AL-TAHADY UNIVERSITY
FACULTY OF SCIENCE
CHEMISTRY DEPARTMENT

M.Sc Thesis Entitled:

SOME REACTIONS OF

ARYLGLCINOYLHYDRAZONES

SUBMITTED BY:

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UNDER SUPERVISION OF:

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Some Reactions of Arylgycinoyl Hydrazones

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SOME REACTIONS

OF

ARYLGLCINOYLHYDRAZONES

بسم الله الرحمن الرحيم

(فأما الزبد فيذهب جفاء وأما ما ينفع الناس فيمكث في الأرض)

صدق الله العظيم

من سورة الرعد

الآية ((17))

Acknowledgment

*First of all, I am greatly thankful to **Allah**, the most gracious creator of the universe for health, Patience and the ability of thinking and start working of my research.*

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Last but not least, due thanks are extended to AL-Tahady University, Faculty of Science, and the Chemistry Department.

GAMILA SULIMAN ABU-ZID

THIS THESIS IS DEDICATED WITH

MY LOVE

TO

My mother,father,

brothers,sisters

and

My baby

ABSTRACT

ABSTRACT

Tittle of thesis : " SOME REACTIONS OF *ARYLGLCINOYL-HYDRAZONES* ".

Condensation of **(202)** with a number of monosaccharides, namely, D-mannose and D-galactose gave the respective hydrazones **(I-IV)**. Acetylation of **(I-III)** with acetic anhydride in pyridine at room temperature gave, the *per-O*-acetyl derivatives **(V-VII)**.

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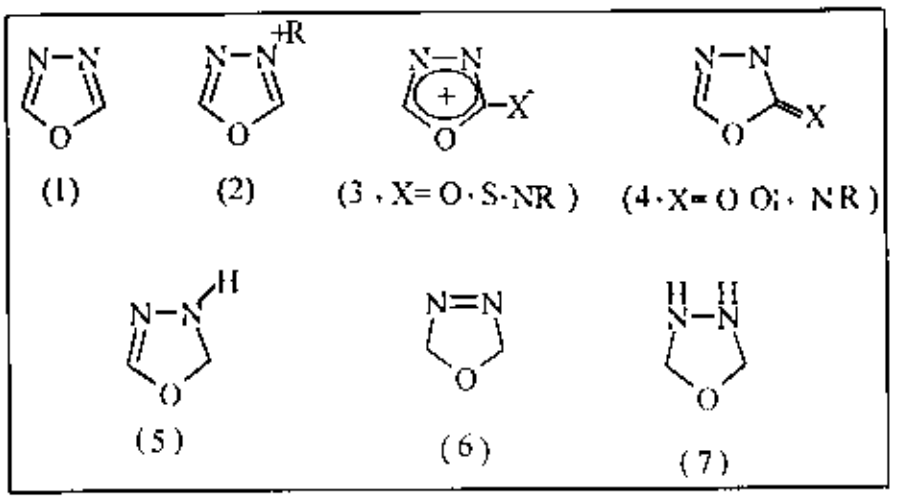
CONTENTS

INTRODUCTION

Introduction:-

1,3,4-Oxadiazole **1** is a thermally stable neutral aromatic molecule[1]. Other aromatic systems are 1,3,4-oxadiazonium cation **2** and the exocyclic conjugated mesoionic 1,3,4-oxadiazoles **3** and 1,3,4-oxadiazolines **4**. Derivatives of the nonaromatic reduced systems such as 2,3-dihydro-1,3,4-oxadiazole (1,3,4-oxadiazoline; **5**), 2,5-dihydro-1,3,4-oxadiazole (1,3,4-oxa- diazoline; **6**), and 2,3,4,5-tetrahydro-1,3,4-oxadiazole (1,3,4-oxadiazoline; 7) are also known as in **Scheme (1).**

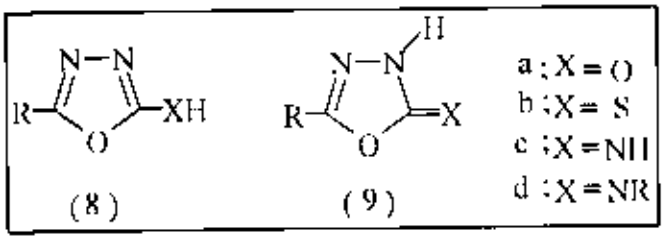


Scheme (1)

Structure and tautomerism of 1,3,4-oxadiazoles:-

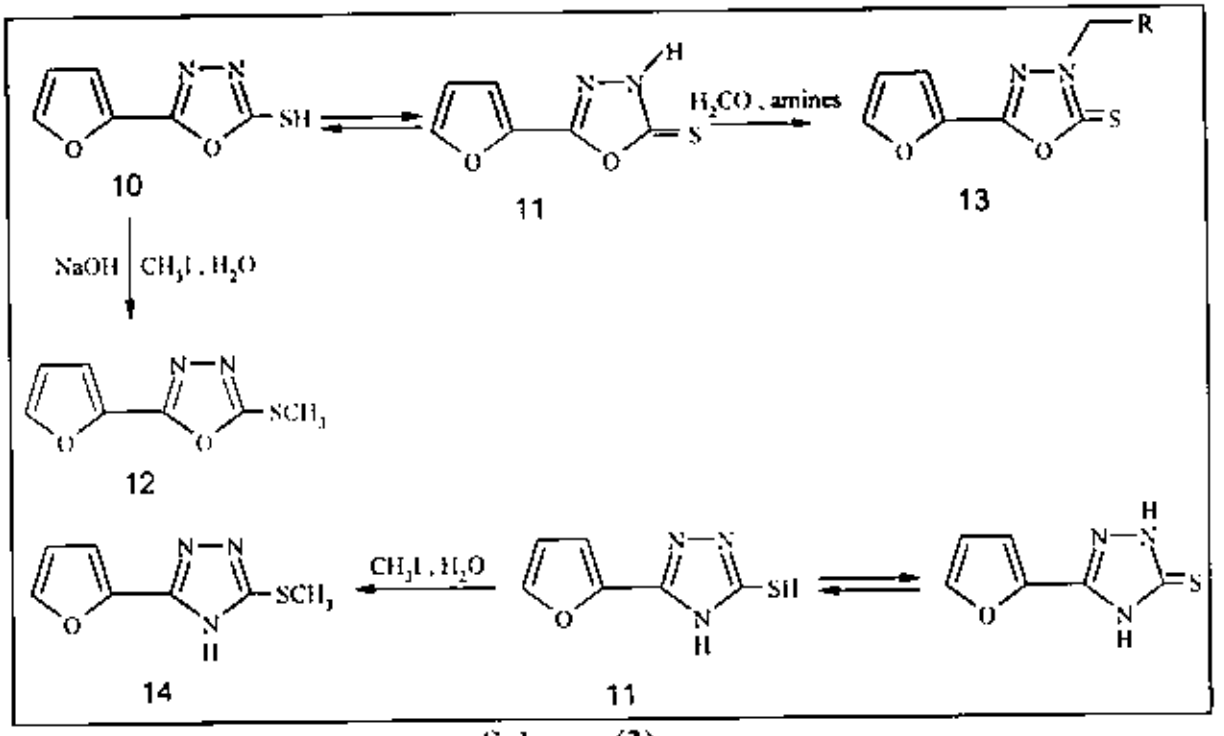
Structural parameters of 1,3,4-oxadiazoles dipole moments and data relating to its UV (λ_{max} calculated to be in the region 193-203 nm) and NMR spectra have been derived [2-5]. Studies on 1,3,4-oxadiazole and its cation indicate a maximum positive charge in the 2- position. Molecular diagrams for 1,3,4-oxadiazoles, 2-phenyl- and 2,5-diphenyl 1,3,4-oxadiazole, and oligomeric oxadiazoles have been derived and conjugation between the rings is found to be similar to that in polyphenyls [6]. 2-Hydrdoxy- **8a**, 2-mercapto- **8b**, and 2-amino **8c**-1,3,4-

oxadiazoles are in equilibrium withthe tautomeric oxadiazolines **9a**, **9b**, and **9c** respectively. Evidence from **UV** [7], and **IR** spectra supports structure **9a** for 1,3,4-oxadiazoline-5-ones and structure **9b** for 1,3,4-oxadiazoline-5-thiones [8].



Scheme (2)

It has been observed that extensive thiol-thione tautomarism exists in compounds **10** and **11**. In the ^{1}H-NMR the signal of the -SH protons were recorded, although they were very weak and also the ready synthesis of the Mannish bases **12**, **13**, **14** confirmed the tautomerism [9,10]. It has been reported that the crystal structures of **10** and **11** like compounds correspond to the thione form [11-13], but the reaction conditions for the synthesis of **12** prove that **10** can be in the thiol form too. The crystal structures of **10** and **11** [11,12] corresponded to the thione form, but they showed thiol-thione tautomerism in solution.



Scheme (3)

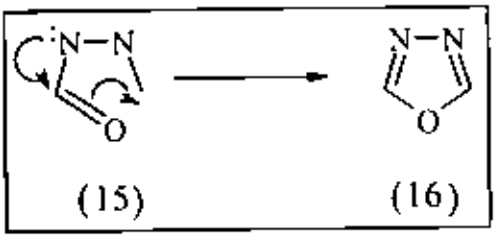
Synthesis of 1,3,4-oxadiazoles:-

Most 1,3,4-oxadiazoles are best obtained by synthesis from acyclic precurcors. Such reactions are mainly one-bond or two-bond cyclizations. For convenience, cyclizations of intermediates formed from two reactants are classed as one-bond cyclization if the intermediate can be isolated.

Ring synthesis:-

Cyclization with the formation of one bond:

The only common mode of cyclization is the formation of O-C(2) bond, usually by nucleophilic attack of the carbonyl oxygen of an amide group at the carbon atom which becomes C(2) in the 1,3,4-oxadiazole ring [13].

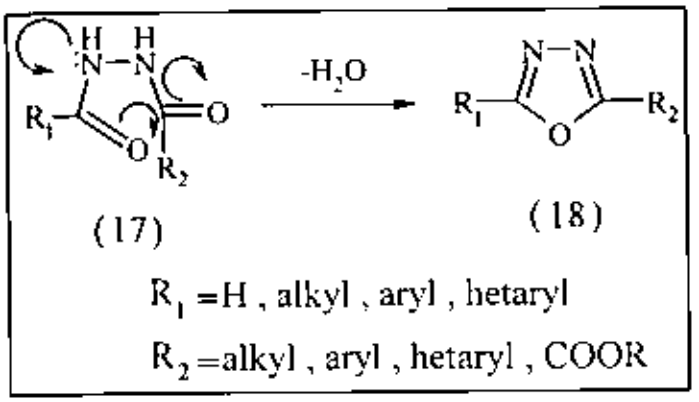


(15) (16)

Scheme (4)

From 1,2-diacylhydrazines and related compounds:

The most widely applicable route to 2,5-dialkyl-, 2-alkyl-5-aryl and 2,5-diaryl-1,3,4-oxadiazoles is the thermal or acid catalyzed cyclization of 1,2-diacylhydrazines [14].



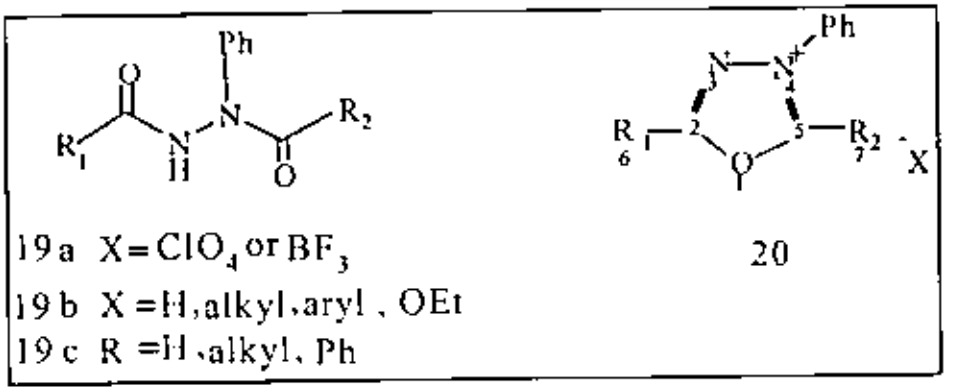
(17) (18)

R_1 =H , alkyl , aryl , hetaryl

R_2 =alkyl , aryl , hetaryl , COOR

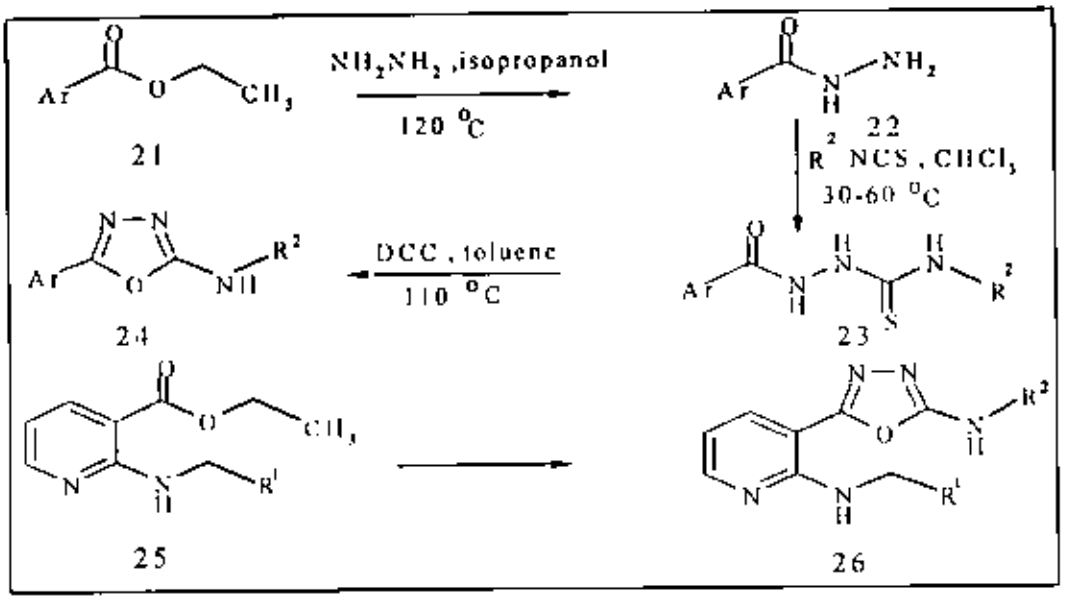
Scheme (5)

1-Phenyl-1,2-diacetylhydrazines **(19 a-c)** cyclize in acetic acid to form oxadiazolium salts[15] **20** :



Scheme (6)

Ester **21** was treated with hydrazine monohyrate to yield hydrazide **22**, which reacted further with an isothiocyanate to form thiocarbazide intermediate **23**. Finally, **23** was cyclized to produce the oxadiazole **24**.Oxadiazole analogue **26** similar to **24** were synthesized by the displacement of chlorine atome form 2-nicotinic acid ethyl ester **25** by a variety of amines under thermal conditions [16].

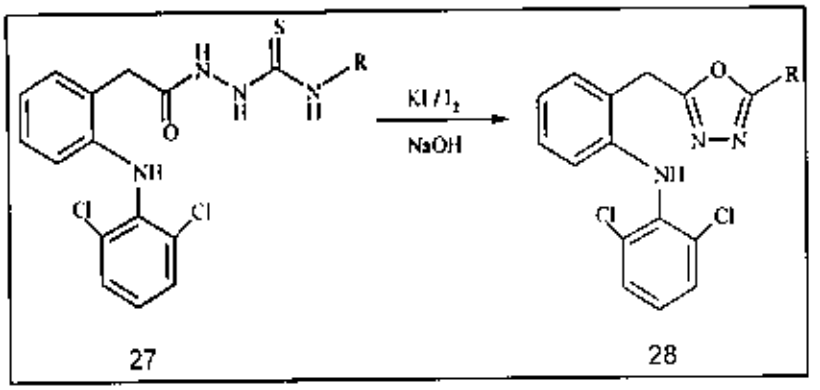


R^1 = 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, 3,4-$F_2C_6H_3$,

R^2 = 2,3-dihydrobenzo[1,4-dioxin]-6-yl, benzo[1,3-dioxol]-5-yl, 4-methoxy phenyldihydrobenzo[1,4-dioxin]-6-yl.

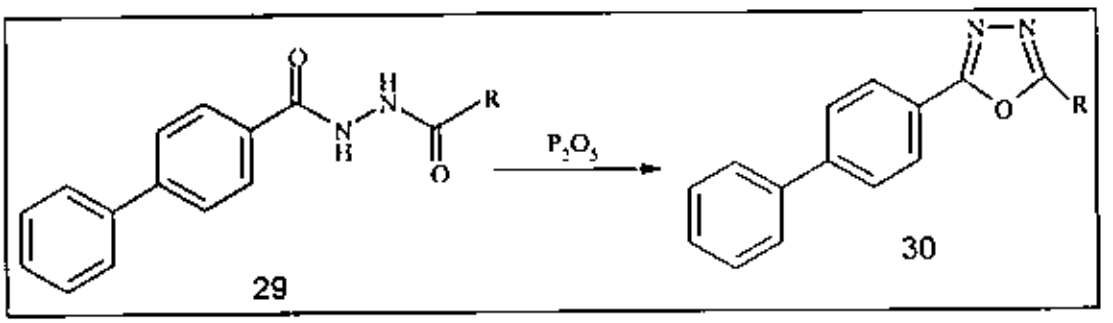
Scheme (7)

The thiosemicarbazides **27** were oxidatively cyclized to2-arylamino-5-substituted-1,3,4-oxadiazoles **28** by elimination of H_2S using iodine and potassium iodide in ethanolic sodium hydroxide [17].



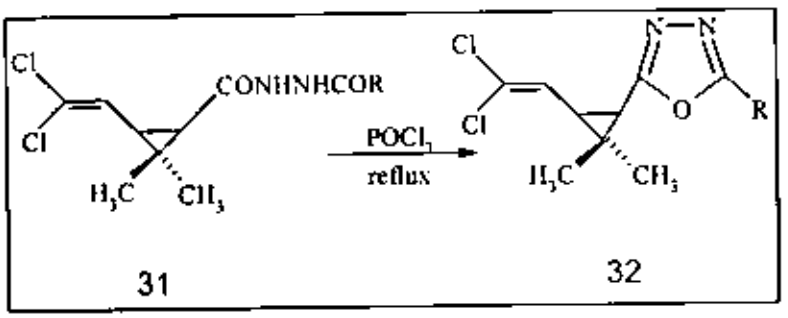
Scheme (8)

Compounds **29** were cyclized to 1,3,4-oxadiazoles **30** with phosphorus pentaoxide [18].



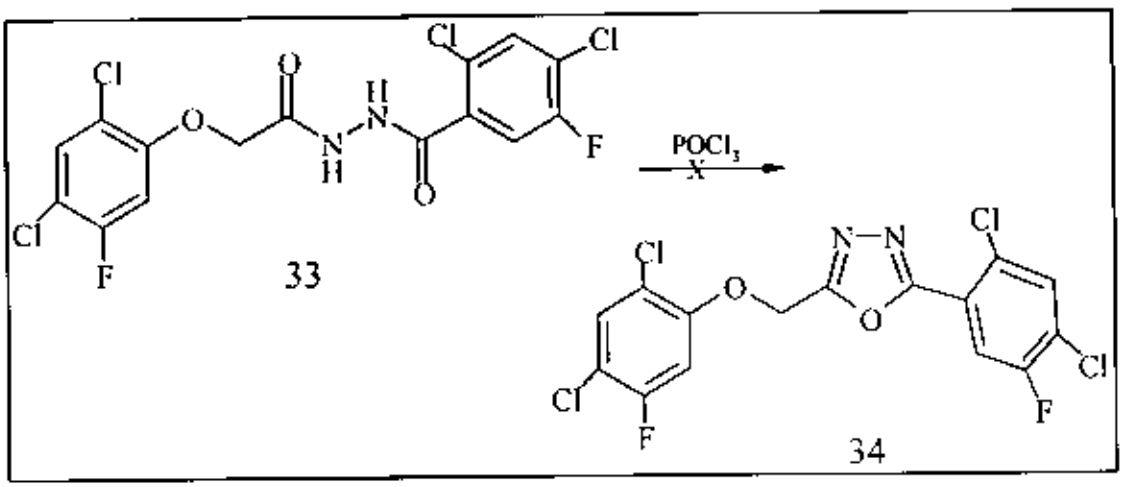
Scheme (9)

A symmetrical 2,5-disubstituted 1,3,4-oxadiazoles are usually synthesized from *N,N'*-diacylhydrazines [19]. By this method, compound **32** (R = 2,4-dichloro-5-fluorophenyl) were prepared via *N,N'*-diacyl-hydrazine [20] **31**.

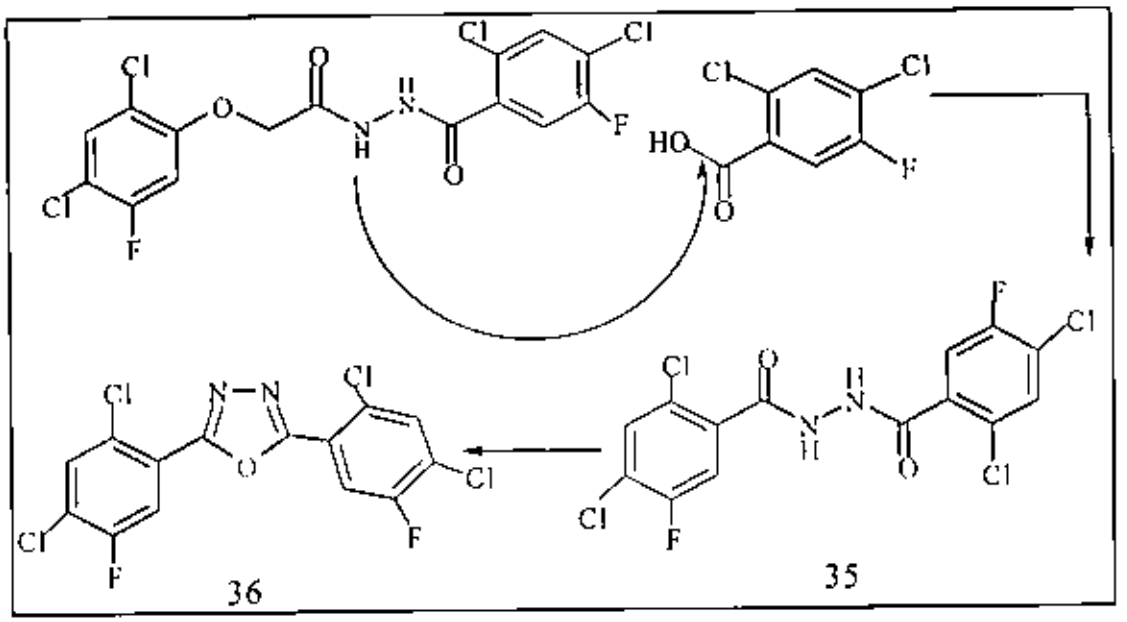


Scheme (10)

The symmetrical 2,5-bis(2,4-dichloro-5-fluorophenyl)-1,3,4-oxadiazole (DCFPO) was synthesized from 4-fluorophenoxyacetic acid hydrazide and 2,4-dichloro-5-fluorobenzoic acid because the expected product was asymmetrical 2-(2,4-dichloro-5-fluorophenyle)-5-(4-fluorophenoxymethyl)-1,3,4-oxadiazole[21]. Because 2,4-dichloro-5-fluorobenzoic acid was in excess we believe that an exchange reaction occurs between the carboxylic acid and the diacylhydrazine which was formed via the mechanism shown bellow[20].

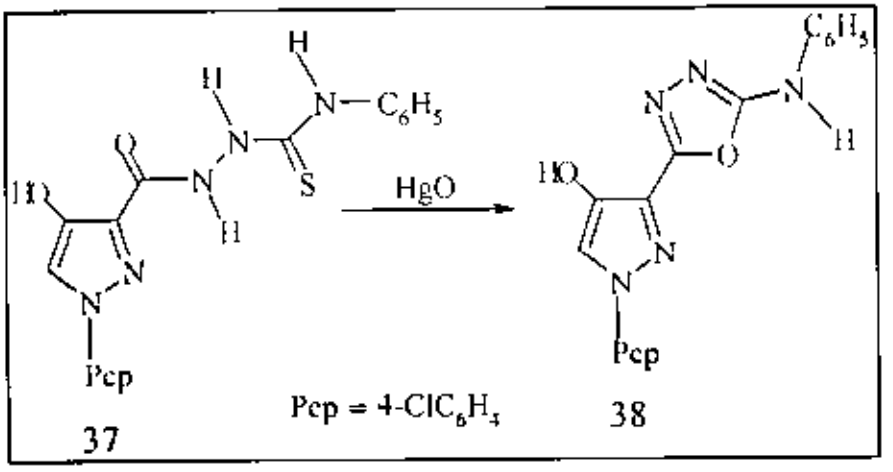


Scheme (11)



Scheme (12)

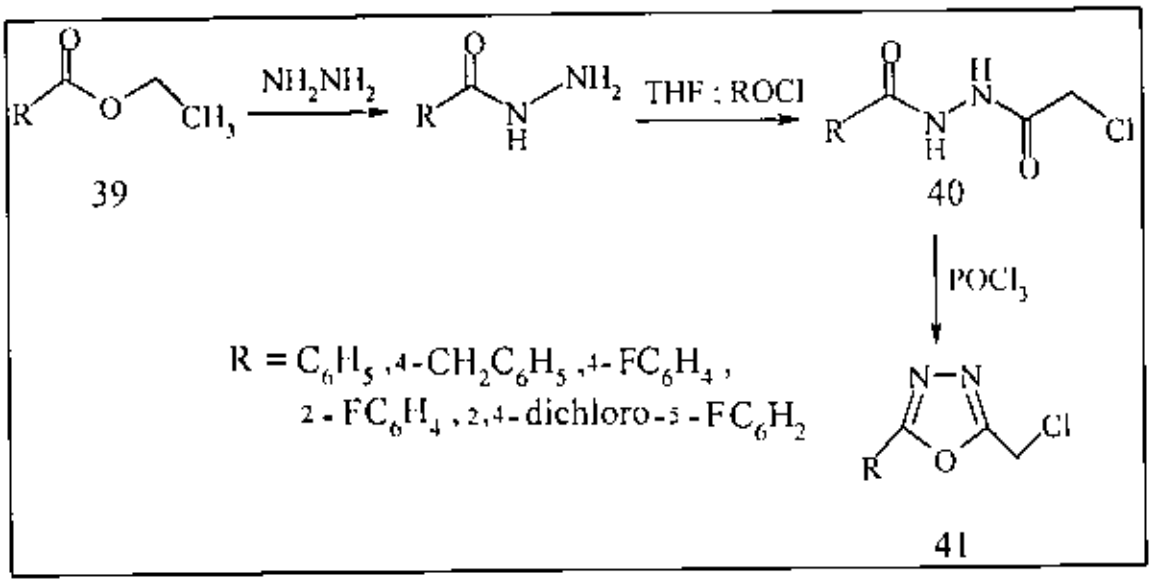
Cyclization of **37** to 5-(1-(4-chlorophenyl)-4-hydroxy-1*H*-pyrazole-3- yl)-2-phenylamino-1,3,4-oxadiazole **38** could be achieved by boiling of the former with mercuric oxide in absolute ethanol [21].



Scheme (13)

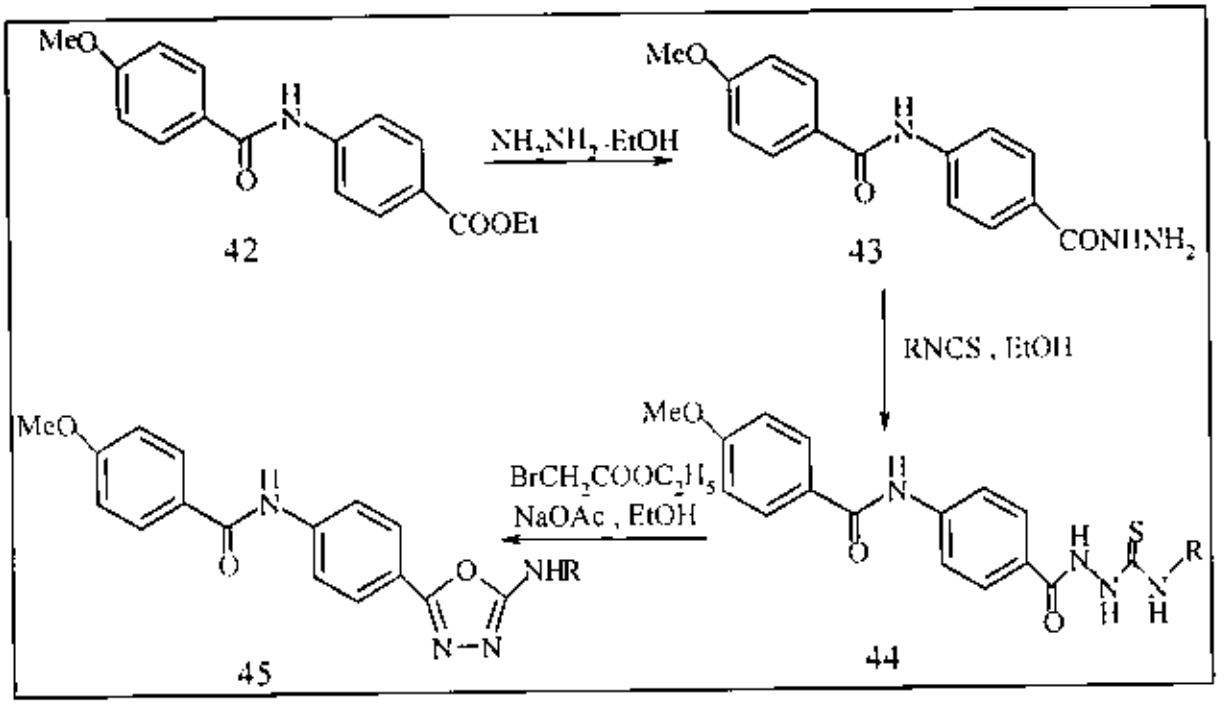
Starting from different esters, monoacylhydrazines, *N,N'*-diacyl-hydrazines and asymmetrical 2,3-disubstitued -1,3,4-oxadiazoles were prepared. All the key intermediate 5-aryl-2-chloromethyl-1,3,4-

oxadiazoles were prepared by the cyclodehydration of *N*-chloroacetyl-*N*-aroylhydrazines in boiling $POCl_3$ [22].



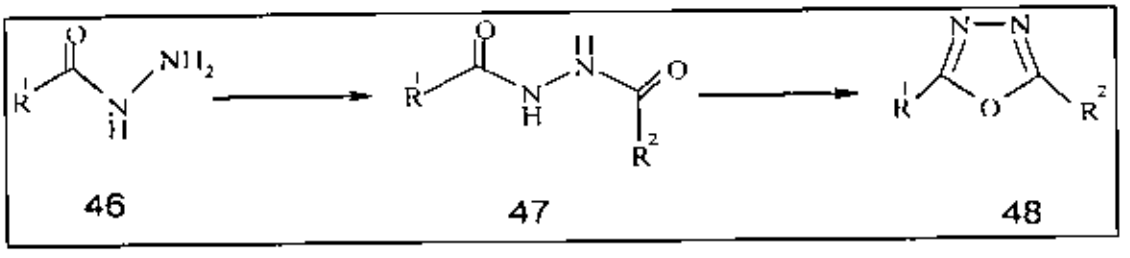
Scheme (14)

Formation of the desired thiadiazolidinone from the thiosemicarbazide derivative **44** failed and instead 1,3,4-oxadiazoles **45** were obtained[23] .



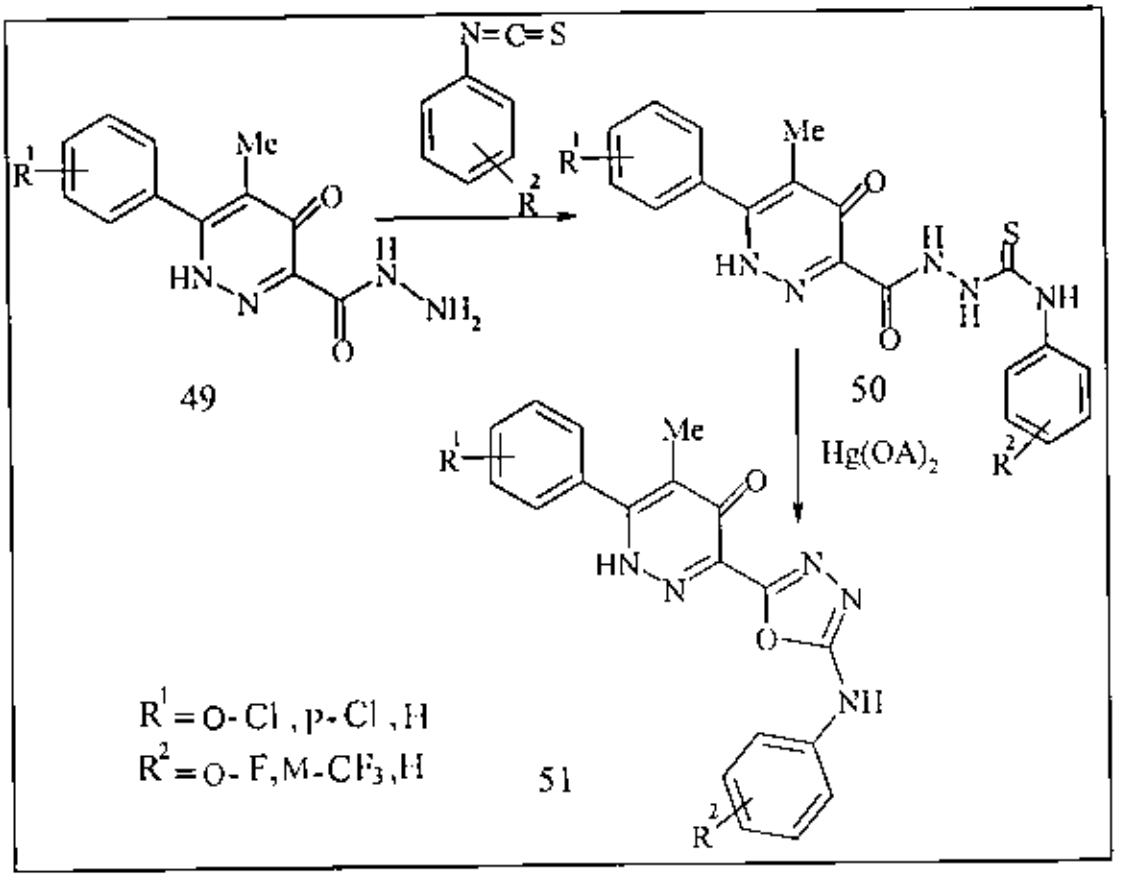
Scheme (15)

Substituted 1,3,4-oxadiazoles **48** have been synthesized by traditional synthesis via cyclization of diacylhydrazides **47.**



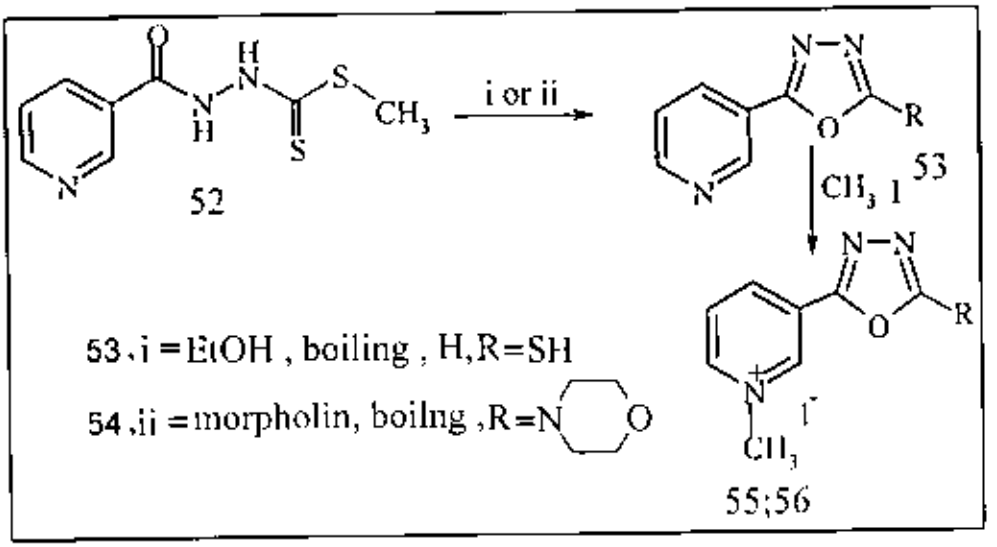
Scheme (16)

The thiosemicarbazide derivative [24] **50** prepared from the acid hydrazide [25] **49** was used in the synthesis of the 1,3,4-oxadizole derivative **51** on treatment with $Hg(OAc)_2$ [26].



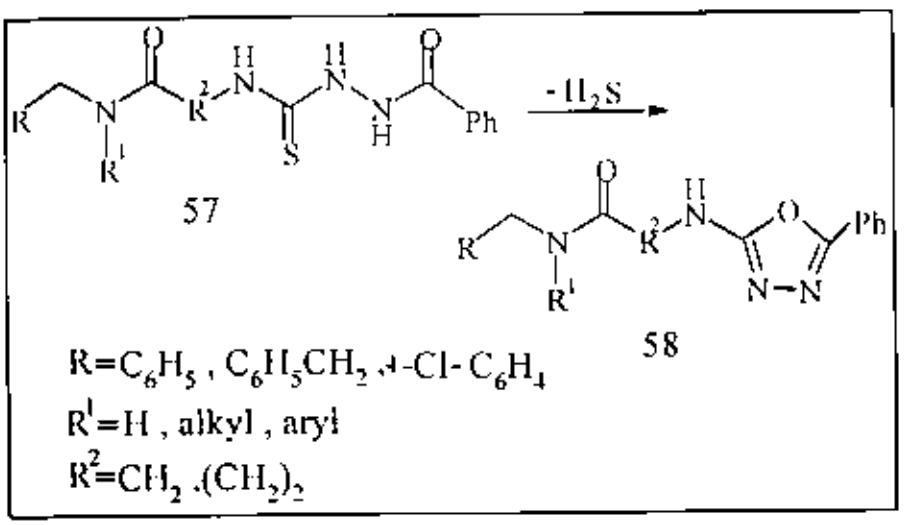
Scheme (17)

3-Isonicotionoyldithiocarbazate **52** which was synthesized earlier [27,28], was used in a practical approach for the synthesis of 1,3,4-oxadiazole derivatives [29] 53 and 54.



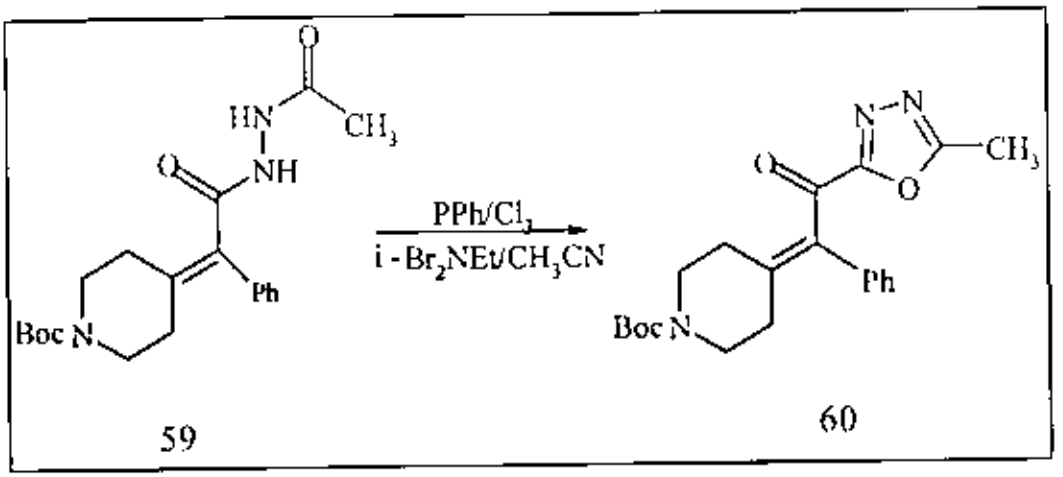
Scheme (18)

A solid phase approach has reported the 1,3,4-oxadiazole synthesis via cyclodehydration of a diacylhydrazide intermediate. Attemptes were directed towards cyclodesulphurisation of the acylthiosemicarbazide intermediate **57** [30].



Scheme (19)

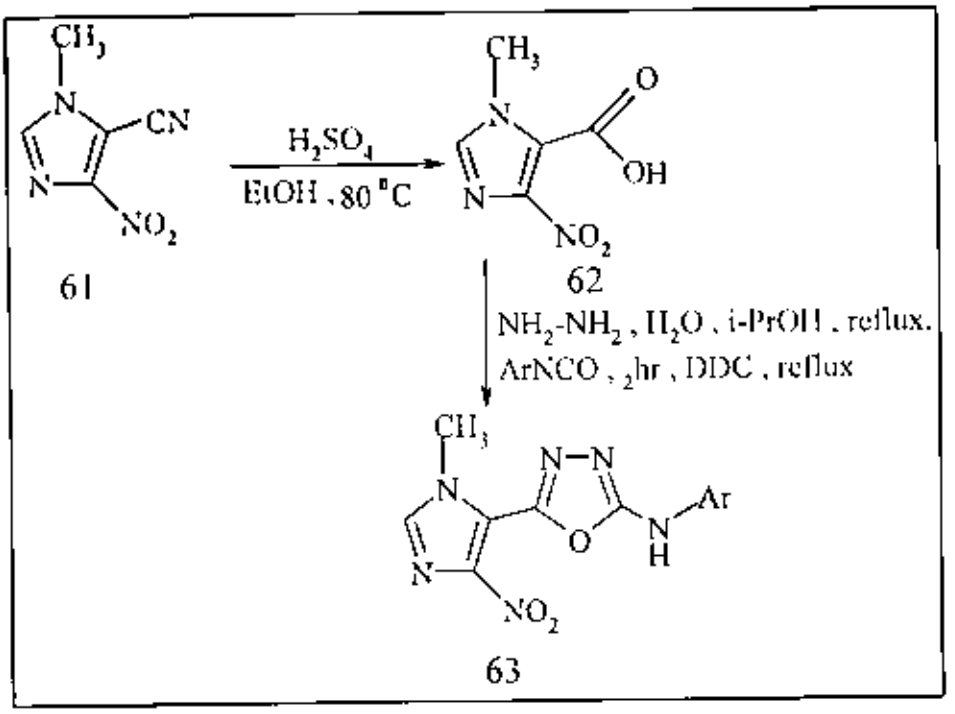
When a solution of diacylhydrazide **59** was treated with hexachloro- ethane in acetonitrile in the presence of (Hu-nig) base and PPh_3, a very fast cyclization occurred at room temperature. Subsequent routine aqueous workup afforded the desired oxadiazole in good yield.



59 60

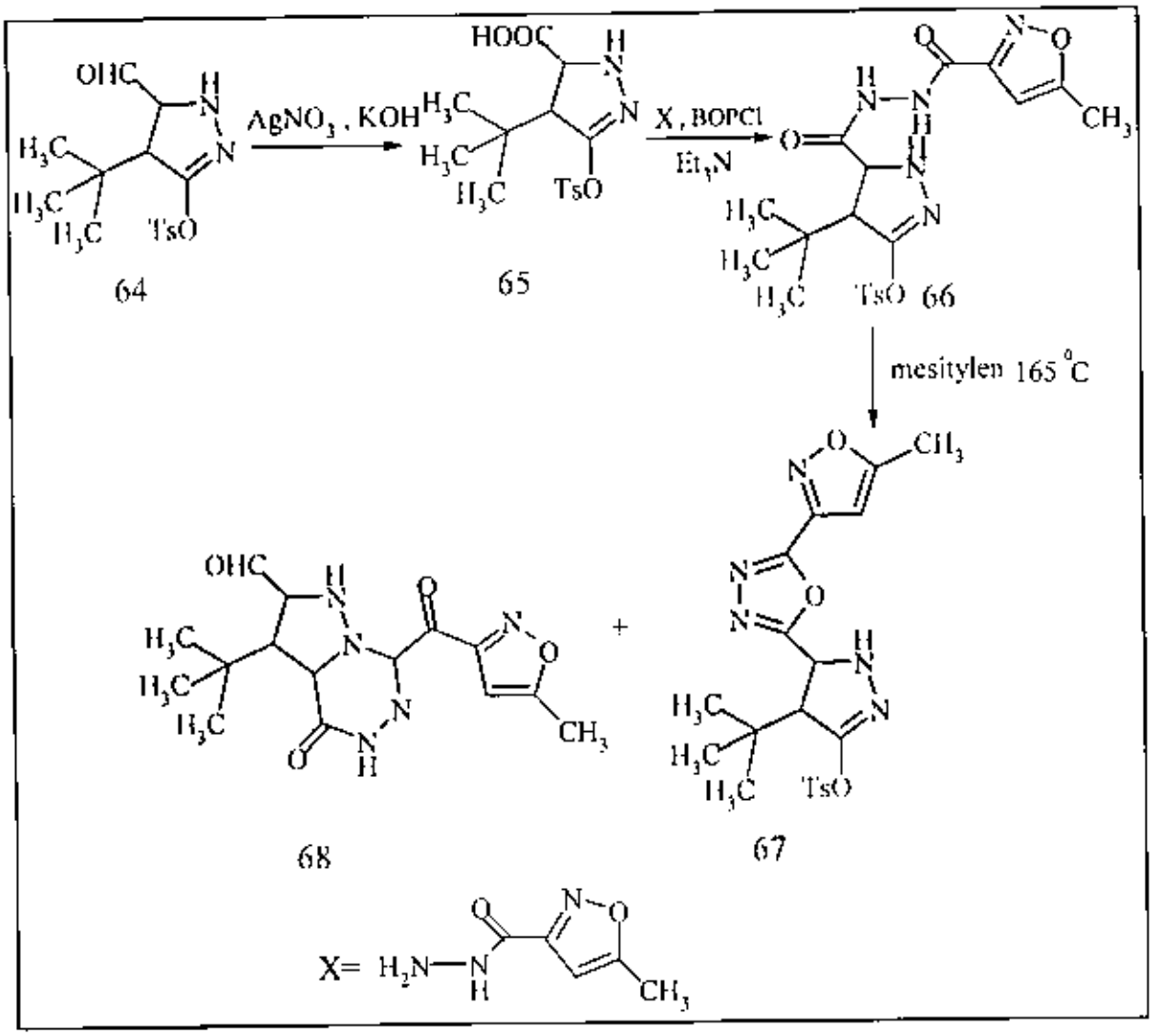
Scheme (20)

These conditions are very mild and the olefin functionality does not seem to interfere with the course of the reaction. A wide variety of functional groups are tolerated, for example, bromomethyl and silyoxmethyl [31] .The acid **62** was converted to a series of 1,3,4-oxadizoles **63** (55-74% overall yield) via the published route [32]. The synthetic sequence involved the formation of acid hydrazide, its reaction with arylthiocyanate, and DCC promoted heterocyclization of the respective thiosemicarbazone derivative in refluxing toluene [33].



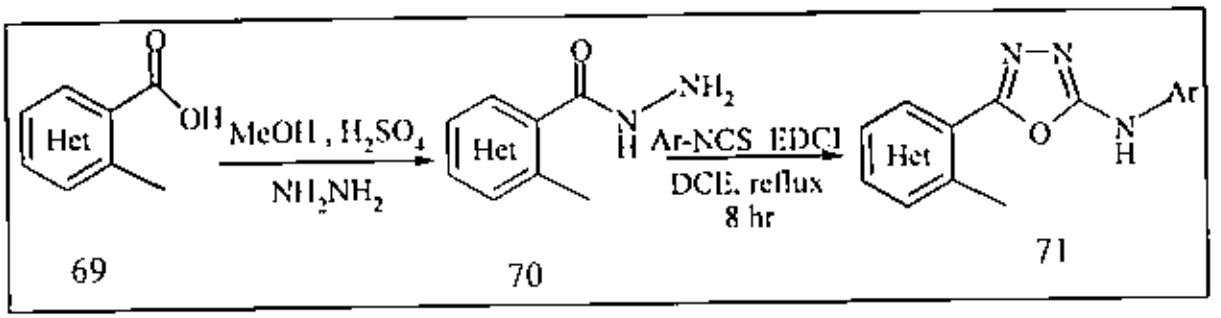
Scheme (21)

Oxidation of the pyrazoloaldehyde **64** to the corresponding carboxylic acid **65** was achieved with $AgNO_3$/KOH, and coupling with the isoxazole hydrazide gave the required cyclisation precursor **66**. However, all attempts to prepare the pyrazolotriazinone skeleton **68** were accompanied with formation of the 1,3,4-oxadiazole **67** as the major product (4:1 upon acid catalysed cyclisation) [34].



Scheme (22)

Commercially a vailable methyl picolinic or quinolinic acids **69** were refluxed in anhydrous methanol with catalytic amount of concentrated H_2SO_4 followed by the addition of anhydrous hydrazine. The resulting crude hydrazides **70** were allowed to react with a series of arylisothiocyanates (Ar-NCS) in dichloromethane. The targeted aminooxadiazole **71** were conveniently isolated in 78-92% yields [35].



Scheme (23)

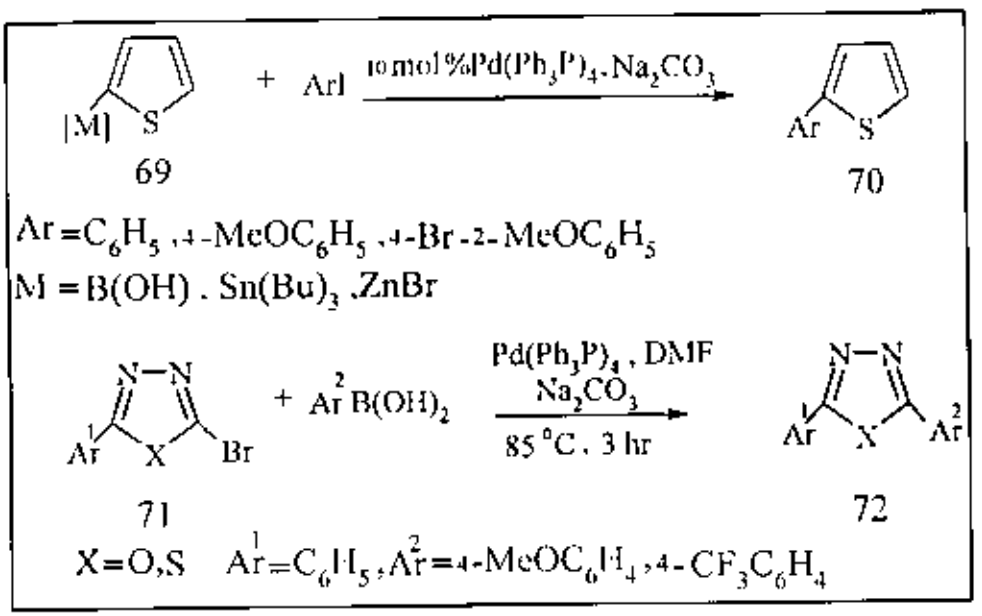
Reactions of 1,3,4-oxadiazoles:

Electrophilic substitution at carbon

The relatively low electron density at carbon, coupled with the possibility of protonation at nitrogen, makes electrophilic substitution at carbon difficult. A further problem is acid-catalyzed ring cleavage, particularly with alkyloxadiazoles. No examples of nitration or sulphonation of the oxadiazole ring have been reported and attempted brominations were unsuccessful. A low yield of 2-(2-furoyl)-5-phenyl-1,3,4-oxadiazole is treated with 2-furoyl chloride in the presence of trimethylamine [36].

An alternative general strategy that employs palladium-catalyzed cross-coupling reactions as the key steps providing access to a wide range of 2,5-diaryl heteropentalenes via a uniform route was presented. Palladium-catalyzed cross-coupling reactions of various heteropentalene derivatives have been well documented although this application to the synthesis of heteropentalene remains unexplored [37].

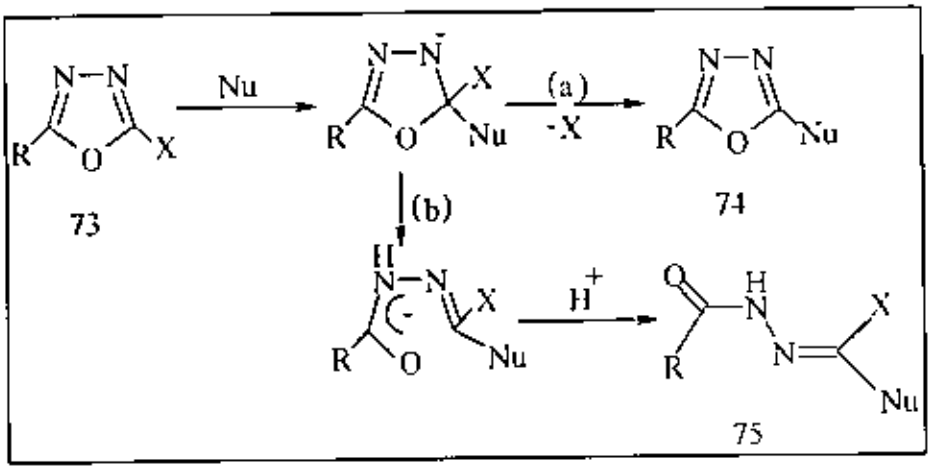
Examples of 2,5-diarylfurans, N-methylpyrroles, 1,3- thiazoles, 1,3-oxazoles, 1,3,4-thiadiazoles and 1,3,4-oxadiazoles **72** were prepared in 63-93% isolated yields following the Suzuki [38] protocol of couplings of iodobenzene with the corresponding 2-thiophene organometallic reagent **69**, thus a general versatile approach to the synthesis of 2,5-diarylthiophenes, furans, pyrroles, 1,3-oxa and thiazoles, 1,3,4-oxa and thiadiazoles was presented. The methodology consists of three steps: (1) a palladium-catalyzed cross-coupling reaction (2) a regio-and chemoselective bromination and (3) a Suzuki coupling [39].



Scheme (24)

Reaction of nuclephiles at carbon

The attack of a nucleophile at carbon in 73 leads either to nucleophilic displacement (path a) or ring cleavage (path b), the latter being the most common result.



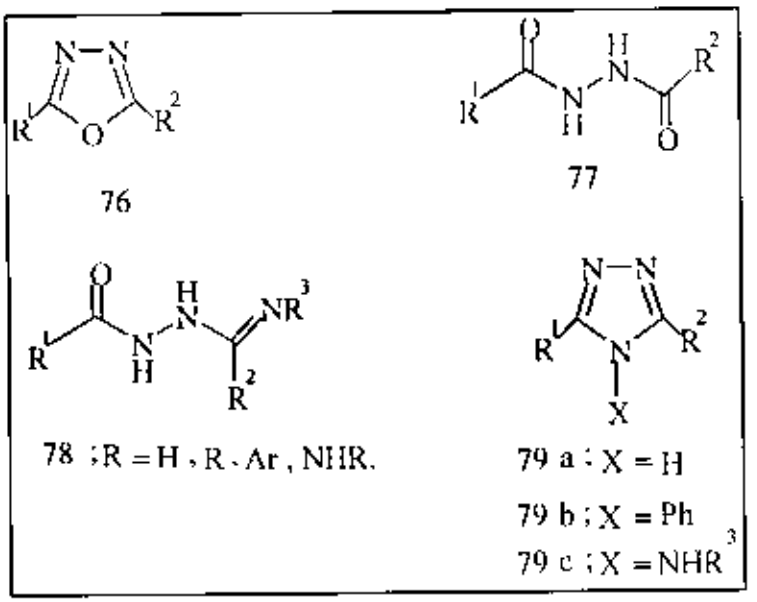
Scheme (25)

Nucleophilic displacement

Treatment of 2-chloro- (**73**: X = Cl) or 2-methylsulphonyl-1,3,4-oxadiazole with amines. thiourea or azide ion yields the corresponding 2-substituted oxadiazoles (Nu = NHR or NR^1R^2, SH or N_3 respectively). Conversion into the hydroxyloxadiazole (Nu = OH) (an oxadiazolin-5-one) is effected using aqueous acid or alkali. A low yield of the 2-chloro compound (**73**; X = Cl, R = Ph) is obtained by heating the corresponding 2-hydroxyoxadiazole in phosphorus oxychloride with phosphorus pentachloride. Oxadiazole (**73**; X = Cl or SO_2Me) react with hydrazine to give 1,2-bis(oxadiazol-2-yl)-hydraziens [40].

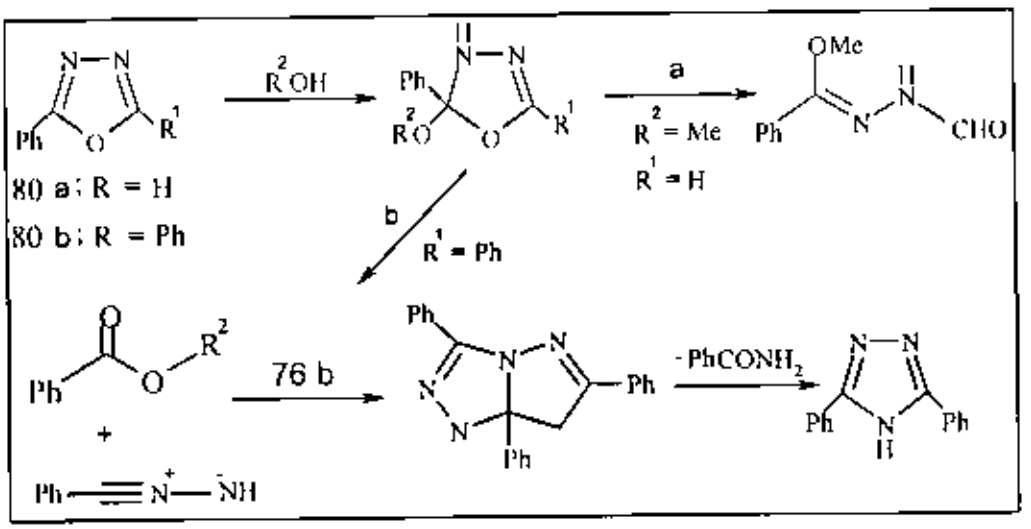
Nucleophilic attack with ring cleavage:

The most frequently encountered result of the reaction of 1,3,4-oxadiazoles with a nucleophile is ring opening to a hydrazine derivatives **75.** This may undergo further reaction such as hydrolysis, or cyclization to a 1,2,4-triazole **79** where X or Nu is an amino group [41]. Alkyl- and aryl-1,3,4-oxadiazoles **76** undergo acid- or base-catalyzed ring opening in water. Susceptibility to hydrolysis increases with solubility. Henc alkyloxadiazoles ring-open more readily than aryloxadiazoles and 2,5-diaryl-1,3,4-xoadiazoles are fairly stable in dilute acid or alkali at 100 ^{0}C. The initial product of hydrolysis is a diacylhydrazine **77** which suffer further hydrolysis under more vigorous conditions.



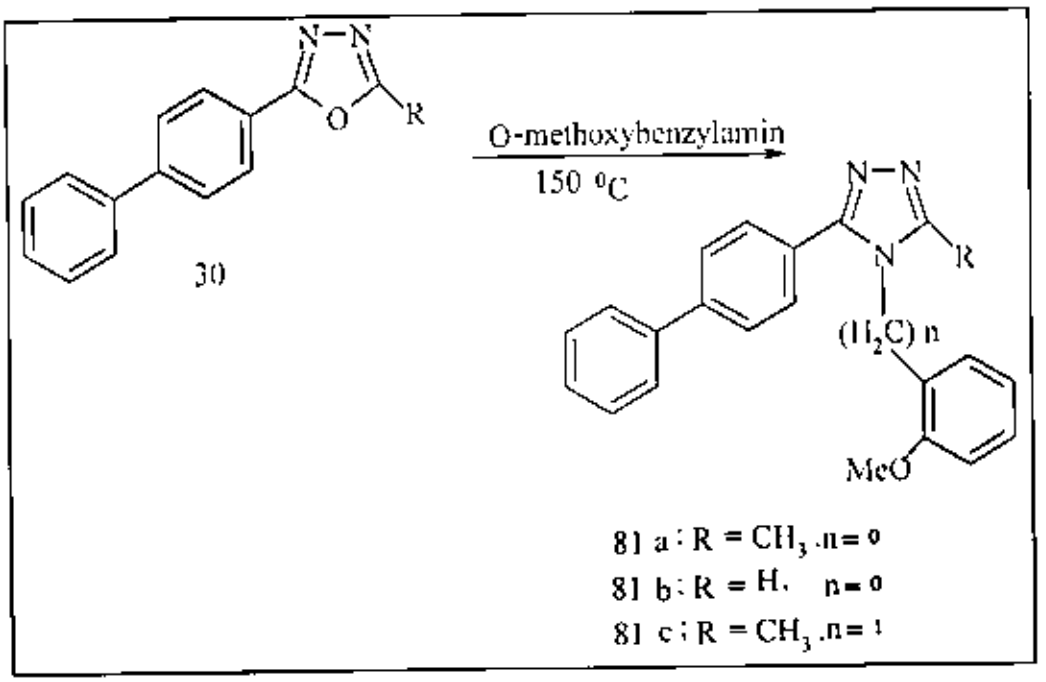
Scheme (26)

The reaction of 1,3,4-oxadiazoles with ammonia, primary amines or hydrazine provides a useful synthesis of 1,2,4-triazoles. In some cases, the initial ring cleavage product **74** may be isolated. Good yields of triazoles **79a**, **79b**, and **79c** are obtained on heating oxadiazoles **76** with formamide in ethylene glycol [42], with aniline, or with hydrazines [43]. In contrast, 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole reacted with hydrazine to form an *s*-tetrazine derivative [44].2-phenyl- **80a** and 2,5-diphenyl-1,3,4-oxadiazole **80b**, in either electronic excited states, undergo nucleophilic attack by lower MW alcohols to give adducts with ring opening (path a) or undergo cycloelemination (path b) with subsequent formation of a triazole [45].



Scheme (27)

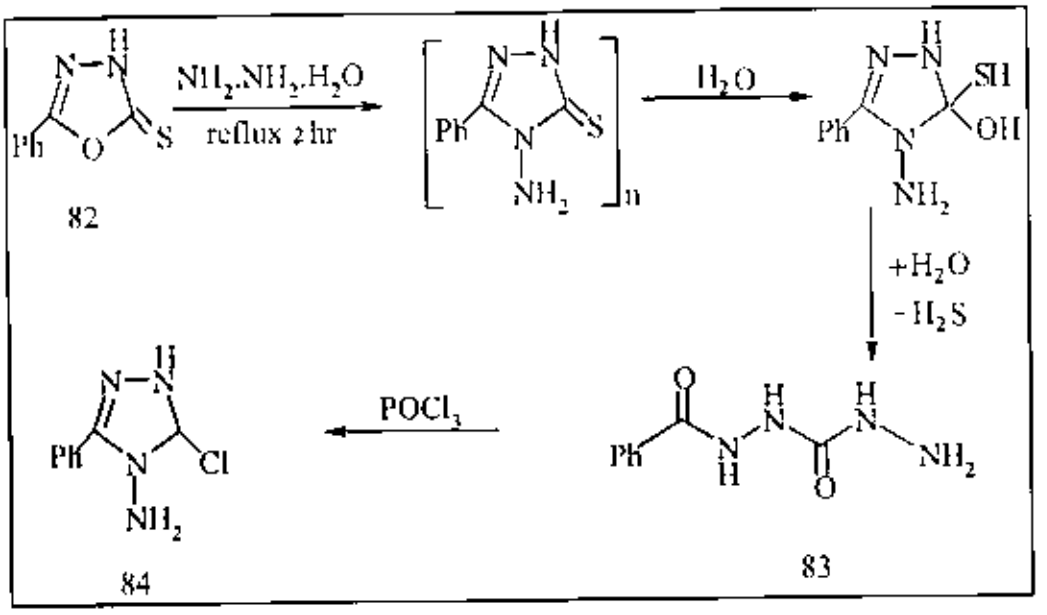
Compound **30** was subjected to a substitution reaction with ananisol or a benzyl amine to afford the 1,2,4-triazole compounds **81** [18].



Scheme (28)

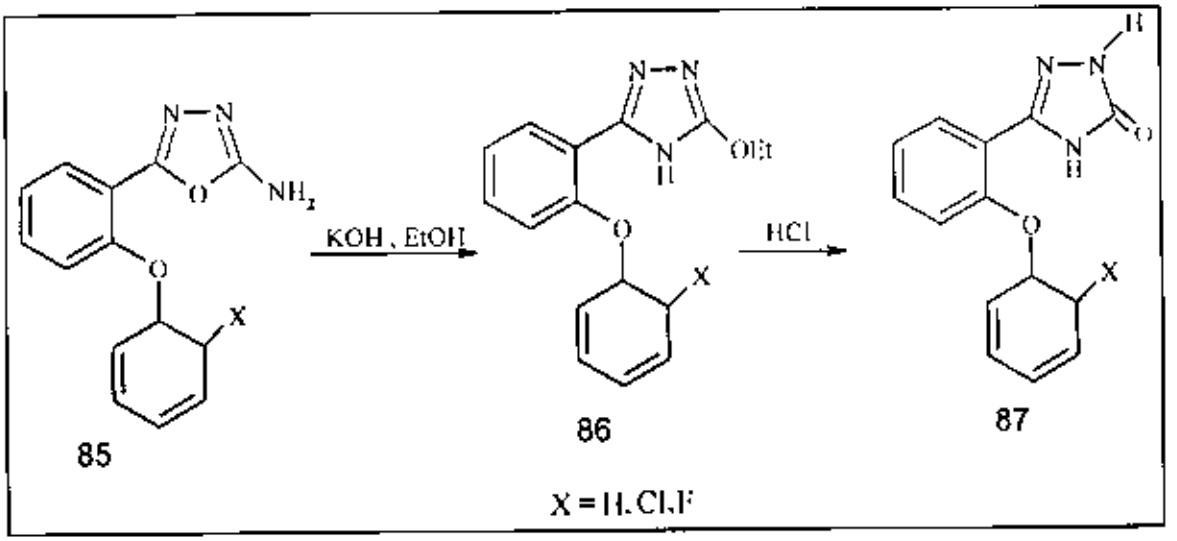
One of the most important methods of obtaining the 1,2,4-triazole system is based on recyclization reactions of 1,3,4-oxadiazoles under the action of amines and hydrazines [46].Thus it was found that [47-52] that 4-amino-3-mercapto-5-sustituted- (4H)-1,2,4-triazoles were synthesized by the reaction of 5-substituted-1,3,4-oxadiazoles-2-thione with hydrazine hydrate in refluxing water [51], n-butanol or dioxin [52] for 3-4 h with hydrogen sulphide evolution. It has been found that treatment of 5-phenyl-1,3,4-oxadiazole-2-thione **82** with hydrazine hydrate in refluxing n-butanol. until hydrogen sulphide evolution was finished (48h), affords a benzylcarbo hydrazide **83**

identifired by elemental analysis, IR and NMR spectra. Treatment of compound **83** with phosphorus oxychloride afforded triazole **84**[53].



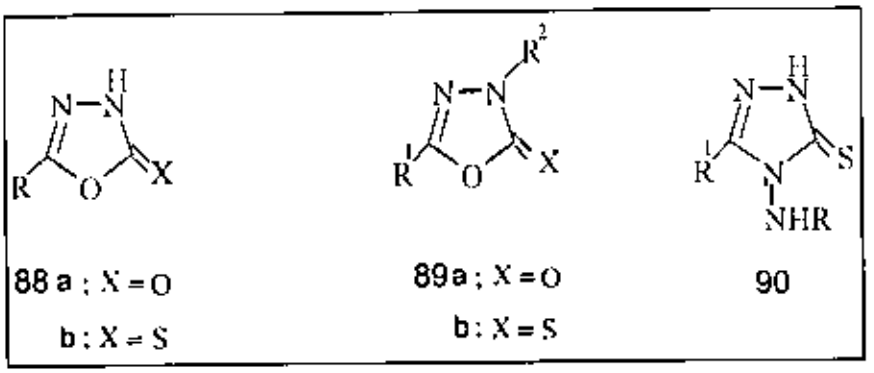
Scheme (29)

Compound 2-amino-5-(2-phenoxyphenyl)-1,3,4-oxadiazole **85** was rearranged to 3-ethoxy-5-(2-phenoxyphenyl)-1,2,4-triazole **86** upon treatment with ethanolic potassium hydroxide. Acid hydrolysis of **86** provided 5-(2-phenoxyphenyl)-1,2,4-triazole-ones[54,55] **87**.



Scheme (30)

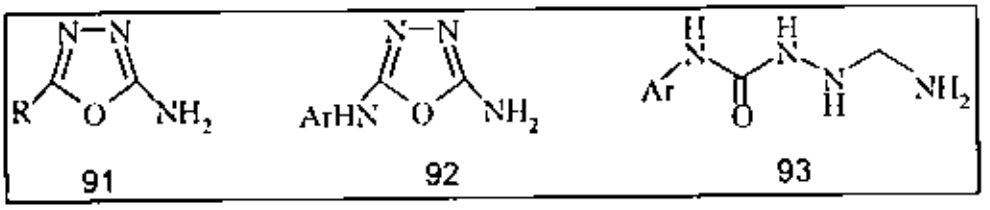
Oxadiazolinones **88** undergo ring opening in hot water to form hydrazinocarboxylic acids (170; R^2 = OH) which decarboxylate to acylhydrazines. These acylhydrazines may subsequently attack the ring of the starting oxadiazole causing cleavage to 1,5-dicarbinohydrazides. Oxadiazolinethiones **88b** are more resistant to nucleophilic attack and thione (**88b**; R = 5-nitro- 2-furyl) is stable in hot water. Oxadiazolinone (**88a**; R^1 = R^2 = Me) is converted into the corresponding thione by the action of phosphorus pentasulphide [56].



Scheme (31)

Ring cleavage of oxadiazolines **88** with ammonia, amines or hydrazines yields acyl semicarbazides. Thione (**88b**; R = 5-nitro-2-furyl) forms stable salts with amines which, in some cases, suffer ring opening on heating. 2-Aryloxadiazolinethiones (**88b**; R = aryl) react with hydrazines $RNHNH_2$ to give triazoline thiones **89** [52].

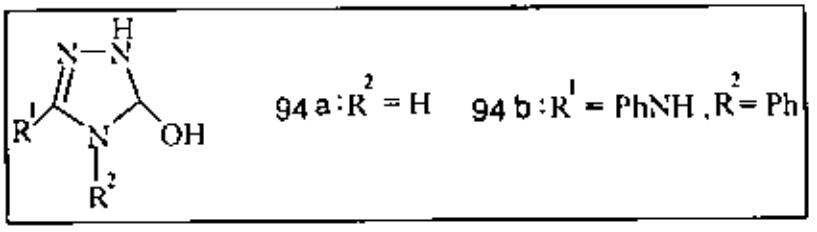
It is well known that some 1,3,4-oxadiazolium salts cleave to semicarbazide derivatives in acid medium and converted to 1,2,4-triazolinone in alkali [57].Acid catalyzed cleavage of 2-aminooxadiazoles **91** generally leads to extensive decomposition. Hydrazine derivatives **93** may be isolated after heating diamines **92** in hydrochloric acid, whereas 2,5-diamino-1,3,4-oxadiazole is stable in hot 6M hydrochloric acid.



91 92 93

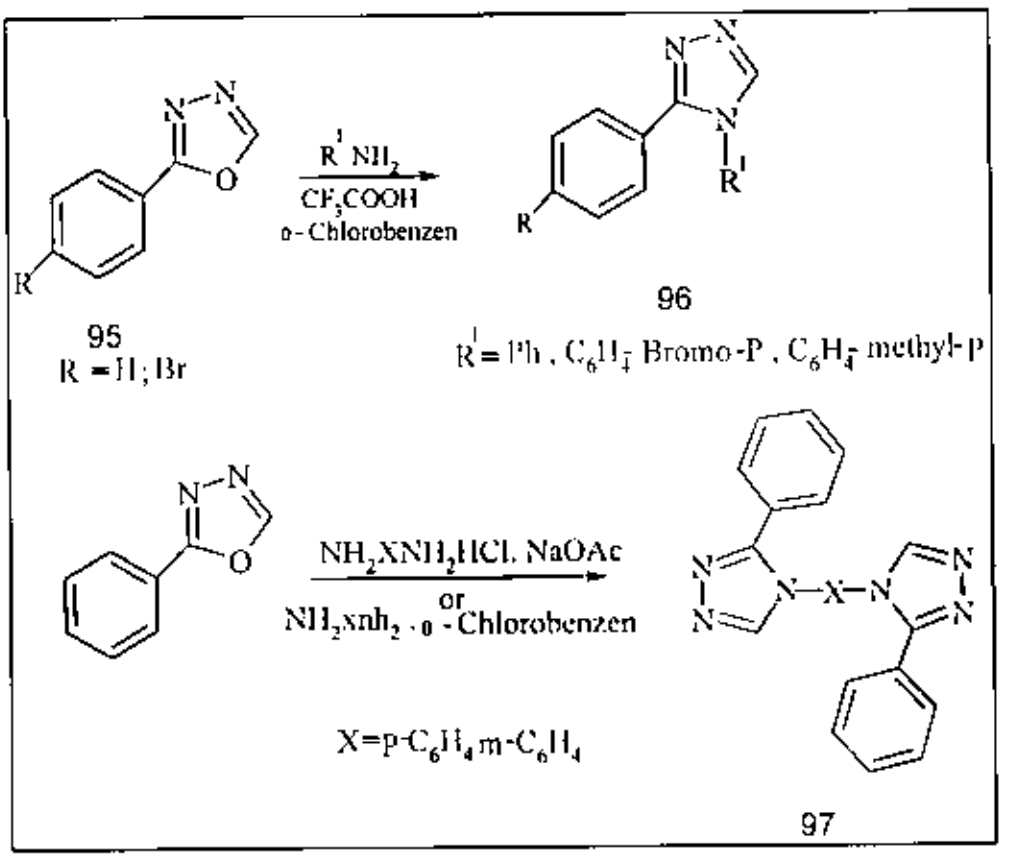
Scheme (32)

Heating aminooxadaizoles **91** with aqueous sodium hydroxide usually resulted in ring cleavage followed by cyclization to triazolinone **94a** In a similar manner, 2,5-dianilino-1,3,4-oxadiazole is converted into the aminotria- zolinone **94b** [58].



Scheme (33)

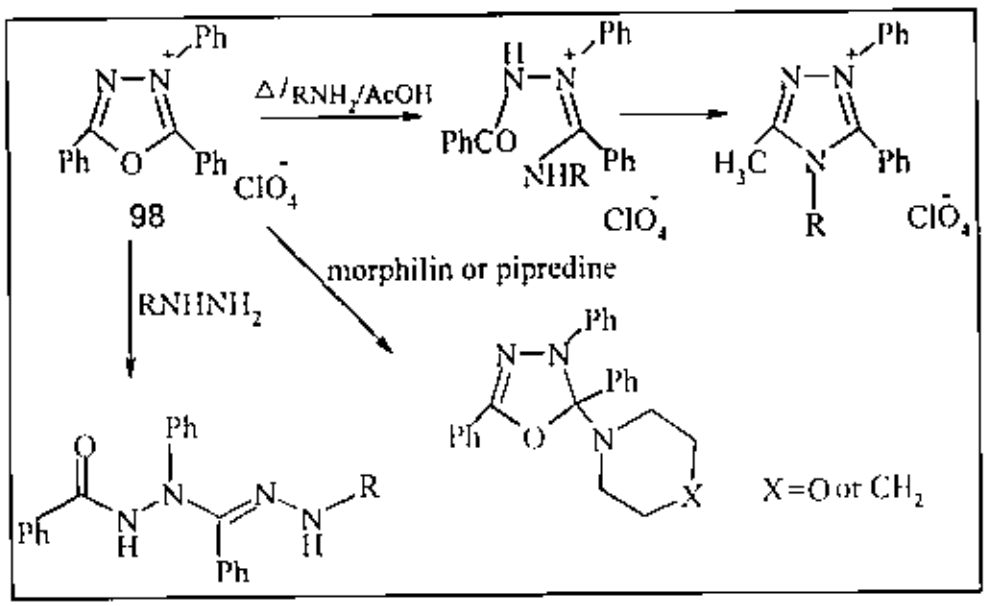
Conversions of 1,3,4-oxadiazoles into 1,2,4-traiazoles are used for obtaining both monotriazoles and polytriazoles [59]. Thus recyclization of compound **95** by using aniline trifluoroacetate, which was prepared *in situ* from aniline and teifluoroacetic acid. And heating the mixture at 190^{0}C in *o*-dichlorobenzene gives 3,4-diphenyl-1,2,4-triazole **96** in 95%. The same method was extended to the synthesis of 3,3'- and 4,4'- bridge linked bistriazoles, precursors of triszol biscarbenes. On interacting oxadiazole **95** with 4-phenylendiamine hydrochloride in the presence of 2 equiv. sodium acetate in *o*-dichlorobenzene 4,4'-*p*-phenylenebis-1,2,4-triazole **97** was *m*-phenylendiamine dihydrochloride gave only 24% bistriazole 97 (x= *m*-Ph) [60].



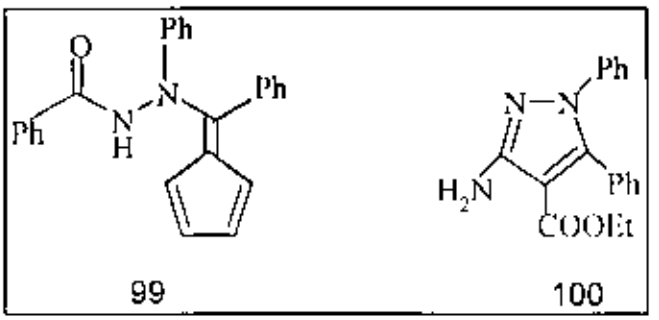
Scheme (34)

Nucleophiliic attack on 1,3,4-oxaadizolium salts occurs under mild conditions and it is usually followed by ring cleavage, often with subsequent recyclization to another heterocycle. Typical reactions are shown by the trihenyloxadiaaazolium salt **98**[61]. With hydrogen sulphide, salt **98**cleaves to a thioacylhydrazine and with cyclopenta- dienyl anion ring opening to the hydrazine derivative takes place **99**. A similar reaction occurs with ethyl cyanoacetate in the presence of triethylamine but the ring cleavage prouduct was unstable and reacts further to give pyrazole**99** [62].

2-Amino-3-phenacyl-1,3,4-oxadi- azolium salts rearrange to imidazolinones in alkali and yield immidazoles on treatment with amines in liquid ammonia[41].



Scheme (35)

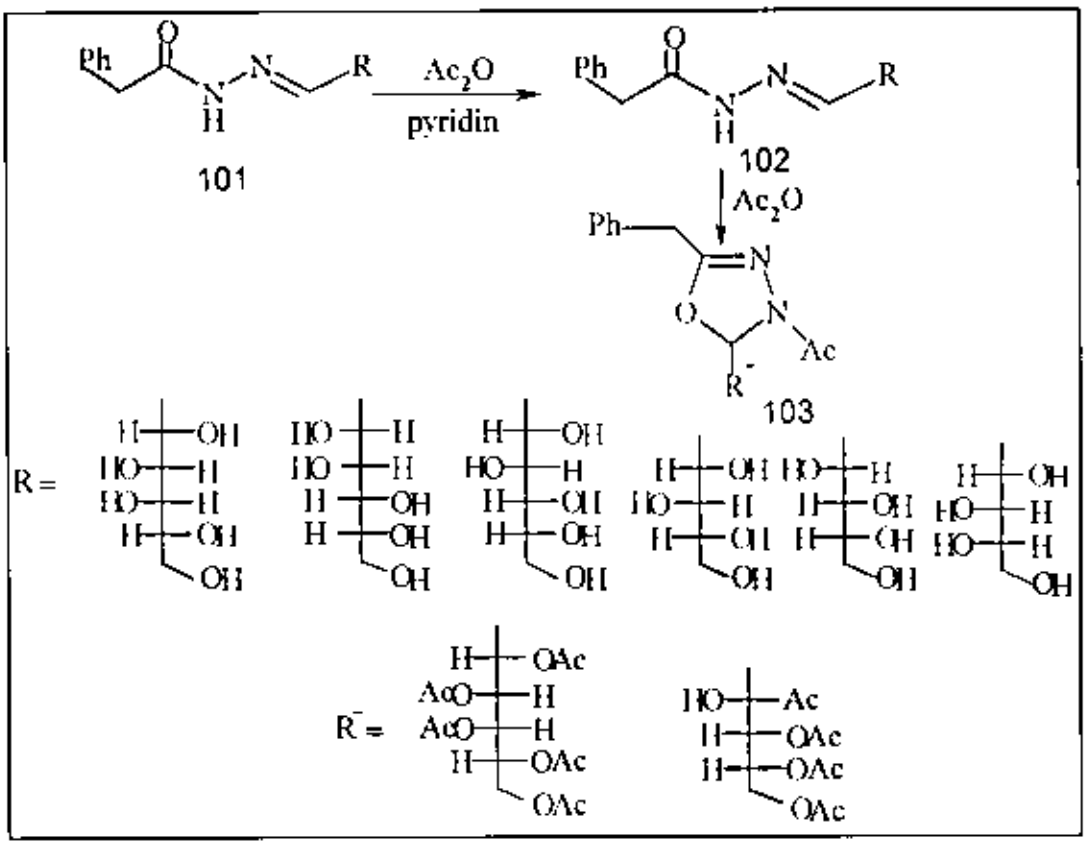


Scheme (36)

On heating with benzoic acid, 2-alkoxy-5-phenyl-1,3,4-oxadiazoles yield 2,5-diphenyl-1,3,4-oxadiazole. The mechanism for the reaction probably involves nucleophilic attack by benzoate anion on the initially formed 3-benzoyl-1,3,4-oxadiazolium benzoate [63].

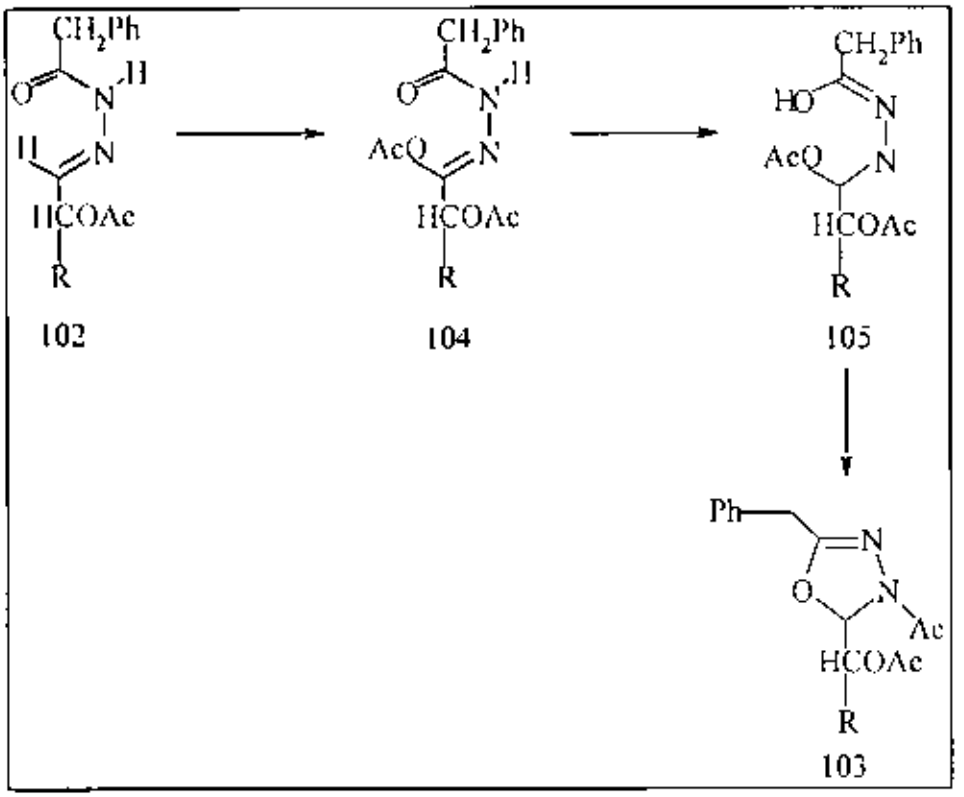
1,3,4-oxadiazole nucleosides

1,3,4-oxadiazolines are of great significance, as shown by their growing patent literature [64] as fungicidal and bactericidal agents and some of them have analgetic, antipyritic, antiphlogestic, paralytic, anticompulsive, as well as hypnotic, sedative [65-68] , and antiviral activity against HIV [69,71] .Recently, synthesis of acyclo-nucleosides has attracted much attention [65-68] which may result in possible enhancement of biological activity resulting from the attachment of carbohydrates to such heterocycles [73-77] . 2,3,4,5,6-Penta-*O*-acetyl-aldeehydo-D-galactose 2-acetylhydrazone was reported [78] to give 3-acetyl-5-methyl-2-(1,2,3,4,5-penta-*O*-acetyl-D-galactito-pentitol-1-yl)-1,3,4-oxadiazoline on reaction with boiling acetic anhydride.When 2,3,4,5,6-Penta-*O*-aldeehydo-D-galactose (phenylacetyl)hydrazone was boiled with acetic anhydride it afforded apure product **103** after repeated crystallization [79].



Scheme (37)

The mechanism of formation of these oxadaizolines propably starts with introduction of the acetic anhydride molecule into the C=N of the hydrazone residue (where there are partially positive centers, presumably the carbon atom attacked by the acetate anion, and the acetyl ion that becomes attached to the nitrogen atom) to give the intermediate **104**; this route is similar to that obtaining for the benzaniline[80] and simple ketone hydrazones[81] on reaction with acetic anhydride. This intermediate **104** then readily loses an acetic acid.

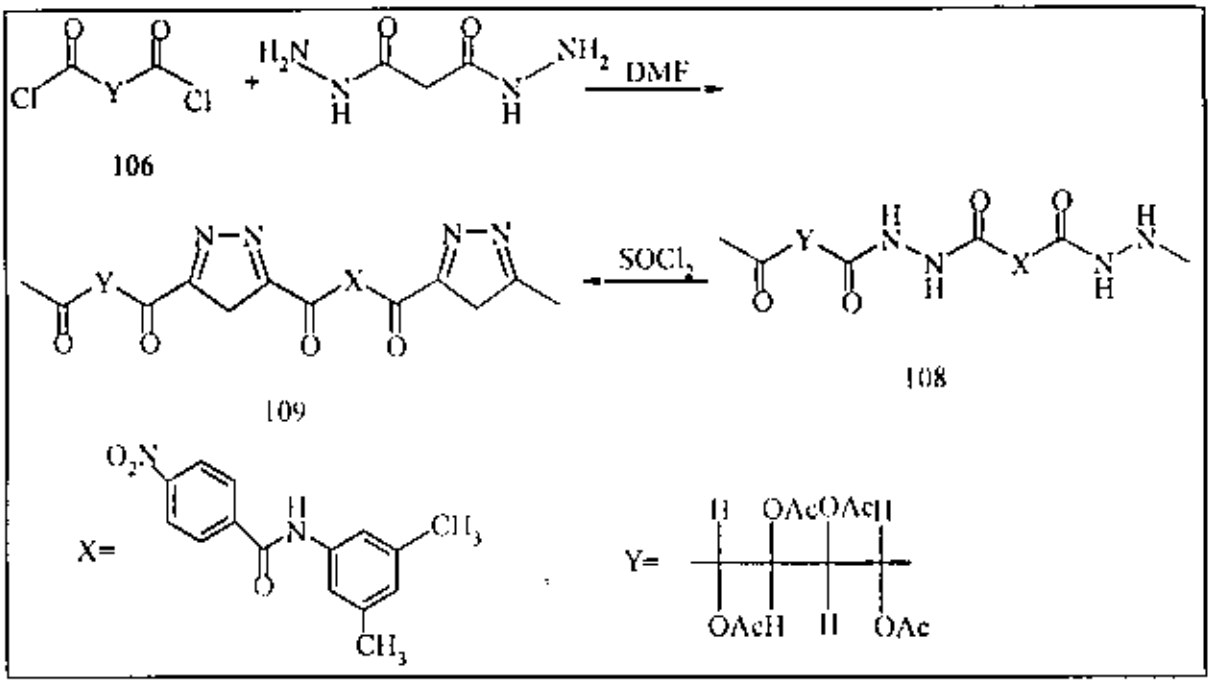


Scheme (38)

Acetylated and de-*O*-acetylated carbohydrate containing polyamides were prepared using low temperature solution polycondensation of 2,3,4,5-tetra-*O*-acetylglactaroyl dichloride with aromatic as well as aliphatic diamines [82].

O-acetylation of these polyamides to produce hydroxylated polymers of high viscosity was carried out by stirring with conc. ammonia in methanol at room temperature [83,84]. High molecular weight polyhydrazides, which have very interesting solubility behavior, were prepared by the low temperature solution polycondensation of diacyldichlorides with hydrazine hydrate or diacid dihydrazides [85].

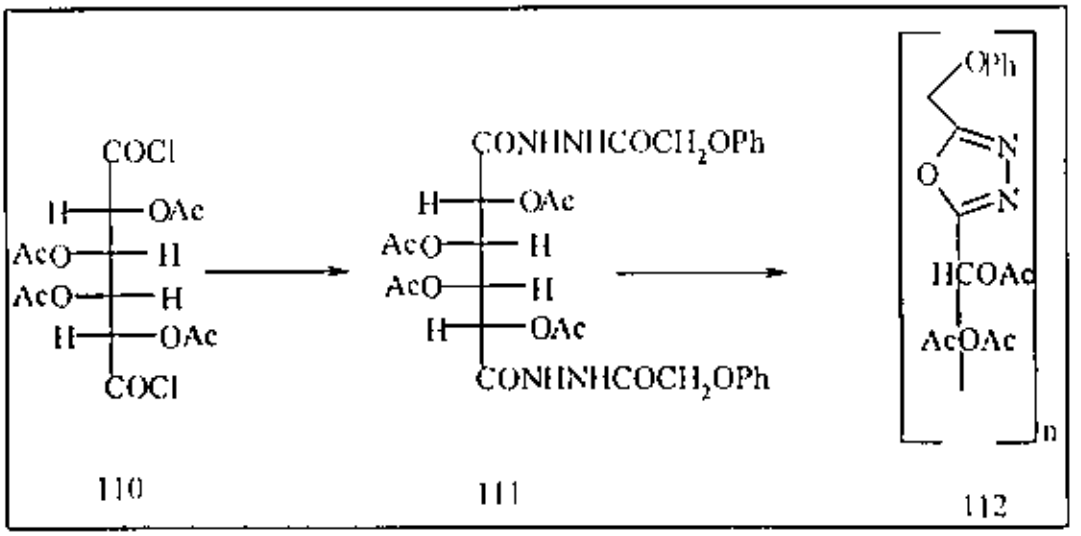
New copolyhydrazides, which contain spacer geouos consisting of carbohydrates, methylene groups or aromatic moieties and also having pendant groups, were synthesized by low temperature solution polycomdensation of diacid dihydrazides with diacid dichlorides in DMF. One example of the prepared copolyhydrazides **108** was cyclized into copoly(1,3,4-oxadiazole); which was treated with ammonia for de-*O*-acetylation to give de-*O*-acetylated carbohydrate containing co-polyhydrazide [86].



Scheme (39)

Condensation of 2,3,4,5-tetra-*O*-acetylgalactardiol dichloride **110** with two molar equivalents of phenoxyacetylhydrazine gave a colorless

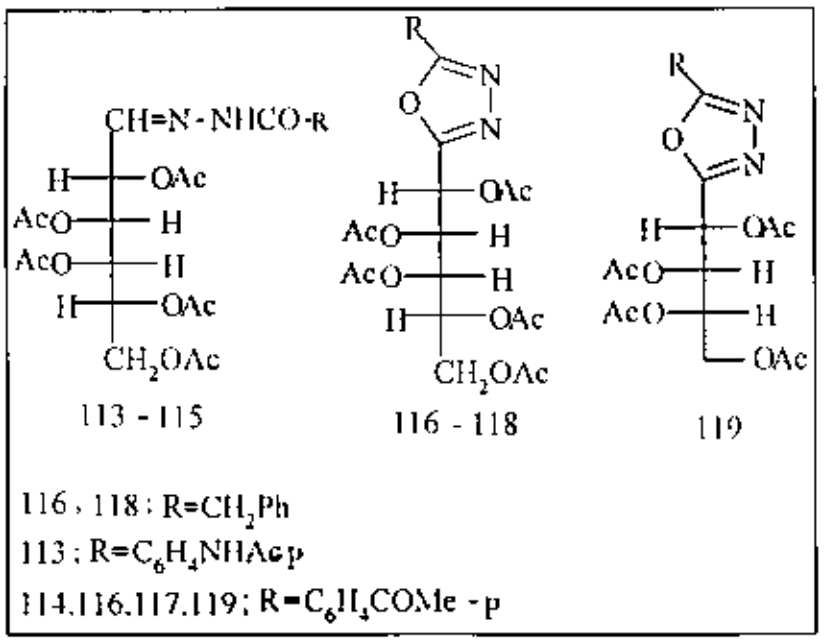
prouduct formulated as 2,3,4,5-tetra-*O*-acetylgalactaric acid bis-(phenoxyacetyl) hydrazide **111**. Dehydration of **111** was effected with a solution of thionyl chloride in *N,N*-dimethylformamide or pyridine, or with dicyclohexyl carbodiimide in pyridine, to give 1,2,3,4-tetra-*O*-acetyl1,4-bis[5-(phenoxymethylen)-1,3,,4oxadddiazol-2-yl]-galacto-tetritol **112** [87]. A similar dehydration of hydrazides, using phosphoryl chloride, has also been reported [88].



Scheme (40)

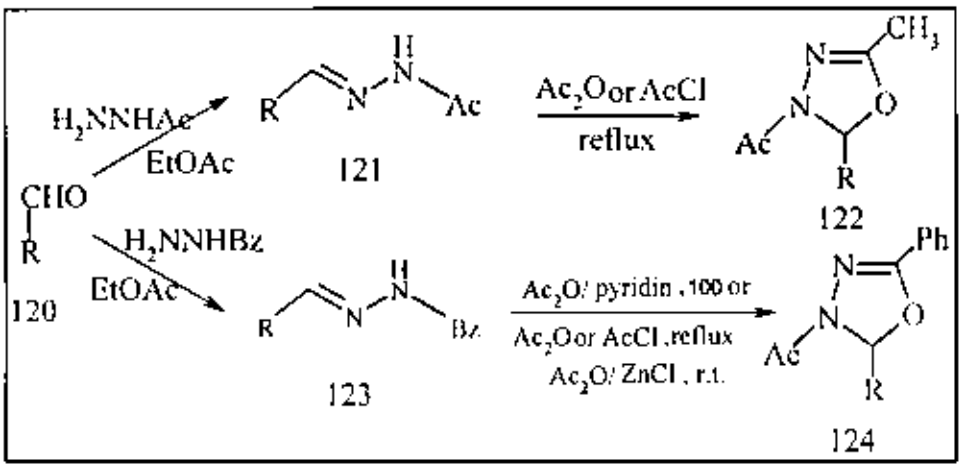
A variety of sugar aroylhydrazones have been prepared and their acetylation with acetic anhydride has been studied [89,90]. On attempting dehydrogenation of sugar aryolhydrazones with mercuric oxide, no change was noted, whereas iodine-mercuric oxide effected the reaction [91].

Thus on applying this reagent to (4-acetamidobenzoyl) hydrazone **113**, [4-(methoxycarbonyl)benzoyl]hydrazone **114**, and (phenylacetyl) hyydrazone **115** of penta-*O*-acetyl-aldehydo-D-galactose, crystalline products were afforded that had been shown to be 5-substit-Uted 2-(1,2,3,4,5-penta-O-acetyl-D-galacto-pentitol-1-yl)-1,3,4-oxadiazoles **116-118**, two hydrogen atoms being lost during the cyclization. Similar dehydrogenation of tetre-*O*-acetyl-aldehydo-L-arabinose (phenylacetyl)hydrazone afforded **119**[87].



Scheme (41)

The crud product obtained from **121** by treatment with boiling acetic anhydride (or boiling acetyl chloride) had been shown to be a mixture of diastereoisomers and crystallization of from ethyl acetate gave a pure product which was assigned the structure 3-acetyl-5-methyl-2-(D-galacto-1,2,3,4,5-pentaacetoxypentyl)-1,3,,4-oxadiazoline **122**. Likewise, treatment of **123** with boiling acetic anhydride or acetyl chloride, or acetic anhydride-zinc chloride at room temperature, gave a mixture of diastereoisomeric 3-acetyl-2-(D-galacto-1,2,3,4,5-penta- acetoxypentyl)-5-phenyl-1,3,,4-oxadiazolines **124** and not the N-acetyl-N-benzoylhydrazone[91].

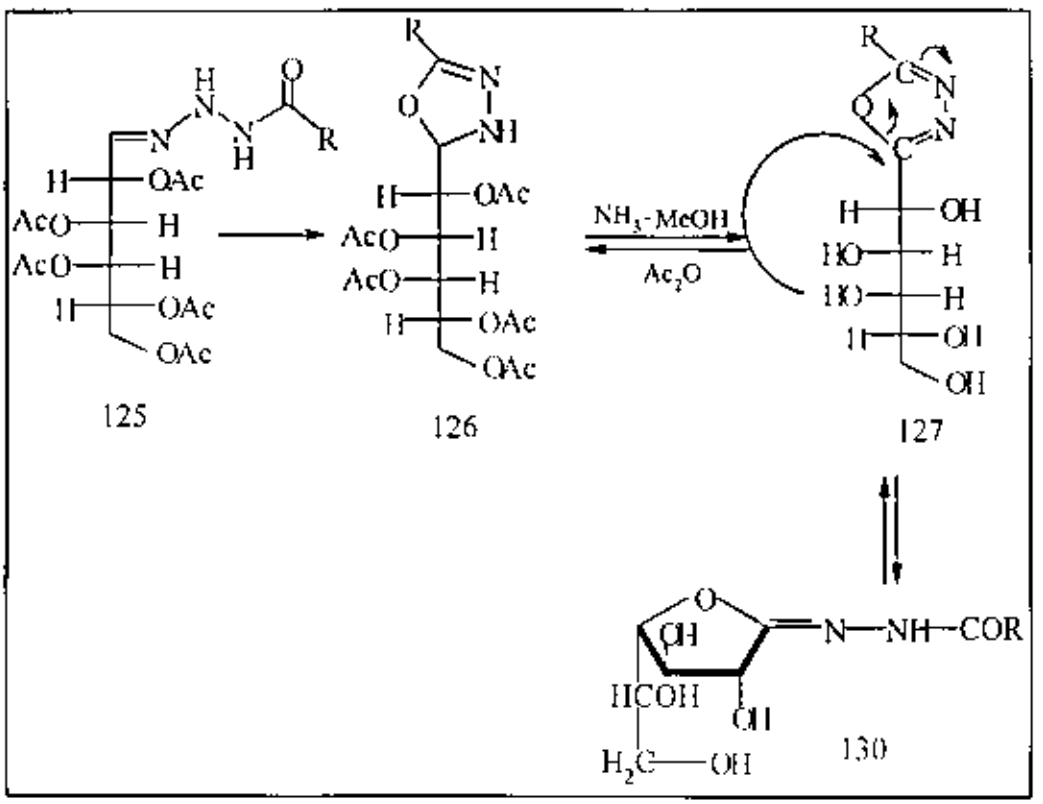


Scheme (42)

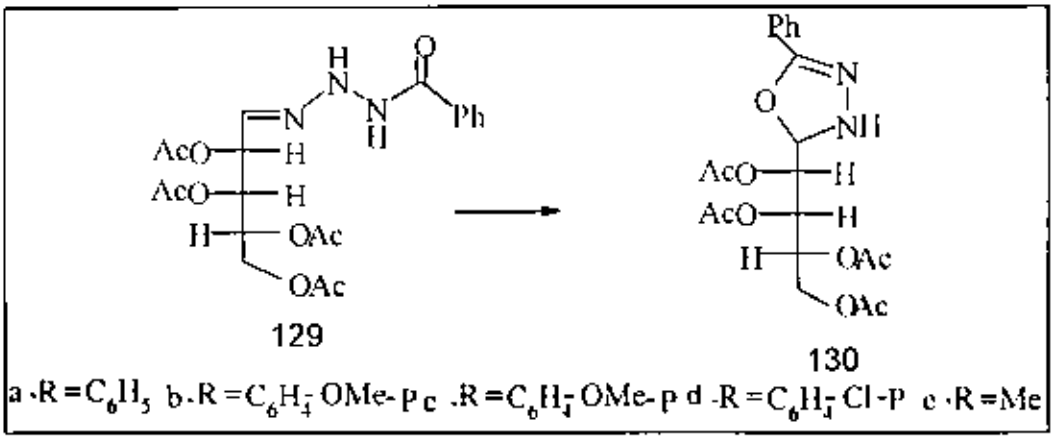
Oxidation of D-galactose benzoyl- and 4-substituted benzoylhydrazone acetates **125a, 125b, 125d** and of D-arabinose benzoylhydrazone **128a** with iodine-mercuric oxide yielded the expected oxadiazoles **126a, 126b,126d and 129a**. Thus, when penta-*O*-acetyl-aldehydo-D- galactose benzoylhydrazone[92]

125a was treated with iodine-mercuric oxide, a reagent known [93-95] to convert 1,2-bis(aroylhydrazones) into 1,2,3-triazoles, it afforded a crystalline product **126a** that had an elementary analysis agreeing with the dehydrogenated hydrazone.

The dehydrogenated product was assigned by also spectral data the structure **126a**, namely, 2-(D-galacto-1,2,3,4,5-pentaacetoxypentyl)-5-phenyl-1,3,4-oxadiazole [129] . The oxidation of saccaride aroylhydrazon acetate to the corresponding 5-aryl-2-(polyacetoxyalkyl)-1,3,4-oxadiazole was also successfully applied to: *a)* penta-*O*-acetyl- aldehydo-D-galactose 4-tolyl **125b** and (p-chlorobenzoyl) hydrazone **125d** [91] , which afforded 2-(D-galacto-1,2,3,4,5-pentaacetoxypentyl)-5- (4-tolyl)- and 5-(4-chlorophenyl)-1,3,,4-oxadizole , respectively, and *b)*tetra-*O*-acetyl-aldehydo-D-arabinose benzoylhydrazone **129a**, which gave 5-phenyl-2-(D-arabino-1,2,3,4-tetraacetyloxybutyl)-1,3,4-oxadiazole **130a** [96].

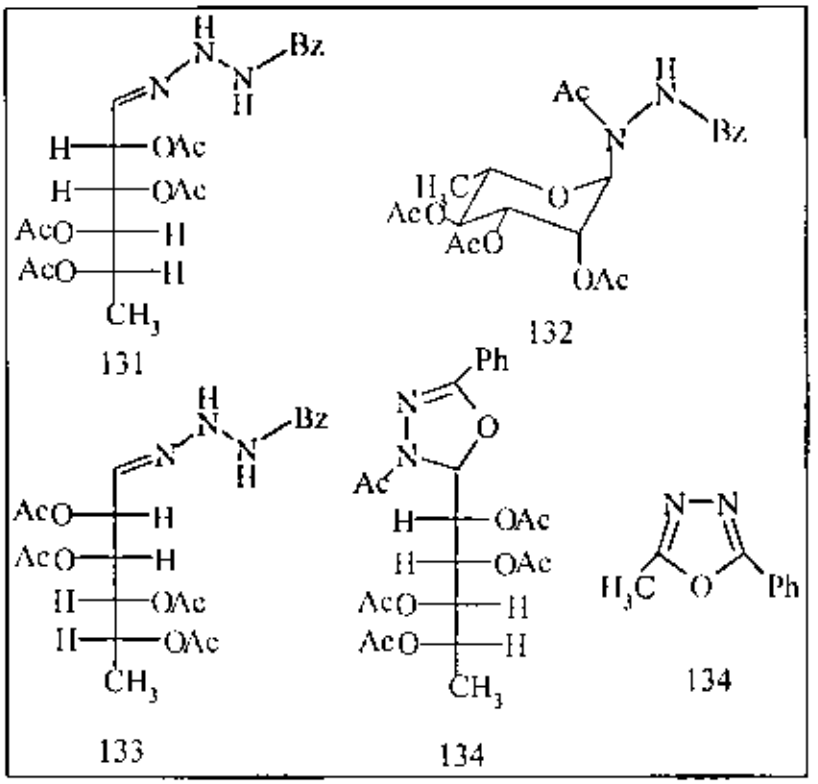


Scheme (43)



Scheme (44)

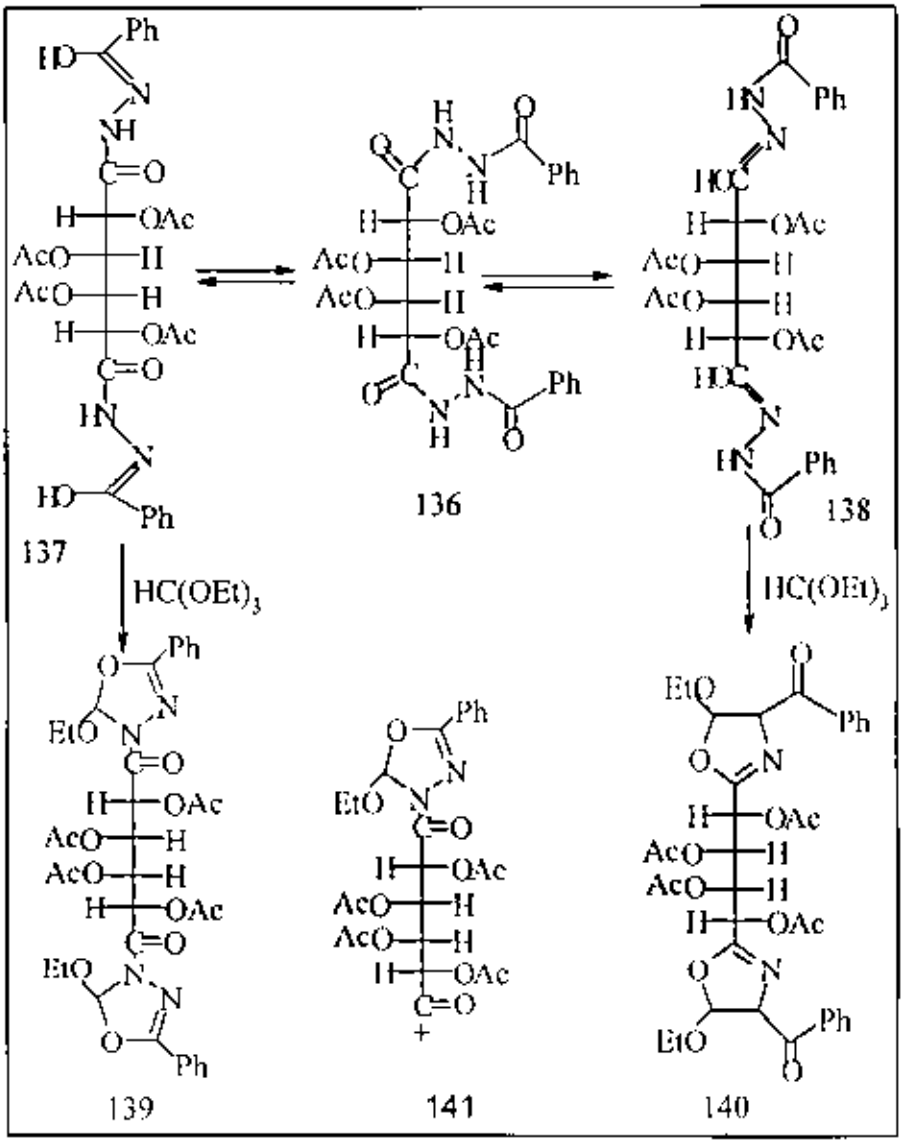
The acyclic tetraacetate **131**, was synthesized unambiguously by reaction of tetre-*O*-acetyl-aldehdo-L-rhamnose [97] with benzoylhydrazine, was amorphous and had solubility and physical constants similar to those of amorphous penta-*O*-acetyl-aldehydo-D-mannose benzoylhydrazone **133** prepared from penta-*O*-acetyl-aldehydo-D-mannose ethyl himiacetal [98] by reaction with benzoylhydrazine, but markedly different from those of **132**. Moreover, treatment of authentic sample of **133** with acetic anhydride and anhydrous zinc chloride gave 3-acetyl-5-phenyl-2-(L-manno-1,2,3,4-tetra-acetoxypentyl)-1,3,4-oxadiazoline **134**. Under similar conditions. the tetraacetate **132** gave after chromatograph purification 1,2,3,4-tetra-*O*-actyl-α-L-rhamnopyranose as a syrupy product and 2-methyl-5-phenyl-1,3,4-oxadiazole **135** [79].



Scheme (45)

Synthesis of saccharide bis(1,3,4-oxadiazoline) derivative **139** by using another approach, namely, condensative cyclization [99-101] . Thus refluxing 2,3,4,5-tetra-*O*-acetylgalactaric acid bis(benzoylhydrazide) [102] **136** with triethylorthoformate afforde a product whose spectral and analytical data are in agrrement with both structures **139** and **140** arising from the condensation of triethylorthoformate with the two enolic forms of **136** (**137** and **138**), and cannot distinguish between them. However, the mass spectrum showed, in addition to the molecular ion at *m/e* 726, fragment **130** at m/e 535.

The latter would only be expected from **139**, and accordingly, the product is assigned the structure of the 1,6-bis(2-ethoxy-2,3-dihydro-5-phenyl-1,3,4-oxadiazol- 3-yl) derivative of tetra-*O*-acetylgalactaric acid. The assignment implies that under the conditions of the reaction the enolic structure **137** is the predominant existing entity[103].

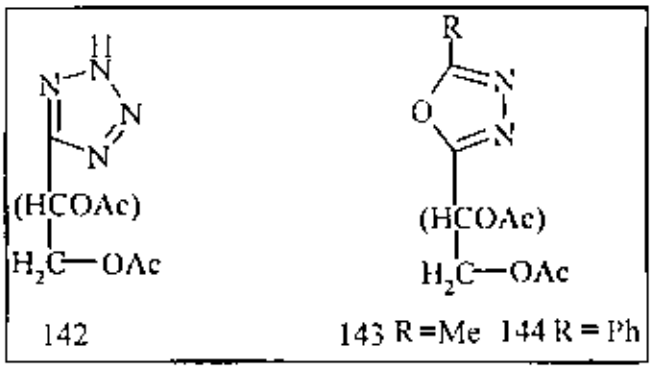


Scheme (46)

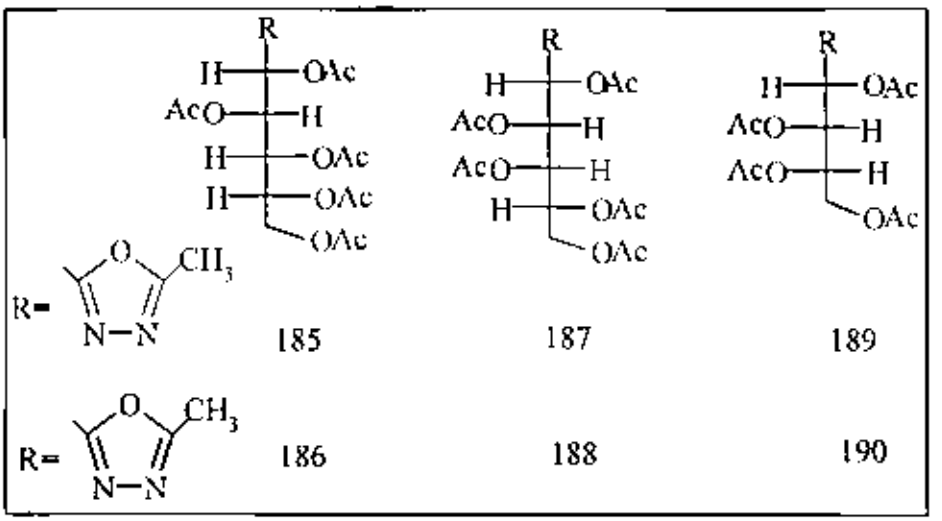
The reaction of 5-alkyl- and 5-aryl-tetrazoles **142** with acylchlorides or acid anhydrides afforded the corresponding oxadiazoles in moderate yields [106-104] . Thus, treatment off 5-(polyacetoxyalkyl) tetrazoles with acetic anhydride or benzoyl chloride, yields 2-methyl-**143** or 2-phenyl-5-(polyacetoxyalkyl)-1,3,4-oxadiazole **133** respectively [107] .

Reaction of 5-(D-gluco-1,2,3,4,5-pentaacetoxypentyl)tetrazole [108] with acetic anhydride afforded2-methyl-5-(D-gluco-1,2,3,4,5-pentaacetoxypentyl)-1,3,4 oxadiazole **185**, and the reaction with benzoyl chloride produced 5-(D-gluco-1,2, 3,4,5-pentaacetoxypentyl)-2-phenyl-1,3,4-oxadiazole **186**.

Similar reactions applied to 5-(D-galacto-1,2,3,4,5-butaacetoxypentyl) tetrazole [109] and 5-(L-arabino-1,2,3,4,5-tetraacetoxybutyl)tetrazole [108] gave 2-methyl-5-(D-galacto-1,2,3,4,5-pentaacetoxypentyl)-1,3,4-oxadiazole **187**, 5-(D-galacto-1,2,3,4,5-penta-acetoxypentyl)-2-phenyl-1,3,4-oxadi- azole [94] **188**, 2-methyl-5-(L-arabino-1,2,3,4-tetra-acetoxybutyl)-1,3,4-oxadiazole **138** and 2-phenyl-5-(L-arabino-1,2,3,4-tetra-acetoxybutyl)-1,3,4-oxadiazole **190** [107].

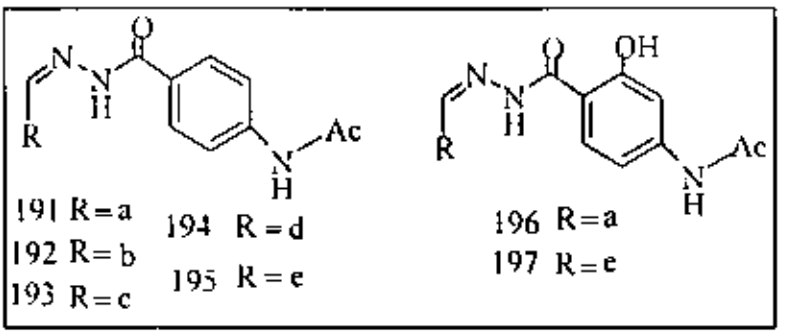


Scheme (47)

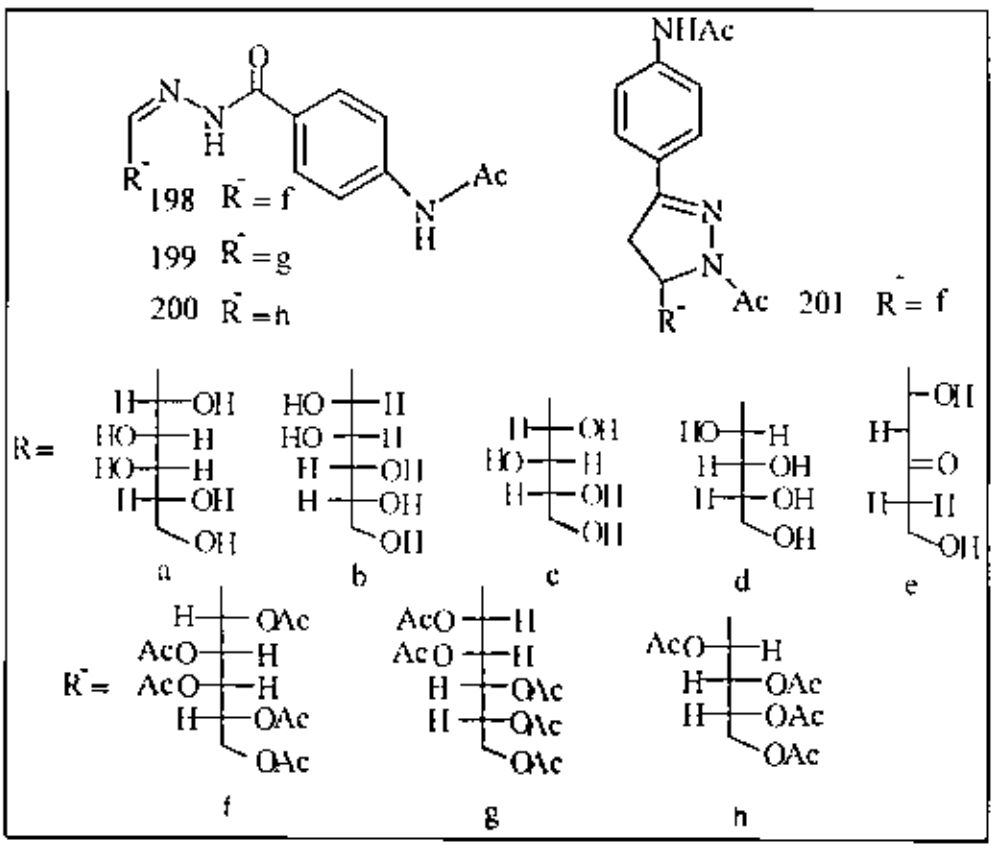


Scheme (48)

Acetylation of **191-193** with acetic anhydride in pyridine afforded the corresponding per-*O*-acetyl derivatives **198-200**. On the other hand, treatment of **198** with boiling acetic anhydride caused its cyclization giving the corresponding oxadiazoline formulated as 5-(4-acetamido phenyl)-3-acetyl-2-(penta-*O*-acetyl-D-galactopentitol-1-yl)-1,3,4-oxadiazoline **201** [88].



Scheme (49)



Scheme (50)

RESULTS AND DISCUSSION

Results and Discussion

The combinatorial approach in organic synthesis and the synthesis of library of compounds become major objectives for various laboratories around the world in order to search for biologically active compounds. Hydrazine and its derivatives have attracted much attention because of the diversity of compounds and heterocyclic rings that can be formed from them. The N-arylglycines such as N-(4-ethoxyphenyl) and N-(4-butoxy phenyl)glycines have very high antitubercular activity[108] in vivo. The respective substituted arylamines showed inhibitory activity against tubercle bacilli in vitro test, but with high toxicity [109]. Furthermore. 1,3,4-oxadiazoles and 1,3,4-oxadiazolines can be fungicidal and bactericidal agents and have analgetic, antipyritic. antiphlogestic, anticompulsive, paralytic hypnotic and sedative

properties[65-68] as well as antiviral activity against HIV[49] and tyrosinase inhibiting effect[110].

Sugar N-arylaminoacetyl hydrazones (I-IV)

The starting materials N-arylglycin hydrazides **202** were synthesized as reported earlier by treating the ethyl esters-N-arylglycinoylesters with hydrazine hydrate[220].

Reaction of 4-substituted phenylglycinoyl hydrazides **202** with equivalent amounts of D-mannose and D-galactose, in boiling ethanol containing catalytic amount of acetic acid gave the respective hydrazones **I-IV.**

The structures of the synthesized sugar hydrazones were established by the analytical and spectral data (IR and ^{1}H NMR).

D-Mannose-N-phenylamino- acetylhydrazone (I).

The colorless condensation product of D-mannose with carbohydrazidese gave elemental analysis data that agreed with the molecular formala $C_{14}H_{21}N_3O_6$ which is hydeogen atoms less than that of the expected hydrazone . The infrared spectrum of the product showed C=N absorption at 1604 cm^{-1}, and OH absorption at 3365 cm^{-1}. The product was, therefore, assigned the structure of D-Mannose-N-phenylamino- acetylhydrazone **(I)**.

D-Manooose-N-(4-tolyl)aminoacetylhydrazone (II):

The analytical data revealed a molecular formula $C_{14}H_{21}N_3O_6$ for **II.** The IR spectrum showed an absorption band at 3387 cm^{-1}due to the hydroxyl groups in addition to a band in the carbonyl frequency region at 1674 cm^{-1} corresponding to amide group.The ^1H NMR spectrum of the hydrazone **II**, confirmed the presence of sugar protons in the range δ 3.15-5.70 ppm, the C-1 methine proton as doublet at 7.47 ppm and the aromatic protons in the region δ 6.55-7.55 ppm. Moreover, The assignments of which have been based on their chemical shift equivalences to the assigned structure of other sugar hydrazones.
The C-1 of the sugar residue appeared in the range δ 149. 88 ppm and the carbonylamide group at δ 171.08 ppm.

D-Galactose-N-phenylaminoacetylhydrazone (III):
Condensation of 202 with D-mannose gave also the respective hydrazone III. The IR spectrum of III showed C=N absorption at 1620 cm^{-1}, and OH absorption at 3322 cm^{-1}.The elemental analysis gave a value greening with the molecular formula $C_{15}H_{23}N_3O_6$.

D-Galactose-N-(4-tolyl)aminoacetylhydrazone (IV):

Carbohydrazide 202 was also allowed to react with D-galactose to give the sugar hydrazone IV. It's elemental analysis agreed with the molecular formula $C_{15}H_{23}N_3O_6$, and it's spectrum showed in addition to the C=O group at 1674 cm^{-1} and OH at 3371 cm^{-1}.

O-Acetylated derivatives of sugar N-arylaminoacetyl-hydrazones (V-VII):

Acetylation of sugar N-arylaminoacetylhydrazones **I,III,IV** gave products whose structures based on the condition of acetylation. Thus, acetylation of **I,II,IV** with acetic anhydride in pyridine at room temperature afforded colorless crystalline *O*-acetyl derivatives **V-VII.**

2',3',4',5',6'-Penta-O-acetyl-D-mannose-N-phenylaminoacetyl-hydrazone (V):

acetylation of **I** with acetic anhydride in pyridine afforded a crystalline product V. It's structure was conclusively confirmed by it's elemental analysis and it's IR spectrum showed in addition to the OCN group at 1675 cm^{-1} the acetyl group at 1750 cm^{-1}.

The ^1H NMR spectrum of the acetyl derivatives V showed the *O*-acetyl-methyl groups as singlets in the range δ 1.95-2.15 ppm. The C-6 methylene protons appeared as doublet of doublet and multiplets at 4.05 and 4.11 ppm. The rest of the alkyl chain protons appeared in the range δ 4.50-5.40 ppm due to H-3, H-4,H-5 and H-2 protons followed by the aromatic protons, and the C-1 methine proton as doublet at δ 7.25ppm.

2',3',4',5',6',-Penta-O-acetyl-D-mannose-N-(4-tolyl)aminoacetyl-hydrazone (VI):

The reaction of the corresponding D-Manooose-N-(4-tolyl) -aminoacetylhydrazone (II) with acetic anhydride in pyridine was also investigated.

Thus IR spectrum of the colorless crystalline product showed a band at 1751 cm^{-1}, due to acetic ester, the amide absorption band at 1661 cm^{-1}.

2',3',4',5',6',-Penta-O-acetyl-D-galactose-N-(4-tolyl)amino-acetylhydrazone (VII):

2',3',4',5',6',-Penta-O-acetyl-D-galactose-N-(4-tolyl)amino-acetylhydrazone (VII) was also preponed by reaction the the IV with acetic anhydride in pyridine at room temperature. IR spectrum showed two absorption bands in the carbonyl frequency region at 1750 (OAc) and 1670 (C=O).

EXPERIMENTAL

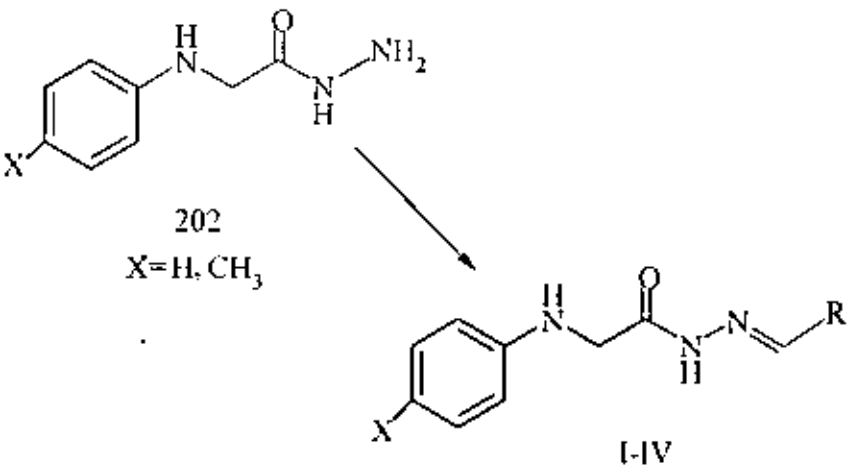
EXPERIMENTAL

Melting points were determined with a kolfer block apparatus and are uncorrected. NMR spectra were recorded on a varian Gemini 200 NMR Spectra at 300 MHz for ^{1}H NMR. Or on a brucker Ac-250 FT spectrometer at 250 MHz for ^{1}H NHR. The progress of thereactions was monitored by TLC using aluminm silica gel plates 60 F 245. Elemental analyses were performed at the Microanalytical data centre at Faculty of Science.

Sugar N-arylaminoacetyl hydrazones (I-IV)

General procedure:

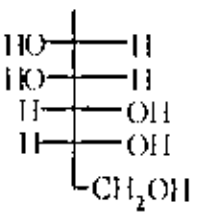
To a well stirred solution of the respective monosaccharid (0.01 mole) in water (2 ml), and glacial acetic acid (0.2 ml) was added the appropriate N-arylaminoacetyl hydrazide 202 (0.01 mol) in etanol (10 ml). The mixture was heated under reflux for 3 hrs and the resulting solution was concentrated and left to cool. The precipitate was filterd off, washed with water and ethanol, then dried and crystallized form ethanol.

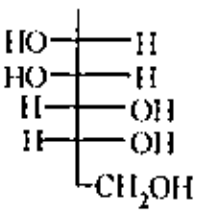


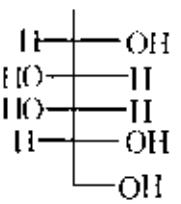
202

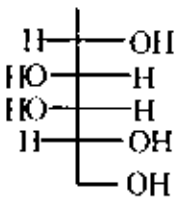
X=H, CH_3

I-IV

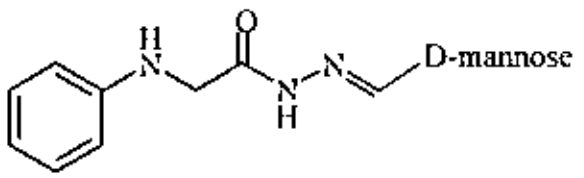
I R =  ,X=H

II R =  ,X=CH_3

III R =  ,X=H

IV R =  ,X=CH_3

D-Mannose-N-phenylaminoacetylhydrazone (I):



I

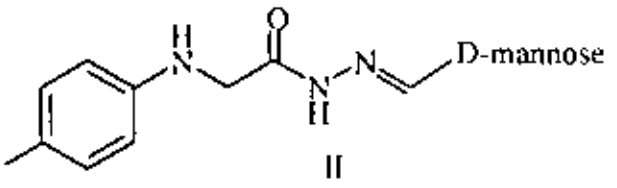
The molecular formula $C_{14}H_{21}N_3O_6$

Melting points 195-197 °C

Yield: 83.0%;

IR (KBr) Y_{max}/cm^{-1}: 3365 (OH), 1661 (C=O), 1604 (C=N). ^1H NMR (DMSO-d_6), (δ ppm): 3.55 (m, 2H, H-6', H-6''), 3.70 (m, 1H, H-5'), 3.80 (d, 2H, CH_2), 4.05 (m, 2H, -3', H-4'), 4.20 (dd, 1H, H-2')4.35 (m, 2H, 2OH), 4.40 (d, 1H, OH), 5.20 (d, 1H, OH), 5.65 (d, 1H, OH), 5.90 (t, 1H, NH), 6.65 (m, 3H, Ar-3H), 7.15 (m, 2H, Ar-2H), 7.40 (d, 1H, H-1'); 11.20 (s, 1H, NH). Anal. Calcd. For $C_{14}H_{21}N_3O_6$: C, 51.37; H, 6.64; N, 12.84. Found: C, 51.05; H, 6.32; N, 13.20%.

D-Manooose-N-(4-tolyl)aminoacetylhydrazone (II):



II

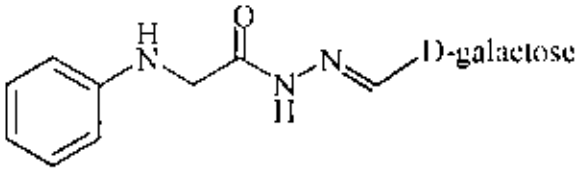
The molecular formula $C_{15}H_{23}N_3O_6$

Melting points 210-211 ^{0}C

Yield: 82.5%.

IR(KBr)Y_{max}/cm^{-1}:3322 (OH), 1661 (C=O), 1620 (C=N), ^{1}H NMR (DMSO-d_6), (δ ppm): 2.15 (s, 3H, CH_3), 3.50 (m, 2H, H-6',H-6"), 3.70 (d, 2H, CH_2), 4.04 (m, 1H, H-5'), 4.25 (m, 2H, H-3', H-4'), 4.35 (dd, 1H, H-2'), 4.45 (d, 1H, OH), 4.50 (d, 1H, OH), 5.20 (m, 2H. 2OH), 5.40 (d, 1H, OH), 5.75(t, 1H, NH), 6.50 (m, 2H, ArH-3,5), 7.05 (m, 2H, ArH-2,6), 7.40 (d, 1H, H-1'), 10.50 (s, 1H, NH). Anal. Calcd. For $C_{15}H_{23}N_3O_6$: C, 52.78; H, 6.78; N, 12.31. Found: C, 52. 43; H, 6.39; N, 12.25%.

D-Galactose-N-phenylaminoacetylhydrazone (III):



III

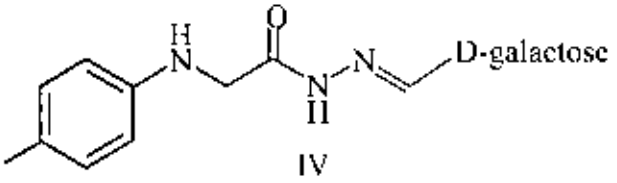
The molecular formula $C_{14}H_{21}N_6O_6$

Melting points 179-181 ^{0}C

Yield: 81%

IR (KBr)Y_{max} /cm^{-1}: 3387 (OH), 1674 (NCO),1605 (C=N). ^{1}H NMR (DMSO-d_6), (δ ppm):3.15-3.25 (m, 2H, H-6', H-6''), 3.35 (m, 2H, H-5', H-4'), 3.40 (dd, 1H, = 5.8 Hz, H-3'), 3.70 (d, 2H, CH2), 3.90 (dd, 1H, H-2'), 4.95 (m, 2H, 2OH), 5.15 (d, 1H, OH), 5.20 (d, 1H, OH), 5.70 (d, 1H, OH), 5.95 (t, 1H, NH), 6.60 (m, 3H, Ar-3H), 7.47 (d, 1H, H-1'), 7.65 (m, 2H, Ar-2H), 9.50 (s, 1H, NH). Anal. Calcd. For $C_{14}H_{21}N_6O_6$: C, 51.37; H, 6.46; N, 12.48. Found: C,51.42; H, 6.18; N, 12.50%.

D-Galactose-N-(4-tolyl)aminoacetylhydrazone (IV):



IV

The molecular formula $C_{15}H_{23}N_3O_6$

Melting points 183-184 ^{0}C

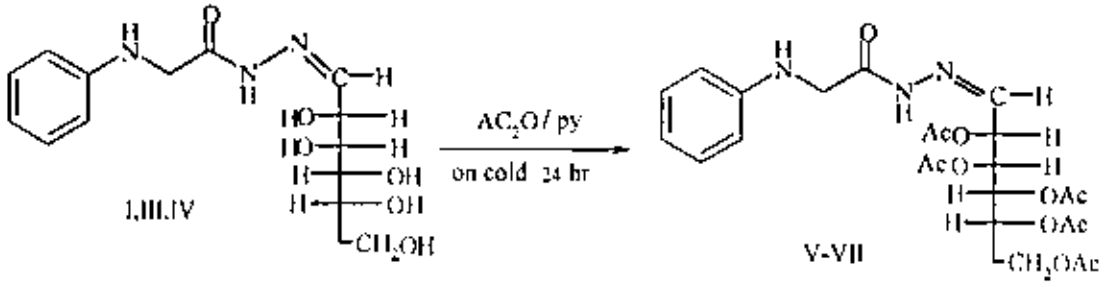
Yield: 78.5%

IR (KBr)Y_{max}/cm^{-1}:3371 (OH), 1674 (C=O), 1618 (C=N), ^{1}H NMR (DMSO-d_6), (δ ppm): 3.4 (m, 2H, H-6', H-6"), 3.50 (m, 1H, H-5'), 3.80 (d, 2H, CH_2),4.05 (m, 1H, H-4'), 4.25 (dd, 1H, H-3'), 4.28 (dd, 1H, H-2'), 4.40 (d, 1H, OH), 4.50 (m, 2H, 2OH), 4.90 (d, 1H, OH), 5.40 (d, 1H, OH), 5.75 (t, 1H, NH), 6.50 (m, 2H, Ar-2H), 6.90 (m, 2H, Ar-2H), 7.40 (d, 1H, H-1'), 11.10 (s, 1H, NH). Anal.Calcd. for $C_{15}H_{23}N_3O_6$: C, 52.78; H, 6.78; N, 12.31. Found: C, 52.51; H, 6.45; N, 12.55%.

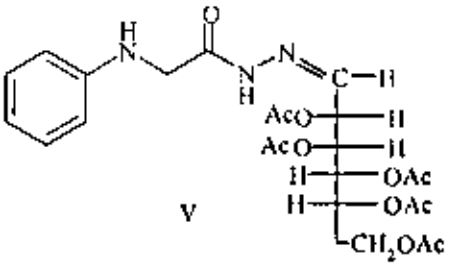
O-Acetylated derivatives of sugar N-arylaminoacetyl-hydrazones (V-VII):

General Procedure:

A cold solution of sugar N-arylaminoacetyl hydrazones **I,III,IV** (2 mmol) in dry pyridine (5 ml) was treated with acetic anhydride (5 mol). The reaction mixture was left overnight with occasional shaking. It was poured onto crushed ice and the separated product was filtered off, washed repeatedly with water, dried and crystallized from ethanol-water mixture. Crystallized from ethanol-water mixture.



2',3',4',5',6'-Penta-O-acetyl-D-mannose-N-phenylamino-acetyl-hydrazone (V):



V

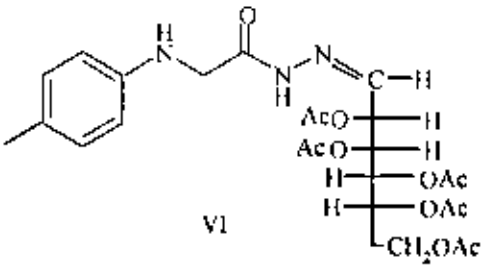
The molecular formula $C_{24}H_{27}N_3O_{11}$

Melting points 110-112 ^{0}C;

Yield: 72%;

IR (KBr)Y_{max}/cm^{-1}: 3450 (NH) 1750 (OAc), 1675 (C=O). ^{1}H NMR (DMSO-d_6), (δ ppm): 1.95, 2.05, 2.10, 2.14, 2.17 (5s, 15H, 5CH_3), 4.05 (dd, 1H, 2.6 Hz, H-6'), 4.11 (m,1H, H-6"), 4.25 (d, 2H, CH_2),4.50 (m, 1H, H-5'), 4.60 (m, 1H, H-4'), 5.15 (dd, 1H, H-3'), 5.50 (dd, 1H, H-2'), 7.05 (d, 1H, H-1'), 7.20 (m, 3H, Ar-3H), 7.45 (m, 2H, Ar-2H), 9.80 (s, 1H, NH). Anal. Calcd. For $C_{24}H_{27}N_3O_{11}$: C, 54.04; H, 5.09; N, 7.88. Found: C, 54.30; H, 5.10; N, 7.52%.

2',3',4',5',6',-Penta-O-acetyl-D-mannose-N-(4-tolyl)aminoacetyl-hydrazone (VI):



VI

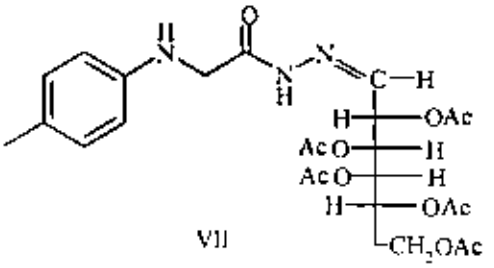
The molecular formula $C_{25}H_{29}N_3O_{11}$

Melting points 118-119 ^{0}C;

Yield: 79.0%;

IR (KBr)Y_{max}/cm^{-1}: 3440 (NH), 1751 (OAc), 1661 (C=O). ^{1}H NMR (DMSO-d_6), (δ ppm): 1.80, 1.89, 1.92, 1.98, 2.05, 2.15 (6s, 18H, 6CH_3), 4.07 (dd, 1H, H-6'), 4.11 (m, 1H, H-5'), 4.20 (d, 2H, CH_2), 5.10 (m, 1H, H-4'), 5.15 (t, 1H, H-3'), 5.33 (t, 1H, H-2'), 7.15 (d, 1H, H-1'), 7.20 (d, 2H, Ar-2H), 7.45 (d, 2H, Ar-2H), 11.40 (s, 1H, NH). Anal. Calcd. For $C_{25}H_{29}N_3O_{11}$, C, 54.85; H, 5.33; N, 7.67. Found: C, 54.70; H, 4.95; N, 7.60%.

2',3',4',5',6',-Penta-O-acetyl-D-galactose-N-(4-tolyl)amino-acetylhydrazone (VII):



VII

The molecular formula $C_{25}H_{29}N_3O_{11}$

Melting points 112-114 ^{0}C:

Yield: 77.0%;

IR (KBr)Y_{max}/cm-1: 1670 (C=O), 1750 (OAc). ^{1}H NMR (DMSO-d_6), (δ ppm): 1.95, 2.05, 2.14, 2.17 (5s, 15H, $5CH_3$), 4.05 (dd, 1H, H-6'), 4.11 (m, 1H, H-6''), 4.25 (d, 2H, , CH_2), 4.50 (m, 1H, H-5'), 4.60 (m, 1H, H-4'), 5.15 (dd, 1H, H-3'), 5.50 (dd, 1H, J = 2.4 Hz, CH_2), 7.05 (d, 1H, H-1'), 7.20 (m, 3H, Ar-3H), 7.45 (m, 2H, Ar-2H), 9.80 (s, 1H, NH). Anal. Calc. for $C_{25}H_{29}N_3O_{11}$: C, 54.85; H, 5.33; N, 7.67. Found: C, 54.80; H, 5.30; N, 7.78%.

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قســـم الكيميـــاء

حـــول البحـــث

((بعـــض تفاعـــلات آريـــل جـــلايسينويل هيـــدرازون))

مقدمـــة مـــن الطـــالبة

جميـــلة سليمـــان أبـــوزيد الزيـــداني

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الدكتور / محمـــد طـــه عبـــد العـــال .....
(مشـــرف الرســـالـــة)

الدكتور / مـــدحت محمـــود المبيـــض .....
(ممتحـــن داخلـــي)

الدكتور / عبـــد الله حمـــد غيـــث .....
(ممتحـــن خارجـــي)

يعتمد

أمين اللجنة الشعبية لكلية العلوم

جامعة التحدي

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