Synthesis of Some Substituted 1,2,3-Triazole Derivatives via 1,3-Cycloaddition Reaction of Phenacylazides and Some Substituted Propargyl Compounds

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Abstract:

Some propargyl esters (5a-g) were prepared from the reaction of propargyl alcohol (2) with the corresponding acid chlorides (1a-g). Also some propargyl imides (6a-c) were prepared from the reaction of the corresponding imide sodium salts (4a-c) with propargyl bromide (3). The two series of compounds (5a-g,6a-c) were allowed to undergo 1,3-cycloaddition reaction with phenacyl azide (9) which intern prepared from the reaction of phenacyl bromide (7) and sodium azide (8) to form the final substituted 1,2,3-triazoles (10a-j). The above synthesized compounds were characterized by IR spectroscopy and are discussed.

Keywords: 1,2,3-Triazole, cycloaddition reaction

Introduction:

There were a versatile methods in literatures for the preparation of triazole compounds including cyclization of thiosemicarbazide derivatives[1-6], decomposition of o-azidobenzene[7,8], reductive cyclization of azides[9], nucleophilic attacks of active methylene on azides, followed by cyclization[10]. A related triazole synthesis utilizes phosphorous Ylids and some phenyl, suphonyl, tosyl and benzoyl azides[11,12]. It should be noted that prolonged heating of aryl azides with sodium ethoxide alone also produces triazoles[13]. The formation of the triazolo [4,5-d] pyrimidine ring system from substituted triazoles has been effected in different ways[14]. Triazole dicarboxy amides has been cyclised with hypobromide to afford 3-glycosido-5,7-dihydroxy triazolo [4,5-d] pyrimidines[15]. Some fused ring triazo to compound like triazolo [4,5-d] pyridine or 1,2,3,4,6-penta azaindene was first prepared by treating 6-methyl-4,5-diaminopyridine with nitrous acid[16]. It was found that some substituted triazoles produced by treatment indazole with nitrilimines followed by hydrolysis in acidic media[17]. Hydroxy and amino-1,2,3-triazoles were synthesized by addition of azide to olefins followed by elimination of molecule of alcohol or amine from the corresponding triazole[18,19].

The other method of triazole synthesis is by addition of azides to triple bonds. The reaction of azides and acetylene yields 1,2,3-triazoles directly. In the synthesis of the parent ring benzyl azide was reacted with acetylene yielding 1-benzyl-1,2,3-triazole which was converted to 1,2,3-triazole by catalytic hydrogenolysis[20,21]. In the addition to unsymmetrical acetylenes the orientation is controlled by electronic effects[22]. This addition reaction has used for the preparation of a large number of substituted triazoles using various types of azides and acetylenes[23-26]. It was found that the reaction of aliphatic ketones with alkyl or aryl azides in the presence of potassium t-butoxide yielded 5-phenyl hydroxyl-1,2,3-triazoles[27].

The recent work on the synthesis of 1,2,3-triazoles includes the Cu-catalyzed stepwise cycloaddition of azides to terminal alkynes[28], synthesis via three component coupling reaction of inactivated terminal alkynes, allyl carbonate and trimethyl silyl azide under Pd(0)-Cu(I) bimetallic catalysis[29]. 1,2,3-Triazoles were prepared in good yields by cycloaddition of allyl azides to enol ethers under solventless conditions[30]. The Pd catalyzed synthesis of 1H-triazoles from alkenyl halides and sodium azide[31] and other 1,2,3-triazole compounds has been prepared by [3+2] cycloaddition reactions of 2-aryl-1-cyano or 2-aryl-1-carbethoxy-1-nitroethenes with $TMSN_3$[32].

Among the new synthetic applications of the triazole compounds are the 1,3-dipolar cycloaddition reaction of nonfluorescent-3-aziocomarins and terminal alkynes which afforded intense fluorescent 1,2,3-triazole products[34]. Four new hydroxyl benzotriazole derivatives have been synthesized. These compounds along with their parent unsubstituted 1-hydroxy benzotriazole (HOBT) have been examined for the cleavage of p-nitrophenyl hexanoate (PNPH) and p-nitrophenyl phosphate (PNPDPP) in comicelles with monovalent cetyl trimethyl ammonium bromide (CTABr)[35]. Triazole based antifungal drugs such as voriconazole has been efficiently synthesized and showed low toxicity[36]. N-Substituted glycine peptide (peptidomimetics) oligomers were used as substrates for azide-alkyne [3+2] cycloaddition conjugation reactions[39]. The [3+2] cycloadditions have been employed to link polypeptide chains, synthesize dendrimers and conjugate derivatives to the exterior of viral particles[38-40]. The approach used for multi-site conjugation of alkyne or azide-containing groups onto peptoid scaffold[41] and further more applications[42,43].

In this investigation new derivatives of triazole compound were prepared and discussed in an attempt to study their biological effect which is our next goal.

Experimental:

The IR spectra were recorded on Bruker. The melting points were measured using Electrothermal type 2300 instrument. Succinic and maleic anhydrides were prepared following the same published procedure[44]. Phthalic anhydride was commercially available from Fluka Company. Compounds (4a-c) were prepared from the well established procedure[45]. Their potassium salts were prepared using elsewhere reported procedure[46]. Compounds (1a-f) were supplied by either BDH or Fluka Companies and were used directly without further purifications.

Synthesis of β-acetylthiopropanoic acid[47]

This acid was prepared by dropwise addition of thioacetic acid (0.01 mol) to a stirred acrylic acid (0.01 mol). After complete addition, the mixture was further stirred for 24 hr. To the thick mass ether (10 ml) was then added. The precipitated solid was filtered off and dried in air, m.p. 52-54 °C, total yield 50%.

Synthesis of β-acetyl thiopropionyl chloride[48] (1g)

To β-acetyl thiopropanoic acid (0.01 mol) dissolved in (100 ml) dry ether was added (3.6 g, 0.03 mol) of thionyl chloride (drop-wise) with continuous stirring for 15 min. The stirring was continued for further 3 hrs. The solvent was evaporated under reduced pressure. The resulted acid chloride had p.b. 118 °C, 78% yield.

General procedure for the synthesis of alkyl and aryl propargyl sulfonate and carboxylate[49] (5a-g)

Propargyl alcohol (0.56 g, 0.01 mol) was mixed with (0.01 mol) of compounds (1a-g), and (0.01 mol) of triethylamine in 100 ml of dry benzene. The mixture was refluxed for one hour, and filtered. The filtrate was distilled to remove the solvent. The oily product was washed with 10% sodium carbonate solution, then with water and dried on $CaCl_2$ (anhydrous). The boiling points of the resulted compounds are indicated in Table (1).

Table (1): Boiling and melting points of propargyl esters (5a-g) and propargyl imides (6a-c)

Comp. No.	5a	5b	5c	5d	5e	5g	6a	6b	6c
b.p., m.p. (°C)	113	152	127	167	186	118	211-214	228-229	187-189
Yield (%)	45	53	48	61	57	78	78	73	66

General procedure for the synthesis of N-propargyl imides (6a-c)[50]

To a flask equipped with reflux condenser containing (0.01 mol) of potassium imide is added 0.01 mol of propargyl bromide. The mixture was refluxed for 1 hr. then cooled. The potassium bromide was removed by filtration, and then cold water added to the filtrate to precipitate imides. The N-propargyl imides were filtered and dissolved in ether Ether was removed from the filtrate under reduced pressure to afford the crude products which were crystallized from EtOH/pet. ether (40-60 °C). The resulted compounds (6a-c) are described in Table (1).

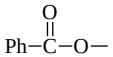
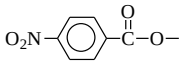
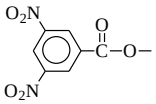
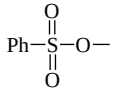
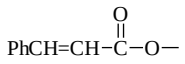
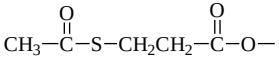
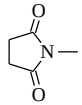
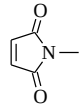
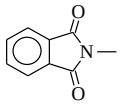
Synthesis of phenacyl azide[51] (9)

A solution of (20 g, 0.1 mol) of phenacyl bromide in 75 ml of ethanol and (12 ml, 0.2 mol) of glacial acetic acid was cooled to 0-5 °C. To this mixture was added a cold solution (13.0 g, 0.2 mol) of sodium azide in 15-20 ml of water and the resulting mixture was allowed to stand in the cold box for 24 hrs with intermittent shaking. The crystalline product, m.p. 16-17 °C, was collected and recrystallized from a mixture of diethyl ether and petroleum ether, b.p. 40-60 °C, wt. 14.9 g (93% yield), m.p. 17 °C.

Synthesis of 1-phenacyl-1H-1,2,3-triazole-4-substituted methylene carboxylate[52] (10a-j)

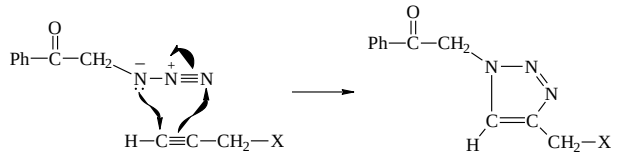
Phenacyl azide 9 (0.01 mol) was dissolved in ethanol (50 ml). The propargyl ester or imide was added to the solution. The mixture was heated under reflux for 24 hrs. After removing the solvent under reduced pressure, the residue was recrystallized from ethanol, m.p. of the resulted compounds are indicated in Table (2).

Table (2): IR absorption spectral data for compounds (10a-j)

Comp. No.	X	m.p. °C	Yield %	IR ν (cm^{-1}) KBr									
				C-O	C-N	C=O Ketonic	C=O Ester	C=C , C---C , N=N aromatic	C=C Triazole	N-O	S=O	C-S	C=O Imide
10a		127-129	69	1216	1342	1673	1731	1599 , 1489	1554	-	-	-	-
10b		152-154	85	1224	1354	1688	1722	1607 , 1429	1566	-	-	-	-
10c		76-78	64	1270	1294	1660	1722	1599 , 1472	1578	1522	-	-	-
10d		168-170	78	1276	1309	1664	1738	1600 , 1493	1561	1519	-	-	-
10e		157-160	69	1284	1319	1667	-	1597 , 1490	1523	-	1176	-	-
10f		178-181	52	1189	1352	1631	1723	1601 , 1469	1563	-	-	-	-
10g		193-195	74	1213	1383	1641	1725	1598 , 1470	1581	-	-	738	-
10h		184-187	58	-	1328	1676	-	1598 , 1469	1561	-	-	-	1770,1718
10i		237-239	53	-	1338	1639	-	1589 , 1414	1560	-	-	-	1786,1731
10j		204-207	41	-	1279	1638	-	1603 , 1413	1560	-	-	-	1771,1726

Results And Discussion:

As mentioned in the introduction, the orientation of 1,3-cycloaddition of unsymmetrical acetylenes is controlled by electronic effects[22]. It was claimed by other researchers that the addition is also controlled by steric effects[19,52,53] which means that the favoured addition is as follows:

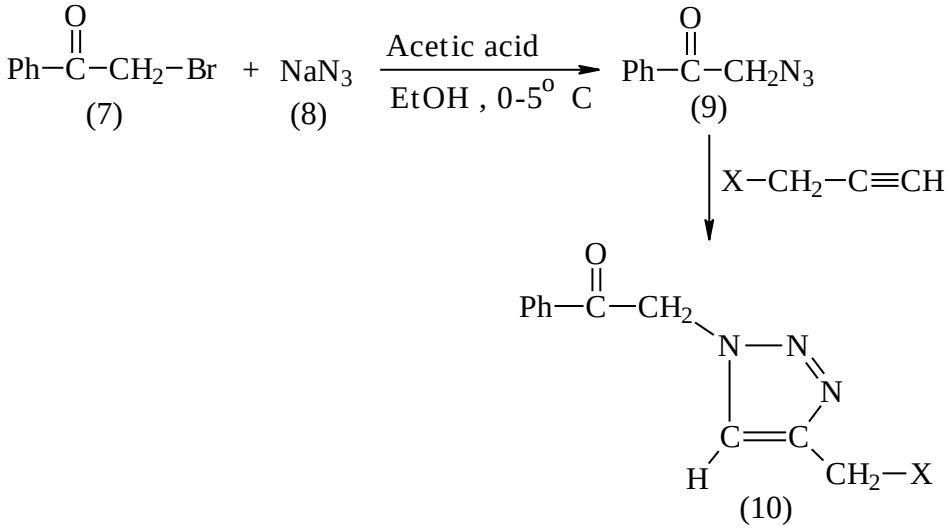


The above mechanism is supported by the formation of just one product which was followed by preparative thin layer chromatography using silica gel and toluene-ethyl acetate mixture as eluant. The above suggestion of the formation of the triazoles (10a-j) (Scheme 1) does not ignore the possibility of the formation of the other isomer which could not be identified even with ^{1}HNMR which might be due to the similarity of the chemical environment of the protons in either position 4 or 5 in the triazole ring[52]. So the less hindered triazoles (10a-j) are believed to be the main products on the basis of steric considerations. This assignment is quite compatible with the reported results of other researchers[54,55]. TLC results revealed the absence of other isomer.

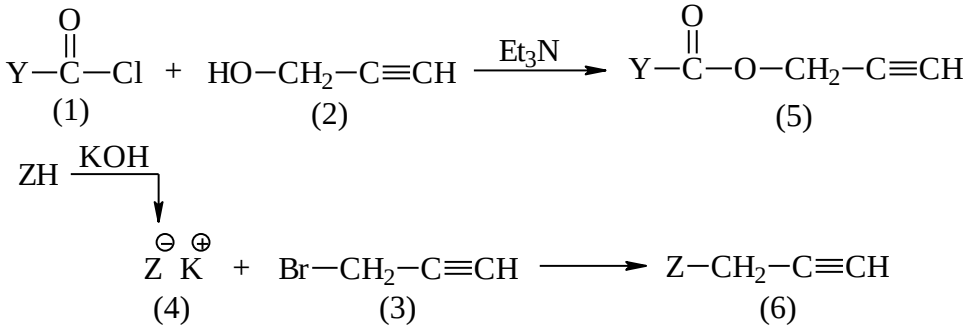
Table (2) showed the IR results of the synthesized triazole compounds in which the C-O stretching absorption bands ranged from 1213-1284 cm^{-1} according to the environment of the C-O group which showed the maximum of 1284 cm^{-1} for compound 10e due to the sulfonate withdrawal group. The ketonic C=O group of the phenacyl moiety ranging around 1631-1688 cm^{-1}, while the C=O group of ester exhibited stretching absorption ranging between 1722-1738 cm^{-1} together with the triazole C=C bond exhibited around 1600 cm^{-1} along with the C⋯C which showed lower values as indicated in the table. The N=N stretching absorption for triazole compounds appeared nearly around 1400 cm^{-1} which was assigned within the same absorption region of the C⋯C stretching for all compounds, see Table (2). The stretching absorption bands for the imide moieties (the two carbonyl groups) usually appeared as two bands for symmetric and asymmetric and are indicated in the same table. The first assigned at (1718-1726 cm^{-1}) and the other at (1770-1786 cm^{-1}) respectively. The aromatic C=C absorption bands of the triazole substituent are appeared at nearly the same absorption of the triazole C=C absorption bands as indicated in Table (2).

Moreover, other simple chemical tests were performed including $Cu(NH_3)_2^+Cl^-$, $Ag^+(NH_3)_2NO_3^-$ which gave negative test of the acetylenic hydrogen in compounds (10a-j), 2,4-Dinitrophenyl hydrazine gave positive test for the formation of the corresponding hydrazone indicating the presence of the phenacyl group within the final compound structure.

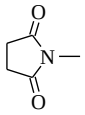
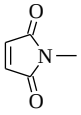
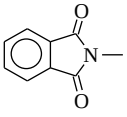
Furthermore, the final compounds (10a-g) showed +ve ferric hydroxamate test for the presence of an ester moiety within the final product structure. The presence of N,S elements was also chacked using simple sodium fusion element test including compounds 10e and 10g. The above results may give further evidence for the formation of the triazole containing these functional groups within its structure. It is important to note that compounds 5 and 6 (Scheme 2) are identified by the presence of the -C≡C- triple bond by IR which usually appeared at 2200-2210 cm^{-1} and the terminal acidic hydrogen test.



Scheme (1)



	Y
1a	CH_3
1b	Ph
1c	4-$NO_2C_6H_4$
1d	3,5-di$NO_2C_6H_3$
1e	YCO- = $PhSO_2$
1f	PhCH=CH-
1g	$CH_3COSCH_2CH_2$-

	Z
4a	
4b	
4c	

Scheme (2)

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تحضير عدد من مشتقات ١،٢،٣-ترايازول المعوضة من خلال تفاعل الاضافة الحلقية للفيناسيل ازيد مع بعض مركبات البروبارجيل المعوضة

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[١] *قسم الكيمياء، كلية التربية، جامعة الموصل، الموصل، جمهورية العراق*

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[٣] *قسم الكيمياء، كلية التربية للبنات، جامعة الموصل، الموصل، جمهورية العراق*

الملخص:

تم تحضير بعض الاسترات البروبارجيلية وهي المركبات (5a-g) من تفاعل بروبارجيل الكحول وهاليدات الحوامض المقابلة (1a-g)، كما تم تحضير بعض الايمايدات البروبارجيلية (6a-c) من تفاعل ملح الايمايد المقابل مع بروبارجيل البروميد (٣). تم مفاعلة هاتين السلسلتين المتمثلة بالمركبات (6a-c,5a-g) مع ازيد الفيناسيل (٩) الذي بدوره تم تحضيره من مفاعلة بروميد الفيناسيل (٧) مع ازيد الصوديوم (٨)، وكان ناتج هذا التفاعل هو تكوين المركبات الحلقية (الترايازولات المعوضة) وهي تمثل المركبات (10a-j) . تم تشخيص النواتج باستعمال طيف الـ IR وتمت مناقشته