International Journal of Chemistry and Pharmaceutical Sciences

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R E S E A E C H A R T I C L E

Synthesis of diethyl (2-benzoylamino-2-(2-hydroxyethoxy) methyl) phosphonate

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A B S T R A C T

The title compound, diethyl (2-benzoylamino-2-(2-hydroxyethoxy) methyl) phosphonate was synthesized in high yield by O-alkylation reaction between diethyl (2-azido-2-benzoylaminomethyl) phosphonate and ethane-1,2-diol in different solvents in the presence of various bases. The structure of this product was established on the basis of NMR spectroscopy (1H, 13C), and MS data.

Keywords: α-amino ester, O-alkylation, ethane-1,2-diol, diethyl (2-azido-2-benzoylaminomethyl) phosphonate, α-aminoacids.

A R T I C L E I N F O

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MS-ID: IJCPS3778

PAPER-QRCODE

A R T I C L E H I S T O R Y: Received 21 Nov 2018, **Accepted** 10 December 2018, **Available Online** 27 January 2019

Citation: El Houssine Mabrouk, *et al. Synthesis of diethyl (2-benzoylamino-2-(2-hydroxyethoxy) methyl) phosphonate*. *Int. J. Chem, Pharm, Sci.*, 2019, 7(1): 26-29.

C O N T E N T S

1. Introduction

Amino phosphonates are phosphorus structural analogs of a-amino acids [1,2]. The medicinal importance and biological effects of α-amino phosphonate derivatives as antibiotics [3], herbicides, fungicides, insecticides [4], enzyme inhibitors [5], HIV protease [6], plant growth regulators [7] anti-thrombotic agents [8], peptidases and proteases [9], had stimulated scientific research to develop many synthetic procedures for them. Based on this background over the last few years we

have synthesized and reported [10-12] some bioactive, antimicrobial, anti-cancer and anti-oxidant phosphates.

Among the various synthetic protocols described for the synthesis of α-amino phosphonates [13] nucleophilic addition of phosphites to imines i.e., Kabachnik-Fields reaction [14] proved to be a convenient route. For the efficient and capitulate oriented synthesis of α-amino phosphonates various other synthetic methodologies have been reported by using different catalysts. For this reason, we considered it interesting to synthesize new compound of α-phosphonic amino acid, in order to study their biological activitie.

2. Materials and Methods

General

Melting points were determined with an Electro thermal melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC-250 MHz spectrometer in $CDCl_3$ with TMS as an internal standard; coupling constants are reported in Hz. NMR data are listed in ppm and are reported relative to tetra-methylsilane (^{1}H, ^{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 visualised under UV light or by exposure to vaporised iodine. Mass spectra were recorded by electrospray on a micromass ESl Platform II.

Typical procedure

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.

Diethyl-(2-benzoylamino-2-(2-hydroxyethoxy)-methyl) phosphonate 2:

Yield = 76 %. Rf : 0.7 (ether / MeOH). ^{1}H NMR (250 MHz, $CDCl_3$): δppm = 1.20 (3H, t, J=7 Hz, CH_3) ; 1.24 (3H, t, J=7 Hz); 4.04 (2H, m, OCH_2); 4.14 (2H, m, OCH_2); 4.48 (m, 1H, OH); 4.70 (m, 2H, OCH_2); 4.84 (m, 2H, CH_2OH); 6.10 (1H$_\alpha$, dd, $^2J_{H\text{-}P}$=20.35 Hz, $^3J_{H\text{-}H}$=9.80 Hz); 7.14 (1H, m, NH); 7.63-7.85 (m, 5H, Harom). ^{13}C NMR ($CDCl_3$, ppm) δC 170.41 (CO), 133.42, 130.79, 128.91 (2C), 127.86 (2C) (C_6H_5 aromatic carbons), 82.41 (-CH-), 73.80 (OCH_2), 67.42 (COH), 66.32 (2C) (CH_3CH_2O), 17.50 (2C) (CH_3CH_2O). M.S. (FAB+): 332 [M + H]+, $C_{14}H_{22}PNO_6$.

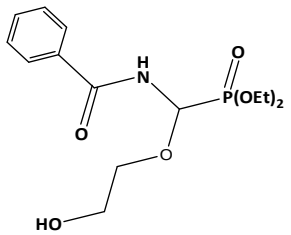

Fig 1: Diethyl (2-benzoylamino-2-(2-hydroxyethoxy) methyl) phosphonate 2

3. Results and Discussions

Following the research done on the synthesis of new α-phosphonic amino esters by our team [15,16], 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-(2-hydroxy ethoxy) methyl) phosphonate 2.

Our strategy is based on the *O*-alkylation of diethyl (2-azido-2-benzoylaminomethyl) phosphonate 1 with ethane-1,2-diol in different solvents in the presence of various bases. Azide derivative 1 was prepared using Steglich method [17] and the procedure of our team[15]. Diethyl (2-azido-2-benzoylaminomethyl) phosphonate 1 was obtained by the reaction 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.

For the reaction of ethane-1,2-diol with azide 1, our estimate was to have two products 2 and 3 with the predominance of one over another, but the spectroscopic data obtained showed the existence of only a single product: diethyl (2-benzoylamino-2-(2-hydroxyethoxy) methyl) phosphonate 2 (Scheme 1).

As shown in scheme 1, the *O*-alkylation reaction was 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 yield was characterized by nuclear magnetic resonance and mass spectrometry. The results are summarized in Table 1.

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**). The reaction was of low yield in THF. The reactions was conducted at room temperature in dry acetone in the presence of DIEPA (diisopropylethylamine) gave the best results.

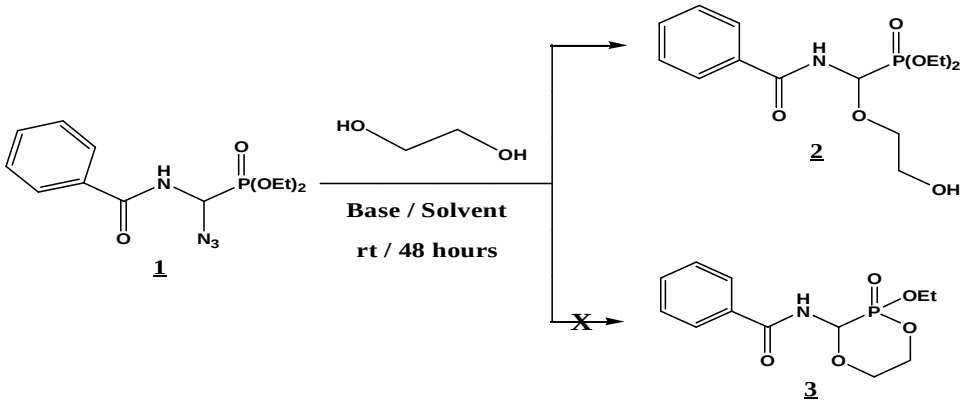

Fig 2: O-alkylation of ethane-1,2-diol with diethyl (2-azido-2-benzoylaminomethyl) phosphonate 1

Table No 1: Synthesis of diethyl (2-benzoylamino-2-(2-hydroxyethoxy) 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 (%)
Ethane-1,2-diol	diethyl (2-benzoylamino-2-(2-hydroxyethoxy)-methyl) phosphonate **2**	48	20	38	52	70	76

4. Conclusion

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-(2-hydroxyethoxy) methyl) phosphonate. The nucleophilic substitution of phosphonic azide with ethane-1,2-diol occurred under very mild conditions and led after about 48 hr to the desired product with a satisfactory yield.

5. Acknowledgment

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

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