SYNTHESIS OF MONO-SUBSTITUTED AND SIMMETRICALLY 2,5-DISUBSTITUTED 1,3,4-OXADIAZOLES¶

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Abstract. In recent years 1,3,4-oxadiazoles have received considerable attention due to their wide range of biological activities and practical importance. They form an important class of five-member heterocyclic compounds with a variety of derivatives. This review will focus on several methods of synthesis for mono-substituted and symmetrically 2,5-disubstituted 1,3,4-oxadiazoles.

Keywords: mono-substituted 1,3,4-oxadiazoles, symmetrically 2,5-disubstituted 1,3,4-oxadiazoles.

1. Introduction

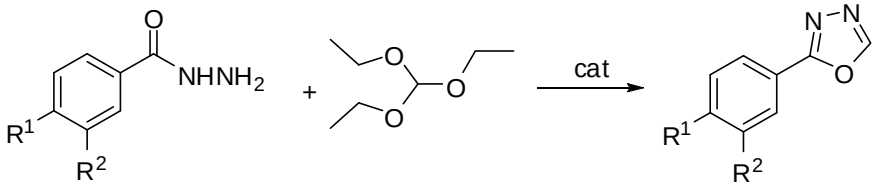
In the last decade a large amount of experimental data on synthesis and study of substituted 1,3,4-oxadiazoles has been accumulated in literature. Available data on the synthesis of substituted 1,3,4-oxadiazoles was previously summarized in a series of reviews [1-28]. This review will focus on the studies published over the last 10 years, as well as those unmarked in publications [1-28].

The specificity of 1,3,4-oxadiazole ring determines its high lability. According to this, the presented group of compounds can be transformed into substances with different cycle sizes, chemical nature of substituents, and number of heteroatoms. It should be noted that substituted 1,3,4-oxadiazoles have been used in medicinal chemistry [29-33], chemistry of pesticides [34], polymer chemistry [35-37], and material sciences [38-40].

2. Synthesis of mono-substituted 1,3,4-oxadiazoles

In earlier articles it was reported that sulfuric acid impregnated with silica gel catalyzes synthesis of 5-aryl-1,3,4-oxadiazoles **2a-e** [41].

Scheme 1



1a R^1=R^2=H
1b R^1=Cl, R^2=H
1c R^1=H, R^2=NO_2
1d R^1=OMe, R^2=H
1e R^1=F, R^2=H

2a R^1=R^2=H 85-91%
2b R^1=Cl, R^2=H 92%
2c R^1=H, R^2=NO_2 88%
2d R^1=OMe, R^2=H 90%
2e R^1=F, R^2=H 90%

It's been shown that heterocyclization of hydrazides **1a-c** with triethyl orthoester lasts 10 minutes, at room temperature without solvent, giving 5-aryl-1,3,4-oxadiazoles **2a-c** in 91%, 92% and 88%, yields respectively.

Another group of researchers reported the synthesis of 1,3,4-oxadiazole **2a**, under microwave irradiation of the mixture of hydrazide **1a** and triethyl orthoester on the surface of Nafion-NR50 (P_4S_{10}/Al_2O_3), however yield didn't exceed 85% [42]. A higher yield was observed (up to 90%) for target products **2d**, **2e** in presence of substituents (OMe and F) in the 4-position of the aromatic ring in the initial acyl hydrazides **1d**, **1e**.

The synthesis of 5-aryl-1,3,4-oxadiazoles **2a-c** catalyzed by 40 mol-% of $KAl(SO_4)_2 12H_2O$ is also known in literature [43]. Formation of 1,3,4-oxadiazoles **2a**, **2b** and **2c** in 89%, 95% and 93% yields, respectively, was observed upon heating the reaction mixture at 100°C for 6 h.

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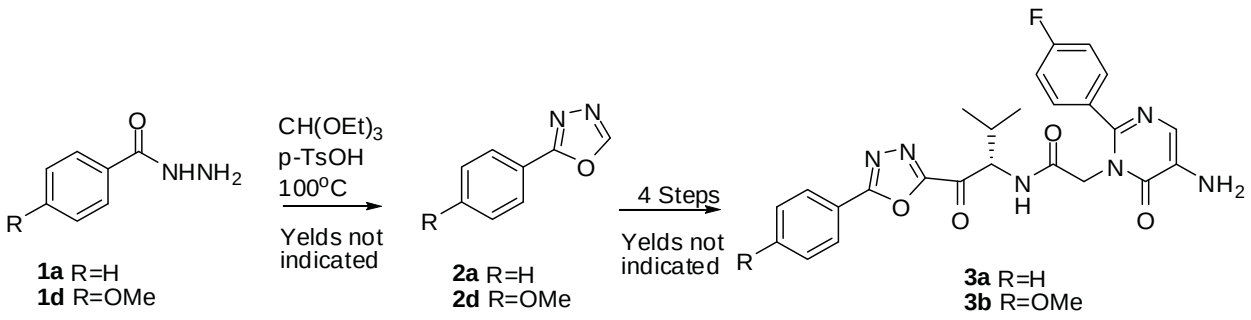
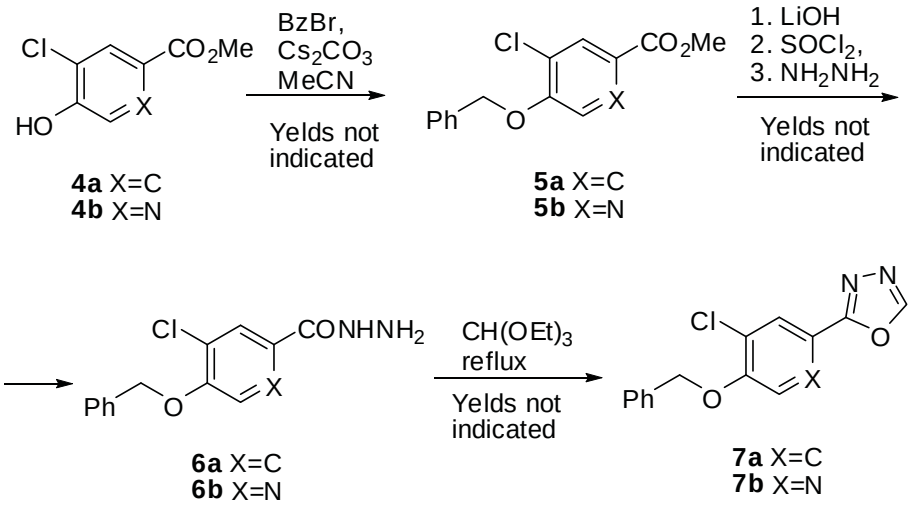
1,3,4-oxadiazoles **2a**, **2d** were obtained by heating the corresponding hydrazides **1a**, **1d** with triethyl orthoester up to 100°C in the presence of catalytic amounts of p-TsOH. Authors [44], used products **2a**, **2d** for the synthesis of the not peptide type inhibitors for human pancreatic elastase illustrated in structures **3a**, **3b** (Scheme 2).

Scheme 2



New inhibitors of biosynthesis of pathogenic bacteria were obtained by initial benzylation of hydroxy esters **4a**, **4b** in 2009 by the authors [45] (Scheme 3).

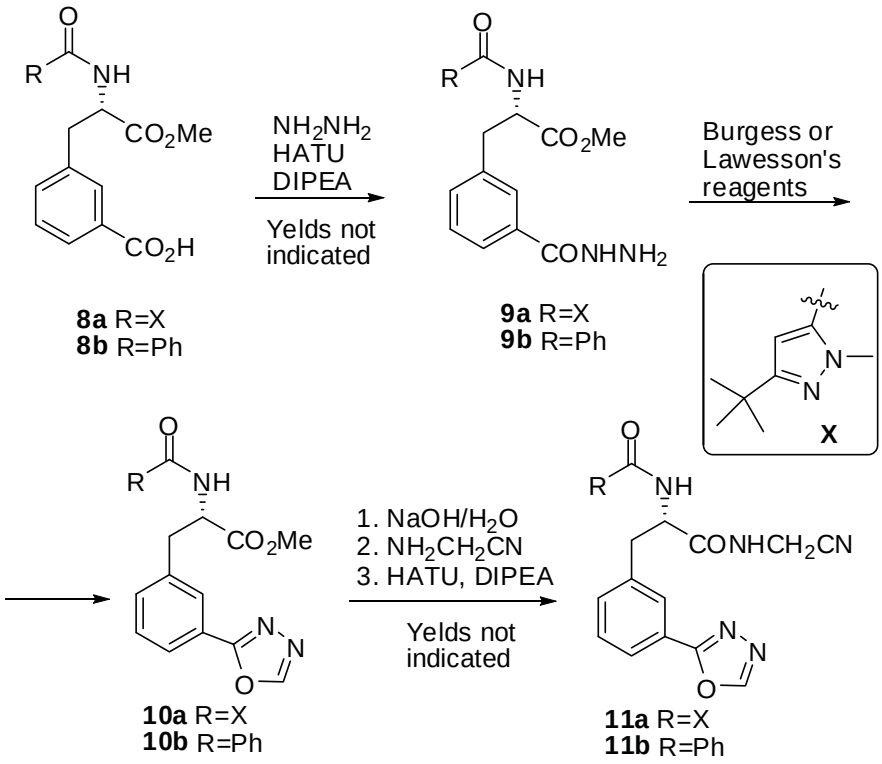
Scheme 3



Hydrazinolysis of esters **5a**, **5b** has led to the products **6a**, **6b**. It's been shown that heating of hydrazides **6a**, **6b** reflux in the solution of triethyl or trimethyl orthoester with distillation of the formed alcohol, facilitate the reaction of heterocyclization with the 1,3,4-oxadiazoles **7a**, **7b** formation. It was established that the product **7a** has a higher bioactivity in comparison with the bioactivity of the nitrogen-containing analogue **7b**.

Another group of researchers reported [46] about synthesis of cathepsin K inhibitors (Cathepsin K), which provokes human breast cancer (Scheme 4).

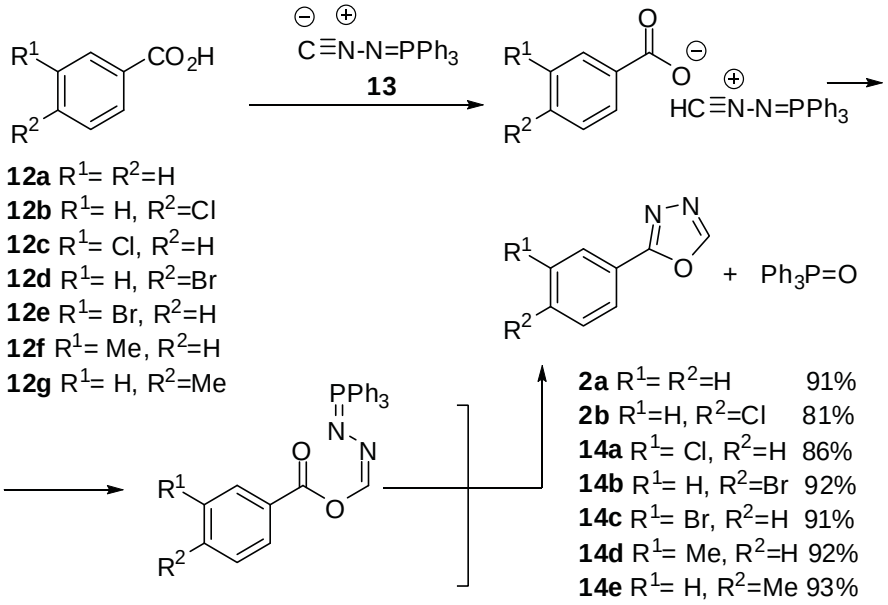
Scheme 4



Regioselective synthesis of hydrazides **9a**, **9b** from the acids **8a**, **8b** was the precursor of heterocyclization. It was found that the latter reaction is realized in presence of 1-methoxy-N-trimethylammoniosulfonyl-methanimidate (Burgess reagent) under microwave irradiation, or in THF solution at 40°C in presence of 2,4-bis(methoxyphenyl)-1,3,2,4-dithiaphosphetane-2,4-disulfide (Lavenson reagent). 1,3,4-Oxadiazoles **10a**, **10b** were further transformed into the target amides **11a**, **11b**.

In conclusion it should be noted a number of publications on the synthesis of 2-aryl-1,3,4-oxadiazoles involving benzoic acids **12a-12g** and (N-isocyananimino) triphenylphosphorane **13** [47-50] according to the scheme 5.

Scheme 5



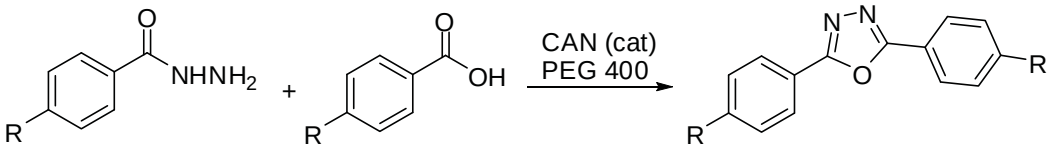
The reaction is carried out in methylene chloride at room temperature with ratio of reagents 1:1. The yields of final products **2a**, **2b**, **14a-14e** practically don't depend on the position or chemical nature of the substituent in initial benzoic acids **12a-12g**. This approach avoids transformation of the carboxyl group into hydrazide one and its cyclization into target 2-aryl-1,3,4-oxadiazoles.

Thus, two alternative approaches to monosubstituted 1,3,4-oxadiazoles have been reviewed, one of them can be carried out directly from benzoic acids and (N-isocyananimino) triphenylphosphorane, or by cyclization of benzoic acid hydrazide in presence of orthoesters.

3. Synthesis of symmetrically 2,5-disubstituted 1,3,4-oxadiazoles

One-pot synthesis of 2,5-diphenyl-1,3,4-oxadiazole **17a** has been realized by heating of benzoic acid hydrazide **1a** and benzoic acid **12a** in polyethylene glycol [51] (Scheme 6).

Scheme 6

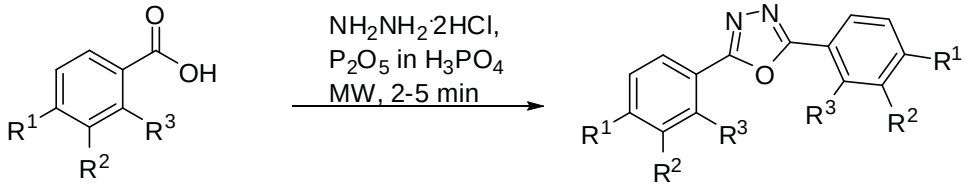


1a R=H	**12a** R=H	**17a** R=H 98%
1b R=Cl	**12b** R=Cl	**17b** R=Cl 97%
1d R=OMe	**12g** R=Me	**17c** R=Me 95%
15a R=OH	**16a** R=OH	**17d** R=OH 91%
15b R=Me	**16b** R=OMe	**17e** R=OMe 98%
15c R=NO_2	**16c** R=NO_2	**17f** R=NO_2 95%

Full conversion of the initial **1a**, **12a** catalized by 5 mol% $InCl_3$, CuO, $NbCl_5$, $FeCl_3$, I_2, $CuSO_4$ and CAN for 11, 8.5, 9, 9.5, 7, 8 and 5 hours, gave 2,5-diphenyl-1,3,4-oxadiazole **17a** with yields 87%, 79 %, 82%, 73%, 76%, 83% and 98% respectively. In the similar conditions 2,5-diaryl-1,3,4-oxadiazoles **17b-17f** have been synthesized in high yields using 5 mol% CAN, acids **12b**, **12g**, **16a-16c**, and hydrazides **1b**, **1d**, **15a-15c**. Another, less efficient synthesis of 2,5-diphenyl-1,3,4-oxadiazole **17a**, involved the consequent addition of 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate and then 1-methoxy-N-trimethylammoniosulfonyl-methanimidate (Burgess reagent) to the mixture of hydrazide of benzoic acid **1a** and benzoic acid **12a** [52, 53]. The reaction is carried out at room temperature in THF solution, and the yield of **17a** does not exceed 88%.

Microwave irradiation of the mixture containing benzoic acid **12a**, $NH_2NH_2 \cdot 2HCl$ and P_2O_5 in H_3PO_4 make it possible to synthesize symmetrical 1,3,4-oxadiazole **17a** in 2 minutes [54] (Scheme 7).

Scheme 7

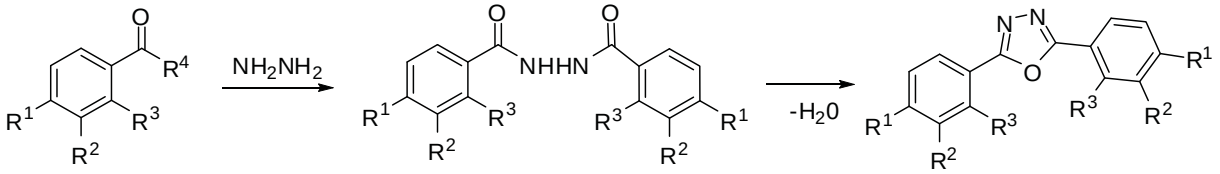


12a $R^1=R^2=R^3=H$	**17a** $R^1=R^2=R^3=H$ 80%
12b $R^1=Cl$, $R^2=R^3=H$	**17b** $R^1=Cl$, $R^2=R^3=H$ 95%
12g $R^1=Me$, $R^2=R^3=H$	**17c** $R^1=Me$, $R^2=R^3=H$ 98%
12f $R^1=R^3=H$, $R^2=Me$	**17d** $R^1=OH$, $R^2=R^3=H$ 30%
16a $R^1=OH$, $R^2=R^3=H$	**17e** $R^1=OMe$, $R^2=R^3=H$ 92%
16b $R^1=OMe$, $R^2=R^3=H$	**19a** $R^1=R^3=H$, $R^2=Me$ 97%
18a $R^1=R^3=H$, $R^2=OMe$	**19b** $R^1=R^3=H$, $R^2=OMe$ 91%
18b $R^1=R^3=H$, $R^3=OH$	**19c** $R^1=R^3=H$, $R^3=OH$ 64%

For the transformation of substituted benzoic acids **12b-12f**, **16a**, **16b**, **18a, 18b** to the corresponding 2,5-diaryl-1,3,4-oxadiazoles **17b-17e**, **19a-19c,** it's necessary to increase the reaction time up to 5 minutes. In most cases, the products of heterocyclization were obtained in high yields (91% - 98%), except the hydroxy-derivatives **17d**, **19c**, which were obtained in 30% and 64% yields respectively.

Alternative approach to the method discussed above, is a procedure of preliminary obtaining diarylhydrazines **22a-22h** from acids **12a**, **12g**, **16b**, **20a** or from chloranhydrides **21a-21f** [55-58] scheme 8.

Scheme 8



12a R^1=R^2=R^3=H, R^4=OH
12g R^1=Me, R^2=R^3=H, R^4=OH
16b R^1=OMe, R^2=R^3=H, R^4=OH
20a R^1=F, R^2=R^3=H, R^4=OH
21a R^1=R^2=R^3=H, R^4=Cl
21b R^1=R^3=H, R^2=R^4=Cl
21c R^1=R^2=H, R^3=OH, R^4=Cl
21d R^1=R^2=H, R^3=F, R^4=Cl
21e R^1=R^3=H, R^2=NO_2, R^4=Cl
21f R^1=Me, R^2=R^3=H, R^4=Cl

22a R^1=R^2=R^3=H
22b R^1=Me, R^2=R^3=H
22c R^1=OMe, R^2=R^3=H
22d R^1=F, R^2=R^3=H
22e R^1=R^3=H, R^2=Cl
22f R^1=R^2=H, R^3=OH
22g R^1=R^2=H, R^3=F
22h R^1=R^3=H, R^2=NO_2

17a R^1=R^2=R^3=H 71-98%
17c R^1=Me, R^2=R^3=H 65-100%
17e R^1=OMe, R^2=R^3=H 75%
19c R^1=R^3=H, R^3=OH 98%
23a R^1=F, R^2=R^3=H 78-100%
23b R^1=R^3=H, R^2=Cl 91%
23c R^1=R^2=H, R^3=F 93%
23d R^1=R^3=H, R^2=NO_2 94%

The limiting stage of the transformation: acid (anhydride) → hydrazide → 2,5-bis-(aryl)-1,3,4-oxadiazole, in most cases is the reaction of dehydration. When heating hydrazide **22b** in $POCl_3$ reflux for 8 hours, the yield of 2,5-bis-(4-methylphenyl)-1,3,4-oxadiazole **17c** did not exceed 65% [55]. The quantitative yield of the latter compound was obtained by using the ratio of 1 eq. of 2-chloro-1,3-dimethylimidazolinium chloride (DMC) to 2 eq. of Et_3N in the solution of CH_2Cl_2 at room temperature [56]. In the latter case, the reaction time was increased up to 21 hours. This method has been used for the synthesis of compounds **17a**, **23a**. The yield and time of the reaction was 86% (16 hours) and 100% (20 hours), respectively. It was also found that $ZrCl_4$ catalyzes diarylhydrazines cyclization in CH_2Cl_2 at room temperature [57]. 1,3,4-oxadiazoles **17a**, **17e**, **23a** have been synthesized in 3 hours in 71%, 75% and 78% yields respectively.

It should be mentioned that the synthesis of symmetrical 2,5-disubstituted 1,3,4-oxadiazoles from chloranhydrides **21a-21f** without isolation of intermediate diarylhydrazines **22a, 22b, 22e, 22f, 22g, 22h** [58]. Cyclization is realized with $BF_3 \cdot Et_2O$ in 1,4-dioxane reflux for 1-2 hours giving products **17a, 17c, 19c, 23b, 23c, 23d** in 98%, 97%, 98%, 91%, 93% and 94% yields, respectively.

4. Conclusions

Hereby, the various ways of synthesis for mono-substituted and symmetrically 2,5-disubstituted 1,3,4-oxadiazoles have been analyzed. The important structural characteristic of 2,5-disubstituted 1,3,4-oxadiazoles is the presence of two aromatic rings with a diversity of substituents spaced by a heterocycle. This fact opens up new opportunities for a wide variety of derivatives, which can serve as new useful substances for medicinal chemistry, polymer chemistry and material sciences. It should also be noted that the literature publications contain data on the synthesis of asymmetrical disubstituted 1,3,4-oxadiazoles, discussion of which will be presented in a separate review.

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