Pergamon

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Tetrahedron Letters 44 (2003) 8441–8444

TETRAHEDRON LETTERS

Nucleophilic aromatic substitution of hydrogen through lithiated phosphine borane complexes and *N*-phosphorylphosphazenes

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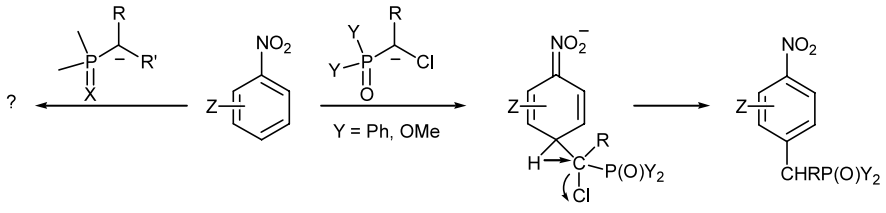
Received 29 July 2003; revised 3 September 2003; accepted 12 September 2003

Abstract—Organophosphorus compounds containing nitroaryl and cyanoaryl groups have been prepared in good yield through nucleophilic aromatic substitution of hydrogen using α-lithiated phosphazenes and phosphine borane complexes as nucleophiles. In all cases, nearly exclusive replacement of the hydrogen in the *para* position with respect to the activating group has been observed.

Nucleophilic aromatic substitution, S_NAr, offers a convenient route for the functionalisation of arenes and heteroarenes with a well-established synthetic utility in the preparation of biologically active molecules. Direct replacement of hydrogen in electron-deficient aromatic rings, S_NAr^H, has additional advantages over the classical displacement of nucleofugal groups and it has become a very efficient method for introducing regio- and chemoselective functionalised alkyl groups into activated aromatic compounds.[1] In carbocyclic aromatic rings the activation is almost exclusively attained through the nitro group.[2] In regard to the nucleophile, the use of phosphorus-stabilised carbanions is particularly attractive due to the importance of organophosphorus compounds in organic synthesis. Examples reported for the preparation of organophosphorus compounds with nitroaryl groups by means of S_NAr processes are based on vicarious nucleophilic substitution.[3] This reaction scheme involves the elimination of a leaving group linked to the nucleophilic centre. Thus, these methods are limited by the need of an auxiliary leaving group that promotes β-elimination for the rearomatisation of the initially formed σ adduct (Scheme 1).

We have previously noted in a synthesis of diazadiphosphorines through addition of lithiated phosphorylphosphazenes to the cyano group of aryl nitriles, that for *p*-nitrobenzonitrile, an S_NAr reaction takes place exclusively.[4] In a similar way, we have also observed the formation of by-products derived from the nucleophilic aromatic substitution of hydrogen in the reaction of lithium phosphine borane complexes with aryl nitriles.[5] It is worth noting that in this latter case the activation of the aromatic nucleus was achieved through the cyano group. The aim of the present paper is to devise a general method for preparing valuable functionalised aromatic compounds through aromatic nucleophilic substitution of hydrogen using phosphorus-stabilised carbanions that do not require α-leaving groups.



Scheme 1.

Keywords: nucleophilic aromatic substitution; phosphazene anions; phosphine borane anions; nitro compounds; arylnitriles.
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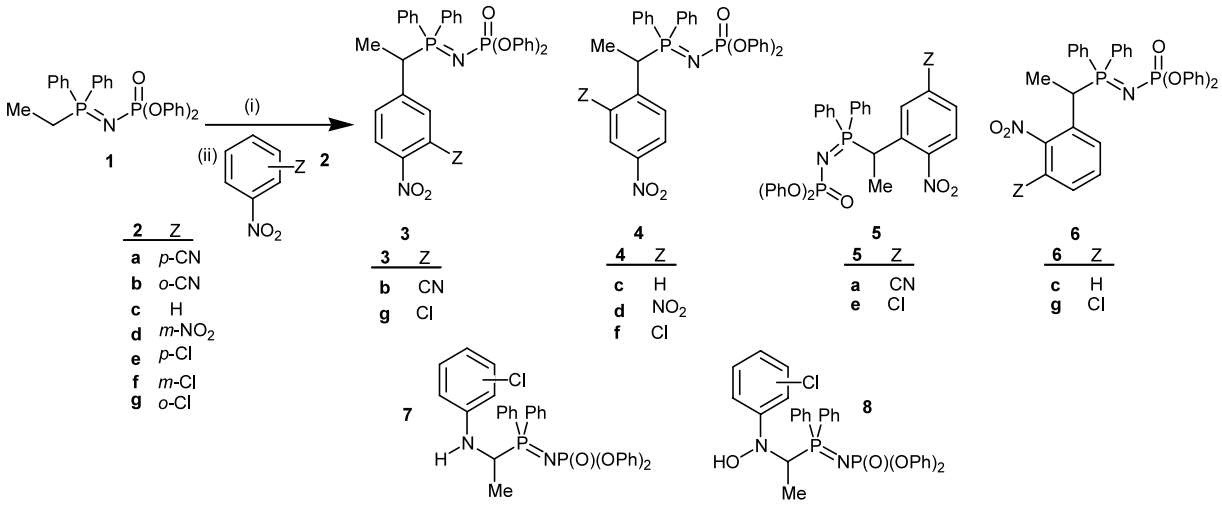
doi:10.1016/j.tetlet.2003.09.095



Scheme 2. *Reagents and conditions*: for **2a**–**b**: (i) $LiBu^n$ 2.5 equiv., THF, −30°C, 30 min; (ii) $ArNO_2$ 2.5 equiv., THF, −90°C, 48 h. For **2c**–**g**: (i) $LiBu^n$ 1 equiv., THF, −30°C, 30 min; (ii) $ArNO_2$ 1 equiv., THF, −90°C, 12 h.

Phosphazene **1** was chosen as a model compound for testing the optimum conditions for S_NAr reactions in a series of nitrobenzenes (Scheme 2). Nucleophilic aromatic substitution was the only reaction observed when a solution of the lithium phosphazene **1** and *p*- or *o*-nitrobenzonitrile **2a**–**b** in THF was stirred at −90°C over 48 h, using a ratio of phosphazene/$LiBu^n$/nitrile of 1:2.5:2.5. In both cases only one regioisomer, **5a** and **3b**, respectively, were obtained, albeit **3b** in significant lower yield (28% of **3b** versus 81% of **5a**). Addition of the external oxidising agent DDQ to promote the departure of the hydride ion[2a,6] did not improve the yield of **3b**.[7] The use of the co-ordinating agent HMPA proved to be more efficient.[8] The reaction of lithiated **1** with **2b** in the presence of 6 equivalents of HMPA to give **3b**, almost duplicated the yield obtained (Table 1, entries 1 and 2).

Generalization of the process to nitroarenes **2c**–**g** showed that the performance of the reaction improved by the use of DDQ or HMPA. Thus, treatment of nitrobenzene **2c** with lithiated **1** in the presence of 6 equiv. of HMPA gave **4c** in 56% yield, whereas in the absence of co-solvent a disappointing 6% yield was obtained. Except for nitrobenzene **2c**, oxidative treatment with 1.2 equivalents of DDQ improved the extension of the aromatic substitution (Table 1, synthesis of **4d**, **4f**, and **5e**), or the selectivity of the process (Table 1, formation of **3g**). For the nitrobenzene derivatives bearing a chlorine substituent **2e**–**g**, displacement of the nuclear halogen was not observed. This result agrees with the well-established statement that the unsubstituted positions of nitroarenes are attacked faster than those substituted by good leaving groups.[9] Interestingly, in the reaction with chlorinated nitrobenzenes low yields of by-products **7**–**8** were isolated, probably arising from single electron-transfer processes.[10] The formation of these by-products could be avoided by addition of DDQ, with subsequent increase in the yield of the S_NAr^H products, except for the *ortho* derivative. As expected, for **2a** and **2e** the nucleophile enters exclusively in the *ortho* position providing **5a** and **5e**, respectively. For the other nitrobenzenes substitution occurs predominantly *para* to the nitro group. Formation of *ortho* adducts **6** were only detected in very small amounts in the reaction of the lithium phosphazene **1** with nitrobenzene **2c** and *o*-chloronitrobenzene **2g** (Scheme 2, Table 1 entry 7). For the derivative **2g**, the addition of 1.2 equiv. of the oxidant increased the selectivity of the process, directing the addition exclusively to the *para* position (Table 1, entry 2). These results indicate that the regiochemistry of the addition is controlled by the size of the lithium phosphazene **1**. All new compounds obtained were purified through column chromatography and characterised by their spectroscopic data.[11] The $\delta(^{31}P)$ (average: δ 19.1 and −8.5 ppm for the PN and PO, respectively) and $^2J_{PP}$ (average 35.7 Hz) values measured in the ^{31}P NMR spectra showed that all of them retained the phos-

Table 1. Distribution of products (%)[a] obtained in the reaction of lithiated **1** with nitro aryls **2**

Comp.	2						
	a	**b**	**c**	**d**	**e**	**f**	**g**
3		28					36[f]
3		53[b]					24[c,g]
4			6	23		10[e]	
4			56[b]	79[c]		62[c]	
5	81				29[d]		
5					53[c]		
6			9				7

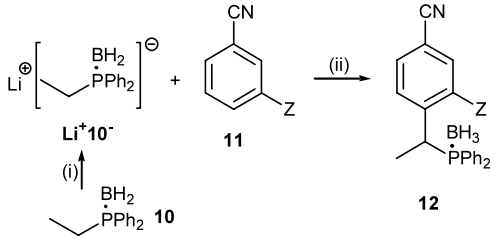
[a] Crude yield.
[b] Metalation in the presence of 6 equiv. of HMPA.
[c] Addition of DDQ (1.2 equiv.).
[d] Also obtained 13% of compound **7**.
[e] Also obtained 17% of compound **8**.
[f] Also formed **8** (9%) and **7** (≈1%).
[g] Also obtained 7% of compound **8**.

phazene moiety of the starting material. The substitution pattern was established from the 2D HMBC spectra based on the correlations observed for the methine proton adjacent to the phosphorus.[12]

Lithium phosphine borane complex **10** also acted as an efficient nucleophile for S_NAr^H processes with electron deficient aromatic systems. We previously showed that the reaction of **Li$^+$10$^-$** with *m*-chlorobenzonitrile **11a**, in the presence of HMPA, afforded the substitution compound **12a** as a by-product (21% yield).[5] Treatment of the crude reaction with 1.2 equiv. of DDQ at –90°C prior to the hydrolytic work-up and then stirring the reaction for an additional hour at room temperature, directed the process exclusively towards the substitution, affording **12a** in 64% yield (Scheme 3, Table 2).

The higher activation of the aromatic nucleus of **11b** allowed the substitution to be achieved in the absence of DDQ, to give compound **12b** in 87% yield. However, the yield decreased to 25% for the fluorinated nitrile **11c** and could not be improved by addition of DDQ. Most importantly, neither **11b** nor **11c** gave rise to products of conjugate addition to the aromatic ring. As in the case of phosphazene **1**, competition with halogen displacement was not observed in the reactions of lithiated **10** with **11a** and **11c**. Compound **12b** precipitated from diethyl ether, while **12a** and **12c** were isolated by column chromatography (ethyl acetate:hexane, 1:10). The substitution pattern was determined by following the same procedure applied to the nitrophosphazenes **3**–**6**.

In summary, two types of non-functionalised phosphorus-stabilised carbanions, derived from phosphazenes and phosphine borane complexes, were satisfactorily used as nucleophiles in the nucleophilic aromatic substitution of hydrogen. For phosphazenyl anions, the S_NAr process is promoted by the strong electron withdrawing nature of the NO_2 group, whereas with the phosphine borane complex derivatives, activation of the aromatic nucleus is achieved by the cyano group. High regioselectivities and yields were generally obtained. The process described allows the introduction of organophosphorus moieties of particular interest into aromatic rings.



Scheme 3. *Reagents and conditions*: (i) LiBu^s (1.2 equiv.), THF, HMPA (6 equiv.), –90°C, 30 min; (ii) 1.2 equiv. of **11**, –90°C, 12 h.

Table 2. Products **12** obtained by reaction of **Li$^+$10$^-$** with arylnitriles **11**

11	Z	12	Yield (%)
a	Cl	**a**	21
a[a]	Cl	**a**	64
b	CN	**b**	87
c	F	**c**	25
c[a]	F	**c**	17

[a] Addition of 1.2 equiv. of DDQ.

Acknowledgements

Financial support by the Ministerio de Ciencia y Tecnología (Project PPQ2001-3266) is gratefully acknowledged. C.M.A.S. thanks the Ministerio de Ciencia y Tecnología for a doctoral fellowship.

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11. Spectral characterisation of **4f**. Oil. Yield 62%. IR (KBr), ν (cm^{-1}) 1638, 1261, 1095. ^{1}H NMR (300.13 MHz, $CDCl_3$), δ (ppm): 1.63 (dd, $^3J_{HH}$ 7.3 Hz, $^3J_{PH}$ 17.4 Hz, 3H), 4.47 (dq, $^3J_{HH}=^2J_{PH}$ 7.3 Hz, $^4J_{PH}$ 3.1 Hz, 1H), 6.92–7.42 (m, 14H), 7.5–7.67 (m, 6H), 7.9–8.03 (m, 3H). ^{13}C NMR (75.46 MHz, $CDCl_3$), δ (ppm): 15.33 (d, $^2J_{PC}$

3.3 Hz), 36.2 (dd, $^{1}J_{PC}$ 70.3 Hz, $^{3}J_{PC}$ 3.6 Hz), 120.39 (d, $^{3}J_{PC}$ 5.4 Hz), 120.46 (d, $^{3}J_{PC}$ 5.1 Hz), 121.92 (d, $^{4}J_{PC}$ 2.7 Hz), 123.80 (d, $^{4}J_{PC}$ 1.8 Hz), 123.91 (d, $^{5}J_{PC}$ 0.9 Hz), 124.05 (d, $^{5}J_{PC}$ 1.2 Hz), 127.31 (d, $^{1}J_{PC}$ 96.4 Hz), 127.87 (dd, $^{1}J_{PC}$ 104.5 Hz, $^{3}J_{PC}$ 4.2 Hz), 128.26 (d, $^{3}J_{PC}$ 12.8 Hz), 129.22 (d, $^{3}J_{PC}$ 12.3 Hz), 129.36 (d, $^{4}J_{PC}$ 0.9 Hz), 129.38 (d, $^{4}J_{PC}$ 0.9 Hz), 131.31 (d, $^{2}J_{PC}$ 10.8 Hz), 131.46 (d, $^{3}J_{PC}$ 4.5 Hz), 132.00 (d, $^{2}J_{PC}$ 9.9 Hz), 132.48 (d, $^{4}J_{PC}$ 3.3 Hz), 132.91 (d, $^{4}J_{PC}$ 3.0 Hz), 134.63 (d, $^{2}J_{PC}$ 7.8 Hz), 142.48 (d, $^{3}J_{PC}$ 5.4 Hz), 146.85 (d, $^{5}J_{PC}$ 3.0 Hz), 152.25 (d, $^{2}J_{PC}$ 7.8 Hz), 152.28 (d, $^{2}J_{PC}$ 7.8 Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$), δ (ppm): 18.29 (d, $^{2}J_{PP}$ 35.6 Hz), –9.09 (d, $^{2}J_{PP}$ 35.6 Hz). Anal. calcd for $C_{32}H_{27}ClN_2O_5P_2$ (616.98): C, 62.30; H, 4.41; N, 4.54. Found: C, 62.21; H, 4.36; N, 4.45. MS, m/z: 617 (100%, M^+).

12. For example, for **3b** the C*H*P proton at δ 4.13 ppm correlates with two methine carbons *meta* to the nitro group at δ 134.9 (d, $^{3}J_{PC}=4.8$ Hz) and 135.85 (d, $^{3}J_{PC}=3$ Hz) ppm, whereas the corresponding proton of **4f** (δ 4.47 ppm, q, $^{3}J_{HH}=^{2}J_{PH}=7.3$ Hz, $^{4}J_{PH}=3.1$ Hz) showed correlations with the CH carbon *meta* to the nitro group at δ 131.46 ppm (d, $^{3}J_{PC}=4.5$ Hz) and the *ipso*-carbon bearing the chlorine substituent (δ 142.48 ppm, d, $^{3}J_{PC}=$ 5.4 Hz).