GLOBAL JOURNAL OF ENGINEERING SCIENCE AND RESEARCHES

SYNTHESIS OF DIETHYL (2-BENZOYLAMINO-2-(PHENOXY) METHYL) PHOSPHONATE

El Houssine Mabrouk [*1] **& Khalid Boukallaba**[2]
[*1]Laboratory of Organic Chemistry, Faculty of Sciences Dhar El Mehraz, University Sidi Mohamed BenAbdellah, Fez, B.P.:1796-Fès Atlas, Morocco

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ABSTRACT

α-Amino esters possess a broad range of applications ranging from agro chemistry to medicine. We developed a simple, efficient, and environmentally benign method for the Synthesis of Diethyl (2-benzoylamino-2-(phenoxy) methyl) phosphonate by *O*-alkylation of diethyl (2-azido-2-benzoylaminomethyl) phosphonate with phenol. The structure of the newly synthesized compound was 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, the α-phosphonic aminoester was obtained in acceptable yields by this methodology.

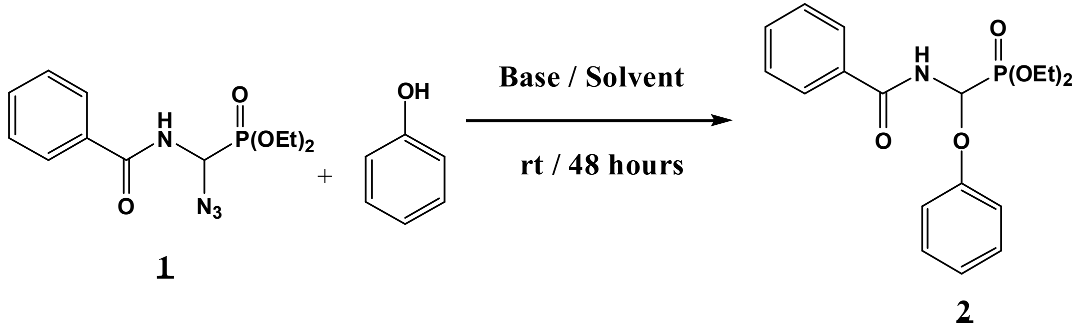
Keywords: *α-amino ester, O-alkylation, phenol, diethyl (2-azido-2-benzoylaminomethyl) phosphonate.*

I. 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-Amino phosphonates are also found as constituents of natural products. These important compounds have been synthesized by various routes. Among the literature methods [5-13], 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.

II. RESULT & DISCUSSION

Following the research done on the synthesis of new α-phosphonic aminoesters by our team [16-18], 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-(phenoxy) methyl) phosphonate **2**. Our strategy is based on the O-alkylation of diethyl (2-azido-2-benzoylaminomethyl) phosphonate **1** with phenolic alcohol (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.



Scheme 1. O-alkylation of phenol with diethyl (2-azido-2-benzoylaminomethyl) phosphonate 1

As shown in scheme 1, the *O*-alkylation reactions were conducted at room temperature in different solvents (acetone, CH_3CN, and THF) in the presence of various bases (Et_3N, DIEPA) for 48 hours. The compound **2** synthesized with satisfactory yields was characterized by nuclear magnetic resonance and mass spectrometry. The results are summarized in Table **1**.

Table 1. Synthesis of diethyl (2-benzoylamino-2-(phenoxy)methyl) phosphonate 2.

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(%)**
phenol	Diethyl (2-benzoylamino-2-(phenoxy)-methyl) phosphonate **2**	48	12	30	40	55	68

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 (Table **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.

III. METHOD & MATERIAL

To a stirred solution of 2.86 mmol of alcohol (oxygen compound) and 3.12 mmol of diisopropylethylamine or triethylamine in 10 mL of dry acetone or anhydrous acetonitrile, 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 O-alkylated phosphonate.

Yield = 68 %. Rf : 0.6 (ether / MeOH). ^1H NMR (250 MHz, $CDCl_3$): δppm = 1.21 (3H, t, J=7 Hz, CH_3) ; 1.25 (3H, t, J=7 Hz); 4.06 (2H, m, OCH_2); 4.16 (2H, m, OCH_2); 6.12 ($1H_\alpha$, dd, $^2J_{H-P}$=20.35 Hz, $3J_{H-H}$=9.80 Hz); 7.14 (1H, m, NH); 7.24-7.68 (8H, m, $8H_{Benzi}$); 7.85 (2H, m, H_{Benzi}). ^{13}C NMR ($CDCl_3$, ppm) δC 171.4 (CO), 116.20 (2C), 121.4, 127.47 (2C), 128.84 (2C), 130.8 (2C), 132.29, 133.52, 165.70 (C_6H_5 aromatic carbons) , 88.41 (-CH-), 68.92 (2C) (CH_3CH_2O), 17.54 (2C) (CH_3CH_2O). M.S. (FAB+): 364 [M + H]+, $C_{18}H_{22}PNO_5$.

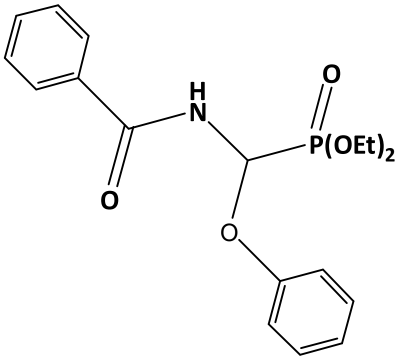


Figure 1: Diethyl (2-benzoylamino-2-(phenoxy) methyl) phosphonate 2

IV. CONCLUSION

The nucleophilic substitution of Phosphonic azide with phenol occurred under very mild conditions and led after about 48 hours to the desired product with a satisfactory yield.

V. ACKNOWLEDGEMENTS

We thank the CNR for financial support of this work (PROTARS D13/03, Morocco)

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