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Synthesis of some substituted 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles from 2-(2,3-dimethylphenyl amino) benzoic acid

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الخلاصة

تم في هذا البحث تحضير عدد من معوضات ١،٣،٤-اوكسادايازول و ١،٣،٤-ثايادايازول و ١،٢،٤-ترايازول. حول حامض ٢-(٢،٣-ثنائي مثيل فنيل امينو) بنزويك إلى استر الاثيل المقابل من خلال تفاعله مع الايثانول المطلق بوجود حامض الكبريتيك المركز. تم مفاعلة استر الاثيل مع الهيدرازين المائي في الايثانول ليعطي هيدرازيد الحامض. وأعطى الهيدرازيد ثايوسيميكاربازيد معوض عند معاملته مع ثايوسيانات الامونيوم. تم مفاعلة الثايوسيميكاربازيد مع محلول هيدروكسيد الصوديوم ومع حامض الكبريتيك المركز ليعطي ٥-(٢،٣-ثنائي مثيل فنيل امينو فنيل)-١،٢،٤-ترايازول-٣-ثايول و ٢-(٢،٣-ثنائي مثيل فنيل امينو فنيل)-٥-امينو-١،٣،٤-ثايادايازول على التوالي. تم مفاعلة الهيدرازيد مع معوضات البنزالديهايد ليعطي الهيدرازونات المقابلة والتي تم حولقتها إلى ١،٣،٤-وكسادايازول ثنائي التعويض. بينما أعطى تفاعل الهيدرازيد مع حامض الفورميك ومفاعلة ١-فورميل هيدرازين الناتج مع PbO_2 مركب ١،٣،٤-اوكسادايازول أحادي التعويض. في حين أعطى تفاعل الهيدرازيد مع ثنائي كبريتيد الكاربون في محلول هيدروكسيد البوتاسيوم الكحولي ٢-(٢،٣-ثنائي مثيل فنيل امينو فنيل)-١،٤،٣-اوكسادايازول-٥-ثايول.

شخصت تراكيب المركبات المحضرة بالطرق الفيزياوية والطيفية.

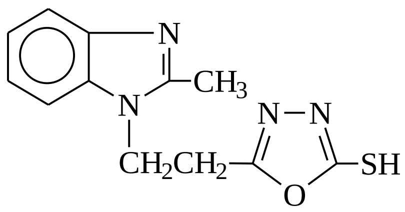
ABSTRACT

In this paper the synthesis of some substituted 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles was achieved. 2-(2,3-dimethyl phenyl amino) benzoic acid was esterified to its ethyl ester by its reaction with absolute ethanol in presence of concentrated sulfuric acid. The ethyl ester was treated with hydrazine hydrate in ethanol to give the corresponding hydrazide. The hydrazide was converted to substituted thiosemicarbazide by its reaction with ammonium thiocyanate. The thiosemicarbazide was treated with sodium hydroxide solution and with sulfuric acid to give 5-(2,3-dimethyl phenyl amino phenyl)-1,2,4-triazole-3-thiol and 2-(2,3-dimethyl phenyl amino phenyl)-5-amino-1,3,4-thiadiazole respectively. The acid hydrazide was treated with substituted benzaldehyde to give hydrazones which cyclized to disubstituted 1,3,4-oxadiazole, while the reaction of hydrazide with formic acid followed by cyclization of formyl hydrazine by PbO_2 to give monosubstituted 1,3,4-oxadiazole. Finally, treatment of hydrazide with carbon disulfite in alcoholic potassium hydroxide gave 2-(2,3-dimethyl phenyl amino phenyl)-1,3,4-oxadiazole-5-thiol. The structures of the synthesized compounds were confirmed by physical and spectral means.

INTRODUCTION

The synthesis of substituted 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles draw the attention of the research workers due to their chemical and biological importance. Some substituted 1,3,4-oxadiazole show antibacterial activity(1), as compound (1)(2).

While 3-substituted-5-(4-pyridyl)-1,3,4-oxadiazole-2-one show antiviral activity(3). Other 1,3,4-oxadiazoles act as antifungal(4), whereas compound (2) effected on the central nervous system as anticonvulsant(5). It was found that 1,5-bis (4-dimethyl aminophenyl)-1,3,4-oxadiazole acts as steel corrosion inhibitors(6).



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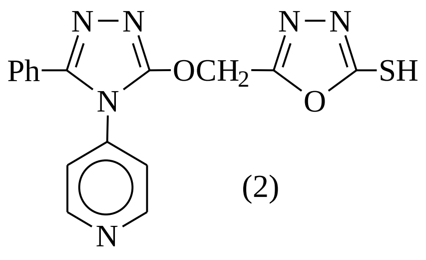
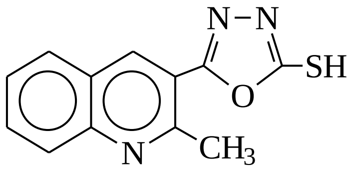


(2)

Substituted 1,3,4-oxadiazoles were synthesized by using a number of starting materials such as acid hydrazides which were converted to substituted 1,3,4-oxadiazoles by their reaction with carbon disulfide in dry pyridine(7), or in ethanolic potassium hydrazide(8,9), as in the case of the synthesis of 2-(2-methyl quinoline-3-yl)-1,3,4-oxadiazole-5-thiol (3)(10).

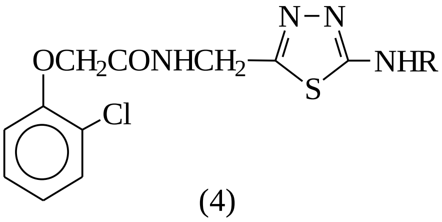


(3)

Substituted thiosemicarbazide were converted to 1,3,4-oxadiazoles by their reaction with lead oxide(11).

Substituted 1,3,4-thiadiazoles are associate with many types of biological activities such as antibacterial and antifungal agent(12) reduce glucose level in blood(13) and act on some cancer tissues(14).

1,3,4-Thiadiazoles were synthesized by various methods, thiosemicarbazide was treated with carboxylic acid or presence of concentrated sulfuric acid to give 5-amino-2-substituted-1,3,4-thiadiazole(15), or from phthalic anhydride and thiosemicarbazide in presence of concentrated sulfuric acid(16), whereas substituted thiosemicarbazides were cyclized by using phosphoric acid to give 1,3,4-thiadiazoles as compound (4)(17).

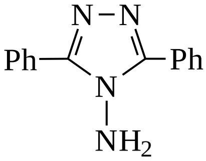


(4)

1,2-Diacyl hydrazine was cyclized to substituted 1,3,4-thiadiazoles by its reaction with phosphorous pentasulfide in xylene(18).

1,2,4-Triazoles showed antiviral, anti-inflammatory and antinociceptive properties(19), anticancer(20) and antibacterial activity(21).

1,2,4-Triazoles were synthesized from the reaction of substituted thiosemicarbazide with aqueous sodium hydroxide(22,23) or with hydrazine hydrate(24), whereas disubstituted 1,2,4-triazoles were synthesized by heating the hydrazides at high temperature as in the case of compound (5)(25).



(5)

In this paper the synthesis of some substituted 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles is reported.

EXPERIMENTAL

All chemicals were purchased from Flucka and BDH Chemical Ltd. The melting points were measured on an Electrothermal 9300 Engineering LTD and were uncorrected. IR spectra were recorded on Infrared Spectrophotometer Model Tensor 27, Bruker Co., Germany, using KBr discs. UV spectra were recorded on Shimadzu, UV-160, UV-Visible Recording Spectrophotometer.

Ethyl 2-(2,3-dimethyl phenyl amino) benzoate (1)

2-(2,3-Dimethyl phenyl amino) benzoic acid (2.57 g, 0.01 mole) was dissolved in abdsolute ethanol (50 ml), concentrated sulfuric acid (4 ml) was added slowly with cooling. The reaction mixture was refluxed for (3) hours, the solvent then evaporated under reduced pressure, the solid product was recrystallized from ethanol (Tables 1 and 2).

Acid hydrazide (2)

A mixture of ethyl ester (1) (2.55 g, 0.01 mole) and hydrazine hydrate (10 ml, 0.2 mole) in absolute ethanol (70 ml) was refluxed for (3) hours. The solvent was evaporated under reduced pressure to give hydrazide as green powder (Tables 1 and 2).

Substituted thiosemicarbazide (3)

A mixture of acid hydrazide (2) (3.14 g, 0.01 mole), ammonium thiocyanate (2.28 g, 0.03 mole), hydrochloric acid (4 ml) in absolute ethanol (25 ml) was refluxed for 22 hrs. The solvent was evaporated and residue poured on crushed ice with stirring, the solid formed, filtered dried and recrystallized from ethanol (Tables 1 and 2).

2,3-Dimethyl phenyl aminophenyl-1,2,4-triazole-3-thiol (4)

A mixture of substituted thiosemicarbazide (3) (1.48 g, 0.005 mole) and 1% aqueous sodium hydroxide (7.5 ml) was refluxed for 3 hrs., the mixture was treated with charcoal and the charcoal then removed by hot filtration. The solution was acidified by 10% hydrochloric acid with cooling, the precipitated was filtered, and recrystallized from ethanol (Tables 1 and 2).

2,3-Dimethyl phenyl aminophenyl-5-amino-1,3,4-thiadiazole (5)

Concentrated sulfuric acid (10 ml) was added to substituted thiosemicarbazide (3) (1.48 g, 0.05 mole). The mixture was heated on water bath at 90 °C with stirring for 2 hrs., the mixture then poured onto ice-water and neutralized with concentrated ammonium hydroxide solution with cooling, the formed precipitate was filtered, washed with cold water, dried and recrystallized from benzene (Tables 1 and 2).

1- Acyl-2-formyl hydrazine (16)

A mixture of acid hydrazide (2) (2.55 g, 0.01 mole), formic acid (0.46 g, 0.01 mole) in ethanol (20 ml) was refluxed for 3 hrs. The mixture was cooled and the solid was filtered, dried and recrystallized from ethanol (Tables 1 and 2).

Hydrazones (6-10)

Benzaldehyde / substituted benzaldehyde (0.01 mole) acid hydrazide (2) (2.55 g, 0.01 mole) in ethanol (20 ml) was refluxed for 2 hrs. The solvent was condensed, then the precipitate was filtered and recrystallized from benzene (Tables 1 and 2).

Cyclization of 1-acyl-2-formyl hydrazine and hydrazones into substituted 1,3,4-oxadiazoles (11-15 , 17)

To a homogenous solution of hydrazones (6-10) and 1-acyl-2-formyl hydrazine (16) (0.01 mole) in glacial acetic acid, PbO_2 (2.39 g, 0.01 mole) was added to the reaction mixture and stirred with mechanical stirrer at 25 °C for 1 hrs. The reaction mixture was diluted with ice-water and left to stand for 24 hours. The precipitate was filtered and recrystallized from benzene (Tables 1 and 2).

2- (2,3-dimethyl phenyl aminophenyl-2-yl)-1,3,4-oxadiazole-5-thiol (18)

To a mixture of acid hydrazide (2) (1.275 g, 0.005 mole), alcoholic potassium hydroxide solution (0.5%), (0.5 g of KOH dissolved in 100 ml ethanol) CS_2 (12 ml) was added slowly. The mixture was refluxed for 12 hrs., the solution was evaporated, diluted with ice-water, acidify with diluted HCl, filtered and dried (Tables 1 and 2).

Table 1: Physical data of compounds (1-18)

Comp. No.	Molecular formula	Yield (%)	m.p. (°C)	Colour
1	$C_{17}H_{19}NO_2$	70	208-210	Gray
2	$C_{15}H_{17}N_3O$	85	192-194	Green
3	$C_{16}H_{18}N_4OS$	62	176-178	Paler yellow
4	$C_{16}H_{16}N_4S$	45	208-210	White
5	$C_{16}H_{16}N_4S$	43	276-278	White
6	$C_{22}H_{21}N_3O$	50	200-202	White
7	$C_{22}H_{20}N_3OCl$	83	220-222	Pale green
8	$C_{22}H_{20}N_4O_3$	76	265-267	Pale brown
9	$C_{24}H_{25}N_3O$	58	205-207	Dark orange
10	$C_{24}H_{25}N_3O_3$	65	183-185	Dark yellow
11	$C_{22}H_{19}N_3O$	45	158-160	Yellow
12	$C_{22}H_{18}N_3OCl$	77	210-212	Pale brown
13	$C_{22}H_{18}N_4O_3$	63	198-200	Pale brown
14	$C_{22}H_{23}N_3O$	35	234-236	Pale yellow
15	$C_{24}H_{23}N_3O_3$	55	275 dec.	Pale yellow
16	$C_{16}H_{16}N_2O_2$	43	206-208	White
17	$C_{16}H_{15}N_3O$	56	137-139	White
18	$C_{16}H_{17}N_3OS_2$	30	> 300	White

RESULTS AND DISCUSSION

In the present work the synthesis of some substituted 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles was studied starting from 2-(2,3-dimethyl phenyl amino) benzoic acid due to its medical importance (Scheme 1). The acid was esterified to its ethyl ester (1) by its reaction with absolute ethanol in presence of concentrated sulfuric acid. The resulting ester was treated with hydrazine hydrate in ethanol to give the corresponding hydrazide (2). The IR spectra of the ester (1) shows νcm^{-1} at 1730 (C=O) and 3246 (N-H) and for the hydrazide (2) νcm^{-1} 1650 (C=O) and 3380 (N-H). The hydrazide (2) was then converted to thiosemicarbazide (3) by its reaction with ammonium thiocyanate/ concentrated hydrochloric acid. The substituted thiosemicarbazide (3) was treated with aqueous sodium hydroxide and with concentrated sulfuric acid to give 5-substituted-1,2,4-triazole-3-thiol (4) and 2-substituted-5-amino-1,3,4-thiadiazole (5) respectively.

The IR spectra of compound (3) show νcm^{-1} 3418 (N-H), 1669 (C=O) and 1118 (C=S), while compound (4) shows νcm^{-1} 3325 (N-H), 1642 (N=C) and 1090 (C=S), compound (5) shows absorption νcm^{-1} at 3380 (N-H). 1638 (C=N) and 1030 (C-O-C).

The hydrazide (3) was treated with benzaldehyde or substituted benzaldehyde to give the hydrazones (6-10), the hydrazone, were cyclized to 2,5-disubstituted-1,3,4-oxadiazoles (11-15) by their reaction with lead dioxide, the hydrazones (6-10) show IR spectra νcm^{-1} at 3431-3380 (N-H), 1700-1673 (C=O), 1640-1613 (C=N) and 1508, 1312 (NO_2) for compound (8). The compounds (6-10) were treated with lead oxide to give 2-(2,3-dimethyl phenyl aminophenyl)-5-aryl phenyl-1,3,4-oxadiazoles (11-15). The IR spectra for compounds (11-15) νcm^{-1} 3423-3301 (N-H), 1638-1614 (C=N) and 1141-1084 (C-O-C). Some substituted 1,3,4-oxadiazoles were synthesized from acid hydrazide (2) by its reaction with formic acid to give 1-formyl-2-acyl hydrazine (16), the later compound was cyclized to 2-substituted 1,3,4-oxadiazole (17) by its reaction with PbO_2. The acid hydrazide (2) was treated with carbon disulfide in ethanolic potassium hydroxide to give 2-substituted-1,3,4-oxadiazole-5-thiol (18). The IR spectra of compound(16) νcm^{-1} 3383 cm^{-1} 3383 (N-H), 2651 (CHO), for compound (17) νcm^{-1} 3455 (N-H) 1631 (C=N) and 1080 (C-O-C) while compound (18) shows νcm^{-1} at 3313 (N-H), and 1116 (C=S) (Tables 1 and 2).

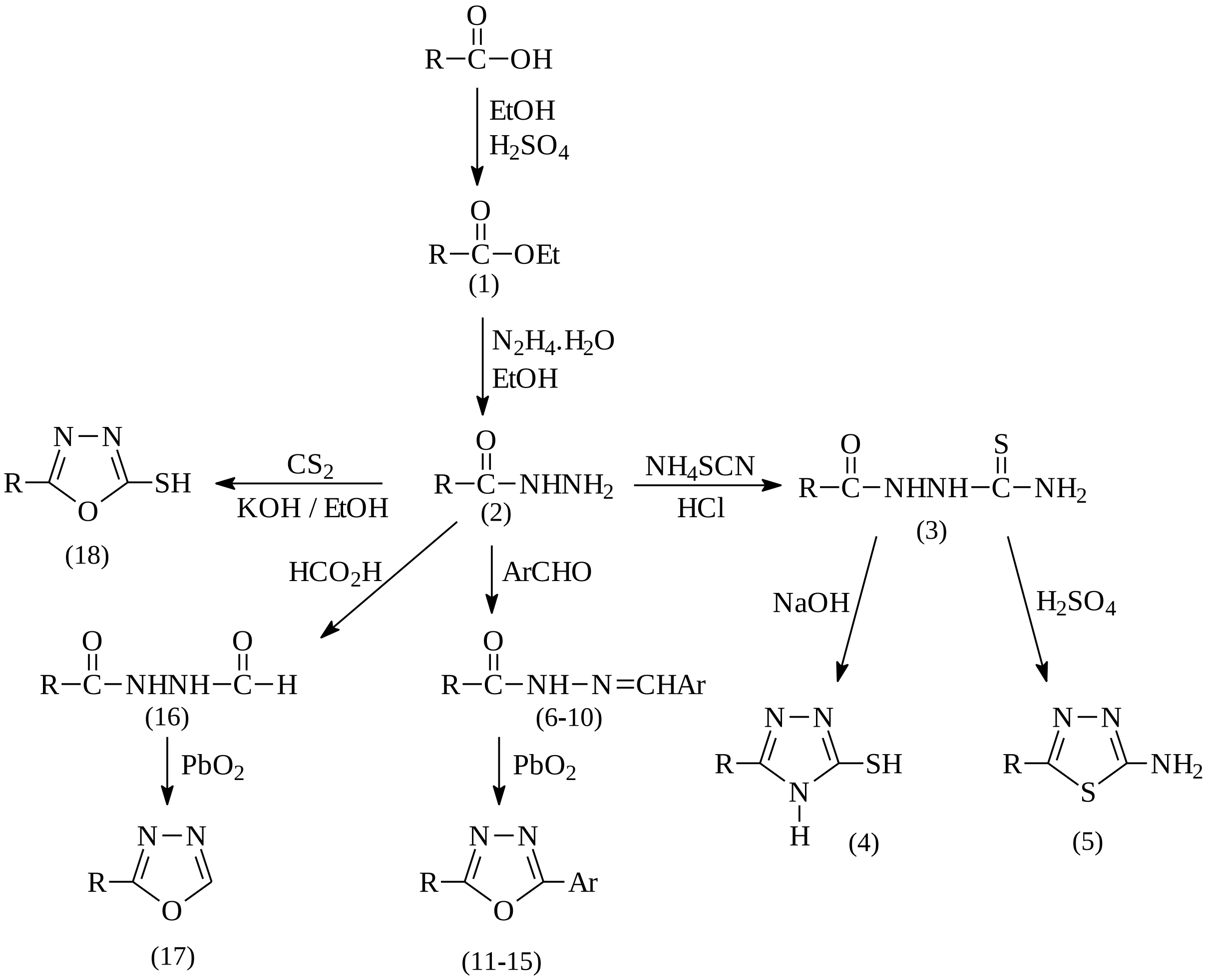
The purity of the synthesized compounds was tested by using TLC technique and the R_f values were calculated (Table 3).

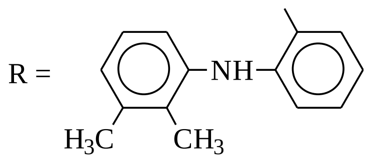
Table (2): Spectral data of compounnds (1-18)

Comp. No.	υ cm^{-1} IR (KBr)					λ_{max} UV EtOH
	C=O	N-H	C=S	C=N	others	
1	1730	3246				238, 284
2	1650	3380				272, 198
3	1669	3418	1118			240
4		3325	1090	1642		248, 242
5		3320		1638	1030 (CSC)	276, 242
6	1700	3410		1613		334, 262
7	1682	3415		1627		286, 246
8	1687	3380		1623	1508, 1312 (NO_2)	296
9	1694	3431		1640		290, 242
10	1673	3416		1621		346, 242
11		3301		1614	1084 (COC)	312, 266
12		3418		1624	1088 (COC)	294, 208
13		3390		1630		294, 272
14		3416		1638	1179 (COC)	386, 244
15		3423		1623	1141 (COC)	326, 244
16	1660	3383			2651 (CHO)	276, 218
17		3455		1631	1080 (COC)	288
18		3313	1116			290

Table (3): The R_f values of some of the synthesized compounds (EtOH)

Compound No.	R_f value
2	0.94
3	0.91
11	0.96
12	0.92
13	0.85
14	0.87
15	0.83
17	0.95
18	0.97





Comp. No.	Ar
6,11	C_6H_5
7,12	4-ClC_6H_4
8,13	4-$NO_2C_6H_4$
9,14	3,4-MeC_6H_3
10,15	3,4-$OMeC_6H_3$

Scheme (1)

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