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Synthesis of some new Bis-1,2,3-triazoles derivatives as urease inhibitors

[1]Zeyad Kadhim Oleiwi, [1]Ibtesam Faris Mohammed and [2]Ahmed Neamah Thamer

[1]Al-Furat Al-awsat Technical University - Al-Kufa technical institute/ Pharmacy department/ najaf - Iraq
[2]The General Directorate of Education in Najaf Al - Ashraf Dr. Enad Ghazwan Preparatory School for Boys// najaf – Iraq

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ABSTRACT

This research include synthesis of some new Bis-1,2,3-triazole from the reaction of an aryl azides and propargylic phenyl ethers. The propargylic ether was prepared from resorcinol by its reaction with propargyl bromide , while an aryl azides were result from treatment of diazoniume salts of an aniline derivatives with sodium azide. The triazole derivatives finally synthesized from the reaction of an figazide derivatives with acetylenic ether via Cu(I) click chemistry . The compounds were identified by FTIR, ^{1}H NMR and ^{13}C NMR. The biological activity of synthesized derivatives was examined against urease enzyme. the result was found that Tr2 ,Tr3compounds inhibit the activity of the urease to hydrolyse urea into CO_2 and NH_3,while Tr1 do not show any effect .

INTRODUCTION

Heterocyclic compounds containing nitrogen plays important role in agrochemical and Pharmaceuticals, The basic heterocyclic rings present in the various medicinal agents are mainly 1, 2, 3-triazole and 1, 2, 4-triazole [1] The 1,2,3-triazole ring system has been the subject of considerable research mainly due to its usefulness in synthetic organic chemistry and also because of the pharmacological properties shown by some of its derivatives. [2] It exhibit various biological effects [3] e.g., antiviral , antibacterial , antifungal , and anticancer activities [4-7] The 1,2,3-triazole moiety is a constituent part of many modified nucleosides or carbanucleosides with antiviral, anti-HIV or cytostatic activities [8-10]. However, the scope of triazole chemistry is not confined to drug discovery, There are an increasing number of applications in numerous other areas of modern chemical sciences, such as bioconjugation [11], supramolecular chemistry, [12] and polymer sciences [13].

MATERIALS AND METHODS

II-1-Synthesis of aryl azide

An aniline derivative (0.01 mole) was dissolved in 25 ml of dilute HCl in a Round Bottomed flask. Reaction mass was cooled to (-10 -5)°C. Sodium nitrite (1.1 mole) was added in small portions (4 portions) to the reaction mass by maintaining the temperature at (-10 -5)°C and maintained the reaction for 10 min.. A solution of sodium azide (1.2 mole 10 ml of water) was added in a drop wise manner to the reaction mixture at 0°C. After addition maintained the reaction at 0°C for 10 min.

II-2-Synthesis of propargylic aryl ether

To a round bottom flask was added the phenol derivative (1 mole), dissolved in 20 ml of acetone and (1.3 mole) of K_2CO_3 and (2.5 mole.) of propargyl bromide were added, the heterogeneous mixture was heated to reflux overnight. After TLC analysis had shown complete conversion of the starting materials, the mixture was cooled to room temperature, and then quenched by the addition of sat. aq. NH_4Cl. The resulting mixture was partitioned with Et2O, the organic layer separated, and the aqueous layer was extracted with Et2O. The combined organic layers were dried over $MgSO_4$. Concentration under reduced pressure gave the desired target structure.

II-3-Synthesis of triazole derivatives

A solution of propargyl ether (3.0 mmol , 0.894 g) in DMSO (5mL) was added to the suspension of sodium ascorbate (0.1107 g, 0.3 mmol) and $CuSO_4.5H_2O$ (0.748, 0.3 mmol) in DMSO (4mL).The mixture was stirred for (10 min) and to this was added azide derivatives The mixture was heated to 50°C with stirring for (24 h.). The reaction mixture was diluted with distilled water (30 mL), extracted with EtOAc (3×30 mL), the combined organic layers were washed with sat. NaCl (2× 20 mL), dried over Na_2SO_4, and evaporated to dryness under reduced pressure. The residue was flash chromatographed (silica gel, 2:1 to 1:2**)**

RESULTS AND DISCUSSION

III-1-Synthesis of propargylic aryl ether

The compound (1) was synthesized from the reaction of resorcinol with propargyl bromide in the presence of potassium carbonate as catalyst and acetone as solvent . the propargylic ether identified by FT.IR and show the following data: 3292 ($\upsilon_{\text{C–H acetylenic}}$),3052 ($\upsilon_{\text{C–H aromatic}}$), 2123 ($\upsilon_{\text{C=C acetylenic}}$), 1595($\upsilon_{\text{C=C aromatic}}$), 1257($\delta_{\text{C–H aromatic}}$)

III-2-Synthesis of aryl azide

The compound (2) was prepared by the reaction of diazoniume salt of amine with sodium azide , the resultant compound was an aryl azide derivatives according to the following data FT.IR and show the following peaks : (G1= NO_2)3100 ($\upsilon_{\text{C–H aromatic}}$),2127 ($\upsilon_{\text{N=N=N, of azide}}$), 1579 ($\upsilon_{\text{C=C aromatic}}$), 1517 ($\upsilon_{\text{O=N=O}}$),1286($\delta_{\text{C–H aromatic}}$).
(G2=benzoate) 3111($\upsilon_{\text{C–H aromatic}}$),2983 ($\upsilon_{\text{C–H, CH3}}$),2123 ($\upsilon_{\text{N=N=N, of azide}}$),1716 ($\upsilon_{\text{C=O of ester}}$),1600($\upsilon_{\text{C=C aromatic}}$),1278($\upsilon_{\text{C–O of ester}}$) (G3= di chloro) 3111($\upsilon_{\text{C–H aromatic}}$), 2120 ($\upsilon_{\text{N=N=N, of azide}}$), 1600($\upsilon_{\text{C=C aromatic}}$) .

III-3-Synthesis of Bis-1,2,3-Triazoles

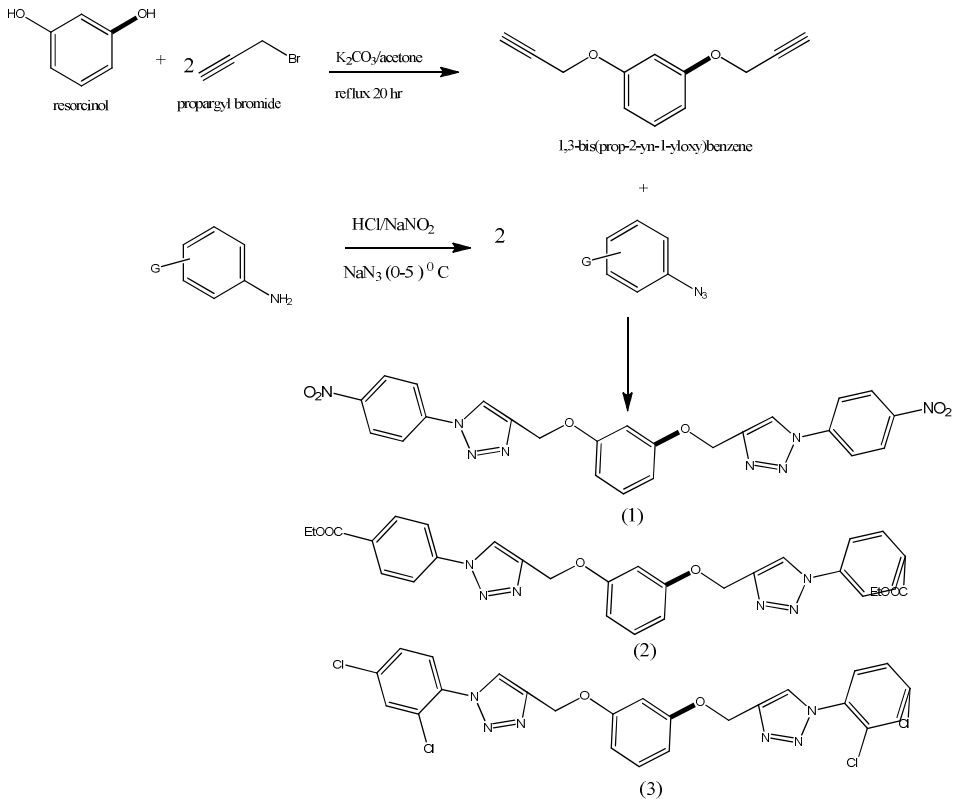
The triazole derivatives were synthesized via click chemistry by the reaction of propargylic derivatives with aryl azide in the presence of Cu(I) as catalyst and DMSO as solvent , the spectral analysis gives the following values for each of FT.IR

(1) at $\bar{\upsilon}$ cm^{-1} : (KBr)3288 ($\upsilon_{\text{C–H aromatic of triazole}}$), 3145 ($\upsilon_{\text{C–H aromatic of}}$),1724 ($\upsilon_{\text{C=C}}$ of triazole), 1595 ($\upsilon_{\text{C=C aromatic}}$), 1492 ($\upsilon_{\text{O=N=O}}$),1286($\delta_{\text{C–H aromatic}}$), disappearance of other peaks of alkyne and azide . ^{1}H NMR spectrum Fig. ( ), 400 MHz, DMSO-d_6) for the compound showed the following signals at δ (ppm): 5.26 (s, 2H, of two $OCH_{2\text{ of ether}}$), 6.57-8.26) (m, of three benzene rings), 8.54 (2H, two triazole rings) 9.19 (1H, of CH-NO_2 of benzene rings) . ^{13}C NMR spectrum Fig. (23), (100MHz, DMSO-d_6) showed the following signals at δ (ppm): 78.26 [(2 ×O**C**H_2 of ether], 97.09 (1C of OCH_2-**C**H-OCH_2), 104-159((m C of aromatic carbon of benzene and triazole ring).

** The signals around 2.5 ppm and 40.00 ppm in ^{1}H &^{13}C NMR spectra respectively are attributed to DMSO and 3.3 in ^{1}H NMR for H_2O.*

(2) 3200 ($\upsilon_{\text{C–H aromatic of triazole}}$), 3145 ($\upsilon_{\text{C–H aromatic of}}$), 1760 ($\upsilon_{\text{C=O}}$ of ester) 1710 ($\upsilon_{\text{C=C}}$ of triazole), 1600 ($\upsilon_{\text{C=C aromatic}}$) ,1286($\delta_{\text{C–H aromatic}}$), disappearance of other peaks of alkyne and azide. ^{1}H NMR spectrum Fig. ( ), 400 MHz, DMSO-d_6) for the compound showed the following signals at δ (ppm):): 1.33-1.36 [m, 6H, of $2CH_{3\text{ of ethyl (ester)}}$] 2.08 [m, 4H, of $2CH_{2\text{ of ethyl (ester)}}$)] 5.22 (s, 2H, of two $OCH_{2\text{ of ether}}$), 6.29-7.26) (m, of three benzene rings), 8.17 (2H, two triazole rings) 9.10 (1H, of CH-COOEt of benzene rings) . ^{13}C NMR spectrum Fig. (23), (100MHz, DMSO-d_6) showed the following signals at δ (ppm): 25.29 (2C of CH_3 of acetate) 39.30-40.36 (2C of CH_2 of acetate)78.26 [(2 ×OCH_2 of ether], 108.24 (1C of OCH_2-CH-OCH_2), 110-148((m C of aromatic carbon of benzene and triazole ring),158(1C of COOEt).

(3) 3188 ($\upsilon_{\text{C–H aromatic of triazole}}$), 3155 ($\upsilon_{\text{C–H aromatic of}}$), 1688($\upsilon_{\text{C=C}}$ of triazole), 1595 ($\upsilon_{\text{C=C aromatic}}$), ($\delta_{\text{C–H aromatic}}$), disappearance of other peaks of alkyne and azide . ^{1}H NMR spectrum Fig. ( ), 400 MHz, DMSO-d_6) for the compound showed the following signals at δ (ppm): 5.16 (s, 2H, of two $OCH_{2\text{ of ether}}$), 6.59-7.78) (m, of three benzene rings), 8.01 (2H, two triazole rings) 8,72 (1H, of CH-Cl of benzene rings) . ^{13}C NMR spectrum Fig. (23), (100MHz, DMSO-d_6) showed the following signals at δ (ppm): 78.26 [(2 ×OCH_2 of ether], 97.09 (1C of OCH_2-CH-OCH_2), 108-157((m C of aromatic carbon of benzene and triazole ring).



Scheme (1) synthesis of triazole derivatives

II-3- Studying the biological activity of synthesized compounds. The biological activity of the synthesized compounds were tested against the activity of urease enzyme (which is catalyze urea to ammonia and carbon dioxide). The enzyme was immobilize on each one of synthesized compound by taking one concentration of each compound with enzyme and stirring the mixture for 10 min. The triazoles derivatives show different inhibition action toward the enzyme shown in figure (1).

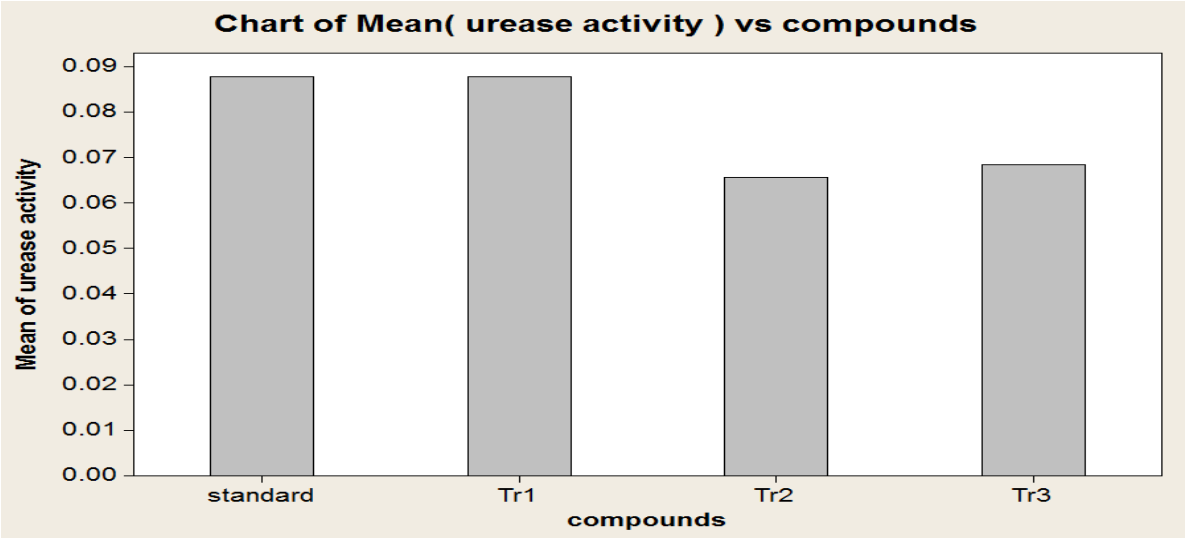


Figure (1) the effect of synthesized compounds on urease activity

Some of these compounds (Tr2,Tr3) show high inhibition action on the enzyme , while (Tr1)do not show any effect on the activity .

The activities of enzyme with different compound were calculated from the amount of liberated ammonia per 5 min as shown in table (2).

Table (2) show the amount of liberated ammonia and enzyme activities

	Name of compound	Absorbance	Ammonia concentration	Urease activity
1	standard	0.180	0.439	0.0878
2	Tr1	0.180	0.439	0.0878
3	Tr2	0.170	0.329	0.0658
4	Tr3	0.172	0.340	0.0680

** The amount of liberated ammonia were calculate from relationship*
(ammonia concentration = Absorbance-0.41/0.091) which is obtain from calibration curve figure (2) .
**The enzyme activity were calculate by relationship*
(Urease activity = amount of liberated ammonia /time) .
**The time was 5 min*

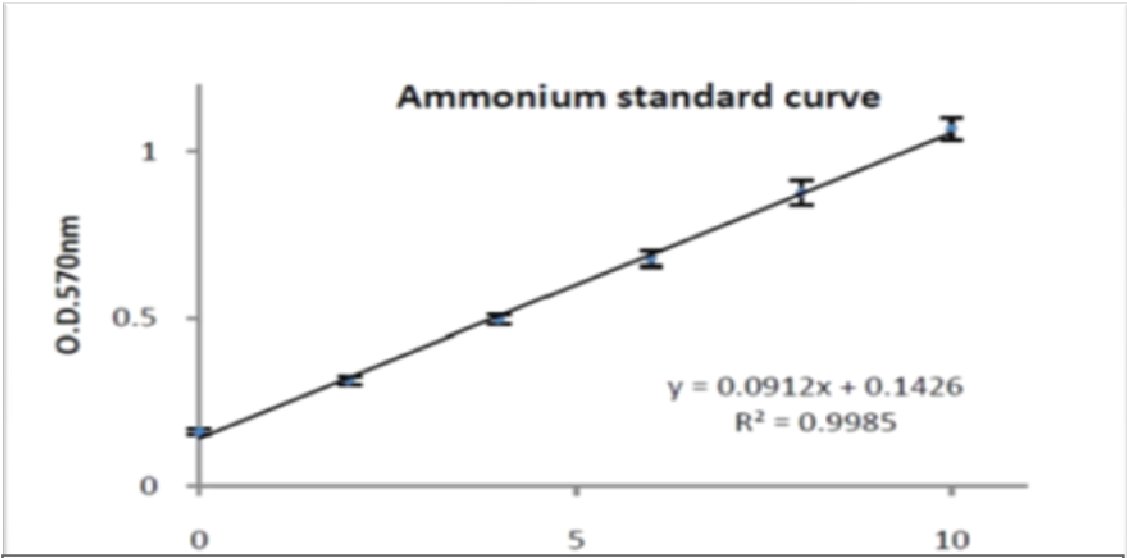


Figure (2) calibration curve for librated ammonia

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