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Abstract: A rapid and green synthesis of 2,5-disubstituted 1,3,4-oxadiazoles is reported. The title compounds were prepared by the reaction of different acyl hydrazides and orthoesters in the presence of silica sulfuric acid under solvent-free

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conditions. In this new process, reactions were run at ambient temperature and completed in a short period of time with high yields.

Keywords: heterogeneous catalysis, heterocycles, 1,3,4-oxadiazoles, silica sulfuric acid, solvent free

INTRODUCTION

Heterocycles form by far the largest of classical divisions of organic chemistry and are of immense importance biologically, industrially, and indeed to the functioning of any developed human society. The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic, as are many additives and modifiers used in industry. Searching for simple and efficient methods for generation of libraries of novel heterocyclic compounds is in demand.[1,2]

Substituted 1,3,4-oxadiazoles are of considerable interest in medicinal chemistry,[10–20] pesticide chemistry,[3] and polymer[4–6] and material science.[7–9] As a consequence of these characteristics, oxadiazoles have an impact in numerous drug discovery programs, including muscarinic agonists,[10] benzodiazepine receptor partial agonists,[11] dopamine transporters,[12] antirhinovirals,[13] growth hormone secretagogoues,[14] fungicides,[15] central nervous system (CNS) stimulants, and anti-inflammatory, hypotensive,[16] insecticidal,[17,18] bactericidal,[19] and anticonvulsant agents.[20] Because of these properties, the synthesis of this group of compounds has attracted significant interest. There are several methods for their synthesis in the literature, which can be classified in to four main routes: (i) cyclization of diacyl hydrazides **2** in the presence of a dehydrating agent,[21–26] (ii) oxidation of acyl hydrazones **3**,[27,28] (iii) reaction of acyl hydarzides with orthoesters in the presence of an acidic catalyst,[29–32] and (iv) solid-phase synthesis (Figure 1).[33–37] In addition to these procedures, some other methods could also be found in the literature.[38–40] 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. Unfortunately, most of the procedures that have been described for this reaction use toxic reagents or solvents, have long reaction times, or use a domestic microwave oven, which could not be adapted to an industrial scale and furthermore repeatability is low.

The principles of green chemistry dictate that chemical transformations should be designed to minimize (a) required energy input, either mechanical or thermal, and (b) the use of harmful organic solvents.

Many reactions proceed efficiently under solvent-free conditions.[41,42] Indeed, in many cases, solid-state organic reactions occur efficiently and more selectively than those of their solution counterparts, because

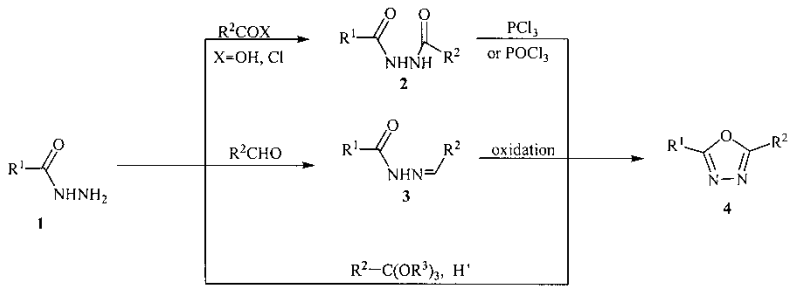


Figure 1. General methods for the synthesis of 1,3,4-oxadiazoles.

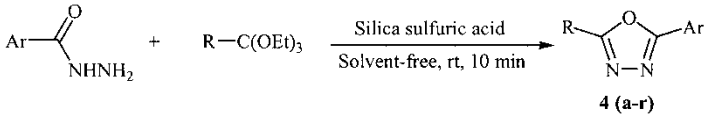
molecules in a crystal are arranged tightly and regularly.[43] For synthesis of our target compounds, a solvent-free reaction was selected.

RESULTS AND DISCUSSION

Here we report a procedure for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles. Recently we found silica sulfuric acid is a green, reusable, and versatile acidic catalyst for organic synthesis.[44–46] Upon simple mixing of neat orthoesters with an acyl hydrazide in the presence of catalytic amounts of silica sulfuric acid, an immediate conversion to 2,5-disubstituted 1,3,4-oxadiazole was observed (Scheme 1). The results summarized in Table 1 establish the scope of this reaction.

The orthoesters were liquid at room temperature, thus making the process easier. As the reactions were run neat and only 1 equivalent of each reagent was needed, there were no problematic side products; the only side product was ethanol, which was a solvent for washing and separating the catalyst; the workup was straightforward and included separating the solid catalyst. In addition, the reactants were not especially sensitive to air or water, so no precautions needed to be taken. It is noteworthy that the reactions were completed in 10 min. To our knowledge, this is the first example of direct synthesis of disubstituted oxadiazoles at room temperature in a very short period of time.

To emphasize the effect of the catalyst, the model reaction between 4-chlorobenzhydrazide and triethyl orthopropionate was described, and different acidic catalysts were subjected to the reaction. All the reactions were run in the same conditions, and similar amounts of catalysts



Scheme 1.

Table 1. Synthesis of mono- and disubstituted oxadiazoles toward the reaction of acyl hydrazides and orthoesters in the presence of silica sulfuric acid at room temperature in 10 min

Product[a]	Ar	R	Yield (%)[b]	Mp (°C)
4a	4-ClC_6H_4	H	92	132–133[32]
4b	4-ClC_6H_4	CH_3	90	109–111[8]
4c	4-ClC_6H_4	C_2H_5	94	90–91[32]
4d	4-ClC_6H_4	$(CH_2)_2CH_3$	90	70–72[32]
4e	4-ClC_6H_4	$(CH_2)_3CH_3$	87	66–67[32]
4f	4-ClC_6H_4	Ph	90	162–163[27]
4g	3-$O_2NC_6H_4$	H	88	125–126
4h	3-$O_2NC_6H_4$	CH_3	85	156–158
4i	3-$O_2NC_6H_4$	$(CH_2)_2CH_3$	93	64–65
4j	3-$O_2NC_6H_4$	$(CH_2)_3CH_3$	80	70–71
4k	3-$O_2NC_6H_4$	Ph	85	150–151[27]
4l	Ph	CH_3	93, 90, 91, 84, 86[c]	65–67[29]
4m	Ph	Ph	90	135–136[27]
4n	Ph	H	91	150–152
4o	Ph	C_2H_5	93	104–105
4p	Ph	$(CH_2)_2CH_3$	89	75–76
4q	Ph	$(CH_2)_3CH_3$	95	70–72
4r	4-Pyridyl	Ph	87	148–150[28]

[a]The products were characterized by comparison of their spectroscopic and physical data with authentic samples synthesized by reported procedures.

[b]Isolated yield based on acyl hydrazide.

[c]The catalyst was recycled for five runs.

(30 mol%) were used. As can be seen in Table 2, satisfactory results were obtained only with silica sulfuric acid.

To investigate the possibility of recycling the catalyst, the reaction of benzhydrazide and triethyl orthoacetate in the presence of 30 mol% of silica sulfuric acid was investigated. After completion of the reaction, ethanol was

Table 2. Effect of acidic catalyst on the reaction of 4-chlorobenzhydrazide and triethyl orthopropionate[a]

Catalyst	Yield (%)
p-TsOH	42
$NaHSO_4$	33
$NaHSO_3$	28
H_2SO_4	25
Montmorillonite K-10	48
Silica sulfuric acid	94

[a]All the reactions were run in 10 min.

added, and the mixture was filtered to separate the catalyst. The recycled catalyst was used for further runs. No decrease in catalytic activity of silica sulfuric acid was observed even after five runs (Table 1, **4l**).

In conclusion, a very simple, efficient, and ecofriendly synthesis of 2,5-disubstituted oxadiazoles has been devised. Several symmetrical and unsymmetrical 1,3,4-oxadiazoles were synthesized to show the diversity of the method. We believe this method could be addressed for the combinatorial synthesis of oxadiazoles in drug discovery programs.

EXPERIMENTAL

Products **4** (**a**–**f**), **4** (**k**–**m**), and **4r** are known compounds, and their physical data, IR, and ^{1}H NMR spectra were essentially identical with those of authentic samples. Other products that are new were characterized by their spectroscopic data (IR, ^{1}H and ^{13}C NMR, and MS). Melting points were obtained in open capillary tubes and also on the Electrothermal 9100 apparatus and are not corrected. Mass spectra were recorded on a Shimadzu QP 1100 BX mass spectrometer. IR spectra were recorded on KBr pellets on a Shimadzu IR-470 spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined on a Bruker 300 DRX Avance instrument at 300 and 75 MHz, respectively.

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

Acyl hydrazide (1 mmol), orthester (1.2 mmol), and silica sulfuric acid (0.11 g, equal to 0.3 mmol H^+) were placed in a round-bottomed flask. The resulting mixture was stirred magnetically at ambient temprature. Upon completion of the reaction, as confirmed by thin-layer chromatography (TLC) (eluent: *n*-hexane/ethyl acetate: 3/1), ethanol (2 mL) was added, and the mixture was filtered to separate the catalyst. The ethanol was evaporated under reduced pressure, and the products were recrystallized from ethanol for further purity.

Selected Data for New Compounds

2-(3-Nitrophenyl)-1,3,4-oxadiazole (**4g**): mp 125–126°C. IR (KBr): 1611, 1583, 1524, 1462, 1059 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.75–8.59 (m, 4H, Ar-H), 8.93 (s, 1H, C_5-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 122.07, 125.194, 126.43, 130.57, 132.68, 148.66, 174.81. MS (EI, 70 eV) (m/z, %): 191 (M^+, 100), 150 (48), 117 (25), 90 (78).

2-Methyl-5(3-nitrophenyl)-1,3,4-oxadiazole (**4h**): mp 156–158°C. IR (KBr): 1586, 1561, 1467, 1062 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.68 (s, 3H,

CH_3), 7.71–8.84 (m, 4H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 11.17, 121.63, 125.57, 126.01, 130.42, 132.28, 148.61, 163.06, 164.54. MS (EI, 70 eV) (m/z, %): 205 (M^+, 100), 150 (48), 104 (32), 76 (30), 15 (45).

2-Propyl-5(3-nitrophenyl)-1,3,4-oxadiazole (**4i**): mp 64–65°C. IR (KBr): 1597, 1560, 1470, 1066 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.08 (t, $J = 7.4$ Hz, 3H), 1.92 (sex, $J = 7.42$ Hz, 2H), 2.95 (t, $J = 7.45$ Hz, 2H), 7.71–8.84 (m, 4H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.62, 20.08, 27.31, 121.62, 125.73, 125.92, 130.38, 132.32, 148.6, 162.86, 167.73. MS (EI, 70 eV) (m/z, %): 234 (MH^+, 50), 205 (100), 150 (40), 104 (30), 76 (30), 43 (45).

2-Butyl-5(3-nitrophenyl)-1,3,4-oxadiazole (**4j**): mp 70–71°C. IR (KBr): 1593, 1558, 1471, 1003 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.99 (t, $J = 7.16$ Hz, 3H), 1.45–1.9 (m, $J = 7.19$ Hz, 4H), 2.97 (t, $J = 7.4$ Hz, 2H), 7.7–8.84 (m, 4H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.58, 22.17, 25.17, 28.55, 121.63, 125.72, 125.94, 130.38, 132.34, 148.59, 162.85, 167.93. MS (EI, 70 eV) (m/z, %): 248 (MH^+, 25), 205 (100), 150 (25), 104 (30), 76 (46), 57 (35), 41 (40).

2-Phenyl-1,3,4-oxadiazole (**4n**): mp 150–152°C. IR (KBr): 1598, 1574, 1481, 1070, 712, 691 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz) δ: 7.45–7.83 (m, 5H, Ar-H), 8.10 (s, 1H, C_5-H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 127.91, 128.93, 129.05, 132.34, 160.39, 165.69. MS (EI, 70 eV) (m/z,%): 147 (MH^+, 21), 105 (100), 77 (100), 51 (35).

2-Ethyl-5-phenyl-1,3,4-oxadiazole (**4o**): mp 104–105°C. IR (KBr): 1573, 1533, 1483, 1057, 795, 689 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.12 (t, $J = 6.75$ Hz, 3H), 2.31 (q, $J = 6.75$ Hz, 2H), 7.34–7.84 (m, 5H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 9.61, 27.33, 127.75, 128.65, 131.31, 132.38, 165.38, 172.64. MS (EI, 70 eV) (m/z, %): 174 (M^+, 45), 136 (23), 105 (100), 77 (73), 51 (23).

2-Propyl-5-phenyl-1,3,4-oxadiazole (**4p**): mp 75–76°C. IR (KBr): 1575, 1533, 1484, 1072, 891, 689 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.93 (t, $J = 7.3$ Hz 3H), 1.66 (sex, $J = 7.3$ Hz, 2H), 2.28 (t, $J = 7.27$ Hz, 2H), 7.27–7.84 (m, 5H, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 13.61, 18.92, 35.89, 127.39, 128.56, 131.21, 132.28, 164.9, 171.33. MS (EI, 70 eV) (m/z, %): 188 (M^+, 21), 160 (20), 136 (25), 105 (100), 77 (85), 51 (60).

2-Butyl-5-phenyl-1,3,4-oxadiazole (**4q**): mp 70–72°C. IR (KBr): 1599, 1552, 1481, 1086, 805, 689 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz) δ: 0.89 (t, $J = 7.3$ Hz, 3H), 1.33 (sex, $J = 7.3$ Hz, 2H), 1.53 (quin, $J = 7.35$ Hz, 2H), 2.17 (t, $J = 7.4$ Hz, 2H), 7.46–7.87 (m, 5H, Ar-H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 14.18, 22.16, 27.67, 33.46, 127.86, 128.88, 132.21,

132.96, 165.95, 172.12. MS (EI, 70 eV) (m/z, %): 202 (M^+, 45), 178 (25), 138 (48), 105 (100), 77 (92), 57 (65).

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