* and *para* to the nitro group. Subsequent oxidation of σ^H-adducts with potassium permanganate gave diphenyl(nitroaryl)phosphine oxides.

Key words: phosphine oxides, nucleophilic aromatic substitution, nitroarenes, carbanions

Organophosphorus compounds have found wide application as intermediates and reagents in organic synthesis.[1] For instance, phosphines are key reagents in important processes such as Mitsunobu,[2,3] Wittig,[3,4] Appel,[3,5] Staudinger[3,6] and many other reactions. Phosphines are indispensable ligands for transition metal catalysts that promote a great variety of reactions.[7] Due to this, a variety of methods for the synthesis of substituted phosphines and phosphinoxides have been developed.[1,8]

In spite of the great interest in synthesis of phosphines and phosphinoxides, those containing nitroaryl substituents are almost unknown. We have found very few papers reporting synthesis of diphenyl(nitrophenyl)phosphines and their oxides. The reaction of alkyl diphenylphosphinite with *o*-dinitrobenzene gave diphenyl-*o*-nitrophenylphosphinoxide in a kind of aromatic Michaelis–Becker reaction.[9] An alternative approach is direct or electrochemical nitration of triphenylphosphine, which gives products of mono- and dinitration.[10]

In this letter we report that diphenyl-[*o*(*p*)-nitroaryl]phosphinoxides can be synthesized via oxidative nucleophilic substitution of hydrogen (ONSH) in nitroarenes with anion of diphenylphosphine.

Oxidative nucleophilic substitution of hydrogen in nitroarenes and other electron-deficient arenes is presently a well-developed method for introduction of nitrogen, oxygen and carbon substituents into electron-deficient aromatic rings.[11,12a] The reaction proceeds via addition of respective nucleophiles: ammonia,[12b] hydroxyl anion,[12c] carbanions[12d–12g] or Grignard reagents[12h,i] to nitroaromatic rings in positions occupied by hydrogen followed by oxidation of the produced σ^H-adducts with external oxidants. For ONSH a variety of solvent–oxidant systems can be used.[13] Particularly efficient is a solution of potassium permanganate in liquid ammonia that serves as efficient ammination agent of highly electron-deficient heteroarenes, oxidative variant of the Chichibabin reaction.[10b] Since liquid ammonia is an excellent solvent for generation and reactions of carbanions, we have used this system for ONSH in nitroarenes with variety of carbanions.[10] The reaction proceeds satisfactorily with carbanions of high nucleophilicity; hence σ^H-adducts thus formed are relatively stable and can be subsequently oxidized.

Taking into account the high nucleophilicity of diphenylphoshine anion we expected that it should add to nitroarenes in positions *ortho* and *para* to the nitro group giving σ^H-adducts and that addition should proceed completely. Subsequent oxidation of these σ^H-adducts should give diphenyl(nitroaryl)phosphines or phosphine oxides, products of the ONSH reaction.

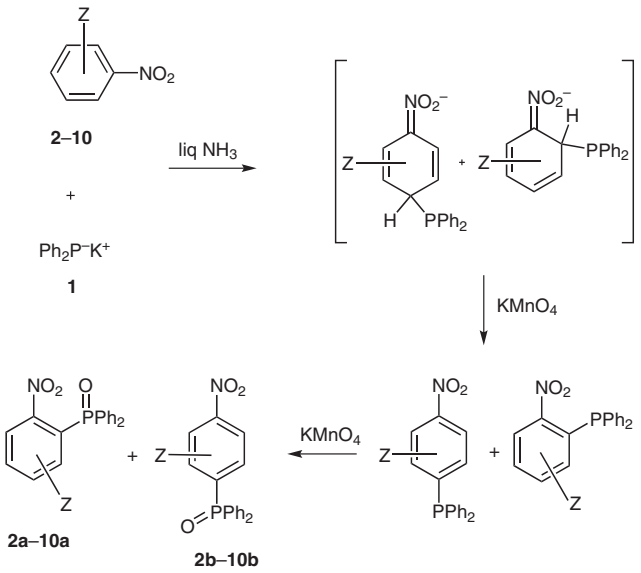
Indeed, addition of commercially available THF solution of potassium salt of diphenylphosphine anion **1** to a solution of nitrobenzene **2** in liquid ammonia and treatment of the resulting mixture after 15 minutes with potassium permanganate gave the expected diphenyl(nitrophenyl)phosphine oxide as a mixture of *ortho*- (**2a**) and *para*- (**2b**) isomers in a total yield of almost 60% (Scheme 1, Table 1). According to our previous observations,[12d] the use of two equivalents of $KMnO_4$ should assure complete oxidation of σ^H-adduct and phosphine. Thus, after addition of the diphenylphosphine anion to nitrobenzene, two oxidation processes proceeded consecutively, oxidation of the σ^H-adducts to the corresponding nitrophenyl diphenylphosphines and subsequent oxidation of the phosphines to phosphinoxides. One cannot exclude *a priori* an alternative pathway, oxidation of the trivalent phosphorous in the σ^H-adduct to produce σ^H-adduct of diphenylphosphinoxides followed by oxidation of the latter.

To clarify this point we have oxidized the σ^H-adduct of diphenylphosphine with an insufficient quantity of potassium permanganate and obtained a mixture of the corresponding phosphine and phosphinoxide. This result suggest that oxidation of the σ^H-adducts to diphenyl(nitroaryl)phosphines is the initial process.

Under identical conditions other nitroarenes reacted with **1** producing the expected diphenyl(nitroaryl)phosphine oxides (Scheme 1, Table 1).[14,15]

The reaction of nitrobenzene and *ortho* and *meta* substituted nitrobenzenes with potassium diphenylphosphide always gave mixtures of *p*- and *o*-nitroaryldiphenylphosphinoxides that were very difficult to separate by conven-

SYNLETT 2008, No. 19, pp 2938–2940
Advanced online publication: 12.11.2008
DOI: 10.1055/s-0028-1087354; Art ID: G29806ST



Scheme 1 Reaction of potassium diphenylphosphide with nitroarenes.

Table 1 Results of ONSH in Nitroarenes with Diphenylphosphine Anion

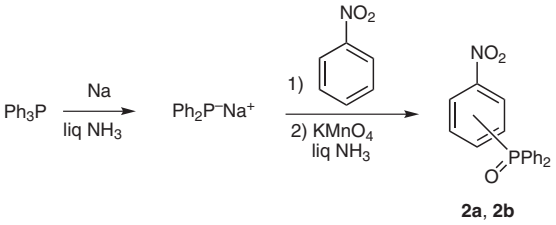
Entry	Nitroarenes		Products	Regioisomer ratio[a]	Overall yield (%)
	Z				
1	H	**2**	**2a/2b**	87:13	58
2	2-Cl	**3**	**3a/3b**	83:17	60
3	2-Br	**4**	**4a/4b**	91:9	33
4	3-Cl	**5**	**5a/5b**	80:20	70
5	3-Br	**6**	**6b**	100:0	37
6	3-F	**7**	**$7a_1$/$7a_2$/7b**	58:33:9	54
7	4-Cl	**8**	**8a**	0:100	35
8	4-F	**9**	**9a**	0:100	41
9	1-NN[b]	**10**	**10a/10b**	94:6	41

[a] Isomer ratio (*para*/*ortho*) was determined using ^{31}P NMR spectroscopy.
[b] 1-NN: 1-nitronaphthalene.

tional chromatographic techniques. Attempts to change solvents, temperature and oxidants resulted in lower yields of the nitroarylated phosphines and did not affect regioselectivity of the reaction.

On the other hand, the reaction of *p*-fluoro- and *p*-chloronitrobenzene with **1** gave exclusively single products of the ONSH, diphenyl(*o*-nitroaryl)phosphine oxides. It should be stressed that even when *p*-fluoronitrobenzene was used in this reaction, we did not find in the reaction mixture diphenyl(*p*-nitrophenyl)phosphine oxide, product of S_NAr of fluorine.

It is known that diphenylphosphine salts can be obtained by direct cleavage of triphenylphosphine with lithium, sodium or potassium.[16] We have therefore attempted to perform one-pot reaction starting with Ph_3P. Treatment of triphenylphosphine with sodium in liquid ammonia gave a dark solution containing undoubtedly sodium salt of diphenylphosphine that upon addition of an excess of nitrobenzene followed by oxidation with potassium permanganate gave the expected product, a mixture of **2a** and **2b** in 45% yield (Scheme 2).[17]



Scheme 2

In this communication we have presented a new method for the synthesis of diphenyl(nitroaryl)phosphine oxides utilizing oxidative nucleophilic substitution of hydrogen in nitroarenes with diphenylphosphine salts, that could be extended on other electron-deficient arenes.

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(14) **Representative Procedure**: To a stirred solution of nitrobenzene (246 mg, 2.00 mmol) in liquid ammonia (ca. 10 mL), at –78 °C was added dropwise a solution of diphenylphosphine potassium salt (0.5 M solution in THF, 2.0 mL, 1.0 mmol). After 15 min, solid potassium permanganate (396 mg, 2.00 mmol) was added. The dark mixture was stirred for further 5 min, and treated with excess of solid ammonium chloride. After evaporation of ammonia the residue was suspended in EtOAc (20 mL), stirred for 10 min and filtered through a small pad of celite. The organic phase was washed once with H_2O, dried with anhyd Na_2SO_4 and evaporated. Column chromatography on silica gel (EtOAc) gave a mixture of *o*- and *p*-nitrophenyl diphenylphosphinoxide (178 mg, 58% yield) as an oil.

(15) Selected analytical data:
Mixture **2a**/**2b**: light orange oil. ^{1}H NMR (400 MHz, $CDCl_3$; *para* isomer): δ = 8.30 (dd, *J* = 2.1, 8.8 Hz, 2 H), 7.89 (dd, *J* = 11.0, 8.8 Hz, 2 H), 7.63–7.74 (m, 4H), 7.55–7.63 (m, 2H), 7.46–7.55 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$; *para* isomer): δ = 149.9 (d, *J* = 3 Hz), 140.3 (d, *J* = 98 Hz), 133.2 (d, *J* = 11 Hz), 132.6 (d, *J* = 3 Hz), 132.0 (d, *J* = 10 Hz), 128.8 (d, *J* = 12 Hz), 128.6, 123.3 (d, *J* = 12 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 27.70 (s, *para* isomer), 28.39 (s, *ortho* isomer). MS (EI, 70 eV): *m*/*z* (%) = 323 (48) [M$^+$], 322 (100), 277 (26), 201 (12), 77 (13).
Compound **6b**: 159–161 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (m, 1 H), 8.18 (ddd, *J* = 8.6, 2.1, 1.4 Hz, 1 H), 7.69–7.77 (m, 4 H), 7.60–7.76 (m, 3 H), 7.45–7.59 (m, 4 H). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 29.59 (s). MS (EI, 70 eV): *m*/*z* (%) = 402 (100)[M$^+$], 356 (20), 322 (22), 201 (43), 77 (23).
Compound **8a**: mp 210–211 °C (MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07–8.11 (m, 2 H), 7.63–7.80 (m, 5 H), 7.54–7.62 (m, 2 H), 7.33–7.53 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.2, 140.5 (d, *J* = 13 Hz), 136.3 (d, *J* = 7.5 Hz), 133.0 (d, *J* = 2.1 Hz), 132.3 (d, *J* = 2.5 Hz), 131.6 (d, *J* = 10 Hz), 131.5, 128.6 (d, *J* = 13 Hz), 126.5 (d, *J* = 5 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 29.50 (s). MS (ESI$^+$): *m*/*z* = 358 [M + H]$^+$.
Compound **9a**: mp 162–163 °C (MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12–8.30 (m, 1 H), 7.63–7.81 (m, 5 H), 7.55–7.62 (m, 3 H), 7.36–7.53 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.6 (d, *J* = 3 Hz), 132.2, 131.9 (d, *J* = 10 Hz), 130.2, 129.0 (d, *J* = 13 Hz), 128.5 (d, *J* = 9 Hz), 128.4 (d, *J* = 9 Hz), 124.1 (dd, *J* = 8, 26 Hz), 120.3 (m), 120.0 (m). ^{31}P NMR (162 MHz, $CDCl_3$): δ = 30.01 (s). MS (ESI$^+$): *m*/*z* = 342 [M + H]$^+$.

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(17) **One-Pot Procedure**: To a suspension of triphenylphosphine (262 mg, 1.00 mmol) in liquid ammonia at –78 °C, sodium metal was added (26 mg, 1.10 mmol). The resulting mixture was stirred for 1 h and to the dark red solution nitrobenzene (369 mg, 3.00 mmol) in THF (1 mL) was added. After 15 min the mixture was treated with solid $KMnO_4$, and after 5 min solid ammonium chloride was added. Workup as in ref. 14 gave a mixture of **2a** and **2b** (138 mg, 45% yield).