

Alum ($\text{KAl}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$): An Efficient and Inexpensive Catalyst for the One-pot Synthesis of 1,3,4-Oxadiazoles under Solvent-Free Conditions

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Summary. Alum ($\text{KAl}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$) catalyzed the efficient synthesis of mono- and disubstituted 1,3,4-oxadiazoles by the condensation of acyl hydrazides with orthoesters under solvent-free conditions at 100°C. This methodology offers significant improvements for the synthesis of oxadiazoles with regard to the yield of products, simplicity in operation, inexpensive reagents, and green aspects by avoiding toxic catalysts and solvents.

Keywords. Heterocycle; Oxadiazole; Solvent-free; Alum.

Introduction

Molecules containing a 1,3,4-oxadiazole core have been shown to have a broad range of important biological activities including antibacterial [1], antimicrobial [2], hypotensive [3], insecticidal [4], herbicidal, and antifungal [5] properties. Consequently, the synthesis of this heterocycle has attracted considerable attention and a wide variety of methods have been used for its assembly [6]. By far the most common strategy involves the dehydrative cyclization of diacylhydrazides, usually with strongly acidic reagents such as POCl_3 [7], SOCl_2 [8], P_2O_5 [9], H_2SO_4 [10], or *PPA* [11]. More recently, however, several methods have been developed using essentially neutral conditions and cyclization mediators such as Tf_2O [12] and *HMDS/TBAF* [13], as well as solid supported cyclization reagents [14]. Among them one simple and efficient method is the reaction of acyl hydrazides

with different orthoesters in the presence of an acid catalyst which afforded the 2,5-disubstituted 1,3,4-oxadiazoles [15]. Unfortunately, most of the procedures which have been described for this reaction entail using toxic reagents or solvents, long reaction times, or using domestic microwave ovens which could not be adapted to an industrial scale and furthermore repeatability was low in this method.

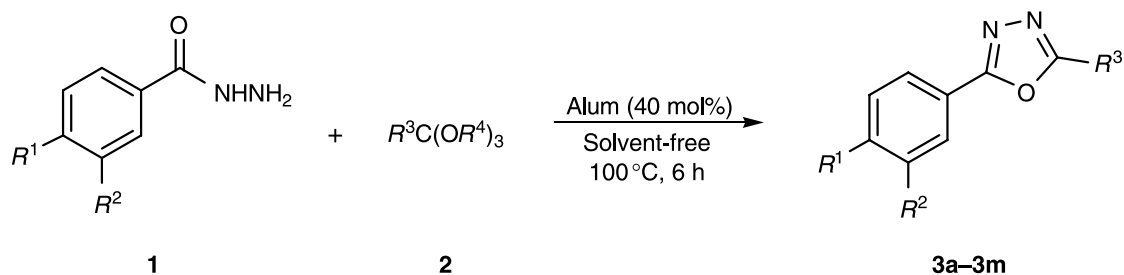
There is an increasing interest in the use of environmentally benign reagents, conditions, and particularly to solvent-free procedures. Avoiding organic solvents during the reactions in organic synthesis leads to a clean, efficient, and economical technology [16].

In continuation of our interest in using solid acidic catalysts in synthesis of heterocyclic compounds [17] we report herein a one-step synthesis of substituted oxadiazoles from acyl hydrazides and orthoesters in the presence of $\text{KAl}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$ (alum) [18] as a solid catalyst, under solvent-free conditions. This method appeared to be efficient and economical, with a wide range of applications.

Results and Discussion

For optimizing the reaction conditions, reaction of *p*-chlorobenzohydrazide (**1**; $R^1 = \text{Cl}$, $R^2 = \text{H}$) and trimethyl orthoformate (**2**; $R^3 = \text{H}$, $R^4 = \text{Me}$) in the presence of a catalytic amount of alum at different temperatures was investigated under solvent-free

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Scheme 1

Table 1. Synthesis of 1,3,4-oxadiazoles in the presence of catalytic amounts of alum under solvent-free condition at 100°C in 6 h

Product	R ¹	R ²	R ³	R ⁴	Yield/% ^a	Mp/°C	Ref. ^b
3a	Cl	H	H	<i>Me</i>	95	133–134	[15d]
3b	Cl	H	<i>Me</i>	<i>Et</i>	82	106–107	[16k]
3c	Cl	H	<i>n-Pr</i>	<i>Et</i>	93	76–78	[15d]
3d	Cl	H	<i>n-Bu</i>	<i>Me</i>	87	69–71	[15d]
3e	Cl	H	<i>Et</i>	<i>Et</i>	90	93–94	[15d]
3f	Cl	H	<i>Ph</i>	<i>Et</i>	95	160–162	[19]
3g	H	NO ₂	<i>Ph</i>	<i>Et</i>	85	147–149	[15e]
3h	H	NO ₂	H	<i>Me</i>	93	125–126	–
3i	H	NO ₂	<i>Me</i>	<i>Et</i>	85	156–158	–
3j	H	H	<i>Ph</i>	<i>Et</i>	92	138–139	[19]
3k	H	H	<i>Me</i>	<i>Et</i>	86	65–67	[15e]
3l	H	H	H	<i>Me</i>	89	150–152	–
3m	H	H	<i>Et</i>	<i>Et</i>	92	104–105	–

^a Yield of isolated product based on acyl hydrazide

^b The products were characterized by comparison of their spectroscopic and physical data with authentic samples synthesized by the procedures given in the references

condition. It was found that the best result was obtained with 40 mol% of alum at 100°C. The reaction was completed within 6 h and the expected product (**3a**) was obtained in 95% yield (Scheme 1). After screening several *Lewis* acids we found that alum was the best promoter for this reaction.

Different kinds of substituted aromatic acyl hydrazides were subjected to the reaction with a variety of orthoesters and the corresponding 2-mono- or 2,5-disubstituted 1,3,4-oxadiazoles were isolated in good to excellent yields (Table 1). It is noteworthy that conducting similar reactions in *EtOH* under reflux conditions after 2 days gave only a few percent of the desired products.

In conclusion, we developed a simple one-step method for the preparation of unsymmetrically substituted 1,3,4-oxadiazoles from the corresponding commercially available acyl hydrazides and orthoesters. The method offers several advantages including high yield of products, short reaction times, and ease of work-up procedure.

Experimental

Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were recorded on a FT-IR 102MB BOMEM apparatus. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. ¹H and ¹³C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz.

General Procedure for the Synthesis of 1,3,4-Oxadiazoles

To a mixture of 2 mmol acyl hydrazide and 2 cm³ orthoester 2.04 mmol alum were added and mixed thoroughly in a round bottom flask and heated at 100°C. After the reaction was completed, which was indicated by TLC (eluent: *n*-hexane/ethyl acetate = 2/1), the mixture was allowed to cool to room temperature and cold water was added to the mixture. The solid product was filtered off and washed with 3 × 10 cm³ water. Finally, the crude product was recrystallized from *EtOH* to afford the pure products **3a–3m** in fairly good yields.

Products **3a–3g**, **3j**, and **3k** are known compounds and their physical data, IR, ¹H, and ¹³C NMR spectra were essentially identical with those of authentic samples. Products **3h**, **3i**, **3l**, and **3m** are new compounds and they were characterized by their spectroscopic data (IR, ¹H and ¹³C NMR, and MS).

2-(3-Nitrophenyl)-1,3,4-oxadiazole (3h, C₈H₅N₃O₃)

Mp 125–126°C; IR (KBr): $\bar{\nu}$ = 1611 (C=N), 1524, 1462, 1059 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ = 7.75–8.59 (m, 4H, Ar-H), 8.93 (s, CH) ppm; ¹³C NMR (CDCl₃, 75 MHz): δ = 122.06, 125.19, 126.43, 130.57, 132.68, 148.66, 174.81 ppm; MS: *m/z* (%) = 191 (M⁺, 100), 150 (48), 117 (25), 90 (78).

2-Methyl-5(3-nitrophenyl)-1,3,4-oxadiazole (3i, C₉H₇N₃O₃)

Mp 156–158°C; IR (KBr): $\bar{\nu}$ = 1586, 1561, 1467, 1062 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ = 2.68 (s, CH₃), 7.71–8.84 (4H, m, Ar-H) ppm; ¹³C NMR (CDCl₃, 75 MHz): δ = 111.69, 121.63, 125.57, 126.01, 130.42, 132.28, 148.61, 163.61, 164.54 ppm; MS: *m/z* (%) = 205 (M⁺, 100), 150 (48), 104 (32), 76 (30), 15 (45).

2-Phenyl-1,3,4-oxadiazole (3l, C₈H₆N₂O)

Mp 150–152°C; IR (KBr): $\bar{\nu}$ = 1598, 1574, 1481, 1070, 712, 691 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MHz): δ = 7.45–7.83 (m, 5H, Ar-H), 8.10 (s, CH) ppm; ¹³C NMR (CDCl₃, 75 MHz): δ = 127.91, 128.93, 129.05, 132.34, 160.39, 165.69 ppm; MS: *m/z* (%) = 147 (M + 1, 25), 146 (M⁺, 22), 105 (100), 77 (100).

2-Ethyl-5-phenyl-1,3,4-oxadiazole (3m, C₁₀H₁₀N₂O)

Mp 104–105°C; IR (KBr): $\bar{\nu}$ = 1573, 1533, 1483, 1057, 795, 689 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ = 1.12 (t, *J* = 6.75 Hz, CH₃), 2.31 (q, *J* = 6.75 Hz, CH₂), 7.34–7.784 (m, 5H, Ar-H) ppm; ¹³C NMR (CDCl₃, 75 MHz): δ = 9.61, 27.33, 127.57, 128.65, 131.31, 132.38, 165.38, 172.64 ppm; MS: *m/z* (%) = 174 (M⁺, 45), 136 (23), 105 (100), 77 (73), 51 (23).

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