Synthesis of 5H-Oxadiazoline Derivatives from Oxime Isatin

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Abstract

A series of heterocyclic compounds 1,2,4-5H oxadiazol [4a-e,5a-c] derivatives were prepared by the reaction of aldehyde and ketone with amidoxime in which the latter was obtained from the reaction of corresponding nitrile with hydroxyl amine hydrochloride. The prepared compounds were characterized by IR spectra.

الخلاصة

يتضمن البحث تحضير بعض مشتقات 1،2،4-5H-اوكساديازول من تفاعل الالديهايد والكيتون مع الاميدو اوكزيم المحضر من تفاعل النتريلات المقابلة مع الهيدروكسيل امين هيدروكلوريد وتم تشخيص المركبات الناتجة باستخدام طيف الاشعة تحت الحمراء.

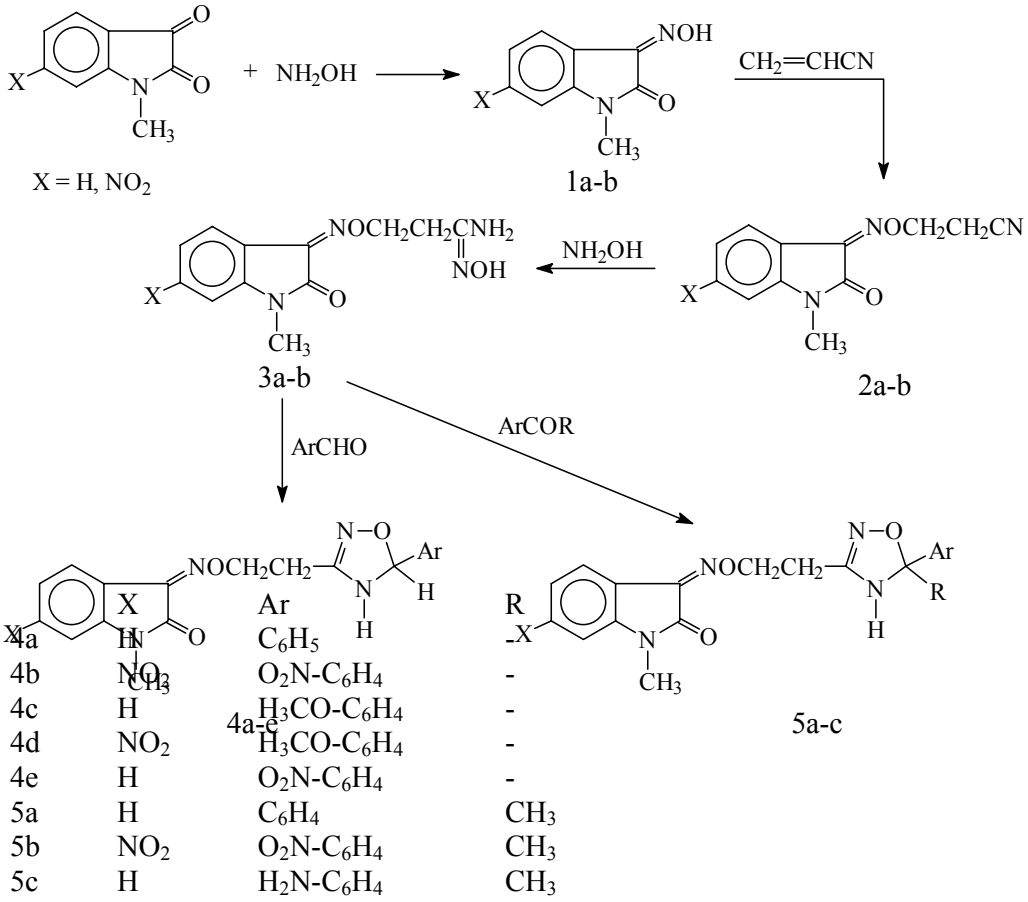
Introduction

1,2,4-Oxadiazole rings occur widely in biologically active synthetic compounds. Numerous 1,2,4-oxadiazoles have been suggested as potential agonists for cortical muscarinic[1-4], benzodiazepine[5,6], $5HT_{ID}$ (5-hydroxy tryptamine) receptors[7] and as antagonists for 5-HT_3[8], histamine H_3 receptors[9], or the porcine 5-HT_{1B} receptor[10]. They showed activity as antirhinoviral agents[11], growth hormone secretagoues[12], anti-inflammatory agents[13], antitumor agents[14] and antinociceptive effect of tramadol[15]. They also inhibit the SH_2 domain of tyrosine kinase[16,17], monoamine oxidase[18], human neutrophil elastase[19] and human DNA topoisomerases[20]. Finally, tropane derivatives of 1,2,4-oxadiazoles display high affinity for the cocaine binding site of the dopamine transporter[21].

1,2,4-Oxadiazoles were prepared by coupling of amidoximes with either activated carboxylic acid derivatives such as acid chloride[22,23], fluorides[24] or anhydride[25,26], carboxylic acid in the presence of coupling agents including dicyclohexyl carbodiimide[27], 2-(dimethyl amino) isopropyl chloride[28,29] and 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyl uranium tetrafluoroborate[30,31] or chiral O-amino acid[32]. Other methods to

prepare 1,2,4-oxadiazoles include 1,3-dipolar cycloadition of imidazoline 3-oxide with alkyl or aryl isothiocyanate[33-35] and cyclic nitrone with styrene[36] or O-pinene[37]. The objective of this investigation was to

prepare a new 1,2,4-5H-oxadiazole derivatives.



	X	Ar	R
4a	H	C_6H_5	-
4b	NO_2	O_2N-C_6H_4	-
4c	H	H_3CO-C_6H_4	-
4d	NO_2	H_3CO-C_6H_4	-
4e	H	O_2N-C_6H_4	-
5a	H	C_6H_4	CH_3
5b	NO_2	O_2N-C_6H_4	CH_3
5c	H	H_2N-C_6H_4	CH_3

Scheme (1)

Xperimental

Uncorrected melting points were determined using Electrothermal 9300 melting points apparatus. I.R. spectra were recorded on Infrared Spectrophotometer Model Tensor 27 Bruker Co., Germany.

Preparation of (6-nitro) or N-methyl isatin oxime (1a-b):

A mixture of (0.05 mole) N-methyl isatin or 6-nitro-N-methyl, (0.1 mole, 3.5 gm) hydroxyl amine hydrochloride and (0.05 mole, 2 gm) sodium hydroxide in (50 ml) of water, was refluxed for (30 min.), cooled,

filtered and recrystallized from ethanol.

Preparation of (6-nitro) or N-methyl isatin oxime propionitrile(2a-b):

To a solution of compound (1) (0.05 mole) in 100 ml of dry dioxane and (0.05 mole) of sodium methoxide added (0.05 mole) of acrylonitrile dropwise with stirring for 20 min. and the solution was stirred for 48 hrs. The solvent was evaporated and the solid was recrystallized from water. Melting point, percent yields and I.R. spectral data are listed in Table (1).

Preparation of 3-[(6-nitro) or N-methyl oxime isatin ethyl] 5-substituted 1,2,4(5H)-oxadiazoline (4a-e) and (5a-c):

(0.005 mole) of compounds (3a-b) were mixed with (0.005 mole) of aldehyde or ketone in 20 ml of ethanol and refluxed for 3 hrs. The solvent was evaporated and the solid was recrystallized from 75% ethanol.

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Compounds (2a-b) were prepared by the reaction of isatin oxime with equivalent amount of the acrylonitrile.

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IR spectra of these compounds showed the major absorption bands at (1614-1632 cm^{-1}), (1670-1689 cm^{-1}) and (2181-2196 cm^{-1}) which are related to stretching vibration C=N, C=O and C≡N respectively. Amidoximes (3a-b) were synthesized from the reaction of the

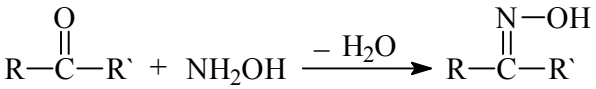
Preparation of (6-nitro) or N-methyl isatin oxime ethylene amido oxime (3a-b):

(0.05 mole) of compound (2a or 2b) was dissolved in 50 ml of 50% ethanol, (0.1 mole) sodium carbonate was added, thereafter (0.2 mole) hydroxyl amine hydrochloride was added. The reaction mixture was heated on steam bath for 90 min. The amidoxime which separated on cooling was filtered off and recrystallized from ethanol to obtain prism crystal. Melting point, percent yields and I.R. spectral data are listed in Table (1).

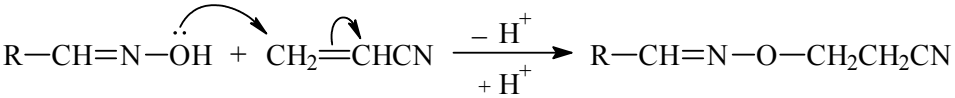
Melting point, percent yields and I.R. spectral data are indicated in Table (2).

RESULTS AND DISCUSSION

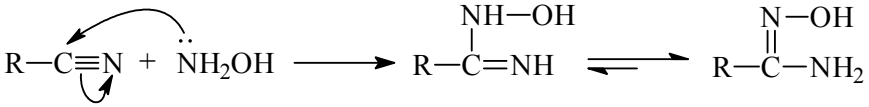
Compounds (1a,b) were prepared by the reaction of isatin or 6-nitroisatin with hydroxylamine hydrochloride in basic media to afford the oximes



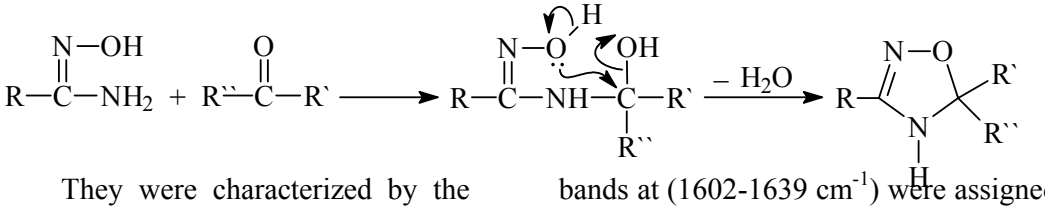
This reaction is occurring through nucleophilic addition of hydroxyl group of oxime to carbon-carbon double bond



corresponding isatin oxime propionitrile (2a-b) with hydroxyl amine hydrochloride by the nucleophelic addition of amino group in hydroxylamine to the nitrile group (C≡N).



Their structure were verified by IR spectra which showed the following main signals (1609-1613 cm^{-1}) for C=N, (1664-1675 cm^{-1}) for C=O, (3129-3454 cm^{-1}) for amine stretching absorption together with hydroxyl absorption band. The final compounds (4a-e) and (5a-c) were synthesized from the reaction of the corresponding amidoxime with aldehyde and ketone respectively. The mechanism of the reaction was accomplished by nucleophilic attack of NH_2 group of amidoxime on carbon of carbonyl group, then, the resulted compound was underwent elimination of H_2O molecular to give oxadiazoline.



They were characterized by the following absorption bands (Table2) (1654-1699 cm^{-1}) for C=O stretching vibration of amide, while the absorption bands at (1602-1639 cm^{-1}) were assigned to C=N stretching vibration and (3155-3434 cm^{-1}) related to NH.

Table (1): Physical constants and IR spectral data for compounds (1a-b, 2a-b, 3a-b)

Comp. No.	m.p. °C	Yield %	IR □ cm^{-1}				
			C=N	C=O	C≡N	N-H	O-H
1a	191-192	84	1608	1675	-	-	3536
1b	250-252	78	1620	1692	-	-	3411
2a	170-172	67	1614	1670	2196	-	-
2b	> 300	60	1632	1689	2181	-	-
3a	211-212	81	1613	1675	-	3135	3339
3b	128-130	74	1609	1664	-	3129	3454

Table (2): Physical constants and IR spectral data for compounds (4a-e) and (5a-d)

Comp. No.	m.p. °C	Yield %	IR □ cm^{-1}		
			C=N	C=O	N-H
4a	225 d.	64	1614	1688	3203
4b	270 d.	70	1639	1699	3390
4c	163-165	72	1610	1683	3155
4d	220 d.	59	1602	1654	3222
4e	82-84	67	1613	1680	3339
5a	250 d.	75	1626	1677	3348
5b	240 d.	62	1615	1671	3310
5c	95-97	60	1634	1670	3434

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