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The Synthesis of Benzylphosphine Oxides *via* Aromatic Vicarious Nucleophilic Substitution of Hydrogen

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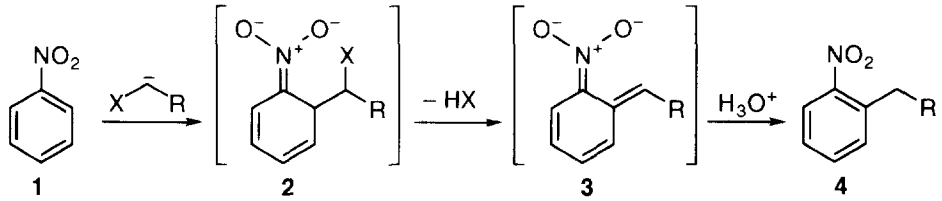
Abstract: A range of substituted nitrobenzenes react with the anion of choromethyldiphenylphosphinoyl oxide to give the substituted nitrobenzyldiphenylphosphine oxide by vicarious nucleophilic substitution. The novel stereoselective synthesis of *E*–stilbenes via a one–pot vicarious nucleophilic substitution/Horner–Wittig reaction is described.

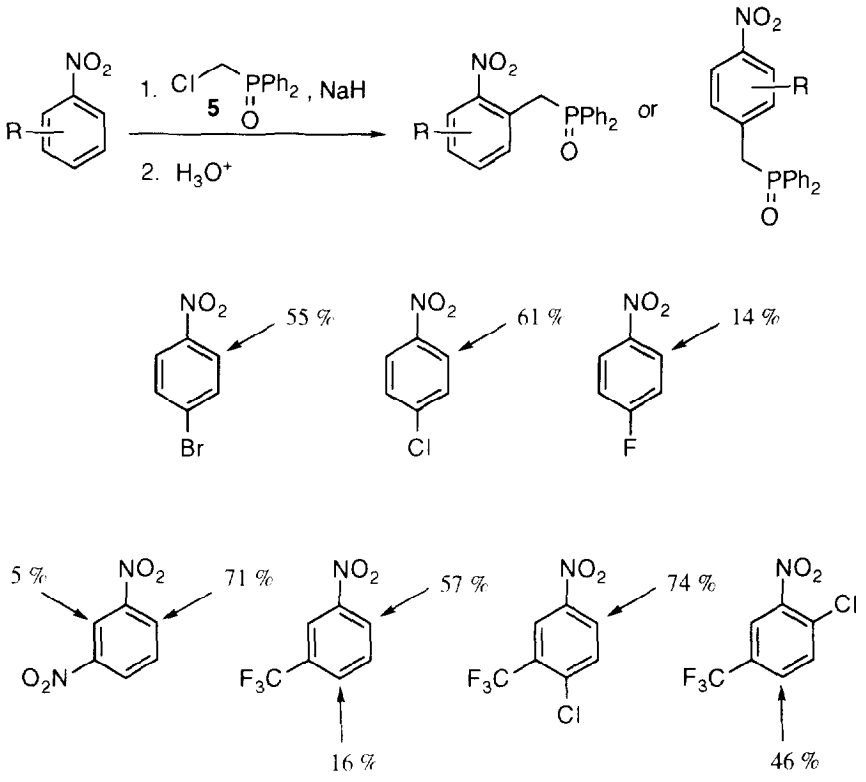
The development of new mild methods for the efficient regio–controlled synthesis of substituted aromatic compounds is an important area of modern organic synthesis. Vicarious nucleophilic substitution[1,2] (VNS) is one such protocol that offers an efficient method for the synthesis of a variety of aromatic and heteroaromatic systems. The reaction is characterised by reaction of a nucleophile — that also bears a nucleofuge (X) at the same nucleophilic centre — with an electron deficient arene **1**. Elimination of HX from the Meisenheimer intermediate **2** generates the intermediate **3** which yields the substituted arene **4** upon work–up. This protocol, pioneered by Makosza and his co–workers,[3] offers a strategy for the functionalisation of arenes complementary to existing methods such as electrophilic substitution,[4] *ortho*–lithiation,[5] and conventional nucleophilic aromatic substitution.[6] We currently have a need to make benzylicphosphine oxides for the stereoselective synthesis of *E*–stilbenes.[7] We now report the synthesis of benzylicphosphine oxides possessing an electron-deficient benzyl group, via vicarious nucleophilic substitution, and their subsequent Horner-Wittig reaction.



1 **2** **3** **4**

Chloromethyldiphenylphosphine oxide **5** was obtained simply, in a two-step operation, by reaction of chlorodiphenylphosphine with formaldehyde in concentrated hydrochloric acid followed by treatment of the resulting alcohol with thionyl chloride.[8] We first attempted to repeat the known addition of **5** to *p*–chloronitrobenzene by treatment with KOH in DMSO.[9] In our hands, this procedure was inefficient at best.

However, when the anion of **5** is generated by use of sodium hydride in anhydrous DMSO, the VNS reaction with *p*–chloronitrobenzene proceeded in 61% yield. A variety of substituted nitrobenzene derivatives were similarly treated with **5**. Addition to *p*–chloro, *p*–bromo and *p*–fluoro nitrobenzenes takes place,[10] as expected, exclusively *ortho* to the nitro group, albeit in poor yield in the *p*–fluoro case. Addition to the more electrophilic 1,3–dinitrobenzene is very efficient (76% total yield) giving the 6-substituted isomer as the major product. Reactions of nitrobenzene derivatives bearing a trifluoromethyl group are equally as efficient; the 6–substituted isomer is the major product from reaction of 3-trifluoromethylnitrobenzene with the 4–substituted product as the minor isomer. When the 4 position is blocked by chlorine, as in 3-trifluoromethyl-4-chloronitrobenzene, the 6–substituted isomer is the exclusive product. When the six position is blocked, as in 3-trifluoromethyl-6-chloronitrobenzene, the 4–substituted isomer is the only product formed in the reaction with **5**; however, the rate of reaction is much slower.



Regiochemistry (shown as isolated yields) in the reaction of **5** with substituted nitrobenzenes.

With the series of benzylphosphine oxides in hand we first attempted the Horner Wittig reaction of **7** (Ar^1 = 2-NO_2-5-ClC_6H_3) with benzaldehyde (Table, entry 1). The stilbene *E*–**8a** was indeed formed with the expected *trans* selectivity, but in disappointing yield. Similarly reaction of **7** (Ar^1 = 2-NO_2-5-BrC_6H_3) with *p*–nitrobenzaldehyde (Table, entry 2) gave the stilbene *E*–**8b**. Increasing the reaction time and temperature did not increase the yield of *E*–**8b** and only lead to the decomposition of the anion of **5**.

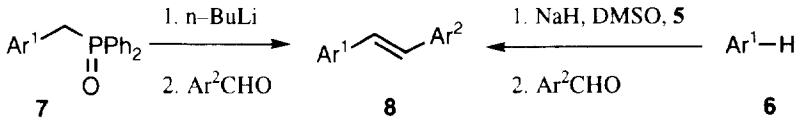
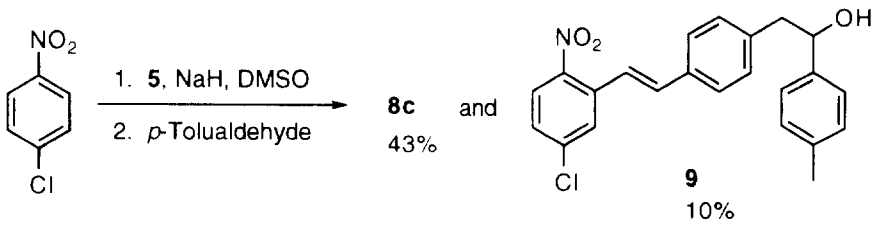


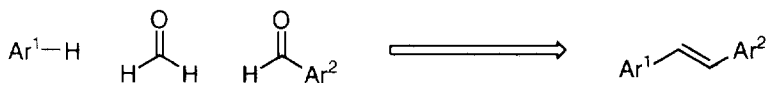
Table : Synthesis of *E*-stilbenes **8a–e**

Entry	Ar^1	Ar^2	Transformation	Stilbene	Yield (%)
1	$2\text{-}NO_2\text{-}5\text{-}ClC_6H_3$	C_6H_5	**7** → **8**	**8a**	31
2	$2\text{-}NO_2\text{-}5\text{-}BrC_6H_3$	$4\text{-}NO_2C_6H_4$	**7** → **8**	**8b**	36
3	$2\text{-}NO_2\text{-}5\text{-}ClC_6H_3$	C_6H_5	**6** → **8**	**8a**	47
4	$2\text{-}NO_2\text{-}5\text{-}ClC_6H_3$	$4\text{-}MeC_6H_4$	**6** → **8**	**8c**	43
5	$2\text{-}NO_2\text{-}5\text{-}ClC_6H_3$	$4\text{-}ClC_6H_4$	**6** → **8**	**8d**	43
6	$2\text{-}NO_2\text{-}5\text{-}Cl\text{-}4\text{-}(CF_3)C_6H_2$	C_6H_5	**6** → **8**	**8e**	32

The anion generated by deprotonation of **7** is actually the same anion, of type **3**, generated in VNS reaction in the synthesis of the phosphine oxide. We therefore thought that the yields of stilbene might be improved if the anion is used directly. Such an approach effectively constitutes a one–pot VNS–Horner-Wittig reaction. Quenching the product of the VNS reaction of **6** (Ar^1 = $2\text{-}NO_2\text{-}5\text{-}ClC_6H_3$) with benzaldehyde gave the expected *E*-stilbene 47% (Table, entry 3); the yield is significantly better than the corresponding reaction of **7** (Ar^1 = $2\text{-}NO_2\text{-}5\text{-}ClC_6H_3$)(Table, entry 1). Indeed we have found that yields of stilbene are generally higher when the one–pot VNS–Horner-Wittig reaction is used (Table, entries 4–6). Only in one case did we identify a by-product; reaction of **6** (Ar^1 = $2\text{-}NO_2\text{-}5\text{-}ClC_6H_3$) with *p*–tolualdehyde gave the stilbene *E*–**9** in addition to *E*–**8c** (Table, entry 4). This is clearly associated with the high acidity of the methyl group of *E*–**8c**. In other cases the unidentified products were baseline material.



Even though the yields of the reaction **6** → **8** are only moderate, the process is nevertheless an intriguing one for the synthesis of functionalised stilbenes. The overall process effectively represents the combination of an arene, formaldehyde and a substituted benzaldehyde.



Standard procedures:

Synthesis of benzyldiphenylphosphine oxides.—To a stirred mixture of sodium hydride (25 mmol, 60% dispersion in oil) in dry DMSO (10 ml), under nitrogen, was added a solution of chloromethyldiphenylphosphine oxide **5** (10 mmol) and the nitroarene (11 mmol) in dry DMSO (15 ml). The mixture was stirred at room temperature until the reaction is complete (by nmr). The mixture was poured into dilute hydrochloric acid (2%) and extracted with dichloromethane (3 × 50 ml). The organic extracts were washed with water, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography (SiO_2).

Synthesis of E–Stilbenes.—The VNS reaction is carried out as above. When the reaction is complete the aldehyde (15 mmol) is added. The mixture is stirred at 60-70 °C until the Horner–Wittig reaction is complete. Standard aqueous work–up (see above) and chromatography gave the alkene.

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Notes and References

1. Chupakhin, O. N.;V. N. Charushin, H. C. van der Plas, *Nucleophilic Aromatic Substitution of Hydrogen*, Academic Press Inc., London, 1994.
2. For reviews of aromatic vicarious nucleophilic substitution see Makosza, M. *Chimia*, 1994, **48**, 499-500; Makosza, M.; Winiarski, J. *Acc. Chem. Res.*, 1987, **20**, 282–287; Makosza, M. *Synthesis*, 1991, 103–111; Makosza, M.; Golinski, J.; Barran, J. *J. Org. Chem.*, 1984, **49**, 1488–1494; Makosza, M.; Ludwiczak, S. *Synthesis*, 1986, 50–52; Makosza, M. 1989, *Russ. Chem. Rev.*, **58**, 747–757.
3. Makosza, M.; Winiarski, J. *J. Org. Chem.*, 1980, **45**, 1534–1535; Makosza, M.; Ludwiczak, S. *J. Org. Chem.*, 1984, **49**, 4562–4563; Makosza, M.; Winiarski, J. *J. Org. Chem.*, 1984, **49**, 1494–1499; Makosza, M.; Golinski, J.; Barran, J.; Dziewonskabaran, D. *Chem. Lett.*, 1984, 1619–1622; Makosza, M.; Owczarczyk, Z. *Tetrahedron Lett.*, 1987, **28**, 3021–3022; Makosza, M.; Kinowski, A.; Ostrowski, S.; *Synthesis*, 1993, 1215–1217; Makosza, M.; Stalewski, J. *Tetrahedron*, 1995, **51**, 7263–7276; Makosza, M.; Stalewski, J. *Tetrahedron*, 1995, **51**, 7263–7276.
4. Taylor, R. *Electrophilic Aromatic Substitution*, Wiley, Chichester, 1990.
5. Beak, P.; Snieckus, V. *Acc. Chem. Res.*, 1982, **15**, 306–312; H. W. Gschwend, H. Rodriguez, *Org. React.*, 1976, 26, 1.
6. Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier, New York, 1968.
7. Brown, K. M.; Lawrence, N. J.; Liddle, J.; Muhammad, F.; Jackson, D. A. *Tetrahedron Lett.*, 1994, **35**, 6733–6736.
8. Marmor, R. S.; Seyferth, D. *J. Org. Chem.*, 1969, **34**, 748–749.
9. Makosza, M.; Golinski, J. *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 451–452.
10. All compounds gave satisfactory spectroscopic data and correct microanalytical figures.

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