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A facile procedure for the one-pot synthesis of unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles

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Abstract—Unsymmetrically 2,5-disubstituted 1,3,4-oxadiazoles were efficiently synthesized from the cyclization–oxidation reaction of acyl hydrazones. Also, the synthesis of the title compounds was achieved by the condensation of acyl hydrazides and aromatic aldehydes in the presence of ceric ammonium nitrate in dichloromethane.

Heterocycles form by far the largest of classical divisions of organic chemistry and are of immense importance biologically and industrially. The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic while countless additives and modifiers used in industrial applications ranging from cosmetics, reprography, information storage and plastics are heterocyclic in nature. One striking structural feature inherent to heterocycles, which continue to be exploited to great advantage by the drug industry, lies in their ability to manifest substituents around a core scaffold in defined three-dimensional representations.

1,3,4-Oxadiazoles are a class of heterocycles which have attracted significant interest in medicinal and pesticide chemistry,[1,2] and polymer and material science.[3,4] Among the 1,3,4-oxadiazoles, 2,5-unsymmetrical disubstituted derivatives have attracted considerable attention because of their biological[5] and electrochemical properties.[3]

Several synthetic methods have been reported for the preparation of symmetrical disubstituted 1,3,4-oxadiazoles. One of the popular methods involve cyclization of diacylhydrazines prepared from the reaction of acyl chlorides and hydrazine. Several cyclodehydrating agents such as BF_3–OEt_2,[6] 1,1,1,3,3,3-hexamethydisilazane,[5] triflic anhydride,[7] phosphorus pentoxide,[8] polyphosphoric acid,[1a] thionyl chloride,[9] phosphorus oxychloride[10] and sulfuric acid[11] have been used. Due to the high reactivity of acyl chlorides their reaction with unprotected hydrazine results in the formation of diacyl hydrazides. Using 2-acylpyridazin-3-one as a mild acylating agent is a good method for the synthesis of unsymmetrical derivatives, reported by Park et al.[12]

One-pot syntheses of 1,3,4-oxadiazoles from hydrazine with carboxylic acids have also been reported.[13] Another synthetic route for the preparation of these compounds is via acylation of tetrazoles.[14] 1,3,4-Oxadiazoles have also been prepared by oxidation of acyl hydrazones with different oxidizing agents.[15–17] Reaction of acyl hydrazides with orthoesters in the presence of an acidic catalyst,[18] and solid phase syntheses of oxadiazoles[19] are other approaches for the synthesis of this group of compounds.

Ceric ammonium nitrate (CAN), was introduced by Smith et al. in 1936.[20] CAN has received considerable attention as an inexpensive and easily available catalyst for various organic reactions such as oxidation, oxidative addition, nitration, photo-oxidation, deprotection, graft polymerization, etc.[21]

Keywords: Heterocycles; 1,3,4-Oxadiazole; Ceric ammonium nitrate; Cyclization–oxidation.
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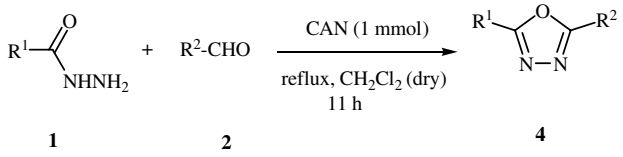
As a part of our ongoing investigation on developing versatile and efficient methods for the synthesis of important heterocyclic compounds,[22] we report here a new procedure for the synthesis of unsymmetrically 2,5-disubstituted 1,3,4-oxadiazoles.

First, the synthesis of 1,3,4-oxadiazoles was investigated through a two-step pathway (Scheme 1). Thus, the reaction of acyl hydrazides with aromatic aldehydes in the presence of catalytic amounts of CAN resulted in formation of the corresponding acyl hydrazones **3**. As shown, acyl hydrazones **3** bearing a variety of other functional groups were prepared in good to excellent yields in a short period of time (Table 1).

Subsequently, compounds **3** underwent cyclization–oxidation using CAN under solvent-free conditions (Scheme 1, Table 1). This step occurred in 20 min under mild conditions at room temperature. Sensitive functional groups such as methoxy, nitro, hydroxyl and pyridyl remained unaffected during the reaction.

The ability of CAN to promote both steps led us to investigate the one-pot synthesis of unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles starting from the same substrates.

When acyl hydrazides **1** and aromatic aldehydes **2** were stirred in dry dichloromethane under reflux in the presence of CAN, the corresponding 2,5-disubstitued 1,3,4-oxadiazoles **4** were obtained in moderate to good yields after 11 h (Scheme 2). The results are summarized in Table 2. The products were isolated by simple aqueous work-up followed by filtration.



1 **2** **4**

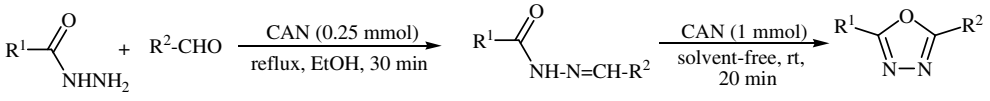
Scheme 2.

Aliphatic aldehydes were also investigated in this reaction but unfortunately, a mixture of compounds was produced and the desired oxadiazoles were obtained in low yields (Table 2, entries 19 and 20).

In conclusion, this investigation constitutes a novel and efficient route for the construction of unsymmetrical disubstituted 1,3,4-oxadiazoles. To the best of our knowledge this is the first report on the one-pot synthesis of this valuable heterocyclic core from cheap and easily available aldehydes.

1. General procedure for the synthesis of acyl hydrazones

A mixture of acyl hydrazide (1 mmol), aromatic aldehyde (1 mmol) and ceric ammonium nitrate (0.25 mmol) in ethanol (5 mL) was heated under reflux with stirring for 30 min. Water (5 mL) was added and the precipitated product was filtered and recrystallized from DMF and water.



1 **2** **3** **4**

Scheme 1.

Table 1. Synthesis of acyl hydrazones **3** and 1,3,4-oxadiazoles **4**

Entry	R^1	R^2	Product **3**		Product **4**	
			Yield[a,b] (%)	Mp (°C)	Yield[a] (%)	Mp (°C)
1	Ph	Ph	87	203–205[24]	71	133–135[27]
2	Ph	4-O_2N–C_6H_4	90	240–242[25]	76	200–203[27]
3	Ph	3-O_2N–C_6H_4	85	188[26]	80	144–146[28]
4	Ph	4-Cl–C_6H_4	82	218–220[25]	72	158–159[28]
5	Ph	4-Me–C_6H_4	90	217[25]	84	143–145[29]
6	Ph	4-MeO–C_6H_4	95	145[25]	64	145–146[27]
7	4-Cl–C_6H_4	Ph	92	230[24]	73	163–164[28]
8	4-Pyridyl	Ph	83	159[23]	67	150[23]
9	4-Pyridyl	4-O_2N–C_6H_4	89	190–192[23]	69	198[23]
10	4-Pyridyl	3-O_2N–C_6H_4	87	267[23]	73	125[23]
11	4-Pyridyl	4-Cl–C_6H_4	77	210[23]	78	170–172[23]
12	4-Pyridyl	4-Me–C_6H_4	81	190–192[23]	75	129–13025
13	4-Pyridyl	4-MeO–C_6H_4	79	158[23]	63	188[23]
14	4-Pyridyl	2-HO–C_6H_4	80	260–262[23]	72	225–226[23]

[a] The products were characterized by comparison of their spectroscopic and physical data with those reported in the literature.
[b] Isolated yield based on the aldehyde.

Table 2. One-pot synthesis of 2,5-disubstituted 1,3,4-oxadiazoles **4**

Entry	R^1	R^2	Yield[a] (%)	Mp (°C)
1	Ph	Ph	48	139–140[16b]
2	Ph	4-O_2N–C_6H_4	51	202–204[16b]
3	Ph	3-O_2N–C_6H_4	45	143–146[16b]
4	Ph	4-Cl–C_6H_4	60	160–162[16b]
5	Ph	4-Me–C_6H_4	67	145–146[16b]
6	Ph	4-MeO–C_6H_4	45	149–151[16b]
7	Ph	2-Furyl	42	98–100[30]
8	Ph	3-Pyridyl	52	108–109[32]
9	Ph	2,4-Cl_2–C_6H_3	55	98–100[33]
10	4-Cl–C_6H_4	4-MeO–C_6H_4	59	152–153[33]
11	4-Cl–C_6H_4	Ph	65	158–160[16b]
12	4-Pyridyl	Ph	48	153[23]
13	4-Pyridyl	4-O_2N–C_6H_4	45	198–199[23]
14	4-Pyridyl	3-O_2N–C_6H_4	47	118–121[23]
15	4-Pyridyl	4-Cl–C_6H_4	56	168–170[23]
16	4-Pyridyl	4-Me–C_6H_4	62	130–132[23]
17	4-Pyridyl	4-MeO–C_6H_4	49	180–183[23]
18	4-Pyridyl	2-HO–C_6H_4	43	230–231[24]
19	Ph	Et	25	104–105[33]
20	4-Cl–C_6H_4	*n*-Pr	30	76–78[31]

[a] Isolated yield based on the aldehyde.

2. General procedure for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles

1-Aroyl-benzylidene hydrazine derivative **3** (0.75 mmol) and ceric ammonium nitrate (1 mmol) were ground in a pestle and mortar at room temperature without any solvent for 20 min. Dichloromethane (5 mL) was added followed by addition of water (5 mL). The organic phase was separated and dried over $MgSO_4$. The mixture was concentrated and the solid residue was recrystallized from dichloromethane (Table 1).

3. General procedure for the one-pot synthesis of 2,5-disubstituted 1,3,4-oxadiazoles

To a solution of acyl hydrazides (1 mmol) and aromatic aldehyde (1 mmol) in dry dichloromethane (5 mL) was added ceric ammonium nitrate (1 mmol). The reaction mixture was stirred for 11 h at reflux. Water (5 mL) was added and the mixture was extracted with chloroform (3×5 mL). The organic layer was separated and dried over $MgSO_4$. The solvent was evaporated and the crude product was recrystallized from dichloromethane to give the desired product (Table 2).

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33. *2-(2,4-Dichlorophenyl)-5-phenyl-1,3,4-oxadiazole (entry 9, Table 2)*: mp: 98–100 °C. IR (KBr) ν/cm^{-1}: 1588, 1450, 1101, 836, 701. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.43–7.46 (m, 1H, Ar–H), 7.54–7.62 (m, 4H, Ar–H), 8.08–8.17 (m, 3H, Ar–H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 121.73, 123.58, 127.01, 127.69, 129.17, 131.24, 131.91, 132.05, 133.81, 138.13, 162.36, 165.21. MS (EI, 70 eV) (*m*/*z*, %): 290 (M^+, 25), 152 (23), 121 (20), 105 (100), 77 (52).
2-(4-Chlorophenyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (entry 10, Table 2): mp: 152–153 °C. IR (KBr) ν/cm^{-1}: 1612, 1497, 1259, 1090, 830, 740. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.90 (s, 3H, OCH_3), 7.03 (d, $J = 7.74$ Hz, 2H, Ar–H), 7.51 (d, $J = 7.50$ Hz, 2H, Ar–H), 8.05–8.08 (m, 4H, Ar–H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 55.49, 114.55, 116.18, 122.54, 128.07, 128.74, 129.43, 137.77, 162.46, 163.32, 164.68. MS (EI, 70 eV) (*m*/*z*, %): 286 (M^+, 60), 195 (20), 152 (23), 135 (100), 111 (25), 77 (20).
2-Ethyl-5-phenyl-1,3,4-oxadiazole (entry 19, Table 2): white solid, mp: 104–105 °C. IR (KBr): ν/cm^{-1}: 1573, 1533, 1483, 1057, 795, 689. ^1H NMR ($CDCl_3$, 300 MHz): δ (ppm): 1.12 (t, $J = 6.75$ Hz, 3H, CH_3), 2.31 (q, $J = 6.75$ Hz, 2H, CH_2), 7.34–7.51 (m, 3H, Ar–H), 7.83 (d, $J = 7.80$ Hz, 2H, Ar–H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 9.61, 27.33, 127.57, 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).