A Convenient Syntheses and Antibacterial Activities of Symmetrical and Unsymmetrical 2,5-Disubstitutded-1,3,4-Oxadiazoles

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(Received 31st October, 2005, revised 16th December, 2005)

Summary: Eighteen symmetrical and unsymmetrical 2,5-disubstituted-1,3,4-oxadiazoles have been synthesized by a simple and convenient method in high yields (82-91%). The method was compared with the reported method in respect of yields. All products were identified by spectroscopic analyses. Some of these compounds were screened *in vitro* for their antibacterial activity.

Introduction

During the past two decades 1,3,4-oxadiazole derivatives are becoming an important member in heterocyclic family not only because of their wide usage as dyes, photosensitive and photoelectric material [1], but also because of their broad spectrum in biological activities such as HIV-activity [2], antibacterial, antifungal [3], antimalarial [4], anticonvulsant [5], anti-inflammatory [6], muscle relaxants [7], antimitotic [8], antitumor [9] activities and as agrochemicals [10]. All these findings prompted us to synthesize various symmetrical and unsymmetrical 2,5-disubstituted-1,3,4-oxadiazoles and screened them for their antibacterial activities.

Results and Discussion

The common synthetic approaches to oxadiazoles involve cyclization of diacylhydrazines [11]. A variety of reaction conditions influence the cyclization reaction. Typically, the reaction is prompted by heat and anhydrous reagents including thionylchloride [12], phosphorus oxychloride [13], phosphorus pentaoxide [14], triphenylphospine [15] and triflic anhydride [16]. Usually 2,5-disubstituted-1,3,4-oxadiazoles are synthesized from *N,N'*-diacylhydrazines [17]. Therefore, we report here a simple and convenient method for the synthesis of symmetrical and unsymmetrical 2,5-disubstituted-1,3,4-oxadiazoles from *N,N'*-diacylhydrazines (Scheme-1).

Nine carboxylic acid hydrazides (**1a-i**) on stirring with 1.1 mole equivalent of benzoyl chloride or 4-nitrobenzoyl chloride in dry acetonitrile at room temperature furnished the corresponding *N,N'*-diacylhydrazines (**2a-r**). Each of these *N,N'*-diacylhydrazine underwent cyclization *via* dehydration on refluxing in thionyl chloride yielding corresponding 2,5-disubstituted-1,3,4-oxadiazoles (**3a-r**) in high yields ranging from 82-91% (Scheme-1). The reported method [18] was also used to synthesize various compounds **3a-r** in order to compare yields. This method involved reaction of nine carboxylic acid hydrazides (**1a-i**) with benzoic acid and separately with 4-nitrobenzoic acid in presence of phosphorus oxychloride to corresponding 2,5-disubstitued-1,3,4-oxadiazoles (**3a-r**) in 68-70% yields (Scheme-1). Therefore, the present procedure from *N,N'*-diacylhydrazines is more convenient and found to be much better in respect of yields (82-91%)

Products *N,N'*-diacylhydrazines (**2a-r**) were characterized by the data given in Table-2. Compounds 2,5-disubstituted-1,3,4-oxadiazoles (**3a-r**) were confirmed by IR, ^{1}H NMR and mass spectral data displayed in Table-3. The characteristic (C=O) and (N–H) stretching of (**2a-r**) were absent in IR spectra of (**3a-r**). The two absorption bands at 1570-1640 cm^{-1} and 1255-1299 cm^{-1} are assigned to (C=N) and

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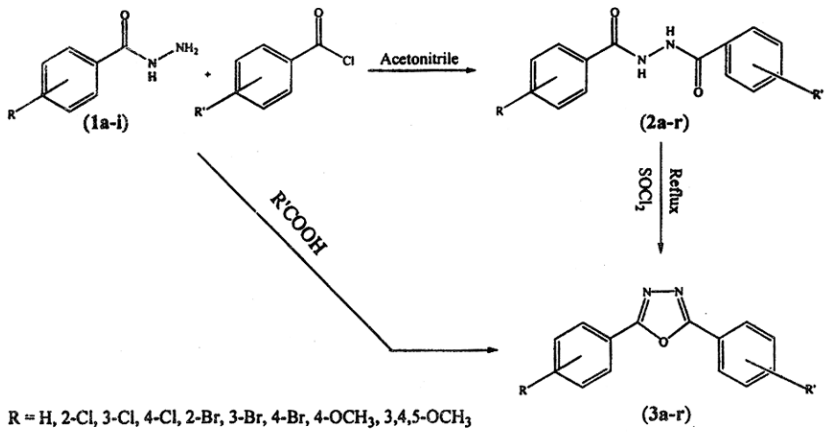

Scheme-1

(N–N=C) functional groups. Whereas absorption bands at 1050-1090 cm^{-1} is characteristic of (C–O–C) [19]. The molecular ions have been detected by using EI-MS.

Antibacterial Activity

Nine selected compounds were screened *in vitro* for their antibacterial activities against four strains of bacteria using agar diffusion technique [20]. The chloramphenicol was taken as standard drug at the same concentration. The screening results are given in Table-1, indicating most of the compounds tested exhibited significant activities against different strains of bacteria. The investigation on the structure-activity relationship showed that halogens and nitro substituents on phenyl ring enhance the antibacterial action of most of the tested compounds.

Table-1: The Antibacterial Activities of Some of the Synthesized Compounds

Compound	*S. aureus*	*E. coli*	*P. aeruginosa*	*B. subtilis*
3a	11	13	12	17
3d	15	19	13	21
3e	21	14	16	18
3h	16	17	9	12
3m	23	25	17	21
3n	21	23	15	25
3p	16	18	19	21
3q	9	17	11	14
3r	21	12	9	19
Chloramphenicol (Standard)	25	24	24	25

Diameter of inhibition zone in mm, concentration 5 mg/ml, agar diffusion method, incubation at 37°C for 24 h

Table-2: Physical Data of *N,N'*-Diacylhydrazines (2a-r)

Comp.	R	R'	M.P. °C (Yield%)	IR ν_{max}/cm^{-1}
2a	Ph	Ph	241-243 (83)	3292 (N-H), 3011 (ArH),1641(C=O)
2b	2-ClPh	Ph	220-221(85)	3235 (N-H), 3031 (ArH)1651 (C=O)
2c	3-ClPh	Ph	215-217(87)	3233 (N-H), 3023 (ArH),1665 (C=O)
2d	4-ClPh	Ph	255-257(91)	3182 (N-H), 3012 (ArH),1671 (C=O)
2e	2-BrPh	Ph	212-213(75)	3213 (N-H), 3017 (ArH),1671 (C=O)
2f	3-BrPh	Ph	223-225 (77)	3234 (N-H), 3031 (ArH),1665 (C=O)
2g	4-BrPh	Ph	237-239 87	3192 (N-H), 3015 (ArH),1661 (C=O)
2h	4-OCH_3Ph	Ph	245-247(91)	3283 (N-H), 3017 (ArH),1665 (C=O)
2i	3,4,5-OCH_3Ph	Ph	191-193(89)	3241 (N-H), 3011 (ArH),1643 (C=O)
2j	Ph	4-NO_2Ph	260-263(75)	3191 (N-H), 3023 (ArH),1672 (C=O)
2k	2-ClPh	4-NO_2Ph	227-229 (77)	3188 (N-H), 3011 (ArH),1651 (C=O)
2l	3-ClPh	4-NO_2Ph	216-218 (79)	3207 (N-H), 3017 (ArH),1647 (C=O)
2m	4-ClPh	4-NO_2Ph	277-279 (90)	3241 (N-H), 3017 (ArH),1643 (C=O)
2n	2-BrPh	4-NO_2Ph	235-237 (72)	3197 (N-H), 3019 (ArH),1647 (C=O)
2o	3-BrPh	4-NO_2Ph	230-231 (74)	3185 (N-H), 3013 (ArH),1651 (C=O)
2p	4-BrPh	4-NO_2Ph	251-253 (81)	3183 (N-H), 3027 (ArH),1669 (C=O)
2q	4-OCH_3Ph	4-NO_2Ph	231-233 (91)	3181 (N-H), 3011 (ArH),1655 (C=O)
2r	3,4,5-OCH_3Ph	4-NO_2Ph	180-182 (82)	3217 (N-H), 3037 (ArH),1649 (C=O)

Experimental

General

All melting points were determined with a Büchi 434 melting point apparatus and are uncorrected. ^1H NMR spectra were recorded in acetone-d_6 / DMSO- d_6 on a Bruker 400 MHz spectrometer using TMS as an internal standard, chemical shifts are reported in δ (ppm) and coupling constants in Hertz. IR spectra were carried out in KBr discs on FT-IR FTS 300 MX spectrometer. EI-MS spectra were recorded with Finnigan MAT 312 and MAT 311A spectrometer. Thin layer chromatography (TLC) was performed on precoated silica gel $60F_{254}$ aluminium sheets (Merck).

N,N'-Diacylhydrazines (2a-r)

General Procedure

Benzoyl chloride and 4-nitrobenzoyl chloride (5.1 mmol) were added separately in portions to a

Table-3: Characterization of 2, 5-disubstituted-1,3,4-oxadiazoles (**3a-r**).

Comp.	R	R	M.P.(°C)/ Yield(%)	IR ν_{max}/cm^{-1}	^1H NMR (Acetone-d_6/ DMSO-d_6 δ, J (Hz)	EI-MS(%)
3a	Ph	Ph	140-142 82	3110, 1600, 1550, 1265, 1076	7.45-7.66 (m, 10H, ArH)	222 (M^+, 47), 165 (20), 105 (100), 77 (45)
3b	2-ClPh	Ph	175-177 85	3101. 1631. 1279. 1067	7.50-7.68 (m, 9H, ArH)	256 (M^+, 27), 210 (11), 150 (29), 139 (100), 111 (45), 77 (22), 76 (29)
3c	3-ClPh	Ph	165-167 83	3116. 1592. 1267, 1076	7/55-7.69 (m, 8H, ArH) 7.95 (s, 1H, ArH)	256 (M^+, 21), 139 (100), 111
3d	4-ClPh	Ph	195-196 91	3028, 1617, 1270, 1071	7.56-7.68 (m, 7H, ArH) 8.18 (d, 2H, J = 8.0, ArH)	256 (M^+, 67), 210 (11), 150 (29), 139 (100), 111 (47), 77 (21), 76 (29)
3e	2-BrPh	Ph	153-155 82	3062, 1617, 1278, 1068	7.65-7.91 (m, 9H, ArH)	300 (M^+, 11), 202 (81), 200 (84), 185 (98), 183 (100), 157 (34), 155 (35), 139 (30, 105 (9), 77 (19), 76 (39)
3f	3-BrPh	Ph	163-165 81	3048, 1624, 1290, 1070	7.66-7.81 (m, 8H, ArH) 7.92 (d, 1H, J = 8.1, ArH)	300 (M^+, 11), 202 (82), 200 (83), 185 (91), 183 (100), 157 (33), 155 (35), 77 (19), 76 (39)
3g	4-BrPh	Ph	201-203 89	3063, 1602, 1267, 1070	7.78-7.85 (m, 7H, ArH), 8.15 (d, 2H, J = 8.0, ArH)	300 (M^+, 35), 185 (98), 183 (100), 157 (34), 155 (35), 105 (9), 77 (9), 76 (39)
3h	4-OCH_3Ph	Ph	169-170 91	3021, 1603, 1271, 1063	3.83 (s, 3H, CH_3O), 6.93-7.62 (m, 9H, ArH)	252 (M^+, 67), 221 (11), 150 (29), 135 (100), 111 (45), 77 (45), 76 (16)
3i	3,4,5-OCH_3	Ph	181-183 89	3025, 1611, 1289, 1081	3.81 (s, 9H, CH_3O), 7.13 (s, 2H, ArH), 7.35-7.59 (m, 5H, ArH)	312 (M^+, 48), 211 (1), 165 (19), 105 (100), 77 (45), 76 (17)
3j	Ph	4-NO_2Ph	190-192 83	3116, 1601, 1265, 1076	7.60-7.67 (m, 5H, ArH), 8.21 (d, 2H, J = 8.1, ArH), 8.46 (d, 2H, J = 8.1, ArH)	267 (M^+, 48), 165 (20), 150 (14), 105 (100), 77 (45), 76 (16), 51 (18)
3k	2-ClPh	4-NO_2Ph	185-186 85	3029, 1622, 1257, 1072	7.73-8.12 (m, 6H, ArH), 8.39 (d, 2H, J = 8.0, ArH)	301 (M^+, 67), 210 (11), 199 (12), 150 (29), 139 (100), 111 (45), 104 (26), 76 (29), 75 (28)
3l	3-ClPh	4-NO_2Ph	176-177 91	3043, 1620, 1255, 1072	7.65-7.91 (m, 6H, ArH), 8.32 (d, 2H, J = 8.0, ArH)	301 (M^+, 61), 210 (7), 199 (11), 139 (100), 111 (45), 76 (27), 75 (19)
3m	4-ClPh	4-NO_2Ph	210-212 83	3044, 1620, 1255, 1072	7.66 (d, 2H, J = 7.1, ArH), 8.13-8.25 (m, 6H, ArH)	301 (M^+, 67), 199 (13), 139 (100), 111 (46), 76 (28)
3n	2-BrPh	4-NO_2Ph	163-165 82	3041, 1623, 1271, 1070	7.67-7.79 (m, 6H, ArH), 8.25 (d, 2H, J = 7.2, ArH)	345 (M^+, 11), 185 (91), 183 (100), 157 (31), 155 (37), 76 (39)
3o	3-BrPh	4-NO_2Ph	191-193 84	3045, 1602, 1269, 1071	7.43-7.68 (m, 6H, ArH), 8.35 (d, 2H, J = 7.2, ArH)	345 (M^+, 2), 185 (67), 183 (100), 157 (35), 155 (39), 76 (21)
3p	4-BrPh	4-NO_2Ph	221-223 85	3021, 1607, 1261, 1067	7.43-8.21 (m, 8H, ArH)	345 (M^+, 39), 185 (69), 183 (100), 157 (37), 155 (41), 76 (31)
3q	4-OCH_3Ph	4-NO_2Ph	193-195 90	3051, 1619, 1277, 1063	3.81 (s, 3H, OCH_3), 7.29-7.89 (m, 6H, ArH), 8.21 (d, 2H, J = 7.2, ArH)	297 (M^+, 29), 135 (100), 107 (7), 76 (35)
3r	3,4,5-OCH_3Ph	4-NO_2Ph	189-191 91	3041, 1621, 1271, 1072	3.79 (s, 9H, OCH_3), 6.95 (s, 2H, ArH), 7.96 (d, 2H, J = 8.0, ArH), 8.34 (d, 2H, J = 8.0, ArH)	357 (M^+, 7), 195 (100), 167 (11), 104 (19), 76 (37)

suspension of carboxylic acid hydrazide **1a-i** (5.0 mmol) in dry acetonitrile (50 ml). The reaction mixture was stirred for 5-7 h at room temperature. The excess solvent was removed *in vacuo* and solid product was filtered and recrystallized with aqueous ethanol to afford *N,N'*-diacylhydrazines (**2a-r**) in 72-91% yields. The product **2a** (83%) had m.p. 241-243°C (lit. 238-240°C, yield 67%). The physical data are given in Table-2.

*1,3,4 Oxadiazoles (**3a-r**)*

General Procedure

A mixture of an appropriate *N,N'*-diacylhydrazine **2a-r** (2 mmol) and thionyl chloride

(10 ml) was refluxed for 2 h. The resulting mixture was poured on to crushed ice and stirred vigorously. The solid product thus obtained was filtered off, washed with water and recrystlalized with aqueous ethanol to afford 2,5-disubstituted-1,3,4-oxadiazoles (**3a-r**) in 82-91% yields. The physical data are listed in Table-3.

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