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Synthesis of 1,2,3-triazole derivatives from azidoacetamide via cyclo-addition reaction

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Abstract

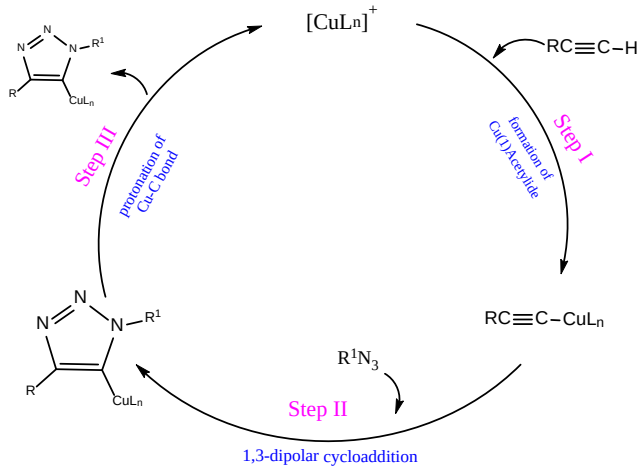
This research involves synthesis of some new 1,2,3-triazol derivatives from compounds starting from reaction azido oxazole compounds [V] with ether propargyl $[III]_{a-c}$ that formation by reaction propergyl bromide with n-propanol , n-butanol , n-pentanol presence sodium hydroxide in DMF .Where the reaction via 1,3-dipolar cycloaddition as in Scheme (1) where product compounds triazole ether in good yields .

Key Words : Oxazole , ether propergyl , triazole.

INTRODUCTION

Triazole ring system has got considerable fame due to the versatile biological activities of a huge number of its derivatives. Many of such compounds are important as agrochemicals [1-3]. There is a continuous need for the development of new drugs as the currently available drugs are becoming ineffective due to the drug resistance developed by pathogens. Moreover, life threatening infections caused by pathogenic fungi are increasingly becoming very common [4-6]. Triazole compounds have shown a great efficacy against antifungal infections. In 1944, Woolly discovered excellent antifungal properties of azole derivatives which led to the invention of fluconazole, variconazole, albaconazole and itraconazole [7-10].Further structural modifications of this ring system are expected to result in potential candidates for antifungal agents. These modifications are carried out by using different functionalities, aliphatic chains, aromatic rings and heterocyclic ring systems[11-14]

The recent workon the synthesis of 1,2,3-triazoles includes the Cu-catalyzed stepwise cycloaddition of azides to terminal alkynes[15]



Scheme 1: 1,3-dipolar cycloaddition of organic azides to alkynes

Synthesis via three component coupling reaction in activated terminal alkynes[16]

EXPERIMENTAL PART

Chemicals and Instruments

Chemical reagents and starting materials were obtained from Ajax and Sigma-Aldrich.

Synthesis of propargyl ethers [III][17]

Alcohol $[I]_{a-c}$ (0.002 mol) was dissolved in DMF(6 mL) and NaOH (0.32gm, 0.008 mol) were added. The mixture were stirred in a salt-ice bath for 15 min then propargyl bromide [II] (0.25 mL, 0.002 mmol) was added dropwise. The reaction mixture allowed to stir for 24 h, at r.t. The reaction mixture was partitioned between Et2O (30 mL) and water (50 mL) and the aqueous layer extracted with more Et2O (3 x 30 mL). The combined organic extracts were dried over Na_2SO_4, and evaporated to dryness under reduced pressure .

Synthesis of azido acetamide derivatives [V]

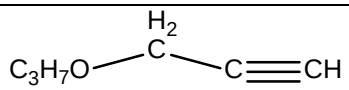
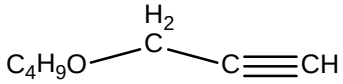
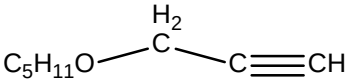
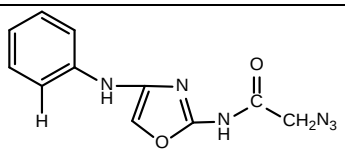
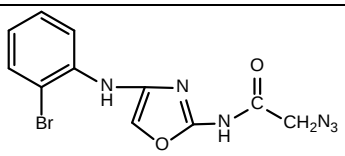
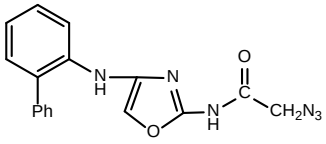
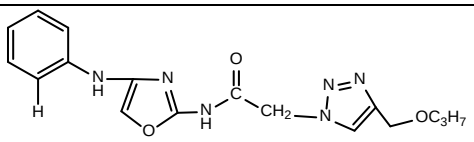
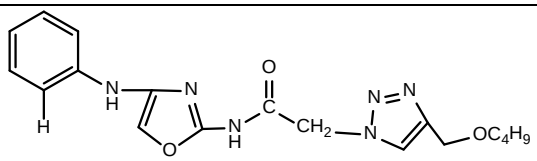
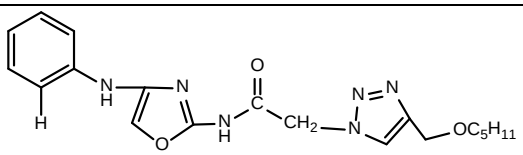
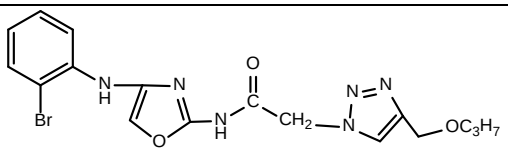
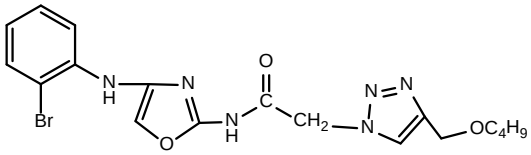
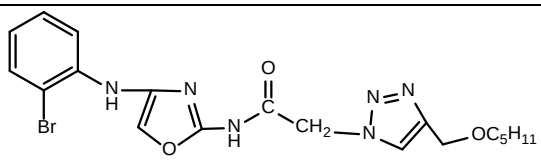
To a solution of compound chloroacetamide derivative [IV] (0.522gm , 0.002mol) in 3mL DMF added Sodium azide (0.26gm , 0.004mol) then added ammonium chloride (0.212gm , 0.004mol) and stirring then the mixture refluxed for (4hrs) after that the resulting solution cool then added in water ice and the product obtained collected .

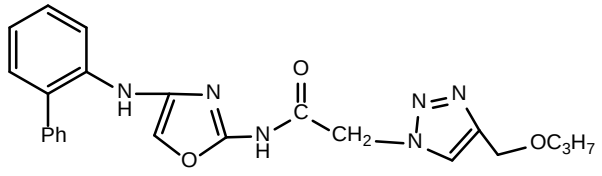
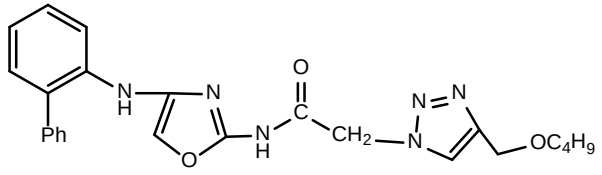
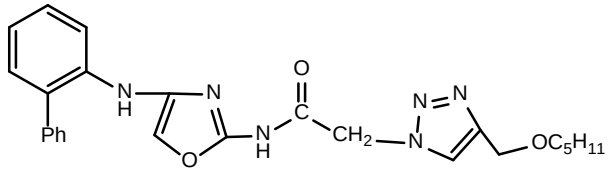
Synthesis of 1,2,3-triazoles [VI]

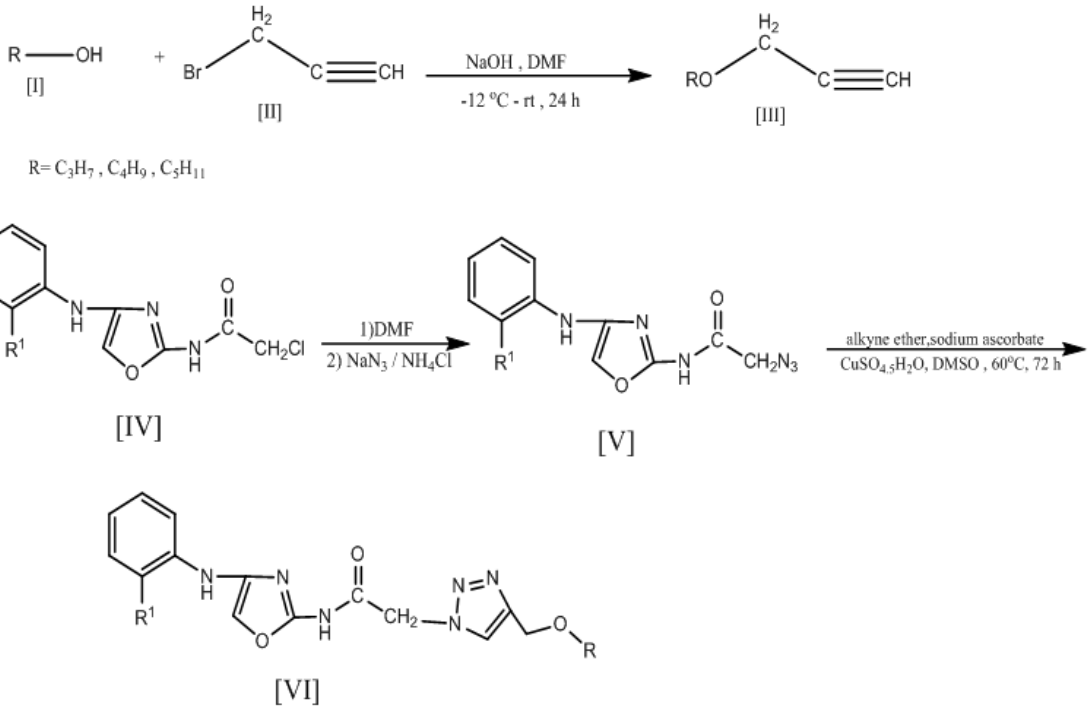
Compound [III] Propargyl ether (alkyne) (0.001 mol) and chloroacetamide [IV] (0.001 mol) were added to a suspension of sodium ascorbate (0.0198 g, 0.0001 mol) and CuSO4·5H2O (0.0125 g, 0.00005 mol) in DMSO (7 mL). The mixture was heated to 66°C and stirred for 72 h. The reaction mixture was diluted with water (35 mL), extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine (2×25 mL), dried over Na2SO4, and evaporated to dryness under reduced pressure. The residue was chromatographed (silica gel, EtOAc/n-hexane1:6 – 1:2) and the main fraction recrystallized from light petroleum (40-60oC) gave appropriate triazoles.

The physical properties for these compounds we listed in table (1)

Table (1) : The Nomenclature,structure formula,Molecular formula yields and physical properties of these compounds

COMP No	Nomenclature	M.P oC	Yield%	Color
$[III]_a$		-	76	Yellow
$[III]_b$		-	68	Yellow pale
$[III]_c$		-	72	Yellow oil
$[V]_a$		73-75	69	Yellow
$[V]_b$		120-122	81	Yellow oil
$[V]_c$		128-131	55	Yellow pale
$[VI]_a$		115-119	61	White
$[VI]_b$		122-124	67	White
$[VI]_c$		130-132	71	White
$[VII]_a$		175-178	75	Yellow
$[VII]_b$		182-185	77	Yellow
$[VII]_c$		194-197	72	Yellow

$[VIII]_a$		218-220	66	Yellow pale
$[VIII]_b$		225-228	63	Yellow pale
$[VIII]_c$		237-241	64	Yellow pale



Scheme 2: Synthetic route of 1,2,3-triazole derivatives

Compound	R	R^1
5_a	$-C_3H_7$	H
5_b	$-C_4H_9$	H
5_c	$-C_5H_{11}$	H
6_a	$-C_3H_7$	Cl
6_b	$-C_4H_9$	Cl
6_c	$-C_5H_{11}$	Cl
7_a	$-C_3H_7$	C_6H_5
7^b	$-C_4H_9$	C_6H_5
7_c	$-C_5H_{11}$	C_6H_5

RESULTS AND DISCUSSION

Straight chain alcohols were etherified with propargyl bromide in the presence of NaOH in DMF and gave the n-alkyl propargyl ethers [III]

FT-IR spectrum of *n*-propyl propargyl ether **[III]$_a$** showed the following bands (3304)cm^{-1} (**C-H** acetylenic) stretching bands, 2917, 2848 **(C-H** aliphatic**)** stretching bands, 2121cm^{-1} (**C≡C**) stretching bands, 1111-1062 (**C-O**). The bands at 3314 and 2121 are very good evidences of formation of the alkyne. FTIR spectrum of *n*-butyl propargyl ether **[III]$_b$** showed the following bands 3304 (**C-H** acetylenic) stretching bands, 2917cm^{-1}, 2848cm^{-1} **(C-H** aliphatic**)** stretching bands, 2122 (**C≡C**) stretching, 1265-1104 (**C-O**). Again the bands at 3311 and 2116 are very good proofs of formation of propargyl ether **[III]$_c$** showed the following bands 3301cm^{-1} (**C-H** acetylenic) stretching bands 2917cm^{-1}, 2848cm^{-1} **(C-H** aliphatic**)** stretching bands, 2122cm^{-1} (**C≡C**), 1265-1104 (**C-O**) stretching. Once more the same scenario with compound **[III]$_c$** .

H NMR (300 MHz, CDCl3) for **[III]$_c$** □ppm: 0.83 (t, 3H, H8`), 1.39 (t, 3H,$H_3$ `), 1.60 (m, 2H, H2`), 2.40 (t, , 2H, H_1), reaction of the chloroacetamide derivatives **[IV]** with sodium azide in DMF afforded azidoacetamide derivatives **[V]** in very good yield. FT-IR spectrum of azidoacetamide **[V]$_a$** showed the following bands (KBr): stretching band 3256 for N-H 3052cm^{-1} (**C-H** aromatic) stretching bands at 2929cm^{-1}, 2865cm^{-1} **(C-H** aliphatic**)** stretching bands at 2108 (**-N≡N**), 1658 **(C=O)** stretching, 1602, 1494 **C=C** aromatic stretching, FT-IR spectrum of 4- chloro azidacetamide **[V]$_b$** showed the following stretching band\ 3257cm^{-1-} (N-H) , 3082cm^{-1} stretching band **C-H** aromatic ,stretching bands 2921, 2852 **C-H** aliphatic stretching, 2108 (**-N≡N**), stretching band 1657 **(C=O)** strething, 1597, 1521 **(C=C** aromatic**)** stretching, FT-IR spectrum of 4-phenylazidoacetamide **[V]$_c$** showed the following bands (KBr): stretching band 3256 for N-H , 3083 **C-H** aromatic stretching bands 2923, 2864 **C-H** aliphatic stretching band , 2106 (**-N3**) stretching, 1668 aliphatic**)** stretching, 1668 **(C=O)** stretching band 1587 **(C=C** aromatic ring**)** terminal alkynes **(2)** with phenacyl azide derivatives gave the targete

1,2,3-triazoles in good yields. FT-IR spectrum of N-phenyl-2-(4-propoxymethyl)-1H-1,2,3-triazole-1yl)acetamide **[VI]$_a$** showed the following bands cm^{-1}(KBr): stretching band 3259cm^{-1} ,3085cm^{-1} (**C-H** aromatic) stretching band 2918cm^{-1}, 2853cm^{-1} **(C-H** aliphatic**)** stretching, 1670cm^{-1} **(C=O)** stretching, 1605cm^{-1}, 1443cm^{-1} **(C=C** aromatic**)** stretching, 1173cm^{-1}, 1084cm^{-1} (**C-O**) the disappearance of the azide band at 2108 cm-1 and the terminal alkyne bands at 3311 and2115 cm-1 is a very good evidence for the formation of compound **[VI]$_a$** .

FT-IR spectrum of N-phenyl-2-(4-butoxymethyl)-1H-1,2,3-triazole-1yl)acetamide **[VI]$_b$** showed the following bands cm^{-1} (KBr): stretching band 3256cm^{-1} and 3104cm^{-1} (**C-H** aromatic) , stretching band 2920cm^{-1}, 2849cm^{-1} **(C-H** aliphatic**),** stretching band 1668 **(C=O)** carbonyl group , stretching band 1579cm^{-1}, 1439cm^{-1} **(C=C** aromatic**)** , the disappearance of the azide band at 2108cm^{-1} and the terminal alkyne bands at 3309cm^{-1} and 2114 cm^{-1} is a very good evidence for the formation of compound **[VI[$_b$.**

FT-IR spectrum of N-phenyl-2-(4-pentoxy methyl)-1H-1,2,3-triazole-1yl)acetamide **[VI]$_c$** showed the following bands cm^{-1} (KBr): stretching band 3259cm^{-1} and 3114cm^{-1} (**C-H** aromatic) , stretching band 2928cm^{-1}, 2857cm^{-1} **(C-H** aliphatic**),** stretching band 1664cm^{-1} **(C=O)** carbonyl group , stretching band 1575cm^{-1}, 1436cm^{-1} **(C=C** aromatic**)** , the disappearance of the azide band at 2108cm^{-1} and the terminal alkyne bands at 3309cm^{-1} and 2114 cm^{-1} is a very good evidence for the formation of compound **[VI[$_c$** . FT-IR spectrum of N-(4-bromophenyl-2- (4-propoxyymethyl)-1H-1,2,3-triazole-1yl)acetamide **[VII]$_a$** showed the following bands cm^{-1}(KBr): 3257cm^{-1} for N-H 3092cm^{-1} for (**C-H** aromatic) stretching , 2931cm^{-1}, 2863cm^{-1} **(C-H** aliphatic**)** stretching, 1665cm^{-1} **(C=O)** stretching, 1601cm^{-1}, 1450cm^{-1} **(C=C** aromatic**)** stretching, 1043cm^{-1} (**C-O**), the disappearance of the azide band at 2108cm^{-1} and the terminal alkyne bands at 3310CM^{-1} and 2115 cm^{-1} is a very good evidence for the formation of compound **[VII]$_a$.**

FT-IR spectrum of N-(4-bromophenyl)-2-(4-((butoxymethyl)-1H-1,2,3-triazol-1-yl)acetamide **[VII]$_b$** showed the following bands cm-1(KBr): 3256cm-^{1} for N-H 3088cm^{-1} (**C-H** aromatic) stretching , 2928cm^{-1}, 2856cm^{-1} **(C-H** aliphatic**)** stretching, 1661cm^{-1}**(C=O)** stretching, 1604cm^{-1}, 1558cm^{-1} **(C=C** aromatic**)** stretching, 1176cm^{-1}, 1080cm^{-1} (**C-O**) bending oop, the disappearance of the azide band at 2108 cm^{-1} and the terminal alkyne bands at 3309cm^{-1} and 2115cm^{-1} is a very good evidence for the formation of compound **[VII]$_b$.**

FT-IR spectrum of N-(4-bromophenyl)-2-(4-((pentoxymethyl)-1H-1,2,3-triazol-1-yl)acetamide **[VII]$_c$** showed the following bands cm-1(KBr): 3256cm^{-1} for N-H , 2924cm^{-1}, 2856cm^{-1} **(C-H** aliphatic**)** stretching, 1660cm^{-1}**(C=O)** stretching, 1619cm^{-1}, 1585cm^{-1} **(C=C** aromatic**)** stretching, 1161cm^{-1}, 1065cm^{-1}(**C-O**), the disappearance of the azide band at 2108 cm^{-1} and the terminal alkyne bands at3309cm^{-1} and 2115 cm^{-1} is a very good evidence for the formation of compound **[VII]$_c$.**

FT-IR spectrum of N-([1,1'-biphenyl]-4-yl)-2-(4-(propoxymethyl)-1H-1,2,3-triazol-1-yl)acetamide **[VIII]$_a$** showed the following stretching bands cm-1(KBr):3256cm^{-1} for N-H , 3031cm^{-1} (**C-H** aromatic) stretching , 2930cm^{-1}, 2860cm^{-1} **(C-H** aliphatic**)** stretching, 1674cm^{-1} **(C=O)** stretching, 1600cm^{-1}, 1553cm^{-1} **(C=C** aromatic**)** stretching, 1181cm^{-1}, 1110cm^{-1} (**C-O**)

FT-IR spectrum of N-([1,1'-biphenyl]-4-yl)-2-(4-(butoxymethyl)-1H-1,2,3-triazol-1-yl)acetamide **[VIII]$_b$** showed the following bands cm-1(KBr):stretching band 3256cm^{-1} for N-H, 2925cm^{-1}, 2856cm^{-1} **(C-H** aliphatic**)** stretching, 1671cm^{-1} **(C=O)** stretching, 1583cm^{-1} **(C=C** aromatic**)** stretching, 1175cm^{-1}, 1068cm^{-1} (**C-O**)

FT-IR spectrum of N-([1,1'-biphenyl]-4-yl)-2-(4-((pentyloxy)methyl)-1H-1,2,3-triazol-1-yl)acetamide **[VIII]$_c$** showed the following bands cm^{-1}(KBr): stretching band 3256cm^{-1} for N-H , 3029cm^{-1} (**C-H** aromatic) ,stretching band 2920cm^{-1}, 2849cm^{-1} **(C-H** aliphatic**)** stretching, 1684cm^{-1} **(C=O)** stretching, 1581cm^{-1}, 1550cm^{-1} **(C=C** aromatic**)** stretching, 1170cm^{-1}, 1066cm^{-1} (**C-O**) .

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