Review
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1,3,4-OXADIAZOLES: SYNTHESIS STRATEGIES AND APPLICATIONS

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Abstract. *1,3,4-oxadiazoles are an extensive class of heterocyclic compounds. They have found applications in various fields of science and technology: pharmacy, polymers, fluorophores, optoelectronics, etc. Nowadays, there are many scientific papers on the synthesis of 1,3.4-oxadiazoles. However, the information in terms of 1,3.4-oxadiazoles is fragmentary and nonspecific. This review presents various approaches to the synthesis of 1,3,4-oxadiazoles described in the literature over the last 5-15 years, as well as examples of practical applications of this class of compounds.*

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Introduction

Oxadiazoles are present in nature as four isomers (Fig. 1); among them 1,3,4-oxadiazole (**d**) is the most investigated due to the availability of synthesis methods and wide application.

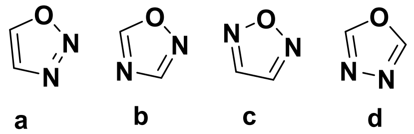
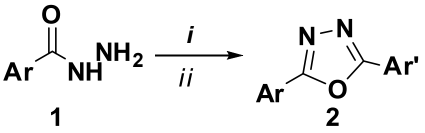


Fig. 1. Natural isomers: **a** - 1,2,3-oxadiazole, **b** - 1,2,4-oxadiazole, **c** - 1,2,5-oxadiazole, **d** - 1,3,4-oxadiazole.

The chemical composition of oxadiazoles, in particular 1,3,4-oxadiazoles, is characterised by their unique heterocyclic structure. It provides them with important biological and physicochemical properties. These compounds attract the attention of researchers due to the variety of methods for their synthesis and the prospects for their application in medical and polymer chemistry. This review presents the strategies for the synthesis of the 1,3,4-oxadiazole moiety as well as applications of these heterocycles.

Main body

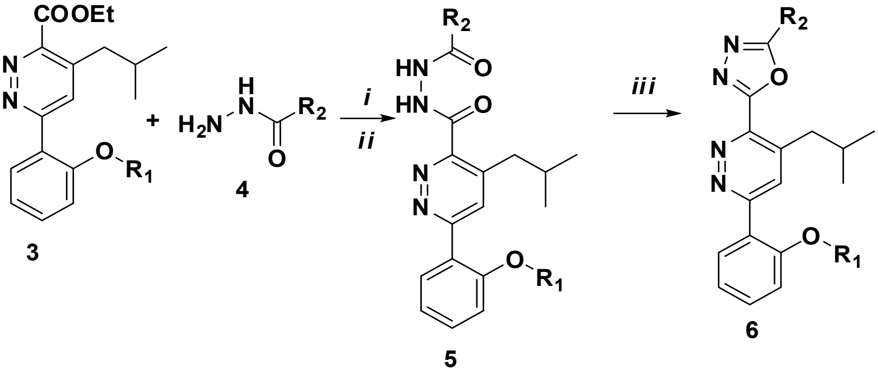
Cyclisation by dehydrating agents. The main method for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles is the interaction of carboxylic acid hydrazides with chlorohydrides with further cyclisation in rather aggressive reagents, for example, by the traditional method – phosphorus chlorooxide [1-4]. A paper [5] describes a method in which intermediates – carbohydrazides – were previously obtained by the interaction of acyl- or arylhydrazides with carboxylic acids in the presence of HATU (*O*-(7-azabenzotriazol-1-yl)-*N*, *N*',*N*'-tetramethyluronium hexafluorophosphate) and DCC (*N,N'*-dicyclohexylcarbodi-imide) followed by cyclisation in the presence of phosphorus chlorooxide (Scheme 1).



i: Ar'COCl, Py or Ar'COOH, HATU, DCC; *ii*: $POCl_3$

Scheme 1

Carboxylic acid esters can also be used as initial substrates. Rebeck et al. [6] consider the use of ethyl ether **3** as a precursor reagent. It is hydrolysed under the action of LiOH and further combined with *N*-acylhydrazides **4** under the action of EDCI/HOBt (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide / 1-hydroxybenzotriazole) to form intermediates **5** in good yield. Dehydration of *N,N'*-diacylhydrazides **5** using POCl **3** gives compound **6** with an α-helical mimetic oxadiazole-pyridazine-phenyl framework with a yield of 45-53% (Scheme 2).

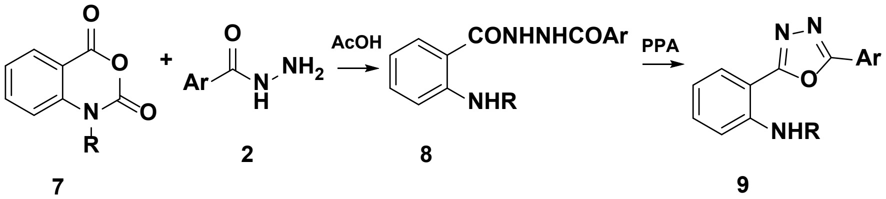


R_1, R_2 = **a**: Ph, *i*-Pr; **b**: Ph, Bn; **c**: *i*-Pr, *i*-Pr; **d**: *i*-Pr, Bn

i: LiOH, THF/H_2O; *ii*: EDCl, HOBt, DCM; *iii*: $POCl_3$, MeCN, reflux, 12 h

Scheme 2

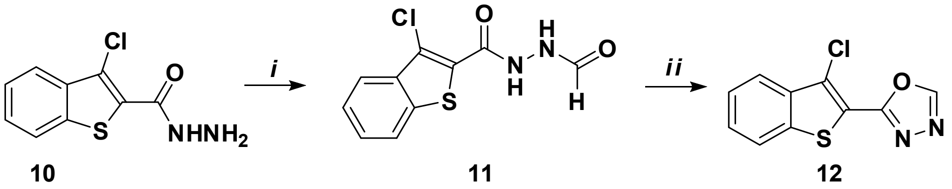
Another method for the obtaining of 2,5-disubstituted-1,3,4-oxadiazoles is the cyclodehydration reaction by the action of sulfuric acid (H_2SO_4), polyphosphoric acid (PPA), and trifluoroacetic acid on carboxylic acid hydrazides [7-9]. Hence, [10] describes the reaction of isatoic anhydrides **7** with the corresponding hydrazides in acetic acid forming 1-(2-R-aminobenzoyl)-2-aroylhydrazines **8**. The latter undergo cyclisation in the presence of PFC to form 2,5-diaryl-substituted 1,3,4-oxadiazoles **9** with a yield of 35-42% (Scheme 3).



R = Me, $PhCH_2$, Et; Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$

Scheme 3

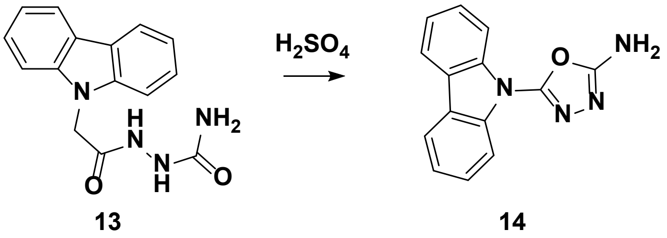
Examples of the use of dehydrating agents are described in [11, 12]. Unsubstituted 1,3,4-oxadiazoles are obtained in two stages: the first stage is boiling of carbohydrocarbazide **10** in excess formic acid to obtain 3-chloro-2-(*N*-formylhydrazide)benzo[*b*]thiophene **11**. At the second stage it is exposed to intramolecular cyclisation under the impact of phosphorus (V) oxide in xylene (Scheme 4) [12]. The product yield was 98%.



i: HCOOH, reflux; *ii*: P_2O_5

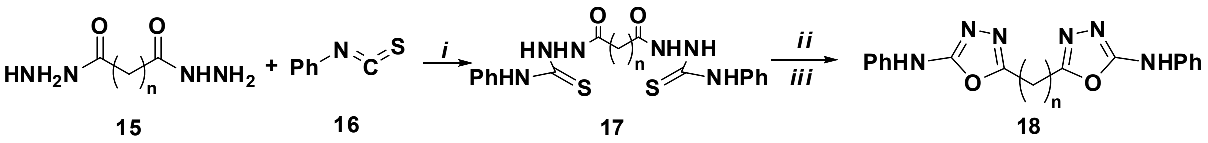
Scheme 4

The synthesis of 2-amino-5-(*N*-carbazylmethyl)-1,3,4-oxadiazole **14** is based on the use of sulfuric acid as a dehydrating agent at the room temperature (Scheme 5). This leads to a high product yield of 82% [13].



Scheme 5

Another way to create an oxadiazole moiety is by cyclodehydration of semicarbazides. An example is the oxidative cyclisation of oxalyldiphenylthiosemicarbazides **17** in the presence of an alkaline I_2/KI solution [14, 15] (Scheme 6).



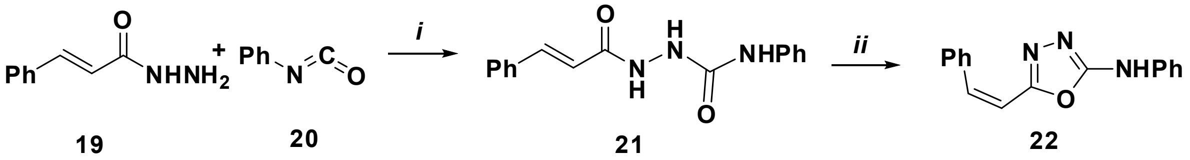
n = 0, 1, 2, 3, 4

i: EtOH; *ii*: EtOH, NaOH/KI; *iii*: I_2

Scheme 6

Similar works were conducted by scientific groups [16, 17]. They showed the possibility of oxidative cyclisation of alkyl- and/or arylthiosemicarbazides and thiosemicarbazide in alkaline iodine solution to obtain 1,3,4-oxadiazoles in 43-75% yield for alkylthiosemicarbazides and 53-64% for arylthiosemicarbazides.

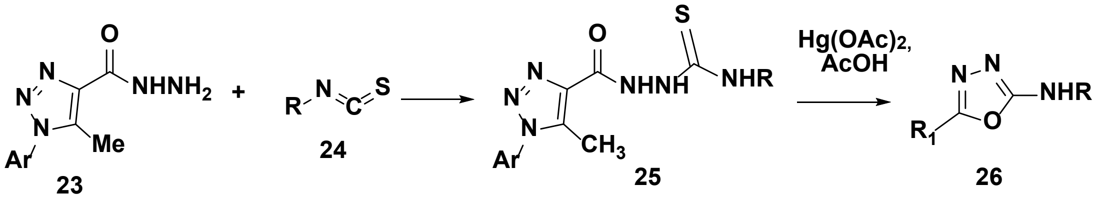
Aziz et al. [18] described a strategy for the synthesis of 1,3,4-oxadiazole derivatives containing a multiple bond. 1-Cinnamoyl-4-phenylsemicarbazide **21** was synthesised by reaction of phenylisocyanate **20** with cinnamic acid hydrazide **19** followed by acid-catalysed intramolecular cyclisation with sulphuric acid. This led to the synthesis of 2-cinnamoyl-5-aminophenyl 1,3,4-oxadisole **22** with a yield of 78% (Scheme 7).



i: $CHCl_3$, reflux, 1h; *ii*: H_2SO_4, stirring

Scheme 7

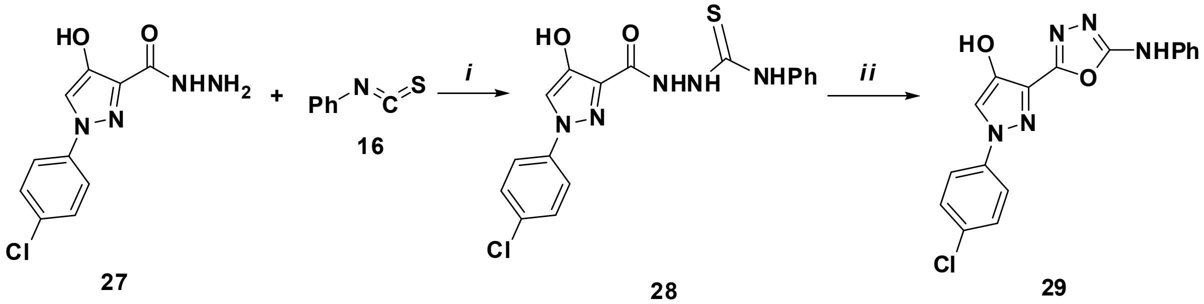
Ring-locking of thiosemicarbazide **25** can be performed in the presence of mercury acetate ($Hg(OAc)_2$) in acetic acid with a yield of 41-50% of the target products [19]. As shown in [20], the use of glacial acetic acid on boiling increases the yield of 1,3,4-oxadiazoles to 83-94% (Scheme 8).



Ar = 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$

Scheme 8

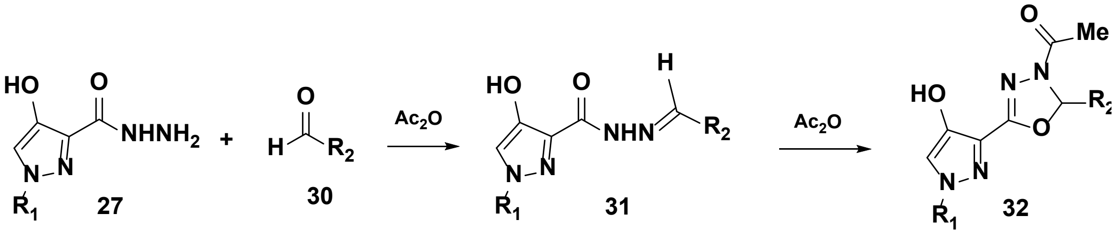
In [21], a cyclisation method considers the use of mercuric oxide as a dehydrating compound. Hence, thiosemicarbazides **28** were obtained by nucleophilic addition reaction of hydrazide 1-(4-chlorophenyl)-4-hydroxy-1*H*-pyrazole-3-carboxylic acid **27** with phenylisothiocyanate **16**. It was further cyclised to 1,3,4-oxadiazole **29** by boiling it (**28**) with mercuric oxide in absolute ethanol. However, this method has a disadvantage – low yield of the product (31%) (Scheme 9).



i: $CHCl_3$, reflux, 1h; *ii*: HgO, EtOH

Scheme 9

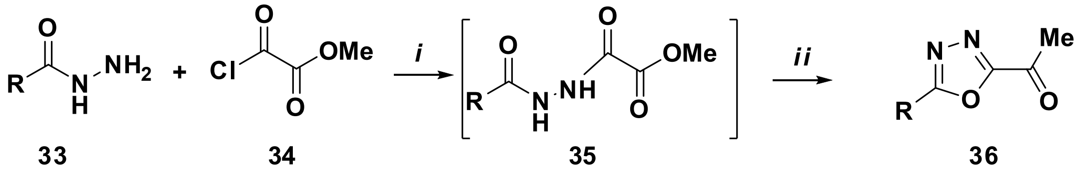
Another example of the use of dehydrating agents is the method of interaction of aryl-substituted hydrazides with aldehydes of various structures in acetic anhydride or acetic anhydride/acetic acid medium (Scheme 10) [21, 22].



R_1 = 4-ClC_6H_4, R_2 = 2,4-$F_2C_6H_3$

Scheme 10

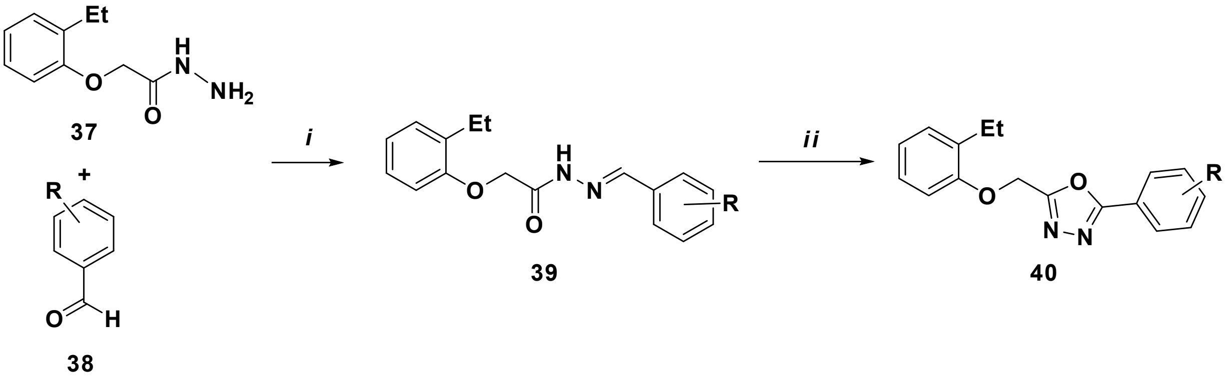
p-Toluene sulfochloride can be used in the cyclisation reaction of diacylhydrazide to 1,3,4-oxadiazole [23-28]. Hydrazide **33** participates in the nucleophilic substitution reaction with methyloxalyl chloride **34** in the presence of triethylamine. It forms intermediate diacylhydrazide **35**, which is cyclised by the action of *p*-toluenesulfonyl chloride (TsCl) to 1,3,4-oxadiazole **36** with a yield of 75-94% (Scheme 11).



i, ii: TsCl, TEA

Scheme 11

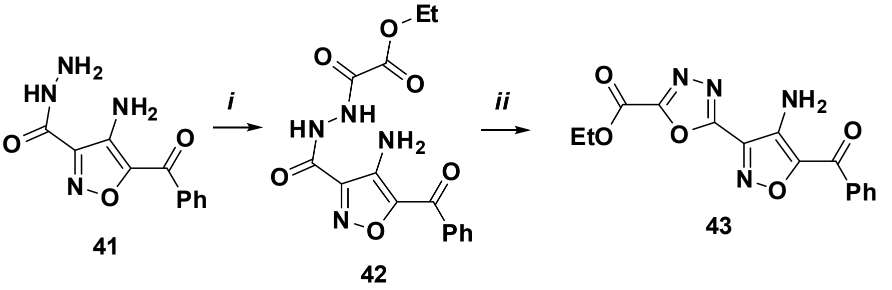
In [29], the authors showed a synthesis method based on the formation of Schiff base **39** by the interaction of aromatic aldehydes **38** with hydrazides of carboxylic acids **37**. They were further cyclised into 1,3,4-oxadiazoles **40** in the presence of iodobenzene diacetate with a yield of 70-75% (Scheme 12).



i: EtOH; *ii*: $PhI(OAc)_2$

Scheme 12

Scheme 13 shows the possibility of using thionyl chloride as a cyclising agent [30]: compound **41** was treated with ethyloxalyl chloride in anhydrous pyridine to obtain compound **42**. It was cyclised in acidic medium with thionyl chloride to ethyl-5-(4-amino-5-benzoylisoxazol-3-yl)-1,3,4-oxadiazol-2-carboxylate **43** (68% yield).

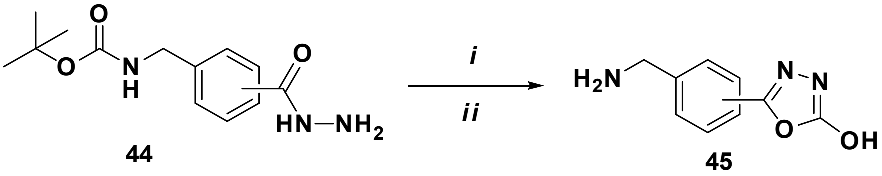


i: ClCOCOOEt; *ii*: $SOCl_2$

Scheme 13

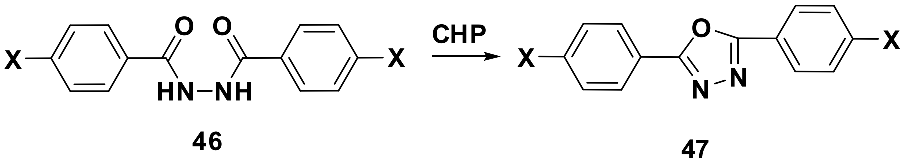
Cyclisation by other methods. A number of different methods of cyclisation without the use of dehydration reagents are described. These methods have the following advantages: less toxic reagents, simpler reaction conditions, higher product yields, ease of product isolation, etc.

For example, Desforges et al. [31] proposed a method for the cyclisation of hydrazides **44** to 1,3,4-oxadiazoles **45** in DMFA/Et$_3$N at 0 °C with the introduction of *N*,*N*'-carbonyldiimidazole (CDI) and subsequent removal of *Boc*-protection. This method provides the target products with yields of 88-91% (Scheme 14).



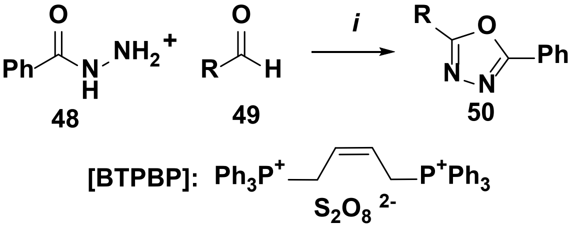
a: 2-CONHNH$_2$, b: 3-CONHNH$_2$, c:4- CONHNH$_2$
i: CDI, Et$_3$N, DMF, rt, 16h; *ii*: HCl
Scheme 14

An alternative method for the synthesis of 2,5-bis(aryl)-1,3,4-oxadiazoles **47** is the thermal cyclodehydration of 1,4-bis(4-aryl)-hydrazide **46** in *N*-cyclohexyl-2-pyrrolidone (CHP) with a yield of 70-88% (Scheme 15) [32].



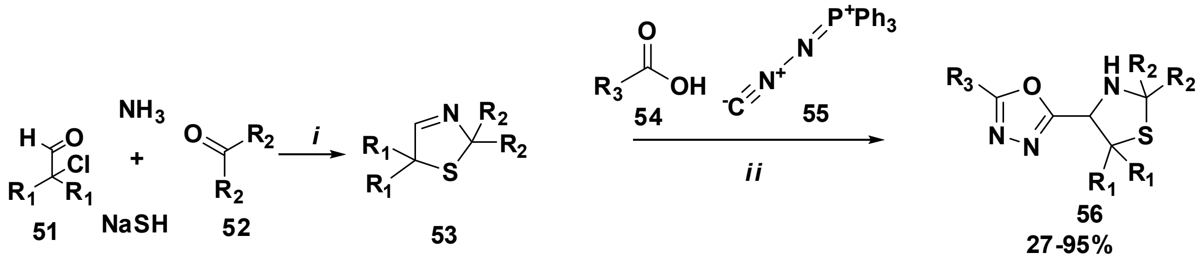
Scheme 15

An efficient, one-step synthesis of 2,5-disubstituted-1,3,4-oxadiazoles with high yield is known [32]. Target products are obtained directly from acylhydrazide and aromatic aldehydes using 1,4-bis(triphenylphosphonium)-2-butenoperoxodisulfate (BTPBP) as an oxidant in non-aqueous and aprotonic solvents (Scheme 16).



R = Ph, 4-ClC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 4-IC$_6$H$_4$,
4-BrC$_6$H$_4$, 3-NO$_2$C$_6$H$_4$, 3-ClC$_6$H$_4$, 2,4-Cl$_2$C$_6$H$_3$
i: [BTPBP], CHCl$_3$, reflux
Scheme 16

In 2014, Martens et al. [34] developed the synthesis of thiazolidin-4-yl-1,3,4-oxadiazoles **56**. It involves intramolecular aza-Wittig-cyclisation under mild conditions; the yield is from satisfactory to good (Scheme 17).

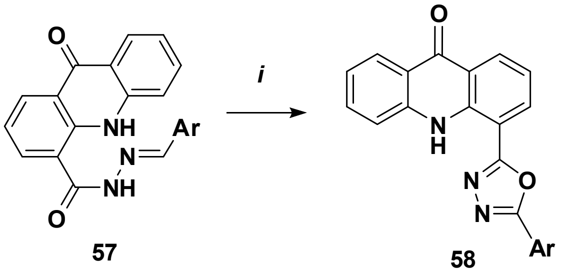


i: $CHCl_3$, 5 °C to rt; *ii*: THF, rt, 15h
Scheme 17

This synthetic method involves the interaction of Azinger products **53**, carboxylic acids **54** and (isocyanoimino)triphenylphosphorane **55** (the synthesis of this reagent is described in [35]).

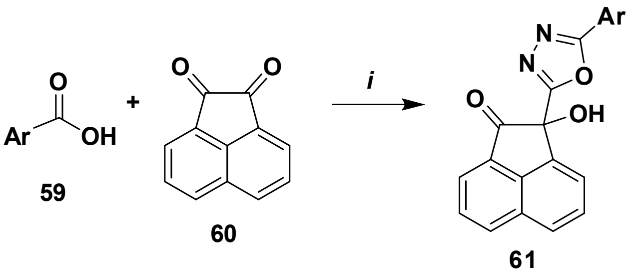
This reaction is distinguished by the occurrence of intramolecular aza-Wittig-cyclisation instead of Mumm rearrangement, which is typical for acylimidates.

One of the ways to form 1,3,4-oxadiazole cycle is the oxidative cyclisation reaction of arylidene hydrazides under the impact of such oxidants as Br_2, HgO, $KMnO_4$ [36]. The interaction of arylidene hydrazide **57** with bromine in acetic acid medium in the presence of sodium acetate gave compounds **58** in 60% yield (Scheme 18).



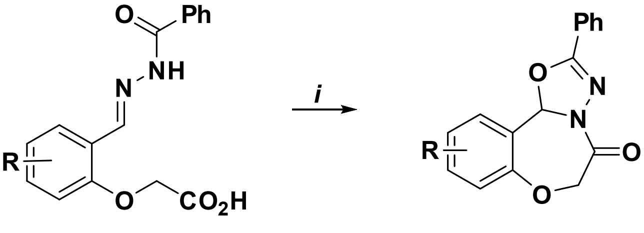
i: AcONa, Br_2, AcOH, 100 °C, 24h
Scheme 18

Another method described for the preparation of 1,3,4-oxadiazoles is the use of ultrasonic irradiation of aromatic carboxylic acids **59** and acenaphthenquinone **60** [37]. The reaction was performed in the presence of (*N*-isocyanimino)triphenylphosphorane and acetonitrile as solvent. The yield was 67-85% (Scheme 19). Comparison of procedures with and without ultrasound showed a significant reduction in time: 15 min with ultrasound compared to 24 h without ultrasound. The compounds **61** obtained are used as drugs for the treatment of tropical parasitic diseases such as trypanosomiasis and leishmaniasis.



i: (*N*-isocyanimino)triphenylphosphorane, CH_3CN, ultrasound, 25 °C, 15 min
Scheme 19

Hydrazonecarboxylic acids **62** are subjected to intramolecular cyclisation in the presence of pyvaloyl chloride, *i*-Pr_2NEt and catalytic amounts of DABCO to form a series of substituted condensed tricyclic 2,3-dihydro-1,3,4-oxadiazoles **63** with high yields (Scheme 20) [38].

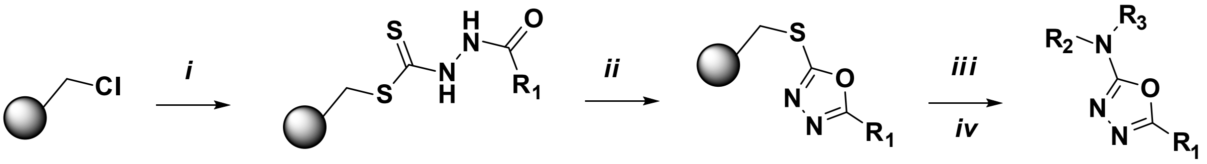


62 **63**

R = H; 4-Me; 4-MeO; 4-Cl; 2-Br; 3-Br
i: *i*-Pr_2NEt; DABCO; *t*-BuCOCl
Scheme 20

Synthesis of 1,3,4-oxadiazoles on a solid polymer carrier. Solid-phase synthesis is a challenging approach to produce a variety of organic compounds on insoluble carriers. Compounds synthesised on solid carriers can be released without a trace of the linker used to bind the intermediates during the synthesis. A large number of synthetic strategies have been developed for the obtaining of products by solid-phase on a carrier. The advantages of solid-state synthesis are as follows: rather easy isolation, absence of the solvents, possibility of parallel syntheses, no solubility issues of intermediate and final products [39, 40]. Today, solid-phase synthesis methods are widely used in organic synthesis, especially in the field of drug discovery, where time-efficient syntheses of compound libraries for high-throughput screening as well as specialised libraries for optimising the lead compound are essential [41-43].

An example of solid-phase synthesis is the obtaining of 1,3,4-oxadiazoles on a dithiocarbazate linker [44]. This allows obtaining the target products with high yields. First, a solid carrier (Merrifield resin) **63** is obtained. It is modified into acyldithiocarbazates **64** by reaction with various hydrazides and carbon disulfide (Scheme 21). These intermediates undergo dehydration cyclisation to give carrier-bound 1,3,4-oxadiazoles **65**. Next, a solid carrier removal is conducted to form the product **66**. This method provides the target heterocycles in high yield. The exception is being the use of dibenzylamine, which is sterically hindered and less nucleophilic. This synthetic approach allows ones to convert the intermediate **64** into different heterocycles, depending on the reagents [45-49].

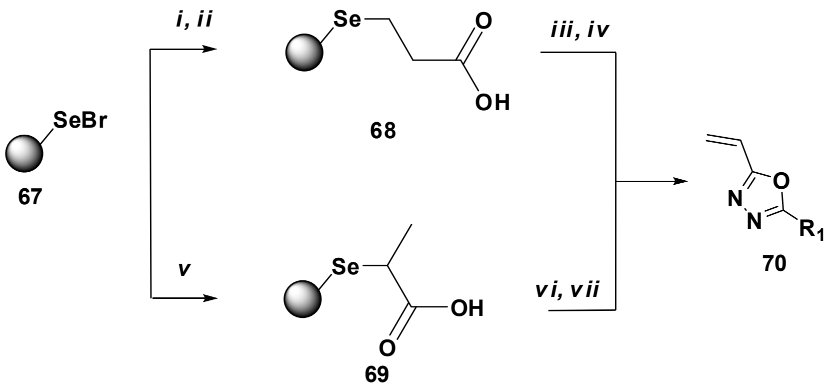


63 **64** **65** **66**

R_1 = Ph, 3-FC_6H_4, 4-$F_3CC_6H_4$; 4-tret-BuC_6H_4; R_2R_3N = piperidinio, morpholino, cyclohexylamino
i: $R_1CONHNH_2$, CS_2, NaH, NMP, rt, 12h; *ii*: TsCl, TEA, DCE, 60 °C, 24 h; *iii*: *m*-CPBA, 1 N aq NaOH, 1,4-dioxane, rt, 6 h; *iv*: R_2R_3NH, 1,4-dioxane, 100 °C, 24 h
Scheme 21

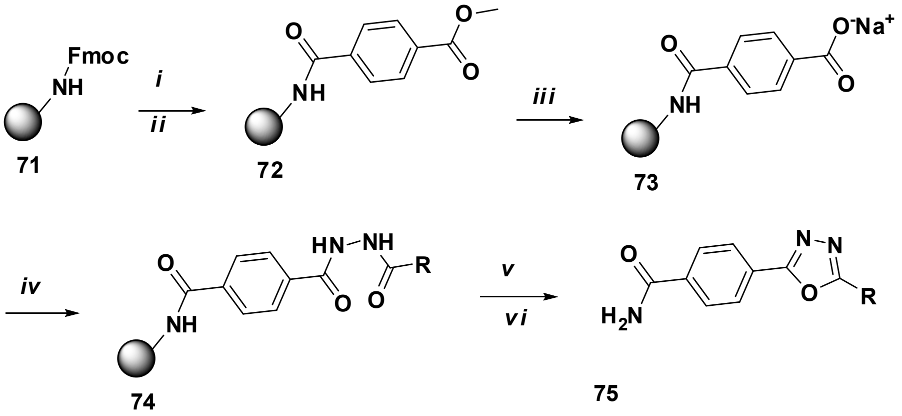
Sheng et al. [50], [51] presented the synthesis of vinyl substituted 1,3,4-oxadiazoles **70** using polymer-bound α-selenopropionic acid **67**. In this method, the activated carboxyl group reacted with hydrazide. The activated acyclic precursor was cyclised under the action of $POCl_3$ to give the target products **70** (Scheme 22).

It is also possible to use acid-sensitive Rink's resin as a solid carrier [52]. Scheme 23 shows the synthesis of 1,3,4-oxadiazoles, which involves the addition of monomethyl terephthalate to Rink's resin **71** with removal of the amino group protection in the presence of hexafluorophosphate benzotriazol-1-yl-oxytripyrrolidinophosphonium (PyBOP) and *N,N*-diisopropyl ethylamine (DIPEA). This led to the formation of the methyl ester **72**.



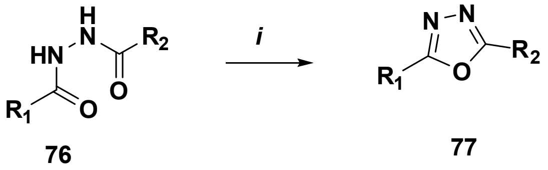
R = Ph, *i*-C_3H_7, $C_6H_5CH_2$, 4-$CH_3OC_6H_4$, 4-ClC_6H_4, 4-$NO_2C_6H_4$
i: $NaBH_4$, THF/DMF, rt, 10h; $ClCH_2CH_2COOEt$, rt, 5h; *ii*: LiOH, THF, H_2O, rt, 24h;
iii: DCC, $R_1C(NH_2)=NOH$, dioxane, 50 °C, 15h, then 95 °C, 5 h;
iv: H_2O_2, THF, 0 °C, 10 min, then rt, 1.5h; *v*: $LiBH_4$, THF, rt, 1 h, then MeCHBrCOOH, rt, 6 h;
vi: EDC, $R_2C(NH_2)=NOH$, DMF,65 °C, then 115 °C, 5 h; *vii*: H_2O_2, THF, 0 °C, 30 min, then rt, 20 min.
Scheme 22

The methyl ether **72** was then exposed to basic hydrolysis and formed carboxylate anion **73**. The latter reacted with the corresponding acylhydrazines to form 1,2-diacylhydrazine **74**. Its heating in the presence of DIC (*N,N'*-diisopropylcarbodiimide) and DMFA and subsequent cleavage from the solid carrier with trifluoroacetic acid in dichloromethane gave 2,5-disubstituted 1,3,4-oxadiazoles **75** with good yield (> 60%, total yield in six steps) and purity (> 71%) (Scheme 23).



i: 20 % piperidine in DMF; *ii*: monomethyl terephthalate, PyBOP, DIPEA, DMF; *iii*: 2M NaOH, THF;
iv: $RCONHNH_2$, PyBOP, DIPEA, DMF; *v*: DIC, DMF; 100 °C, 18 h; *vi*: TFA:DCM (1:1).
Scheme 23

Transition-metal catalysed condensation. Couturier et al. [53] described a method for the obtaining of 1,3,4-oxadiazole ring from *N,N'*-acylhydrazines **76** by the action of catalytic amounts of palladium (Scheme 24). The yield of the products was 30-71%.

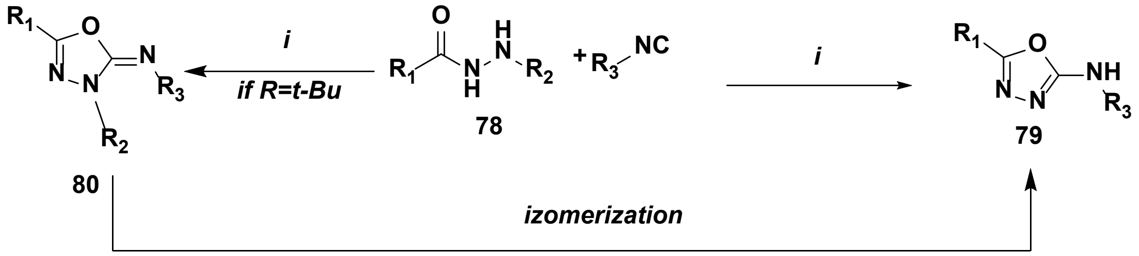


$R_1 = R_2$ = Ph, Me, Et, 4-$CH_3C_6H_4$, 4-$MeOC_6H_4$, 4-ClC_6H_4

i: 3 % $Pd(PPh_3)_4$, 0.9 equiv PPh_3 1.2 equiv $(PhCO)_2O$, decalin, 175 °C

Scheme 24

In [54], they proposed a strategy for transmetallic catalysis by palladium of the reaction between hydrazide and isocyanides. The yields of the target compounds are satisfactory to good using benzoylhydrazides with acetyl moiety as leaving group (Scheme 25).



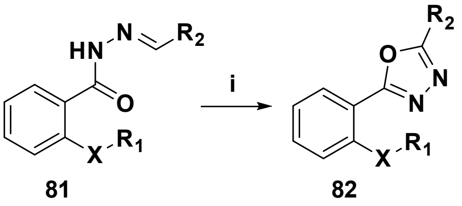
R_1 = Ar, Het, Alk; R_2 = H, Ac, R_3 = *t*-Bu, cyclohexyl

i: $Pd(OAc)_2$, (5%mol), toluene, 80 °C, O_2

Scheme 25

Transition metals (4d- and 5d-elements) have proven to be effective in activating C^{sp2}-H bonds. This resulted in functionalized compounds in the formation of C^{sp2}-C^{sp3} and C^{sp2}-heteroatom bonds. The prominent examples are reactions on palladium catalysts. The development of such processes involving less expensive and more common metals is in high demand for manufacturing. In this context, copper has gained particular interest in the last decade, demonstrating its ability to undergo different types of transformations [55-57].

The synthesis of substituted oxadiazoles is one of the examples of copper nanocatalysts. They were obtained by aerobic functionalisation of the imine C^{sp2}-H from *N*-aroyl-*N*-arylidenehydrazines [58]. The synthesis technique allows ones to obtain isolated products with high yields (75-90%) under moderate heating conditions (80°C) (Scheme 26).



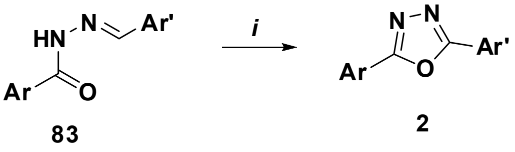
R_1 = allyl, benzyl; R_2 = Py, 2,6-$F_2C_6H_3$, C_6F_5

i: CuONPS; Cs_2CO_3; DMSO, air, 80 °C

Scheme 26

After three catalytic reaction runs, the copper catalysts showed the same morphology (SEM and TEM analyses) and structure (X-ray diffraction data) as those observed before use, but showed a slight decrease in yield. These studies have shown the possibility of cyclic application of cheaper catalysts (compared to palladium catalysts) for the synthesis of heterocyclic structures.

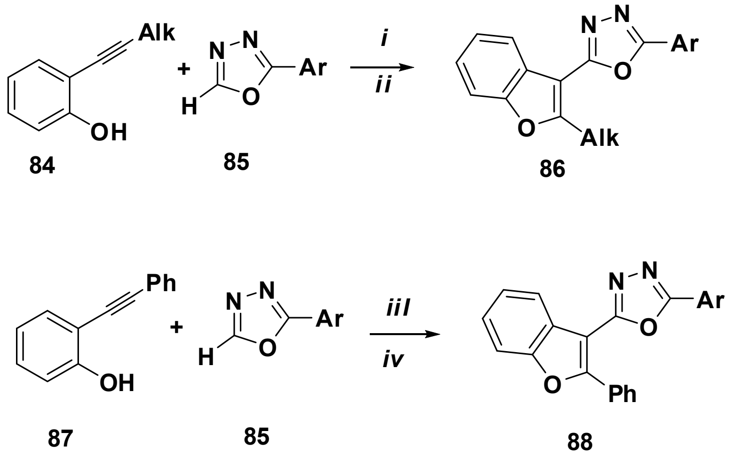
Copper (II) salts can be used as a catalyst. The reaction is characteristic for the preparation of diarylproizodnye 1,3,4-oxadiazoles (Scheme 27), is selective and gives good yield (54-93%) [59, 60]:



i: 10% $Cu(OTf)_2$, air, 1 equiv Cs_2CO_3

Scheme 27

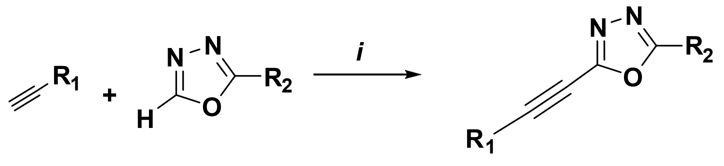
The reaction for the obtaining of 2,5-substituted 1,3,4-oxadiazoles can also be performed on copper catalysts. Miura et al. [61, 62] reported the synthesis of biaryl heterocycles **86**, **89** via a tandem oxycoupling/oxidative coupling process. For example, 2-alkynylphenols **84**, **87** react with 1,3,4-oxadiazole **85** using 1,10-phenanthroline, CuF_2 and base at room temperature. This provides obtaining of diheteroaryl products in good to moderate yields (Scheme 28). The 2:1 copper/ligand ratio was found to be crucial for the efficiency of the reaction. Oxygen is required for this reaction because the reaction in a nitrogen atmosphere gives poor yields of the target substances.



i: 2 equiv CuF_2, 4equiv 1,10-phenanthroline; ii: 3 equiv K_3PO_4, air, DMF, rt, 4-48 h; iii: 20% mol equiv CuF_2 2 equiv 1,10-phenanthroline 2 equiv MnO_2; iv: 3 equiv K_3PO_4, air, DMF, rt, 8-12 h

Scheme 28

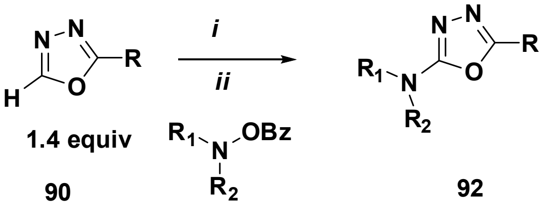
Another example of direct cross-coupling of alkynes and azoles under catalysis by copper (II) chloride in oxygen atmosphere is presented in [63]. 1,3,4-Oxadiazoles **90** react with terminal alkynes **89**. This allows ones to obtain the hetero-bonded product **91** with good yield (Scheme 29).



89 **90** **91**

$R_1 = C_6H_5$, 4-tolyl, $PhCH_2CH_2$, 4-$CF_3C_6H_4$, R_2 = 4-tolyl, *t*-Bu, cyclohexenyl
i: 1 equiv $CuCl_2$, 2 equiv Na_2CO_3, 1 atm O_2, DMAc,120 °C
Scheme 29

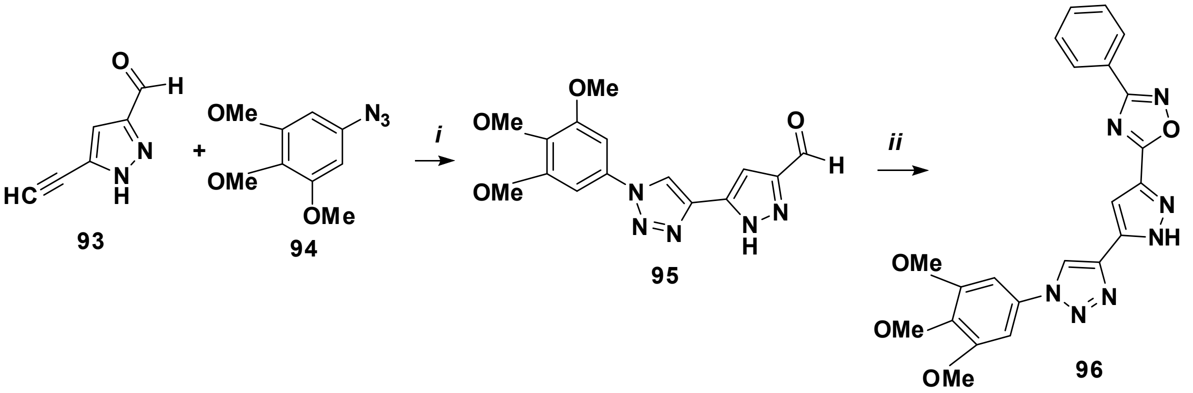
In 2020, according to Knochel et al. [64], the synthesis strategy by zincation/catalysis with copper salts can be applied to 1,3,4-oxadiazoles. The 1,3,4-Oxadiazoles **90** can be introduced into the reaction with zinc to form the corresponding diheteroarylzinc derivatives. They are further subjected to electrophilic amination (Scheme 30). This method showed very good tolerance to functional groups, in particular with esters, halides, and NH-amides.



90 **92**

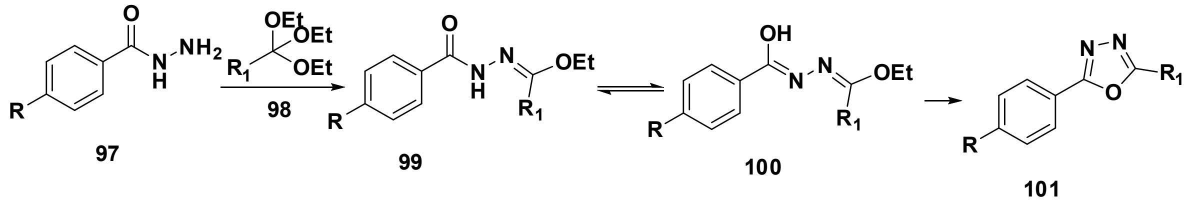
R = Pr, Bn; R_1R_2N = morpholino
i: $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (0.75 equiv), THF, rt; *ii*: $Cu(OTf)_2$, (15 mol%), THF, rt
Scheme 30

A method for the preparation of 1,3,4-oxadiazole/1,2,3-thiazole hybrid **96** has been developed [65]. By interaction of 5-ethyl-1*H*-pyrazol-3-carbaldehyde **93** with 5-azido-1,2,3-trimethoxybenzene **94** and copper (II) iodide in water-alcohol medium, triazole **95** was obtained. It was further interacted with aryl nitriles in hydroxylamine medium. This resulted in the formation of the target product **96** (Scheme 31).



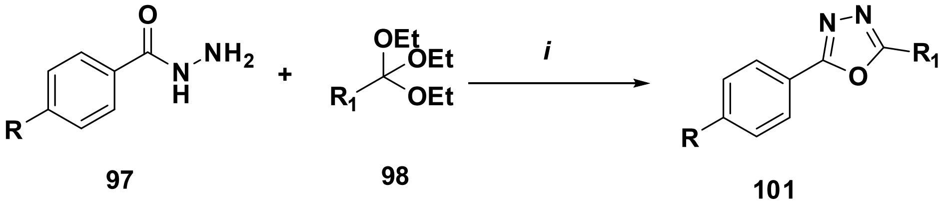
i: CuI, EtOH/H_2O, 60°C, 6h; *ii*: C_6H_5CN, $NH_2OH{\cdot}HCl$, Et_3N, *t*-BuOH, 80°C, 18 h
Scheme 31

One-pot synthesis. Ainsworth [66] studied the one-pot synthesis of 1,3,4-oxadiazole derivatives by the interaction of acid hydrazides **97** with orthoformates **98**. The disadvantage of this reaction is the high excess of orthoformate and the long time. According to Ainsworth, the process involves condensation of the acid hydrazide with an orthoester to form a 1-alkoxymethylene-2-aryl hydrazide derivative **99**. This is cyclised via the enolic form **100** to the corresponding oxadiazole ring **104** (Scheme 32).



Scheme 32

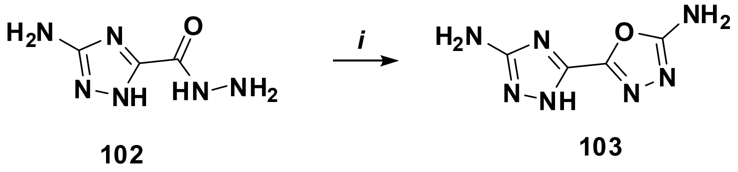
Recently, Polshettivar et al. [67] presented a one-pot synthesis of various 1,3,4-oxadiazole derivatives by a method developed by Ainsworth under microwave irradiation using Nafion polymeric membrane materials (Nafion NR50) as a catalyst. The reaction was conducted without solvent (Scheme 33). Interactions of various substituted benzoic acid hydrazides **97** with orthoesters **98**, conducted at 80 °C under microwave irradiation, gave excellent yields (80-90%) of 1,3,4-oxadiazoles **101** in only 10 min (Scheme 33).



i: Nafion NR50; MW, 80 °C

Scheme 33

A one-step method for the synthesis of 2-(1,2,4-triazol-5-yl)-1,3,4-oxadiazole derivatives **103** by action on carboxylic acid hydrazides **102** bromocyanide was presented in [68] (Scheme 34).



i: BrCN

Scheme 34

Application. Derivatives of 1,3,4-oxadiazoles are an important class of bioactive heterocycles with a wide range of pharmaceutical and biological activities: antibacterial [69-71], anticancer [72-75], antituberculosis [76, 77], and are also inhibitors of a large spectrum of enzymes [78, 79]. Known examples of commercial drugs with a 1,3,4-oxadiazole moiety are thiodazosin [80] and nesapidil [81], which are antihypertensive agents; antibiotics such as furamisole [82], which contain an oxadiazole core. 2-Amino-1,3,4-oxadiazoles have demonstrated biological activity as myorelaxants and antimitotic agents [83, 84]. The examples of structures and applications of 1,3,4-oxadiazoles with pharmaceutical activity are presented below.

Chavez et al. [85] synthesised a gold (I) complex containing 1,3,4-oxadiazole (Fig. 2). It showed favourable activity against murine melanoma.

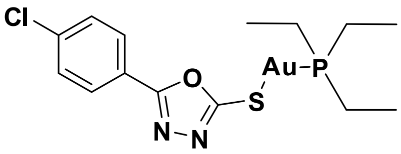


Fig. 2. The active ingredient against murine melanoma

The synthesis of 4-{5-[(pyridin-4-yl)amino]-1,3,4-oxadiazol-2-yl}phenol, which shows analgesic activity, was reported in [86]. It is shown that in comparison with aspirin, the effect of the preparation presented in Fig. 3, is superior to the known one.

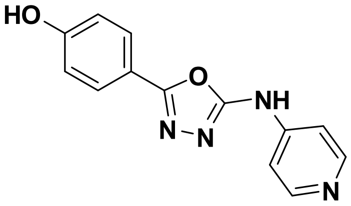


Fig. 3. Structural formula of 4-{5-[(pyridin-4-yl)amino]-1,3,4-oxadiazol-2-yl}phenol

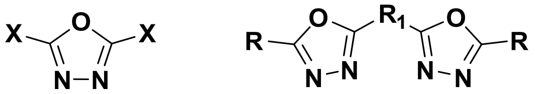
Organic π-conjugated molecules with semiconducting and/or luminescent properties have potential applications as emitting/charge transfer layers in devices such as organic light-emitting diodes (OLEDs), organic field-effect transistors (OFETs), organic thin-film transistors (OTFTs), and photovoltaic cells [87, 88].

In [89], the authors investigated 44 symmetrical oxadiazoles from the charge transfer point of view using computer modelling techniques. Therefore, we used data on the structure of molecules in the solid state obtained from the Crystallographic Structure Database (CSD). Two types of molecules were analysed: planar and non-planar; among them small and large molecules were distinguished [90].

Small planar molecules show high reorganisation energies for both hole and electron transfer. This is due to the uniform distribution of electron density throughout the molecule (delocalisation). Due to the dense packing, such molecules have large values of the charge transfer integral. This contributes to efficient charge transfer.

Large planar oxadiazole molecules have lower reorganisation energies due to better delocalisation of electronic states. The high packing density in the solid state provides large transfer integrals, promoting balance in charge transport (Fig. 4).

Such research techniques are used to develop new components of OLED materials, improving their charge transfer efficiency.

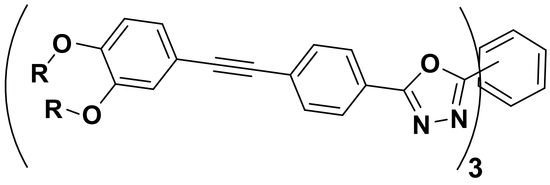


X: Ph, $-CH_3$, $-C(CH_3)_3$, $-OCH_3$, $-OC(CH_3)_3$, $-NH_2$, *p*-tolyl

R_1 = 4-C_6H4, 2-C_6H_4, 5,5'-biphenyl, 2,2'- biphenyl, 2-pyridine

Fig. 4. Some structures under study

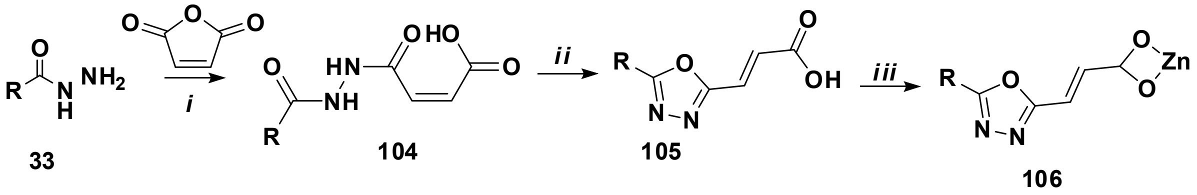
The authors [91] synthesised and investigated two molecules based on 1,3,4-oxadiazole: FD16 and FD12 (Fig. 5). They form columnar mesophases over a wide temperature range. Compound FD12 when cooled forms a transparent vitreous film with preserved liquid crystal order and bright blue luminescence (quantum yield 26%). It makes it a perspective for LEDs and OLEDs. Both molecules form luminescent gels in the decane with a columnar arrangement of molecules. The optical properties of the gels depend on the length of the alkyl chain: the gel of FD12 has a blue emission and that of FD16 has a bluish green emission. The change in molecular structure affects macroscopic properties, demonstrating the potential for fine-tuning optical properties in soft organic materials.



FD12: R=$C_{12}H_{25}$; FD16: R=$C_{16}H_{33}$

Fig. 5. Structure of 1,3,4-oxadiazole-based FD12 and FD16 molecules

The usage of derivatives of 1,3,4-oxadiazoles in the creation of materials emitting deep blue colour is well known [92]. *O*-hydroxyphenyl substituted 1,3,4-oxadiazoles were obtained. They are able to form stable organometallic complex compounds used as organic light-emitting diodes. The complex compounds obtained were studied by UV-visible spectroscopy. The studies showed that the obtained compounds emit in the blue-green region with an anomalously high Stokes shift (6546-14053 cm^{-1}).

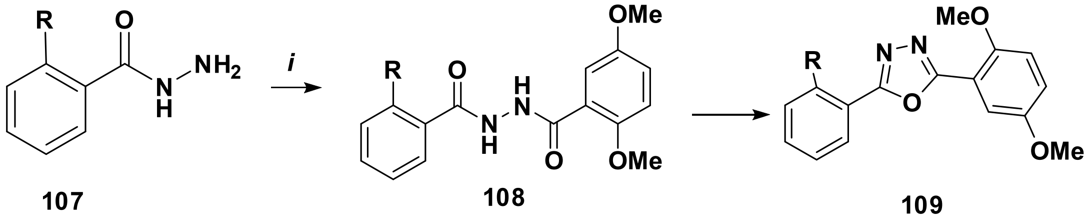


R= 4-Me$_2$NC$_6$H$_4$; 3,4,5-(MeO)$_3$C$_8$H$_2$

i: AcOH; *ii*: POCl$_3$, DMF; *iii*: KOH, Zn(OCOCH$_3$)$_2$

Scheme 35

The impact of solvent properties and introduced groups in the substituted 1,3,4-oxadiazole molecule has also been studied [93]. The luminescence spectra in toluene and acetonitrile showed a peak in the long wavelength region with an anomalously large Stokes shift (10471-10799 cm^{-1}). It occurs as a result of intramolecular excited-state proton transfer (ESIPT) from the phenolic and hydroxyl groups to the nearest nitrogen atom in the heterocycle. However, in highly polar DMSO the spectrum has a peak in the short-wavelength region with normal Stokes shift. This shows the inhibitory effect of highly polar DMSO on the obtained structures.



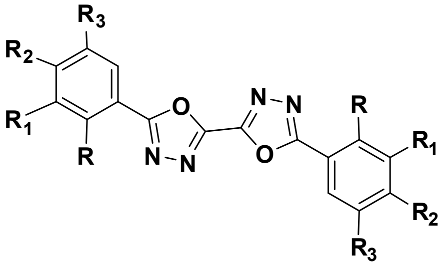
R = H, OH, OCH$_3$

i: 2, 6 - (MeO)$_2$C$_6$H$_3$COCl, NEt$_3$

Scheme 36

The use of aprotonic solvents allows the obtained compounds to be used as phosphors in the short-wave region.

The researchers [94] also studied the effect of methoxy groups on the heterocyclic core: both symmetrically substituted and non-symmetrically substituted. Hence, the introduction of a methoxy group into symmetrical phenyl substituted derivatives of bi-1,3,4-oxadiazole can effectively cause the occurrence of luminescent properties (red shifts) of the compound (Fig. 6). Moreover, all monosubstituted compounds show higher quantum yields in different solvents than the polysubstituted ones. All experimental data are proved by theoretical quantum calculations.



1. $R=R_1=R_2=R_3=H$; 2. $R_1=R_3=OCH_3$, $R=R_2=H$; 3. $R_1=R_2=R_3=OCH_3$, $R=H$

Fig. 6. Methoxy-substituted derivatives of 1,3,4-oxadiazole

The same researchers considered structures containing an additional benzene ring (Fig. 7) [95]. Molecule **C** shows an increase in fluorescence with increasing solvent polarity. It is also more capable and stable to charge transfer due to the geometry of the molecule. This is confirmed by theoretical analysis of the electron density and charge map.

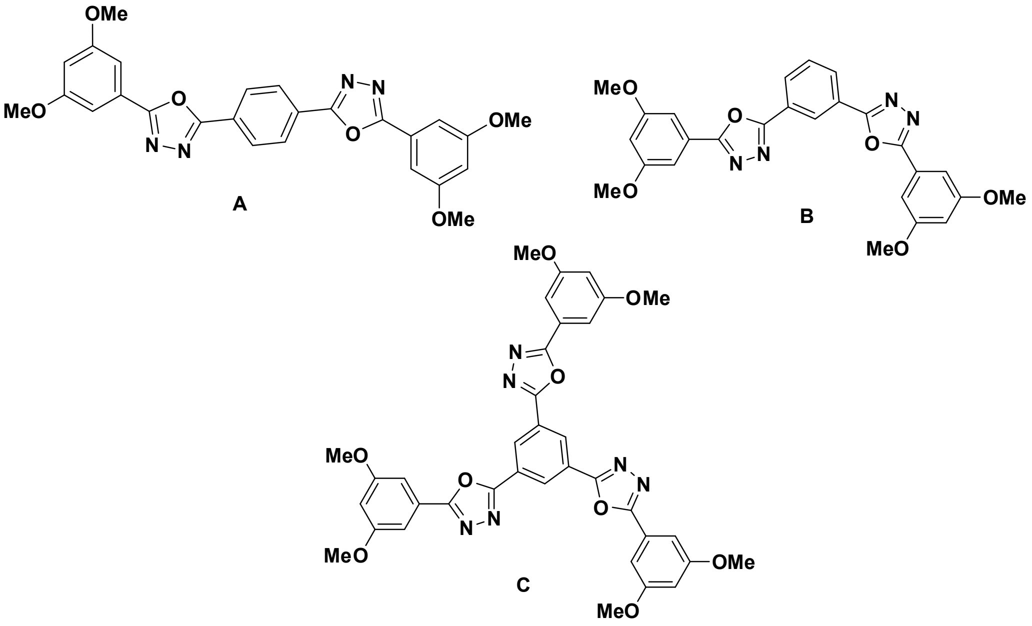


Fig. 7. Methoxyphenyl substituted 1,3,4-oxadiazoles

Researchers [96] synthesised a series of five donor-π-acceptor emitting materials consisting of an acceptor fragment of 1,3,4-oxadiazole (Fig. 8), which was symmetrically or asymmetrically substituted with dendritic carbazole donors (TTAC and terCBz). All materials containing TTAC donors have been shown to demonstrate TADF with blue to green emission in the solid state.

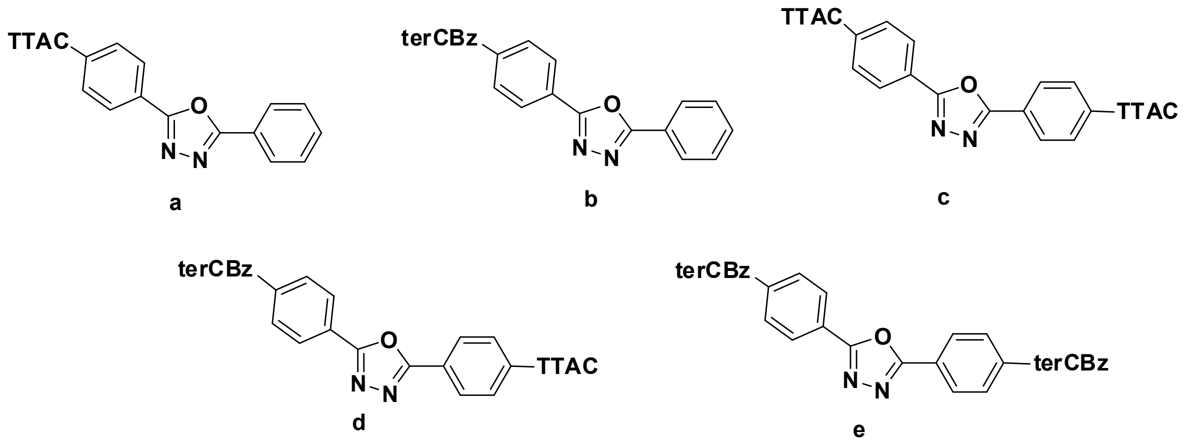


Fig. 8. Donor-π-acceptor emitting materials consisting of an acceptor fragment of 1,3,4-oxadiazole

The paper [97] describes the development of a novel oxadiazole-based fluorescent chemosensor: 2-(2-hydroxyphenyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (HMOD). The fluorescence properties were studied at the complex compound with zinc (II) in a solution of ethanol: buffer (pH=7.0) = 9:1. The emission of fluorescence intensified at wavelength λ=430 nm after the addition of zinc to the solution. According to the results, HMOD is a highly selective and sensitive chemosensor for the determination of Zn^{2+} in the presence of other metal ions. This fluorescent probe can be used as a potential candidate in various biological environments.

The authors [97] used *ab initio* HF and DFT methods to investigate the ground and excited state properties of a series of quinoid derivatives of 1,3,4-oxadiazole (Fig. 9). More negative charges were transferred to the centred oxadiazole unit intramolecularly as the electron-donating ability of the substituted groups increased. As a result, the HOMO-LUMO gap decreased and the absorption and emission peaks shifted toward red. Properties such as excitation energy, emission energy, solvent shift, and relative intensity of absorption peaks in different solvents were determined by TDDFT calculations, which were in agreement with experimental results.

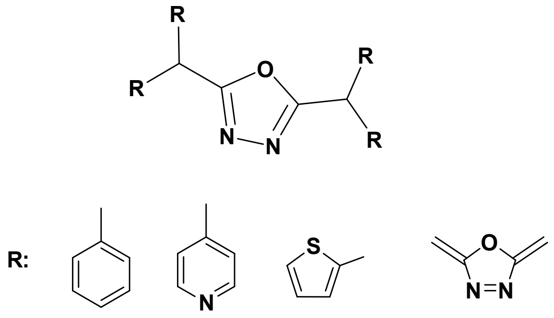
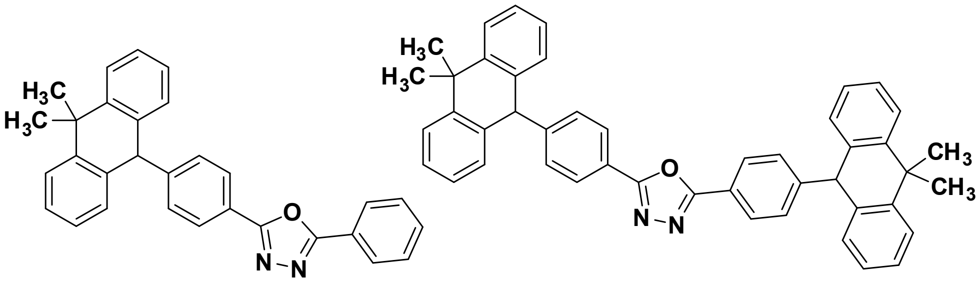


Fig. 9. Molecular structure for the calculation model

In the study [98], molecules **a** and **b** were considered for the application of various quantum chemical calculations (Fig. 10). DFT and TD-DFT methods were used. After performing the calculations, molecule **b** with a symmetrical structure has the potential to be used as a deep blue colour emitter.



a b

Fig. 10. Molecules used in the studies [100]

The authors [99] described the synthesis and luminescent properties of the compound shown on Fig. 11. The chemosensor can interact with Zn^{2+} at a 1:1 ratio and shows a highly selective and sensitive fluorescence response to Zn^{2+} compared to other metal ions in aqueous acetonitrile solution.

The fluorescence enhancement process was mainly due to the stable electrophilic attack of Zn^{2+} ion on the phenolic oxygen atom. The oxygen atom has the properties of electron enrichment and effective prevention of torsional motions of two aryl fragments in the 2-hydroxy-phenyl-1,3,4-oxadiazole group. They accompany the formation of a new complex with a rigid planar structure and blocking of non-radiative transitions.

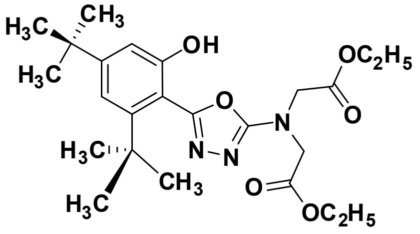


Fig. 11. Chemosensor

Studies [100] discuss the effect of thiophene links on the 1,3,4-oxadiazole ring and its fluorescence properties. The number of thiophene bonds shows a shift of the spectra towards the long wavelength region.

However, these compounds (Fig. 12) possess photoluminescence, emitting blue to green light in THF solution with emission maximum in the range of 434 to 537 nm. They also keep these properties in the solid state, as in the prototypes of ‘host-guest’ OLED devices. This provides them with a perspective in the creation of new components.

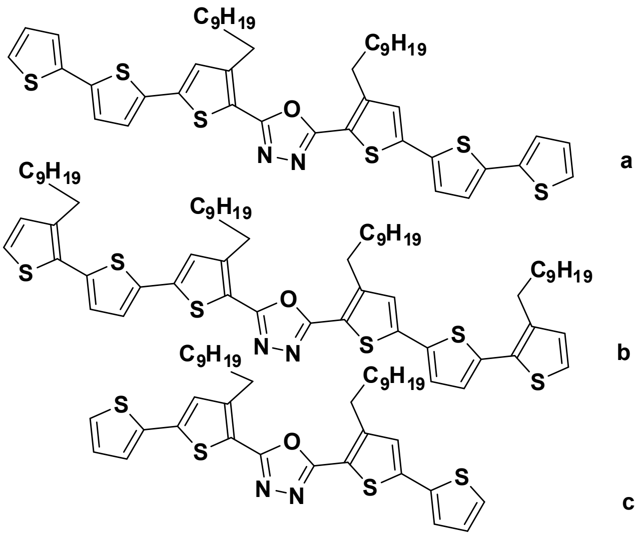


Fig. 12. Thiophene substituted 1,3,4-oxadiazoles

The authors [101] synthesised a liquid crystal dendrimer containing an oxadiazole heterocycle (Fig. 13). The properties of liquid crystals in dendrimers are significantly improved compared to mesogenic precursors. X-ray studies have revealed interesting structural details concerning the packing of these compounds in their mesophases. Based on the experimental results, some supramolecular models have been proposed. In particular, interactions between neighbouring layers or columns are observed. The degree of interaction depends on the length of the gap and the oxadiazole isomer.

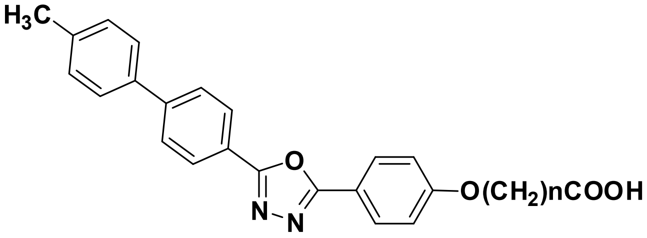


Fig. 13. Liquid crystalline dendrimer based on 1,3,4-oxadiazole

Conclusions

Derivatives of 1,3,4-oxadiazoles are promising compounds for drug preparation. Compounds that have an oxadiazole moiety in their structure are used to treat arthritis, asthma, intestinal inflammation, as well as cancer and viruses. They have a wide range of biological activities, including antibacterial, anticonvulsant, and analgesic effects. They are also antagonists of the histamine H_4 receptor and have cytotoxic effects.

Despite the great variety of drugs used in practical medicine, their effectiveness is reduced due to the emergence of resistant forms of tumours and microorganisms, the presence of side effects. Therefore, the development of new drugs and active pharmaceutical substances is an urgent task for studying the chemistry of 1,3,4-oxadiazoles.

Moreover, 1,3,4-oxadiazoles are used in the production of dyes and polymers, photo-emitting technology, as starting compounds for heat-resistant photographic films, for corrosion inhibition, creation of chiral catalysts and metal-selective chemosensors.

Therefore, this extensive use of 1,3,4-oxadiazole derivatives proves the relevance of these compounds universal application.

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