Characterization of the Structure of 9-([1-[(4-methyl-2-phenyl-4,5-dihydrooxazol-4-yl)methyl]-1*H*-1,2,3-triazol-4-yl)methyl]-9*H*-carbazole Using 2D ¹H-¹⁵N HMBC Experiment

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Abstract

The title compound, 9-([1-[(4-methyl-2-phenyl-4,5-dihydrooxazol-4-yl)methyl]-1*H*-1,2,3-triazol-4-yl)methyl]-9*H*-carbazole was synthesized in high yield by 1,3-dipolar cycloaddition reaction of 4-(azidomethyl)-4-methyl-2-phenyl-4,5-dihydrooxazole and 9-(prop-2-ynyl)-9*H*-carbazole in toluene at reflux. The structure of this product was established on the basis of NMR spectroscopy (¹H, ¹³C, ¹⁵N and 2D ¹H-¹⁵N HMBC) in addition to the elemental analysis and MS data.

Keywords

1,2,3-triazole, Oxazoline, 1,3-dipolar cycloaddition, ¹H-¹⁵N correlation

Introduction

1,2,3-Triazoles are an important class of heterocycles due to their wide range of applications as synthetic intermediates and pharmaceuticals [1,2]. Several therapeutically interesting 1,2,3-triazoles have been reported, including anti-HIV agents, antimicrobial, anticancer, antibacterial, antifungal, anti-tubercular compounds [3,4], corrosion inhibitors [5], β₃-selective adrenergic receptor agonists [6], kinase inhibitors [7,8] and other enzyme inhibitors [9,10]. The 1,2,3-triazole moiety is also present in a number of drugs, for example, the β-lactam antibiotic tazobactam [11] and the cephalosporin cefatrizine [12]. In addition to this, the heterocycle 2-oxazoline has drawn tremendous attention due to their extensive applications in chemistry, biochemistry and pharmacology [13-16]. This heterocycle is found in the structure of many biologically active natural products [17]. It is also known as important intermediates in organic transformations [18].

Material and Methods

¹H NMR spectra were recorded on a Bruker Avance™ 400 spectrometer and Bruker Avance 300 spectrometer respectively at 400.13 MHz and 300.13 MHz (Faculty of Chemistry of Strasbourg, University of Strasbourg - France and Centre Universitaire Régional

d'Interface, Sidi Mohamed Ben Abdellah University, Fez - Morocco). Chemical shifts (δ) are given in ppm. The residual solvent proton peak was used as reference for calibration (DMSO-*d*₆: 2.50ppm and CDCl₃: 7.26ppm). The coupling constants *J* are given in Hz. Peaks are described as singlet (s), doublet of doublets (dd) and multiplet (m). ¹³C NMR spectra were recorded on a Bruker Avance™ 400 spectrometer and Bruker Avance 300 spectrometer respectively at 100.62 MHz and 75.47 MHz. All spectra were measured under broadband decoupled conditions. The residual solvent peaks were taken as reference (DMSO-*d*₆: 39.43 and CDCl₃: 77.08 ppm). ¹⁵N NMR spectra were recorded on a Bruker Avance™ 400 spectrometer at 40.55 MHz. 2D NMR spectra were also recorded on a Bruker Avance™ 400 spectrometer. All spectra were recorded at 25°C. The reaction was followed by TLC. TLC analyses were carried out on 0.25mm thick precoated silica gel plates (Merck Fertigplatten Kieselgel 60F₂₅₄) and spots were visualized under UV light or by exposure to vaporized iodine. The purification was performed by column chromatography on silica gel columns 60 Merck (Kieselgel 60F₂₅₄ Merck Fertigplatten) using ether/hexane 4:1 as eluant.

Discussion

In this paper, we examine the 1,3-dipolar cycloaddition reaction

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between 4-(azidomethyl)-4-methyl-2-phenyl-4,5-dihydrooxazole and 9-(prop-2-ynyl)-9H-carbazole in 5 mL of toluene at reflux with constant stirring during 72 hours (Scheme) [19]. Two regioisomers (1) and (2) were obtained in an 80:20 ratio, the major isomer was found to elute second.

Scheme: Synthesis of two regioisomers (1) and (2).

According to the literature data and the results obtained by the various members of our team [20-23], the 1,3-dipolar cycloaddition reaction between alkynes and azides leads to two regioisomers with different proportions, where the 1,4-isomer is generally more prominent than 1,5-isomer. The assignment of structures to triazoles isomers is essentially based on ^1H NMR and ^{13}C NMR spectroscopic study [24-26].

In simple cases where signals of triazole's protons are well resolved and are not covered by other signals of the spectrum, we observed that the triazolic proton $\text{C}^5\text{-H}$ is more deshielded than the proton $\text{C}^4\text{-H}$ [20].

On one hand, the spectroscopic study by ^{13}C NMR, conducted in the laboratory [20,27] shows that the tertiary carbon C^4 of

Figure 1: ^1H NMR spectrum in CDCl_3 (aliphatic moiety) of compound (1).

Figure 2: ^1H NMR spectrum in CDCl_3 (aliphatic moiety) of compound (2).

1,2,3-triazole ring of the 1,5-isomer is more deshielded than the tertiary carbon C⁵ of the 1,4-isomer.

In our case, ¹H NMR spectra (at 300 MHz) showed that the signals corresponding to triazole's protons are covered by other signals of the aromatic protons. So, to support the proposed structures to their corresponding products, a thorough spectroscopic study was carried out on the regioisomers (1) and (2).

The comparative study of ¹H NMR spectra at 300.13 MHz of the two regioisomers (Figure 1 and Figure 2) shows that the protons of methylene group located between the carbazole ring and the triazole ring are less apart in the isomer (1) than in the isomer (2). It is the same for protons of methylene oxazoline, which shows that the two methylene groups do not have the same environment this is due to the steric hindrance of the carbazole that lies just below the rest of the molecule the isomer (2).

The comparison of ¹³C NMR spectra of these regioisomers shows the deshielding of the tertiary carbon (123.24 ppm) located in position 4 of 1,2,3-triazole ring of the minor product (2) with respect to the tertiary carbon (120.32 ppm) located in position 5 of 1,2,3-triazole ring of the major product (1) (Table 1) consistent with the literature [24-26].

On the other hand, the comparison between the ¹H NMR spectrum (at 400MHz) in DMSO (Figure 3) of major product (1) and the crude product (mixture of two regioisomers (1) + (2)) allowed us to locate so specifies the signals corresponding to the triazole's proton C⁴-H (7.91 ppm) and C⁵-H (7.90 ppm) of the two regioisomers.

It is found that the C⁴-H is slightly deshielded compared to C⁵-H

Table 1: Chemical shifts of tertiary (C_t) and quaternary (C_q) carbon atoms.

Compound	δ_c in ppm (CDCl ₃ , 75.47 MHz)	
	C-4 (1,5-isomer)	C-5 (1,4-isomer)
(1)	123.24 (C _t)	140.20 (C _q)
(2)	144.20 (C _q)	120.32 (C _t)

contrary to what is described in the literature, including the work done in our laboratory. The opposite phenomenon is due to the anisotropic effect of the carbazolic ring: the proton C⁴-H of minor regioisomer is located in the precession cone of the aromatic ring. While in the case of the major regioisomer, the C⁵-H proton does not undergo the same effect.

Compound (1)

White solid; mp = 146-148°C; R_f = 0.25(ether). δ_H (ppm, CDCl₃, 300.13MHz): 1.41(3H, CH₃, s); 4.01-4.49(2H, CH₂(4,5-dihydrooxazole), AB, J = 9.0Hz); 4.35-4.46(2H, CH₂-triazole, AB, J = 14.03 Hz); 5.45-5.57(2H, CH₂-carbazole, AB, J = 16.8Hz); 7.19-8.06(9H_{arom} + H⁵-1,2,3-triazole, m). δ_C (ppm, CDCl₃, 75.47MHz): 24.87; 37.98; 57.08; 70.80; 75.18; **120.32(C_t)**; 144.32(C_q); 119.41-134.64 (18C_{arom}); 162.97. **MS-EI:** [M]⁺ = 421. Elemental analysis: calcd.: C 74.10; H 5.46; N 16.62; Found: C 73.84 ; H 5.14 ; N 16.38.

Compound (2)

White solid; mp = 208-210°C; R_f = 0.35(ether). δ_H (ppm, CDCl₃, 300.13MHz): 1.57(3H, CH₃, s); 4.53(2H, CH₂(4,5-dihydrooxazole), AB, J = 9.0Hz); 4.55(2H, CH₂-triazole, dd, J₁ = 14.39Hz, J₂ = 14.45Hz); 5.73(2H, CH₂-carbazole, AB, J = 17.1 Hz); 7.15-8.11(9H_{arom} + H⁴-1,2,3-triazole, m). δ_C (ppm, CDCl₃, 75.47MHz): 25.61; 37.64; 55.56; 71.60; 75.05; **123.24(C_t)**; 140.20(C_q); 119.78-133.46 (18C_{arom}); 162.68. **MS-EI:** [M]⁺ = 421. Elemental analysis: calcd.: C 74.10; H 5.46; N 16.6; Found: C 74.14 ; H 5.38 ; N 16.65.

In order to remove any ambiguity and irrevocably confirm the structure of each of two regioisomers, we studied the structure of the major compound (1) by ¹⁵N NMR.

The ¹⁵N NMR spectrum (at 40.55 MHz) of the compound (1) has five signals corresponding to five nitrogen atoms in the molecule (Figure 4). The assigning each signal to its corresponding nitrogen atom is carried out based on the 2D ¹H-¹⁵N HMBC experiment that have been used in the characterization of 1,2,3-triazole derivatives [27].

Figure 3: ¹H NMR spectrum of major isomer (in red) and of crude product (in blue).

Figure 4: ^{15}N NMR spectrum of compound (1) in DMSO- d_6 .

Figure 5: 2D ^1H - ^{15}N HMBC of compound (1) in DMSO- d_6 .

The interaction ^1H - ^{15}N has allowed us to make the following observations (Table 2, Figure 5):

- Correlation between aromatic system protons of carbazole ring, the protons of the methylene group attached to the carbazole ring and nitrogen whose chemical shift is 118.93 ppm, allowing us to assign this signal to nitrogen N-5.
- Correlation between the three methyl protons, the two protons

of the methylene group linked to the triazole nucleus and nitrogen whose chemical shift is 236.02 ppm, which justifies the attribution of this signal to the oxazoline cycle nitrogen N-1.

- Interaction between the methylene protons related to the triazole ring, the triazolic proton C⁵-H and the nitrogen whose chemical shift is 244.37 ppm. This signal is assigned to the nitrogen N-2 situated in position 1 of the 1,2,3-triazole ring.

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Figure 6: Assignment of each signal to its nitrogen atom.

Table 2: Listing of ^{15}N NMR spectral data for (**1**) in $\text{DMSO}-d_6$, including results obtained by heteronuclear multiple bond coherence shift-correlated (HMBC).

^1H δ (ppm, DMSO)	δ_{N} (ppm, DMSO)	Correlation $^1\text{H}-^{15}\text{N}$
5.5849	118.93	$2\text{H}(\text{CH}_2\text{-carbazole})$, N-5
7.6076	118.93	$\text{H}(\text{aromatic})$, N-5
1.4559	236.02	$3\text{H}(\text{CH}_3)$, N-1
4.4816	236.02	$2\text{H}(\text{CH}_2\text{-triazole})$, N-1
4.4816	244.37	$2\text{H}(\text{CH}_2\text{-triazole})$, N-2
7.9001	244.37	$\text{H}(\text{C}^5\text{-H of triazole})$, N-2
5.8549	351.35	$2\text{H}(\text{CH}_2\text{-carbazole})$, N-4
7.9001	351.35	$\text{H}(\text{C}^5\text{-H of triazole})$, N-4
4.4816	364.27	$2\text{H}(\text{CH}_2\text{-triazole})$, N-3
7.9001	364.27	$\text{H}(\text{C}^5\text{-H of triazole})$, N-3

- Correlation between the methylene protons related to the carbazole ring, the triazolic proton $\text{C}^5\text{-H}$ and nitrogen whose chemical shift is 351.35 ppm. This enables to assign the signal corresponding to the nitrogen N-4 located in position 3 of the 1,2,3-triazole ring.

- Interaction between the methylene protons related to the triazole ring, the triazolic proton $\text{C}^5\text{-H}$ and nitrogen whose chemical shift is 364.27 ppm. The corresponding signal is attributed to the nitrogen N-3 situated in position 2 of the 1,2,3-triazole ring.

The assignment of each signal to its nitrogen atom is based on the correlation $^1\text{H}-^{15}\text{N}$ (Figure 6). Indeed, analysis of the different correlations presented in the $^1\text{H}-^{15}\text{N}$ HMBC NMR spectrum of the major compound (**1**), we can assign accurately to each nitrogen; the corresponding chemical shift. Hence, the identification of this compound has been confirmed.

On the basis of this spectroscopic study, we can conclude, then, for the substrates and conditions probed here, the 1,4-isomer was found to be the major isomer. Therefore, the allocation of each structure to its corresponding compound is well established.

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