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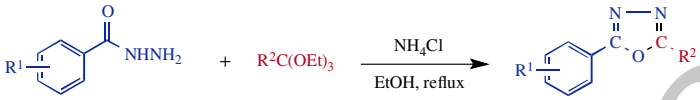

1-8 **9 a-d** **10-17 (a-d)**
30 examples

R^1 = H, 4-CH_3, 4-OCH_3, 3-Br, 2-Cl, 4-Cl, 2-NO_2, 4-NO_2
R^2 = H, CH_3, CH_3CH_2, Ph

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Efficient synthesis of 1,3,4-oxadiazoles promoted by NH_4Cl

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ABSTRACT

An efficient and inexpensive approach to the synthesis of 2-substituted and 2,5-disubstituted 1,3,4-oxadiazoles from arylhydrazides and orthoesters is reported using catalytic NH_4Cl. The conditions are mild, and thus, compatible with a variety of functional groups. The optimized reaction is performed using 30 mol% of NH_4Cl in 100% EtOH and is generally complete within 1 h for non-aromatic orthoesters and 2-10 h for aromatic orthoesters. The reaction permits both electron-releasing and electron-withdrawing groups on the arylhydrazide substrate. Most products are formed in high yield and require only minimal purification. Compared with earlier reports, the current reactions proceed in shorter time and require less of the orthoester.

The 1,3,4-oxadiazole scaffold has attracted considerable attention in the field of medicinal chemistry.[1] This interest stems from their wide range of biological activities including anticancer,[2] antifungal,[3,4] antibacterial,[5] antimicrobial,[6,7] anti-inflammatory,[8,9] anticonvulsant,[10,11] analgesic,[12] and as inhibitors of HIV integrase[13] and angiogenesis.[14] Many commercial drugs, such as the antihypertensives tiodiazosin[15] and nesapidil,[16] the antibiotic furamizole,[17] the HIV-integrase inhibitor raltegravir[13] and the anticancer agent zibotentan,[2] contain the oxadiazole nucleus (Figure 1). In drug research, the oxadiazole moiety can serve as a bioisostere for carboxylic acids, esters and amides.[18-22] These rings are also important structural components of agrochemicals such as herbicides,[23] pesticides[24] and plant growth regulators.[25-27] Beyond their medicinal and agricultural uses, oxadiazoles find application in the field of organoelectronics due to their electron transporting properties.[28-31]

Due to the broad commercial potential of 1,3,4-oxadiazoles, numerous methods for their synthesis have been developed over the years. Most approaches are either multi-step or involve the cyclization of hydrazides using harsh conditions such as phosphorus oxychloride, thionyl chloride, sulfuric acid, zirconium(IV) chloride, XtalFluor-E®, Burgess reagent, Deoxo-Fluor®, acid chlorides, Nafion® NR50 or acetic acid, under reflux or microwave heating.[32] Due to the caustic nature of these reagents, sensitive functional groups are often incompatible with these earlier methods. To address this problem, we have developed a mild protocol, which involves the formation of 1,3,4-oxadiazoles from arylhydrazides and orthoesters promoted by catalytic NH_4Cl.

In recent years, we have found that NH_4Cl is a highly efficient and mild catalyst for the synthesis of benzo-fused heterocycles such as benzimidazoles, benzoxazoles and benzothiazoles,[33] and also for the preparation of α-aminonitriles using a variant of the Strecker synthesis.[34] To extend the scope of this catalyst, optimization studies were performed for the current reaction using benzhydrazide (1.0 eq) and triethyl orthoformate (1.1 eq). The optimized transformation occurred using 30 mol% of NH_4Cl in refluxing ethanol, which afforded a 96% yield of the corresponding oxadiazole in less than 1 h. Lower catalyst loadings gave slow and often incomplete reaction, while more catalyst gave no additional rate enhancement. The use of absolute EtOH proved essential to achieve maximum conversion for these reactions. Attempts to use other solvents (THF, dichloroethane, CH_3OH, dioxane, CH_3CN, benzene, 10:1 EtOH:H_2O or 1:1 EtOH:H_2O) either produced lower yields or required longer reaction times (Figure 2). The current procedure represents a considerable improvement over a previously published uncatalyzed route that required 18 h and a five-fold excess of the orthoester.[35]

The scope of this reaction was studied by refluxing a series of arylhydrazides with various triethyl orthoesters in EtOH using 30 mol% of NH_4Cl. Our results are summarized in Table I. The mild reaction conditions offered a wide range of functional group tolerance on the arylhydrazide including methyl, methoxy, chloro, bromo and nitro. In most cases, the yields were high, and the products were formed cleanly. Solid products were isolated directly from the reaction mixture and did not require further purification. Oils required purification by elution through a

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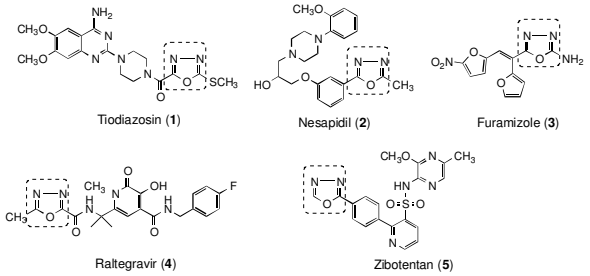


Figure 1. Drugs containing an oxadiazole ring

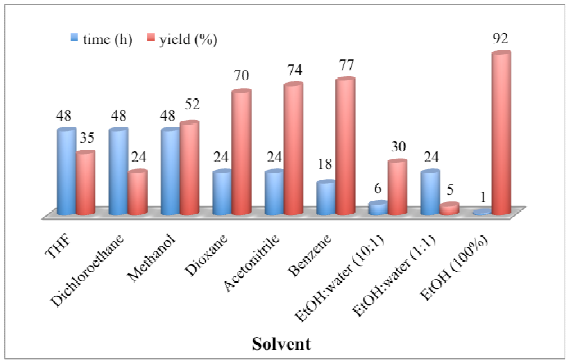
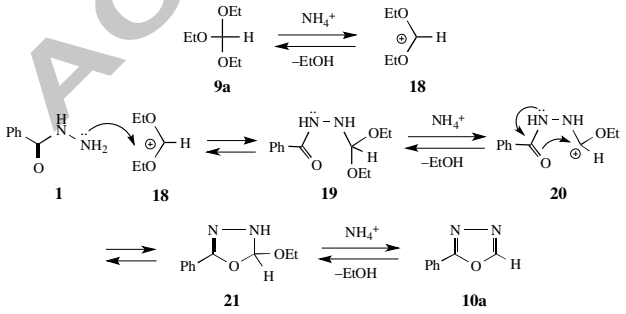


Figure 2. Effect of solvent with time in the reaction

short column of silica gel. The reaction was successful with both electron-releasing and electron-withdrawing substituents on the arylhydrazide reactant. The yield of oxadiazole was only decreased when an electron-withdrawing group was positioned *ortho* to the hydrazide carbonyl. This presumably results from an electronic effect, which should exert a greater impact on the carbonyl reactivity from this position. Most notably, the presence of an electron-withdrawing chloro or nitro at the *ortho* position of the arylhydrazide resulted in lower yields, especially with non-aromatic orthoesters.

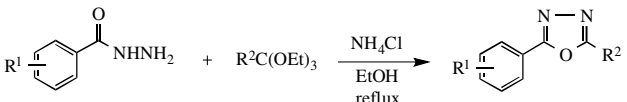
Several observations were made regarding the series of orthoesters used in these reactions. With respect to reaction times, orthoformate, orthoacetate and orthopropionate were completely consumed in less than 1 h, while orthobenzoate required extended reaction times of 2-10 h. However, orthobenzoate seemed to give the most consistent yields, while the smaller orthoesters afforded more variable results.

A proposed mechanism for oxadiazole formation is given in Scheme 1. Initial protonation and loss of EtOH from **9a** would



Scheme 1. Proposed mechanism for formation of oxadiazole **10a** from **1** and **9a**.

Table 1. Synthesis of 2- and 2,5-disubstituted 1,3,4-oxazoles



1-8
1 (R^1 = H)
2 (R^1 = 4-CH_3)
3 (R^1 = 4-OCH_3)
4 (R^1 = 3-Br)
5 (R^1 = 2-Cl)
6 (R^1 = 4-Cl)
7 (R^1 = 2-NO_2)
8 (R^1 = 4-NO_2)

9 (a-d)
a (R^2 = H)
b (R^2 = CH_3)
c (R^2 = CH_2CH_3)
d (R^2 = Ph)

10-17 (a-d)
(refer to table)

Entry	R^1	R^2	Time	Yield (%)
10a	H	H	30 min	95[b]
10b	H	CH_3	45 min	93[b]
10c	H	CH_3CH_2	45 min	98[a]
10d	H	Ph	2.5 h	96[a]
11a	4-CH_3	H	30 min	88[b]
11b	4-CH_3	CH_3	45 min	53[b]
11c	4-CH_3	CH_3CH_2	45 min	95[b]
11d	4-CH_3	Ph	2.5 h	96[a]
12a	4-OCH_3	H	30 min	98[a]
12b	4-OCH_3	CH_3	45 min	90[b]
12c	4-OCH_3	CH_3CH_2	45 min	93[b]
12d	4-OCH_3	Ph	2 h	97[a]
13a	H	H	30 min	82[b]
13b	CH_3	CH_3	45 min	89[b]
13c	CH_3CH_2	CH_3CH_2	45 min	86[b]
13d	Ph	Ph	3 h	80[b]
14a	2-Cl	H	30 min	28[b]
14d	2-Cl	Ph	3 h	97[a]
15a	4-Cl	H	30 min	90[b]
15b	4-Cl	CH_3	45 min	75[b]
15c	4-Cl	CH_3CH_2	45 min	95[a]
15d	4-Cl	Ph	3 h	70[b]
16a	2-NO_2	H	1 h	22[b]
16b	2-NO_2	CH_3	1 h	25[b]
16c	2-NO_2	CH_3CH_2	1 h	38[b]
16d	2-NO_2	Ph	10 h	55[b]
17a	4-NO_2	H	1 h	74[b]
17b	4-NO_2	CH_3	1 h	81[b]
17c	4-NO_2	CH_3CH_2	1 h	69[b]
17d	4-NO_2	Ph	6 h	92[b]

[a]Product was isolated by filtration. [b]Product was isolated by column chromatography

give the ether-stabilized carbocation **18**. Attack on this species by hydrazide **1** to give **19** would be followed by protonation and loss of a second molecule of EtOH to give **20**. Ring closure to generate **21** and elimination of EtOH would then afford oxadiazole **10a**.

In summary, we have developed an efficient and inexpensive approach to the synthesis of 2-substituted and 2,5-disubstituted 1,3,4-oxadiazoles using NH_4Cl as catalyst. The conditions are mild, and thus, compatible with a variety of functional groups. The optimized reaction is performed using 30

mol% of NH_4Cl in 100% EtOH and is generally complete within 1 h for orthoformate, orthoacetate or orthopropionate, and 2-10 h for orthobenzoate. In most cases, the yields are high, and the isolated products require only minimal purification. The reaction is successful with electron-releasing and electron-withdrawing groups on the arylhydrazide substrate and proceeds smoothly for both non-aromatic and aromatic orthoesters. Compared with earlier reports, the current reactions proceed in shorter time and require considerably less orthoester.

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