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Synthesis of some 2-Aryl -1,3,4-Thiadiazoline-2-One Derivatives

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ABSTRACT

To synthesis of some new heterocyclic compounds containing 1,3,4-thiadiazole moieties. Many of 5-alkyl-3-(4-substituted-2-butyn-1-yl) -1,3,4-thiadaizoline-2(3H)-one (15a-e and 16a-e) have been prepared by the reactions sequences starting from the acid hydrazides (1 and 2). All the products are well known for their useful biological activities. The structures of all compounds were confirmed by physical and spectral methods.

Keywords: 1,3,4-thiadiazole-2-one, Manich reaction**.**

تحضير بعض مشتقات 2- اريل - 4,3,1- ثاياديازولين -2- اون

الملخص

تم تحضير بعض المركبات الحلقيـة غير المتجانسـة الحاوية على حلقـة 4,3,1- ثاياديـازول ، كما تم تحضير مركبات 5- أريـل-3- (4- معوضات- 2- بيوتا ين-1- أيـل)-4,3,1- ثاياديـازول-2(3H)-اون (15a-e and 16a-e) وذلك عن طريق سلسلة من التفاعلات المتعاقبة ابتدءا من هيدرازيـدات الحوامض (1و2)، ومن المعروف أن كل المركبات الناتجة تمتلك فعالية بايولوجية جيدة و تم إثبات الـصيغ التركيبية للمركبات المحضرة من خلال استخدام الطرائق الفيزيائية والطيفية المتوفرة.

الكلمات المفتاحية: 4،3،1- ثاياديازول -2- اون، تفاعل مانيخ.

INTRODUCTION

Numerous 1,3,4- thiadiazole derivatives are classes of heterocycles, which have a wide range of biological activities in medicinal chemistry including potential antimicrobial agent (Aly and Alsyed, 2006), (Vosooghi *et al*., 2005), antibacterial (Dobholkar *et al.*, 2009), anticonvulsant and muscle relaxant (Siddiqui *et al*., 2009), (Almasirad *et al*., 2007), also such these compounds exhibited significant inhibitory activity agent (Mohammad *et al.*, 2009), others such compounds have fungicidal activity (Chen *et al.*, 1999) and as antiamebic agent (Singh and Longer, 1989).

Acetylenic compounds were found to be high significant in medical science, since the medical compounds of acetylenic system have a higher activity and lower toxicity (AL-Ajely *et al*., 2003). Some of the acetylenic derivatives showed both oxetermrine and acetylcholine antagonistic activity (Zuhair Muhi-Elden *et al.,* 1981). Several acetylenic amines showed anticholinergic activity and ability to inhibit tremors (Dahlbom and Mollberg, 1963).

In view of these observations, it was thought to synthesize some 5-alkyl-3-(4-substituted-2-butyn-1-yl)-1,3,4-thiadiazole-2(3H)-ones (15a-e) and (16a-e) have been expected to posses an antagonistic activity towards acetylcholine and oxotremorine (Zuhair Muhi- Elden *et al.,* 1985).

Accordingly, we describe here an approach to synthesize some acetylene compounds containing 1,3,4 thiadiazole moiety as depicted in (scheme 1) to improve the expected biological activities of such compounds.

EXPERIMENTAL

Melting points were determined using electro thermal 9300 melting point apparatus and are uncorrected. IR Spectra were recorded by Bruker 96565 Spectroscopy as (KBr disk). UV Spectra were recorded on Shimadzu (UV-1600) UV-Visible Spectrophotometer using methanol as a solvent. All the starting material were used either from Fluka or Aldrich chemical products. The secondary amines were use with further purification. The acid hydrazides (1 and 2) were prepared as previously described by (EL-Khwass, 1989). (Noori, 1999), m.p. (173-174^{0}C) (Adams and 141-143^{0}C). (Noori, 1999) respectively .

Preparation of potassium-3-substituted methyl dithiocarbazates (3 and 4) (Hoggarth, 1952).

To a mixture of acid hydrazide (1and 2) (0.01 mole) in absolute ethanol (50 ml) containing potassium hydroxide (0.015 mole, 0.84 gm) carbon disulfide (0.015 mole, 1.71gm) was added, then the reaction mixture stirred at room temperature for (24 hours). Yellow precipitate of the corresponding compounds was separated, dry ether (100 ml) was added to complete the precipitation of the formed salts. The products was filtered off, washed with dry ether and crystallized from aqueous ethanol. Physical data of compounds (3and 4) are listed in Table (1).

Preparation of methyl-3-substituted methyl dithiocarbazates(5and 6) (Noori, 1999):

Methyl iodide (0.01 mole, 0.15 gm) was added to a stirred solution of compounds (3and 4) (0.009 mole) in (50ml) of water for two hours. The white solid was filtered washed with water and crystallized from aqueous methanol to give the corresponding products (5 and 6) as a pale yellow crystals. Physical data of these products are listed in Table (1).

Preparation of 5-alkyl -2-methylthio-1,3,4-thiadiazoles (7 and 8) (Noori, 1999):

Methyl dithiocarbazates (5 and 6) was dissolved in a minimum amount of concentrated sulfuric acid (3 ml) at room temperature, the mixture was poured on ice. The pale-yellow precipitate was filtered off and crystallized from aqueous methanol to give the products (7 and 8). Physical data of the two products are shown in Table (1).

Preparation of 5-alkyl-2-methylsulfonyl-1,3,4-thiadiazole (9 and 10)(Ludwig *et al.*, 1973):

The 5- alkyl–2 - methylthio -1,3,4-thiadiazoles (7 and 8) (0.05 mole) was dissolved in glacial acetic acid (10ml), potassium permanganate (1.58 gm,3%) was added and the mixture was stirred at (40 C°) for three hours. The reaction mixture was decolorized with sodium hydrogen sulphite at (0 C°).The crude solid product was collected and crystallized from aqueous ethanol to give the products (9 and 10). The physical data of these products are listed in Table (1).

Preparation of 5-alkyl-1,3,4-thiadiazoline-2(3H)-one (11 and 12) (Zuhair Muhi-Elden *et al*., 1985):

5-alkyl-2-methylsulfonyl-1,3,4-thiadiazoles (9 and 10) (0.005 mole) was added to (10ml) aqueous sodium hydroxide solution. The mixture was refluxed for a half hour ,and the product was acidified with diluted acetic acid. The crude solid product was collected and recrystallized from aqueous methanol to give pure products (11 and 12). Physical data for compounds (11 and 12) are listed in Table (1).

Preparation of 5-alkyl-3-proporgyl-1,3,4-thiadiazoline-2(3H)-ones (13 and 14) (Zuhair Muhi-Elden *et al*., 1985):

To a solution of (0.005 mole) of 5-alkyl-1,3,4-thiadiazoline-2(3H)-ones (11 and 12) in (30 ml) of ethanol, (0.01 mole) of potassium hydroxide was added slowly, the stirred solution was refluxed for (15 minutes) and (0.11 mole, 13.1 gm) of propargylbromide was added drop-wise. The stirred mixture was refluxed for an additional (2 hours). After cooling , 250 ml of water was added, the crude solid products was collected and crystallized from methanol. Physical data for compounds (13 and 14) are listed in Table (1).

Preparation of 5-alkyl-3-(4-substituted-2-butyn-1-yl)-1,3,4-thiadiazoline-2(3H)-one (15a-e and 16a-e) (Zuhair Muhi-Elden *et al*., 1985):

Appropriate secondary amine (0.003 mole) was added to a mixture of 5-alkyl-3-proporgyl -1,3,4-thiadiazoline-2(3H)-one (13 and 14) (0.003mol), paraformaldehyde (0.003 mole) and catalytic amount of cuprous chloride in (10ml) hydrogen peroxide (30%), the mixture was heated at (70-80)c° for (3 hours) with continuous stirring. The products (15a-e and 16a-e) was filtered and recrystallized from aqueous methanol. The physical data for these products are shown Table (2).

Table 1: Physical data of compounds(3-14).

Compd. No.	M.P. C°	Yield %
3	238 - 41	68
4	257 - 59	73
5	183 - 85	53
6	191-194	45
7	123 - 26	56
8	113 -15	47
9	85 - 88	52
10	76 -78	43
11	153 - 55	41
12	184 - 88	67
13	112 - 115	71

Table 2: Physical data of compounds (15a -e) and (16a-e).

Compd. No.	M.P. C°	Yield %
15a	94 -96	32
15b	91 -93	43
15c	154 - 56	33
15d	211 - 14	36
15e	223 -26	47
16a	117 - 20	35
16b	120 - 22	46
16c	149 - 51	41
16d	203- 06	45
16e	231-35	52

RESULTS AND DISSCUSION

During the course of our interest work towards the synthesis of new heterocyclic compounds of potential activity, acid hydrazides (1 and 2) are used to synthesize many acetylenic-tert-amine derivatives containing 1,3,4-thiadiazole moiety, which are well-known for their useful biological and pharmacological activities (Zuhair Muhi -Elden *et al.,* 1985).

Acid hydrazides (1 and 2) are used for synthesis a potassium 3-substituted dithiocarbazates (3 and 4) by its reaction with carbon disulfide and potassium hydroxide in an absolute ethanol. Methylation of compounds (3 and 4) with methyl iodide under reflux afforded the corresponding methylthio derivatives (5 and 6), the I.R spectra of these

products exhibited characteristic carbonyl bands in 1668Cm^{-1} and 1703 $Cm^{-1}$and NH stretching appeared at 3196 $Cm^{-1}$and 3134 Cm^{-1}.(Noori, 1999), (Yong and Wood , 1955).

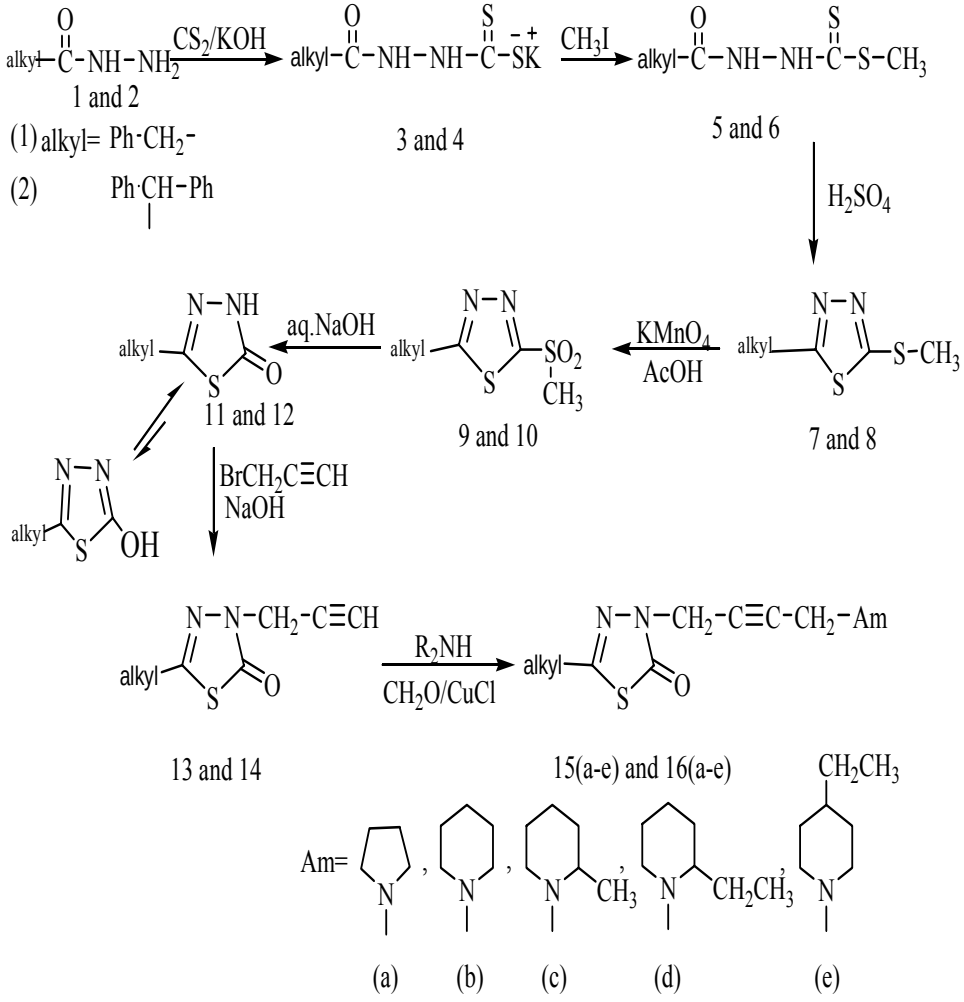
Ring closure of compounds (5 and 6) in an acidic media is well known method for the synthesis of compounds (7 and 8) (Yang *et al.*,1955), their I.R spectra showed absorption for (C═N) band at 1635 $Cm^{-1}$and 1656 Cm^{-1}, also at 1087 $Cm^{-1}$and 1095 Cm^{-1}due to C─S─C bonds. UV spectra of compounds (7 and 8) showed λ_{max} (MeOH) at 268 nm and 260 nm.

Oxidation of compounds (7 and 8) by potassium permanganate in acidic medium yielded compounds (9 and 10) respectively. The IR spectrum for these compounds disclose the presence of C═N at 1642 Cm^{-1} and 1658 Cm-1and sulfonyl group at 1310 Cm^{-1} and 1335 Cm^{-1} . The UV spectrum of these compounds have λ_{max} (MeOH) at 259 nm and 248 nm.

Hydrolysis of compounds (9 and 10) with (15%) aqueous solution of sodium hydroxide converted them to 5-alkyl-1,3,4-thiadiazoline-2-(3H)-one (11 and 12). The IR spectra of these compounds were consistent with the presence of (C═N) at 1635 $Cm^{-1}$and 1643 Cm^{-1} , NH group at 3050 Cm^{-1} and 3064 Cm^{-1}, C═O group at 1635 Cm^{-1} and 1690 NH group at 3050 $Cm^{-1}$and 3064 Cm^{-1}. Although compounds (11 and 12) may exist in two tautomeric forms, keto and enole, we observed that keto form was predominated since the IR spectra showed no absorption band at 3400-3500 Cm^{-1} related the enole form. The UV spectrum of these compounds have λ_{max} (MeOH) at 267 nm and 259 nm.

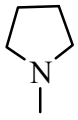
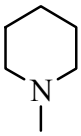
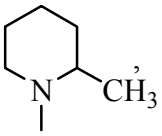
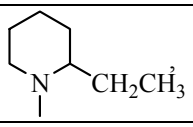
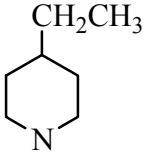
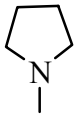
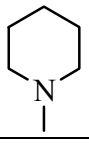
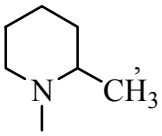
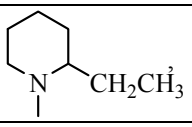
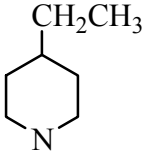
The reaction of 5-alkyl-1,3,4-thiadiazole-2-(3H)-ones (11 and 12) with alcoholic sodium hydroxide followed by the addition of propagyl bromide obtained 5-alkyl-3-alkylnyl-1,3,4-thiadiazole-2(3H)-ones(13 and 14), the IR spectra of these compounds are characterized by the present of (≡ CH) at (3266 $Cm^{-1}$and 3275 Cm^{-1}), C═O at (1735 Cm^{-1}, 1722 Cm^{-1}) and (CH for ArH) at (3026 Cm^{-1} and 3018 Cm^{-1}) bands. While, the UV spectrum of these compounds have λ_{max} (MeOH) at 254 nm and 258 nm.

The Mannich reaction of 5-alkyl-3-alkyl-1,3,4-thiadiazoline-2-(3H)-one (13 and 14) with paraformaldehyde and the appropriate amines in the presence of catalytic amount of cuprous chloride afforded the 5-alkyl-3-(4-tert-amino-2-butynyl)-1,3,4-thiadiazole-2-(3H)-ones (15a-e and 16 a-e). The structure of these products was deduced according the I.R and UV spectra which are in agreement to the published data in the same acetylenic compounds (Parikh , 1974) Table (3).


alkyl-C(=O)-NH-NH2
CS2/KOH
alkyl-C(=O)-NH-NH-C(=S)-SK
CH3I
alkyl-C(=O)-NH-NH-C(=S)-S-CH3
1 and 2
3 and 4
5 and 6
(1) alkyl= Ph·CH2-
(2) Ph·CH(Ph)-
H2SO4
KMnO4
AcOH
aq.NaOH
BrCH2C≡CH
NaOH
11 and 12
9 and 10
7 and 8
13 and 14
R2NH
CH2O/CuCl
15(a-e) and 16(a-e)
Am=
(a)
(b)
(c)
(d)
(e)

(Scheme 1)

Table 3: Spectral data of compounds (15 a-e) and (16 a-e).

Comp. No.	Am	IR(kBr) γ,Cm^{-1}					UV, λ max (nm) (MeOH)
		C=O	C=N	C≡C	C-S-C	CH-Ar	
15a		1713	1592	2105(vw*)	1035	3053	268
15b		1708	1588	2098(vw)	1079	3042	255
15c		1718	1610	2118(vw)	1068	3050	243
15d		1722	1612	2122(vw)	1072	3033	239
15e		1707	1623	2100(vw)	1090	3047	244
16a		1705	1604	2090(vw)	1075	3055	259
16b		1700	1595	2113(vw)	1083	3028	248
16c		1709	1598	2105(vw)	1072	3031	241
16d		1710	1623	2108(vw)	1083	3041	253
16e		1698	1611	2117(vw)	1094	3052	264

⋆vw (very weak)

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