ORIGINAL ARTICLE

# SYNTHESIS OF NEW α-AMINO PHOSPHONATES

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|Received | 24 August 2017| |Accepted | 15 September 2017| |Published 24 September 2017 |

## ABSTRACT

**Background**: we reported in this paper another part of our investigations concerning the preparation of diethyl (2-benzoylamino-2-(phenylsulfanyl) methyl) phosphonate and diethyl (2-benzoylamino-2-(4-chloro- phenylsulfanyl) methyl) phosphonate **2**-**3**, with the aim to have access to new active biomolecules with a good yield through *S*-alkylation reaction. **Objectives**: α-Amino esters possess a broad range of applications ranging from agrochemistry to medicine. We developed a simple, efficient, and environmentally benign method for the Synthesis of new racemic phosphonic α-amino esters by *S*-alkylation of diethyl (2-azido-2-benzoylaminomethyl) phosphonate with aromatic thiols (thiophenol and 4-chloro thiophenol). The structures of the newly synthesized compounds were supported by $^{1}$H NMR, $^{13}$C-NMR and mass spectral data. This method has advantages of mild condition, no environmental pollution, and simple work-up procedures. Most importantly, compounds of α-phosphonic aminoesters are obtained in acceptable to moderate yields by this methodology. **Methods:** The *S*-alkylation of diethyl (2-azido-2-benzoylaminomethyl) phosphonate with aromatic thiols (thiophenol and 4-chloro thiophenol) are performed in different solvents (acetone and acetonitrile) for 48 h at room temperature in the presence of various bases ($Et_3N$ and DIEPA). **Results**: The products **2**-**3** synthesized with a satisfactory yields were characterized by nuclear magnetic resonance and mass spectrometry. **Conclusions**: we have developed an environmentally friendly, mild condition protocol and convenient procedure for the preparation of new phosphonic α-aminoesters derivatives starting from the appropriate azide derivative **1**. The nucleophilic substitution of azide with different thiols (thiophenol and 4-chloro thiophenol) occurred under very mild conditions and led after a reaction time of about 48 hours to the desired products with a satisfactory yields.

***Keywords**: α-amino ester, S-alkylation, thiophenol, diethyl (2-azido-2-benzoylaminomethyl) phosphonate.*

## 1. INTRODUCTION

The synthesis of α-amino phosphonates has attracted much attention recently due to their structural analogy to α-amino acids [1] and significant biological activities. Indeed, a number of potent antibiotics [2], enzyme inhibitors [3] and pharmacological agents [4] are α-aminophosphonates as well as their derivatives, notably peptides. α-Aminophosphonates are also found as constituents of natural products.

These important compounds have been synthesized by various routes. Among the literature methods [5, 6, 7, 8, 9, 10, 11, 12, 13], the Kabachnik–Fields reaction is one of the most convenient approaches to α-aminophosphonates [14, 15].
For this reason, we considered it interesting to synthesize new compounds of α-phosphonic amino acid, in order to study their biological activities.

## 2. RESULTS AND DISCUSSION

Following the research done on the synthesis of new α-phosphonic aminoesters by our team [16, 17, 18], and to study the effect of solvent and base on the yield of the reaction of synthesis of new α-phosphonic aminoesters, we reported in this paper another part of our investigations concerning the preparation of diethyl (2-benzoylamino-2-(phenylsulfanyl)methyl) phosphonate and diethyl (2-benzoylamino-2-(4-chloro- phenylsulfanyl) methyl) phosphonate **2**-**3**. Our strategy is based on the *S*-alkylation of diethyl (2-azido-2-benzoylaminomethyl) phosphonate **1** with aromatic thiols (thiophenol and 4-chloro thiophenol) (Scheme 1) in different solvents in the presence of various bases. Azide derivative **1** was prepared using Achamlale's version [16] of the Steglich reaction [18]. Diethyl (2-azido-2-benzoylaminomethyl) phosphonate **1** was obtained by the reaction [16] of sodium azide with the diethyl (2-bromo-2-benzoylaminomethyl) phosphonate. The title compound is stable and can be stored for an unlimited time without any signs of decomposition. The diethyl (2-bromo-2-benzoyl-aminomethyl) phosphonate also can be used and gives satisfactory results; the azide **1** is used especially for its stability.



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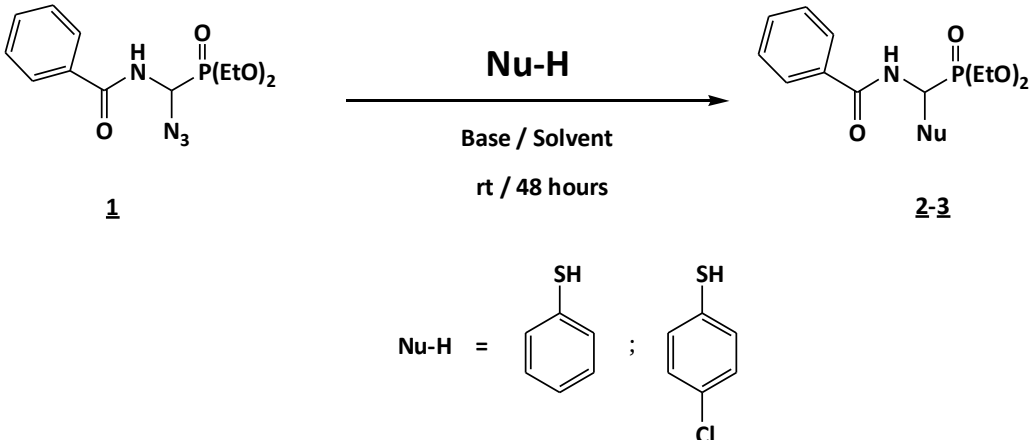


**Scheme 1.** *S*-alkylation of aromatic thiols (thiophenol and 4-chloro thiophenol) with diethyl (2-azido-2-benzoylaminomethyl) phosphonate **1**.

The *S*-alkylation reactions were carried out in different solvents (acetone, $CH_3CN$, and THF) for 48 hours at room temperature in the presence of various bases ($Et_3N$, DIEPA). The products **2**-**3** synthesized with satisfactory yields were characterized by nuclear magnetic resonance and mass spectrometry. The results are summarized in Table 1.

**Table 1:** Synthesis of diethyl (2-benzoylamino-2-(phenylsulfanyl) methyl) phosphonate **2** and diethyl-(2-benzoylamino-2-(4-chloro- phenylsulfanyl) methyl) phosphonate **3**.

| Nu-H | Product | Reaction Time (h) | $Et_3N$ THF | $Et_3N$ $CH_3CN$ | $Et_3N$ Acetone | DIEPA $CH_3CN$ | DIPEA Acetone |
|---|---|---|---|---|---|---|---|
| | | | Yield (%) | Yield (%) | Yield (%) | Yield (%) | Yield (%) |
| Thiophenol | Diethyl (2-benzoylamino-2-(phenylsulfanyl) methyl) phosphonate **2** | 48 | 25 | 40 | 52 | 68 | 80 |
| 4-Chloro thiophenol | Diethyl (2-benzoylamino-2-(4-chlorophenylsulfanyl)-methyl) phosphonate **3** | 48 | 30 | 41.5 | 54 | 70.5 | 84 |

DIEPA: diisopropylethylamine.
$Et_3N$: triethylamine.
THF: Tetrahydrofuran.
$CH_3CN$: Acetonitrile.

It should be noted that the yield of pure product **3** was slightly increased, which is consistent with the presence of halogen atoms on the system thiophenol (nucleophilic agent) whose the (+M) mesomeric effect outweighs the inductive effect attractor (-I).

In summary, the solvents played an important role in the nucleophilic substitution of α-phosphonic α-azido-aminoester. Further studies established that absolute acetone also was the best choice among the solvents (acetone, $CH_3CN$, and THF) screened (Tables 1). All reactions were of low yields in THF. All reactions were conducted at room temperature in dry acetone in the presence of DIEPA (diisopropylethylamine) gave the best results.

## 3. MATERIELS AND METHODES

### 3.1. General

Melting points were determined with an Electrothermal melting point apparatus and are uncorrected. NMR spectra ($^1H$, $^{13}C$) were recorded on a Bruker AM 300 (operating at 300.13 MHz for $^1H$, at 75.47 MHz for $^{13}C$) spectrometer. NMR data are listed in ppm and are reported relative to tetra-methylsilane ($^1H$, $^{13}C$); residual solvent peaks being used as internal standard. All reactions were followed by TLC. TLC analyses were carried out on 0.25 mm thick precoated silica gel plates (Merck Fertigplatten Kieselgel 60F254) and spots were visualized under UV light or by exposure to vaporized iodine. Mass spectra were recorded by electrospray on a micromass ESl Platform II.

### 3.2. Typical procedure for N-alkylation

To a stirred solution of 2.86 mmol of thiols (sulfur compounds) and 3.12 mmol of diisopropylethylamine in 10 mL of dry acetone, 2.6 mmol of diethyl (2-azido-2-benzoylaminomethyl) phosphonate were added. The mixture was stirred at room temperature and the reaction was followed by TLC (Kiesegel Merck 60F254). The solvent was evaporated under reduced pressure. The residue was quenched with saturated aqueous solution of ammonium chloride (20 mL) and extracted with dichloromethane (20 mL × 3). The organic phase was dried in sodium sulfate ($Na_2SO_4$) and the solvent was removed under reduced pressure. The product was purified by column chromatography on silica gel using ether or ether/methanol as eluant to afford pure *S*-alkylated phosphonate.

### 3.3. Diethyl (2-benzoylamino-2-( phenylsulfanyl) methyl) phosphonate 2:

Yield = 80 %. Rf: 0.53 (ether / MeOH). $^1$H NMR (250 MHz, $CDCl_3$): δppm = 1.27 (3H, t, J=7 Hz, $CH_3$) ; 1.32 (3H, t, J=7 Hz); 4.10 (2H, m, $OCH_2$); 4.20 (2H, m, $OCH_2$); 6.10 (1H$_\alpha$, dd,, $^2J_{H\text{-}P}$=20.35 Hz, $^3J_{H\text{-}H}$=9.80 Hz ); 7.08(1H, m, NH); 7.25-7.60 (8H, m, 8H$_{Benzi}$); 7.85 (2H, m, H$_{Benzi}$). M.S. (FAB$^+$): 380 [M + H]$^+$, $C_{18}H_{22}PNO_4S$.

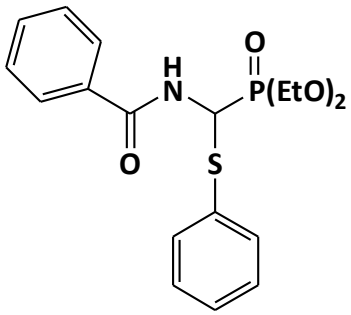


**Figure 1:** Diethyl (2-benzoylamino-2-(phenylsulfanyl) methyl) phosphonate **2**

### 3.4. Diethyl (2-benzoylamino-2-(4-chlorophenylsulfanyl) methyl) phosphonate 3:

Yield = 84 %. Rf: 0.60 (ether / MeOH). $^1$H NMR (250 MHz, $CDCl_3$): δppm = 1.27 (3H, t, J=7 Hz, $CH_3$) ; 1.32 (3H, t, J=7 Hz); 4.10 (2H, m, $OCH_2$); 4.20 (2H, m, $OCH_2$); 6.10 (1H$_\alpha$, dd,, $^2J_{H\text{-}P}$=20.35 Hz, $^3J_{H\text{-}H}$=9.80 Hz ); 7.08(1H, m, NH); 7.25-7.60 (7H, m, 7H$_{Benzi}$); 7.85 (2H, m, H$_{Benzi}$). M.S. (FAB$^+$): 414.5 [M + H]$^+$, $C_{18}H_{21}ClPNO_4S$.

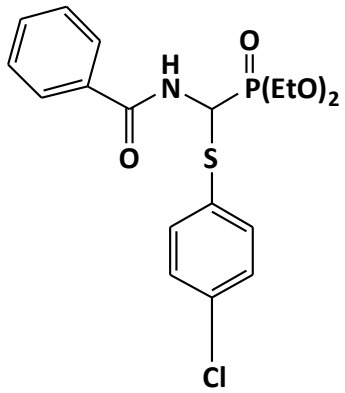


**Figure 2:** Diethyl (2-benzoylamino-2-(4-chloro phenylsulfanyl) methyl) phosphonate **3**

## 4. CONCLUSION

- In order to study their biological activities, we considered it interesting to synthesize new compounds of α-phosphonic amino acid.

- In summary, we have developed an environmentally friendly, mild condition protocol and convenient procedure for the preparation of new phosphonic α-aminoesters derivatives starting from the appropriate azide derivative **1**. The nucleophilic

substitution of azide with different thiols (thiophenol and 4-chloro thiophenol) occurred under very mild conditions and led after a reaction time of about 48 hours to the desired products with satisfactory yields.

- The nucleophilic nature of the reagents has an immediate influence on the α-hydrogen acidity and its possible effect the reactivity of the α-amino acids.

**Acknowledgment** We thank the CNRST for financial support of this work (PROTARS D13/03, Morocco).

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**Cite this article: El Houssine Mabrouk, and Khalid Boukallaba.** SYNTHESIS OF NEW α-AMINO PHOSPHONATES. *Am. J. innov. res. appl. sci. 2017; 5(4): 246-249.*