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Review Article

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Synthetic routes to some azolyl-triazoles

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ABSTRACT

Published data on the methods of preparation pyrrolyl, isoxazolyl, oxazolyl, and oxadiazolyltriazole and triazolyltetrazoles are summarized and described systematically. The review is divided according to the type of azole connected to triazole ring.

Keywords: pyrrolyltriazole; isoxazolyltriazole; oxazolyltriazole; oxadiazolyltriazole; triazolyltetrazoles

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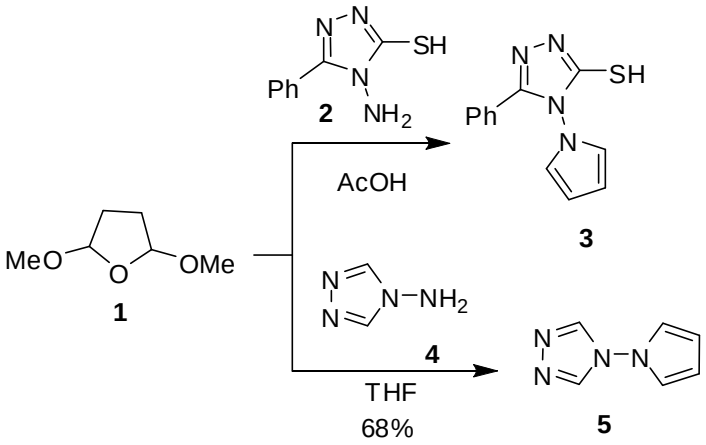
INTRODUCTION

The biologically important triazole moiety has been incorporated into many drugs or drug candidates covering a variety of therapeutic areas. Several therapeutically active compounds containing 1,2,3-triazoles have been reported, such as antimicrobials, anti-HIV agents, and kinase inhibitors [1-4]. Certain 1,2,4-triazole derivatives are of interests due to their bioactivity, including antibacterial [5-7] and antifungal [8,9] properties. Recently there has been considerable interest in the synthesis and properties of bi-heterocycles, due to their wide range of application. For example, 2,2`-bi-1,3,4-thiadiazole derivatives exhibit interesting photoluminescence and electroluminescence and are used as thermotropic liquid crystals[10, 11]. 3,3`-Bis-1,2,4-triazoles have proved to possess bactericidal, fungicidal, and anthelmintic activities [12], imidazolyltriazoles are useful for inhibition of the production of cytokines [13] and (1,2,3-triazolyl)-1,2,3-oxadiazole derivatives used as potentiating NO-dependent activation of soluble forms of guanylate cyclase [14]. In the view of the above facts and in connection to our previous review articles about biologically active heterocyclic systems [15-18], we decided to prepare this review to present for reader a survey of the literature of the different azoles linked directly with triazole nucleus, also some of the commercial applications are mentioned.

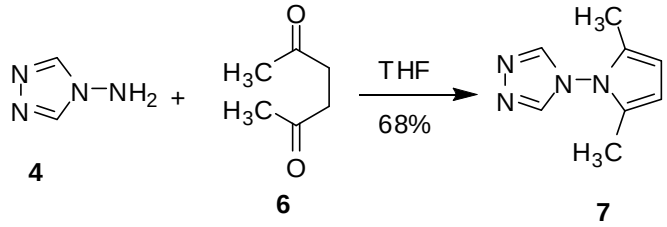
2. Pyrrolyltriazoles

4-Amino-3-mercapto-5-phenyl-1,2,4-triazole **2** was converted to 4-(1-pyrroyl) derivative **3** by reaction with 2,5-dimethoxytetrahydrofuran **1**in refluxing acetic acid [19]. Also, the pyrrolotriazole **5** prepared from 4-amino-1,2,4-triazole **4** by condensation with 2,5-dimethoxytetrahydrofuran **1** (Scheme 1) [20].



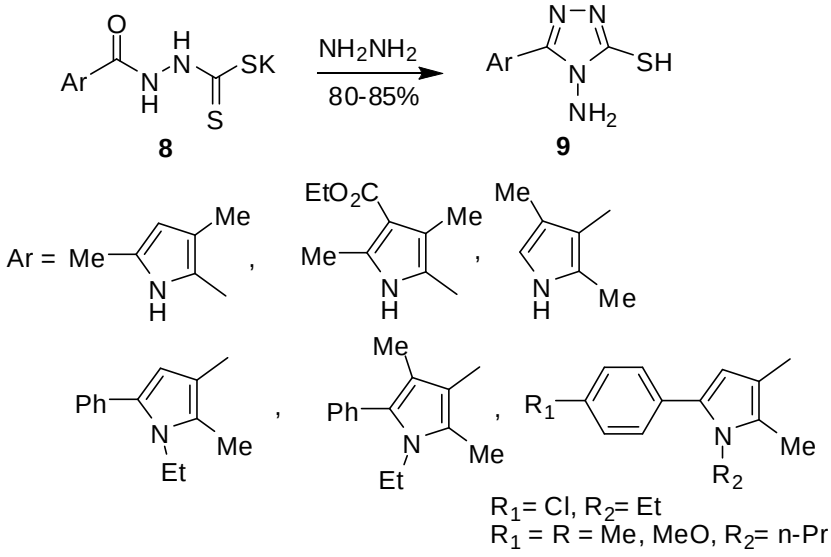
Scheme 1

4-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-4*H*-1,2,4-triazole **7** was prepared from 4-amino-1,2,4-triazole **4** by condensation with acetonylacetone **6** (Scheme 2) [20].



Scheme 2

4-Amino-5-(substituted pyrrolyl)-4*H*-1,2,4-triazole-3-thiols **9** were prepared by cyclization of hydrazinecarbodithionic acids **8** after heating with hydrazine hydrate (Scheme 3) [21].

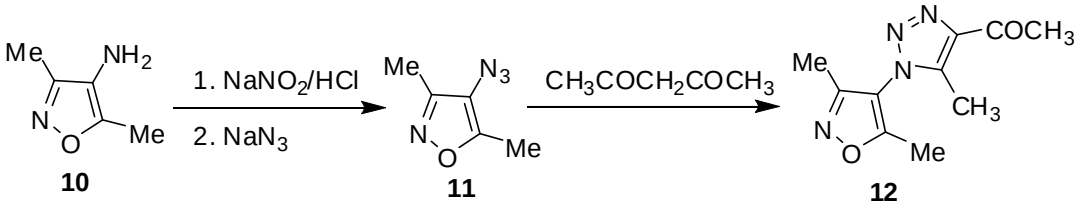


Scheme 3

3. Isoxazolyltriazoles

3.1. Isoxazolyl-1,2,3-triazoles

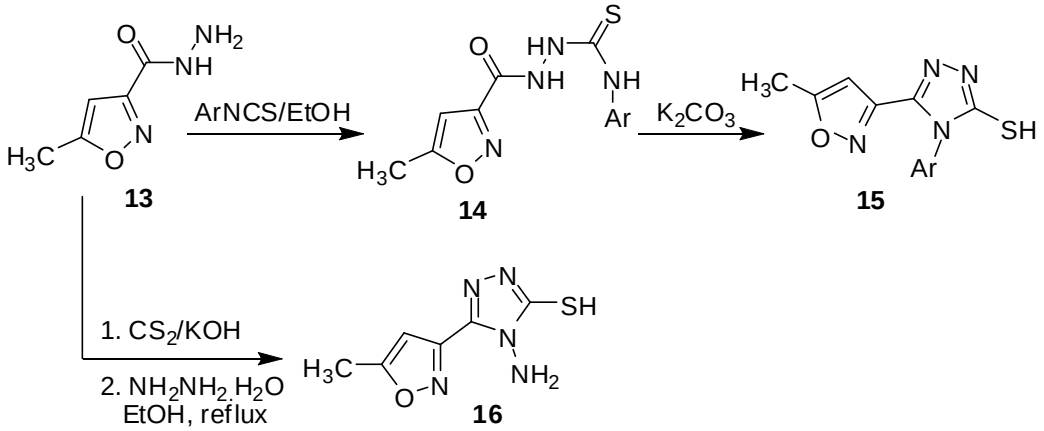
The diazonium salt from aminodimethylisoxazole **10** was more stable and at 0 °C, reacted with sodium azide to give 65% **11** which on reaction with acetyl acetone afforded 10% the isoxazolyltriazole **12** (Scheme 4) [22].



Scheme 4

3.2. Isoxazolyl-1,2,4-triazoles

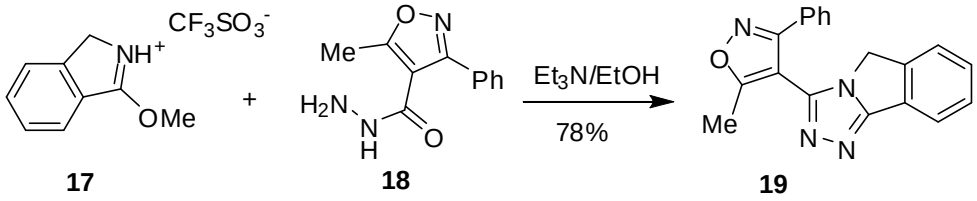
5-Methylisoxazole-3-carbohydrazide **13** reacted with arylisothiocyanates and then cyclization in the presence of 2 mol/L aqueous potassium carbonate solution to give 4-aryl-5-(5-methylisoxazol-3-yl)-1,2,4-triazol-3-thiols **15** [23, 24]. Whereas 4-amino-5-mercapto-3-(5-methylisoxazol-3-yl)-1,2,4-triazole **16** was prepared by treatment of **13** with carbon disulphide followed by reaction with hydrazine hydrate (Scheme 5) [25-27].



Ar = Ph, (2-Me, 3-Me, 4-Me; 2-Cl, 3-Cl, 4-Cl, 2-Br, 3-Br, 4-Br,2-MeO, 4-MeO, 2-EtO, 4-EtO)C_6H_4; 3,4-$(CH_3)_2C_6H_3$

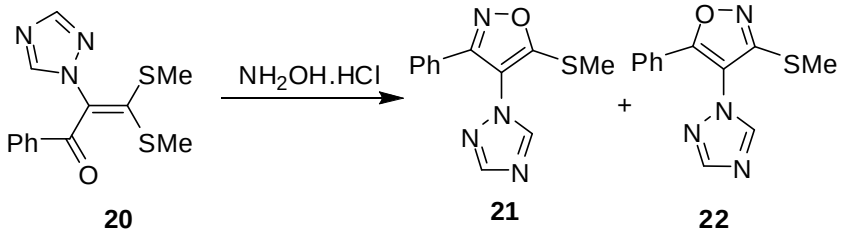
Scheme 5

Refluxing of 3-methoxy-1*H*-isoindolium triflate **17** and 5-methyl-3-phenyl-4-isoxazoloyl hydrazide **18** in the presence of triethyl amine in ethanol gave 78% 3-(5-methyl-3-phenylisoxazol-4-yl)-5*H*-[1,2,4]-triazolo[3,4-*a*]isoindole **19** which act as GABA-A α5 receptor subunit ligands useful as cognition enhancers for treatment of Alzheimer's disease (Scheme 6) [28].



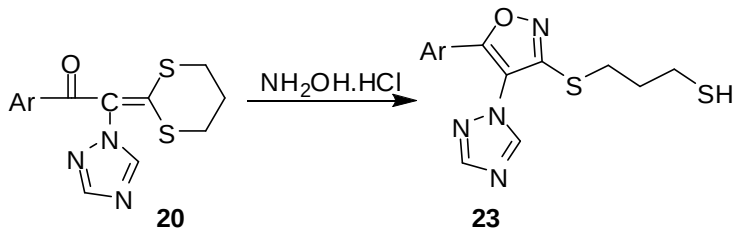
Scheme 6

Reaction of 3,3-bis(methylthio)-1-phenyl-2-(1*H*-1,2,4-triazol-1-yl)prop-2-en-1-one **20** with hydroxylamine hydrochloride gave a mixture of isomeric isoxazoles **21** and **22** (Scheme 7) [29].



Scheme 7

Substituted isoxazolyl-1,2,4-triazoles **23** were obtained by reaction of cyclic β-oxo-α-(1,2,4-triazolyl)ketene *S*,*S*-acetals **20** reacted with hydroxylamine hydrochloride under basic conditions (Scheme 8) [30].

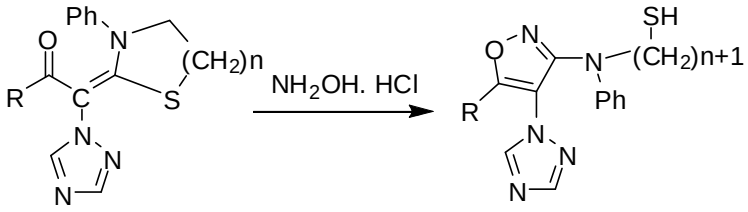


20 **23**

Ar = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-BrC_6H_4

Scheme 8

Cyclic α-oxo-α-(1,2,4-triazol-1-yl)ketene *N*,*S*-acetals **24** react with hydroxylamine hydrochloride under basic conditions affording (3-mercaptoalkylamino)isoxazolyl-1,2,4-triazoles **25** (Scheme 9) [31].



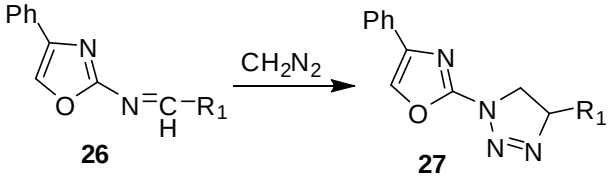
24 **25**

R = (un)substituted Ph; n = 1, 2

Scheme 9

4. Oxazolyltriazoles

Triazolines **27** were prepared from cycloaddition reaction of imine **26** and diazomethane (Scheme 10) [32].



26 **27**

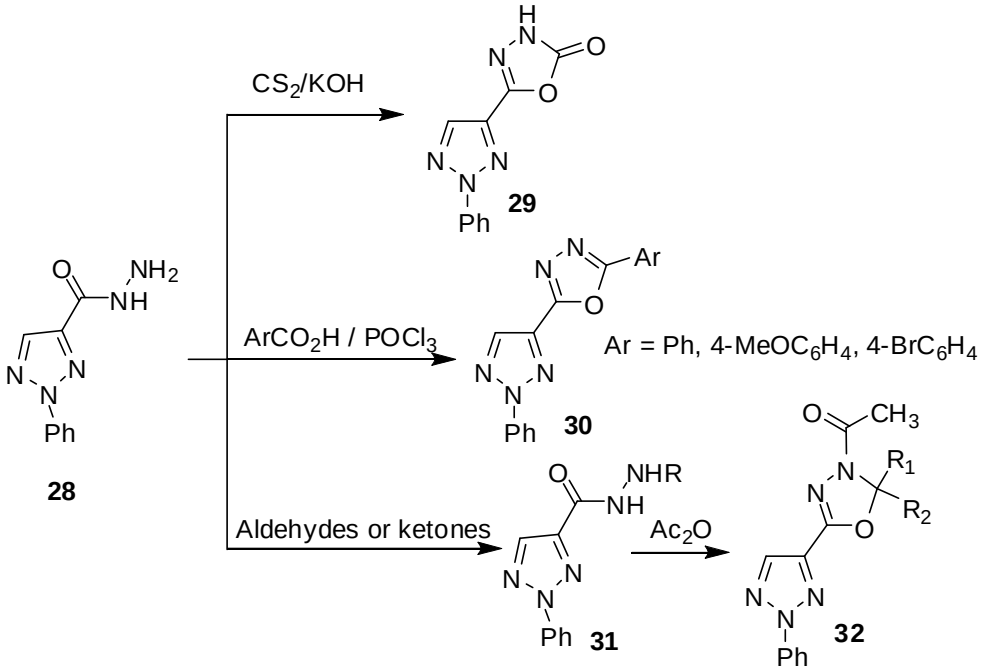
R_1 = anisyl, $O_2NC_6H_4$, ClC_6H_4, HOC_6H_4, $Me_2NC_6H_4$

Scheme 10

5. Oxadiazolyltriazoles

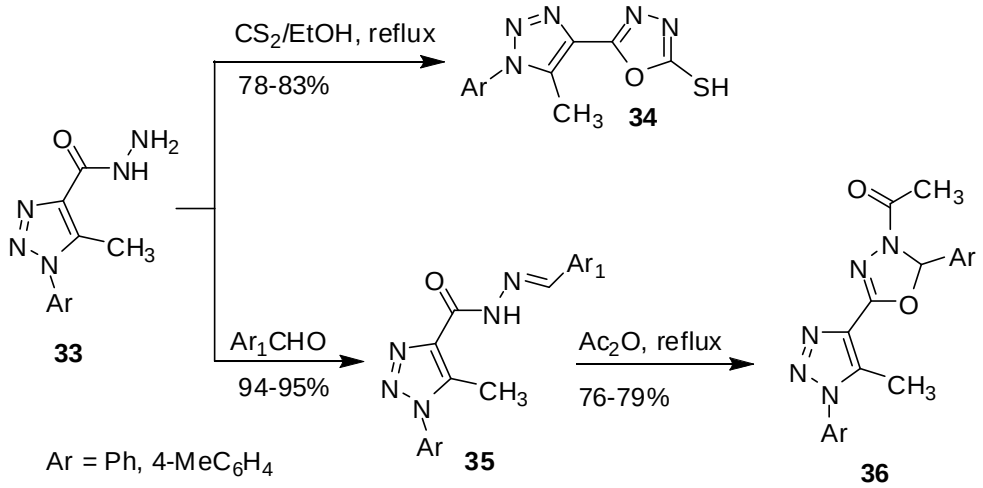
5.1. Oxadiazolyl-1,2,3-triazoles

Reaction of 2-phenyl-1,2,3-triazole-4-formylhydrazine **28** with CS_2/KOH gave the oxadiazole derivative **29**. Also, condensation of **28** with aromatic acids in phosphorus oxychloride yielded oxadiazole derivative **30.** While the reaction of **28** with aldehydes and ketones afforded hydrazones **31**. Cyclization of **31** with acetic anhydride gave the desired dihydroxadiazole derivatives **32** (Scheme 11) [33].



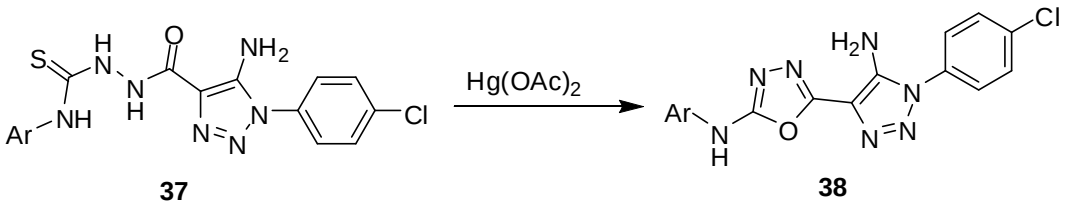
Scheme 11

2-[1,2,3-Triazol-4-yl]-1,3,4-oxadiazole derivatives **34** and **36** were synthesized by various pathways starting from 1-aryl-5-methyl-1,2,3-triazol-4-formhydrazide **33** by condensation with carbon sulfide or reaction with aromatic aldehydes followed by ring closure (Scheme 12) [34].



Scheme 12

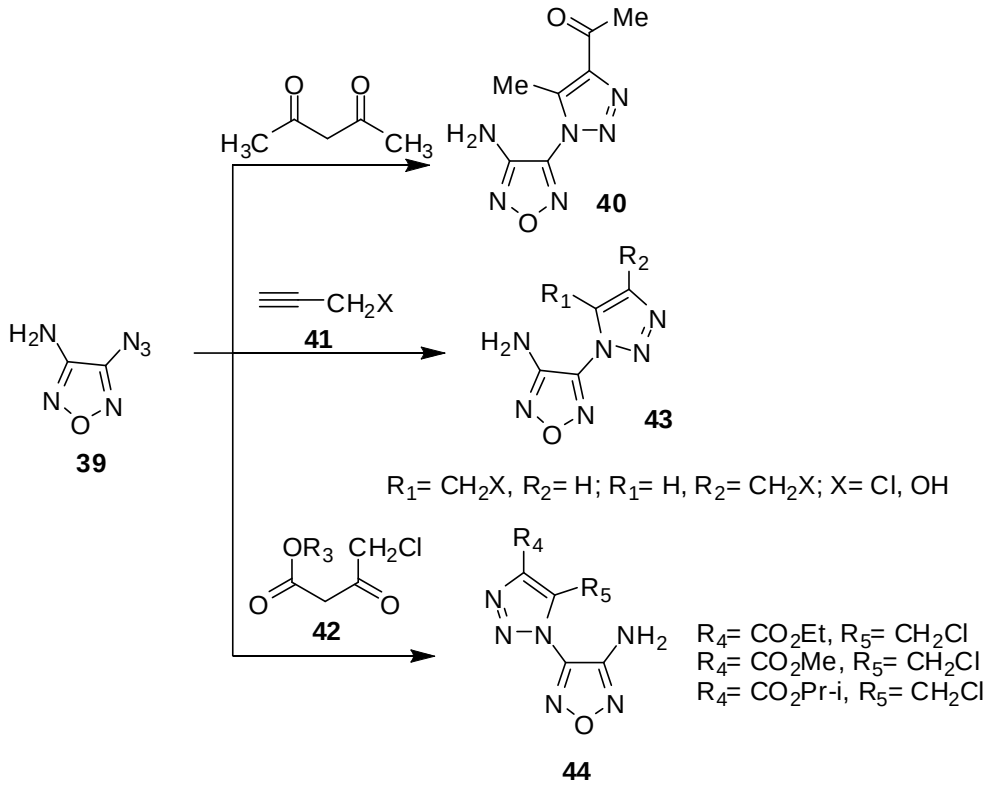
Cyclization of 1-[5-amino-1-(4-chlorophenyl)-1,2,3-triazol-4-ylcarbonyl]-4-arylthiosemicarbazides **37** with mercuric acetate under heating gave 2-arylamino-5-[5-amino-1-(4-chlorophenyl)-1,2,3-triazol-4-yl]-1,3,4-oxadiazoles **38**. The latter compounds showed antibacterial activity against Escherichia coli and Staphylococcus aureus (Scheme 13) [35].



37 **38**

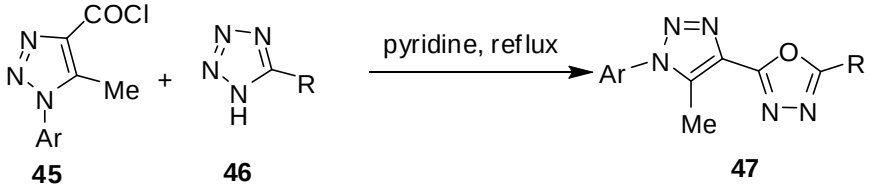
Scheme 13

Cycloaddition of 4-amino-3-azidofurazan **39** with acetyl acetone led to the formation of 1-(1-(4-amino-1,2,5-oxadiazol-3-yl)-5-methyl-1*H*-1,2,3-triazol-4-yl)ethanone **40**. While the reaction with propargyl compounds **41** allowed forming oxadiazolyltriazoles **43** presence of pyridine. Compounds **44** were synthesized by reactions of **39** with the corresponding alkyl chloroacetoacetates **42** (Scheme 14) [36].



Scheme 14

5-Substituted tetrazoles **46** react with 1-aryl-5-methyl-1*H*-1,2,3-triazole-4-carbonyl chlorides **45** to give the corresponding 1,3,4-oxadiazoles **47** having a triazolyl substituent in the 5-position in 54-83% yield (Scheme 15) [37].

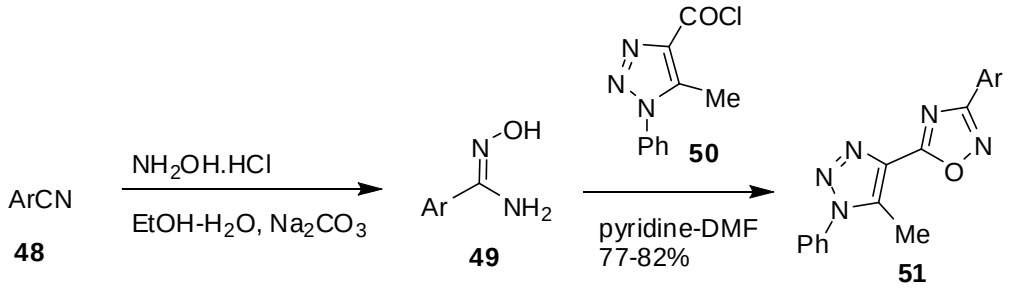


Ar = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 4-FC_6H_4, 2-MeOC_6H_4, 3-MeOC_6H_4

R= Ph, 2-MeC_6H_4, 4-MeC_6H_4, 2-ClC_6H_4, 2-furyl

Scheme 15

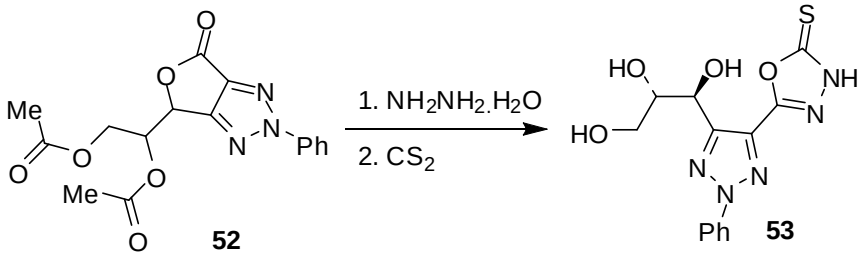
1,2,4-Oxadiazolyl triazoles **51** were obtained starting from corresponding acid chloride **50** by reaction smoothly with amide oximes **49** (Scheme 16) [37].



Ar= Ph, 4-MeC_6H_4

Scheme 16

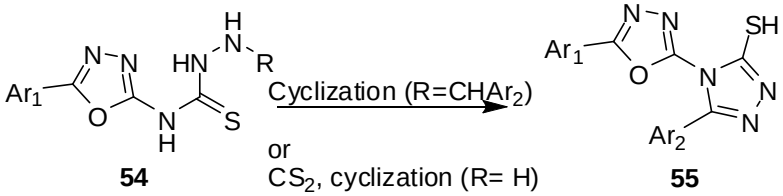
Reaction of 2-phenyl-2,6-dihydro-6-(1,2-diacetoxyethyl)-4*H*-furo[3,4-*d*-1,2,3-[triazol-4-one **52** with hydrazine hydrate followed by treatment with carbon disulfide yielded binuclear heterocycles **53** (Scheme 17) [38].



Scheme 17

5.2. Oxadiazolyl-1,2,4-triazoles

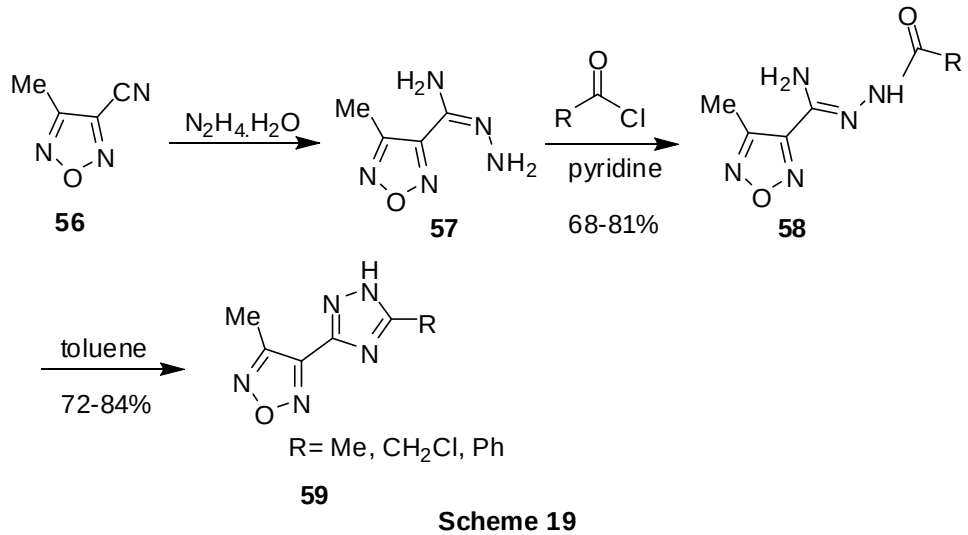
Oxadiazoles **55**, had fungicidal activity comparable to that of dithiane M-45 at 1000 ppm, were prepared via cyclization of the thiosemicarbazides (**54**, R =$CHAr_2$) or reaction of (**54**, R = H) with CS_2 and subsequent cyclization (Scheme 18) [39].



Ar_1 = Ph, o-, p-ClC_6H_4, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$; Ar_2= Ph, p-ClC_6H_4, 4-MeC_6H_4

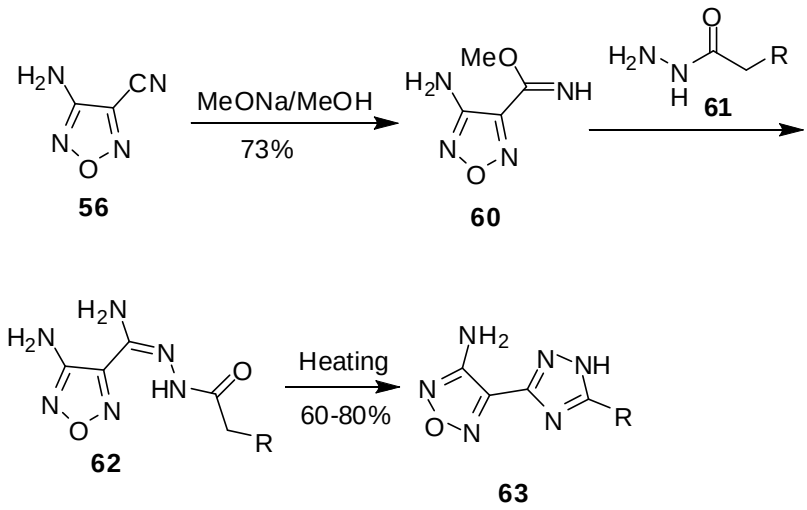
Scheme 18

Treatment of 4-methyl-1,2,5-oxadiazole-3-carbonitrile **56** with hydrazine hydrate in isopropyl alcohol afforded the corresponding amidrazone **57** in 78% yield. A room temperature reaction of amidrazone **57** with commercial aliphatic acid chlorides and benzoyl chloride in chloroform in the presence of pyridine gave acylamidrazones **58** in high yields. Dehydration of **58** by refluxing their solutions in toluene using a Dean-Stark trap giving triazoles **59** (Scheme 19) [40].



Scheme 19

The route to compounds **63** involve thermal dehydration of acylamidrazones **62** obtained from aliphatic acid hydrazides **61** containing various functional substituents and methyl 3-aminofurazan-4-carboximidate **60**, which is prepared from 3-amino-1,2,5-oxadiazole-4-carbonitrile **56** (Scheme 20) [41].

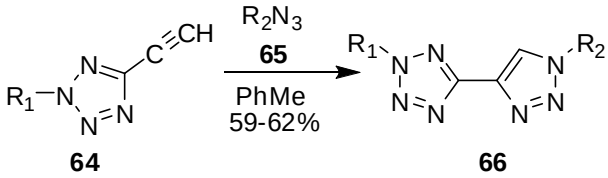


Scheme 20

6. Triazolyltetrazoles

6.1. 1,2,3-Triazolyltetrazoles

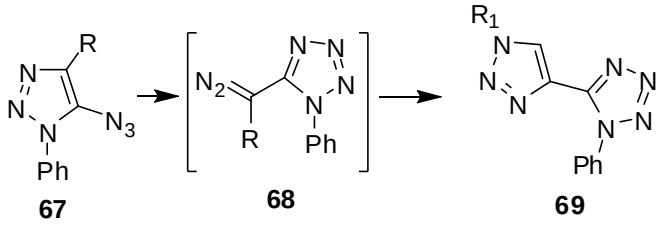
1-Subs.-4-(2-ethyltetrazolyl)-1,2,3-triazoles **66** were obtained by reaction of ethynltetrazole **64** and azide **65** in refluxing toluene (Scheme 21) [42, 43].



R_1= Et, Me; R_2 = Ph, CH_2CH_2Cl

Scheme 21

5-Azido-1-phenyltriazoles **67** can thermally isomerize to diazo substituted tetrazoles **68** and immediately ring-closed to triazoles **69** (Scheme 22) [44].

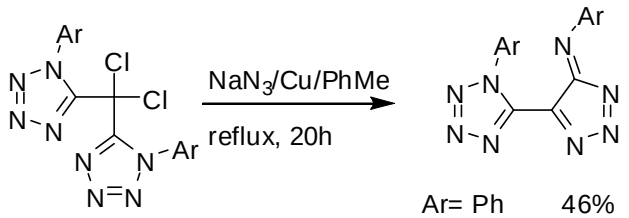


67 **68** **69**

R=CH:NR$_1$; R$_1$ = Ph, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, Et, CMe$_3$, CH$_2$Ph, OH

Scheme 22

Bis(1-aryl-5-tetrazolyl)dichloromethanes **70** were refluxed with sodium azide and powdered Cu in toluene for 20 h to give **71** (Scheme 23) [45].

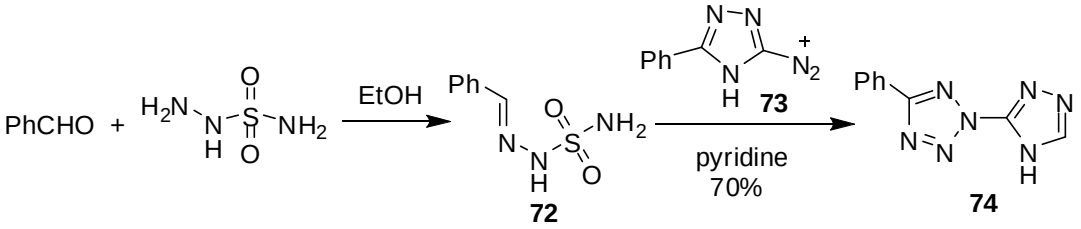


70 **71**

Scheme 23

6.2. 1,2,4-Triazolyltetrazoles

5-Phenyl-2-(4*H*-1,2,4-triazol-3-yl)-2*H*-tetrazole **74** was prepared in 70% yield by reaction of benzaldehyde with hydrazinesulfonamide followed by reaction of **72** with 5-phenyl-4*H*-1,2,4-triazole-3-diazonium salt **73** in pyridine (Scheme 24) [46].



72 **73** **74**

Scheme 24

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