

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

Minoo Dabiri,^{a,*} Peyman Salehi,^{b,*} Mostafa Baghbanzadeh^a and Mahboobeh Bahramnejad^a

^aDepartment of Chemistry, Faculty of Science, Shahid Beheshti University, Tehran 1983963113, Iran

^bDepartment of Phytochemistry, Medicinal Plants and Drugs Research Institute, Shahid Beheshti University, Tehran, PO Box 19835-389, Iran

Received 7 June 2006; revised 17 July 2006; accepted 25 July 2006

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.

© 2006 Published by Elsevier Ltd.

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 biological⁵ 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 $\text{BF}_3\text{--OEt}_2$,⁶ 1,1,1,3,3,3-hexamethyldisilazane,⁵ triflic anhydride,⁷ phosphorus pentoxide,⁸ polyphosphoric acid,^{1a} thionyl chloride,⁹ phosphorus oxychloride¹⁰ and sulfuric acid¹¹ 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 oxadiazoles¹⁹ 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.

*Corresponding authors. Tel.: +98 21 22431661; fax: +98 21 22431663; e-mail: m-dabiri@sbu.ac.ir

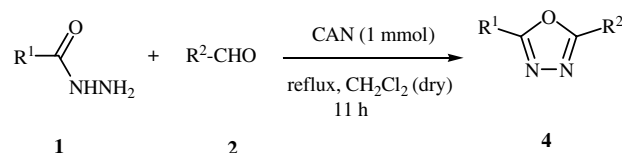
As a part of our ongoing investigation on developing versatile and efficient methods for the synthesis of important heterocyclic compounds,²² we report here a new procedure for the synthesis of unsymmetrically 2,5-disubstituted 1,3,4-oxadiazoles.

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-disubstituted 1,3,4-oxadiazoles 4 were obtained in moderate to good yields after 11 h (Scheme 2). The results are summarized in



Scheme 2.

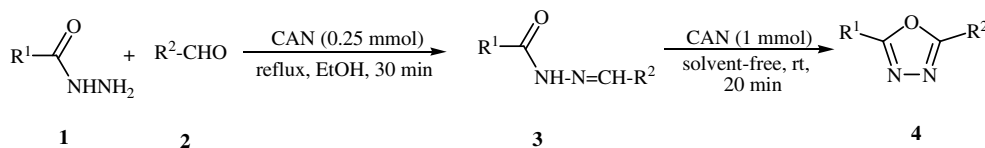
Table 2. The products were isolated by simple aqueous work-up followed by filtration.

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.



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 ₂ N–C ₆ H ₄	90	240–242 ²⁵	76	200–203 ²⁷
3	Ph	3-O ₂ N–C ₆ H ₄	85	188 ²⁶	80	144–146 ²⁸
4	Ph	4-Cl–C ₆ H ₄	82	218–220 ²⁵	72	158–159 ²⁸
5	Ph	4-Me–C ₆ H ₄	90	217 ²⁵	84	143–145 ²⁹
6	Ph	4-MeO–C ₆ H ₄	95	145 ²⁵	64	145–146 ²⁷
7	4-Cl–C ₆ H ₄	Ph	92	230 ²⁴	73	163–164 ²⁸
8	4-Pyridyl	Ph	83	159 ²³	67	150 ²³
9	4-Pyridyl	4-O ₂ N–C ₆ H ₄	89	190–192 ²³	69	198 ²³
10	4-Pyridyl	3-O ₂ N–C ₆ H ₄	87	267 ²³	73	125 ²³
11	4-Pyridyl	4-Cl–C ₆ H ₄	77	210 ²³	78	170–172 ²³
12	4-Pyridyl	4-Me–C ₆ H ₄	81	190–192 ²³	75	129–130 ²⁵
13	4-Pyridyl	4-MeO–C ₆ H ₄	79	158 ²³	63	188 ²³
14	4-Pyridyl	2-HO–C ₆ H 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.

Download English Version:

<https://daneshyari.com/en/article/5288794>

Download Persian Version:

<https://daneshyari.com/article/5288794>

[Daneshyari.com](https://daneshyari.com)