Synthesis and characterization of benzylidene-[1,3,4]thaidiazol -2-yl-amine

Al-Kaddimy H. A. Ahmed*

Received 2/10/2005 ; accepted 1/2/2006

الخلاصة

هذه ألدراسة صممت للتخليق الكيميائي لمشتقات ألـ2-aminothiadiazole وتحويلها إلى قواعد شف Schiff's base مبدأ التخليق لهذه ألمركبات يعتمد على ثلاثة خطوات :
أولاً : الغلق الحراري للـ thiosemicarbazied مع ثنائي كبريتيد الكاربون بوجود هيدروكسيد البوتاسيم المذاب في الايثانول المطلق للحصول على 2-amino-5- mercapto-1,3,4-thiadiazole
ثانياً : الغلق الحراري للـ thiosemicarbazied مع مشتق الحامض الكربوكسيلي بوجود حامض الكبريتيك المركز ليعطي yield 2-amino-5-R-1,3,4-thia diazole.
ثالثاً : تكوين قواعد شف بتفاعل 2-amino-5-R-1,3,4-thiadiazole مع الديهايدات أروماتية في الايثانول.
تم تشخيص المركبات المحضرة عن طريق مطيافية الأشعة فوق البنفسجية والمرئية ومطيافية الأشعة تحت الحمراء ودرجات الانصهار, (جدول 1و2).

ABSTRACT

This study was designed to synthesize chemically 2-aminothiadiazole derivatives and conversion to Schiff's base. The principle synthesis of these compounds was to involve three steps:
First : by thermal cyclization of thiosemicarbazied with carbon disulfide in the presence of potassium hydroxide dissolved in anhydrous ethanol to yield 2-amino-5- mercapto-1,3,4-thiadiazole.
Second : by thermal cyclization of thiosemicarbazied with substituted carboxylic acid and sulphuric acid, to yield 2-amino-5-R-1,3,4-thiadiazole.
Third : Schiff's base formation by reflux of aromatic aldehyde with 2-amino-5-R-1,3,4-thiadiazole in the presence of ethanol.
The chemical structures of all prepared compounds were confirmed by spectral data (UV-visible and IR spectroscopy) tables (1, 2, and 3).

INTRODUCTION :

1,3,4-thiadiazoles constitute an important class of compounds having a wide spectrum of biological activity. 1,3,4-thiadiazoles derivatives are associated with diverse biological activities probably due to toxophoric $-N=\overset{H}{C}-SH \rightleftharpoons -\overset{H}{N}-\overset{|}{C}=S$ grups. The advent of sulfur drugs greatly accelerated the rate of progress in the field of thiadiazole[1,2]. Various derivatives of 1,3,4-thiadiazole have shown antibacterial[3,5], antifungal[6], cardio tonic[7], anti-tubercular[8,9] anti-depressant[10,11], analgesic and anti-inflammatory activities[12,15]. The parent of the series thiadiazoles was first synthesized in 1955[16]. Several investigators have shown that the standard route to 2-amino-1,3,4-thiadiazoles involves the acylation of thiosemicarbazied followed by dehydration[17].
The preparation of 5-phenyl-2-amino-1,3,4-thiadiazole, was described in many reactions. As the initial substance, 1-benzoylthiosemicarbazide is used. Their cyclization happens in the presence of various substances, e.g. conc. sulphuric acid, phosphoric acid, acylchloride, and hydroxides, respectively. In other cases, thiosemicarbazide itself was used as the initial substance, which then reacted with benzoylchloride[17].

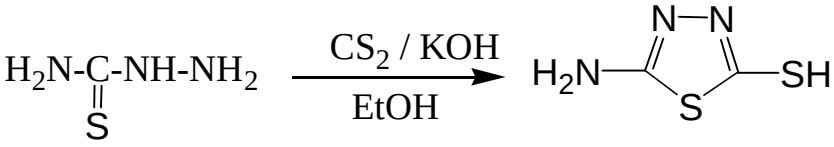
*Applied Science Department, College of Biochemical Technology, Technology University, Baghdad – Iraq.

EXPERIMENTAL:

Synthesis of 2-Amino-5-mercapto-1,3,4-thiadiazole (1)

Potassiumhydroxide (9.0gm, 0.16mole) was dissolved in anhydrous ethanol (40ml) and carbon disulfide (18.3gm, 0.2409mole) was added to solution after the addition of CS_2, thiosemicarbazied (13.5gm, 0.145mole) in anhydrous ethanol (40ml) was added and the mixture was stirred and reflux for 6h. most of the solvent was removed under pressure and the reside was dissolved in water (60ml) and carefully acidified with HCl (15ml). The precipitate was filtered off to give 2-amino-5- mercapto-1,3,4-thiadiazole (1) the crude product was washed with water, then dried .

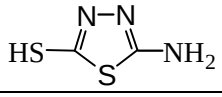
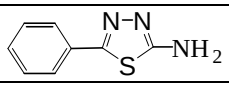
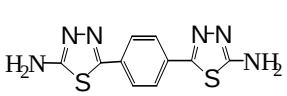
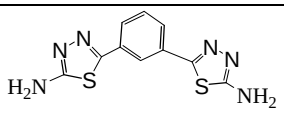
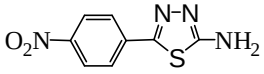
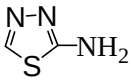
The reaction:



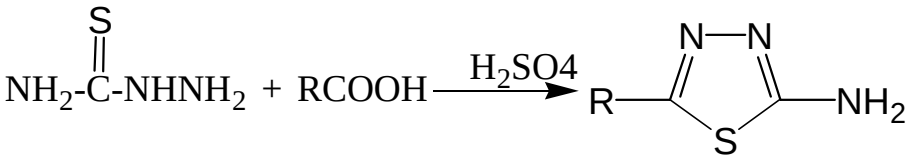
Synthesis of 2-Amino-5-R-1,3,4-thiadiazole (2-5)[18]

The carboxylic acid (0.15mol) and thiosemicarbazide (0.125mol) was stirred in 16ml of concentrated sulfuric acid in a round bottomed flask for 7 hours under reflux. After the reaction was complete the reaction mixture was allowed to cool and poured into ice water. The mixture was basified using concentrated ammonium hydroxide solution. On addition of the base the thiadiazole product precipitated. This was filtered and the crude product obtained. It was recrystallized from aqueous ethanol (10-15%). The pure product was dried over phosphorus pentoxide under vacuum for 24 hours. The chemical structure of compounds identified by melting point and infrared spectroscopy, table (1)

Table 1 . The physical and spectroscopical data of synthesized compounds (1-6).

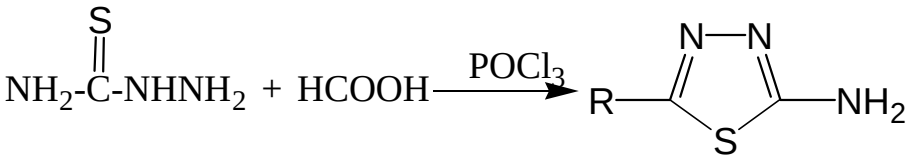
No	NAME	STRUCTURE	YIELD %	M.P. C°	IR spectroscopy					
					NH_2	NO_2	CSC	C-N	=N-N=	C-H Ar
1	5-Amino-[1,3,4]thiadiazole-2-thio		65	230-233	3400 3300	-	740	1630	1060	-
2	5-Phenyl-[1,3,4]thiadiazol-2-ylamine		40	225-231	3270	-	700	1630	1050	3100
3	5,5'-p-phenylene-bis-2-amino-1,3,4-thiadiazole		25	decompose	3300	-	690	1630	1060	3070
4	5,5'-m-phenylene-bis-2-amino-1,3,4-thiadiazole		60	decompose	3400	-	700	1640	1060	3120
5	5-(4-Nitro-phenyl)-[1,3,4]thiadiazol-2-ylamine		55	248-252	3400	1510 1340	690	1630	1070	3150
6	[1,3,4]Thiadiazol-2-ylamine		35	191-195	3290	-	685	1620	1025	-

The reaction:



Synthesis of 2-Amino-1,3,4-thiadiazole (6)[2]

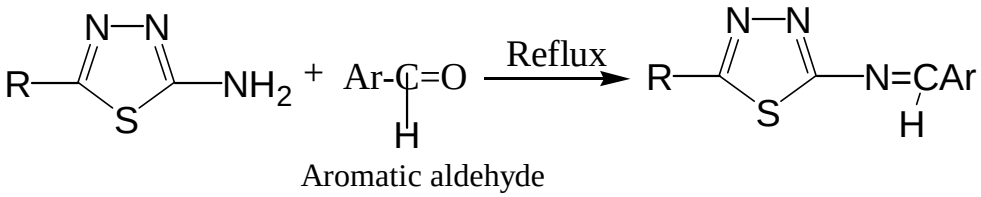
A mixture of formic acid (0.05mol), thiosemicarbazide (0.05mol), phosphorous oxychloride (25ml) was refluxed gently for 5 hours. After cooling, water was added (125ml). The mixture was refluxed for 4 hours and filtered. The solution was neutralized with potassium hydroxide. The precipitate was filtered and washed with distilled water and crystallized from ethanol to give 2-Amino-1,3,4-thiadiazole (6). The chemical structure of compound identified by melting point(191C°) standard (191-195C°) and infrared spectroscopy, table (1)



Synthesis of 5-(Benzylidene-amino)-[1,3,4]thiadiazole derivatives (7-24)[19]

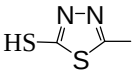
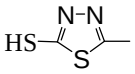
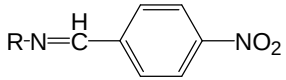
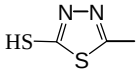
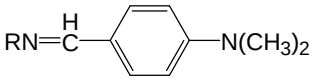
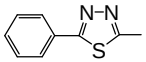
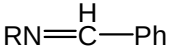
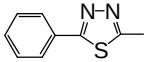
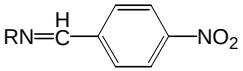
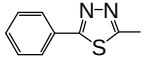
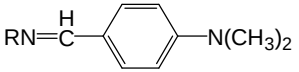
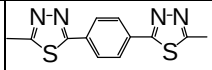
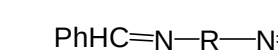
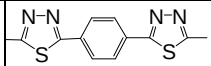
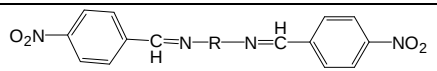
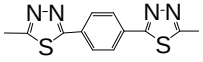
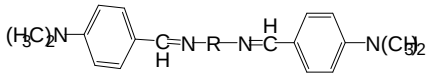
A mixture of 0.01mole 2-amino-5-R-[1,3,4]thiadiazole and 0.01mole of the aromatic aldehyde in 10ml absolute ethanol was refluxed in water bath for 30min. then left to cool in ice-water, The solid was filtered washed with 2% HCl, then recrystallized twice from ethanol. The chemical structure of compounds identified by melting point and infrared spectroscopy, table (2).

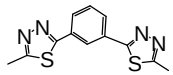
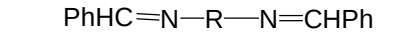
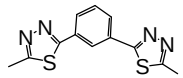
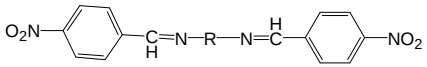
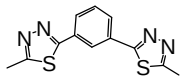
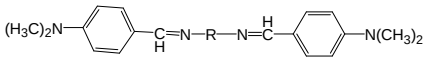
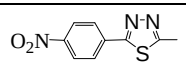
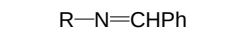
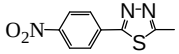
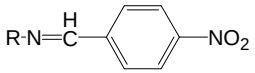
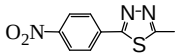
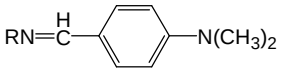
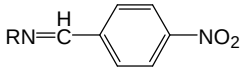
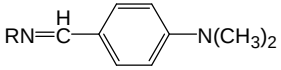
The reaction:



Aromatic aldehyde

Table 2 . The physical and spectroscopical data of synthesized compounds (7-20).

NO	Name	R	Structure	MP	UV-Visible nm	IR-spectra cm^{-1}			
						C-H Aromat	NO_2	C=N	CH_3
7	5-(Benzylidene-amino)-[1,3,4]thiadiazole-2-thiol			140-151	380	3080	-	1575	-
8	5-[(4-Nitro-benzylidene)-amino]-[1,3,4]thiadiazole-2-thiol			189-192	400	3100	1530 1350	1580	-
9	5-[(4-Dimethylamino-benzylidene)-amino]-[1,3,4]thiadiazole-2-thiol			191-195	400	3090	-	1580	2950
10	Benzylidene-(5-phenyl-[1,3,4]thiadiazol-2-yl)-amine			167-172	390	3110	-	1570	-
11	(4-Nitro-benzylidene)-(5-phenyl-[1,3,4]thiadiazol-2-yl)-amine			180-182	420	3150	1525 1340	1575	-
12	(4-Dimethylamino-benzylidene)-(5-phenyl-[1,3,4]thiadiazol-2-yl)-amine			185-189	420 430	3110	-	1575	2905
13	Bis{5-(Benzylidene-amino)-[1,3,4]thiadiazole-2-thiol}-1,4-benzene			167-171	380	3140	-	1575	-
14	Bis{5-((4-nitro)Benzylidene-amino)-[1,3,4]thiadiazole-2-thiol}-1,4-benzene			298-302	400	3110	1535 1355	1590	-
15	Bis{5-(4-N,N-dimethyl)Benzylidene-amino)-[1,3,4]thiadiazole-2-thiol}-1,4-benzene			285-289	420	3150	-	1570	2930

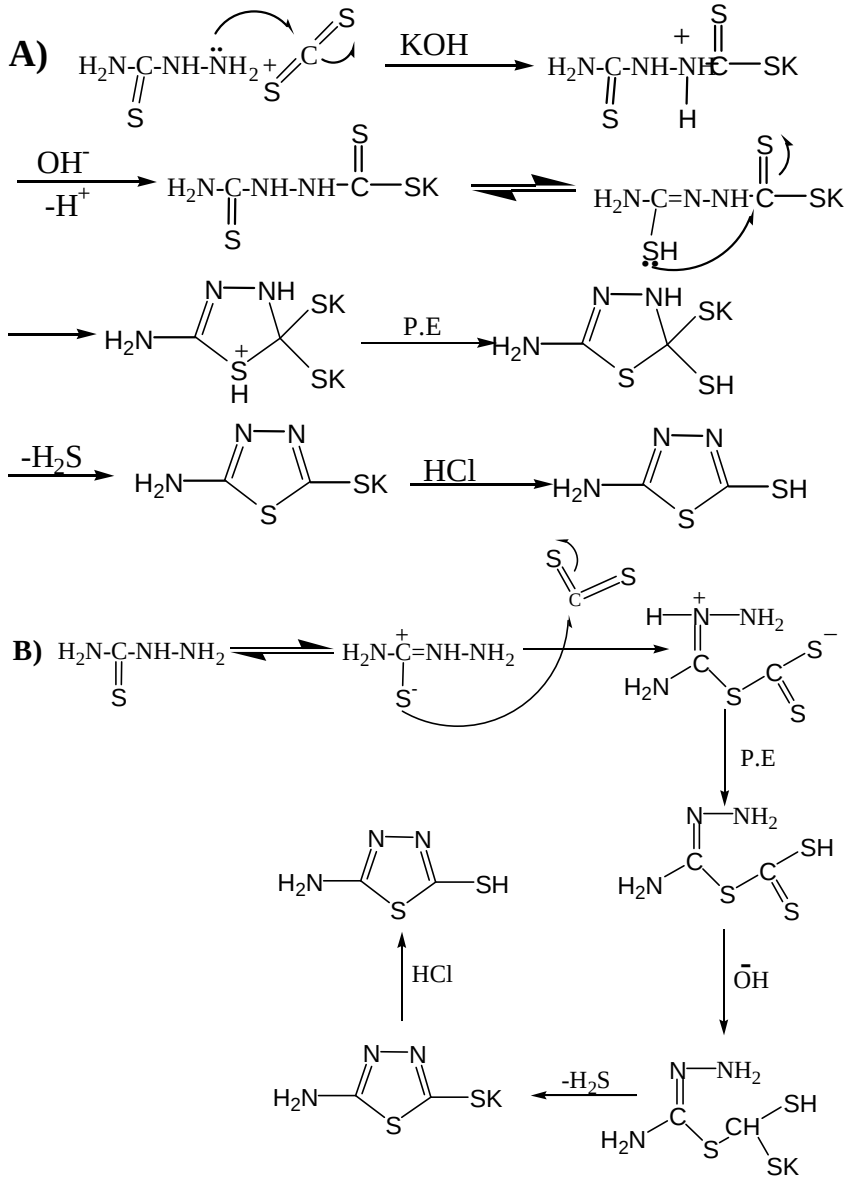
16	Bis{5-(Benzylidene-amino)-[1,3,4]thiadiazole-2-thiol}-1,3-benzene			290-293	420 400	3150	-	1570	-
17	Bis{5-((4-nitro)Benzylidene-amino)-[1,3,4]thiadiazole-2-thiol}-1,3-benzene			255-259	440	3130	1540 1350	1585	-
18	Bis{5-(4-N,N-dimethyl)Benzylidene-amino)-[1,3,4]thiadiazole-2-thiol}-1,3-benzene			297-300	380 420 440	3050	-	1570	2910
19	Benzylidene-[5-(4-nitro-phenyl)-[1,3,4]thiadiazol-2-yl]-amine			179-183	380 400	3100	1525 1340	1575	-
20	(4-Nitro-benzylidene)-[5-(4-nitro-phenyl)-[1,3,4]thiadiazol-2-yl]-amine			201-204	390 410	3120	1515 1340	1580	-
21	(4-Dimethylamino-benzylidene)-[5-(4-nitro-phenyl)-[1,3,4]thiadiazol-2-yl]-amine			298-304	380 445	3095	1520 1340	1570	2930
22	Benzylidene-[1,3,4]thiadiazol-2-yl-amine			152-155	400	3060	-	1570	-
23	(4-Nitro-benzylidene)-[1,3,4]thiadiazol-2-yl-amine			189-193	380 410	3080	1540 1350	1575	-
24	(4-Dimethylamino-benzylidene)-[1,3,4]thiadiazol-2-yl-amine			255-259	390 420	3050	-	1565	2920

RESULTS AND CHARACTERIZATION:

Synthesis of 2-Amino-5-mercapto-1,3,4-thiadiazole (1)

Thermal cyclization of thiosemicarbazied with carbon disulfide in the presence of potassium hydroxide dissolved in anhydrous ethanol yield 2-Amino-5-mercapto-1,3,4-thiadiazole. The chemical structure of compound(1) was identified by melting point 230-233C° (standard is 230-232C°) and infrared spectroscopy (for active groups NH_2=3400,3300, C-N=1630, and =N-N= =1060) table (1)

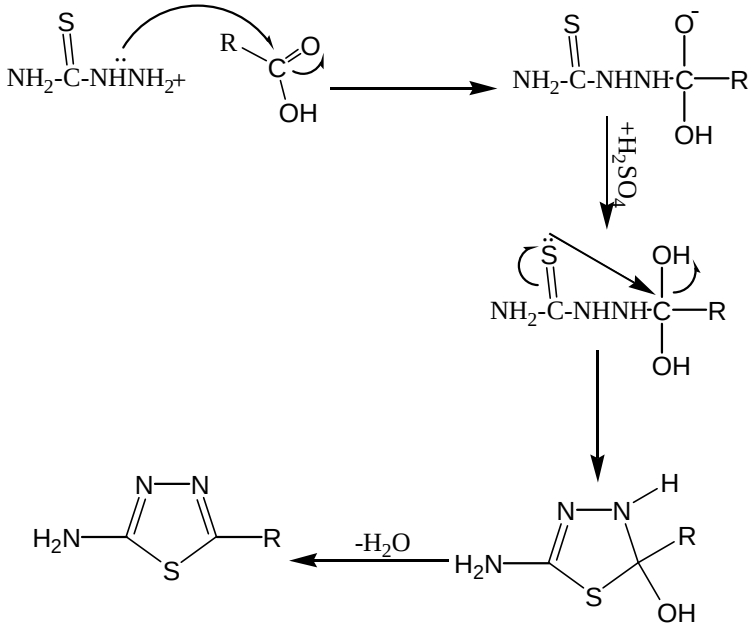
The mechanism[20]**:**



Synthesis of 2-Amino-5-R-1,3,4-thiadiazole (2-6)

The reflux of thiosemicarbazied (0.125mole) and carboxylic acid (0.15mole) in(16ml) H_2SO_4.

The mechanism:



Synthesis of 5-(Benzylidene-amino)-[1,3,4]thiadiazole derivatives (7-24)
A mixture of 0.01mole 2-amino-5-R-[1,3,4]thiadiazole and 0.01mole of the aromatic aldehyde in 10ml absolute ethanol was refluxed in water bath for 30min.

REFERENCES:

1. Amir T Atto, Nazar A. Al-Nasiry, Omar S. Al-Rahbi, Journal of Al-Nahrain University, Vol. 7, No. 1, 2004.
2. Ayad S. Hameed, Nadia A . Saleh and Amar H. AlDujaily, National Journal of Chemistry, 2002, Vol.5, 121-131.
3. S. Rollas, S. Karaku_s, B.B. Durgun, M. Kiraz and H. Erdeniz, Farmaco, 51 (12), 811-814 (1996).
4. A. Varvaresou, A. Tsantili-Kakoulidou, T. Siatra-Papastaikoudi and E. Tiligada, Arzneim.-Forsch./Drug Res., 50, 48-54 (2000).
5. N. Terzio_glu, N. Karal_, A. G¨ursoy, G.¨ Ot¨uk, M. Kiraz and Z. Erturan, Acta Pharmaceutica Turcica, 40, 77-82 (1998).
6. H. Chen, Z. Li and Y. Han, J. Agric. Food Chem., 48, 5312-5315 (2000).
7. Y. Nomoto, H. Taka_, T. H_rata, M. Teran_sh_, T. Ohno and K. Kubo, Chem. Pharm. Bull., 39, 86-90 (1991).
8. A. Foroumadi, M. Mirzaei and A. Sha_ee, Pharmazie, 56 , 610-612 (2001).
9. M.G. Mamolo, V. Falagiani, D. Zampieri, L. Vio and E. Ban_, Farmaco, 56, 587-592 (2001).
10. F. Clerici, D. Pocar, M. Guido, A. Loche, V. Perlini and M. Brufani, J. Med. Chem., 44, 931-936 (2001).
11. A. Varvaresou, T. Siatra-Papastaikoudi, A. Tsotinis, A. Tsantili-Kakoulidou and A. Vamvakides, Farmaco, 53, 320-326 (1998).
12. S. Schenone, O. Bruno, A. Ranise, F. Bondavalli, W. Filippelli, G. Falcone, B. Piucci and S. Sorrentino, Farmaco; 53, 586-589 (1998).
13. S. Schenone, O. Bruno, A. Ranise, F. Bondavalli, W. Filippelli, G. Falcone, L. Giordano and M.R. Vitelli, Bioorg. Med. Chem., 9, 2149-2153 (2001).
14. A.A. Fargnaly, A.A. Bekhit and J.Y. Park, Arch. Pharm. Pharm. Med. Chem., 333, 53-57 (2000).
15. E. Palaska, G. S_ahin, P. Kelicen, N.T. Durlu and G. Alt_nok, Farmaco, 57, 101-107 (2002).
16. J. Geordeler, and O. Tegmeyer, Cem. Ber. 89. 1534(1955).

17. Miloslav Hejsek and Iveta Wiedermannová FACULTAS RERUM NATURALIUM 2001 CHEMICA 40 Accepted August 28, 2001
18. Khalid M. Daoud and Mohammad A. Eisa National Journal of Chemistry, 2002, Vol.7, 438-445.
19. F. A. Hussein and Khalid F. Ali. Iraq, Journal of Chemistry , Vol. 28, No. 3, 2002.
20. هند فاضل ثامر الجبوري "تحضير مشتقات 1و3و4-ثايادايوزول-4-امينو بنزايلدين معوضة -5-امينوبروباين-2-اريل " رسالة ماجستير 1989.