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A mild and facile method for one pot synthesis of 2,5-di-substituted 1,3,4-oxadiazoles at room temperature

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Abstract

2,5-Di-substituted 1,3,4-oxadiazoles **3a-n** have been synthesized as a one pot procedure from the reaction of acid hydrazide **1**, acyl halides **2** and phosphorus pentoxide in acetonitrile at room temperature. High yield, short reaction time (10–15 min), mild condition, and easy work-up are advantages of this methodology.

Keywords: 1,3,4-Oxadiazole; Acid hydrazide; Acyl halide; Phosphorus pentoxide

The synthesis of compounds incorporating 1,3,4-oxadiazole rings in their structure has attracted widespread attention, mainly in connection with their wide range of pharmacological properties such as anti-inflammatory, [1] anticonvulsant [2] and antibacterial activities [3]. They have also shown antimitotic [4] antifungal [5], muscle relaxant [6], anti-mycobacterial [7], insecticidal [8] antimicrobial and anti-HIV activity [9]. Their utility in material science is due to their luminescent and thermal stability [10–12].

1,3,4-Oxadiazoles have been prepared by different methods. One of the most common routes to these compounds involves cyclodehydration of 1,2-diacyl and 1,2-diaroyl hydrazines with a variety of anhydrous reagents such as thionyl chloride [13], phosphorous pentoxide [14], phosphorous oxychloride [15], triflic anhydride [16], acid chloride [17], polyphosphoric acid [18], and sulfuric acid [19]. They have also been prepared from oxidation of acylhydrazones with different oxidizing agents [20–22]. Recently, solid phase synthesis of these compounds under mild conditions was also reported [23–25]. A few one pot methods have also been reported in the literature [26].

Phosphorus pentoxide, is a powerful and inexpensive dehydrating agent which has been used in a variety of organic reactions such as formation of amides, anhydrides, cyclodehydration and condensation reactions [27].

1. Experimental

Evaporation of the solvents was performed using a rotovaper Buchi R 3000. Melting points were taken on a Buchi B-540 melting point apparatus. IR spectra were taken with a Shimadzu IR-408 spectrometer (KBr). The ^{1}HNMR spectra were determined in $CDCl_3$ solution on a Bruker DRX-500 Avance (500 MHz). Merck silica gel 60GF254 was

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Table 1
One pot synthesis of 2,5-di-substituted-1,3,4-oxadizoles **3a-n**[a]

Entry	R^1	R^2	Time (min)	Yield (%)	m.p. (°C)	Lit. m.p. (°C)
a	Ph	Ph	10	97	137–138	136 [21c,22a]
b	Ph	4-NO_2–$C_6H_4^-$	12	88	207	209–210 [21c,30]
c	Ph	4-Cl–$C_6H_4^-$	10	92	162–163	162 [21c,27e]
d	Ph	4-Br–$C_6H_4^-$	10	94	167–168	167 [21c,31]
e	Ph	4-Me–$C_6H_4^-$	10	94	147–148	148 [21c,32]
f	Ph	4-MeO–$C_6H_4^-$	10	98	150–151	150 [21c,22a]
g	Ph	2-furyl–	15	81	103–104	103 [17]
h	Ph	3-NO_2–$C_6H_4^-$	10	90	151–152	147 [21c,22a]
I	Ph	2-NO_2–$C_6H_4^-$	10	87	121–122	121–122 [22a]
j	Ph	2,4-Di–Cl–$C_6H_3^-$	12	89	100–101	98–100 [27e]
k	4-Cl–$C_6H_4^-$	Ph	12	90	161–162	162 [22a,27e]
l	4-Cl–$C_6H_4^-$	4-Cl–$C_6H_4^-$	12	89	243	241–242 [27f]
m	4-Cl–$C_6H_4^-$	4-Me–$C_6H_4^-$	15	90	204–205	204–205 [33]
n	4-Cl–$C_6H_4^-$	4-NO_2–$C_6H_4^-$	12	87	218–219	217–218 [33]
o	CH_3	Ph	75	–	–	–
p	CH_3	4-NO_2–$C_6H_4^-$	90	–	–	–
q	Ph	CH_3	60	–	–	–
r	Ph	2,4-Di–NO_2–C_6H_3	30	–	–	–

[a] The products were characterized by comparison of their spectral and physical data with those of known samples in our previous work [21c] and other methods reported in the literature.

used for analytical and preparative TLC. Acid hydrazides were prepared according to the literature method [28] and silica sulfuric acid was prepared by following procedure. Commercial (98%) sulfuric acid (2 mL) is stirred with a suspension of silica gel (Merk silica gel 60, 70–230 mesh) (20 g) in methanol (40 mL) for 30 min. On evaporation of the solvent at 45 °C a dry white powder is obtained (23.5 g).

1.1. Synthesis of 2,5-di-substituted 1,3,4-oxadiazoles general procedure

Acid hydrazide (1 mmol), benzoyl chloride (1.3 mmol), and phosphorous pentoxide (5 mmol) was dissolved in acetonitrile (10 mL) and stirred at room temperature. After complete conversion (10–15 min) (Table 1) as indicated by TLC (EtOAc/ Petether), the solvent was removed under *vacuo* and the mixture was dissolved in dichloromethane and washed with water (3 × 50 mL). The organic layer was then dried over sodium sulfate and evaporated under *vacuo*. The precipitated solids were further recrystallized from ethanol.

2. Results and discussion

As part of our ongoing interest on developing efficient methods for the synthesis of useful heterocycles [29], we wish to report a general and convenient method for the synthesis of 1,3,4-oxadiazoles from readily available starting materials. This research is an easy and one pot procedure for the synthesis of 2,5-disubstituted-1,3,4-oxadiazoles, in which after treatment of acid hydrazides **1** with different acyl halides **2** in acetonitrile and in the presence of phophorus pentoxide at room temperature, 2,5-disubstituted-1,3,4-oxadiazoles **4a-n** were obtained in high yield (Scheme 1, Table 1).

In search of an efficient method to convert compounds **1** and **2** to the corresponding 2,5-diphenyl-1,3,4-oxadiazole (entry a), 1 mmol of different catalyts ($ZrCl_4$, silica sulfuric acid, and phosphorus pentoxide) and a variety of solvents (CH_2Cl_2, DMSO, DMF, EtOH, CH_3CN etc.) were used initially at both room temperature and under reflux condition. Among these, phosphorus pentoxide in acetonitrile at room temperature gave the best results. In order to further improve the yield of the reaction, optimization of the molar ratio of P_2O_5 was carried out at room temperature using different amounts of P_2O_5 in CH_3CN. As indicated in Table 1, the reaction of benzoic acid hydrazide with benzoyl chloride in acetonitrile and in the presence of 5 molar excess of P_2O_5 went to completion within 10 min with a yield of 97%. Further amounts of P_2O_5 had no significant effect on the yield of reaction. In a similar manner, compounds **3b-n** were prepared at room temperature (Table 1). The reaction of acetic acid hydrazide with benzoyl chloride after 70 min