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Review of synthesis of mono, bis and tris-1,3,4- oxadiazole and N-substituted-2,5-disubstituted-1,3,4- oxadiazole.

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Abstract:

In this minireview, the method of syntheses of mono, bis and tris-1,3,4-oxadiazole and N-substituted-2,5-disubstituted-1,3,4- oxadiazole is reviewed. To the best of my knowledge, reviews on the mono 1,3,4-oxadiazoles are extensive while now reviews are reported to cover the syntheses of the bis and tris counterparts. The bis and tris 1,3,4-oxadiazoles and N-substituted-2,5-disubstituted-1,3,4-oxadiazole and their precursors and derivatives are promising candidates for many different applications in industry notably the medicinal and pharmaceutical industries.

Keywords:

1,3,4-oxadiazole, bis-1,3,4-oxadiazole tris-1,3,4-oxadiazole, *N*-acetyl-1,3,4-oxadiazoline, Hydrazide, Hydrazone

1. Introduction:

Heterocyclic compounds in general, and these containing nitrogen atom in particular are of great interest to researchers in the fields of medicinal and pharmaceutical chemistry (**Jonnalagadda *et.al*., 2020**). Heterocyclic compounds possessing at least one nitrogen atom alone or along with other heteroatoms, have shown a characteristic biological activity, that makes these compounds a focal point of research and applications in the field of medicinal and pharmaceutical (**Heravi & Zadsirjan, 2020; Frank & Szőllősi, 2021, Jampilek, 2019, Wdowiak *et.al*., 2021)**. In addition; they have applications in other scientific fields for example; in light emitting and dyes **(Matache et.al., 2016**, **Gather *et.al*., 2019)**. Among the huge pool of known heterocyclic; compounds contain 1,3,4-oxadiazol moiety in their frame received a significant interest of researchers notably in medicinal chemistry and drug syntheses. The outcome of the researches on syntheses and examinations of the biological effects of 1,3,4-oxadiazole containing compounds and their derivatives, led to commercializing of drugs possess the 1,3,4-oxadiazole moiety in their structures. For examples; Zibotentan **1** is an anticancer agent developed by AstraZeneca company and was approved by the FDA for the treatment of prostate cancer
(Siwach & Verma, 2020; Sudeesh & Gururaja, 2017). Raltegravir **2** was also approved to Merck company by the
FDA along in combination with other antiretroviral agent for the treatment of HIV-1 Infection **(Hicks & Gulick, 2009)**. Furamizole **3** which has very strong anti-bacterial activity and Nesapidil **4** as anti-hypertensive agent **(Singh & Chauhan, 2013; Siwach & Verma, 2020)** (**Figure 1**).

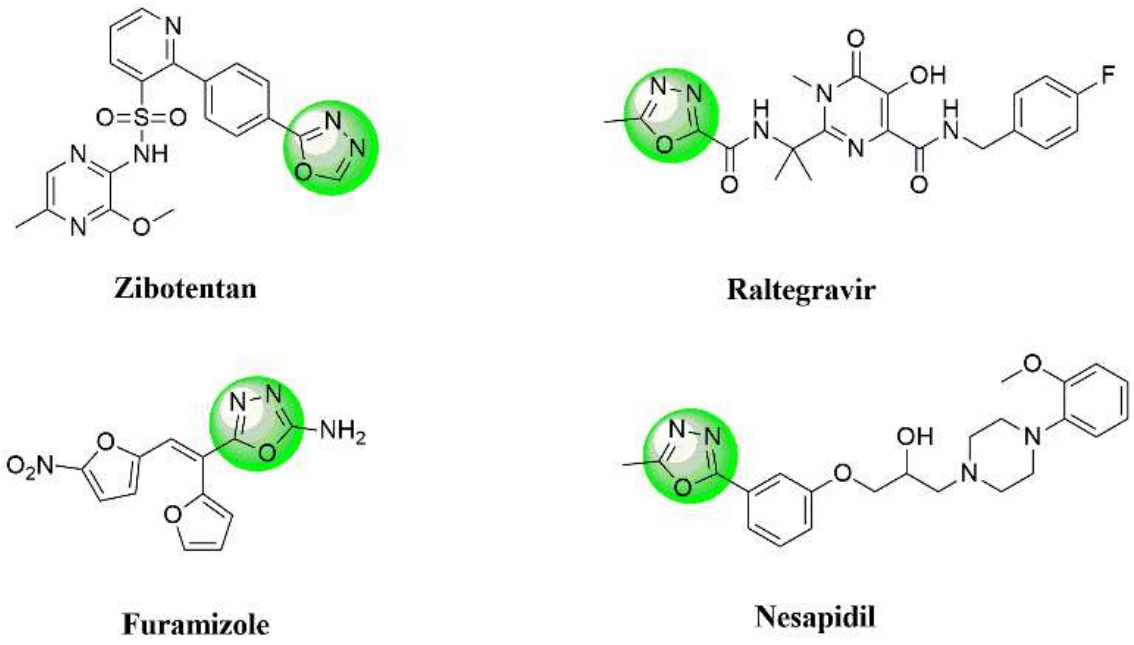


Fig.1: In market drugs contains 1,3,4-oxadiazole ring.

Oxadiazole is a five-member ring with molecular formula $C_2H_2N_2O$. It possesses one oxygen, two carbons, two nitrogen atoms. The oxadiazole moiety is derived from furan in which two methinylene groups (–CH=) replaced by two pyridine type nitrogen (-N=). The molecular formula of oxadiazole enabled the existence of different isomeric structure for this molecular formula. Indeed; four

different isomers of oxadiazole are known and their isolation, syntheses and characterization are well established. The four isomers of oxadiazole are 1,3,4-oxadiazole **1**, 1,2,4-oxadiazole **2 (Demkowicz *et.al.*, 2020, Lima et.al., 2018**), 1,2,3-oxadiazole **3** and 1,2,5- oxadiazole **4** (**Figure 2**).

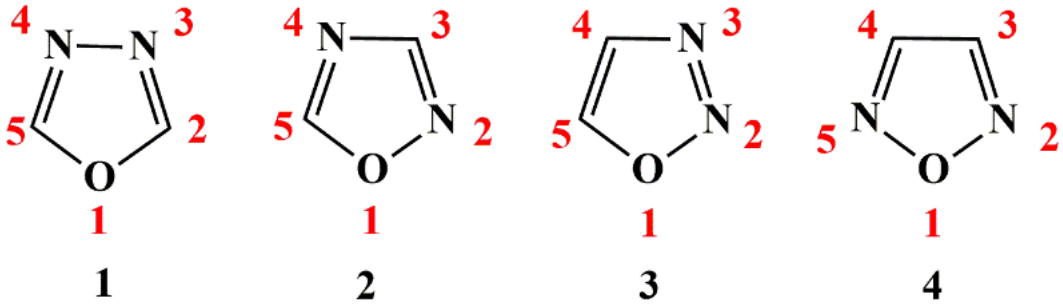
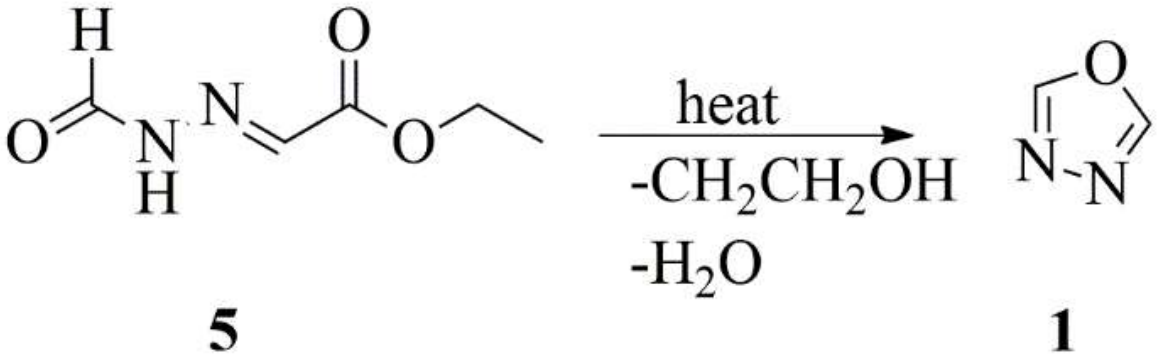


Fig.2: The four isomeric structures of oxadiazole moiety

In term of stability of the four different isomeric structure; the 1,3,4-oxadiazol isomer is considered as the most stable one, and the 1,2,3-oxadiasole is the only unstable isomer. The stability of 1,3,4-oxadiazole ring is due back to different reasons for example; the energy value of aromatic stability, amount of hardness and bonds length. However; the present of substituted groups on the oxadiazole ring are playing significant roll and effect on the stability of the oxadiazole ring. The unique stability of the 1,3,4-oxadiazole moiety and their derivatives encouraged researchers to investigate in depth their syntheses and possible applications notably in the fields of medicinal, drug designing and pharmaceutical chemistry.

Routes for the Synthesis of 1,3,4-oxadiazole Derivatives

The first synthesis of the un-substituted 1,3,4-oxadiazole ring was reported by Ainsworth in 1965 (**Ainsworth, 1965)**. The Ainsworth synthesis of the 1,3,4-oxadiazole **1** was based on the thermolysis of ethyl 2-(2-formylhydrazono) acetate **5** (**Scheme 1**).



Scheme 1: Ainsworth synthesis of 1,3,4-oxadiazole

Ainsworth synthesis was the inspiration for the scientist to designing different routes not just for the generation of the un-substituted 1,3,4-oxadiazole but also for synthesis of different substituted 1,3,4-oxadiazole. The researcher's efforts led to synthesis of 2,5-disubsititued 1,3,4-oxadiazole derivatives as well as tri-substituted derivatives where the third substituent located at one of the two nitrogen atoms of the 1,3,4-oxadiazole nucleus and leading to the formation of *N*-substituted-2,5-disubstituted-2,3-dihydro-1,3,4- oxadiazole (**Figure 3**).

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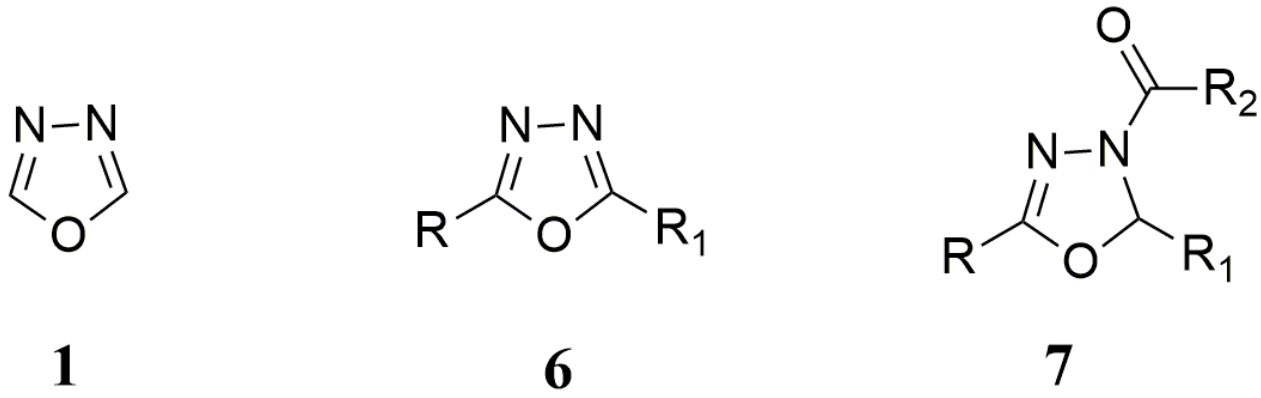

Fig.3: Structure of un-substituted **1**, 2,5-disubtstituted **6** and 3-*N*-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazole **7**

The understanding of the 1,3,4-oxadiazole structure and the limited possibilities for existence of substituent groups; paved the way for researchers towards the dressing of different synthetic routs for generation of different substituted 1,3,4-oxadiazole based on the available candidates starting materials and reagents. In the structure of **6** various substituent groups *i.e.* R and R_1 can be attached to end up with 2,5-disubstituted-1,3,4-oxadiazole. The R group on **6** can be aliphatic, aromatic or heterocyclic substituent. On the other hand; R_1 can be amino, or substituted amino group, thiol or substituted thiol as well as aliphatic, aromatic or heterocyclic substituent. The synthesis of 2,5-disubstituted-1,3,4-oxadiazoles of type **6** utilizing different synthetic routes, starting material and reagents is well reported in literature. However, and up to date; the generation of the 2,5-disubstituted-1,3,4-oxadiazole **6** can be achieved through six different reactions as summarized in (**Figure 4**).

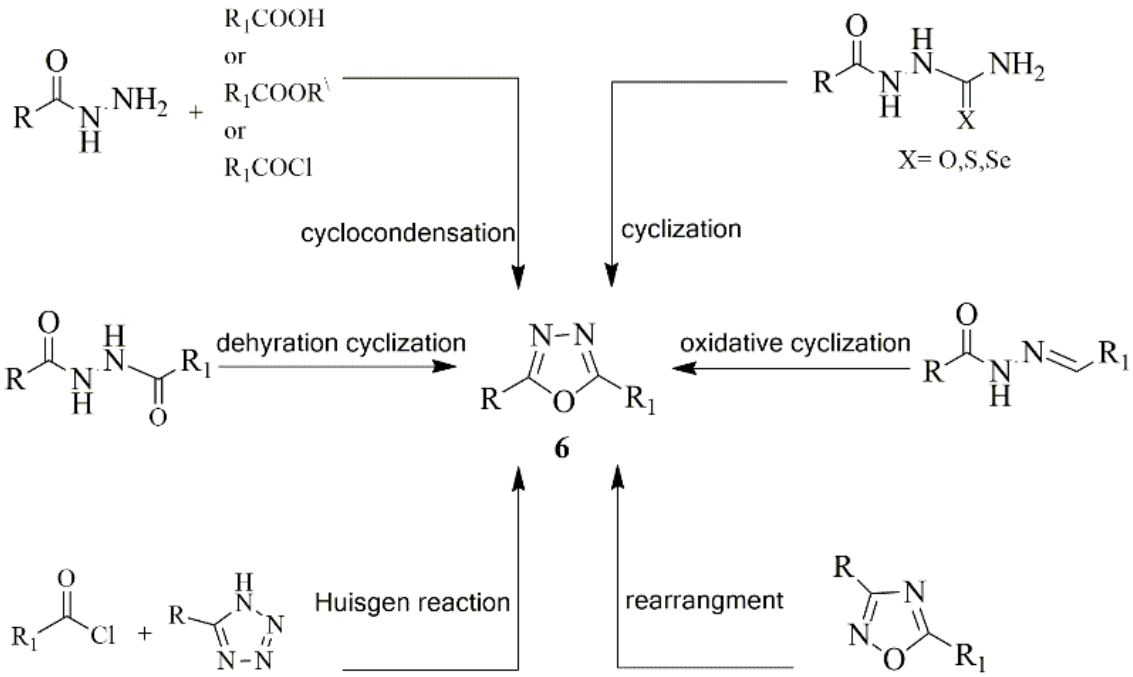

Fig.4: Routes towards the synthesis of 2,5-disubstituted-1,3,4-oxadiazole.

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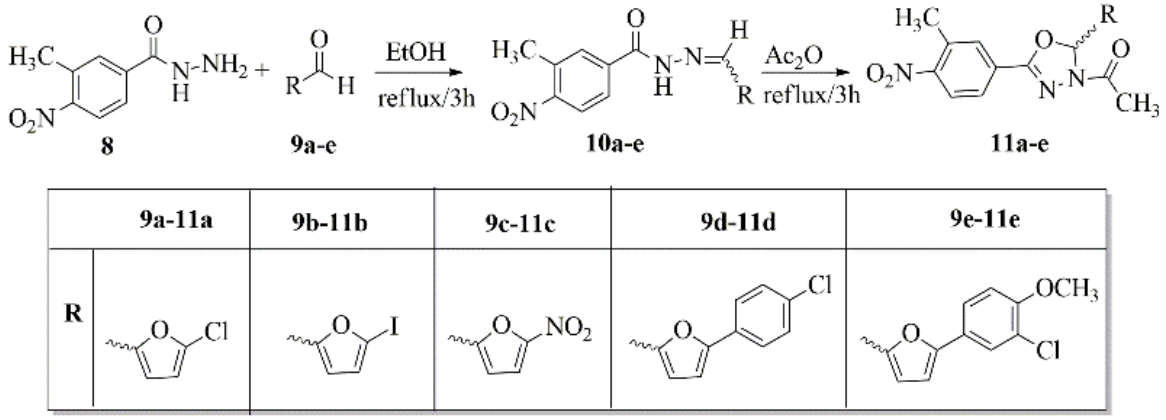
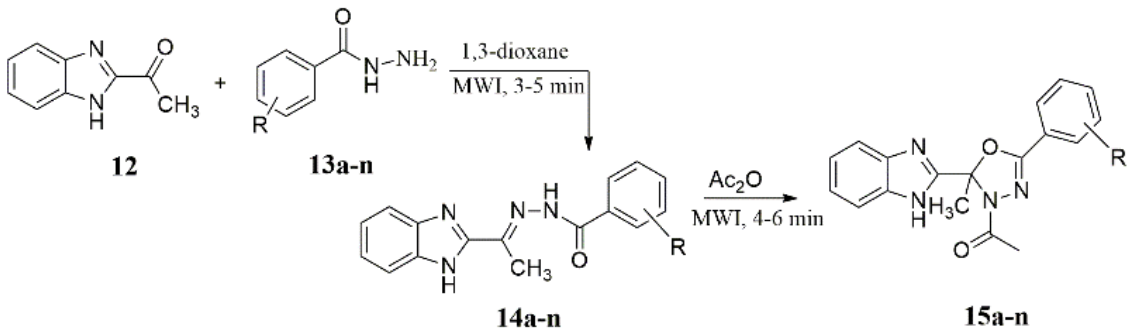
Among the different available protocols for synthesis of 2,5-disubstitutied-1,3-4-oxadiazol **6**; both the dehydration

cyclization of diacyl hydrazide and the oxidative cyclization of hydrazide hydrazone are the most investigated methods for generation of 2,5-disubstitutied-1,3-4-oxadiazole. The oxidative cyclization of hydrazide hydrazone has an advantage over the other protocols because it enables the syntheses of *N*-substituted-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazole **7**. The two steps synthesis of **7**, required in the first step the generation of hydrazide-hydrazone. This is normally synthesized from the condensation of acid hydrazide with aldehydes or ketones. A huge number of hydrazide-hydrazone including mono, *bis*, *tris* and *tetra* hydrazide-hydrazone moiety have been synthesized and were converted *into N*-substituted-2,5-disubstituted-2,3-dihydro-1,3,4- oxadiazole. The synthesis of new series is still on going to meet the demand for researchers for designing new compounds for various applications. For example, about synthesis of novel mono hydrazide-hydrazone and their conversion into *N*-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazolines; Paruch et al reported the synthesis of a series of new hydrazide-hydrazone derivatives of 3-methyl-4-nitrobenzohydrazide **8**. The target *N*-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazolines **11a-e** was obtained in their work *via* refluxing of the synthesized hydrazide-hydrazone **10a-e** in acetic anhydride for 3h. A part of Paruch *et al* work is represented in **Scheme 2**.



Scheme 2: Synthesis of *N*-acetyl 1,3,4-oxadiazole by Paruch *et al*

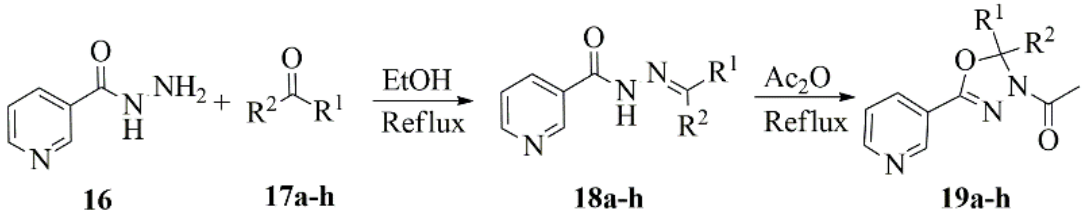
Paruch *et al* tested their novel compounds for potential antimicrobial activity and cytotoxicity and some of them showed good and promising results as reported (**Paruch *et al, 2020***). The synthesis of *N*-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazolines was also achieved through utilizing of microwave radiation that led to the target compounds in shorter time than the traditional refluxing. For example; Desai *et al* reported the synthesis of a series of benzimidazole bearing 1,3,4-oxadiazole derivatives (**Desai *et.al.,* 2014**). The aim of Desais work was to combine two active pharmacophores namely; benzimidazole and *N*-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazolines within a single compound. The work principle of Desai *et. al* based on the generation of new hydrazide-hydrazone derivatives **14a-n** from 1-(1H-benzo[d]imidazol-2-yl)ethanone **12** and different substituted acid hydrazides **13a-n** under microwave radiation (**Scheme 3**). The target hybrid compounds **15a-n** were obtained *via* the reaction of the prepared hydrazide-hydrazone **14a-n** with acetic anhydride under microwave radiation for 4-6 min (**Scheme 3**).



13a, 14a,15a: R= H
13b, 14b,15b: R= 3-Cl
13c, 14c,15c: R= 4Cl
13d, 14d,15d: R= 4-F
13e, 14e,15e: R= 3-Me
13f, 14f,15f: R= 4-Me
13g, 14g,15g: R= 3-NO_2
13h, 14h,15h: R= 4-NO_2
13i, 14i,15i: R= 3-OH
13j, 14j,15j: R= 4-OH
13k, 14k,15k: R= 3-OCH_3
13l, 14l,15l: R= 4-OCH_3
13m, 14m,15m: R= 3-Br
13n, 14n,15n: R= 4-Br

Scheme 3: Desai synthesis of benzimidazole bearing 1,3,4-oxadiazole derivatives.

The synthesis of hydrazide-hydrazone as precursor for the synthesis of *N*-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazolines from the condensation of acid hydrazide and carbonyl compound is not limited for utilizing aldehydes. Ketones was also used and both cyclic and acyclic ketones were used to generate the hydrazide-hydrazone derivatives, which in turn were successfully converted into *N*-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazolines. For example; Morjan *et.al* reported the synthesis of novel series of hydrazide hydrazone derivatives **18a-h** *via* the condensation of nicotinic acid hydrazide **16** with different cyclic and acyclic ketones **17a-h** (**Scheme 4**). The conversion of **18a-h** to *N*-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazolines was achieved upon refluxing **18a-h** in acetic anhydride (**Morjan et.al 2014**).

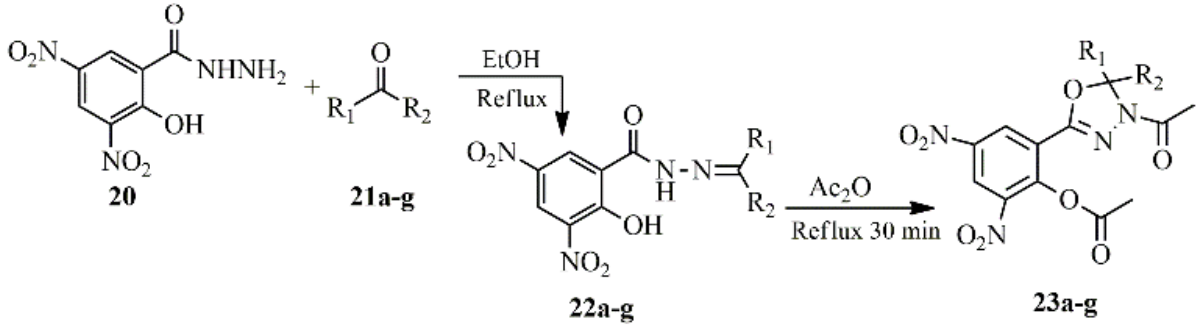


17a, 18a, 19a: $R_1 = CH_3$, $R_2 = CH_3$
17b, 18b, 19b: $R_1 = CH_3$, $R_2 = CF_3$
17c, 18c, 19c: $R_1 = CH_3$, R_2 = 4F-Ph
17d, 18d, 19d: $R_1 = CH_3$, $R_2 = C_6H_{11}$
17e, 18e, 19e: $R_1 + R_2 = C_4H_8$
17f, 18f, 19f: $R_3 + R_4 = C_5H_{10}$
17g, 18g, 19g: $R_3 + R_4 = C_6H_{12}$
17h, 18h, 19h: $R_3 + R_4 = C_7H_{14}$

Scheme 4: Synthesis of *N*-acetyl 1,3,4-oxadiazole by Morjan *et.al*

A recent example for the synthesis of *N*-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazolines was also reported by Morjan *et.al*. They reported the synthesis of a new series of *N*-acylhydrazone of 2-hydroxy-3,5-dinitrobenzohydrazide **22a-g** and their conversion into *N*-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazolines derivatives **23a-g** *via* refluxing of **22a-g** in acetic anhydride (**Scheme 5**).

They reported that the conversion of *N*-acylhydrazone **22a-g** into the *N*-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazolines **23a-g** was accompanied with concurrent acetylation of the phenolic OH of **22a-g**. In Morjan et.al. work; the formation of compound **23e** was undoubtedly confirmed by X-ray analysis (**Morjan *et.al.,* 2022**).

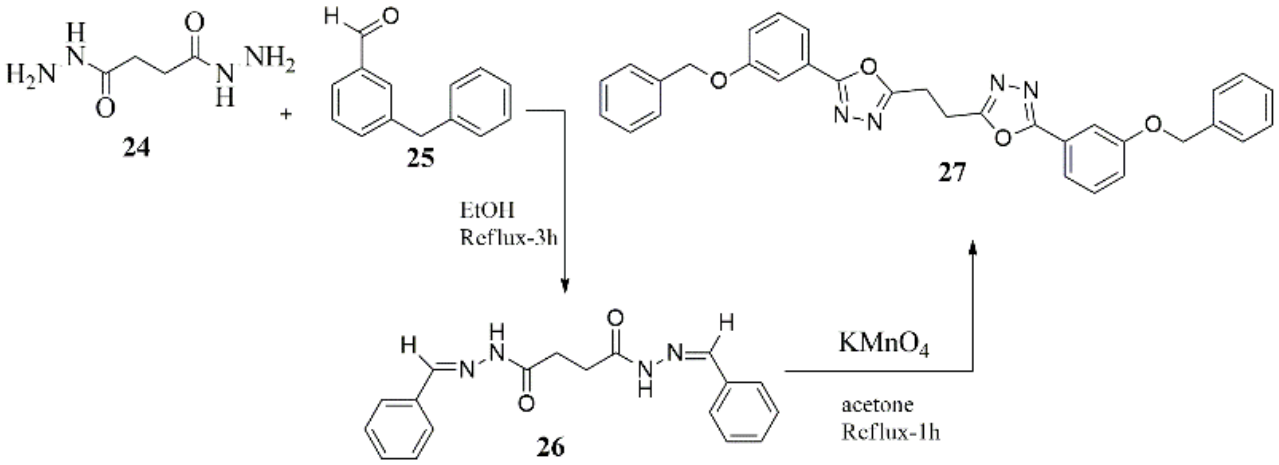


21a, 22a, 23a: $R_1 = H$, $R_2 = Ph$ **21d, 22d, 23d:** $R_1 = CH_3$, $R_2 = Ph$
21b, 22b, 23b: $R_1 = H$, $R_2 = 4\text{-ClPh}$ **21e, 22e, 23e:** $R_1 = R_2 = CH_3$
21c, 22c, 23c: $R_1 = H$, $R_2 = 4\text{-OMePh}$ **21f, 22f, 23f:** $R_1 + R_2 = C_5H_{10}$
21g, 22g, 23g: $R_1 + R_2 = C_7H_{14}$

Scheme 5: *N*-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazolines of 2-hydroxy-3,5-dinitrobenzohydrazide

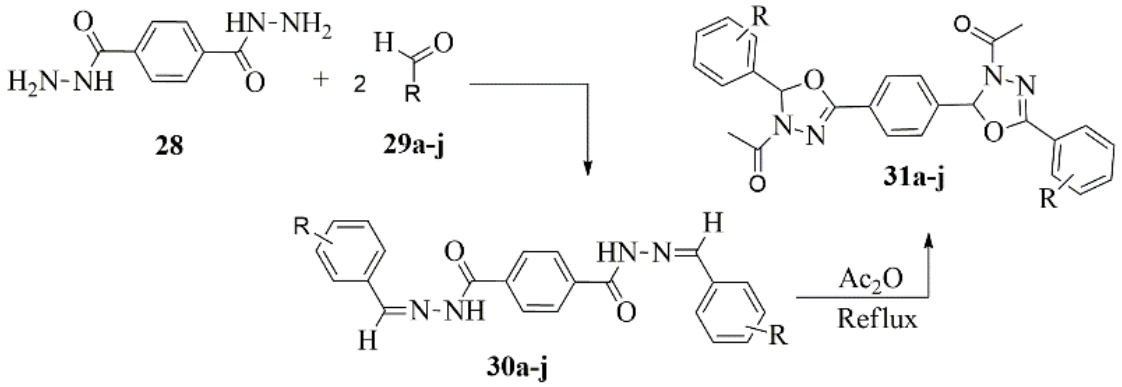
***Bis*-*N*-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazolines**

The synthesis of *N*-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazolines was extended to design and synthesize a new compound possesses two moieties of *N*-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazolines in a single molecule. In fact; there is no much reported data for this type of compounds. The major requirements for the generation of the *Bis*-type molecules that posing the *N*-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazolines are diacid as starting materials for the generation of the dihydrazide. The different types of di-carboxylic acid *i.e.* aliphatic aromatic and heterocyclic di-carboxylic acid and their di-hydrazide derivatives are reported in literature and many of them are commercially available. For examples; oxalic acid dihydrazide, succinic acid dihydrazide and adipic acid dihydrazide are commercially available. On the other hand; heterocyclic dihydrazide for example; pyridine-2,6-dicarbohydrazide and furan-3,4-dicarbohydrazide and aromatic diacidhydrazide for example; isophthalic acid and terephthalic acid hydrazides are also reported and some of them are commercially available. Although of the availability of different dicarboxylic acids; their conversion into diacid hydrazone still limited and the reported data showed some examples for such as this type of conversion. However; only limited examples are reported in literature for the conversion of di-hydrazone into either 1,3,4-oxadiazoles or *N*-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazolines derivatives. For example; Abo-Bakr reported **(Abo-Bakr, 2013**) the utilization of succinic acid dihydrazide for the synthesis of hydrazide-hydrazone **26** which then was used to synthesize a new heterocyclic compound containing *bis*-1,3,4-oxadiazole **27** *via* oxidation with potassium permanganate in refluxing acetone (**Scheme 6**).



Scheme 6: Synthesis of *Bis*-1,3,4-oxadiazole by Abo-Bakr

The aromatic diacids were also converted into di-hydrazide and successfully converted either to *Bis*-1,3,4-oxadiazole or *Bis-N*-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazolines. For example; Li *et.al* reported the synthesis of a series of *Bis-N*-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazolines starting from terephthalic dihydrazide **28** (**Li *et.al.,* 2007**). The condensation of **28** with aromatic aldehydes **29a-j** afforded the corresponding hydrazones **30a-j**. Cyclization of **30a-j** with acetic anhydride in refluxing for 4-5 h afforded bis-l,3,4-oxadiazoline derivatives **31a-j** (**Scheme 7**).

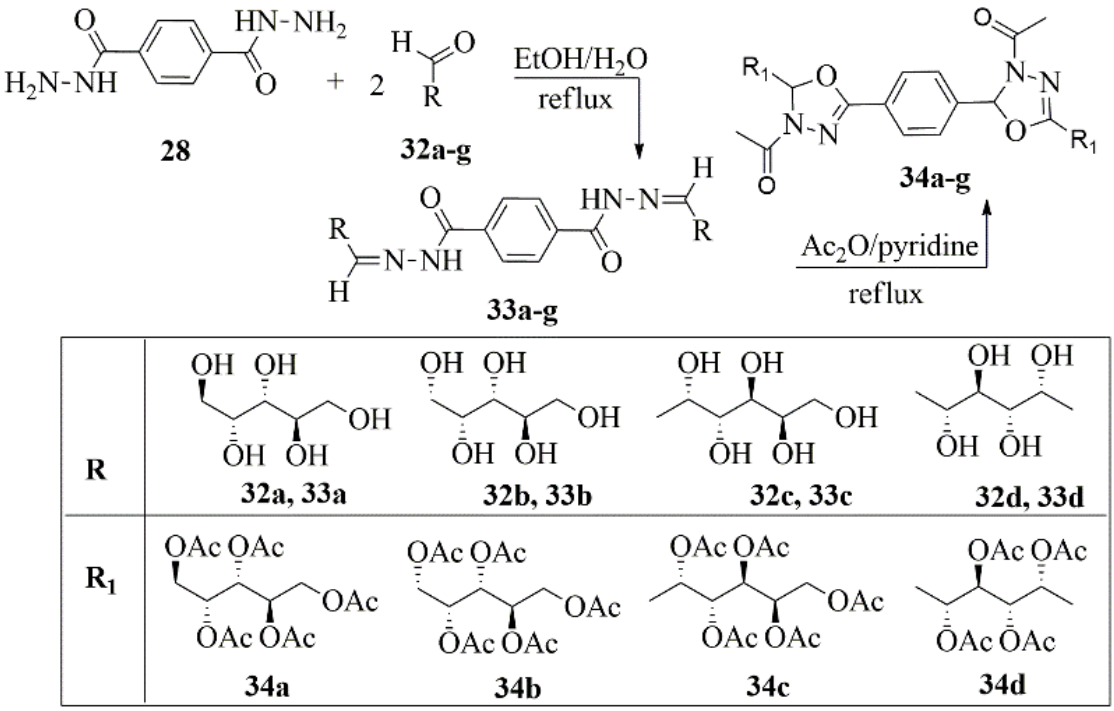


29a ,30a, 31a) R = 4-Cl-Ph
29b ,30b, 31b) R = 2-Cl-Ph
29c ,30c, 31c) R = 2,4-diClPh
29d ,30d, 31d) R = 4-CH_3Ph
29e ,30e, 31e) R = 4-OCH_3Ph
29f ,30f, 31f) R = 4-$N(CH_3)_2$Ph
29g ,30g, 31g) R = 4-OHPh
29h ,30h, 31h) R = 4-NO_2Ph
29i ,30i, 31i) R = 3-NO_2Ph
29j ,30j, 31j) R = Ph

Scheme 7: Synthesis of *Bis*-1,3,4-oxadiazoline by Li *et. al.*

In recent example, Abdelrehim *et. al* reported the synthesis of novel series of *N*-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazolines. Their work based on the synthesis of terephthalic dihydrazide **28** followed by condensation with two equivalent of monosaccharide aldoses (**Abdelrehim *et.al.,* 2022**). In despite to the mixture of products they obtained *i.e.,* bis(sugarhydrazone) or *bis*-glycosylhydrazide structure or the formation of tautomeric equilibrium,

the treatment of the products with acetic anhydride in refluxing pyridine led to the formation of the target derivatives of *N*-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazolines. The formation of *N*-acetyl-1,3,4-oxadiazoline ring was accompanied with concurrent acetylation of all hydroxyl groups of the sugar moieties. A part of Abdelrehim *et.* al. is represented in **Scheme 8**.



Scheme 8: Synthesis of *bis*-1,3,4-oxadiazoline by Abdelrehim *et.* al.

N-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazolines possessing a furan ring was also synthesized and reported by Shiji *et.al* (**Shiji *et.al.,* 2022**). Their work started by esterification of the commercially available 3,4-furandicarboxylic acid **35** to produce the dimethyl 3,4-furandicarboxylate **36**. The dihydrazide was obtained *via* reacting the di-ester **36** with hydrazine hydrate to produce the dihydrazide **37**. The bi-hydrazones **39** were obtained through condensation of different aromatic aldehydes and ketones **38a-c** with the dihydrazide **37**. The target *N*-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazolines **40a-c** was obtained through the cyclodehydration of the bi-hydrazones **39** using acetic anhydride (**Scheme 9**).

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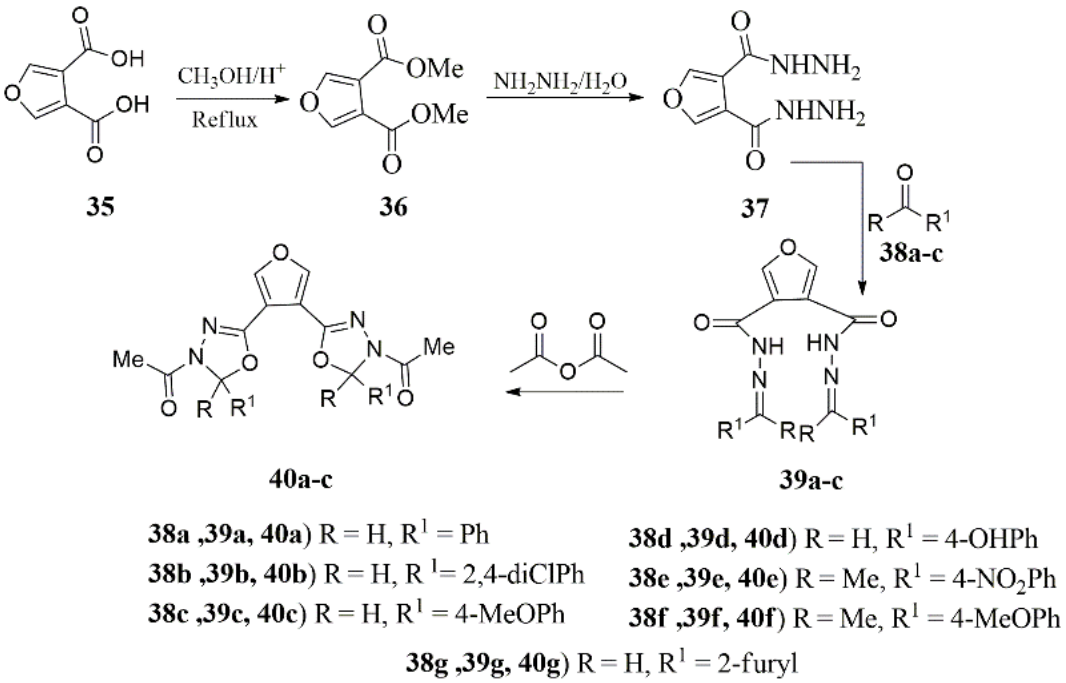
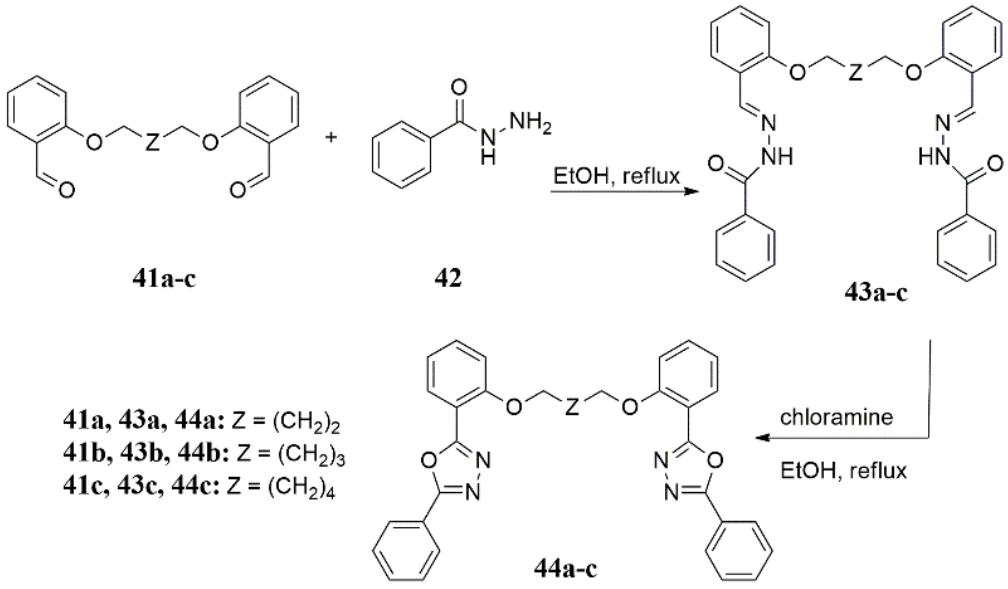


Scheme 9: Synthesis of *bis*-1,3,4-oxadiazoline by Shiji *et.al.*

A new series of *bis*-1,3,4-oxadiazoles possess an aliphatic spacer was recently reported by Sanad *et.al*. They reported the synthesis, antibacterial activity and in silico study of novel *bis*(2,5-disubstituted-1,3,4-oxadiazoles) linked to aliphatic cores through and ether bonds. Some of the new products displayed promising antibacterial activity against the *Staphylococcus aureus* and *Pseudomonas aeruginosa* strains with MIC values range 3.5-55.8 µM. Part of Sanad *et.al*. is shown in (**Scheme 10**).



Scheme 10: Synthesis of *bis*-1,3,4-oxadiazole by Sanad *et.al*.

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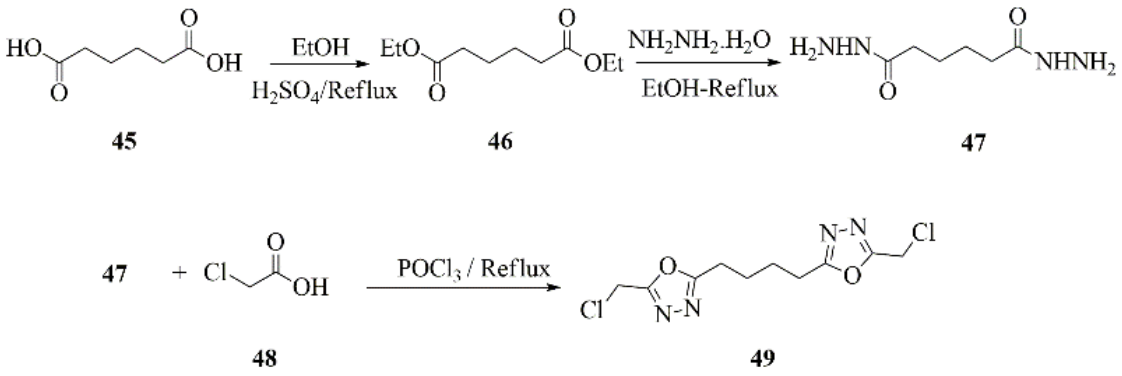
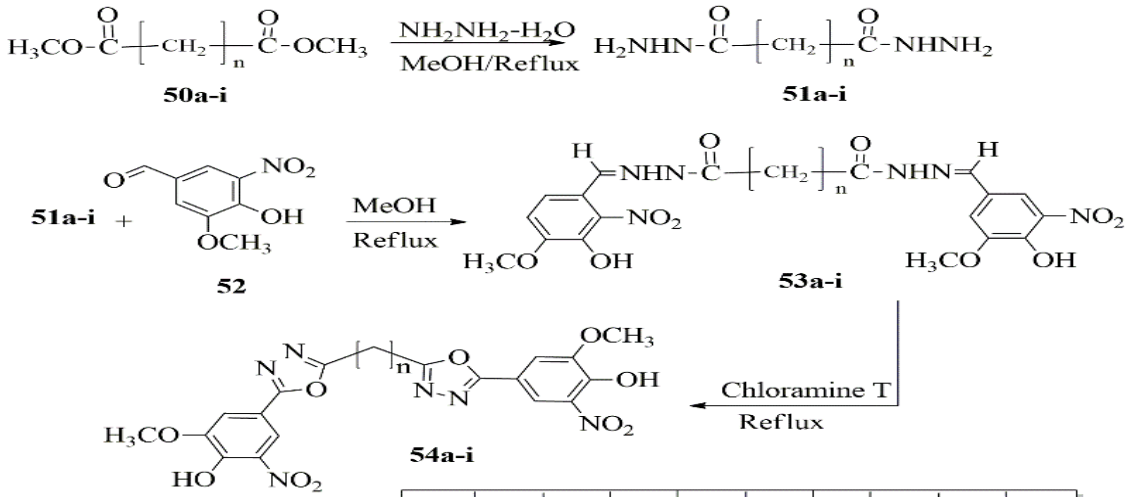
Bis-1,3,4-oxadiazoles possessing an aliphatic spacer was also reported by Rohand *et.al.* Their work started from the esterification of 1,6-hexandioic acid **45.** The obtained di-ester **46** was converted into the di acid hydrazide **47** *via* reaction of the di-ester **46** with hydrazine hydrate. The 1,3,4-oxadiazole was obtained through ring closure reaction upon the treatment of the diacid hydrazide **47** with chloroacetic acid **48** in phosphorus oxychlorid (**Scheme 11**). The chloroethyl substituent group at position 2 of the oxadiazole ring **49** is an active group and further derivatives can be prepared for example via reaction with different amino groups.



Scheme 11: Synthesis of *bis*-1,3,4-oxadiazole by Rohand *et.al*

Another series of bis-1,3,4-oxadiazole possess an aliphatic spacer was reported by Malghe *et.al*. Their work based in the preparation of a series of aliphatic dihydrazide **51a-l** starting from different carbon chain diesters **50a-i** ranging from zero carbon spacer *i.e.* dimethyl oxalate **50a** to dimethyl decanedioate *i.e.* 8 carbon spacer **50i**. The condensation of the different dihydrazide **51a-i** with 4-hydroxy-3-methoxy-5-nitrobenzaldehyde **52** in refluxing methanol afforded the target *bis*-hydrazide-hydrazone derivatives **53a-i**. The *bis*-1,3,4-oxadiazoles derivatives **54a-i** were obtained upon the treatment of **53a-i** with Chloramine-T in refluxing methanol (**Scheme 12**).



	a	b	c	d	e	f	g	h	i
n	0	1	2	3	4	5	6	7	8

Scheme 12: Synthesis of *bis*-1,3,4-oxadiazole by Malghe *et.al*.

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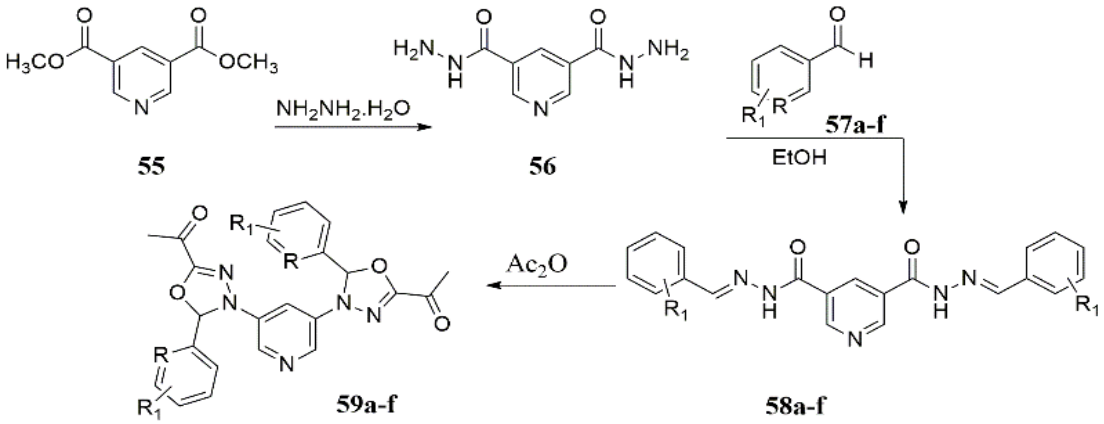
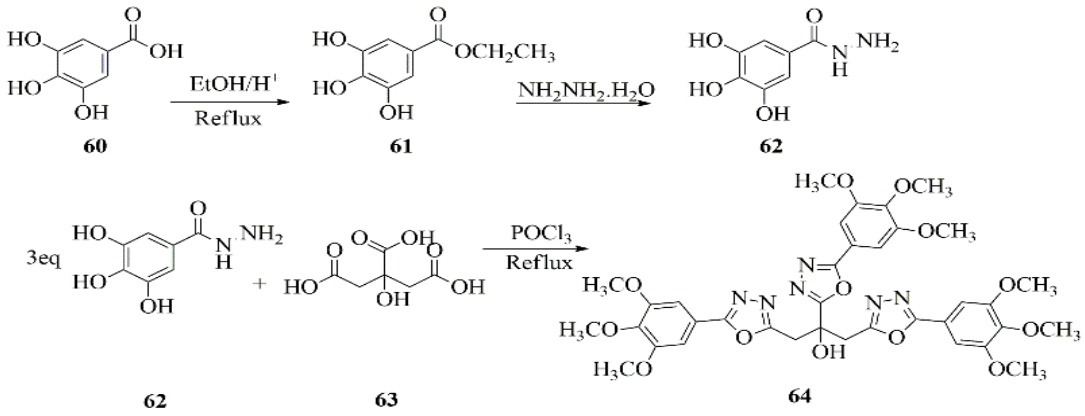
The synthesis of *bis*-1,3,4-oxadiazoline possess a pyridine core was reported by Xiaolin *et.al* (**Xiaolin *et.al.*, 2008**). In their work; the Hydrazinolysis of dimethyl pyridine-3,5-dicarboxylate **55** produced the 3,5-pyridinedicarboxylic acid 3,5-dihydrazide **56**. The Bis-hydrazide-hydrazone **57a-f** were obtained *via* the condensation of the bis-dihydrazide **56** with aldehydes or ketones **57a-f** (**Scheme 13**).



Scheme 13: *Bis*-1,3,4-oxadiazoline possess a pyridine core by Xiaolin *et.al*.

Tris-*N*-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazolines.

A search for the *tris*-*N*-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazolines using Sci-finder data base (Scifinder) gave no hits by both subject search and structure search. The serach then directed to find related structures and the serch was done for *tris* 2,5-disubstituted-1,3,4-oxadiazole using the same data base. The obtained search results showed very limited reported examples. For example; Rabie *et.al* reported the synthesis and antioxidant polyphenolic 1,3,4-oxadiazole compounds properties as promising anti-COVID-19 agents (**Rabie *et.al*. 2021**). In order to achieve their target compound **64**; they started from the commercially available 3,4,5-trihydroxybenzoic acid (gallic acid) **60** which was converted into the ethyl gallate **61** upon refluxing in ethanol. The hydrazide of gallic acid **62** was obtained through the refluxing of **61** with excess hydrazine hydrate $NH_2NH_2.H_2O$. The target compound **64** was obtained through refluxing of **62** and **63** with excess $POCl_3$ as cyclodehydration agent (**Scheme 14**).



Scheme 14: Synthesis of *tris*-1,3,4-oxadiazole by Rabie *et.al*.

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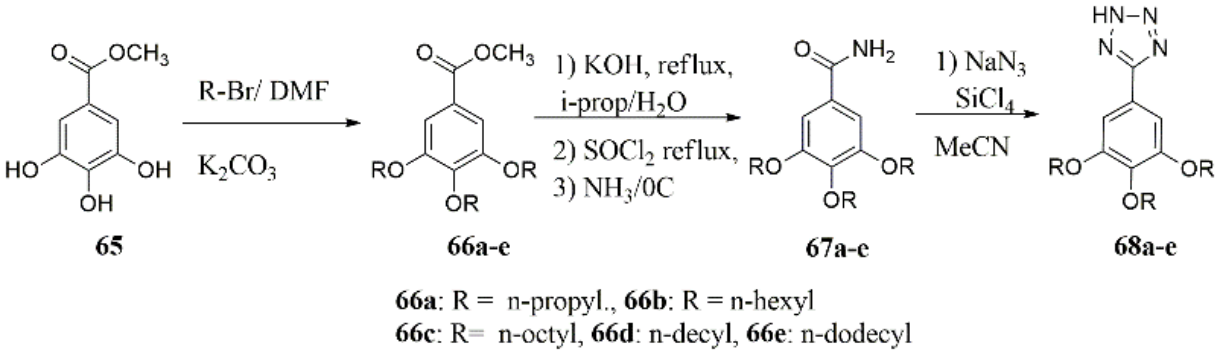
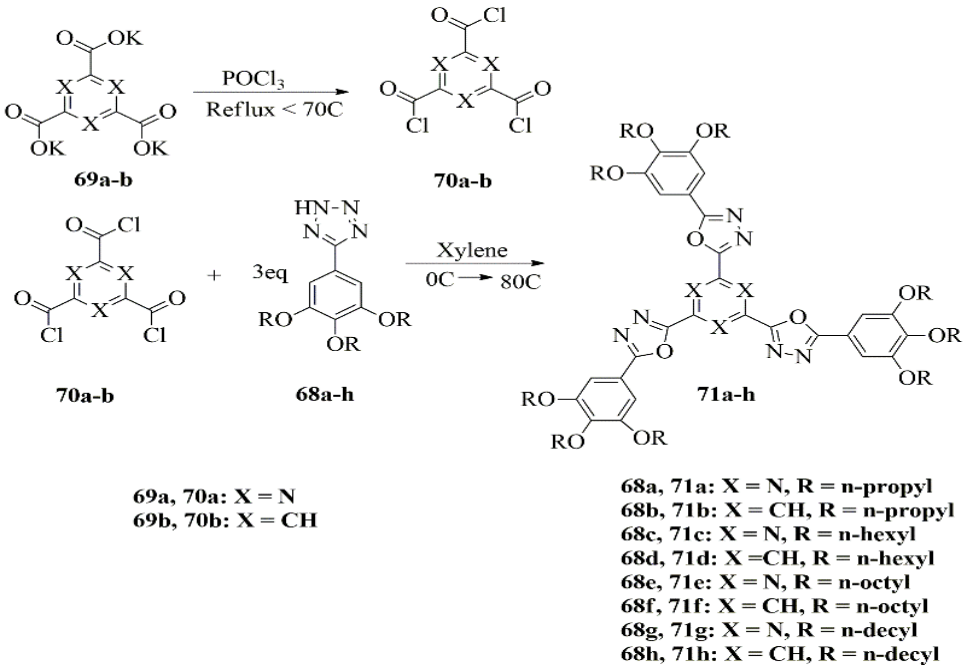
Another example about synthesis of new tris-oxadiazole was reported by Detert *et.al* (**Detert *et.al.* 2019**). Following the convergent synthesis strategy *i.e*. two independent stages; they synthesized a series of tris-oxadiazole utilizing Huisgen reaction of tetrazoles. In a part of Deter *et.al* work; and in order to synthesize the required tetrazoles suitable to be attached to their tris-core; they started from methyl gallate **65**. The first stage target, tetrazoles **66a-e** were achieved through multistep synthesis that involved alkylation, saponification, chlorination/ammonolysis **67a-e** followed by dehydration/ azide transfer with triazidochlorosilane **67a-e**. A part of Detert *et.al* that describes the synthesis of tetrazoles is represented in **Scheme 15**.



Scheme 15: Synthesis of tetrazoles by Deter *et.al*

The target tris-oxadiazoles **71a-h** in Deter at.al. work was achieved through direct reaction between 1 equivalent of 1,3,5-benzenetricarbonyl chloride **70a-b** and the tetrazoles **68a-h** (**Scheme 16**).



Scheme 16: Synthesis of tris-oxadiazoles by Deter *et.al*

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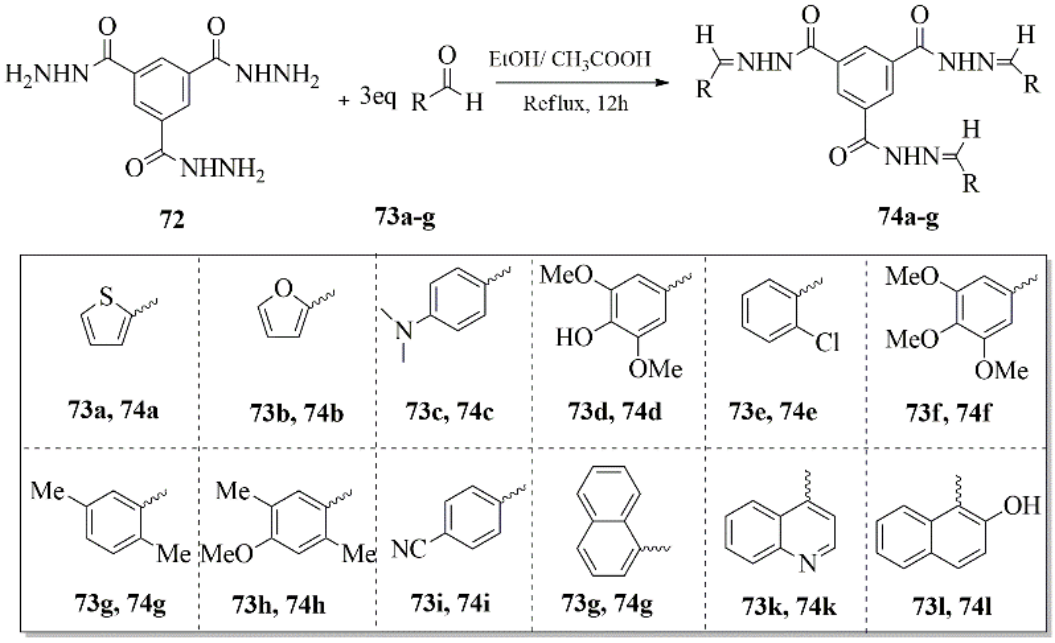
However; and as the results search for the synthesis of *bis* 1,3,4-oxadiazoles was limited, I thought to direct the search their precursors *i.e. tris*-acids hydrazides and their hydrazide-hydrazone derivatives. The literature survey revealed that, different *tris*-hydrazide-hydrazone derivatives are reported, but no indications in literatures about any attempts for their conversion into neither oxadiazole nor oxadiazoline derivatives. For example; Mhaidat *et.al*. recently reported the syntheses and characterization of a new series of hydrazide-hydrazone derivatives **74a-g** through the condensation of tri-mesic-tri-hydrazide **72** with different aromatic aldehydes **73a-g**. The derivatives reported by Mhaidat *et.al*. are potential starting materials for the synthesis of tris-1,3,4-oxadiazoles and/or N-substituted tris-1,3,4-oxadiazolines.



Scheme 17: Synthesis of *tris*-hydrazide-hydrazone derivatives by Mhaidat *et.al*.

In the synthesis of *N*-substituted 1,3,4-oxadiazole, the N-acetyl group is the most common and used substituent. However; it is worthiest to mention here that there are some other reagents that can be used to generate an N substituting 1,3,4-oxadiazoline derivatives. For example; Ferwanah reported the reaction of acetone and cycloalkanone hydrazones with phenylisocyanate produced the 1,3,4-oxadiazolines. In the case of cycloalkanone; the structure of the obtained N-substituted 1,3,4-oxadiazoline was confirmed by x-ray (**Ferwanah, 2005**). Other examples were reported by Awadallah as he reported the reaction of different hydrazone with phenylisocyanate produced the N-substituted 1,3,4-oxadiazoline (**Awadallah, 2006**). Awadallah showed that the 1,3,4-oxadiazoles is not always the products. The structure of the products is affected by the natural of the substituent groups that may produce the acyclic adducts rather than the N-substituted 1,3,4-oxadiazoles moiety.

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