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Synthesis 4-phenyl -1-alkyl-1,2,4-triazoline-5-one derived from D- fructose

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Abstract

The aim of the present work is the synthesis of new carbohydrate derivatives containing 1,2,4-triazole from D-fructose . To obtain these derivatives, the diacetone fructose (1) was chosen as the starting material, which was obtained from the reaction of anhydrous fructose with dry acetone in presence of anhydrous ferric chloride. Oxidation of (1) with potassium permanganate in potassium hydroxide solution gave the acid (2). Esterification of the acid with dimethyl sulphate gave the methyl ester (3). Treatment of the methyl ester (3) with hydrazine hydrate gave the hydrazide (4), which is the desired Chiron. The hydrazide (4) was used for the preparation of 1,2,4-triazole-5-one (6) derivative. These compounds was synthesized by the intramolecular cyclization of the semicarbazide derivative (5), which was obtained from the reaction between the hydrazide (4) and phenylisocyanate. Alkylation of (6) with different alkyl halides give (6a,6b).

All the synthesized compounds were characterized by the following techniques : CHN analysis and FTIR spectra . The antibacterial activity for their compounds were studied against three selected micro-organisms *Eschericha coli* , *Klebsiella* and *Pseudomonas aeruginosa* .

Introduction

1,2,4-Triazole derivatives have been used in many drugs as antiviral[(1)], antibacterial[(2)] and antifungal [(3)]. Most of the known triazole compounds posses low solubility in water ,therefore the new researches include preparation of new carbohydrate derivatives containing 1,2,4-triazole and 1,2,3-triazole[(4-10)], these derivatives have high solubility in water in addition of possessing possible biological activity .

Other 1,2,3-triazoles can be used as corrosion inhibitors [11,12], while some are used as charge-donating materials for electrostatographic development[(13)] . Recently, 1,2,3-triazole links have

emerged as a popular bridging units in carbohydrate chemistry because of the facile efficient method of their introduction, which referred to as "click chemistry"[14].

The present work was directed toward the synthesis of new carbohydrate derivatives containing 1,2,4-triazole from D-fructose**,** these derivatives are expected to have high solubility in water in addition of possessing possible biological activity .

Experimental

General procedure

Melting points were recorded using Electrothermal 9100 melting point apparatus and are uncorrected. The IR spectra (KBr discs or thin films) were recorded on a Perkin-Elmer 1310 infrared spectrophotometer, or a Shimadzu FTIR-800.

(TLC) was performed on aluminum plates per coated with silica-gel f_{254}, supplied by Merck. Column chromatography was carried out with silica-gel 60 (Fluka). Spots were detected with iodine vapor. Elemental analysis (C.H.N) were carried out in College of Science / University Al - Mustansiriya , Baghdad .

Synthesis of Compounds

Compounds (1-4) have been prepared as previously described(9)

Synthesis 1-(1,2:3,4-di-o-isopropylidene-α-D-fructopyranosyl)-4-phenyl-semicarbazide (5)

To a solution of 1,2:3,4-di-o-isopropylidene-α-D-fructonic acid hydrazide (4) (5gm,14mmole) in absolute ethanol (20 ml) , was added with continues stirring phenyl isocyanate (1.87ml,14mmole) and the resulting mixture was stirred overnight. The white precipitate was filtered and recrystallized from ethanol to give white crystals of semicarbazide derivative (5) (6gm, yield 85%), m.p : 242-244.

Synthesis 3-(1,2:3,4 – di-o-isopropylidene -α-D-fructopyranose-5-yl)-4-phenyl-1,2,4-triazole-5-one (6)

1-(1,2:3,4-di-o-isopropylidene-α-D-fructopyranosyl)-4-phenyl-semicarbazide (5) (4gm,9.45mmole) was refluxed with 10% aqueous potassium hydroxide solution (25 ml) for 24 hr. . The reaction mixture was filtered, cooled and neutralized by gradual addition with stirring of 10% acetic acid solution. The formed white precipitate was filtered and recrystallized from ether : petroleum ether to give white crystals of the triazole derivative (6) (3gm , 78 % yield), m.p : 260 °C .

Synthesis 3-(1,2:3,4 – di-o-isopropylidene -α-D-fructopyranose-5-yl)-4-phenyl-1-alkyl-1,2,4-triazoline-5-one (6a,6b)

3-(1,2:3,4 – di-o-isopropylidene -α-D-fructopyranose-5-yl)-4-phenyl-1,2,4-triazole-5-one (6) (0.4gm, 0.49mmole) in dry dioxane (5ml), was added during 20 min. potassium hydroxide (0.03gm ,0.54mmole) with stirring, then the appropriate alkyl halide (0.59mmole) was added dropwise and the reaction mixture was refluxed for 4 hr. . TLC (benzene : methanol, 9:1) showed that the reaction was complete. The reaction mixture was filtered, cooled and filtrate was poured onto cold water.

The resulting aqueous layer was extracted with chloroform (3×10ml), the combined chloroform extracts was evaporated to give the desired 5-alkyloxy derivatives (6a,6b) .table (1) lists the physical properties of the synthesized compounds .

Study of biological activity for compounds

The biological activity of the compounds were studied against selected types of bacteria which include *Eschericha coli* , *Klebsiella* and *Pseudomonas aeruginosa* were cultivated in nutrient agar medium .

Two ***in vitro*** techniques were proceeded for studying antibacterial activity against the two strains , DMSO was used as a solvent and as a control , for both techniques the constructions of the compounds in this solvent were (10^{-3} M) . The first technique was the Disc Sensitivity Test[15], this method involves the exposure of the zone of inhibition towered the diffusion of micro-organism on agar plate. The plates were incubated for 24hr. at 37 C^{o}, the zone of inhibition of bacterial growth around the disc was observed.

Results and Discussion

To prepare triazole compound having saccharide moiety, the hydrazide (4) was seen as a suitable Chiron for this synthetic approach.

The hydrazide (4) was obtained from D – fructose which initially was converted to the diacetone fructose (1) by its reaction with dry acetone in presence of anhydrous ferric chloride as Lewis acid catalyst[16]. The diacetone fructose (1) was then oxidized to diacetone fructonic acid (2) using potassium permanganate in potassium hydroxide solution[9]. This method is similar to that described by Szkrybaio[17] for the synthesis of 2,3:4,5-di-o-isopropylidene-2-keto-D-gluconic acid.

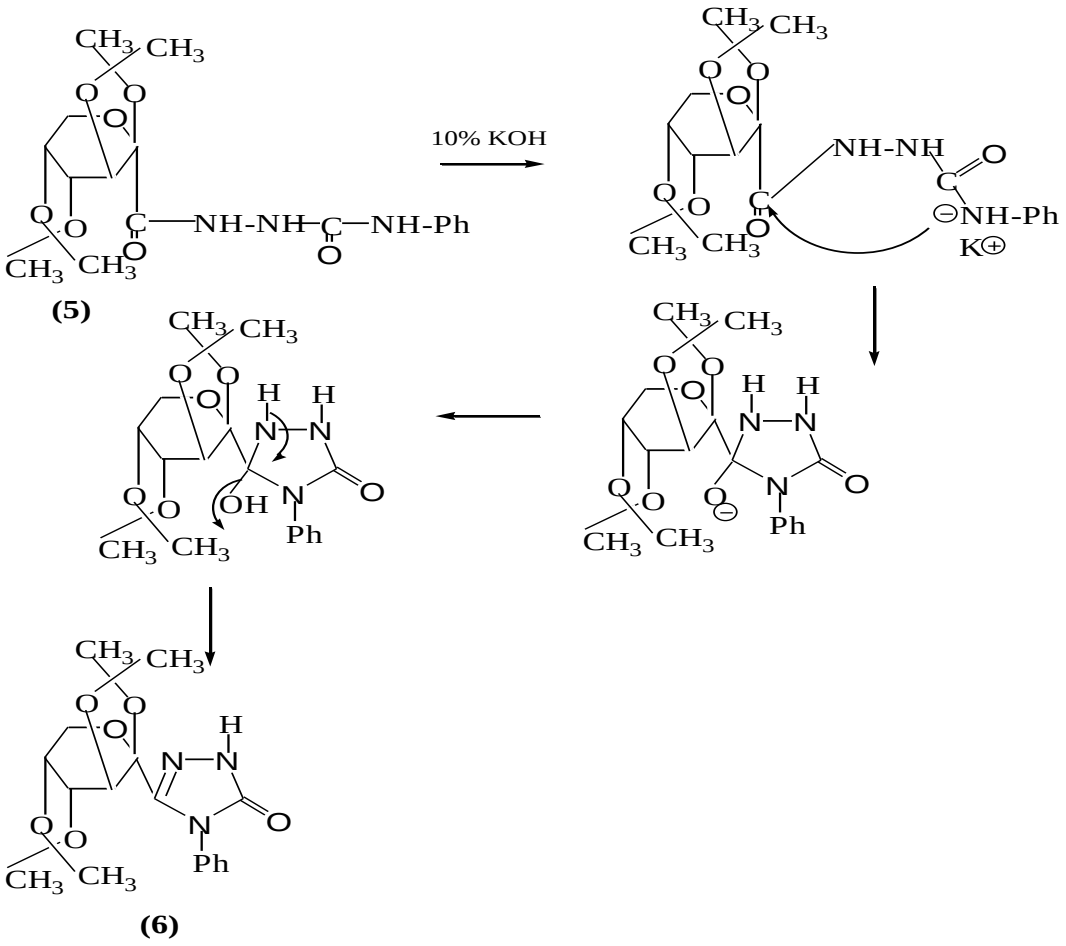
The next step was esterification of the acid (2) to the corresponding methyl ester by refluxing (2) with dimethyl sulphate (DMS)[9].

When the methyl ester (3) was refluxed with 98% hydrazine hydrate it gave after the usual work up the expected hydrazide (4)[9] .

The reaction of acid hydrazide (4) with phenyl isocyanate in ethanol at room temperature gave the semicarbazide (5). The FTIR spectrum of (5) showed stretching bands at 3380 cm^{-1} and 3250 cm^{-1} (amide N-H groups), 1690 cm^{-1} and 1650 cm^{-1} for the amide I and amide II absorptions, the FTIR spectrum also showed a characteristic aromatic band at 3040 cm^{-1} $(C-H)_w$, 1595 cm^{-1} $(C=C)_m$ and out of plane bending at 695 cm^{-1} and 740 cm^{-1} for mono substituted benzene ring .

The reaction of the semicarbazide (5) with 10% KOH under refluxing condition affected intramolecular cyclization through the loss of H_2O giving the desired triazole - one derivative (6).

The formation of (6) may be visualized by the following mechanism :



(5)

(6)

Scheme (1) : The mechanism formation of triazole derivative (6)

The structure of the triazole - one derivative (6) was confirmed by elemental analysis and FTIR Spectra.

The FTIR of the triazole - one derivative (6) showed stretching bands at 3300 cm^{-1} (N-H), 1750 cm^{-1} (C=O) and 1580 cm^{-1} (C=N).

Alkylation triazole - one (6) with different alkyl halides under basic condition gave different alkylated products (6a,6b). The triazole - one (6) is considered as an ambident nucleophile. Under SN^2 mechanism, the N-alkyl halides (MeI, EtCl) are attacked by the better nucleophile, i.e the nitrogen atom to give the N-alkyl derivatives. These observations are in good agreement with literature[18] .

The N-alkyl derivatives showed the same general FTIR spectral features. The only difference from (triazole - one) was the disappearance of (N-H) band. These results are agreement with literature[8] .

Table (1) : Physical properties of prepared compounds

Comp. No.	Colour	M.P. C°	Yield %	Elemental analysis Calc. / (Foud)		
				C%	H%	N%
5	White	242-244	85%	53.26 (52.90)	6.52 (5.83)	10.96 (9.94)
6	White	260	78%	55.89 (54.83)	6.30 (5.75)	11.50 (10.70)
6a	White	>300	73%	56.99 (55.91)	6.59 (5.70)	11.08 (10.20)
6b	White	>300	70%	58.01 (56.97)	6.87 (5.90)	10.68 (9.73)

Biological activity

Biological Screening: Antimicrobial Activity Tests.

The biological activity of some of the prepared compounds was tested against one strain of Gram +ve bacteria (*Klebsiella*), Gram –ve bacteria (*Eschericha coli*, *Pseudomonas aeruginosa*.

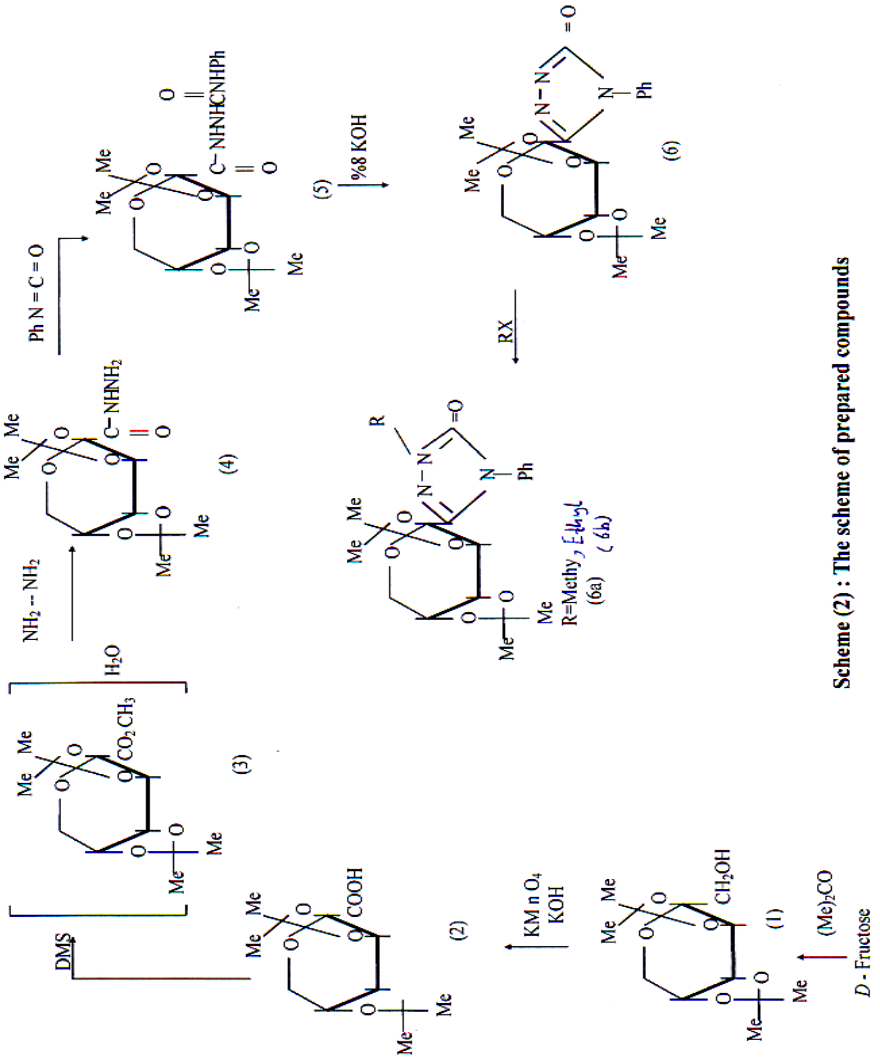
Disc sensitivity test[19]was employed for the *in vitro* study for anti bacterial studies. This method involves the exposure of the zone of inhibition toward the diffusion of microorganism on agar plate. The plates were incubated for 24 hrs. at 37 °C, the zone of inhibition of bacterial growth around the disc was measured.

The resulted are presented in table (2), Compounds (6a, 6b) were nearly as active as the antibiotics against the E. Coli and no effect against other bacteria. and compound (6) shows no effect against all bacteria.

Table (2): Results of antimicrobial activities of the compounds (10^{-3} mg. mL^{-1})

Compound	*Klebsiella*	*E. Coli*	*Pseudomonas aeruginos*
Control (DMSO)	0	0	0
6	0	0	0
6a	0	++	0
6b	0	++	0

Where:
(0) : no effect, 8-10 mm: (++)



Scheme (2) : The scheme of prepared compounds

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تحضير 4-

فنيل – 1 – الكيل – 1,2,4 – ترايأزولين – 5- ون مشتق من D – فركتوز

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الخلاصة

الهدف من هذا البحث هو تحضير مشتقات كاربوهيدراتية جديدة تحتوي على حلقة 4,2,1- ترايزول من الفركتوز. للحصول على هذه المشتقات تم اختيار داي استون فركتوز (1) كمادة اولية والتي تم الحصول عليها من تفاعل الفركتوز اللامائي مع الاسيتون الجاف بوجود كلوريد الحديد اللامائي. اكسدة (1) ببرمنغنات البوتاسيوم في محلول هيدروكسيد البوتاسيوم اعطى مركب الحامض (2). استرة الحامض بثنائي مثيل سلفات اعطى مركب المثيل استر (3). معاملة المثيل استر (3) مع الهايدرازين اعطى مركب الهايدرازايد (4) . تم استخدام مركب الهايدرازايد لتحضير مشتقات 4,2,1- ترايزول -5-ون (6). هذه المركبات حضرت بواسطة الغلق الحلقي لمشتق السيميكاربازايد (5). والذي حضر من التفاعل بين مشتق الهايدرازايد (4) و الفنيل ايزوسيانات . ان الكلة المشتق (6) بهاليدات الاكيل اعطت المشتقات (6a,ab) . شخصت المركبات المحضرة بواسطة التقنيات التالية : تحليل CHN و اطياف الاشعة تحت الحمراء FTIR . تم تقويم الفعالية المضادة للبكتريا المرضية و اختير ثلاث انواع من البكتريا (*Eschericha coli*) و (*Klebsiella*) و (*Pseudomonas aeruginosa*) .