



Full paper/Mémoire

## Synthesis of phosphoenol pyruvates. Theoretical and experimental study



### Synthèse des phosphates d'énols pyruviques. Étude théorique et expérimentale

Amina Ghomri <sup>a,b,\*</sup>, Abdelkrim Atmani <sup>c</sup><sup>a</sup> École préparatoire Sciences et Techniques Tlemcen, BP 165 RP Bel horizon, 13000 Tlemcen, Algeria<sup>b</sup> Laboratoire de thermodynamique appliquée et modélisation moléculaire n° 53, Département de chimie, Faculté des sciences, Université Abou-Bekr-Bekaid, BP 119, 13000 Tlemcen, Algeria<sup>c</sup> Laboratoire des substances naturelles et bioactives (LASNABIO), Département de chimie, Faculté des sciences, Université Abou-Bekr-Bekaid, BP 119, 13000 Tlemcen, Algeria

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## ABSTRACT

A theoretical and experimental study of the reaction of α-chloropyruvate with trialkyl phosphites in toluene is reported. The phosphoenol pyruvate obtained was characterized by (<sup>1</sup>H, <sup>13</sup>C and <sup>31</sup>P) NMR. DFT-based reactivity descriptors are used to explain the main reaction product found experimentally. Global and local reactivity indices, namely global electrophilicity and Parr function, were computed at the B3LYP/6-311(d) level of theory. The solvent's effect on the reactivity indices is elucidated. The computed regioselectivity is in good agreement with experimental outcomes.

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## R É S U M É

Une étude théorique et expérimentale de la réaction des α-chloropyruvates avec les trialkyl phosphites dans le toluène a été réalisée. Les phosphates d'énols obtenues sont caractérisés par RMN (<sup>1</sup>H, <sup>13</sup>C et <sup>31</sup>P). Les descripteurs de réactivité dérivant de la DFT sont utilisés pour expliquer les produits de réaction obtenus expérimentalement. Les indices globaux et locaux de réactivité, à savoir l'électrophilie globale et la fonction de Parr, sont calculés par la méthode B3LYP/6-311G(d). L'effet du solvant sur les indices de réactivité est élucidé. La régiosélectivité calculée est en bon accord avec les résultats expérimentaux.

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## 1. Introduction

A tremendous amount of experimental work has been devoted to the study of the phosphoenols because of their important biological and pharmacological properties [1–4]. Phosphoenols represent important intermediates in organic chemistry for the synthesis of complex organic molecules [5–8].

\* Corresponding author. École préparatoire Sciences et Techniques Tlemcen, BP 165 RP Bel horizon, 13000 Tlemcen, Algeria.

E-mail addresses: ghomriamina@yahoo.fr, am\_ghomri@mail.univ-tlemcen.dz (A. Ghomri).

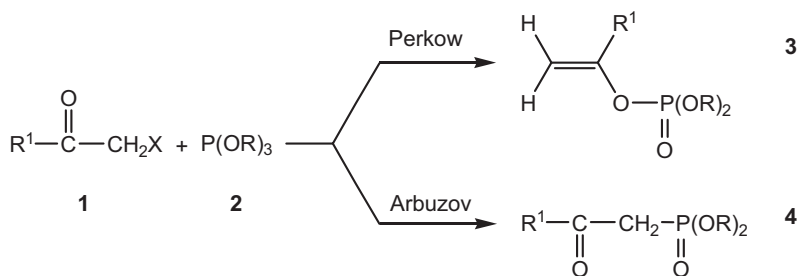


Fig. 1. Competition between the Perkow reaction (formation of phosphoenols) and the Arbuzov reaction ( $\beta$ -ketophosphonate).

The reaction of trialkyl phosphite with  $\alpha$ -halogenated ketones [9,10] leads to a competition between the Perkow reaction (phosphoenol formation) and the Arbuzov reaction ( $\beta$ -ketophosphonate) (Fig. 1). However, a great amount of experimental works devoted to the selective syntheses of phosphoenols can be found in the literature [11–21].

The aim of this work is first to present a simple and selective method of synthesis of phosphoenol pyruvates (PEP). Based on a preceding work [22], we used the  $\alpha$ -chloropyruvates because they present direct precursors of phosphoenol pyruvates and are also easily accessible. We note that, compared with the previous work, our synthesis method has several advantages, such as fairly short reaction times, high yields, mild reaction conditions, absence of catalyst; moreover, it offers ready access to structural variety such as  $\beta$ -substituted phosphoenol pyruvates, not previously available in these series of compounds (Fig. 2).

The second purpose of this study is to evidence the experimental outcomes that state that, in this reaction, the carbon atom of the carbonyl group (C=O) of the  $\alpha$ -halogenoketone is preferred for the electrophilic attack of the trialkyl phosphites  $P(OR)_3$  using theoretical descriptors.

Recently, the popularity and success of density functional theory (DFT) has stimulated many groups to use the Hard and Soft Acids and Bases (HSAB) principle, formulated with DFT [23,24], as a qualitative and quantitative treatment to predict reactivity based upon ground-state properties (density). Furthermore, DFT-based reactivity descriptors, such as condensed Fukui functions [25], local softness [26], local hardness [24b,26], electrophilicity [27], and nucleophilicity indices [28], have proven their utility for the analysis of organic reactions [29–31].

Very recently, Domingo et al. introduced the electrophilic and nucleophilic Parr functions as local indices and showed that these new descriptors provide useful clues for

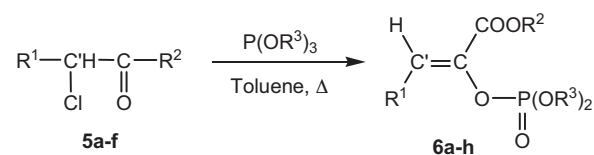


Fig. 2. Reaction of  $\alpha$ -chloropyruvate **5a-f** with trialkylphosphites in toluene.

the characterization of the most electrophilic and nucleophilic centers of molecules, and for the establishment of the regio- and chemoselectivity in polar reactions [32]. The proposed Parr functions were compared with both, the Parr–Yang Fukui functions [33], based on frontier molecular orbitals, and Yang–Mortier condensed Fukui functions [34] based on Mulliken charges. In the present work, we used the electrophilic Parr function as local reactivity indices to justify our experimental finding. To be in agreement with the experimental procedure, the calculations were done in the gas phase then in toluene; the obtained results allow us to discuss the solvent's effect in the determination of the local reactivity indices.

## 2. Theoretical background

### 2.1. Global quantities

Assuming the differentiability of the electronic energy,  $E$ , with respect to  $N$  and  $\nu(r)$ , a series of response functions appear, among which the most important are probably electronegativity ( $\chi$ ) [35] and hardness ( $\eta$ ) [23,36], have been provided with rigorous definitions within the purview of conceptual DFT [25,37]. Electronegativity is the negative of the chemical potential, defined by:

$$\chi = -\mu = -\left(\frac{\partial E}{\partial N}\right)_{\nu(r)} \quad (1)$$

$\mu$  is the Lagrange multiplier associated with the normalization constraint of DFT [25].

Hardness ( $\eta$ ) is defined as the corresponding second derivative,

$$\eta = \left(\frac{\partial^2 E}{\partial N^2}\right)_{\nu(r)} = \left(\frac{\partial \mu}{\partial N}\right)_{\nu(r)} \quad (2)$$

Softness ( $S$ ) is the reciprocal of hardness;  $S = 1/\eta$ .

Using a finite-difference method, the working equations for the calculation of  $\mu$  and  $\eta$  may be given as [25]:

$$\mu = -\frac{I + A}{2} \quad (3)$$

$$\eta = I - A \quad (4)$$

where  $I$  and  $A$  are the ionization potential and electron affinity, respectively. If  $\epsilon_{\text{HOMO}}$  and  $\epsilon_{\text{LUMO}}$  are the energies of the highest occupied and lowest unoccupied molecular

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