Synthesis of some Substituted Multinuclear 1,3,4-Oxadiazoles and 1,3,4-Thiadiazoles

Khalid M. Daoud and Mohammad A.A. Eisa
Chemistry Department, College of Education, University of Mosul, Mosul-Iraq

(NJC)

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Abstract

The synthesis of multinuclear heterocyclic system containing substituted 1,3,4-oxadiazole and 1,3,4-thiadiazole ring was achieved from suitable esters which were converted to the corresponding acid hydrazides by their reaction with hydrazine hydrate in ethanol. The treatment of acid hydrazide with phosgene or with carbon disulfide gave substituted oxadiazole-2-one or 2-thiol respectively. 5-Phenyl-1,3,4-oxadiazole-2-thiol was treated with 2-chloro-5-phenyl-1,3,4-thiadiazole in ethanolic potassium hydroxide solution to give (5-phenyl-1,3,4-oxadiazol-2-yl) (5-phenyl-1,3,4-thiadiazol-2-yl) sulfide, whereas the reaction of 1-[5-(4-aminophenyl)-1,3,4-oxadiazol-2-yl] hydrazine and 5-(4-aminophenyl)-2-amino-1,3,4-thiadiazole with 5-phenyl-2-chloro-1,3,4-thiadiazole gave 1-[5-{4-N-(5-phenyl-1,3,4-thiadiazol-2-yl) aminophenyl}-1,3,4-oxadiazole-2-yl] 2-[5-phenyl-1,3,4-thiadiazol-2-yl] hydrazine and [5-{4-N-(5-phenyl-1,3,4-thiadiazole-2-yl)aminophenyl}-1,3,4-thiadiazol-2-yl] [5-phenyl-1,3,4-thiadiazol-2-yl] amine respectively.

The structure of synthesized compounds was established by physical and spectral means.

الخلاصة

تم في هذا البحث تحضير عدد من معوضات متعدد الحلقات غير المتجانسة الحاوية على 1،3،4-اوكسادايازول و 1،3،4-ثايادايازول. حولت الاسترات الى هيدرازيدات الاحماض الكاربوكسيلية من خلال تفاعلها مع الهيدرازين المائي في الايثانول. اعطت مفاعلة هيدرازيدات الاحماض الكاربوكسيلية مع الفوسجين او مع ثنائي كبريتيد الكاربون معوضات الاوكسادايازول-2-اون و 2-ثايول على التوالي.

تم مفاعلة 5-فنيل-1،3،4-اوكسادايازول-2-ثايول مع 2-كلورو-5-فنيل-1،3،4-ثايادايازول في محلول هيدروكسيد البوتاسيوم الايثانولي ليعطي (5-فنيل-1،3،4-اوكسادايازول-2-يل) (5-فنيل-1،3،4-ثايادايازول-2-يل) كبريتيد. بينما نتج عن تفاعل كل من 1-[5-(4-امينو فنيل)-1،3،4-اوكسادايازوليل] هيدرازين و 5-(4-امينو فنيل)-2-امينو-1،3،4-ثايادايازول مع 5-فنيل-2-كلورو-1،3،4-ثايادايازول، المركبين 1-[5{4-N-(5-فنيل-1،3،4-ثايادايازول-2-يل) امينو فنيل}-1،3،4-اوكسادايازول-2-يل]-2-

[5-فنيل-1،3،4-ثياديازول-2-ايل] هيدرازين و [5-{4-N-(5-فنيل-1،3،4-ثياديازول-2-يل) امينـ و فنيل}-1،3،4-ثياديازول-2-يل] [5-فنيل-1،3،4-ثياديازول-2-يل] امين على التوالي.

شخصت تراكيب المركبات المحضرة بالطرق الفيزياوية والطيفية.

Introduction

The chemical and biological importance of substituted 1,3,4-oxadiazoles and 1,3,4-thiadiazoles draw the intention of many research workers. Some substituted 1,3,4-oxadiazoles possess various biological activities as antibacterial agent[1], antifungal, anti-inflammatory agents[2,3] and their uses in polymer synthesis[4]. Many substituted 1,3,4-thiadiazoles show different uses and activities, they may act as antimicrobials[5], antibacterial, antifungal and antiviral[6,7].

1,3,4-Thiadiazoles were synthesized from thiosemicarbazides by their reaction with concentrated sulfuric acid[8] or hydrogen peroxide[9], while substituted 1,3,4-oxadiazoles were synthesized from acid hydrazide by their reaction with carbon disulfide in pyridine[10]. Substituted hydrazine was treated with phosphorus oxychloride to give the corresponding 1,3,4-oxadiazole[12].

In the present work the synthesis of some new multinuclear 1,3,4-oxadiazoles and 1,3,4-thiadiazoles was reported.

Experimental

The melting points were measured on a Kofler hot stage apparatus and are uncorrected. The IR spectra were recorded on a Pye–Unicam SP 1100 infrared spectrophotometer using KBr discs.

Note: The synthesis of compounds (15, 16, 17 and 19) was achieved following the procedure applied for the synthesis of compounds (7, 8, 9 and 10) respectively, using 2 moles of 2-chloro-5-phenyl-1,3,4-thiadiazole.

2-Amino-5-aryl-1,3,4-thiadiazole (1,18):

Benzoic or p-aminobenzoic acid (0.094 mole) and concentrated sulfuric acid (30 ml, 98%) were mixed thoroughly, with cooling and rapid stirring, thiosemicarbazide (7.8 gm, 0.086 mole) was added in small amounts. After the addition was completed, the solution was heated on a steam bath for 8 hrs. The mixture was cooled and mixed with ice and concentrated ammonium hydroxide to precipitate the free base which was recrystallized from ethanol, Table (1 and 2).

2-Chloro-5-phenyl-1,3,4-thiadiazole (2):

2-Amino-5-phenyl-1,3,4-thiadiazole (5 gm, 0.03 mole), dissolved in hydrochloric acid (100 ml, 37%) at – 5 ^{o}C, then was treated dropwise with sodium nitrite (7 gm, 0.01 mole) in water (25 ml) over a period of 45 min. the 5-phenyl-1,3,4-thiadiazol-2-yl diazonium chloride began to separate as yellow crystals. The reaction mixture was left to stand for 2 hours, then heated on a steam bath for 30 min, a dark red oil was separated from the solution. The oil was crystallized on cooling. The solid was recrystallized from aqueous ethanol as yellow plates.

Benzoic and p-aminobenzoic acid hydrazide (3, 11):

A mixture of ethyl benzoate or ethyl p-aminobenzoate (0.08 mole) and hydrazine hydrate 99% (0.4 mole, 20 ml) in ethanol (70 ml) was refluxed for 3 hrs. The mixture was concentrated and cooled (for the hydrazide 11, the cold water was added to complete the precipitation). The formed precipitate

was filtered and recrystallized from ethanol, Tables (1 and 2).

5-Aryl-1,3,4-oxadiazole-2-one (4, 12):

A solution of (0.1 mole) of acid hydrazide (3 or 11) in a (150 ml) mixture of (1:1) acetone:water, was cooled to 0 °C. To this solution, phosgene (0.1 mole, 9.8 gm) in toluene (39 ml) was added with stirring. The mixture was stirring for 12 hrs. The formed precipitate was filtered and recrystallized from ethanol-water, Tables (1 and 2).

5-Aryl-1,3,4-oxadiazole-2-thiol (5, 13):

Hydrazide (3 or 11) (0.005 mole) was dissolved in potassium hydroxide solution (0.56 gm/100 ml ethanol). To this solution carbon disulfide (6 ml, 0.1 mole) was added with shaking, then refluxed for (20) hrs. The solvent was evaporated under reduced pressure, and the residue then poured into cold water and acidified with dilute hydrochloride acid. The precipitate was filtered and recrystallized from ethanol, Tables(1 and 2).

1-(5-Aryl-1,3,4-oxadiazole-2-yl) hydrazine (6, 14):

A mixture of compound (5 or 13) (0.01 mole) and hydrazine hydrate (99%, 1 ml) in absolute ethanol was refluxed for 3 hrs. The solvent was evaporated under reduced pressure and the residue was collected and recrystallized from ethanol, Tables (1 and 2).

(5-Phenyl-1,3,4-oxadiazol-2-yl) (5-phenyl-1,3,4-thiadiazol-2-yl) sulfide (8):

A mixture of equivalent moles of compound (5), compound (2) and potassium hydroxide in ethanol was refluxed for 20 hrs. The solvent was removed by evaporation and the residue was collected, washed with cold water and recrystallized from ethanol, Tables (1 and 2).

5-Phenyl-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-1,3,4-oxadiazole-2-one (7):

Compound (4) (0.005 mole) was dissolved in pyridine (25 ml). 2-Chloro-5-phenyl-1,3,4-thiadiazole (2) (0.005 mole, 0.98 gm) was added and the mixture was heated under reflux for 24 hrs. On cooling an oily material was separated, which was crystallized from ethanol-water to give golden needles, Tables (1 and 2).

Di(5-phenyl-1,3,4-thiadiazol-2-yl) amine (10):

Compound (1) (0.005 mole) was mixed with 2-chloro-5-phenyl-1,3,4-thiadiazole (2) in ethanol (50 ml), to this mixture, a solution of sodium acetate (0.41 gm/25 ml water) was added. The mixture was refluxed for 3 hrs and poured into a beaker. The reaction mixture was leaved in refrigerator to the next day. Precipitate was filtered, washed with water and recrystallized from ethanol, Tables (1 and 2).

1(5-Phenyl-1,3,4-oxadiazol-2-yl)-2-(5-phenyl-1,3,4-thiadiazol-2-yl) hydrazine (9):

A mixture of compound (6) (0.005 mole), 2-chloro-5-phenyl-1,3,4-thiadiazole (2) (0.005 mole, 0.98 gm) and sodium acetate (0.41 gm) in ethanol was refluxed for 4 hrs. The solvent was removed under reduced pressure, the small residue portion was added to ice-water, precipitate began to appear, filtered and recrystallized from ethanol, Tables(1 and 2).

Results and Discussion

In the present work the synthesis of some substituted multinuclear 1,3,4-oxadiazoles and 1,3,4-thiadiazoles from the corresponding monocyclic five membered ring heterocyclic compounds were achieved (Scheme 1).

Table (1): Physical constants for compounds (1-19)

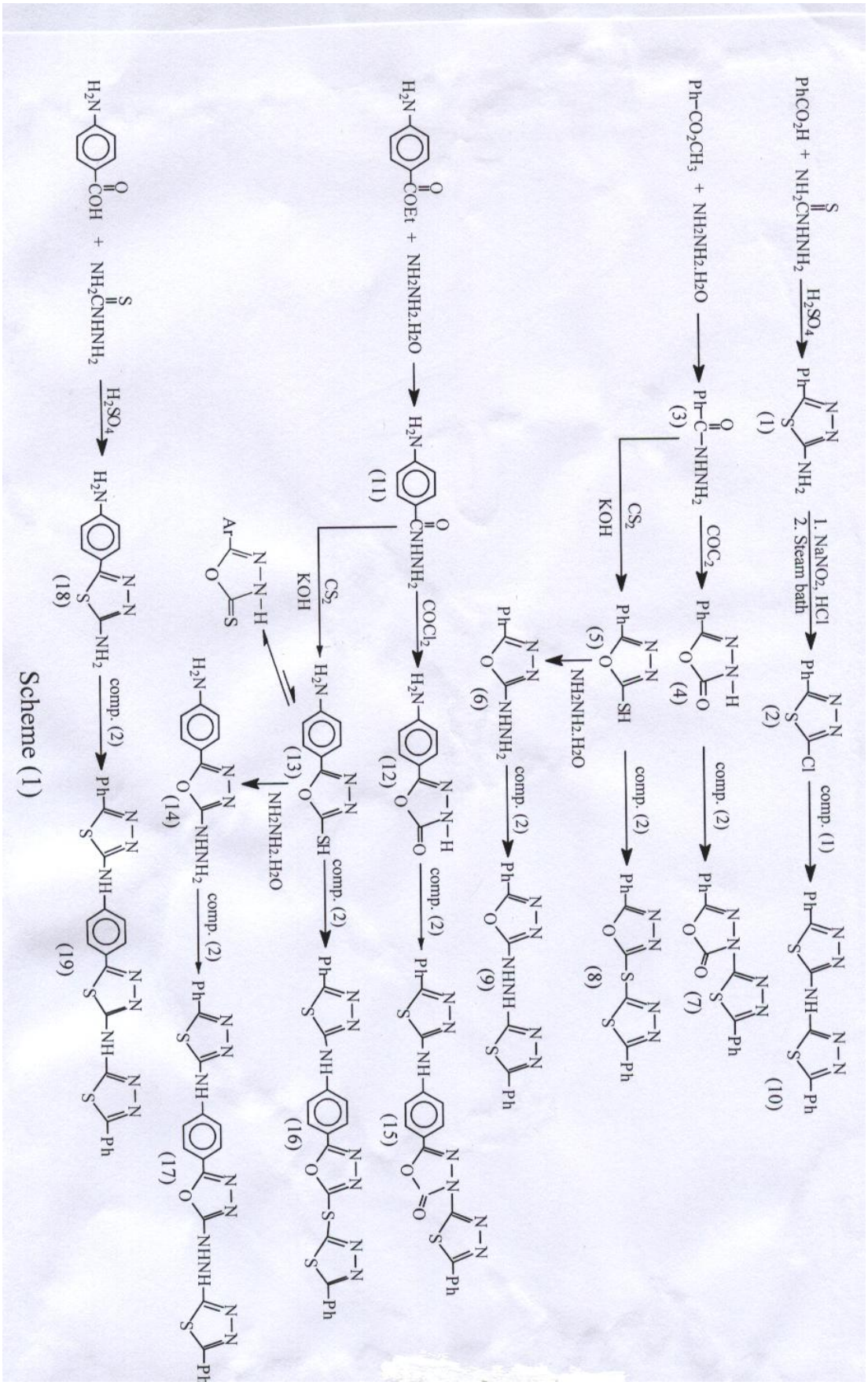
Comp. No.	Molecular formula	Yield (%)	m.p. (°C)
1	$C_8H_7N_3S$	79	221-223
2	$C_8H_5ClN_2S$	77	83-85
3	$C_7H_8N_2O$	83	110-112*
4	$C_8H_6N_2O_2$	67	128-130
5	$C_8H_6N_2OS$	79	218-220**
6	$C_8H_8N_4O$	61	138-140
7	$C_{16}H_{10}N_4O_2S$	62	115-117
8	$C_{16}H_{10}N_4OS_2$	62	210-213
9	$C_{16}H_{12}N_6OS$	63	151-153
10	$C_{16}H_{11}N_5S_2$	65	178-180
11	$C_7H_9N_3O$	71	88-90
12	$C_8H_7N_3O_2$	88	100-102
13	$C_8H_7N_3S$	81	193-195
14	$C_8H_9N_5O$	78	129-130
15	$C_{24}H_{15}N_7O_2S_2$	83	233-235
16	$C_{24}H_{15}N_7OS_3$	71	103-104
17	$C_{24}H_{17}N_9OS_2$	72	110-112
18	$C_8H_8N_4S$	83	209-210
19	$C_{24}H_{12}N_8S_3$	82	119-121

* (Lit.[13] = 112.5 °C)

** (Lit.[14] = 219-220 °C)

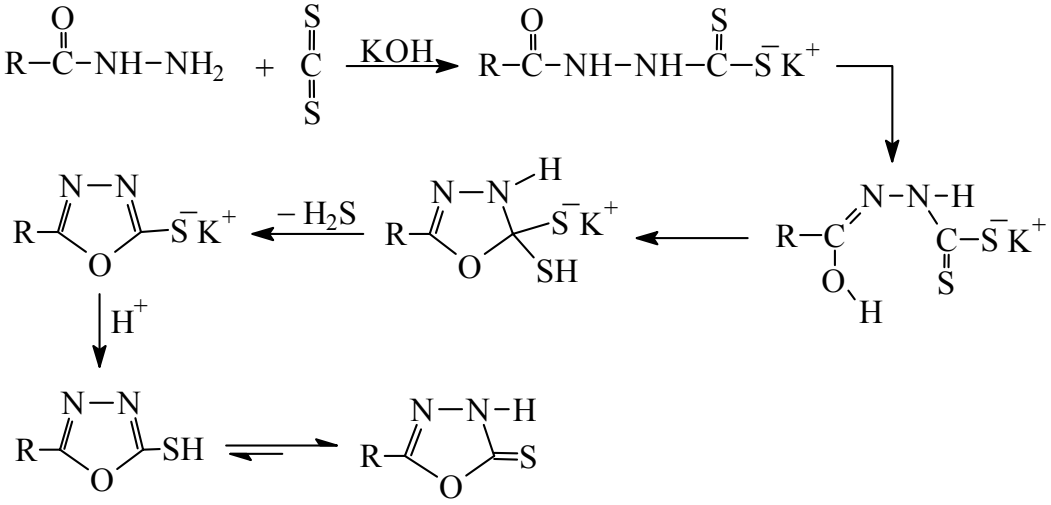
Table (2): IR spectra for compounds (1-19)

Comp. No.	IR ν (cm^{-1})				
	N-H	C=O	C=N	C=S	C-O-C
1	3400	-	1650	-	-
2	-	-	1630	-	-
3					
4	3300	1685	1625	-	1030
5	3350	-	1660	1175	1070
6	3400	-	1630	-	1090
7	-	1690	1630	-	1060
8	-	-	1650	-	1090
9	3390	-	1650	-	1050
10	3450	-	1660	-	-
11	3500	1700	-	-	-
12	3500	1720	1640	-	1090
13	3500	-	1610	1180	1030
14	3500	-	1630	-	1100
15	3400	1695	1655	-	1105
16	3300	-	1675	-	1100
17	3500	-	1625	-	1090
18	3250	-	1650	-	-
19	3400	-	1665	-	-



Scheme (1)

The substituted 1,3,4-oxadiazoles (4,5 and 6) were synthesized from methyl benzoate which was reacted with hydrazine hydrate in ethanol to give acid hydrazide (3). Acid hydrazide (3) then treated with phosgene in acetone:water and with carbon disulfide in potassium hydroxide solution to give 5-aryl-1,3,4-oxadiazole-2-one (4) and 5-aryl-1,3,4-oxadiazole-2-thiol respectively. Compound (4) show IR spectrum ν cm^{-1} 3300 (N-H), 1685 (C=O), 1625 (C=N) and 1030 (C-O-C), whereas compound (5) show ν cm^{-1} 3350 (N-H), 1660 (C=N), 1175 (C=S) and 1070 (C-O-C). the formation of 1,3,4-oxadiazole (5) from hydrazide (3) may proceed through the following mechanism:



Compound (8) was treated with hydrazine hydrate in absolute ethanol to give 1-(5-aryl-1,3,4-oxadiazole-2-yl) hydrazine (6), the IR spectrum for oxadiazole (6) ν cm^{-1} 3400 (N-H), 1630 (C=N) and 1090 (C-O-C). the reaction of substituted 1,3,4-oxadiazoles (4, 5, and 6) with 2-chloro-5-phenyl-1,3,4-thiadiazole (2) gave 5-phenyl-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-1,3,4-oxadiazol-2-one (7), (5-phenyl-1,3,4-oxadiazol-2-yl) (5-phenyl-1,3,4-thiadiazole-2-yl) sulfide (8) and 1-(5-phenyl-1,3,4-oxadiazol-2-yl) hydrazine (9) respectively. The structures of 7, 8 and 9 were established by IR spectrum as well as physical means, as shown in Tables (1 and 2).

2-Chloro-5-phenyl-1,3,4-thiadiazole (2) was prepared by the reaction of benzoic acid and thiosemicarbazide to give 2-amino-5-phenyl-1,3,4-thiadiazole (1). IR spectrum show absorption ν cm^{-1} 3400 (N-H) and 1650 (C=N), thiadiazole (1) then treated with sodium nitrite/ hydrochloride acid followed by heating on a steam bath to give (2).

Ethyl 4-aminobenzoate was converted to 5-(4-aminophenyl)-1,3,4-oxadiazole-2-one (12), 5-(4-aminophenyl)-1,3,4-oxadiazole-2-thiol (13) and 5-(4-aminophenyl)-1,3,4-oxadiazol-2-yl) hydrazine (14), using the sequence shown in Scheme 1. Compound (12) show IR spectrum ν cm^{-1} 1720 (C=O), 1640 (C=N) and 1090 (C-O-C) compound (13) show ν cm^{-1} 1180 (C=S), while compound (14) show absorption at ν cm^{-1} 3500 (N-H), 1630 (C=N) and 1100 (C-O-C).

4-Aminobenzoic acid was treated with thiosemicarbazide in presence of sulfuric acid to give 2-

amino-5-(4-aminophenyl)-1,3,4-thiadiazole (18).

The synthesis of polynuclear heterocyclic compounds (15-17) was achieved by the reaction of substituted 1,3,4-oxadiazoles (12-14) with 2-chloro-5-phenyl-1,3,4-thiadiazole, whereas 2-amino-5-(4-aminophenyl)-1,3,4-thiadiazole (18) gave compound (19). The final products show the expected IR spectrum, Table (2).

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