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Synthesis of 2-Substituted-1,3,4-Oxadiazole Derivatives

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ABSTRACT

Diethyladipate on reaction with Hydrazine hydrate gave Succinohydrazide (1) which on further treatment with Carbon disulfide, Aromatic aldehydes and Cynogen bromide yielded 1,2[di-(2-Mercapto-1,3,4-oxadiazole-5yl)] ethane (2), 1,2[di-(2-Phenyl-1,3,4-oxadiazole-5yl)] ethane (3a-f) and 1,2[di-(2-Amino-1,3,4-oxadiazole-5 yl)] ethane (4) respectively. The structures of the compounds have been elucidated on the basis of spectral analysis.

Keywords: Diethyladipate, Succinohydrazide, Carbon disulfide and Cynogen bromide.

INTRODUCTION

The chemistry of heterocyclic compounds has been an interesting field of study for a long time. The synthesis of novel Oxadiazole derivatives and investigation of their chemical and biological behavior have gained more importance in recent decades for biological, medical and agricultural reasons. Different classes of Oxadiazole compounds possess an extensive spectrum of pharmacological activities. In particular, compounds bearing 1,3,4-Oxadiazole nucleus are known to exhibit unique anti-edema and anti-inflammatory activity [1-4,9]. Differently substituted Oxadiazole moiety has also been found to have other important activities such as analgesic [3,4] antimicrobial [5,6], antimycobacterial [7], anticonvulsant [8], antitumor [9], antimalarial [10] and anti-hepatitis B viral activities [11]. Substituted 1,3,4-Oxadiazoles exhibit antibacterial [12], Pesticidal [13] and antifungal [14] activities.

1,3,4-oxadiazoles are biologically active [15], synthetically useful and important heterocyclic compounds. for these reasons the chemistry of 1,3,4-oxadiazoles have been the subject of many investigations [16-19].One pot synthesis of 1,3,4-oxadiazoles by the reaction of appropriate hydrazide and carboxylic acid has been reported [20]. Cerric ammonium nitrate has received considerable attention as an inexpensive and easily available catalyst for various organic reactions such as Oxidation, Oxidative addition, Nitration, Photo-oxidation, Polymerization etc. In recent report Cerric ammonium mediated synthesis of 1,3,4-Oxadiazoles has also been described [21,22].

MATERIALS AND METHODS

Melting points of all synthesized compounds were determined in open capillary tubes on an electrothermal apparatus and are uncorrected. The progress of reaction was monitored by thin layer chromatography on silica gel coated aluminium plates (Merck) as adsorbent and UV light as visualizing agent. IR spectra (KBr in cm^{-1}) were recorded on a Perkin-Elmer spectrophotometer in the range of 4000-400 cm-1. 1H NMR spectra were recorded on a Varian 500 MHz NMR spectrometer using CDCl3/DMSO-d6 as solvent and TMS as an internal standard (chemical shifts in δppm).

Succinohydrazide (1): General procedure

A mixture of Diethyladipate (0.08 mole), Hydrazine hydrate (3.85 ml, 0.08 mole), and ethanol (10 ml) was refluxed on water bath for 4-5 hrs. The mixture becomes almost solid. This reaction mixture is allowed to cool at room temperature. The white solid so obtained is then filtered and washed with cold ethanol and finally recrystallized from hot water to yield (**1**).

1,2[di-(2-Mercapto-1,3,4-oxadiazole-5yl)] ethane (2)

A mixture of Succinohydrazide (1.0 gm, 0.0068 mole), Carbon disulfide (0.82 ml, 0.0136 mole), and Potassium hydroxide (0.768 gm, 0.014 mole) was refluxed in ethanol (10 ml) on water bath for 5-6 hrs. The reaction is then allowed to cool. The red colored solid so obtained is then filtered and washed with ethanol and finally recrystallized from hot dichloromethane to yield (**2**).

1,2[di-(2-Phenyl-1,3,4-oxadiazole-5yl)] ethane (3a-f)

A mixture of Succinohydrazide (1.0 gm, 0.0068 mole), aromatic aldehydes (0.0136 mole), and Cerric ammonium sulphate (0.5 gm, 0.0008 mole), in Dichloromethane (10 ml) as a solvent was taken in 100 ml round bottom flask and the mixture was refluxed on water bath for 4-5 hrs. After monitoring the reaction on TLC, the reaction mixture was cooled and dumped on to the ice, filtered and recrystallized from ethanol**.**

1,2[di-(2-Amino-1,3,4-oxadiazole-5 yl)] ethane (4)

A mixture of Succinohydrazide (1.0 gm, 0.0068 mole), Cynogen bromide (0.0136 mole), and Sodium bicarbonate (1 g, 0.012 mole), in ethanol (10 ml) as a solvent was taken in 100 mL round bottom flask and the mixture was refluxed on water bath for 4-5 hrs. After monitoring the reaction on TLC, the reaction mixture was cooled and dumped on to the ice, filtered and recrystallized from dimethylformamide to yield (**4).**

The schematic data of the compound **2, 3(a-f)** and **4** are listed in the Table-1.

Antimicrobial evaluation

Representative samples were screened for their antimicrobial and antifungal activity against gram-negative bacteria, E coli and P aeruginosa and gram-positive bacteria, S aureus, and C diphtheriae using disc diffusion method [23,24]. The zone of inhibition was measured in mm and the activity was compared with standard drug. The results of antibacterial screening studies are reported in Table-2.

RESULTS AND DISCUSSION

Diethyladipate on reaction with Hydrazine hydrate gave Succinohydrazide (**1**) which on further treatment with Carbon disulfide, Aromatic aldehydes and Cynogen bromide yielded 1,2[di-(2-Mercapto-1,3,4-oxadiazole-5yl)] ethane **(2),** 1,2[di-(2-Phenyl-1,3,4-oxadiazole-5yl)] ethane **(3a-f)** and 1,2[di-(2-Amino-1,3,4-oxadiazole-5 yl)] ethane **(4)** respectively with good yield.

Further, the representative compounds were screened for their antimicrobial activity against gram negative as well as gram positive bacteria, which shows convincing activity.

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Table-1: Characterization of synthesized compounds 2, 3(a-f) and 4.

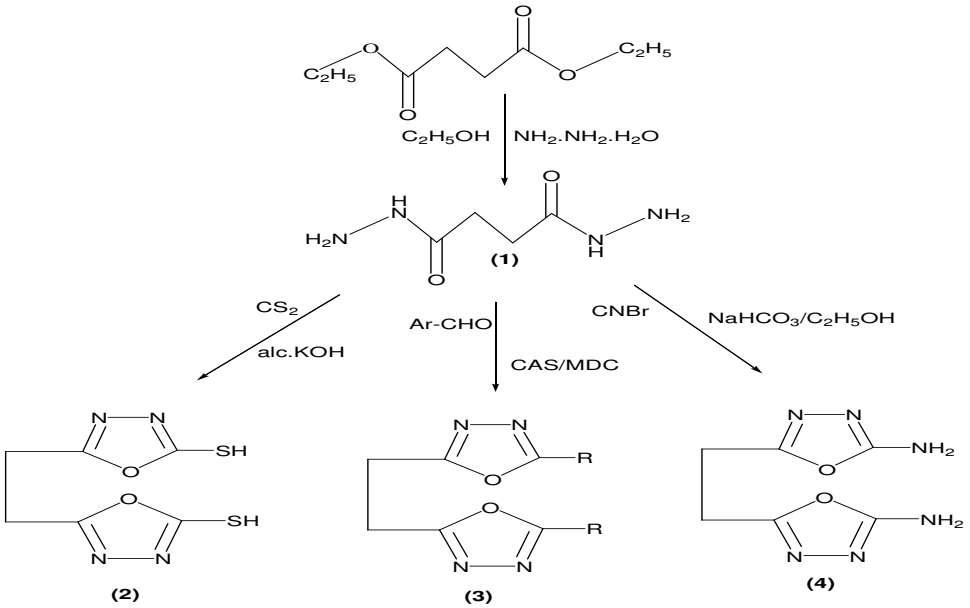
Compd.	R	Mol. Formula	Yield (%)	m.p. (°C)	Spectral data IR (KBr cm^{-1})/^{1}H NMR/^{13}C NMR (ppm) in DMSO-d_6
2	-	$C_6H_6N_4O_2S_2$	52	62-64	IR (KBr): 2581 (S-H), 1363 (C=N). ^{1}H NMR: 2.7 (t, 4H, CH_2), 9.7 (s, 2H, SH). [Found: C,35.27, H,2.57, N,24.35, S,27.85%. Required: C,31.30, H,2.61, N,24.35, S,27.83%.]
3a	C_6H_5	$C_{18}H_{14}N_4O_2$	68	114-115	IR (KBr): 1621-1432 (Ar), 1377 (C=N), ^{1}H NMR: 2.9 (t, 4H, CH_2),7.4 (m,10H,ArH) [Found: C,67.27, H,3.87, N,17.35%. Required: C,67.92, H,4.4, N,17.61%.]
3b	*p*-OCH_3-C_6H_5	$C_{20}H_{18}N_4O_4$	71	97-99	IR (KBr): 1373 (C=N), 1142 (-OCH_3). ^{1}H NMR: 2.9 (t, 4H, CH_2),3.7 (s, 6H, OCH_3), 6.9 (d, 4H), 7.5 (d,4H).^{13}C NMR: 55.3 (OCH_3), 72.4 (CH_2),114.3-128.5 (Ar-C), 152.3 (C=N) [Found: C,63.29, H,4.38, N,14.42%. Required: C,63.49, H,4.76, N,14.81%.]
3c	*p*-Cl-C_6H_5	$C_{18}H_{12}N_4O_2Cl_2$	56	90-94	IR (KBr): 1353 (C=N), 781 (C-Cl). [Found: C,55.31, H,3.04, N,14.21%. Required: C,55.81, H,3.1, N,14.47%].
3d	*o*-OH-C_6H_5	$C_{18}H_{14}N_4O_4$	61	124-127	IR (KBr): 3302 (-OH), 1308 (C=N). [Found: C,61.65, H,4.06, N,16.07%. Required: C,61.71, H,4.00, N,16.00%].

3e	CH=CH-C_6H_5	$C_{22}H_{18}N_4O_2$	58	112-114	IR (KBr): 3021 (CH=CH), 1328 (C=N). [Found: C,70.99, H,4.53, N,15.01%. Required: C,71.35, H,4.86, N,15.14%.]
3f	*p*-OCH_3-m-OH-C_6H_5	$C_{20}H_{20}N_4O_6$	57	93-95	IR (KBr): 3311 (-OH), 1331 (C=N), [Found: C,58.02, H,4.77, N,13.52%. Required: C,58.25, H,4.85, N,13.59%.].
4	-	$C_{18}H_{16}N_6O_2$	64	86-89	IR (KBr): 1381 (C=N), 1267 (NH_2). ^{1}H NMR: 2.9 (t, 4H, CH_2), 8.9 (s, 4H, NH_2). [Found: C,62.10 H,4.48, N,24.06%. Required: C,62.06, H,4.59, N,24.14%].

Table-2: Antibacterial Activity of compound 2, 3(a-f) and 4

Comp.	Zone of inhibition (in mm)			
	Gram Positive		Gram negative	
	S.aureus	C.diphtheria	P.aeruginosa	E.coli
2	22	20	21	19
3a	21	18	20	18
3b	18	19	18	14
3c	16	18	17	18
3d	21	22	16	17
3e	20	21	18	15
3f	18	19	21	14
4	17	21	21	16
Amphicilin trihydrate	26	28	24	21
DMSO	0	0	0	0

* Diameter of the disc was 6mm, concentration of the compounds taken was about 100 µg/mL.



Scheme-1

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