Synthesis of 2- alkyl/phenyl -5-Substituted 1,3,4-Thiadiazoles

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الخلاصة

تم في هذا البحث تحضير عدد من معوضات 2- الكيل/فنيل -5- معوض4,3,1- ثاياداياز ول.

اعطت مفاعلة بنزو نتريل واسيتو نتريل مع ثايوسميكاربازايد بوجود حامض ثلاثي فلورو الخليك 2-الكيل/ اريل -5- امينو 4,3,1- ثاياداياز ول (2,1). تم تحويل الثاياداياز ولات (2,1) الى كلايسينات N- (5- الكيل/ فنيل-4,3,1-ثاياداياز ول -2 - يل) الاثيل (4,3) من خلال تفاعلها مع كلورو خلات الاثيل في الميثانول. وتم تحويل الاسترات الناتجة الى الهيدرازيدات المقابلة (6,5) مع الهيدرازين المائي في الايثانول. اعطى تفاعل الهيدرازيدات مع البنزالديهايد في الايثانول الهيدرازونات (8,7). بينما اعطى تفاعل 4,3,1- ثاياداياز ول (2,1) مع كلورو فورمات الاثيل, كلوريد الاستيل والبنزويل او مع البنزالديهايد/ بارا-ميثوكسي بنزالديهايد معوضات الثاياداياز ول (18,17) و (12-9) و (16-13) على التوالي.

شخصت تراكيب المركبات المحضرة بطيف IR و UV وبالطرق الفيزياوية

ABSTRACT

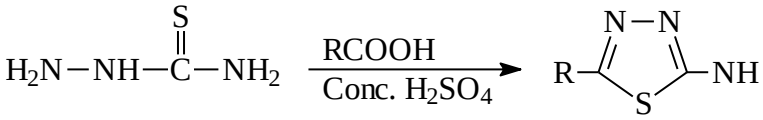
In this paper the synthesis of some 2-alkyl phenyl 5-substituted 1,3,4-thiadiazole is reported, Benzonitrile and Acetonitrile were treated with thiosemicarbazide in presence of trifluroacetic acid to give 2-alkyl/ aryl -5- amino- 1,3,4- thiadiazoles (1,2), which was treated with ethylchloroacetate in methanol to give Ethyl N-(5-alkyl/phenyl -1,3,4-thiadiazole-2- yl) glycinate (3,4), the resultant esters were converted to acid hydrazide (5,6) by their reaction with hydrazine hydrate in ethanol. Reaction of the hydrazides with benzaldehyde in ethanol gave hydrazones

(7,8). Thiadiazols (1,2) were treated with ethyl chloroformate, acetyl and benzoyl chloride or benzaldehyde/ p-methoxybenzaldehyde to give substituted thiadiazoles (17,18), (9-12) and (13-16) respectively.

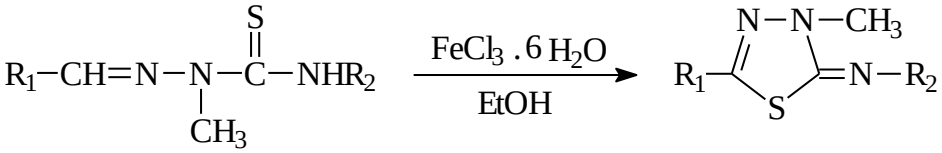
The structure of the synthesis compounds were confirmed by IR, UV. Spectra and physical means.

Introduction

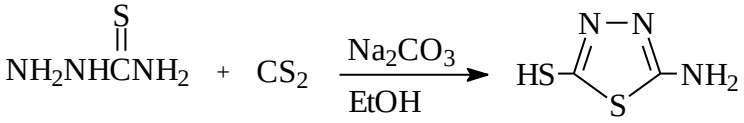
Derivatives of 1,3,4-thiadiazole have been found to possess a wide spectrum of activities[1,2], thiadiazole were studied for anumber of pathological conditions including inflammation[3] or hypertension[4]. The synthesis of substituted 1,3,4-thiadiazole has attracted attention due to their application as anti-inflammatory[5,7], analgesic[8,9], antimicrobial antibacterial[10-12], anticonvulsant[13,14], anticancer[15], antifungal[16,17] and plant growth regulating effect[18]. Substituted 1,3,4-thiadiazoles were synthesis from thiosemicarbazide with carboxylic acid in concentrated sulfuric acid [19].



Also substituted 1,3,4-thiadiazole was synthesized by using ferric chlorid in ethanol with substituted thiosemicarbazide [20].



Whereas synthesis of 1,3,4-thiadiazol containing thiol group were obtained from reaction of thiosemicarbazid with carbon disulphide[21].



Experimental

The melting points were measured on an electro thermal 9300 engineering LTD and are uncorrected, IR spectrum were recorded on infrared spectrophotometer model tensor 27, Bruker Co., Germany, using KBr discs. The U.V spectrum were recorded on UV-Visible Shimadzu 1601spectrophotometer using ethanol as a solvent. All chemicals were purchased from Fluka and BDH chemical Ltd.

2- Alkyl/ phenyl-5-amino -1,3,4-thiadiazole (1,2)[22].

A mixture of acetonitrile/ benzonitrile (0.01mole), thiosemicarbazide (0.01mole,0.9g) in trifloroacetic acid (5ml) was refluxed for 8h the mixture cooled and poured on ice-water (15ml), the

mixture was neutralized with concentrated ammonia then left for 24h. the solid product was filtered off, dried and recrystallized from ethanol-water. Table (1).

Ethyl N-(5-alkyl/phenyl -1,3,4-thiadiazole-2- yl) glycinate (3,4)[23].

A mixture of 2-aminothiadiazole (1,2) (0.01mole), ethyl chloroacetate (0.01mole,1.15g) and potassium carbonate(0.6g) in methanol (25ml) was refluxed for 5h, cool, the solid product was filtered off, dried and recrystallized from methanol- water. Table (1)

N- (5- alkyl/ phenyl -1,3,4-thiadiazole-2-yl) glycine hydrazid (5,6)[23].

The ester (3or4) (0.03 mole) and hydrazine hydrate(0.03 mole,1g)in ethanol (25 ml) were refluxed for 3h, the solvent was evaporated under reduced pressure, the hydrazide was washed with petroleum ether dried and recrystallized from methanol- water. Table (1)

2-(benzylidene amino acetamido amin) 5- alkyl / phenyl – 1,3,4-thiadiazole (Hydrazones) (7,8)[24].

To hydrazide (5 or 6) benzaldehyde (0.01mole,1g) in ethanol (25ml) was added followed by hydrochloric acid (3ml). The mixture was refluxed for 3h, cool and neutralized with dilute sodium hydroxide. The precipitate filtered off, dried and recrystallized from ethanol- water. Table (1)

2-alkyl /phenyl -5- acylamino -1,3,4- thiadiazole (9-12)[22].

A mixture of thiadiazole (1 or 2) (0.01 mole) in dry pyridine (30 ml) and acetyl chloride/ benzoyl chloride (0.01 mole) was refluxed for 4h, the mixture was left to stand at room temperature for 48h, the crystallized product was filtered off, dried and recrystallized from ethanol- water. Table (1)

Hydrazone(13-16)[25].

To thiadiazole (1 or 2) (0.01 mole) in ethanol (8 ml) benzaldehyde or 4- methoxy benzaldehyde (0.03 mole) and sodium hydroxide (3g) were added with cooling and stirring, the mixture was refluxed for 1/2h, cool and neutralized with concentrated hydrochloric acid with cooling. The product was filtered and recrystallized from ethanol- water. Table (1)

Ethyl -2- alkyl/ phenyl -5- (ethoxy carbonyl imino)- 4,5- dihydro-1,3,4- thiadiazole -3- carboxylate (17,18).

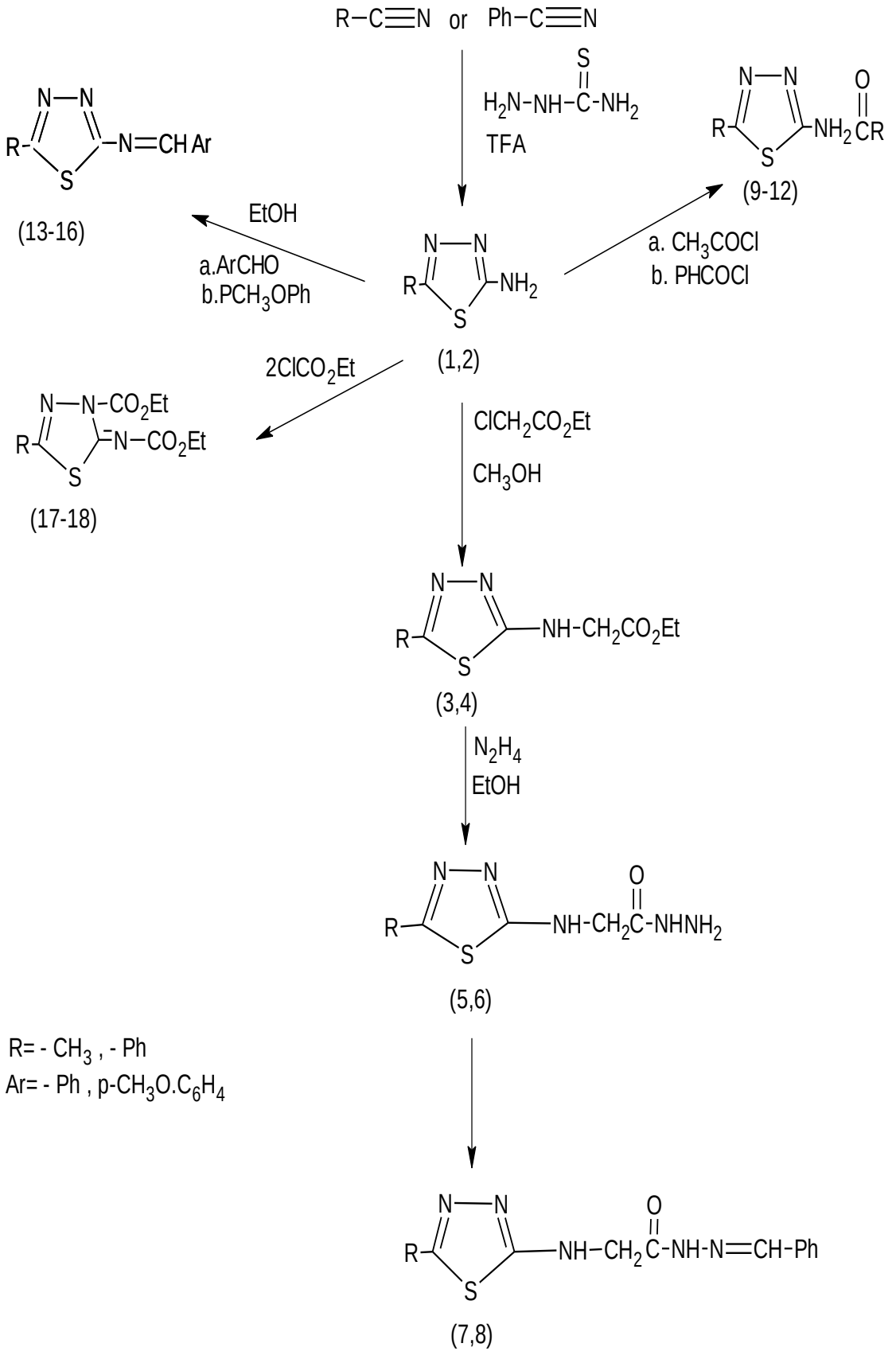
Amixture of thiadiazole (1 or 2) (0.005 mole) in dry benzene (50 ml) and ethyl chloroformate (0.02 mole,2.16g) was refluxed for 6h, the

solvent was evaporated under reduced pressure, the product was recrystallized from ethanol- water. Table (1)

Results and Discussion

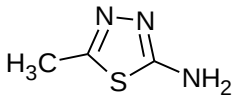
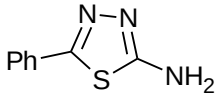
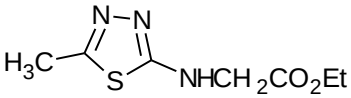
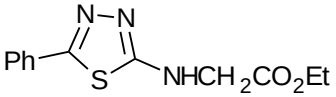
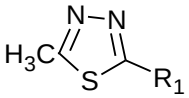
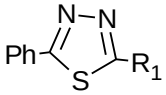
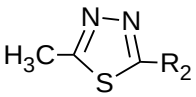
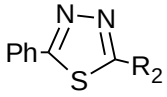
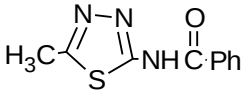
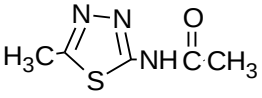
1,3,4-Thiadiazole derivatives were synthesized from benzonitrile and acetonitrile by their reaction with thiosemicarbazide in trifluoroacetic acid which afforded 2-phenyl/ methyl-5- amino -1,3,4- thiadiazole (1,2) Scheme 1, the IR spectra of (1) show absorption at 1575 cm^{-1}(C=N) and 3445 cm^{-1} (N-H), λ_{max}235,331nm. Thiadiazole (1,2) were treated with ethyl chloroacetate in methanol to give ethyl ester (3,4).The absorption band of the –(C=O) group appears in the 1742 – 1748cm^{-1} and the bands at 1640, 1634 cm^{-1} due to(C=N). The esters were treated with hydrazine hydrate in ethanol to give acid hydrazides (5,6). The IR spectra of compounds (5,6) showed the absence of C=O ester absorption and the C=O for hydrazides appear at 1680, 1675 cm^{-1} and for (C=N) at 1522, 1600 cm^{-1}.

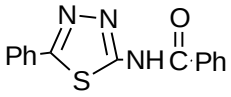
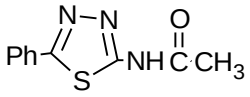
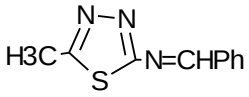
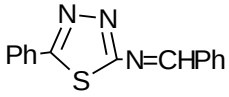
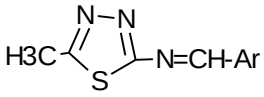
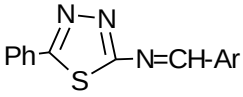
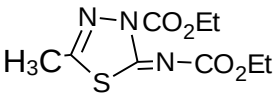
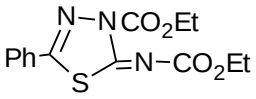
Hydrazides (5,6) were converted to hydrazones (7,8) by their reaction with benzaldehyde in ethanol. In the IR spectra the absorption band of the (C=O) group appears at 1653, 1675 cm^{-1}. thiadiazoles (1,2) were reacted with benzoyl chloride and acetyl chloride to give thiadiazoles (9-12), the (C=O) group in IR spectra appeared at 1653-1688 cm^{-1}. the hydrazones (13-16) were synthesis from 5-amino thiadiazole (1,2) with benzaldehyde or 4- methoxybenzaldehyde IR spectra of compound (13-16) showed absorption at 1629- 1693 cm^{-1}(C=N). The reaction of (1,2) with ethyl chloroformate gave imino thiadiazole (17,18). The IR spectra showed absorption at 1744- 1754^{-1} for (C=O) group and 1627- 1644cm^{-1} for (C=N). Table (1)


R−C≡N or Ph−C≡N
H2N-NH-C(=S)-NH2
TFA
(9-12)
(13-16)
EtOH
a.ArCHO
b.PCH3OPh
a. CH3COCl
b. PHCOCl
(1,2)
2ClCO2Et
(17-18)
ClCH2CO2Et
CH3OH
(3,4)
N2H4
EtOH
(5,6)
R= - CH3 , - Ph
Ar= - Ph , p-CH3O.C6H4
(7,8)

Scheme 1

Table (1): Physical and UV, IR Spectra Data of Synthesised Compound.

Comp. No.	structure	m.p. (C°)	Color	U.V λ max In ethanol	I.R υ cm^{-1}(KBr)			Yield (%)
					C=N	C=O	N-H	
1		157-159	White-yellow	235	1575	-	3445	71
2		144-146	white	331	1664	-	3362	80
3		209-211	White	210	1640	1742	3443	63
4		179-181	White-yellow	220	1634	1748	3441	70
5		oil	yellow	288	1600	1680	3423	60
6		Oil	Red	306	1600	1674	3334	62
7		84-86	yellow	315	1624	1653	3447	90
8		348d	Brown-red	247	1610	1675	3443	74
9		199-201	Yellow	319	1607	1686	3446	92
10		340d	White-yellow	288	1613	1653	3419	41

11		89-91	White	257	1601	1682	3443	81
12		283-285	Yellow-orang	270	1610	1688	3443	60
13		207-209	Brown	292	1681	-	-	87
14		111-113	Red	359	1671	-	-	84
15		348 d	White	270	1629	-	-	67
16		279-281	White	316	1693	-	-	69
17		b.p. 185	Red	279	1644	1754	-	90
18		101-103	brown	312	1627	1744	-	61

Ar = 4-$OCH_3C_6H_4$

R_1=-$NHCH_2CONHNH_2$

R_2=-$NHCH_2CONHN=CHPh$

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