

Regioselective functionalisation of nitrobenzene and benzonitrile derivatives via nucleophilic aromatic substitution of hydrogen by phosphorus-stabilized carbanions

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Abstract—The synthesis of *P*-benzylic products by reaction of anions stabilised by *N*-phosphorylphosphazanyl, *N*-methoxycarbonylphosphazanyl, phosphine borane complex, and phosphine oxide groups by displacement of hydrogen of a variety of electron-deficient benzene derivatives is described. Lithium phosphazenes were the most suitable nucleophiles for the substitution of hydrogen in nitrobenzene and some *ortho*-, *meta*-, and *para*- substituted nitrobenzenes. Lithiated phosphine borane complexes produced efficiently the substitution of the hydrogen at the *para* position of a cyano group in cyanobenzenes, whereas the anion of ethyldiphenylphosphine oxide lead to complex mixtures with all electrophiles assayed. The method reported here represents a convenient alternative to the vicarious nucleophilic substitution for the synthesis of benzylic phosphorus derivatives using phosphorus-stabilised anions that do not bear a leaving group at the carbanionic centre.

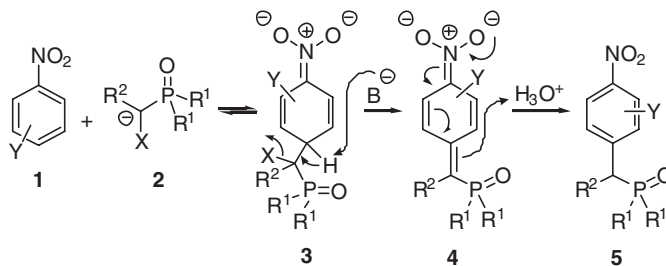
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1. Introduction

The direct functionalisation of electron-deficient arenes via nucleophilic replacement of hydrogen is a process of great interest both in the academia and in the industry.¹ The introduction of a *P*-alkyl substituent into an aromatic system is particularly attractive owing to the possibility of using benzylic phosphorus derivatives into olefination reactions. The end products would be stilbenes, a compound class that have shown important biomedical properties.² Nucleophilic aromatic substitution of hydrogen, S_NAr^H, by phosphorus-stabilised carbanions has been achieved exclusively via vicarious nucleophilic substitution

(VNS),³ and only on nitrobenzenes. The VNS method requires that the nucleophile also contains a nucleofugal group (X) at the reactive centre. Attack of the carbanion **2** formed by deprotonation of the corresponding organophosphorus compound to the nitroarene **1** leads to a Meisenheimer complex **3**, which is in equilibrium with the starting reagents (Scheme 1). This σ -adduct undergoes β -elimination of HX promoted by a second equivalent of base. The resulting nitronate intermediate **4** provides the substituted arene **5** upon work-up.⁴

The organophosphorus reagents used in VNS reactions include chloromethyldiphenylphosphine oxide,⁵ dimethyl



Scheme 1.

Keywords: Phosphazenes; Phosphine-boron complexes; Nucleophilic aromatic substitution; Carbanions; Cyano group.

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α -chlorobenzylphosphonate,^{5a} and 2-(1,3-dithianyl)triphenylphosphonium chloride.⁶ Phosphorus ylides derived from (halomethyl)triphenylphosphonium halides (halide = Cl, Br) failed to give VNS products in the reaction with nitrobenzene.^{5c} Interestingly, Lawrence and co-workers showed that the vicarious nucleophilic substitution products formed in the reaction of the anion of chloromethyl-diphenylphosphine oxide with a series of substituted nitrobenzenes can be transformed into stilbenes in a one-pot process.^{5b,c}

The introduction into an aromatic ring of alkyl side chains bearing phosphorus-containing functional groups through the VNS protocol shows two important limitations. On the one hand, the nucleophile must bear an auxiliary leaving group at the carbanionic centre. On the other, only nitrobenzenes have been used as electrophiles.

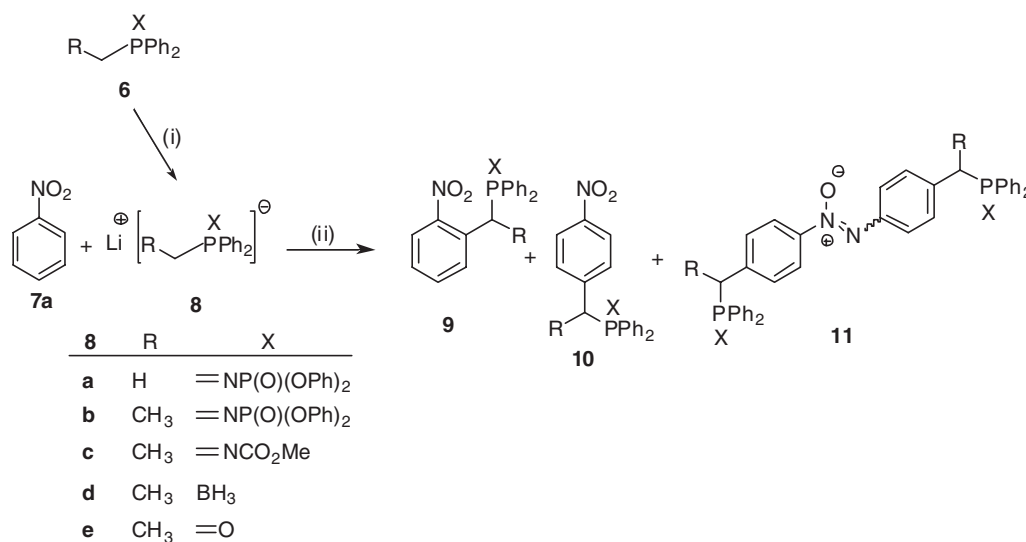
We have recently reported a new method for the direct introduction of alkylphosphorus substituents into nitro- and cyano-benzenes, with high yield and regioselectivity, through nucleophilic aromatic substitution of hydrogen without the requirement of a nucleofuge at the α position with respect to the phosphorus atom.⁷ Generally, aromatization occurred spontaneously in the reaction medium or during work-up. In some cases the use of an external oxidant such as DDQ proved to be beneficial for increasing the yield of S_NAr^H products. Here we wish to report the full details of this investigation showing the scope of the methodology. We have evaluated the feasibility of α -lithiated

N-phosphorylphosphazenes, *N*-methoxycarbonylphosphazenes, phosphine borane complexes, and phosphine oxides, as nucleophiles for the S_NAr^H reactions. The influence of the substituents for activating the aromatic nucleus and the different reactivity of primary and secondary carbanions are also discussed.

2. Results and discussion

2.1. Functionalisation of nitrobenzene and benzonitrile derivatives via S_NAr^H

We initially chose lithiated phosphazenes bearing electron-withdrawing groups at the nitrogen atom **8a–c** as nucleophiles for the reaction with nitrobenzene **7a** based on our experience on the synthetic applications of these anions,⁸ which includes their utilisation in olefination reactions.⁹ The carbanions **8a–c**, generated through metalation of phosphazenes **6a–c** with $LiBu^n$, were allowed to react with **7a** at low temperature in THF (Scheme 2). The results obtained are collected in Table 1 (entries 1–3). High conversions were observed for **8b–c**. The major products isolated consisted of compounds **9** and **10** resulting from the hydrogen substitution at the *ortho* and *para* position to the nitro group, respectively. The later is generated in higher yield except for lithium phosphazene **8a**. This carbanion affords equimolecular amounts of both regioisomers, albeit in very low yield. The poor performance of the reaction of **8a** with nitrobenzene can be ascribed to



Scheme 2. Reagents and conditions: (i) for **6a–c** and **6e** $LiBu^n$ (1 equiv), THF, HMPA (6 equiv), $-30^\circ C$, 30 min; for **6d** $LiBu^s$ (1 equiv), THF, HMPA (6 equiv), $-90^\circ C$, 30 min; (ii) 1 equiv of **7a**, THF, $-90^\circ C$, 12 h.

Table 1. Distribution of products (%) in the reaction of phosphorus-stabilised anions **8a–e** with nitrobenzene

Entry	Nucleophile	R	X	Conversion	S_NAr^H ^a	9 ^b	10 ^b	11 ^b
1	8a	H	=NP(O)(OPh) ₂	18	100	9 (a)	9 (a)	
2	8b	CH ₃	=NP(O)(OPh) ₂	84	77	11 (b)	54 (b)	19 (a)
3	8c	CH ₃	=NCO ₂ Me	76	55	10 (c)	32 (c)	10 (b)
4	8d	CH ₃	BH ₃	58	83	3 (d)	45 (d)	10 (c)
5	8e	CH ₃	=O	94	20		19 (e)	<1% (d)

^a Referred to the % of conversion.

^b Crude yield.

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