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*Dedicated to Professor Zeno Simon*
*on the occasion of his 80th anniversary*

# SYNTHESIS AND THEORETICAL STUDY ON SOME NEW PHOSPHORAMIDATES

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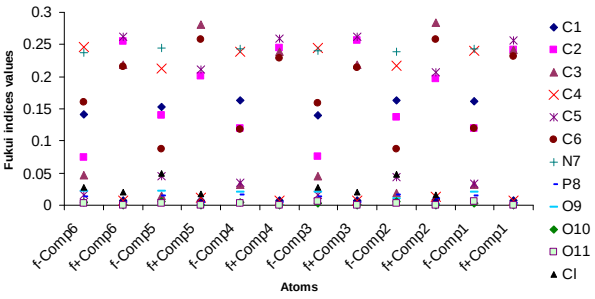
Some new phosphoramidates were prepared by phosphorylation of *orto*-/*meta*-chloroaniline in liquid-solid system, using potassium carbonate as base. The used method is an efficient and convenient one, providing highest yields comparatively with the liquid-liquid system, which use halogenated solvents. The effects of chloro-substituent in the aryl moiety of phosphoramidates, reaction time and yield of reaction were studied. In addition, a theoretical study using DFT method has been carried out. Global chemical reactivity descriptors such as HOMO and LUMO, the global hardness, the softness, Fukui indices and electrostatic potential, have been calculated in order to obtain information about chemical reactivity of new synthesized phosphoramidates.




## INTRODUCTION

Although extensive research was carried on organophosphorous compounds, the interest in this group of chemicals in general and phosphoramidates in particular continues to grow because of their large array of activities and properties reported. Phosphoramidates find extensive applications in agriculture as insecticides[1] and herbicides,[2] in industry as flame retardants[3] and lubricant oil additives[4] and in medicine as antitumor,[5] antiviral,[6] antibacterial,[7] antimalarial[8] and antiprotozoal[9] agents. The reasons for such diversity are based on high alkylating capacity of phosphoramidates and the ability of these molecules to insert in the structure of natural nucleotides.[10]

Beside plethora of applications, phosphoramidates play a key role in organic synthesis. Dialkyl, dibenzyl and diphenyl phosphoramidates are useful in the protection of the amino group.[11] N-arylphosphoramidates have been used for imines synthesis by aza-Wittig reactions[12] and for the preparation of functionalized aziridines by nucleophile cyclizations.[13] Although there is a growing interest in the market in phosphoramidates, the number of published synthetic approaches is relatively reduced.

Amongst the efforts for the synthesis of phosphoramidates, Todd–Atherton reaction is the classical and the most applied one.[14] This method initially used dialkyl phosphite with primary/ secondary alkylamine in the presence of carbon tetrachloride.[15] A number of convenient and valuable modifications of the original method[15a] have been

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introduced (alternative halogen sources such as iodoform,[15b] phosphorylation of amines in an aqueous system in the presence of a catalytic amounts (ca. 5 mol %) of triethylbenzylammonium chloride or tetrabutylammonium bromide[16]). However, the reaction was extended to different nucleophiles, in order to optimize the reaction conditions. It was reported that less nucleophilic amines like aniline[17] can be used in Todd–Atherton reaction, but not successful results was obtained in the case of ortho-substituted aniline.[18]

In our previous works,[19] we have developed a new approach to the preparation of phosphoramidic acid derivatives from unsubstituted, ***meta***- and ***para***-nitroaniline and dialkyl/diarylphosphites in liquid-solid system, using potassium carbonate as base and tetrabutylammonium bromide as catalyst. The method liquid-solid gives low reaction times and higher yields comparatively with liquid-liquid system. Herein, we continue our interest in the chemistry of phosphoramidate derivatives by the synthesis of new compounds and exploring how the variations in the phosphorous substituents influence the reaction times and yield of reaction. This study reports new phosphoramidates prepared by phosphorylation of ***orto***-/***meta***-chloroaniline, in lichid-lichid and lichid-solid systems. The chemical behaviour of chloro-substituted and unsubstitued phosphoramidates at DFT level of theory will be studied, in order to find additional information about their chemical reactivity.

## RESULTS AND DISCUSSION

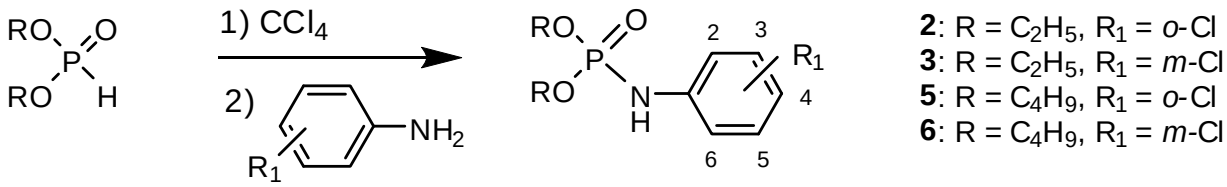
This paper presents the phosphorylation of ***orto***-/***meta***-chloroaniline in liquid-liquid system (methods *a* and *b*) and liquid-solid system (method *c*). The general synthesis of the title compounds is outlined in Scheme 1. The reaction involves a two-step mechanism. In the first step, dialkylphosphite is oxidized to chlorodialkylphosphate, which reacts with chloroaniline in the second step by a nucleophilic substitution, giving corresponding dialkyl-N-aryl-phosphoramidate. No partial dialkylation was detected for these phosphites.

Table 1 presents the comparison between percentage yields for all synthesised phosphoramidates. The influence of anorganic bases on the yield of reaction was investigated. The phosphoramidates obtained by method *c*, where potassium carbonate was used as base, gave better yields. In this case, potassium carbonate strongly reduced saponification reactions, comparatively with sodium hydroxide, used in methods *a* and *b*. It is observed that alkyl phosphite with longer chain and chloro- substituent do not affect the yield of reaction significantly. The experimental elemental analysis data showed good agreement with the calculated values for all synthesised compounds (**2.** found (%): P 11, N 4.8; calcd. (%) P 11.7, N 5.3; **3.** found (%): P 10.9, N 4.7; calcd. (%) P 11.7, N 5.3; **5.** found (%): P 9.1, N 3.8; calcd. (%) P 9.7, N 4.3; **6.** found (%): P 8.9, N 3.7; calcd. (%) P 9.7, N 4.3. It revealed 1:1 stoichiometry for all compounds.

We have noticed that the reaction time influence the yields of reactions. Studies were carried out on the effect of reaction time on the yield of new phosphoramidates obtained by method *c*, with reaction time set at 1, 1.5, 2, 2.5, 3, 3.5 and 4 hour. The results show a change in yield with respect to time. A graph of the phosphoramidates yield against time was plotted to evaluate results (Fig. 1). The results depict that the yield start showing sharp increase after first hour. The good yields were obtained after three hour. The presence of chloro-substituent (either ***ortho***- or ***meta***-) in the aryl moiety of these phosphoramidates determines a phosphorylation longer reaction time (3 h) in comparison with unsubstituted phosphoramidates (2 h).[19a]

Chemical reactivity for all six compounds was investigated by DFT formalism. The HOMO and LUMO energies are computed with B3LYP/6-31G(d) basis set. The frontier molecular orbital HOMO acts as electron donor and hence it is most subjected to an electrophilic attack, while the frontier molecular orbital LUMO is directly associated with electronic deficiency, being most vulnerable to nucleophilic attack. Fig. 2 shows the distributions and energy levels of HOMO and LUMO orbitals (the black colour indicates the positive lobes and the grey colour shows the negative lobes).

The hardness, *H*, can be used to describe the thermodynamic aspects of chemical reactivity. Our theoretical study shows that the distribution range of hardness values is very small with a maximum value of 5.85668 (compound **4**) and minimum value of 5.741718 (compound **5**). f_NN_HOMO is related to the Fukui function, *f*-, and quantifies the atomic sites available for electrophilic attack, and f_NN_LUMO is related to the Fukui function, *f*+, which estimates the centres susceptible to nucleophilic attack.[20]




Scheme 1 – Synthesis of new phosphoramidates (compounds **2**, **3**, **5** and **6**).

*Table 1*

Yields, RMN spectra and quantum-chemical descriptors values for compounds **1** to **6**

| | R=$C_2H_5$ | | | R=$C_4H_9$ | | |
|---|---|---|---|---|---|---|
| | **1*** ($R_1$=H) | **2** ($R_1$=***o***-Cl) | **3** ($R_1$=***m***-Cl) | **4*** ($R_1$=H) | **5** ($R_1$=***o***-Cl) | **6** ($R_1$=***m***-Cl) |
| Method *a* (yield%) | 78 | 58 | 57 | 75 | 65 | 62 |
| Method *b* (yield%) | 43 | 51 | 53 | 40 | 50 | 58 |
| Method *c* (yield%) | 81 | 78 | 72 | 78 | 79 | 75 |
| $^{31}$P-NMR (ppm) | 2.3 | -0.92 | -0.5 | 3 | -0.12 | 0.2 |
| $E_{HOMO}$(eV) | -5.82884 | -6.01722 | -6.0872 | -5.83089 | -6.03863 | -6.10467 |
| $E_{LUMO}$(eV) | 0.02506 | -0.21861 | -0.31477 | 0.025795 | -0.29692 | -0.33017 |
| *EP*(kcal/mol) | -39.443 | -35.608 | -37.353 | -39.410 | -38.698 | -37.581 |
| Global *H* | 5.853905 | 5.798614 | 5.772438 | 5.85668 | 5.741718 | 5.774506 |
| Global *S* | 0.170826 | 0.172455 | 0.173237 | 0.170745 | 0.174164 | 0.173175 |
| f_NN_HOMO | N7; C4 (0.24/0.24) | N7; C4 (0.24/0.22) | C4 (0.24) | N7; C4 (0.24/0.24) | N7; C4 (0.24/0.21) | C4 (0.25) |
| f_NN_LUMO | C5 (0.26) | C3 (0.28) | C2; C5 (0.26/0.26) | C5 (0.26) | C3 (0.28) | C2; C5 (0.26/0.26) |

*EP* = electrostatic potential; *H* = Hardess; *S* = Softness; * for compounds **1** and **4** see reference 19[a]

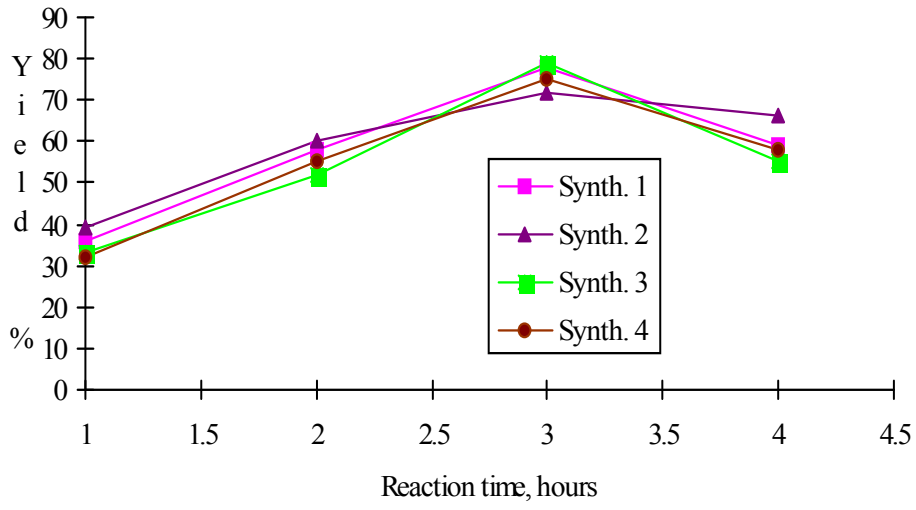



Fig. 1 – Reaction time on the yield of new phosphoramidates.

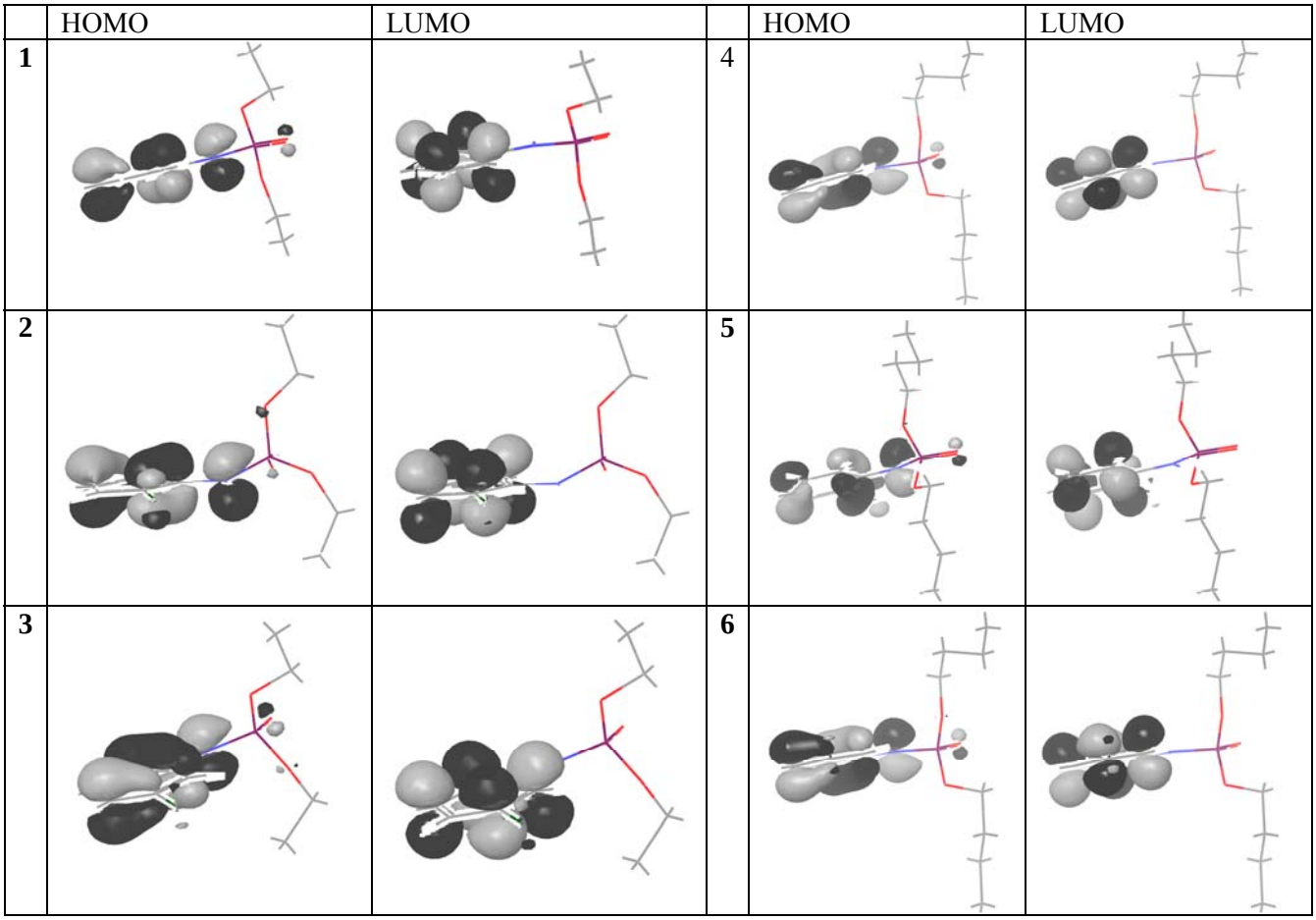



Fig. 2 – Frontier molecular orbitals for compounds **1** to **6**.

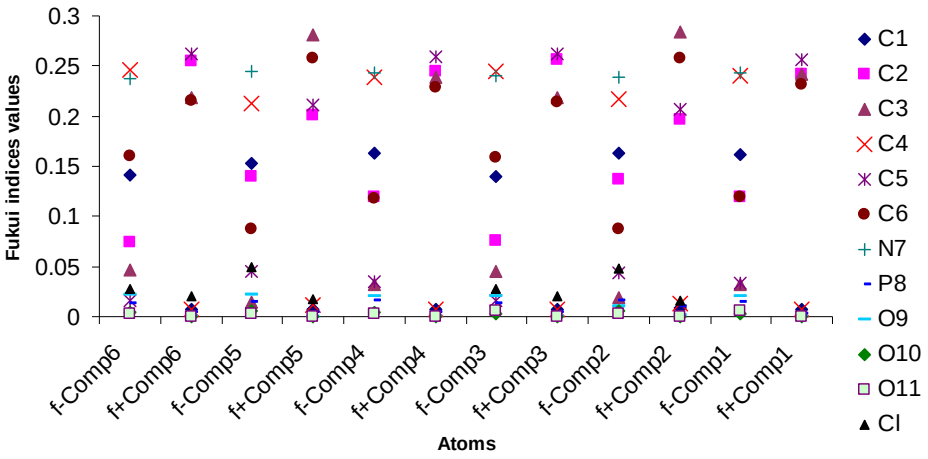



Fig. 3 – Fukui reactivity indices calculated for compounds **1** to **6**.

The highest values of these indices are listed in Table 1. The distribution of Fukui indices with significant values (different from zero) are shown in Fig. 3.

These indices are not reliable to identify the most reactive nucleophilic or electrophilic site inside a molecule being more useful in finding trends in reactivity for a chosen atomic site in a series of related molecules.[21] For studied phosphoramidates series, the atoms susceptible to electrophilic attack are: nitrogen atom and carbon atom of position 4 with similar values, while the carbon atoms of position 2, 3, 5 are susceptible to nucleophilic attack (see Fig. 3).

## MATERIAL AND METHODS

### Experimental details

**General.** All the reagents and solvents were used as received from commercial suppliers, without any further purification. All chemicals used for the synthesis were of analytical grade or laboratory grade and purchased from Aldrich and Merck, Germany. Nuclear magnetic resonance ($^{31}$P-NMR) spectra were recorded on Bruker Avance DRX 400 spectrometer, using $CDCl_3$ as a solvent and 85% $H_3PO_4$ as external standard. Elemental analysis was performed using Kjeldahl and Schöniger methods.

**General procedure for the synthesis.** Four ***orto***- and ***meta***- phosphoramidates from were synthesized by three different methods: liquid–liquid (methods *a* and *b*) and liquid–solid (method *c*).

*Method a.* To a stirred two-phase system of dichloromethane (5 ml) / tetrachloromethane (5 ml) / 25% (w/v) sodium hydroxide (5 ml) and tetrabutylammonium bromide (TBAB) (0.02 g) as catalyst, a mixture of dialkyl phosphite (0.01 mol) and chloroaniline (0.01 mol) in dichloromethane (5 ml) was added drop-wise. The temperature was kept at 0–10°C by external cooling. After completion of addition, the mixture was stirred 1 h at 0–10°C and then 2 h at room temperature. The organic layer was separated, washed with 3% hydrochloric acid (2×10 ml) and water (2 × 10 ml), and dried over anhydrous magnesium sulphate.

*Method b.* To a stirred and cooled (0–10°C) mixture of dialkyl phosphite (0.01 mol) / chloroaniline hydrochloride (0.01 mol) / dichloromethane (5 ml) / tetrachloromethane (5 ml) and tetrabutylammonium bromide (TBAB) (0.02 g) as catalyst, a solution of 25% (w/v) sodium hydroxide (5 ml) was added dropwise. After completed addition, stirring was continued for 1 h at 0–10°C and then for 3 h at room temperature. Then, the organic layer was separated, washed with 3% hydrochloric acid (2 × 10 ml) and water (2 × 10 ml), and dried over anhydrous magnesium sulphate.

*Method c.* To a stirred two-phase system of dichloromethane (5 ml) / tetrachloromethane (5 ml) / potassium carbonate (3 g) and tetrabutylammonium bromide (TBAB) (0.02 g) as catalyst, a solution of dialkyl phosphite (0.01 mol) and chloroaniline (0.01 mol) in 5 ml of dichloromethane was added dropwise. The temperature was kept at 0–10°C by external cooling. After completion of addition, stirring was continued for 1 h at 0–10°C and then for another 3 h at room temperature. The potassium carbonate and potassium chloride were filtered, and the organic layer was separated, washed with 3% hydrochloric acid (2 × 10 ml) and water (2 × 10 ml), and then dried over anhydrous magnesium sulphate.

### Computational details

The chemical behavior of these compounds was theoretically investigated by DFT (Density Functional Theory) methodology.

**Molecular geometry optimization.** Molecular geometry optimizations were carried out initially at semiempirical level using the PM3 method implemented in HyperChem 7.5[22] followed by DFT computations carried out with Jaguar 8.3[21] using the graphical interface Maestro[23] from the Schrödinger package. All calculations were performed using the Becke's three-parameter hybrid method using LYP correlation functional, B3LYP, supplemented with the standard 6-31+G(d) basis sets. The minimum energy structure was confirmed by performing vibrational frequency analysis at the same level of theory, and no imaginary frequencies were obtained.

**Computation of quantum-chemical descriptors.** The theoretical study is focused on computing the eigenvalues of HOMO and LUMO, the global hardness, *H*, the softness, *S*, Fukui indices and electrostatic potential, *EP*. The Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) provide information about the trend of donating/accepting electronic density.[24] The energy gap between HOMO and LUMO directed correlated with hardness-softness offers information regarding the chemical reactivity, polarizability and chemical stability of the molecule.[25] A large HOMO–LUMO gap related to global hardness, *H*, indicates high stability and implicitly low reactivity, and vice versa. The inverse of hardness is defined as softness, *S*.[26] Moreover, the large gap implies low polarizability and the small gap suggests high polarizability. Fukui indices[27] are reactivity indices which provide information about the atoms of a molecule that show a larger tendency to either lose (nucleophilic attack) or accept (electrophilic attack) electron density. The Fukui indices are derived from Mulliken populations and are annotated as f_NN_HOMO for HOMO and

f_NN_LUMO for LUMO, respectively. The atomic sites of molecule which show the highest values of the atomic Fukui indices have the highest reactivity and are susceptible to chemical attacks (see Table 1).

## CONCLUSIONS

A series of new phosphoramidates were synthesized using three different methods. The phosphorylation reaction of ***orto***-/***meta***-chloroaniline with dialkyl phosphite was performed with highest yields in a liquid-solid system, with potassium carbonate as base. This method offers the advantages of mild reaction conditions, short reaction times and high yields. Experimental data indicated that the yield of reaction was not significantly affected by the alkylphosphite with longer chain and chloro- substituent. Regarding reaction time, the presence of chloro- substituent (either ***ortho***- or ***meta***-) in the aryl moiety of these phosphoramidates delays the completion of phosphorylation reaction with one hour in comparison with unsubstituted ones. Global chemical reactivity descriptors of the title molecules, e.g. HOMO and LUMO, the global hardness, *H*, the softness, *S*, Fukui indices and electrostatic potential, *EP* were calculated within the DFT formalism. Low HOMO–LUMO energy gap value suggests the intramolecular charge transfer inside the molecule. The Fukui function helps in identifying the electrophilic/nucleophilic nature of a specific site in a series of related molecules. For studied phosphoramidates series, the nitrogen atoms and carbon atom of position 4 are susceptible for electrophilic attack, and the carbon atoms of position 2, 3, 5 are susceptible for nucleophilic attack.

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