ORIGINAL ARTICLE

European Journal of Advanced Chemistry Research
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Synthesis and Characterization of the Structure of Diethyl [(4-{(1H-Benzo[*d*]Imidazol-1-yl)Methyl}-1H-1,2,3-Triazol-1-yl)(Benzamido)Methyl]Phosphonate Using 1D and 2D NMR Experiments

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ABSTRACT

The biheterocyclic derivative of the phosphonic glycine analogue is prepared selectively by reaction between the α-azidoamino diethyl methylphosphonate and the 1-(prop-2-yn-1-yl)-1H-benzo[d]imidazole. The dipolar -1,3 cycloaddition reaction using Click Chemistry was carried out in a solvent water/ethanol mixture in a ratio of 1:1. Copper sulphate pentahydrate and sodium ascorbate are used in the reaction in catalytic amounts. The compound [diethyl [{4-[(1H-benzo[d]imidazol-1-yl)methyl]-1H-1,2,3-triazol-1-yl}(benzamido) methyl] phosphonate was isolated pure as a white powder, after chromatography on a silica gel column (ethyl acetate/hexane acetate: 1/1). The yield of pure product is 90%, after recrystallization in an ether/hexane mixture. The structure of the -1,4 isomer is attributed to the compound obtained by means of 1D and 2D NMR and based on data from the literature concerning the cycloaddition reaction via Click Chemistry. Two-dimensional NMR spectroscopy played a major role. The analysis of the different correlations between adjacent hydrogens and carbons, and also between hydrogens and distant carbons, confirmed the proposed structure.

Keywords: diethyl α-amino phosphonate, Benzimidazole, Alkyne, Azide, Dipolar -1,3 cycloaddition, 2D NMR experiments.

Published Online: January 10, 2021

ISSN: 2684-4478

DOI :10.24018/ejchem.2021.2.1.42

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I. INTRODUCTION

The phosphonic α-amino acids and their derivatives has a considerable role play in the design of new drugs [1]. Thus, these derivatives have a high potential for diverse biological activity [2], acting as a protease inhibitor agent of West Nile virus [3], anticancer agent [4], antibacterial [5], antioxidant [6]. Their various applications are also oriented in the inhibitory use of bone resorption [7], [8].

This wide range of therapeutic and pharmacological activity [9] has led researchers to promote new methods for the preparation of α-amino phosphonic acid [10], whose main routes are the one-pot reaction of Kabachnick field [11]-[13] and the synthesis of chiral products of α-amino phosphonates [14]-[16]. In this case, the synthesis of new heterocyclic phosphonic amino esters continues to bloom in the literature.

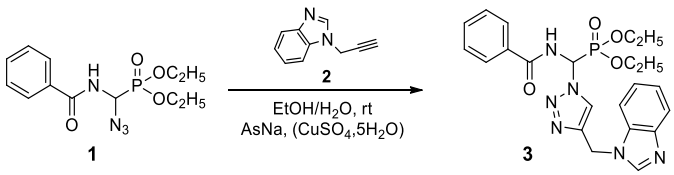
In addition, click chemistry today constitutes an innovative and valuable tool in organic synthesis with applications in various domains, such as medicine [17], biology [18], biomedical field [19], and nanotechnology [20]. In the light of these observations and in the continuity of our previous work on the synthesis of α-heterocyclic phosphonic amino acids [21]-[25], we report in this paper the preparation of a new biheterocyclic phospohonic aminoester, entituled, diethyl [{4-[(1H-benzo[d]imidazol-1-yl)methyl}-1H-1,2,3-triazol-1-yl}(benzamido)methyl] phosphonate.

Thus, we have adopted the strategy using, initially, the synthesis of dipolarophile (2) via a nucleophilic substitution reaction of 1H-benzo[d]imidazole [26] on propargyl bromide (80 wt. % in toluene). Then, we carried out the dipolar cycloaddition reaction via click chemistry between the azide derivative (1) and the alkyne derivative of benzimidazole (2). The -1,4 regioisomer isolated with excellent yield, is characterized by one- and two-dimensional spectroscopy (^{31}P, ^{1}H, ^{13}C).

II. RESULTS AND DISCUSSION

The alkyne derivative (2) is synthesised according to the method reported in the literature [26] via the substitution of bromine by the benzimidazole nucleus, which is characterized by the presence of an acidic proton. Like so, this experiment has enabled us to have and characterize the 1-(prop-2-yn-1-yl)-1H-benzo[d]imidazole (2) with a yield of 78%. The azide dipole (1) was obtained with an overall yield of 85%, adopting a synthesis strategy [16a] consisting of six stages and demanding a strictly anhydrous environment, under an inert atmosphere of nitrogen. The final step to obtain the azide dipole (1) is the action of sodium azide on diethyl benzamidobromomethyl) phosphonate.

The condensation of dipolarophile (2) and azide dipole (1) under the previously specified click chemistry conditions, allowed cyclisation with an efficiency of 90%. (Scheme 1).



Scheme 1. Reaction protocol for the synthesis of product (3).

According to Huisgen's procedure and our previous research [21], [22], 1,3-dipolar cycloaddition leads to the formation of the two 1,4- and 1,5-regioisomers with a predominance of the 1,4-isomer. Nevertheless, in the requirements of Click chemistry [27], [28] regarding the nature of the metal ion used as a catalyst, this reaction selectively leads to a single -1,4 or -1,5 regioisomer. Thus, in the presence of copper II ions [27], only the -1,4-isomer is isolated, whereas in the presence of Rhodium I [28], only the 1,5-isomer is isolated. As far as we are concerned, we have used copper II sulphate and sodium ascorbate in the cyclisation reaction. Only one product is isolated after purification on a silica gel column and recrystallisation in a mixture of solvents: ether/hexane. The solvent mixture (ethyl acetate/hexane: 1/1) was used as a purification eluent. The structure of the 1,4 regioisomer obtained with an excellent yield is proposed through the analysis of its spectra of the coupled and decoupled ^{31}P NMR (Fig. 1B), the 1D ^{1}H and ^{13}C NMR (Fig. 2 and 3), as well as through the examination of the different correlations from the 2D ^{1}H-^{1}H and ^{1}H-^{13}C NMR (Fig. 4, 5 and 6).

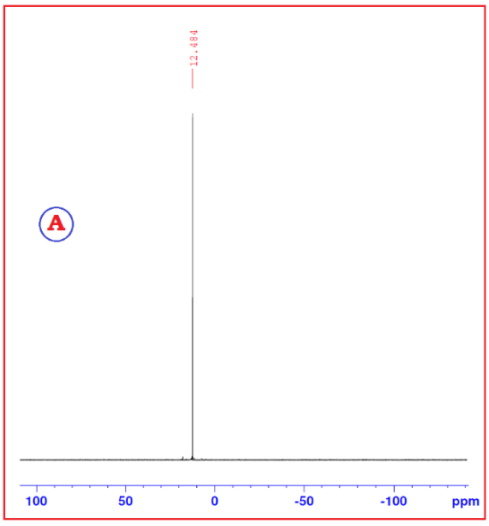


Fig. 1 A. Decoupled ^{31}P NMR spectrum of (3).

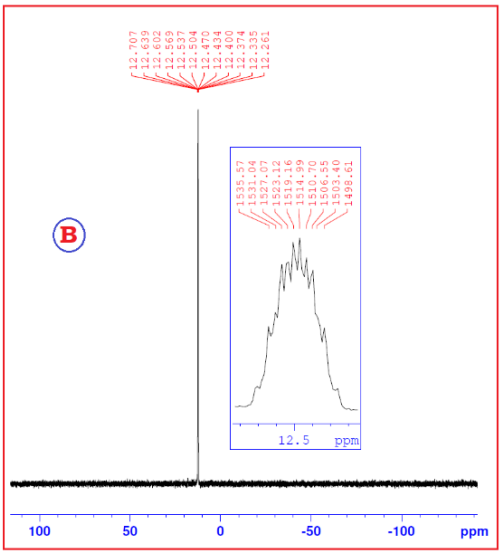


Fig. 1 B. Coupled ^{31}P NMR spectrum of (3).

Thus, its decoupled 31 phosphorus NMR spectrum (Fig. 1A) shows a singlet at 12.48 ppm, while its coupled ^{31}P NMR spectrum (Fig. 1B) shows a single signal centred at 12.48

ppm. The spread of this signal makes it clear that it is a multiplet because of the coupling of phosphorus with neighboring carbons and hydrogens.

Besides, the ^{13}C NMR spectrum of the cycloadduct (3) (Fig. 2) reveals the coupling of phosphorus with:

- Alpha carbon of the phosphonate ($^{1}J_{P\text{-}CH}$ = 183.40 Hz).
- Carbonyl carbon ($^{3}J_{CO\text{-}P}$ = 9 Hz).
- Carbons of the two ethoxy groups ($^{2}J_{OCH2\text{-}P}$ = 6.8 Hz and $^{3}J_{OCH2CH3\text{-}P}$ = 6 Hz).

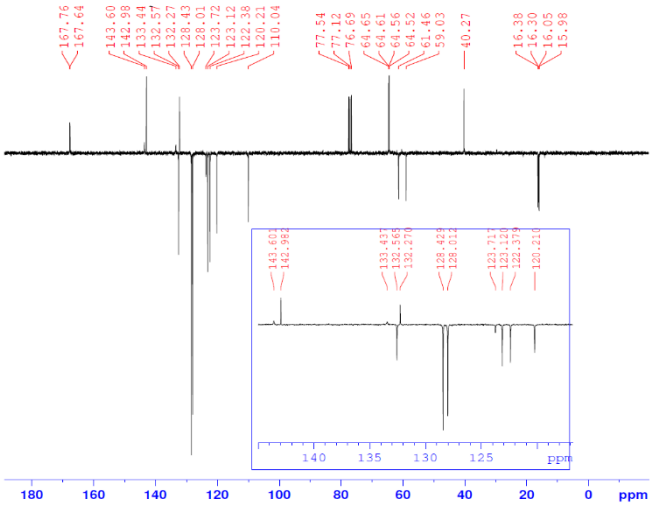


Fig. 2. ^{13}C NMR spectrum of compound (3).

Whereas in ^{1}H NMR (Fig. 3), a signal is revealed in the form of a split double corresponding to the hydrogen atom carried by the alpha carbon of the phosphonate. This is justified by the coupling with both amidic hydrogen -NH and phosphorus ^{31}P, $^{2}J_{CH\text{-}P}$ = 16.80 Hz et $^{3}J_{CH\text{-}NH}$ = 9.90 Hz. In addition, a quadruple split signal corresponding to two protons of the first ethoxy group OCH_2CH_3 is justified by the coupling found both with the coupling constants $^{3}J_{OCH2\text{-}CH3}$ = 7 Hz et $^{3}J_{OCH2\text{-}P}$ = 1.5 Hz. Ultimately, two split quintupled signals are attributed to the two O**CH_aH$_b$** protons of the other ethoxy group because the two protons **H_a** and **H_b** are not magnetically similar. The coupling constants are similar to the above.

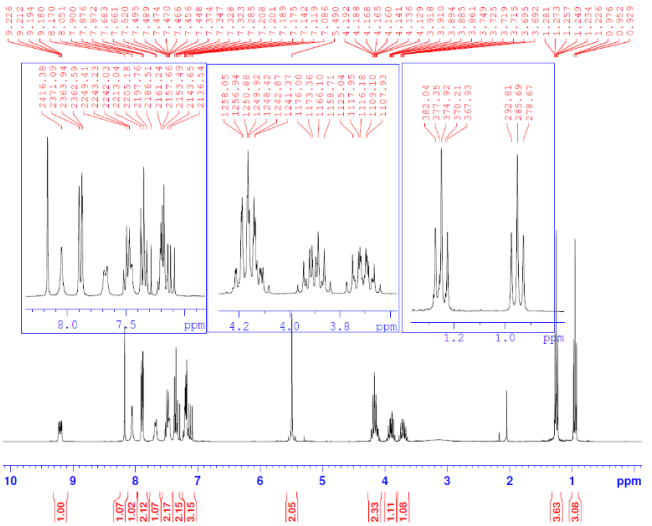


Fig. 3. ^{1}H NMR spectrum of compound (3).

Furthermore, the analysis of the different proton-proton correlations of the cycloadduct (3) also shows a perfect correlation between neighbouring protons (Fig. 4).

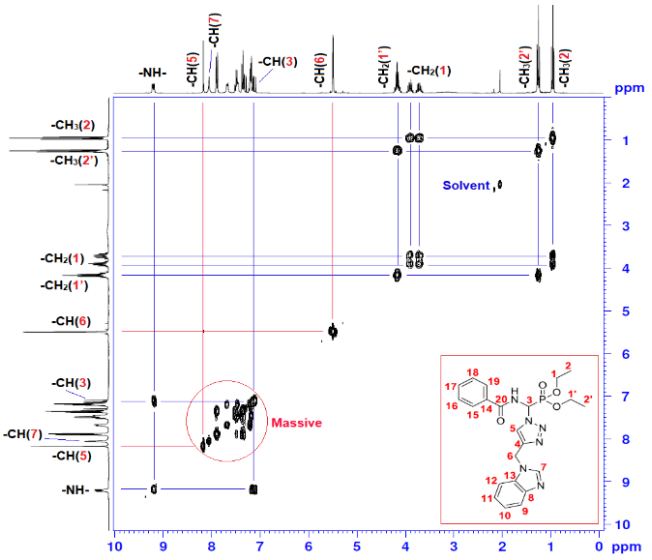


Fig. 4. 2D NMR ^{1}H-^{1}H spectrum of the cycloadduct (3).

The recognition observed in the 1D NMR spectrum, corresponding to the non-equivalence of the two protons **H_a** and **H_b** carried by the carbon 1 atom of the ethoxy group, is also confirmed in 2D heteronuclear NMR (Fig. 5). This phenomenon has also been observed in the literature [31]. Thus, the non-equivalence in NMR of the two protons is due to the existence of molecular asymmetry in relation to these two protons. The two protons have a diastereoisomeric relationship with each other, which is reflected in the NMR spectrum by a difference between their relative chemical displacements. This diastereoisomeric relationship is particularly fulfilled when there is an asymmetric carbon in the molecule. However, the resulting intrinsic non-equivalence is likely to be small and the existence of non-equivalence is generally considered as an indication of a conformational imbalance in the molecule.

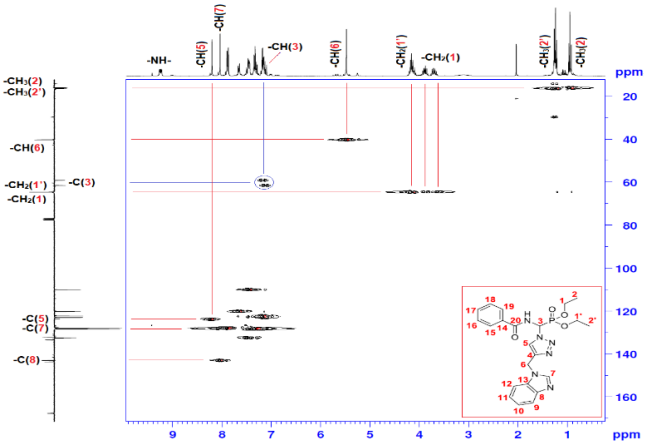


Fig. 5. 2D NMR ^{1}H-^{13}C spectrum of the cycloadduct (3).

The chemical displacements of protons and carbons, as well as their respective correlations, are summarised in the table given below.

TABLE I: THE ARRANGEMENT OF CHANNELS

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TABLE 1: ^{1}H (300.13 MHz) AND ^{13}C (75.47 MHz) NMR SPECTRAL DATA FOR COMPOUND (3) IN $CDCl_3$, INCLUDING RESULTS OBTAINED BY HOMONUCLEAR 2D SHIFT-CORRELATED AND HETERONUCLEAR 2D SHIFT-CORRELATED HMBC. CHEMICAL SHIFTS (IN PPM) AND COUPLING CONSTANTS (*J* IN HZ)

Pos.	δ_H	δ_C	Correlation H-H	Correlation C-H
1	3.69-3.91 (m)	64.52-64.56	$2H^1$-$2H^1$; $2H^1$-$3H^2$	C^1-$2H^1$; C^1-$3H^2$
1’	4.13-4,19 (m)	64.61-64.65	$2H^{1'}$-$2H^{1'}$; $2H^{1'}$-$3H^{2'}$	$C^{1'}$-$2H^{1'}$; $C^{1'}$-$3H^{2'}$
2	0 .95 (t, ^3J = 7)	15.98-16.05	$3H^2$-$3H^2$; $3H^2$-$2H^1$	C^2-$3H^2$; C^2-$2H^1$
2’	1.25 (t, ^3J = 7)	16.30-16.38	$3H^{2'}$-$3H^{2'}$; $3H^{2'}$-$2H^{1'}$	$C^{2'}$-$3H^{2'}$; $C^{2'}$-$2H^{1'}$
3	7.09-7.17 (dd, $^3J_{H\text{-}H}$ = 9.6 and $^2J_{H\text{-}P}$ = 18.6)	59.03-61.46 (d, $^1J_{H\text{-}P}$ = 183.4)	$1H^3$-$1H^3$; $1H^1$-HN	C^3-$1H^3$
4	-	142.98	-	C^4-$1H^5$; C^4-$2H^6$
5	8.17 (s)	123.71	$1H^5$-$1H^5$	C^5-$1H^5$; C^5-$2H^6$
6	5.5 (s)	40.27	$1H^6$-$1H^6$	C^6-$2H^6$
7	8.05 (s)	128.43	$1H^7$-$1H^7$	C^7-$1H^7$
NH	9,23 (dd, $^3J_{H\text{-}H}$ = 9,6 and $^3J_{H\text{-}P}$ = 4,2)	-	HN - HN	-
20	-	164.7	-	C^{20}-NH; C^{20}-$1H^3$; C^{20}-H^{arom}

The Analysis of the 2D ^{1}H-^{13}C NMR spectrum of compound (3) (Fig. 5) indicates a faultless correlation between protons and adjacent carbons and protons and neighboring carbons in some cases. It should also be noted that the realization of this heteronuclear 2D spectrum allowed us to see that the hydrogen atom carried by the carbon in α phosphonate group, which resonates in the form of a doublet between 59.08 and 61.51 ppm, correlates both with its carbon and with carbon 5 carrying the triazole proton in position 5 at 123.72 ppm. This result is consistent with literature data on *click chemistry* [27], that allows us to affect to the cycloaddition product (3) the structure of the 1,4-regioisomer. This structure is also attributed on the basis of the chemical displacements of triazole protons described in the literature [29,30]. Those in position 4 (H_4) (1,5-regioisomer) of the triazole ring are less delineated than their counterparts in position 5 for the -1,4-regioisomer ($\delta_{H4}>\delta_{H5}$). Their signals are usually between 8 and 8.5 ppm. While in ^{13}C NMR, the carbon bearing the triazole proton in position 5 resonates at around 124 ppm (1.4-regioisomer), that in position 4 (1,5-regioisomer) resonates between 134 and 135 ppm. This is probably due to the fact that the -C^5H in the 1,4-regioisomer is in the vicinity of an sp^2-hybridized carbon and an sp^3-hybridized nitrogen. Whereas in the case of –C^4H (1,5-regioisomer), the carbon atom is surrounded by atoms in an sp^2-hybridized state (carbon and nitrogen). This last one is responsible for the deshielding of the carbon carrying the triazole proton in position 4 in the 1,5-regioisomer.

We have also realized the heteronuclear 2D NMR spectrum with far coupling between hydrogen atoms and neighbouring and distant carbons (Fig. 6).

Thus, we notice that the two hydrogens carrying the carbon 6 linking the two heterocycles, do not correlate with the adjacent carbon but correlate both with:

- The three quaternary carbons, 4, 8 and 13 of the triazole and benzimidazole rings.
- The carbon 5 carrying the triazole proton in position 5 (-C^5H).

On the other hand, and contrary to what was observed in the heteronuclear 2D spectrum (Fig. 6), we found a unique correlation of the two hydrogens with the adjacent carbon 6 linking the two heterocycles.

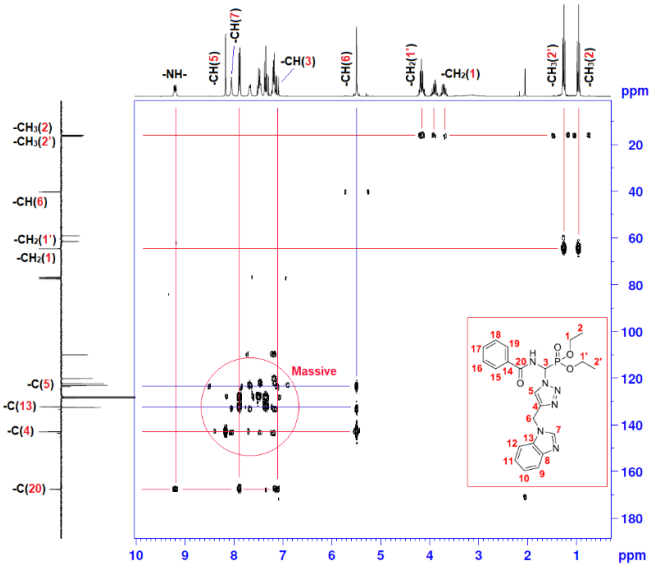

Fig. 6. Distant heteronuclear correlations of compound (3).

In addition, we noted a correlation between the hydrogens and the distant carbons of the ethoxy groups appearing on either side of the diagonal, as well as the absence of correlations between the hydrogens and the adjacent carbons of the ethoxy groups. This is in contrast to what has been obtained for the two-dimensional nuclear magnetic resonance of the carbons and hydrogens of the ethyl phosphonate group (Fig. 6).

Finally, it should be noted that the correlations between hydrogens and aromatic carbons in distant heteronuclear 2D NMR are much higher than in normal heteronuclear 2D NMR.

On the basis of this physico-chemical study, we attribute to the product resulting from the cyloadditioin reaction (3), the structure of the 1,4-regioisomer, entituled diethyl [{4-[(1H-benzo[*d*]imidazol-1-yl)methyl}-1H-1,2,3-triazol-1-yl}(benzamido)methyl]phosphonate.

III. MATERIALS AND METHODS

All solvents were purified following the standard techniques and commercial reagents were purchased from Sigma-Aldrich (St. Louis, MO, USA). Melting point was determined with an Electrothermal melting point apparatus and was uncorrected. NMR spectra (1H and 13C) were recorded on a Bruker AM 300 spectrometer (operating at 300.13 MHz for 1H, at 75.47 MHz for 13C) (Bruker Analytische Messtechnik GmbH, Rheinstetten, Germany). NMR data are listed in ppm and are reported relative to tetramethylsilane (1H, 13C); 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.

To a solution of (690 mg; 2.2 mmol) azide (1) and (345 mg; 2.2 mmol) alkyne (2) in 10 ml of an ethanol-water mixture (1/1), 0.05 equivalent of copper sulphate pentahydrate (CuSO4, 5H2O) and 0.1 equivalent of sodium ascorbate (As-Na) are added. The reaction mixture is stirred at room temperature for 24 hours. After filtration of the precipitate formed, the solvent is evaporated under pressure and the crude is washed with water and extracted with methylene chloride. The organic phase is then dried with magnesium sulphate and the solvent is removed under reduced pressure. The oil obtained is purified by chromatography on a silica gel column (ethyl acetate/hexane acetate).

Yield = 90% (White solid); Rf = 0.4 (ether/ methanol 5%); m.p. = 226-228°C. 1H-NMR (CDCl3, δH ppm): 0.95 (t, 3H, -CH2-CH3, 3J = 7 Hz), 1.25 (t, 3H, -CH2-CH3, 3J = 7 Hz), 3.70-4.20 (m, 1H + 1H + 2H, 2x(-OCH2-CH3)), 5.5 (s, 2H, triaz-CH2-), 7.09-7.17 (dd, 1H, 3JH-H = 9.9 Hz, 2JH-P = 16.8 Hz, NH-CH-P), 7.28-7.68 (m, 5Harom(Ph)).

7.36 (d, 2H, ^{1}J = 8Hz, H_{arom}(Bnzm)), 7.88 (d, 2H, ^{1}J = 8Hz, H_{arom}(Bnzm)), 8.05 (s, 1H, -CH(Bnzm)), 8.17 (s, 1H, -CH(triaz)), 9.18-9.22 (dd, 1H, $^{3}J_{H\text{-}H}$ = 9.6 Hz, $^{3}J_{H\text{-}P}$ = 4.2 Hz, -NH-). ^{13}C-NMR ($CDCl_3$, δ_C ppm): 15.98-16.05 (1C, (-CH_2-CH_3)), 16.30-16.38 (1C, (-CH_2-CH_3)), 40.27 (1C, triaz-CH_2-), 59.03-61.46 (1C, -CH-P, d, $^{1}J_{H\text{-}P}$ = 183,4 Hz), 64.60 (2C, 2x(O-CH_2-CH_3)), 110.04, 120.21, 123.12, 123.38, 128,01, 128.43, 132,27, 132,57, 133.44, 143.60 (13C_{arom}), 123,72 (1C, C_t(triaz)), 142,98 (1C, C_q(triaz)), 167,68 (1C, CO).

IV. Conclusion

In conclusion, the 1,4-regioisomer, namely [{4-[(1H-benzo[d]imidazol-1-yl)methyl]-1H-1,2,3-triazol-1-yl}(benzamido)methyl]diethyl phosphonate, was synthesized in an excellent yield and regioselectively via the condensation of the diethyl (azido(benzamido)methyl)phosphonate (1) and the 1-(prop-2-yn-1-yl)-1H-benzo[d]imidazole (2), operating under click chemistry conditions. Its structure was proposed following an in-depth spectroscopic study using 1D and 2D NMR. The product thus synthesized is currently undergoing biological and anticorrosive activity evaluation.

Acknowledgment

This work was supported by Sidi Mohammed Ben Abdellah University (USMBA) and National Center for Scientific and Technical Research (CNRST).

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