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Alum ($KAl(SO_4)_2 \cdot 12H_2O$): An Efficient and Inexpensive Catalyst for the One-pot Synthesis of 1,3,4-Oxadiazoles under Solvent-Free Conditions

Minoo Dabiri[1,*], **Peyman Salehi**[2], **Mostafa Baghbanzadeh**[1], and **Mahboobeh Bahramnejad**[1]

[1] Department of Chemistry, Faculty of Science, Shahid Beheshti University, Tehran, Iran
[2] Department of Phytochemistry, Medicinal Plants and Drugs Research Institute, Shahid Beheshti University, Tehran, Iran

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Summary. Alum ($KAl(SO_4)_2 \cdot 12H_2O$) 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*/*TBA*F [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.

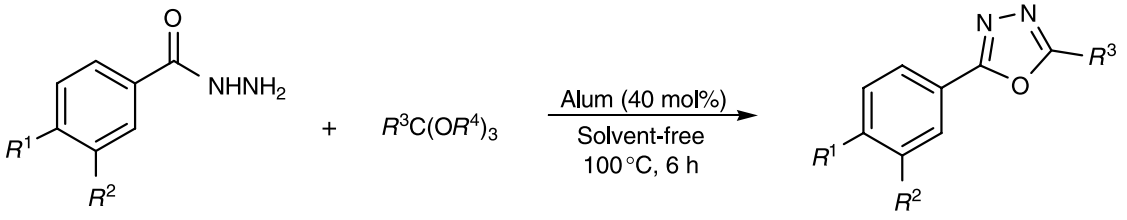
There is an increasing interest in the use of environmentally benign reagents, conditions, and particularly to solvent-free procedures. Avoiding organic solvents during the reactions in organic synthesis leads to a clean, efficient, and economical technology [16].

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 $KAl(SO_4)_2 \cdot 12H_2O$ (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**; $R^1 = Cl$, $R^2 = H$) and trimethyl orthoformate (**2**; $R^3 = H$, $R^4 = Me$) in the presence of a catalytic amount of alum at different temperatures was investigated under solvent-free

* Corresponding author. E-mail: m-dabiri@sbu.ac.ir



1 **2** **3a–3m**

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	*Me*	95	133–134	[15d]
3b	Cl	H	*Me*	*Et*	82	106–107	[16k]
3c	Cl	H	*n-Pr*	*Et*	93	76–78	[15d]
3d	Cl	H	*n-Bu*	*Me*	87	69–71	[15d]
3e	Cl	H	*Et*	*Et*	90	93–94	[15d]
3f	Cl	H	*Ph*	*Et*	95	160–162	[19]
3g	H	NO_2	*Ph*	*Et*	85	147–149	[15e]
3h	H	NO_2	H	*Me*	93	125–126	–
3i	H	NO_2	*Me*	*Et*	85	156–158	–
3j	H	H	*Ph*	*Et*	92	138–139	[19]
3k	H	H	*Me*	*Et*	86	65–67	[15e]
3l	H	H	H	*Me*	89	150–152	–
3m	H	H	*Et*	*Et*	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 *Et*OH 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. ^{1}H and ^{13}C 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 cm^3 orthoester **2** 0.4 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 cm^3 water. Finally, the crude product was recrystallized from *Et*OH 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, ^{1}H, and ^{13}C 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, ^{1}H and ^{13}C NMR, and MS).

2-(3-Nitrophenyl)-1,3,4-oxadiazole (**3h**, $C_8H_5N_3O_3$)
Mp 125–126°C; IR (KBr): $\bar{\nu} = 1611$ (C=N), 1524, 1462, 1059 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.75$–8.59 (m, 4H, Ar–H), 8.93 (s, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 122.06$, 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**, $C_9H_7N_3O_3$)
Mp 156–158°C; IR (KBr): $\bar{\nu} = 1586$, 1561, 1467, 1062 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 2.68$ (s, CH_3), 7.71–8.84 (4H, m, Ar–H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta =$ 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**, $C_8H_6N_2O$)
Mp 150–152°C; IR (KBr): $\bar{\nu} = 1598$, 1574, 1481, 1070, 712, 691 cm^{-1}; ^1H NMR (*DMSO*-d_6, 300 MHz): $\delta = 7.45$–7.83 (m, 5H, Ar–H), 8.10 (s, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 127.91$, 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**, $C_{10}H_{10}N_2O$)
Mp 104–105°C; IR (KBr): $\bar{\nu} = 1573$, 1533, 1483, 1057, 795, 689 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 1.12$ (t, $J =$ 6.75 Hz, CH_3), 2.31 (q, $J = 6.75$ Hz, CH_2), 7.34–7.784 (m, 5H, Ar–H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 9.61$, 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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References

[1] a) Ates O, Kocabalkanli A, Sanis GO, Ekini AC, Vidin A (1997) Drug Res **47**: 1134; b) Dabhi TP, Shah VH, Parikh AR (1992) Indian J Pharm Sci **54**: 98; c) Hui XP, Zhang LM, Zhang ZY, Wang Q, Wang F (1999) Indian J Chem Sect B Org Chem Incl Med Chem **38**: 1066
[2] a) Holla BS, Gonsalves R, Shenoy S (2000) Eur J Med Chem **35**: 267; b) Cesur N, Birteksoz S, Otuk G (2002) Acta Pharm Turcica **44**: 23; c) Laddi UV, Desai SR, Bennur RS, Bennur SC (2002) Indian J Heterocycl Chem **11**: 319
[3] Tyagi M, Kumar A (2002) Oriental J Chem **18**: 125
[4] Zheng X, Li Z, Wang Y Chen W, Huang Q, Liu C, Song G (2003) J Fluorine Chem **123**: 163
[5] Zou XJ, Lai LH, Jin GY, Zhang ZX (2002) J Agric Food Chem **50**: 3757
[6] a) Rigo B, Fassuer D, Cauliez P, Couturier D (1989) Synth Commun **19**: 2321; b) Rigo B, Cauliez P, Fasseur D, Couturier D (1988) Synth Commun **18**: 1247; c) Singh SP, Naithani R, Batra H, Prakash O, Sharma D (1998) Indian J Heterocycl Chem **8**: 103; d) Froeyen P (1991) Phosphorus, Sulfur Silicon Relat Elem **57**: 11; e) Milcent R, Barbier G (1983) J Heterocycl Chem **20**: 77; f) Singh SP, Batra H, Sharma PK (1997) J Chem Res (S) **12**: 468; g) Lutun S, Hasiak B, Couturier D (1999) Synth Commun **29**: 111; h) Isobe T, Ishikawa T (1999) J Org Chem **64**: 6989; i) Tandon VK, Chhor RB (1999) Synth Commun **31**: 1727; j) Natero R, Koltun DO, Ablocki JA (2004) Synth Commun **34**: 2523; k) Sharma GVM, Begum A, Krishna PR (2004) Synth Commun **34**: 2387; l) Yang YH, Shi M (2005) Tetrahedron Lett **46**: 6285; m) Dabiri M, Salehi P, Baghbanzadeh M, Bahramnejad M (2006) Tetrahedron Lett **47**: 6983
[7] a) Hamad ASS, Hashem HI (2002) J Heterocycl Chem **39**: 1325; b) Kerr VN, Ott DG, Hayes FN (1960) J Am Chem Soc **82**: 186
[8] Borg S, Vollinga RC, Labarre M, Payza K, Terenius L, Luthman K (1999) J Med Chem **42**: 4331
[9] Carlsen PHJ, Jorgensen KB (1994) J Heterocycl Chem **31**: 805
[10] Short FW, Long LN (1969) J Heterocycl Chem **6**: 7
[11] Reddy CK, Reddy PSN, Ratnam CV (1983) Synthesis 842
[12] Spiros L, Allen MP, Segelstein BE (2000) Synth Commun **30**: 437
[13] Rigo B, Cauliez P (1986) Synth Commun **16**: 1665
[14] a) Brain CT, Paul JM, Loong Y, Oakley PJ (1999) Tetrahedron Lett **40**: 3275; b) Brain CT, Brunton SA (2001) Synlett 382; c) Brown B, Clemens I, Neesom JK (2000) Synlett 131
[15] a) Ainsworth C (1955) J Am Chem Soc **77**: 1148; b) Leiby RW (1984) J Heterocycl Chem **21**: 1825; c) Shafiee A, Naimi E, Mansobi P, Foroumadi A, Shekari M (1995) J Heterocycl Chem **32**: 1235; d) Khajavi MS, Sadat Hosseini SS, Sefidkon F (1997) Iran J Chem Chem Eng **16**: 68; e) Dabiri M, Salehi P, Baghbanzadeh M, Bahramnejad M (2007) Synth Commun **37**: 1201
[16] Tanaka K, Toda F (2000) Chem Rev **100**: 1025
[17] a) Dabiri M, Salehi P, Mohammadi AA, Baghbanzadeh M (2005) Synth Commun **35**: 279; b) Salehi P, Dabiri M, Baghbanzadeh M, Bahramnejad M (2006) Synth Commun **36**: 2287; c) Dabiri M, Salehi P, Mohammadi AA, Baghbanzadeh M, Kozehgiry G (2004) J Chem Res (S) 570; d) Salehi P, Dabiri M, Zolfigol MA, Bodaghi Fard MA (2003) Tetrahdron Lett **44**: 2889; e) Salehi P, Dabiri M, Zolfigol MA, Baghbanzadeh M (2005) Synlett 1155; f) Salehi P, Dabiri M, Khosropour AR, Roozbehniya P (2006) J Iran Chem Soc **3**: 98; g) Salehi P, Dabiri M, Zolfigol MA, Baghbanzadeh M (2005) Tetrahedron Lett **46**: 7051; h) Salehi P, Dabiri M, Zolfigol MA, Otokesh S, Baghbanzadeh M (2006) Tetrahedron Lett **47**: 2557; i) Baghbanzadeh M, Salehi P, Dabiri M, Kozehgary GH (2006) Synthesis 344; j) Dabiri M, Salehi P, Zolfigol MA, Baghbanzadeh M (2007) Heterocycles **71**: 677
[18] a) Dabiri M, Salehi P, Baghbanzadeh M, Kiani S, Vakilzadeh Y (2007) Monatsh Chem **138**: (in press); b) Azizian J, Mohammadi AA, Karimi AR, Mohammadizadeh MR (2005) J Org Chem **70**: 350
[19] Rostamizadeh S, Ghasem Housaini SA (2004) Tetrahedron Lett **45**: 8753