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Synthesis of some 3,5-disubstituted 1,2,4-oxadiazoles starting from aryl nitriles

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ABSTRACT

The synthesis of some 3,5-disubstituted 1,2,4-oxadiazoles starting from arylnitriles is described. Arylnitriles are converted to arylamidoximes and then condensed with aromatic acid chlorides to form 1,2,4-oxadiazoles. Structures of the products were characterized by analytical data and spectral studies. All compounds of the series were screened for their anti-bacterial and anti-fungal activity. Most of the tested compounds showed moderate antifungal and antibacterial activity comparable with that of the standard drug.

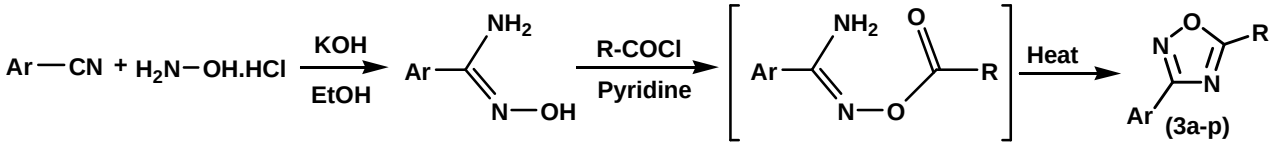
KEYWORDS

1,2,4-Oxadiazoles;
Arylnitriles;
Arylamidoximes;
Antibacterial activity;
Antifungal activity.

INTRODUCTION

Due to the increasing number of novel drug targets the rapid construction and modification of biologically active heterocyclic compounds is becoming more and more important in drug development[1]. 1,2,4-Oxadiazoles are an important class of biologically active compounds[2]. Among nitrogen–oxygen containing heterocycles, the 1,2,4-oxadiazole nucleus is of particular interest for organic and medicinal chemists, because it is present in various biologically active compounds and natural products[4–9]. They have for instance been identified as anti-inflammatory agents[3], antitumor agents[4], 5-HT_3 [5], histamine H_2 and H_3 receptor antagonists[6] as well as monoamine oxidase[7] and β II-tryptase inhibitors[8]. In addition, 1,2,4-oxadiazoles are widely used as hydrolysis-resisting amide bioisosters in the development of peptidomimetics[9]. Many of them also have been found to possess analgesics[10], anti-inflammatory[11], antimicrobial[11], antiviral[12], insecticidal[13], anticonvulsant[14] and pronounced β-adrenoreceptor blocking activity combined with moderate α-adrenoreceptor blocking properties[15].

1,2,4-Oxadiazoles are commonly prepared by reactions of amidoximes with reactive carboxylic acid derivatives[16,17]. Other methods to generate 1,2,4-oxadiazoles include 1,3-dipolar cycloadditions of nitrile oxides to nitriles[16] and the oxidation of 4,5-dihydro-1,2,4-oxadiazoles[17]. 3,5-Diamino-1,2,4-oxadiazoles are accessible starting from N_1-arylalkylamino-N_3-cyano-O-phenylisoureas and hydroxylamine[6]. Improved synthesis of oxadiazoles under microwave irradiation conditions was also studied[18]. The most common route to 1,2,4-oxadiazoles is coupling amidoximes with 1) activated carboxylic acid derivatives such as acid chlorides, fluorides, anhydrides or active esters; 2) carboxylic acid in the presence in the presence of coupling reagents including dicyclohexyl carbodiimide (DCC), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC), 2-diehylaminoisopropyl-



Scheme 1 : Synthesis of 3,5-disubstituted 1,2,4-oxadiazoles

chloride DIC/HOBt, bis(oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl), 2-(1*H*-benzo- triazol-1-yl)-1,1,3,3-tetramethyluroniumtetrafluoroborate (TBTU), 1,1-carbonyldiimidazole (CDI). 3) acyl halides in the presence of palladium catalysts or with aldehyde followed by oxidation. Recently, emphasis has been given to synthesize oxadiazoles having novel functional groups attached to the either to C-3 or C-5 of this ring system.

In view of the above observations and in continuation of our research work of synthesizing heterocyclic compounds of biological interest, the synthesis of oxadiazoles having 3,5-disubstitution starting from arylnitriles were aimed at investigating antibacterial and antifungal properties.

RESULTS AND DISCUSSION

This paper describes the synthesis of some oxadiazoles **(3a-p)** having 3,5-disubstitutions. The synthetic route followed for obtaining the title compounds is outlined in Scheme 1. Amidoximes **(2a-h)** were obtained by the reactions of arylnitriles with hydroxylamine hydrochloride in alcoholic alkaline medium. Condensation of **(2a-h)** with appropriate aromatic acid chlorides in pyridine finally furnished the 3,5-substituted 1,2,4-oxadiazoles **(3a-p)** in good yields. The arylnitriles **(1a-h)** were prepared from aldehydes by conventional method[19].

The structures of the synthesized compounds were established on the basis of spectral and analytical data. The C, H, N analyses of these compounds are in agreement with the calculated values within the limits of experimental error. The characterization data of the synthesized compounds are presented in TABLE 1.

In a typical example, the IR spectrum of compound **(2a)** showed NH asymmetric and symmetric stretching bands of primary amine function at 3313cm^{-1} and 3261cm^{-1} respectively. The C = N stretching band appeared at 1634 cm^{-1}. The absorption band at 3080 cm^{-1} was attributed to the aromatic C-H stretching vibrations. Band at 3361cm^{-1} is attributed to the –OH group stretching vibration. The band due to C = C group was seen at 1603cm^{-1}. In the IR spectra of oxadiazoles **(3a-p)** the C-H stretching and C = N absorption bands were observed in the region of 2900-3100cm^{-1} and 1588-1619cm^{-1} respectively. In the IR spectrum of **(3a)**, the bands due to NH_2 and OH groups were not detectable, demonstrating the disappearance of these groups. The C-O stretching bands appeared at 1271cm^{-1} indicated the formation of the cyclised product. The absorption band for C = N stretching vibration was observed at 1571cm^{-1}.

The exhibited chemical shifts obtained from ^{1}H NMR spectra were also supported the proposed structures of **(2a-p)** and **(3a-p)**. In the ^{1}H NMR spectrum of compound **(2a)**, a singlet seen at δ 10.0 was assigned to the –OH proton and singlet at δ 5.49 ppm to –NH_2 protons. Two protons of pyridine moiety were resonated as two distinct double doublets in the region δ 8.57-8.6 (J = 4.6Hz & 1.7Hz) and δ 7.62-7.64 (J = 4.6Hz & 1.7Hz) integrating for two protons each. The ^{1}H NMR spectrum of 3a also showed two distinct double doublets in the region δ 8.74-8.75 (J = 4.5Hz and J = 1.4Hz) and δ 7.96-7.98 (J = 4.5Hz and J = 1.4Hz) integrating for two protons each of pyridine moiety. The phenyl protons resonated as multiplets in the region δ 8.13-8.16 and δ 7.48-7.59 integrating for two and three protons respectively. In the ^{1}H NMR spectrum of compound **(3a)**, the disappearance of signals arising from –NH_2 and –OH functions of **(2a)**, provided the evidence for cyclisation to yield oxadiazole ring system.

In the FAB-mass spectra of two selected prototypes, **(2a)** and **(3a)**, the existing molecular ions confirmed the molecular weights of these compounds. In the case of compound **(2a)**, the protonated molecular ion peak was observed at m/z, 138 consistent with its molecular formula $C_6H_7N_3O$. The fragmentation of protonated **(2a)** through the loss of NH_3 and NO yielding the tropylium ion was base peak at m/z, 91. The FAB mass spectrum of 3a showed protonated molecular ion

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TABLE 1 : Characterization data of newly synthesized 3,5-disubstituted 1,2,4-oxadiazoles (3a-p)

Compd.	Ar	R	Mol. formula (Mol. wt)	m. p.(°C)	Analysis (%) found (calculated)		
					C	H	N
3a	4-pyridyl	C_6H_5	$C_{13}H_9N_3O$ (233.23)	148	69.86 (69.08)	4.01 (3.83)	18.75 (18.21)
3b	4-pyridyl	2-ClC_6H_4	$C_{13}H_8ClN_3O$ (257.23)	110-112	60.44 (58.54)	3.11 (2.85)	10.91 (10.31)
3c	2-ClC_6H_4	C_6H_5	$C_{14}H_9ClN_2O$ (256.68)	84-86	65.35 (65.45)	3.42 (3.50)	10.81 (10.91)
3d	2-ClC_6H_4	2-ClC_6H_4	$C_{14}H_8Cl_2N_2O$ (291.13)	84	56.98 (57.70)	2.75 (2.50)	9.56 (9.81)
3e	4-OHC_6H_4	C_6H_5	$C_{14}H_{10}N_2O_2$ (238.24)	126-128	70.51 (68.61)	4.19 (3.86)	11.75 (11.26)
3f	4-OHC_6H_4	2-ClC_6H_4	$C_{14}H_9ClN_2O_2$ (272.68)	118-120	61.61 (60.88)	3.30 (4.03)	10.26 (10.81)
3g	4-$OCH_3C_6H_4$	C_6H_5	$C_{15}H_{12}N_2O_2$ (252.26)	80-82	71.31 (70.35)	4.65 (4.75)	10.88 (11.09)
3h	4-$OCH_3C_6H_4$	2-ClC_6H_4	$C_{15}H_{11}ClN_2O_2$ (286.71)	84-86	62.67 (60.78)	3.77 (3.94)	9.85 (8.77)
3i	2-NO_2-4,5-$(OCH_3)_2C_6H_2$	C_6H_5	$C_{16}H_{13}N_3O_5$ (327.29)	152-154	66.85 (65.97)	3.91 (3.97)	12.71 (12.83)
3j	2-NO_2-4,5-$(OCH_3)_2C_6H_2$	2-ClC_6H_4	$C_{16}H_{12}ClN_3O_5$ (361.73)	130-132	53.01 (52.08)	3.12 (3.32)	11.55 (10.81)
3k	4[$OCHCH(CH_3)_2$]C_6H_3	C_6H_5	$C_{18}H_{18}N_2O_2$ (294.34)	80-82	73.45 (73.08)	6.21 (6.92)	9.50 (9.30)
3l	4[$OCHCH(CH_3)_2$]C_6H_3	2-ClC_6H_4	$C_{18}H_{17}ClN_2O_2$ (328.79)	84-86	65.66 (64.69)	5.05 (5.17)	8.56 (8.62)
3m	2,3,5-ClC_6H_2	C_6H_5	$C_{14}H_7Cl_3N_2O$ (325.57)	90-92	51.67 (50.60)	2.12 (2.55)	8.52 (8.80)
3n	2,3,5-ClC_6H_2	2-ClC_6H_4	$C_{14}H_6Cl_4N_2O$ (360.02)	158-160	46.58 (47.66)	1.71 (1.66)	7.80 (8.77)
3o	3-pyridyl	C_6H_5	$C_{13}H_9N_3O$ (223.23)	168-170	69.94 (70.68)	4.08 (4.33)	18.78 (18.81)
3p	3-pyridyl	2-ClC_6H_4	$C_{13}H_8ClN_3O$ (257.67)	90-92	60.43 (59.54)	3.18 (3.40)	10.90 (10.81)

peak at m/z 224 as the most abundant ion. The molecular ion peak observed at m/z 223 was in agreement with its molecular formula $C_{13}H_9N_3O$.

Antibacterial activity studies

The newly synthesized compounds were screened for their antibacterial activity *in vitro* against *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa* and *Klebesilla pneumoniae bacterial strains* by serial dilution method[20]. Serial dilutions of the drug in Muller-Hinton broth were taken in tubes and their p^H was adjusted to 5.0 using phosphate buffer. A standardized suspension of the test bacteria was inoculated and incubated for 16-18 hours at 37°C. The minimum inhibitory concentration (MIC) was noted by seeing the lowest concentration of the drug at which there was no visible growth. Solvent control was also kept. Ciprofloxacin was used as the standard drug. The antibacterial activity results showed that the newly prepared oxadiazoles have moderate activity against the above mentioned organisms. The results are summarized in TABLE 2.

Antifungal activity studies

The synthesized compounds were also screened for their antifungal activity against *Aspergillus flavus, Aspergillus fumigates, Candida albicans* and *Penicillium marneffei* by agar diffusion method[21,22]. The nutrient broth, which contained logarithmic serially two fold diluted amount of test compound and controls were inoculated with approximately 1.6-6 × 10^4 c.f.uml^{-1}. The cultures were incubated for 48h at 35°C and growth was monitored. The lowest concentration (highest dilution) required to arrest the growth of fungus was re-

TABLE 2 : Antibacterial activity of compounds (4a-p)

Compound	MIC in µg/ml and zone of inhibition (in mm)			
	Pseudomonas aeruginosa	*Escherichia coli*	*Klebesilla pneumoniae*	*Staphylococcus aureus*
3a	25(<10)	25(<10)	25(<10)	25(<10)
3b	25(<10)	25(<10)	25(<10)	25(<10)
3c	25(<10)	25(<10)	25(<10)	25(<10)
3d	25(<10)	25(<10)	25(<10)	25(<10)
3e	12.5(11-15)	25(<10)	25(<10)	12.5(11-15)
3f	12.5(11-15)	25(<10)	25(<10)	12.5(11-15)
3g	6.25(16-20)	25(<10)	6.25(16-20)	6.25(16-20)
3h	25(<10)	25(<10)	25(<10)	25(<10)
3i	25(<10)	25(<10)	25(<10)	25(<10)
3j	6.25(16-20)	6.25(16-20)	6.25(16-20)	12.5 (11-15)
3k	25(<10)	6.25(16-20)	25(<10)	25(<10)
3l	25(<10)	25(<10)	6.25(16-20)	25(<10)
3m	6.25(16-20)	6.25(16-20)	25(<10)	25(<10)
3n	25(<10)	25(<10)	25(<10)	25(<10)
3o	6.25(16-20)	25(<10)	25(<10)	6.25(16-20)
3p	6.25(16-20)	25(<10)	25(<10)	12.5(11-15)
Standard (*Ciprofloxacin*)	6.25(25-33)	6.25(30-40)	6.25(23-27)	6.25(22-30)

TABLE 3 : Antifungal activity of compounds, (4a-p)

Compound	MIC in µg/ml and zone of inhibition (in mm)			
	Aspergillus flavus	*Aspergillus fumigatus*	*Candida albicans*	*Penicililum marneffei*
3a	25(<10)	25(<10)	25(<10)	25(<10)
3b	6.25(16-20)	25(<10)	6.25(16-20)	25(<10)
3c	25(<10)	25(<10)	25(<10)	25(<10)
3d	25(<10)	25(<10)	25(<10)	25(<10)
3e	25(<10)	25(<10)	25(<10)	25(<10)
3f	25(<10)	25(<10)	25(<10)	25(<10)
3g	6.25(16-20)	6.25(16-20)	6.25(16-20)	25(<10)
3h	25(<10)	25(<10)	25(<10)	25(<10)
3i	25(<10)	25(<10)	25(<10)	25(<10)
3j	6.25(16-20)	25(<10)	25(<10)	25(<10)
3k	25(<10)	25(<10)	25(<10)	25(<10)
3l	25(<10)	25(<10)	25(<10)	25(<10)
3m	25(<10)	25(<10)	25(<10)	6.25(16-20)
3n	25(<10)	25(<10)	25(<10)	25(<10)
3o	25(<10)	6.5(16-20)	25(<10)	25(<10)
3p	25(<10)	25(<10)	25(<10)	25(<10)
Standard (*Ciclopiroxolamine*)	6.25(25-30)	6.25(25-30)	6.25(27-33)	6.25(22-27)

garded as minimum inhibitory concentrations (MIC). Diameter of the zone of inhibition was measured. Activity of each compound was compared with that of *Ciclopiroxolamine* as standard drug. The antifungal activity results showed that the oxadiazoles synthesized have moderate against the above mentioned organisms and the results are summarized in TABLE 3.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. IR spectra (cm^{-1}) were recorded on a Perkin Elmer 577 spectrophotometer in KBr pellets. ^1H NMR spectra were recorded on a Perkin Elmer (Model RB-12) spectrometer using TMS as an internal standard (chemical shifts are reported in δ scale). The FAB mass spectrum was recorded on JEOL SX 102/DA-6000 Mass spectrometer/Data system using Argon/Xenon (6kv,10Ma) as the FAB gas. C, H, N analysis was carried out on a Vairo-EL (Elementa) model. Purity of the compounds was checked by TLC on silica gel G plates.

Preparation of arylnitriles (1a-h)

Some of the arylnitriles were prepared by the conventional method reported in the literature[19] starting from appropriate aldehydes. Rest of them were purchased and used after purification by distillation.

General procedure for the synthesis of arylamidoximes (2a-h)

To a solution of hydroxylamine hydrochloride 4.58g (0.06 mol) and potassium hydroxide 3.7g (0.06 mol) in 100ml ethanol, arylnitrile (0.06 mol) was added slowly at room temperature and the whole mixture was heated to reflux for 3-4 h. After the completion of reaction, about 50ml of solvent was removed by distillation. The flask content was allowed to cool to 0-5°C, the solid separated was filtered and recrystallized from ethanol.

IR (KBr) ν cm^{-1}: 3504 (O-H str.), 3387 (N-H str.), 3219 (N-H str.), 3079 (C-H str.), 1638 (C = N str.), 1577 (C = C str.), 1275 (C-O str.), 868, 827 (C-Cl str.). ^1H NMR (400 MHz, $CDCl_3$, TMS) δ ppm: 9.74 (s, 1H, OH), 5.42 (s, 2H, NH_2), 7.2 (s, 1H, Ar-CH), 7.53 (s, 1H, Ar-CH). FAB mass: m/z = 241 (M^++H).

General procedure for the synthesis of 3,5-disubstituted 1,2,4-oxadiazoles (3a-p)

The solution of arylamidoxines (0.01 mol) in pyridine (10ml) was cooled and to this solution, acid chlo-

ride (0.01 mol) was added drop wise under stirring. This mixture was heated slowly to reflux and maintained for 10-12 h. After the completion of reaction, it was cooled to room temperature and quenched into ice cold water. The resulting precipitate was filtered, washed with water and recrystallized from methanol or ethyl acetate.

(3b): IR (KBr) ν cm^{-1}: 3161(= C-H str.), 1603(C = N str.). ^1H NMR (400 MHz, $CDCl_3$, TMS) δ ppm: 8.04-8.06 (dd, 2H, J = 5.94 Hz and 1.9 Hz, pyridine moiety), 8.81-8.83 (dd, 2H, J = 5.94 Hz and 1.9 Hz, pyridine moiety), 8.14-8.18 (dd, 1H, J = 10.1Hz and 2.1Hz, ArH), 7.52-7.58 (m, 1H, ArH), 7.43-7.50 (m, 1H, ArH), 7.59-7.63 (m, 1H, ArH). FAB mass: m/z (%) = 257 (M^++1,100%).

(3d): IR (KBr) ν cm^{-1}: 3422((= C-H str.), 1596 (C = N str.), 891-781(C-Cl str.), 1475(C-O str.). ^1H NMR (400 MHz, $CDCl_3$, TMS) δ ppm: 7.5-7.62 (m, 3H, Ar-H), 8.15-8.18 (dd, 1H, J = 7.8 Hz and 1.7 Hz, Ar-H), 7.50-7.62 (m, 3H, Ar-H), 8.15-8.18 (dd, 1H, J = 7.8 Hz and 1.7 Hz, Ar-H). FAB mass: m/z (%) = 291(100%), 292 (M^++H).

(3e): IR (KBr) ν cm^{-1}: 3240 (= C-H str.), 1610(C = N str.), 1210 (C-O str.). ^1H NMR (400 MHz, $CDCl_3$, TMS) δ ppm: 7.10 (s, 1H, OH), 7.80-8.88 (dd, 2H, J = 6.2Hz and 2.1Hz, Ar-H), 8.0-8.1 (dd, 2H, J = 6.2Hz and 2.1Hz, Ar-H), 8.40-8.84 (m, 5H, Ar-H).

(3h): IR (KBr) ν cm^{-1}: 3250 (C-H str.), 1615 (C = N str.), 1243 (C-O str.). ^1H NMR(400 MHz, $CDCl_3$, TMS) δ ppm: 3.82 (s, 3H, OCH_3), 7.80-7.86 (dd, 2H, J = 6.5Hz and 2.3Hz, Ar-H), 8.01-8.1 (dd, 2H, J = 6.5Hz and 2.3Hz, Ar-H), 8.15 (dd, 1H, J = 7.7Hz and 1.7Hz, Ar-H), 8.16-8.61 (m, 3H, Ar-H). FAB mass: m/z (%) = 287, 292(M^++H,100%).

(3j): IR (KBr) ν cm^{-1}: 3105 (= C-H str.), 1581(C = N str.), 1290 (C-O str.). ^1H NMR (400 MHz, $CDCl_3$, TMS) δ ppm: 3.8 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 7.6 (s, 1H, Ar-H), 7.65 (s,1H, Ar-H), 8.1(dd, 1H, J = 7.7Hz and 1.7Hz, Ar-H), 8.1-8.4 (m, 3H, Ar-CH). FAB mass: m/z (%) = 362 (M^++H, 60%), 345, 331, 318, 306, 286, 154.

(3m): IR (KBr) ν cm^{-1}: 3005 (= C-H str.), 1571 (C = N str.), 1271 (C-O str.). ^1H NMR (400 MHz, $CDCl_3$, TMS) δ ppm): 7.55 (s,1H, Ar-H), 7.59 (s,1H, Ar-H), 7.62-7.67(m, 2H, Ar-H), 7.95-7.96 (m,1H, Ar-H), 8.20-8.23 (m, 2H, Ar-H). FAB mass: m/z (%) = 325 (M^+, 20%), 327 (M^++2, 30%), 154 (100%), 136, 120.

(3o): IR (KBr) ν cm^{-1}: 3250 (Ar-H str.), 1615 (C = N str.), 1243 (C-O str.). ^1H NMR (400 MHz, $CDCl_3$, TMS) δ ppm: 7.62 (d, 1H, J = 2.4 Hz, pyridine moiety), 7.8-8.4 (m, 5H, Ar-H); 8.5-8.6 (m, 2H, Py-H), 8.85-8.91 (m, 1H, Py-H). FAB mass: m/z (%) = 223 (M^+, 100%), 224 (M^++H, 30%).

CONCLUSION

A new series of 3,5-disubstituted 1,2,4-oxadiazoles were synthesized with a view to evaluate their biological activity. The screening data showed that the newly prepared compounds exhibited promising antibacterial and antifungal activities.

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