SYNTHESIS AND STUDY ON NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY OF 5-(4-METHYLPHENYL)-1*H*-1,2,3-TRIAZOLE

Received 10-09-2024

*Võ Viết Đại, Thái Thị Thu Thủy, Nguyễn Trần Nguyên**
Chemistry department, University of Science and Education, The University of Da Nang
**E-mail:ntnguyen@ued.udn.vn*

TÓM TẮT

TỔNG HỢP VÀ PHÂN TÍCH PHỔ CỘNG HƯỞNG TỪ HẠT NHÂN CỦA 5-(4-METHYLPHENYL)-1*H*-1,2,3-TRIAZOLE

5-(4-Methylphenyl)-1H-1,2,3-triazole đã được điều chế thành công từ các nguyên liệu đầu là 4-methylacetophenone, ammonium acetate (NH_4OAc) và 4-nitrophenyl azide trong dung môi DMF ở nhiệt độ 90 $^{\circ}$C. Cấu trúc của sản phẩm được khẳng định dựa vào các phương pháp phổ hiện đại như phổ cộng hưởng từ hạt nhân một chiều và hai chiều (1D NMR, 2D NMR), phổ khối phân giải cao (ESI -HRMS). Đặc điểm cấu tạo của dị vòng thơm 1,2,3-triazole đã ảnh hưởng đến độ chuyển dịch hóa học của nguyên tử hydrogen (H) liên kết trực tiếp với nguyên tử nitrogen (N) cũng như nguyên tử hydrogen (H) liên kết với nguyên tử carbon (C) vị trí số 4 của dị vòng triazole thông qua hiệu ứng bất đẳng hướng (anisotropic efect). Phổ khối phân giải cao xuất hiện peak có tỉ lệ m/z tương ứng với khối lượng phân tử của 5-(4-methylphenyl)-1H-1,2,3-triazole.

***Từ khóa**: 1,2,3-Triazole, NH-1,2,3-triazole, triazole.*

1. INTRODUCTION

1,2,3-Triazoles are five-membered heterocycles containing two carbon and three nitrogen atoms which could interact with biological targets *via* hydrogen bonds [1]. Numerous 1,2,3-triazole containing compounds were synthesized and proven to possess a broad spectrum of promising pharmacological activities e.g. anti-inflammatory [2], anti-HIV [3], anticancer [4-6]. Consequently, there have been more and more drugs containing 1,2,3-triazole scaffold in their structure which are available on the market. For instance, tazobactam could be used in combination with piperacillin or ceftolozane to broaden the spectrum of piperacillin antibacterial action [7]. Carboxyamidotriazole has been used in the treatment of lympohma, lung cancer, breast cancer [5].

The synthesis of 1,2,3-triazoles was firstly described in 1967 by Rolf Huisgen *via* the 1,3-dipolar cycloaddition of azides and alkynes at high temperature. However, this method resulted in the mixture of 1,4-disubstituted 1,2,3-triazole and 1,5-disubstituted 1,2,3-triazole [8]. Sharpless and Meldal reported independently the synthesis of 1,4-disubstituted 1,2,3-triazoles *via* the copper(I)-catalyzed azide-alkyne cycloaddition reaction (CuAAC) [9, 10]. In addition, instead of Cu(I) catalyst, the use of Ru(II) catalyst for 1,3-dipolar cycloaddition reaction (RuAAC) between terminal alkynes and azides brought about 1,5-disubstituted 1,2,3-triazoles [11]. It is undoubtedly that

most of synthetic methods resulted in 1,4- or 1,5-disubstituted 1,2,3-triazoles. Moreover, there were only a few synthetic routes towards 5-substituted 1*H*-1,2,3-triazoles, in which copper or palladium-based catalysts were also used for the reaction between either trimethylsilyl azide and alkyne or alkenyl bromide and sodium azide, respectively [12,13]. The use of toxic heavy-metal catalysts restricted the application of above methods in bio-material chemistry and consequently, metal-free synthesis of 1,2,3-triazoles attracted considerable attention in drug discovery [14]. In this study, we reported the synthesis of 5-(4-methylphenyl)-1*H*-1,2,3-triazole from 4-methylacetophenone, ammonium acetate (NH_4OAc) and 4-nitrophenyl azide in DMF solvent without using any metal catalyst [15]. In addition, the structure of desired product was described by modern spectroscopic methods (^{1}H NMR, ^{13}C NMR, ^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC, ^{1}H–^{13}C HMBC).

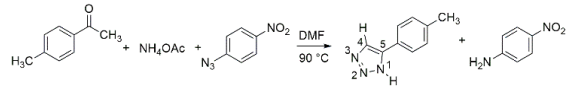
2. EXPERIMENTAL

2.1. General experimental methods

Nuclear magnetic resonance (NMR) spectra of 5-(4-methylphenyl)-1*H*-1,2,3-triazole were recorded with Bruker Avance II+ 500 MHz spectrometer at Chemistry department, Hanoi University of Science, Vietnam National University (VNU-HUS). Chemical shifts (δ) were reported in parts per million (ppm) referenced to the internal (NMR) solvent signal or tetramethylsilane (TMS). High resolution mass spectrum (ESI - HRMS) was acquired on QTOF LC/MS Agilent 6530 at Institute of Chemistry, Vietnam academy of Science and Technology (VAST). 70–230 Mesh silica 60 (E. M. Merck) was used as the stationary phase for column chromatography. All chemicals were received from Merck, Acros.

2.2. Procedure for synthesis of 5-(4-methylphenyl)-1*H*-1,2,3-triazole [15]

4-Methylacetophenone (0.125 ml, 0.94 mmol, 1 equiv.), ammonium acetate (NH_4OAc) (360 mg, 4.7 mmol, 5 equiv.), 4-nitrophenyl azide (200 mg, 1.22 mmol, 1.3 equiv.) and DMF (2 mL) were added to a glass reaction tube with screw cap, which was equipped with a magnetic stirring bar. The reaction mixture was stirred vigorously at 90 °C for 12 hours and thin layer chromatography (TLC) was used to monitor the reaction's progress. Crude product was purified by column chromatography (silicagel, hexane : ethylacetate = 5 : 2) to obtain pure product as a light yellow solid with the yield of 89.1%.

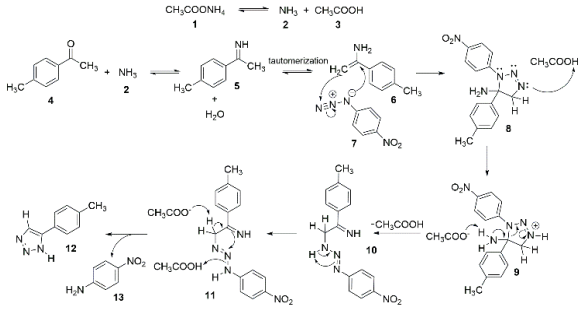


Scheme 1. *Synthesis of 5-(4-methylphenyl)-1H-1,2,3-triazole*

3. RESULTS AND DISCUSSION

The multi-component reaction of 4-methylacetophenone, ammonium acetate and 4-nitrophenyl azide was carried out in dimethylformamide (DMF). Firstly, ammonium acetate (**1**) was dissolved in dimethylformamide (DMF), a polar aprotic solvent and subsequently, converted into ammonia (**2**) and acetic acid (**3**) due to heating at high temperature [16,17]. Ammonia (**2**) played the role of nucleophilic agent and attacked to electrophilic center of carbonyl group (C=O) of 4-methylacetophenone (**4**) to yield imine (**5**) which reversibly converted into enamine (**6**). The reaction between aromatic ketone **4** and NH_3 (**2**) in acidic environment was reversible [18] and according to Le Chatelier's principle [19], the excess

amount of ammonium acetate (5 equiv.) as compared to 4-methylacetophenone (1 equiv.) would shift the equilibrium to the side of imine (**5**) formation. The [3+2] cycloaddition reaction between 4-nitrophenyl azide (**7**) and enamine (**6**) resulted in a key triazoline intermediate (**8**). One of nitrogen atoms of five-membered triazoline ring would be protonated by acidic proton of acetic acid to intermediate **9** which then had the triazoline ring opened to obtain **10**. The intermediate **10** would be tautomerized to **11** and lastly, the triazolization along with the removal of a molecule of 4-nitroaniline (**13**) would lead to desired product, 5-(4-methylphenyl)-1*H*-1,2,3-triazole (**12**) (Scheme 2) [14,15].



Scheme 2. *Mechanism for the synthesis of 5-(4-methylphenyl)-1H-1,2,3-triazole* [14,15]

High resolution mass spectrometry (ESI–HRMS) appeared peak at mass to charge (m/z) ratio of 160.0848 corresponding to the molecular mass of 5-(4-methylphenyl)-1*H*-1,2,3-triazole.

The ^{1}H NMR spectrum of 5-(4-methylphenyl)-1*H*-1,2,3-triazole showed two doublet resonance signals at 7.71 ppm and 7.25 ppm which represented four protons of para-disubstituted benzene ring. In addition, coupling constants *J*(H,H) of these two doublets corresponded to spin – spin coupling between protons of benzene ring which separated by three sigma bond (σ). The formation of 1,2,3-triazole ring was characterized by a singlet peak at the chemical shift of 7.95 ppm representing for proton at the 4-position of nitrogen-containing heterocyclic ring. When 5-(4-methylphenyl)-1*H*-1,2,3-triazole placed in a magnetic field of nuclear magnetic resonance spectrometer, the movement of 6 π electrons of 1,2,3-triazole conjugated ring system would generate their own magnetic field, called anisotropic field. Proton attached to carbon atom at 4-position of 1,2,3-triazole ring lied in the deshielding region of the anisotropic filed and consequently, it resonanced at higher chemical shift, 7.95 ppm, as compared to other normal hydrogen atom bonded to sp^2 hybridized carbon atom. Furthermore, proton bonded to nitrogen atom at 1-position of heterocyclic ring was represented by a broad, low intensity peak at high chemical shift, 12.89 ppm. It was undoubtedly that the moderate quadrupole moment for nitrogen led to peak broadening, named quadrupole broadening, of the attached hydrogen atom (N–H) [20]. Lastly, three hydrogen atoms of methyl group (CH_3) was characterized by a siglet peak at 2.39 ppm (Figure 1).

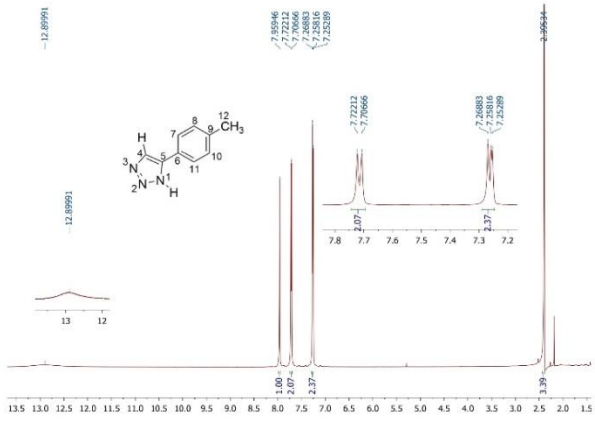


Figure 1. *^{1}H NMR spetrum of 5-(4-methylphenyl)-1H-1,2,3-triazole*

In the ^{13}C NMR spectrum of 5-(4-methylphenyl)-1*H*-1,2,3-triazole, there was a resonance signal at 21.32 ppm

corresponding to carbon atom of methyl group (CH_3). Two high intensity peaks at the chemical shift of 130.02 ppm and 126.40 ppm represented for four carbon atoms at the 7,8,10 and 11-positions of 1,4-disubstituted benzene ring. Furthermore, the spectrum also exhibited three resonance signals at 147.40, 139.10 and 127.19 ppm.

In addition to ^{1}H NMR and ^{13}C NMR, 2D NMR spectra of 5-(4-methylphenyl)-1*H*-1,2,3-triazole were also recorded. 2D ^{1}H – ^{1}H COSY (*homonuclear correlation spetroscopy*) spectrum showed four cross peaks which corresponded to the chemical shifts of four protons of 1,4-disubstituted benzene ring. The existence of these four off-diagonal peaks was the proof of spin – spin coupling between two protons separated by three sigma bonds on the benzene ring.

There were cross peaks in 2D ^{1}H – ^{13}C HSQC spectrum of 5-(4-methylphenyl)-1*H*-1,2,3-triazole resulted from the spin – spin coupling between protons and carbons which were directly attached to each other. Hydrogen atoms resonance at 2.40, 7.25 and 7.96 ppm correlated with carbons resonance at 21.56, 126.40 and 130.02 ppm, respectively. Therefore, peaks at 21.56, 126.40 and 130.02 ppm in ^{13}C NMR spectrum corresponded to C12, C7 and C11 or C8 and C10 and C8 and C10 or C7 and C11, respectively.

In the 2D ^{1}H – ^{13}C HMBC spectrum of 5-(4-methylphenyl)-1*H*-1,2,3-triazole, there was a cross peak arised from the correlation between C12 resonance at 21.56 ppm and two protons resonance at 7.25 ppm as a doublet. Thus, doublet at 7.25 ppm belonged to two chemically equivalent hydrogen atoms H8 and H10, and doublet at 7.71 ppm represents for H7 and H11. On the other hand, 2D ^{1}H – ^{3}C HSQC spectrum of 5-(4-methylphenyl)-1*H*-1,2,3-triazole exhibited the correlation between ^{13}C atoms resonance at 126.40 ppm, 130.02 ppm and protons resonance at 7.71 ppm, 7.25 ppm, respectively. Consequently, two high intensity peaks at 126.40 ppm, 130.02 ppm in ^{13}C NMR would correspond to chemically equivalent carbons C7 and C11, C8 and C10, respectively. In addition, in the 2D HMBC spectrum, all hydrogen atoms H4, H7 and H11 all showed the spin – spin coupling with the same carbon atom resonance at 147.28 ppm. Therefore, resonance signal at 147.28 ppm in ^{13}C NMR spectrum arised from carbon atom at the 5-position (C5). Furthermore, three hydrogen atoms of methyl group ($–CH_3$) and two chemically equivalent hydrogen atoms H7 and H11 showed the spin – spin coupling with the same carbon atom resonance at 139.10 ppm. It meaned that the peak at 139.10 ppm in ^{13}C NMR had to be that of carbon atom at the 9-position (C9). Lastly, based on 2D HMBC spectrum, it could be concluded that resonance peak at 127.19 ppm represented for carbon atom at the 6-position (C6) (Figure 2).

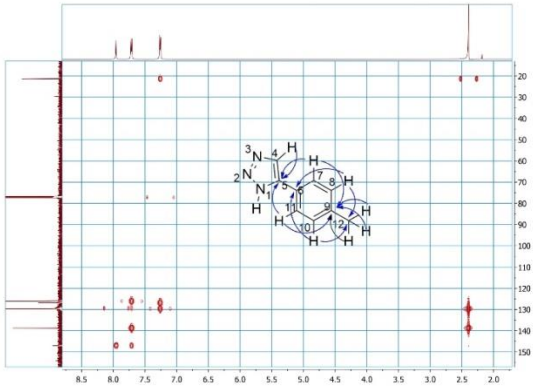


Figure 2*. 2D ^{1}H – ^{13}C HMBC spectrum of 5-(4-methylphenyl)-1H-1,2,3-triazole*

The spectroscopic data of 5-(4-methylphenyl)-1*H*-1,2,3-triazole could be summarized in Table 1.

Table 1. *^{1}H NMR, ^{13}C NMR spectroscopic data of 5-(4-methylphenyl)-1H-1,2,3-triazole (500/125 MHz, $CDCl_3$)*

Position	δ_C	δ_H
1		12.89 (s_{br}, 1 H, −NH)
4		7.96 (s, 1 H, H−triazole)
6	127.19	
7, 11	126.40	7.71 (d, ^{3}J(H,H) = 7.7, 2 H, benzene)
8, 10	130.02	7.25 (d, ^{3}J(H,H) = 8.0, 2 H, benzene)
9	139.10	
12	21.56	2.40 (s, 3 H, CH_3)

4. CONCLUSION

5-(4-methylphenyl)-1*H*-1,2,3-triazole was successfully synthesized *via* the reaction among 4-methylacetophenone, 4-nitrophenyl azide and ammonium acetate in DMF solvent. The structure of desired product was proven *via* modern spectroscopic methods such as nuclear magnetic resonance spectroscopy (1D NMR, 2D NMR) and high resolution mass spectrometry (ESI – HRMS). In the ^{1}H NMR spectrum of 5-(4-methylphenyl)-1*H*-1,2,3-triazole, due to anisotropic effect, inductive effect and quadrupole broadening, hydrogen atom of secondary amino group (NH) of 1,2,3-triazole heterocyclic ring was represented by a broad, low intensity peak at high chemical shift, 12.89 ppm. Moreover, the presence of 1,4-disubstituted benzene ring in the structure of 5-(4-methylphenyl)-1*H*-1,2,3-triazole was characterized by two doublets at the chemical shift of 7.25 ppm and 7.71 ppm.

REFERENCES

[1] Bonandi E, Christodoulou M S, Fumagalli G, Perdicchia D, Rastelli G, Passarella D, (2017). The 1,2,3-triazole ring as a bioisostere in medicinal chemistry. *Drug Discovery Today*, **22(10)**, 1572-1581.

[2] Ali Y, Alam M S, Hamid H, Husain A, Bano S, Dhulap A, (2015). Design, synthesis and biological evaluation of piperic acid triazolyl derivatives as potent anti-inflammatory agents. *European Journal of Medicinal Chemistry*, **92**, 490-500.

[3] Tian Y, Liu Z, Liu J, Huang B, Kang D, Zhang H, (2018). Targeting the entrance channel of NNIBP: Discovery of diarylnicotinamide 1,4-disubstituted 1,2,3-triazoles as novel HIV-1 NNRTIs with high potency against wild-type and E138K mutant virus. *European journal of medicinal chemistry*, **151**, 339-350.

[4] Lal K, Yadav P, (2018). Recent advancements in 1,4-disubstituted 1*H*-1,2,3-triazoles as potential anticancer agents. *Anti-Cancer Agents in Medicinal Chemistry*, **18(1)**, 21-37.

[5] Liang T, Sun X, Li W, Hou G, Gao F, (2021). 1,2,3-Triazole-containing compounds as anti–lung cancer agents: Current developments, mechanisms of action, and structure–activity relationship. *Frontiers in pharmacology*, **12**, 661173.

[6] Slavova K I, Todorov L T, Belskaya N P, Palafox M A, Kostova I P, (2020). Developments in the application of 1,2,3-triazoles in cancer treatment. *Recent Patents on Anti-Cancer Drug Discovery*, **15(2)**, 92-112.

[7] Perry C M, Markham A, (1999).

Piperacillin/tazobactam: an updated review of its use in the treatment of bacterial infections. *Drugs*, **57**, 805-843.

[8] Huisgen R, Szeimies G, Möbius L, (1967). 1.3-Dipolare cycloadditionen, XXXII. Kinetik der Additionen organischer azide an CC-mehrfachbindungen. *Chemische Berichte*, **100(8)**, 2494-2507.

[9] Kolb H C, Sharpless K B, (2003). The growing impact of click chemistry on drug discovery. *Drug discovery today*, **8(24)**, 1128-1137.

[10] Tornøe C W, Christensen C, Meldal M, (2002). Peptidotriazoles on solid phase:[1,2,3]-triazoles by regiospecific copper (I)-catalyzed 1,3-dipolar cycloadditions of terminal alkynes to azides. *The Journal of organic chemistry*, **67(9)**, 3057-3064.

[11] Zhang L, Chen X, Xue P, Sun H H, Williams I D, Sharpless K B, (2005). Ruthenium-catalyzed cycloaddition of alkynes and organic azides. *Journal of the American Chemical Society*, **127(46)**, 15998-15999.

[12] Röhrig U F, Majjigapu S R, Grosdidier A, Bron S, Stroobant V, Pilotte L, Colau D, Vogel P, Van den Eynde B J, V. Zoete V, (2012). Rational design of 4-aryl-1,2,3-triazoles for indoleamine 2,3-dioxygenase 1 inhibition. *Journal of medicinal chemistry*, **55**, 5270-5290.

[13] Barluenga J, Valdés C, Beltrán G, Escribano M, Aznar F, (2006). Developments in Pd catalysis: Synthesis of 1*H*-1,2,3-triazoles from sodium azide and alkenyl bromides *Angewandte Chemie International Edition*, **45**, 6893-6896.

[14] John J, Thomas J, Dehaen W, (2015). Organocatalytic routes toward substituted 1,2,3-triazoles. *Chemical Communications*, **51(54)**, 10797-10806.

[15] Thomas J, Jana S, Liekens S, Dehaen W, (2016). A single-step acid catalyzed reaction for rapid assembly of *NH*-1,2,3-triazoles. *Chemical Communications*, **52(59)**, 9236-9239

[16] Alizadeh A, Rostampoor A, (2024). Synthesis of polycyclic chromeno[4,3,2-ij]Isoquinoline-3-carbonitriles in the presence of ammonium acetate as a dual rule reagent-catalyst. *ChemistrySelect*, **9**, e202400290.

[17] Urbiña-Alvarez J, Rincón-Carvajal S, Gamba-Sánchez D, (2023). Ammonia surrogates in the synthesis of primary amines. *Organic & Biomolecular Chemistry*, **21**, 7036-7051.

[18] Clayden J, Greeves N, Warren S, (2012). Organic Chemistry, 2nd ed., New York: Oxford University Press.

[19] Silberberg M, (2012). Equilibrium: The Extent of Chemical Reactions. Principles of general chemistry, New York: McGraw Hill.

[20] Donald L P, Gary M L, George S K, James R V, (2015). Introduction to spectroscopy, 5th ed., Washington: Cengage Learning.