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Unexpected reactivity between aromatic nitro compounds and $PCl_3/AlCl_3$. A new one-pot synthesis of phenazines

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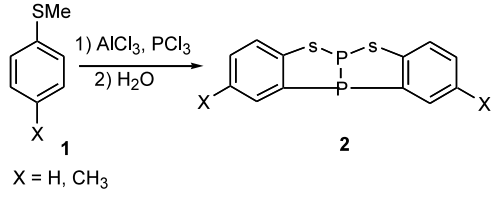
Abstract—The reaction between 4-nitroalkoxybenzenes **7** and $PCl_3/AlCl_3$, when carried out in appropriate molar ratio, gives a prevalent formation of diazenes **8** and 2,7-dialkoxyphenazines **9** with their new chlorinated derivatives **10**–**13**. These compounds are obtained, in satisfactory yield, in a one-pot procedure, in mild conditions, from commercially available and safe starting materials. In this reaction both the reagents PCl_3 and $AlCl_3$ play a fundamental role in obtaining the products, and this method might be applicable to other 4-alkoxynitrobenzenes.

Since the last century the Friedel–Crafts-type reaction using PCl_3 and $AlCl_3$ has been an excellent method for the direct attachment of a phosphorus atom to an aromatic ring to give aryldichlorophosphanes or diarylchlorophosphanes. However, this reaction is very sensitive to the type of substituents present on the aromatic ring[1,2] and in particular it fails completely when thioanisoles are used.[3]

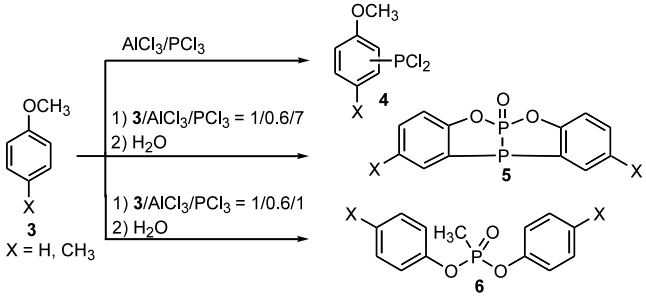
In the past we found[4] that the phosphonation reaction between thioanisoles (**1**) and $PCl_3/AlCl_3$ give, unexpectedly and in high yield, a new heterocyclic system, namely fused [1,2,3]benzothiadiphosphole (**2**) (Scheme 1).

It addition, it is reported[5] that the phosphonation between anisoles **3** and $PCl_3/AlCl_3$ give conflictual results and small amounts of phosphorylation products **4**, together with a large amount of tars. We recently repeated this reaction in order to understand why it was unsuccessful and to explore the possibility to obtain compounds related to **2**. For this purpose we carried out the reaction in different conditions and reagent ratio, and we found a strong dependence of the reaction products on the experimental conditions, it being possible to obtain, by varying the reagent ratio, the formation, as major products, of fused [1,2,3]benzooxadiphosphole[6] (**5**) or of methylphosphonates (**6**). The latter arise from an unexpected insertion of phosphorus atom in the O–CH_3 bond[7] (Scheme 2).

These findings prompted us to check whether the reaction between 4-nitroanisole (**7a**) and $PCl_3/AlCl_3$, reported to fail, might give **5**- and **6**-like compounds or further unexpected results. However, the formation of **5**-like compounds is improbable because of the presence



Scheme 1.



Scheme 2.

Keywords: phosphorus trichloride; phenazines; diazenes; 4-nitroanisole.

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of a nitro group on the aromatic ring, which disfavours the electrophilic attack occurring in the last step of the formation pathway of **5**.[6]

After repeated attempts, varying the reagent ratios and reaction conditions and monitoring the outcome of the reaction by GC–MS analysis, we observed that the use of a reagent ratio **7a**:PCl_3:$AlCl_3$ of 1:3:1 at 50–55°C gives a complex mixture of products (Scheme 3) in which *trans*-1,2-bis(4-methoxyphenyl)diazene (**8a**, 30% yield), 2,7-dimethoxyphenazine (**9a**, 15%) and its chlorinated derivatives (**10a**–**13a**, 30% overall yield) were predominant.

The results obtained with 4-nitroanisole (**7a**) suggested that we should extend the study to other nitro aromatic compounds. In particular, in the same experimental conditions, we carried out the reaction with 4-ethoxy-nitrobenzene, 4-phenoxy-nitrobenzene, 4-bromo-nitrobenzene, 3-methoxy-nitrobenzene, 3-chloro-nitrobenzene, and 4-methoxy-2-methyl-1-nitrobenzene: in all cases traces of anilino derivatives **14**-like were observed in GC–MS, but compounds **8b**–**12b** were otained (**8b**, 7%, **9b**–**12b**, 34% overall) only using 4-ethoxy-nitrobenzene (**7b**). It is noteworthy that **10**–**13** are new compounds and that chlorophenazines are substrates particularly prone to S_NAr and, for this reason, they could be used as versatile starting materials to obtain other phenazinic derivatives.

The major reaction products **8**–**13** were isolated by chromatography on silica gel and fully characterized.[8] In particular, chemico-physical data of compounds **8a**,[9a] **8b**,[9b] **9a**[10] and **9b**[11] were in agreement with published data. Since the formation of phenazinic nucleus was unpredictable, the X-ray diffraction analysis[12] of a single crystal of **10a** unequivocally confirmed the structure and the relative position of the substituents. In addition, the structure of new dichloro isomers **11**–**13** was determined from the analysis of their ^1H and ^{13}C NMR spectral data.

Figure 1 shows the ORTEP drawing of **10a**, whose molecular symmetry is C_S. A second image of the chlorine atom bonded to C(3′) was found in the crystal; therefore the molecular model possesses a statistical inversion centre due to a random packing of molecules related by a pseudo twofold axis to which all the atoms, except chlorine, conform.

The unexpected formation, in a one-pot reaction, of phenazines **9**–**13**, prompted us to carry out the reaction with $AlCl_3$ alone, or with PCl_3 alone, in order to investigate the role played by each reagent. We found that the mixing of 4-nitroanisole (**7a**) with $AlCl_3$ at 50°C does not produce new products, but probably only the reversible formation of a complex due to the coordination of $AlCl_3$ with the oxygen atom, while an increase of the reaction temperature causes a demethylation reaction with formation of 4-nitrophenol. Even the reaction between **7a** and PCl_3 does not allow detectable amounts of products. In conclusion, one can evince that the formation of compounds **8**–**13** is due to the concomitant action of the $AlCl_3$/PCl_3 couple.

The fact that we observed the formation of traces of anilino derivatives **14** with all the substrates suggests the presence of a nitrene as intermediate. The recovering of phenazines and diazenes can also agree with a mechanism involving nitrenic species,[13] from which parallel pathways can depart to give the observed products (Scheme 4).

However, the fact that compounds **8**–**13** are obtained only when nitro derivatives **7a** and **7b** are used, could be explained hypothesizing that the presence in *para* to

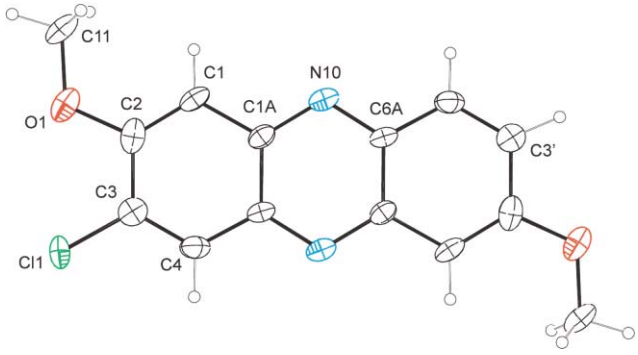
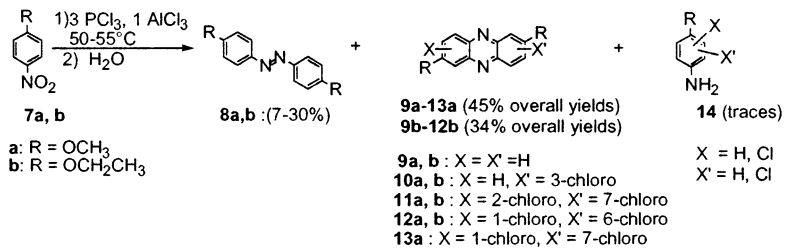
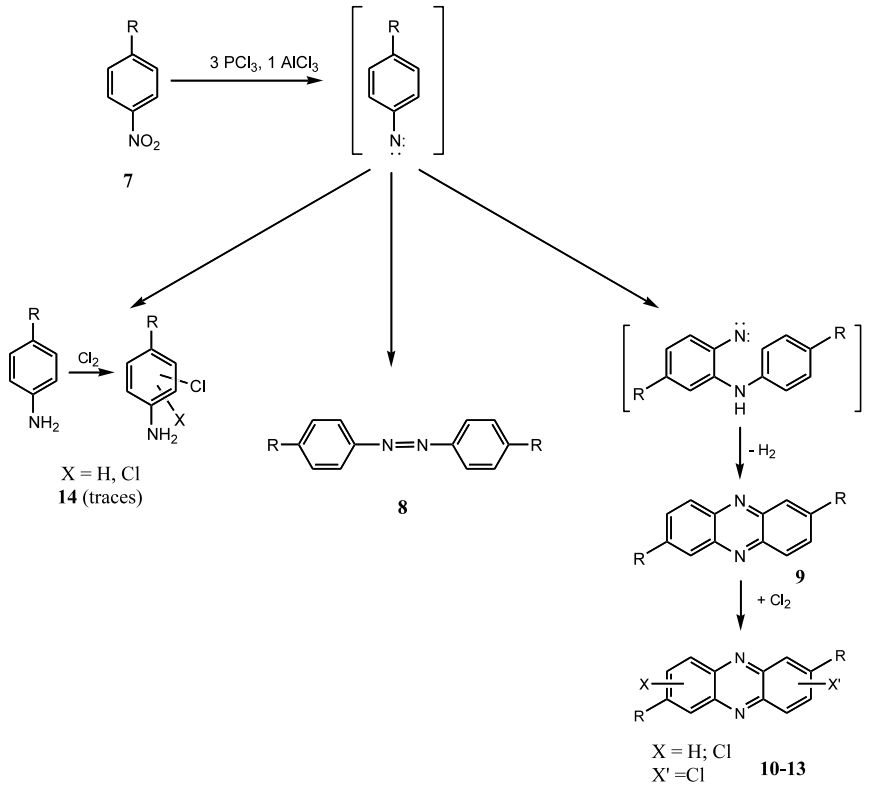


Figure 1. ORTEP drawing of **10a**. Thermal ellipsoids are drawn at the 30% probability level. The crystallographically independent bond distances (Å) and angles (°) are as follows (the molecular model possesses a statistical C_{2V} symmetry in the crystal): N(10)–C(6A) 1.312(7), N(10)–C(1A) 1.372(7), C(1A)–C(1) 1.432(7), C(1)–C(2) 1.340(8), C(2)–C(3) 1.425(9), C(3)–C(4) 1.330(8), Cl(1)–C(3) 1.550(7), O(1)–C(2) 1.376(6), O(1)–C(11) 1.418(7); O(1)–C(2)–C(3) 115.0(6), Cl(1)–C(3)–C(2) 119.2(5), C(1A)–N(10)–C(6A) 116.9(5), C(2)–O(1)–C(11) 118.0(5).



Scheme 3.



Scheme 4.

the nitro group of strong electron-releasing substituents, such as alkoxy groups, stabilizes the nitrene, thus permitting its decay from singlet to triplet state, with consequent formation of intra- and intermolecular coupling products.[13,14] 4-Phenoxy-nitrobenzene and 4-bromo-nitrobenzene bear substituents with an electron-releasing power lower than that of alkoxy groups, while 4-methoxy-2-methyl-1-nitrobenzene could probably have negative steric effects in the cyclization pathway.

It is interesting to note that Cadogan reported[15] that the reaction between nitro- and nitroso compounds and trialkylphosphites produces nitrenic species, but the latter cannot be formed using PCl_3 alone. In addition, it is reported[15b] that the reaction of *p*-nitroanisole with triethyl phosphite does not provide diazenes. This emphasizes the importance, in our case, of the concomitant presence of both, PCl_3 and $AlCl_3$, in the reaction mixture for the formation of diazenes and phenazines.

Furthermore, the finding of chlorinated compounds reveals that the system **7**/PCl_3/$AlCl_3$ is extremely complex and might produce molecular chlorine, probably through oxido-reductive processes. This is supported by the results obtained carrying out reactions between compound **9a** and both PCl_3 and PCl_3/$AlCl_3$: in these cases no chlorinated product was observed, whereas treatment of a solution of **9a** with chlorine gave a mixture of compounds **10a**–**13a**. The yields of chloroderivatives **10**–**13** can thus be increased by simple bubbling of chlorine in the reaction mixture.

It is interesting to note that many syntheses of phenazines are reported in the literature,[16] but they often occur in very low yields, from starting materials difficult to procure or by pyrolysis of azides. Up to now, the best synthesis for the building of phenazinic intermediates seems to be the so-called 'Beirut reaction',[17] in which the reaction between benzofuroxane and hydroquinones allows the formation, in good yields and in mild conditions, of 2-hydroxyphenazines 5,10-dioxide, versatile substrates for easy functional group manipulation.

In conclusion, we found that the reaction between 4-alkoxy-nitrobenzenes (**7a**,**b**) and PCl_3/$AlCl_3$ gives, when carried out in appropriate molar ratio, prevalent formation of 2,7-dialkoxyphenazines and their new chlorinated derivatives. The importance of our method lies in the fact that such heterocycles can be obtained, in satisfactory yield, in a one-pot procedure, in mild conditions and from commercially available and safe starting materials. In this reaction both the reagents, PCl_3 and $AlCl_3$ play a fundamental role in obtaining the products and this method might be applicable to other 4-alkoxynitrobenzenes.

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8. Typical procedure: 4-nitroanisole (**7a**) (4.99 g, 0.033 mol), PCl_3 (8.64 mL, 0.099 mol), and $AlCl_3$ (4.41 g, 0.033 mol) were mixed under nitrogen atmosphere into a dried apparatus equipped with a mechanical stirrer and kept at 0°C with an ice bath. After 1 h, the temperature was increased to 50–55°C and the reaction monitored by GC–MS analysis. After about 24 h, the reaction mixture was treated with water and dried over anhydrous $MgSO_4$. The residue was mixed with silica gel and extracted in continuous with $CHCl_3$ in a Soxhlet apparatus. After concentration 'in vacuo', the flash chromatography of the residue gave compounds **8**–**13**. Compounds **8a**, **8b**, **9a**, **9b** were isolated in 30, 7, 15 and 12% yield, respectively.
   The overall yield of compounds **9a**–**13a** was 45% and of **9b**–**12b** was 34%. Compounds **11b**–**13** were contaminated with traces of other isomers. Compounds obtained in traces were identified by comparison with authentic commercial samples or by GC–MS analysis. Even if compound **10a** was cited in literature,[18] the unique data reported are the molecular peak and the melting point of a sample contaminated with **9a**. Here we report other data on this.
   ***trans*-1,2 Bis(4-methoxyphenyl) diazene** (**8a**): yellow solid, 30% yield, impure of traces of *cis*-isomer, $R_f=0.76$ (*n*-hexane:diethyl ether, 1:1); δ_H (300 MHz, $CDCl_3$): 7.27 (d, 4H, $J=9.1$ Hz), 6.95 (d, 4H, $J=9.1$ Hz), 3.88 (s, 6H, OCH_3), δ_C (75.56 MHz, $CDCl_3$): 161.5, 147.1, 124.3, 114.1, 55.5; MS (*m*/*z*,%): 242 (M^+, 87), 135 (35), 107 (100), 92 (37), 77 (42).
   Selected data for new chloro compounds:
   3-Chloro-2,7-dimethoxyphenazine (**10a**): yellow solid, 22% yield mp: 236–238°C (from dichloromethane) Lit.[18]: 234–237°C, $R_f=0.54$ (*n*-hexane:diethyl ether, 1:1); δ_H (300 MHz, $CDCl_3$): 8.19 (s, 1H,), 8.03 (d, 1H, $J=9.6$ Hz), 7.51 (dd, 1H, $J=9.6$ Hz, $J=2.8$ Hz), 7.49 (s, 1H), 7.38 (d, 1H, $J=2.8$ Hz), 4.11 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3); δ_C (75.56 MHz, $CDCl_3$): 160.7, 155.6, 143.9, 141.9, 140.5, 139.7, 130.6, 130.0, 128.9, 126.3, 106.2, 104.8, 56.7, 55.9: MS (*m*/*z*, %): 276 (M^++2, 35), 274 (M^+, 100), 259 (18), 231 (53), 216 (7), 188 (14); HRMS calcd for $C_{14}H_{11}ClN_2O_2$: 274.0509, found: 274.0512.
   3-Chloro-2,7-diethoxyphenazine (**10b**): yellow solid, 16% yield mp: 146–147°C (from dichloromethane) $R_f=0.60$ (*n*-hexane:diethyl ether, 1:1); δ_H (300 MHz, $CDCl_3$): 8.18 (s, 1H), 8.01 (d, 1H, $J=9.5$ Hz), 7.50 (dd, 1H, $J=9.5$ Hz, $J=2.5$ Hz), 7.44 (s, 1H), 7.34 (d, 1H, $J=2.5$ Hz), 4.30 (q, 2H, $J=7.0$ Hz), 4.23 (q, 2H, $J=7.0$ Hz), 1.60 (t, 3H, $J=7.0$ Hz), 1.54 (t, 3H, $J=7.0$ Hz); δ_C (75.56 MHz, $CDCl_3$): 160.1, 155.0, 143.6, 141.7, 140.2, 139.3, 131.2, 129.7, 128.5, 126.8, 106.4, 104.9, 65.3, 64.3, 14.5 14.4; MS (*m*/*z*, %): 302 (M^+, 72), 274 (20), 246 (100), 217 (33); HRMS calcd for $C_{16}H_{15}ClN_2O_2$: 302.0822, found: 302.0802.
   2,7-Dichloro-3,8-dimethoxyphenazine (**11a**): yellow solid, 3% yield $R_f=0.64$ (*n*-hexane:diethyl ether, 1:1); δ_H (300 MHz, $CDCl_3$): 8.18 (s, 2H,), 7.47 (s, 2H), 4.11 (s, 6H); δ_C (75.56 MHz, $CDCl_3$): 156.0, 142.5, 139.8, 131.0, 129.0, 106.1, 56.7; MS (*m*/*z*, %): 310 (M^++2, 66), 308 (M^+, 100), 293 (35), 265 (39); HRMS calcd for $C_{14}H_{10}Cl_2N_2O_2$: 308.0119, found: 308.0109.
   2,7-Dichloro-3,8-diethoxyphenazine (**11b**): yellow solid, 3% yield, $R_f=0.80$ (*n*-hexane:diethyl ether, 1:1); δ_H (300 MHz, $CDCl_3$): 8.16 (s, 2H,), 7.42 (s, 2H), 4.32 (q, 4H, $J=7.0$ Hz), 1.61 (t, 6H, $J=7.0$ Hz); δ_C (75.56 MHz, $CDCl_3$): 155.3, 142.5, 139.6, 131.3, 128.9, 106.5, 65.3, 14.4; MS (*m*/*z*, %): 336 (M^+, 40), 280 (100), 251 (23), 216 (13); HRMS calcd for $C_{16}H_{14}Cl_2N_2O_2$: 336.0432, found: 336.0439.
   1,6-Dichloro-3,8-dimethoxyphenazine (**12a**): yellow solid, 3% yield, $R_f=0.63$ (*n*-hexane:diethyl ether, 1:1); δ_H (300 MHz, $CDCl_3$): 7.58 (d, 2H, $J=2.7$ Hz), 7.26 (d, 2H, $J=2.7$ Hz), 3.93 (s, 6H); δ_C (75.56 MHz, $CDCl_3$): 159.7, 143.9, 141.0, 133.3, 125.4, 106.7, 56.9; MS (*m*/*z*, %): 310 (M^++2, 64), 308 (M^+, 100), 293 (34), 265 (45); HRMS calcd for $C_{14}H_{10}Cl_2N_2O_2$: 308.0119, found: 308.0122.
   1,6-Dichloro-3,8-diethoxyphenazine (**12b**): yellow solid, 3% yield, $R_f=0.70$ (*n*-hexane:diethyl ether, 1:1); δ_H (300 MHz, $CDCl_3$): 7.54 (d, 2H, $J=2.7$ Hz), 7.32 (d, 2H, $J=2.7$ Hz), 4.26 (q, 4H, $J=7.0$ Hz), 1.62 (t, 6H, $J=7.0$ Hz); MS (*m*/*z*, %): 336 (M^+, 37), 280 (100), 251 (25); HRMS calcd for $C_{16}H_{14}Cl_2N_2O_2$: 336.0432, found: 336.0436.
   1,7-Dichloro-3,8-dimethoxyphenazine (**13a**): yellow solid, 2% yield, $R_f=0.60$ (*n*-hexane:diethyl ether 1:1); δ_H (300 MHz, $CDCl_3$): 8.20 (s, 1H), 7.61 (d, 1H, $J=2.6$ Hz), 7.45 (s, 1H), 7.23 (d, 1H, $J=2.76$ Hz), 4.10(s, 3H), 3.91 (s, 3H); δ_C (75.56 MHz, $CDCl_3$): 157.85, 143.2, 140.4, 132.2, 127.2, 108.4, 56.8; MS (*m*/*z*,%): 310 (M^++2, 63), 308 (M^+, 100), 293 (27), 265 (47); HRMS calcd. for $C_{14}H_{10}Cl_2N_2O_2$: 308.0129, found: 308.0118.
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12. **Crystallographic studies of 10a**: $C_{14}H_{10}Cl_1N_2O_2$, $M=273.69$, monoclinic, space group $P2_1/n$, $a=3.9575(5)$, $b=18.188(2)$, $c=8.7141(9)$ Å, $\beta=102.316(4)°$, $V=612.80(12)$ Å^3, $T=293(2)$ K, $Z=2$, $D_{calcd}=1.483$ mg/m^3, μ(Mo Kα)$=0.310$ mm^{-1}, 6036 reflections collected, 1284 unique which were used in all calculations. The value of the

goodness-of-fit indicator was 0.965. Final $R_1(F)=0.0904$ [$I>2\sigma(I)$] and $wR_2(F^2)=0.2641$ (all data). The crystallographic data for **10a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 200015. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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