Synthesis of 2-Isobutyl, 2-Isobutyl-5-aryl and 2-Isobutyl-5-thiol-1,3,4-Oxadiazoles

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الملخص

تم في هذا البحث تحضير عدد من معوضات 1،3،4-اوكسادايازول من حامض ايسوبيوتريك. تم تحويل الحامض الى اثيل استر المقابل ثم مفاعلته مع الهيدرازين المائي في الايثانول ليعطي هيدرازيد الحامض. اعطت مفاعلة هيدرازيد الحامض مع معوضات البنزالديهايد للهيدرازونات المقابلة. تم تحويل الهيدرازونات المحضرة الى مركبات 2-ايسوبيوتيل-5-اريل-1،3،4-اوكسادايازول من خلال مفاعلتها مع PbO_2 . بينما اعطت مفاعلة الهيدرازين مع حامض الفورميك 1-فورميل-2-اسيل هيدرازين والذي تم تحويله الى 2-ايسوبيوتيل-1،3،4-اوكسادايازول من خلال مفاعلته مع اوكسي كلوريد الفسفور. تم تحضير 2-ايسوبيوتيل-1،3،4-اوكسادايازول-5-ثايول من تفاعل هيدرازيد الحامض وثنائي كبريتيد الكاربون في محلول هيدروكسيد البوتاسيوم.

شخصت المركبات المحضرة بالطرائق الفيزياوية والطيفية.

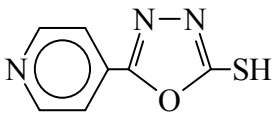
ABSTRACT

In this paper the synthesis of some substituted 1,3,4-oxadiazoles from isobutyric acid was studied. The isobutyric acid was converted into the corresponding ethyl ester, which then treated with hydrazine hydrate in ethanol to give the acid hydrazide. The acid hydrazide was treated with substituted benzaldehyde to give the corresponding hydrazones. The synthesized hydrazones were then converted to 2-isobutyl-5-aryl-1,3,4-oxadiazoles by their reaction with PbO_2. While treatment of acid hydrazide with formic acid and then with phosphorus oxychloride gave 2-isobutyl-1,3,4-oxadiazole. 2-Isobutyl-1,3,4-oxadiazole-5-thiol was synthesized by the reaction of acid hydrazide with carbon disulfide in potassium hydroxide solution.

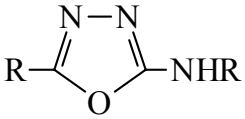
The structures of the synthesized compounds were confirmed by physical and spectral means.

INTRODUCTION

The chemical and biological importance of substituted 1,3,4-oxadiazoles draw attention of many research workers. Some substituted 1,3,4-oxadiazole show applications in dye industry[1], some others have various biological activities as antibacterial[2-4], antifungal[5] and medical uses[6]. Some of 1,3,4-oxadiazoles derivatives act as plant growth regulators[7] active against tuberculosis[8] and parasitic helminthes[9] as compound (I) and (II) respectively.



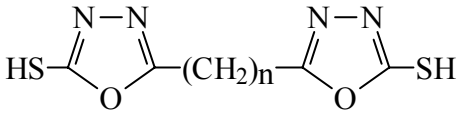
(I)



(II)

Substituted 1,3,4-oxadiazoles were synthesized from corresponding hydrazide by their reaction with carbon disulfide in dry pyridine[9] or ethanolic potassium hydroxide[10]. While thiosemicarbazides were converted into 1,3,4-oxadiazole when treated with iodine in alcoholic sodium hydroxide[11].

Bis-(2-thiol-1,3,4-oxadiazole-5-yl) alkanes (III) were synthesized from the corresponding acid hydrazide by the reaction with carbon disulfide in aqueous potassium hydroxide[12].



n = 2,3

(III)

By using microwave energy, 2,5-disubstituted-1,3,4-oxadiazoles were synthesized from acid hydrazides and carboxylic acids[13].

EXPERIMENTAL

Melting points were measured using Electrothermal 9300 and are uncorrected. The IR spectra were recorded on Brucker FT-IR Spectrophotometer, Tensor 27, using KBr discs. The UV spectra were recorded on UV-Visible Shimadzu 1601 Spectrophotometer.

Synthesis of ethyl isobutyrate (2):

A mixture of isobutyric acid (1) (2.2 g, 0.025 mole) and concentrated sulfuric acid (5 ml) in absolute ethanol (50 ml) was refluxed for 3 hours. The mixture was allowed to cool to room temperature and crushed ice was added with stirring, the mixture was then neutralized with 20% sodium carbonate, extracted with methylene chloride, and the organic layer was dried over $MgSO_4$, filtered and evaporated to give the ethyl ester b.p. (108-110 °C, Lit.[14] b.p. 107-110 °C), yield 83%, IR. □ 1734 cm^{-1} (C=O), U.V. $\square_{max}$ 290 nm.

Synthesis of isobutyric acid hydrazide (3)[15]:

A mixture of ethyl isobutyrate (1.16 gm, 0.01 mole) and hydrazine hydrate (2.5 ml, 0.05 mole) in ethanol (50 ml) was refluxed for 3 hours. The solvent was evaporated under vacuum to give the hydrazide as a solid product which was recrystallized from ethanol to give the titled compound, m.p. (98-100 °C), yield 62%, IR 3350 for (N-H) 1694 cm^{-1} (C=O), UV λ_{max} 288 nm.

Substituted hydrazones (4-8)[16]:

Ethanolic solution of substituted benzaldehyde (0.01 mole, 25 ml) was added to hydrazide (3) (1.02 gm, 0.01 mole). The reaction mixture was then refluxed for 2 hours, and cooled. The forming precipitate was filtered off and recrystallized from ethanol, Table (1).

2,5-Disubstituted-1,3,4-oxadiazole (9-13):

Hydrazones (4-8) were stirred in glacial acetic acid (40 ml) to get homogenous solution. Then PbO_2 (1.3 gm, 0.01 mole) was added, the mixture stirred with mechanical stirrer at (25 °C) for 1 hour. The mixture was diluted with cold water, then the products thus formed as solid after 24 hours, were filtered and recrystallized from ethanol, Table (2).

1-Formyl isobutyric acid hydrazide (14)[17]:

A mixture of hydrazide (3) (2.5 gm, 0.025 mole) and formic acid (10 ml) was refluxed for 30 minutes. The solvent was evaporated under reduced pressure to give the product, which purified by recrystallization from ethanol. IR 1650, 1685 cm^{-1} (2C=O), UV λ_{max} 296 nm, yield 59%, m.p. (151-153 °C).

2-Isobutyl-1,3,4-oxadiazole (15)[18]:

A mixture of 1-formyl isobutyric acid hydrazide (14) (0.01 mole) and phosphorus oxychloride (10 ml) was refluxed for 1 hour. The mixture was then poured on crushed ice. Sodium bicarbonate solution (20%) was added until the solution become basic. The formed precipitate was filtered, washed with water (several times) and recrystallized from ethanol-water, Table (2).

2-Isobutyl-1,3,4-oxadiazole-5-thiol (16)[9]:

To hydrazide (3) (0.005 mole) in potassium hydroxide solution (0.28 gm, 0.005 mole) in (70 ml) 95% ethanol. Carbon disulfide (6 ml, 0.1 mole) was added, and the mixture then refluxed for 16 hours (until H_2S evolve cased). The solvent was evaporated under reduced pressure, the residue then poured onto crushed ice and acidified with dilute hydrochloric acid with cooling and stirring. The solid was filtered and recrystallized from ethanol, Table (2).

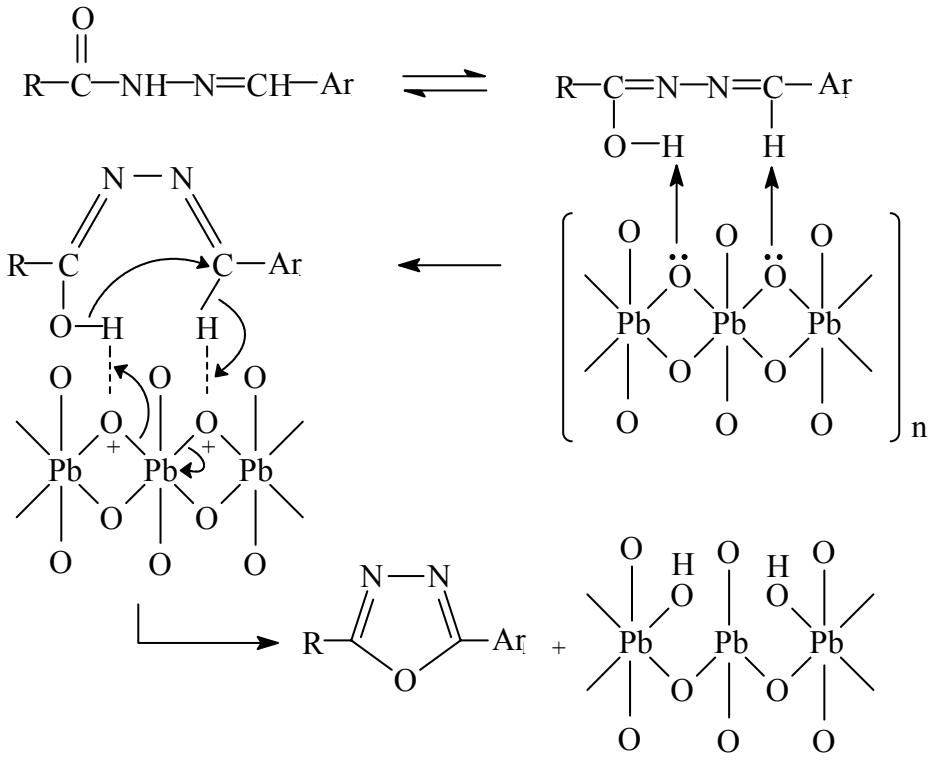
RESULTS AND DISCUSSION

The synthesis of some substituted 1,3,4-oxadiazoles was achieved from isobutyric acid (Scheme 1).

The isobutyric acid (1) was converted to ethyl ester (2) by its reaction with absolute ethanol in acidic medium. The ester showed absorption band in the IR spectrum cm^{-1} at 1734 cm^{-1} due to (C=O) stretching band and maximum absorption in the UV spectrum λ_{max} at 290 nm. The ester (2) was converted to acid hydrazide (3) by its reaction with hydrazine hydrate in ethanol, the IR spectrum showed absorption cm^{-1} at 3350 cm^{-1} due to (N-H) and 1694 cm^{-1} due to (C=O).

The hydrazide (3) was treated with benzaldehyde and substituted benzaldehyde (p-methoxy, p-chloro, o-nitro and o-hydroxy) to give the hydrazones (4-8). The IR spectrum for compound (4) showed absorption cm^{-1} at 3384 cm^{-1} due to (N-H), 1666 cm^{-1} due to (C=O) and 1610 cm^{-1} due to (C=N), UV spectrum showed maximum absorption at 334 nm. While the IR spectrum of compounds (5, 7, and 8) showed absorption cm^{-1} at 2839 cm^{-1} due to (C-H stretching, OCH_3), 1560, 1347 cm^{-1} due to (NO_2) and 3418 due to (OH).

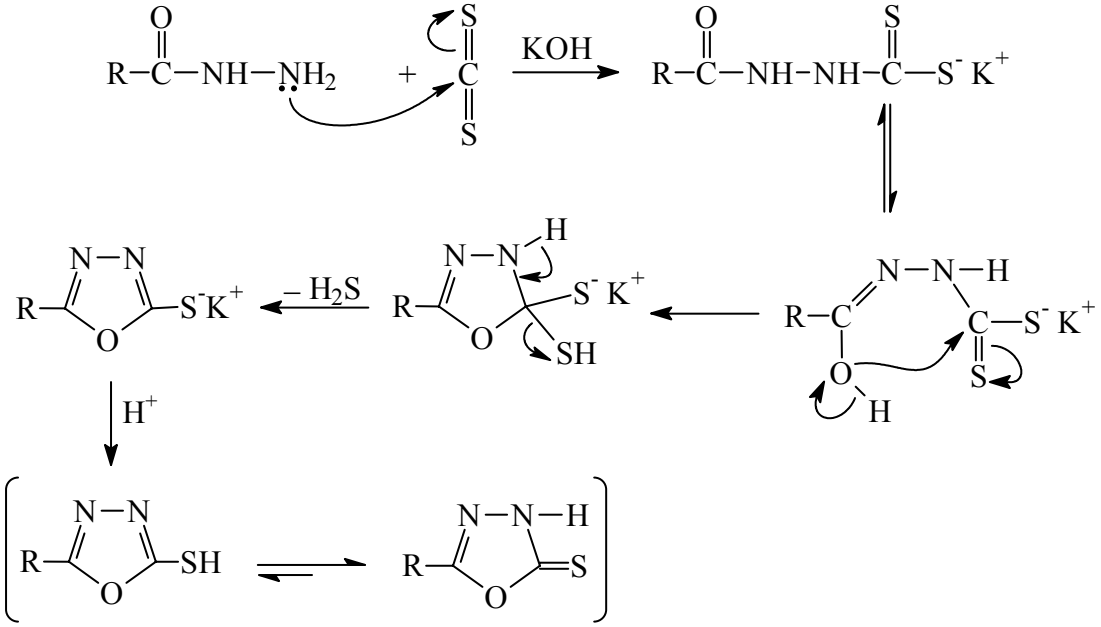
The hydrazones (4-8) were cyclized to the corresponding 1,3,4-oxadiazoles (9-13) by their reaction with lead dioxide in glacial acetic acid, through the following mechanism[19]:



The IR spectrum of compound (9) showed absorption bands cm^{-1} at 1636 cm^{-1} due to (C=N) and 1092 cm^{-1} due to (C-O-C), whereas UV

spectrum showed higher absorption λ_{max} at 322 nm. The IR spectrum of compound (10) showed maximum absorption ν cm^{-1} at 2840 cm^{-1} due to (C-H stretching, OCH_3), and compound (11) showed absorption at 1524 (asy.) and 1345 (sym.) cm^{-1} due to (NO_2), while compound (13) showed absorption band at 3378 due to (OH).

Hydrazide (3) was treated with formic acid to give 1-formyl-2-acyl hydrazine (14), which then converted to monosubstituted 1,3,4-oxadiazole (15). 1-Formyl-2-acyl hydrazine (14) showed in IR stretching absorption bands ν cm^{-1} at 1685 and 1650 cm^{-1} due to 2(C=O). The monosubstituted 1,3,4-oxadiazole (15) showed absorption bands ν cm^{-1} at 1634 cm^{-1} due to (C=N) and 1027 cm^{-1} due to (C-O-C). 2-Isobutyl-1,3,4-oxadiazole-5-thiol (16) was synthesized from the reaction of hydrazide (3) with carbon disulfide in alcoholic potassium hydroxide. Compound (16) showed IR absorption bands ν cm^{-1} at 1634 cm^{-1} due to (C=N), 1048 cm^{-1} due to (C-O-C) and 1212 cm^{-1} due to (C=S) which is the more probable form in thiol-thione tautomerism in this type of compounds. The UV spectrum of compound (16) showed maximum absorption λ_{max} at 356 nm. The formation of 1,3,4-oxadiazole (16) from hydrazide (3) may proceed through the following mechanism[20]:



R = $(CH_3)_2CH$-

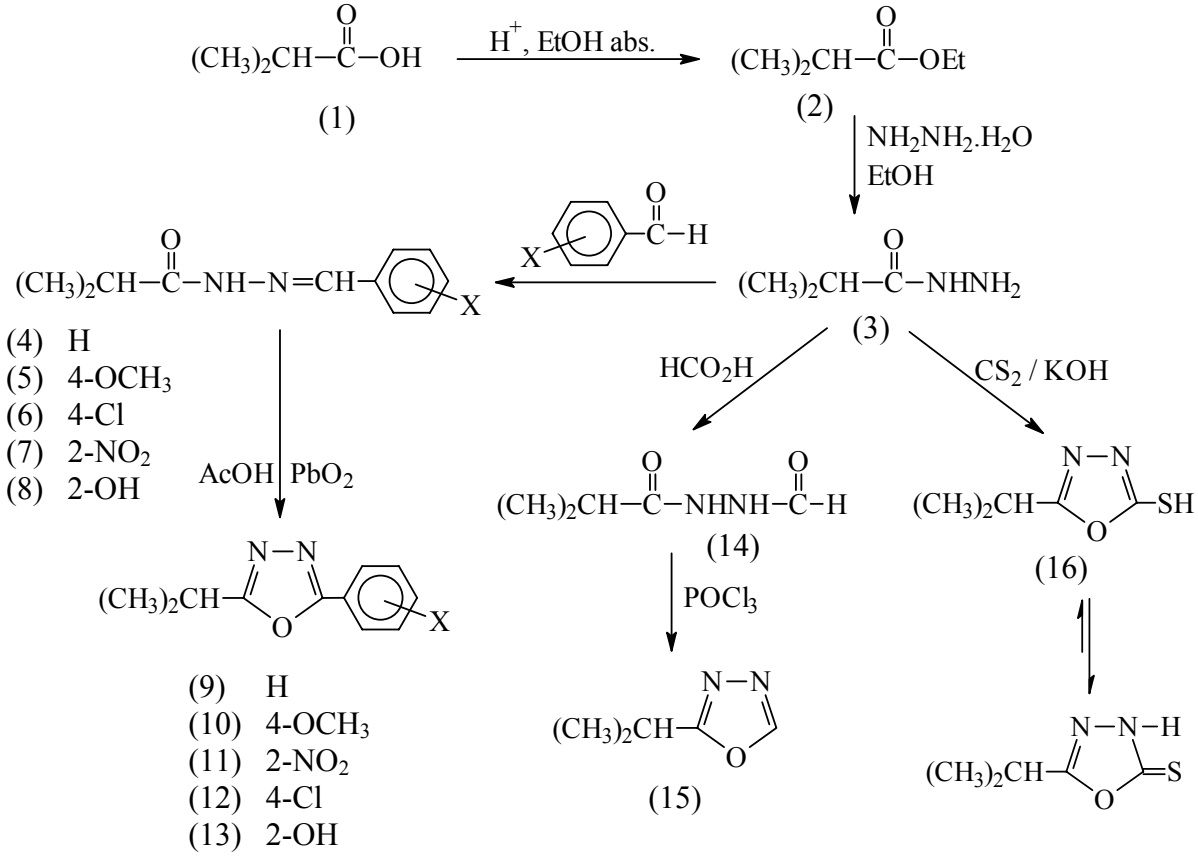
Physical and spectral data of the synthesized compounds are shown in Tables (1 and 2).

Table (1): Physical and spectral data of hydrazones (4-8)

Comp. No.	m.p. °C	Yield %	IR □ cm^{-1}				UV λ_{max} nm EtOH
			N-H	C=O amide	C=N	Others	
4	84-86	98	3384	1666	1610	-	334
5	167-169	59	3446	1683	1619	2839 C-H st. OCH_3)	344
6	52-54	50	3357	1655	1625	-	342
7	70-72	30	3284	1667	1607	1560, 1347 asy. , sym. (NO_2)	314
8	94-92	33	3384	1673	1630	3418 (OH)	362

Table (2): Physical and spectral data of substituted 1,3,4-oxadiazoles (9-16)

Comp. No.	m.p. °C	Yield %	IR □ cm^{-1}			UV λ_{max} nm EtOH
			C=N	C-O-C	Others	
9	112-114	30	1636	1092	-	322
10	128-130	20	1632	1028	2840 C-H st. (OCH_3)	326
11	205-207	37	1626	1141	1524, 1345 asy. , sym. (NO_2)	344
12	212-214	83	1625	1089	-	344
13	200-202	70	1623	1050	3378 (OH)	344
15	120-122	85	1634	1027	-	288
16	146-148	83	1634	1048	1212 (C=S) 3452 (N-H)	356


(CH3)2CH–C(=O)–OH
H+, EtOH abs.
(CH3)2CH–C(=O)–OEt
(1)
(2)
NH2NH2.H2O
EtOH
(CH3)2CH–C(=O)–NHNH2
(3)
X–C6H4–CHO
(CH3)2CH–C(=O)–NH–N=CH–C6H4–X
(4) H
(5) 4-OCH3
(6) 4-Cl
(7) 2-NO2
(8) 2-OH
AcOH PbO2
HCO2H
CS2 / KOH
(CH3)2CH–C(=O)–NHNH–C(=O)–H
(14)
POCl3
(CH3)2CH–C2N2O–SH
(16)
(CH3)2CH–C2N2O
(15)
(CH3)2CH–C2N2O–NH
=S
(9) H
(10) 4-OCH3
(11) 2-NO2
(12) 4-Cl
(13) 2-OH

Scheme (1)

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