Synthesis and Characterization of New Heterocyclic Compounds based on 5,5-dithio bis (1,3,4-thiadiazole -2- amine)

Lamees Bassim Hussien
Department of Chemistry, College of scientific, Mustansiriyah University/Iraq, lamessbassim@uomustansiriyah.edu.iq

Sajida. Munadi. Th.AL-Suraify
Department of Pharmaceutical Chemistry, College of Pharmacy, University of Misan, sajida_munadi@uomisan.edu.iq

Emad M. Al- Kinani
Department of Chemistry, College of scientific, Mustansiriyah University/Iraq

Abstract

The parent compound (5,5-dithio bis(1,3,4-thiadiazole -2- amine) was diazotized to afford the diazonium salt. Diazonium salts continue to attract great interest in the field of organic synthesis due to their various chemical and biological applications observed, especially in recent times. As a result, in this work new (16) compounds were synthesized in many steps. The first step was involved reaction of diazonium salt with active methylene compounds (malononitrile , ethyl cyanoacetate and ethyl acetoacetate) to give derivatives (1,2 and 3) ,respectively .Azide (4) was produced from treatment of diazonium with sodium azide , Moreover, cyclocondensation reaction of azide (4) with ethyl acetoacetate , malononitrile in presence of sodium ethoxide produce tetrazole derivatives (5,6), respectively ,(scheme 1) . Cyclization of compounds (1,2 and 3) were afforded a series of amino pyrazole and pyrazolone derivatives (7-12) ,(scheme 2). Furthermore, compound (6) was a good key for synthesis of new pyrrole, pyrazole and pyrimidine derivatives (13-16). The;;constructions;;of;all;manufactured ;combinations;;were confirmed; according;spectroscopic;;analysis such as UV, FTIR ,1HNMR and 13C-NMR .

Keywords: *azo synthesis, 1,3,4-thiadiazole, pyrazole , pyrazolone , pyrrole and pyrimidine derivatives.*

Introduction

Conversion of thiols to disulfides is important from both biological and synthetic points of view. In biological systems, thiols are oxidized by flavins, cytochromes and dehydroascorbic acid to control the cellular redox potential and prevent oxidative damage. On the other hand, disul_des are important reagents in organic synthesis and can be used to prepare sulfinyl and sulfenyl compounds (Karami et al., 2005). Thiadiazole play a

prominent role in nature. For example, the thiazolium ring present in vitamin B1 serves as anelectron sink and its coenzyme form is important for thedecarboxylation of α-keto acids (Raj et al., 2013) .Thiadiazole scaffold emerges as an interesting structural motif due to the presence of different heteroatoms in its structure and its promising therapeutic activities in the treatment and cure of several diseases (Update, Kotwica-mojzych and Mojzych, 2021) .Azo dyes constitutes one of the largest and important class of synthetic organic compounds containing an azo N=N group generally connected to aromatic rings. Mostly,synthesis of azo compounds involves diazotization of substituted primary aromatic

amines followed by coupling with nucleophiles (Mousway, Khmmas and Jarad, 2013). Azo compounds are a very important class of chemical compounds receiving attention in scientific research. They are highly colored and have been used as dyes and pigments for a long time. Furthermore, they have been studied widely because of their excellent thermal and optical properties in applications such as optical recording medium, toner, ink-jet printing, oil-soluble lightfast dyes , textile fibers ,biochemical studies and organic synthesis (Kirkan and Gup, 2008), (Kamoon, Jawad Al-Mudhafar and Omar, 2020).

Pyrazole is a heteroaromatic compound of 5-membered containing two adjacent nitrogen atoms. NH-Pyrazoles can act both as weak bases and moderately weak acids because they have a pyridine-type proton-acceptor nitrogen atom (C=N) and one pyrrole-type nitrogen atom (N-H) with a proton-donor behavior. Likewise, hydrogen bonding interactions and tautomeric properties of these compounds are strictly related to the nature of their heteroatoms as well as by the electronic effect of the substituent groups on the pyrazole core . They are one of the most studied groups of compounds among the azole family (Castillo and Portilla, 2018), (Karrouchi et al., 2018). Pyrazolones are biologically essential groups for substances with various functions, such as antifungals, antibacterial, anti-inflammatory ,analgesic, antdiabetic, antipyretic, immunosuppressive, hypoglycemic, antiviral, antidepressant, and other biological activities against two types of Gram (+)ve and three types of Gram (-)ve bacteria (Saeed, Zaki Dawood and Qasim, 2020). Pyrrole derivatives are considerable attention of synthetic importance and extensively used in drug discovery and pharmacological activity such as anti-inflammatory (Idhayadhulla et al., 2012). Also it have a wide-range of biological activities; antibacterial, antifungal, antiviral and anticancer (Abd El-Hameed et al., 2021; Abbasi et al, 2021) . Pyrimidines (“m-diazine) were known as the breakdown products of uric acid. The first pyrimidine derivative to be isolated was alloxan (5,5-dihydroxypyrimidine-2,4,6(1H,3H,5H)-trione) in 1818 by Brugnatelli, oxidizing uric acid with nitric acid. Pyrimidines are the heterocyclic aromatic compounds similar to benzene and pyridine ,containing two nitrogen atoms at positions 1 and 3 of the six-membered rings. Pyrimidine has one axis of symmetry about the 2-5 axis; it has three different pairs of bond lengths and four different bond angles (Tolba et al., 2022). Pyrimidine has a great value in medicinal chemistry since it comprises the base for thiamine, uracil and cytosine nitrogen bases which are the building blocks of the nucleic acids . Furthermore, pyrimidine derivatives have registered their importance in the development of various pharmaceuticals of broad spectra of the therapeutically activities such as: anti-microbial , anti-viral, anti- HIV , anti-tubercular , anti-malarial ,analgesic, anti - inflammatory, diuretic , cardiovascular ,hypnotic for the nervous system and antioxidant (Mohsein and Obaid, 2019).

MATERIALS AND METHODS

Melting point were determined on Gallen – Kamp (MFB- 600) melting point apparatus and are;;uncorrected. The FTIR spectrum of the compounds were;;noted on Shimadzu FT-IR 3800 spectrometer as KBr disk .The U.V spectra were performed on Cintra-5-Gbes scientific; equipment. The 1H-NMR and 13C-NMR spectra (solvent DMSO) were verified;;on Bruker 300 MHZ spectrophotometer ;using TMS as internal standard.

General procedures for the synthesis of compounds

Synthesis ;of diazonium salt (Of, 2016)

Stage (1): amine (0.01mol.) was dissolved in (15mL) of concentrated hydrochloric acid and (15mL) of distilled water contained in a small beaker. The mixture was cold at (0°C) in an ice bath.Then a solution of sodium nitrite (1.656g,0.024 mol.) dissolved in (20 mL) of distilled water was added dropwise to the mixture with stirring, the temperature of the ice bath was controlled between (0-5°C).;

Synthesis of compound (1-3) (Patil et al., 2019)

Added aryldiazonium salt solution (from Stage-I) slowly, to the well cooled mixture of, active methylene compound (malononitile, ethyl cyanoacetate, and ethyl acetoacetate) (0.01 mol.) dissolved in 15 ml ethanol and sodium acetate (0.01 mol.) in 4-5 ml of water(to keep the mixture alkaline to litmus).The mixture was stirring for 30 minutes a coloured precipitate was separated, then added 20 ml of concentrated HCl, filtered and recrystallized from ethyl acetate, dry it to give the corresponding hydrazone derivatives .The physical ;properties were given in Table (1).

Compound (1):U.V(EtOH) nm :. (225, 361). FT.IR (KBr) (cm^{-1}) : 1597 (C=N); 2240(C≡N) ,1612,1617 (C=N) of thiadiazole ring, , 3210 (NH), 3202,3320(NH_2), 1680 (C=O) of amide , 480 (S-S): ^{1}HNMR signals (ppm) (DMSO-d_6):6 (S,2H ,NH) , 5.5 (S,4H ,NH_2). ^{13}C NMR : (118, 145, 155, 167).

Compound(2): U.V(EtOH) nm :(231, 380). FT.IR (KBr) (cm^{-1}) : 1497 (N=N); 1685(C=O) of amide , 3250 ,3365 for NH_2 , 1605,1620 (C=N) of thiadiazole ring, 2950 ,2976 ,2890,2865 $CH_{alp.}$, 471 (S-S), 1735 (C=O) of ester , 1225 (C-O),

: ^{1}HNMR signals (ppm) (DMSO-d_6): 5.5 (S,4H ,NH_2). 3.5(S,1H ,C<u>H</u>N=N) , 4.2(q,2H, -O-C<u>H$_2$</u>CH$_3$) ,1.5(T,3H, O-CH$_2$<u>CH$_3$</u>) .^{13}C NMR : (13.5,59, 75, 145, 170, 177).

Compound(3): U.V(EtOH) nm :. (287, 362). 3217 (NH) ,487 (S-S) , 1734 (C=O) of ester , 1695 (C=O) of ketone : ^{1}HNMR signals (ppm) (DMSO-d_6): 2 (S,6H , 2COCH$_3$) , 4.5(S,1H, N<u>H</u>) , 4.2(q,4H, -OC<u>H$_2$</u>CH$_3$),1.5 (T,6H, -OCH$_2$C<u>H$_3$</u>)-: ^{13}C NMR : (13,19,60, 154,200 ,145, 160).

Synthesis of compound (4) (Hassan, 2013)

A solution of sodium azide (0.01 mol.) was added dropwise to an aqueous solution of diazonium salt (from Stage-I). The mixture was stirred for further 1hr. to give compound (4). The physical ;properties were given in Table (1). U.V(EtOH) nm :. (260, 312). FT.IR (KBr) (cm-1) : 2120(N=N-N of azide) ;1615,1622 (C=N) of thiadiazole ring ,491 (S-S) .

Synthesis of compound (5,6) (Hassan, 2013)

To a cold solution of sodium ethoxide (0.01 mol.) and(0.01 mol.) from active methylene groups(ethyl acetoacetate , malononitrile) azide (4) (0.01 mol.) was cautiously added and the mixture was heated under reflux on a water bath for 5 hrs. The resulting (5,6) were separated and recrystallized from suitable solvent . The physical properties were listed in Table compound (5)U.V(ETOH) nm :(210 , 299) , FT.IR(KBr) (cm^{-1}): 2955 $CH_{alp.}$,471 (S-S) , 1610,1615 (C=N) of thiadiazole ring , 940(N-N=N of triazole ring)1710 (C=O) of carboxylic acid , (2500-3350) OH of acid , (1250) C-O; ^{1}H-NMR (DMSO-d$_6$) ppm :2.4(S,6H,2C<u>H$_3$</u>) subst. on ring; 11.2 (S,2H,2O<u>H</u>) ; ^{13}CNMR: (6.5, 16, 145, 150.5, 172).

compound (6) :U.V(ETOH) nm :(220 , 318) , FT.IR(KBr) (cm^{-1}):. ,485 (S-S) , 1614,1622 (C=N) of thiadiazole ring , 952 (N-N=N of triazole ring); 2230 (CN) ; (3230, 3345) NH_2 ; ^{1}H-NMR (DMSO-d_6) ppm : 4 (S,4H,2N<u>H$_2$</u>) subst. on ring ; ^{13}CNMR: (118, 130, 145).

Synthesis of compounds (7-12) (Nofal *et al.*, 2011)

Hydrazine hydrate or phenylhydrazine (0.01 mol) were added to a solution of compounds (1,2 or 3) (0.01 mol) and pyridine 0.5 ml in 30 ml of ethanol. The reaction mixture was heated under reflux for 4-5 h, then cooled to room temperature and the precipitated products that separated upon dilution with water were filtered,washed with water several times, dried and recrystallized from suitable solvents to give compounds (7-12). The physical properties were listed in Table (1).

Compound (7): U.V(ETOH) nm :(243 , 320) , FT.IR(KBr) (cm^{-1}):. ,473 (S-S) , 1617,1628,1643,1639 (C=N) of rings ; 3250 (NH) ; (3230, 3345) NH_2 ; ^{1}H-NMR (DMSO-d_6) ppm : 6.5 (S,4H,2N$\underline{H}_2$) subst. on ring 8 (S,2H,2N$\underline{H}$); ^{13}CNMR: (78, 153, 145).

Compound (8): U.V(ETOH) nm :(265 , 377) , FT.IR(KBr) (cm^{-1}):. ,461 (S-S) , 1610,1638,1635,1641 (C=N) of rings ; 1470(N=N) ; (3390, 3450) NH_2 ;3095 CH_{ar} ; ^{1}H-NMR (DMSO-d_6) ppm : 5.5 (S,4H,2N$\underline{H}_2$) subst. on ring ;(7.2 – 7.5) ar. Protons ; ^{13}CNMR: (81, 129, 145, 148, 160, 118,129,126).

Compound (9): U.V(ETOH) nm :(253 , 384) , FT.IR(KBr) (cm^{-1}):. ,483 (S-S) , 1612,1619,1628 (C=N) of rings ; 1469 (N=N) ; (3365, 3480); 1680 (C=O) of ring; NH_2 ; 3270(NH) ; ^{1}H-NMR (DMSO-d_6) ppm : 4.8 (S,4H,2N$\underline{H}_2$) subst. on ring; 6.5 (S,2H,2 N$\underline{H}$); 3.2 (S,2H,2C$\underline{H}$ of ring) ; ^{13}CNMR: (66, 145, 155, 173).

Compound (10): U.V(ETOH) nm :(240 , 390) , FT.IR(KBr) (cm^{-1}):. ,483 (S-S) , 1623,1629,1637 (C=N) of rings ; 1475(N=N) ; (3371, 3450) NH_2 ; 1685 (C=O) of ring; ;3099 $CH_{ar.}$; 1H-NMR (DMSO-d_6) ppm : ;(7 – 7.6) ar. Protons 5(S,4H,2N$\underline{H}_2$) subst. on ring; 3.4 (S,2H,2C$\underline{H}$ of ring); ^{13}CNMR: (63.5,145, 156, 168, 120,124,128, 140).

Compound (11): U.V(ETOH) nm :(238 , 381) , FT.IR(KBr) (cm^{-1}):. ,468 (S-S) , 1627,1634,1642 (C=N) of rings ; 1466 (N=N) ; (3280) NH ; 1689 (C=O) of ring; ;2876,2934 $CH_{alp.}$; 1H-NMR (DMSO-d_6) ppm : 6(S,2H,2N$\underline{H}$) of ring; 3 (q,2H,2C$\underline{H}$ of ring); 1.5(d, 6H, $2CH_3$)) subst. on ring; ^{13}CNMR: (14.3, 70.5,145,156, 173).

Compound (12): U.V(ETOH) nm :(245 , 399) , FT.IR(KBr) (cm^{-1}):. ,479 (S-S) , 1631,1639,1640 (C=N) of rings ; 1475 (N=N) ; 1684 (C=O) of ring; ;2880,2957 $CH_{alp.}$; 3087 CH_{ar} 1H-NMR (DMSO-d_6) ppm : ;(7 – 7.6) ar. Protons; 3.2 (q,2H,2C$\underline{H}$ of ring); 1.6(d, 6H, $2CH_3$)) subst. on ring; ^{13}CNMR:. (14.8, 68.9,145.5, 155, 169,128,120,124).

Synthesis of compound (13) (Karam, Hussain and Tomma, 2019)

A mixture of(0.05mol.) chloro acetic acid ,(0.05 mol.) of compound (6) were dissolve in (20ml.)of absolute ethanol then the mixture was refluxed for (10hrs.),cooled and poured into crushed ice, the solid product was filtered and recrystallized from ethanol 50% to give compound (13). The physical properties were given in Table (1).

U.V(ETOH) nm :(212,338) , FT.IR(KBr) (cm^{-1}):. ,468 (S-S) , 1637,1625,1630 (C=N) of rings ; 1471 (N=N) ; 3254 (NH) of ring , 3300,3410 (NH_2) subst. on ring , 1760 (C=O) ; (3300-3550) OH of carboxyl group. ^{1}H-NMR (DMSO-d_6) ppm : 4(S, 4H, $2NH_2$)) subst. on ring, 5(S,2H, 2NH) ,11(S,2H,2OH);^{13}CNMR:. (123, 115,133,145.5, 105,165).

Synthesis of compound (14) (Cai *et al.*, 2016)

A mixture of compound (6) (0.05 mol.) in formamide (20 ml) was refluxed for 4hrs. the solid was formed on hot was filtered off,dried and recrystallized from acetone. The physical properties were listed in Table (1).

U.V(ETOH) nm :(278,350) , FT.IR(KBr) (cm^{-1}):. ,462 (S-S) , 1635,1620,1638,1640 (C=N) of rings ; 1467 (N=N) ; 3088 (CH_{ar}), 3320,3430 (NH_2) subst. on ring ,. ^{1}H-NMR (DMSO-d_6) ppm : 4.2(S, 4H, $2NH_2$)) subst. on ring,

8(S,2H, 2CH) of pyrimidine ring, ^{13}CNMR:. (,133,145.5, 157, 105,167.5).

Synthesis of compound (15,16) (Al-Issa, 2012)

A mixture of (6) (0.01 mol.) and urea (or thiourea) (0.01 mol.) was fused in an oil bath at 180 C, for 1h. After cooling and dilution with ethanol (30 ml) the solid product formed was filtered off and recrystallized from chloroform.The physical properties were listed in table (1).

Compound (15) : U.V(ETOH) nm:(229,343); FT.IR(KBr) (cm^{-1}): 470 (S-S) , 1619,1633, 1641 (C=N) of rings (3260, 3411 NH_2), (3630 OH.); ^{1}H-NMR (DMSO-d_6) ppm: 4(S,4H,2N$\underline{H}_2$), 5(S,2H O$\underline{H}$) ; ^{13}CNMR(105,, 133, 145, 163, 174.5).

Compound (16) : U.V(ETOH) nm:(229,343); FT.IR(KBr) (cm^{-1}): 475 (S-S) , 1614,1626,1630, 1647 (C=N) of rings (3330, 3420, (NH2).) 2550(SH); ^{1}H-NMR (DMSO-d_6) ppm: 4(S,4H,2NH_2) , 3(S,2H,2SH):^{13}CNMR((105,, 133, 145, 168, 187).

Table (1): physical properties of synthesized compounds

Comp. NO.	m.p.°C	Yield %	Color	Recryst. Solvent
1	211-213	93	Light yellow	Ethyl acetate
2	120-122	95		Ethyl acetate
3	113-115	87	Pale yellow	Ethyl acetate
4	137-139	81	Off-white	Ethanol 70%
5	119-121	79	White	Ethanol 50%
6	145-147	89	Yellowish	Petroleum ether(60-800)C
7	161-163	77	Dark yellow	Ethanol 50%
8	169-171	75	Light orange	Ethanol 70%
9	210-212	68	Off -white	Dichloromethane
10	188-200	60	Pale yellow	Dichloromethane
11	202-204	59	yellow	Dioxan
12	243-245	55	Dark yellow	Dioxan
13	257-259	90	Brown	Ethanol 50%
14	319 decom	70	yellow	Acetone
15	288-290	87	White	Chloroform
16	266-268	83	Light yellow	Chloroform

Results and discussion

In the present work the synthesis of some new 1,2,3-triazoles , pyrrole, pyrazole and pyrazolinone derivatives were achieved from 5,5-dithio bis(1,3,4-thiadiazole -2- amine) .

The starting material ,diazonium salt was prepared by reaction of 5,5-dithio bis(1,3,4-thiadiazole -2- amine) with sodium nitrite in hydrochloric acid14, which was directly converted to the coupling derivatives (1,2,3) via the reaction with malononitrile , ehylcyanoacetate and ethylacetoacetate, respectively. FT.I.R spectrum of compound (1) was showed presence of an;;absorption band for;;CO of amide at1680 cm−1 and another at 3210 cm-1 corresponding;;to the NH group and3202,3320 for NH2 group. The 1H-NMR spectrum;;of compound (1);indicated;;a signals (ppm) (DMSO-d6) :6 (S,2H ,2NH) , 5.5 (S,4H ,2NH2).;;13C NMR : (118, 145, 155, 167).

It is worthy to note that the IR spectrum of compound (2) was showed the absence of stretching vibration of CN group at 2220 cm−1, due to the hydrolysis of CN to CO-NH2.While 1HNMR spectrum signals (ppm) (DMSO-d6): 5.5 (S,4H ,NH2).;3.5(S,2H ,CHN=N) , 4.2(q,4H, 2 -O-CH2CH3) ,1.5(T,6H, 2O-CH2CH3),,.13C NMR : (13.5,59, 75, 145, 170, 177).

Compounds (1-3) were easily undergoing cyclocondensation reaction with hydrazine hydrate or phenyl hydrazine in boiling ethanol and pyridine under reflux afforded to the corresponding substituted pyrazole or pyrazolone derivatives (7-12). Thus cyclization of (1-3) with hydrazine hydrate yielded the corresponding products (7,9 and 11). On the other hand, reaction of (1-3) with phenyl hydrazine afforded the corresponding derivatives (8,10 and 12) respectively (scheme 2). The physical properties of the synthesized compounds (7-12) were listed in table (1). The structure of the new synthesized compounds [(7-12) had been characterized and identified on the bases of their U.V. ,FT. IR , 1 HNMR and 13 CNMR spectra.

A series of target ;compounds (13-16),;scheme (3) contain substitution pyrazole ,pyrrole and pyrimidine ring were synthesized from compound (6) . Derivative (13) was synthesized from treatment of (6) with chloroacetic acid , the FT.IR spectrum was showed characteristic absorption peak in the regionat (1637,1625,1630) for stretching vibration (C=N) of rings cm-1), and at (3300,3410) cm-1 due NH2 group substitution. on ring , another absorption at 1760 cm-1 due to (C=O)and abroad peak at (3300-3550) cm-1 for OH of carboxyl group.. While the U.V. spectrum was showed a maximum absorption at wavelength at the region (212,338).

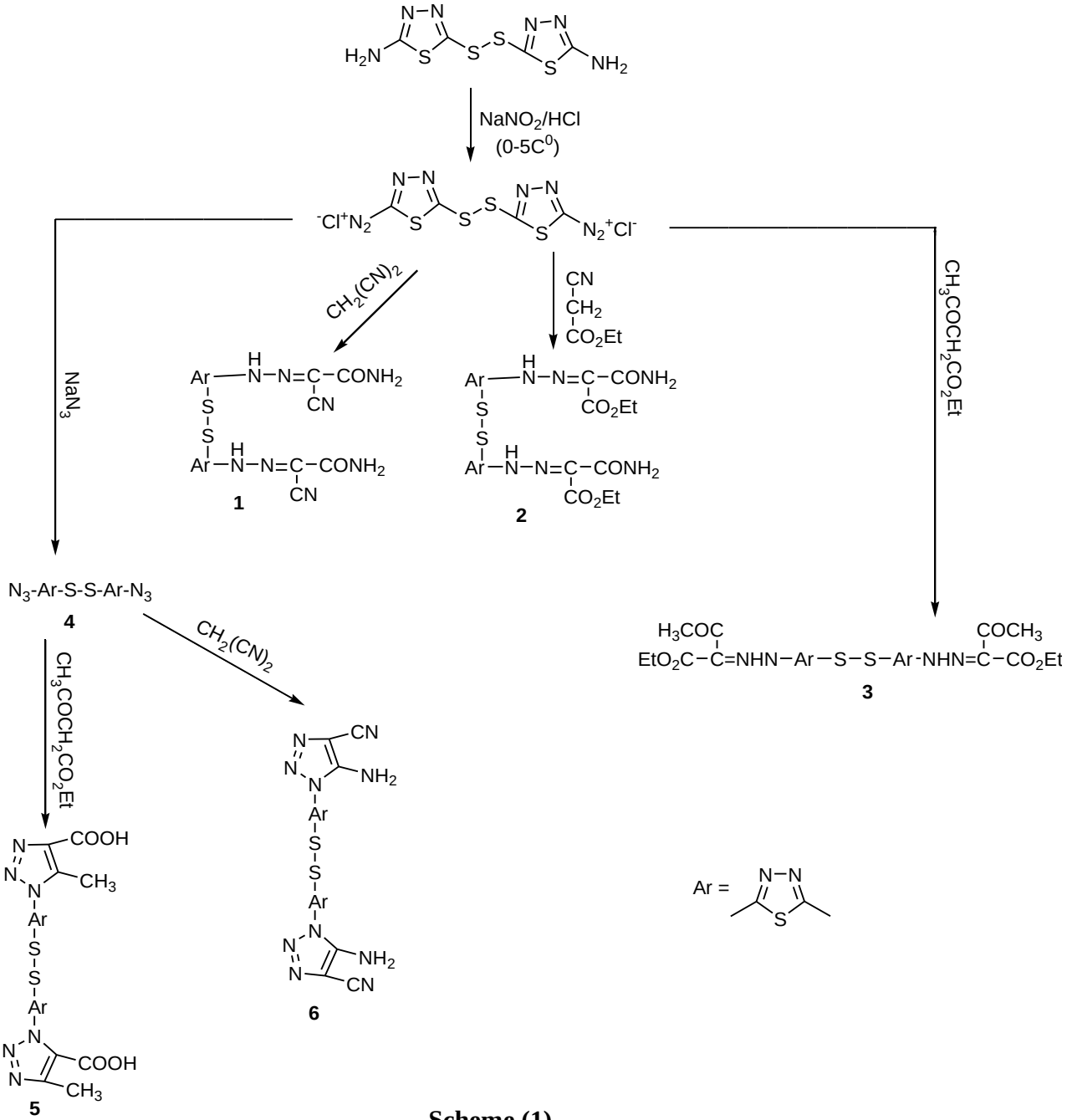
1 H-NMR;spectrum ;of (13);;displayed;indicators; at;4 for assigned; NH2 and 5 for assigned;NH,and at 11 for OH of carboxylic acid,and 13CNMR spectrum was given the following signals in ppm: (123, 115,133,145.5, 105,165).

Cyclization of (6) with formamide produced amino pyrazole derivative(14) , the;IR;spectrum of;composite (3) was showed the;;presence of an;;absorption band for;;NH2 group at;;(3320,3430) cm−1. Also was showed another bands at 1635,1620,1638,1640 for (C=N) of rings.1H-NMR;spectrum of compound (14); showed a sign;;at 4.2 for assigned NH2, and at 8 for CH of pyrimidine ring. 13CNMR spectrum gave the following signals in ppm :133,145.5, 157, 105,167.5.

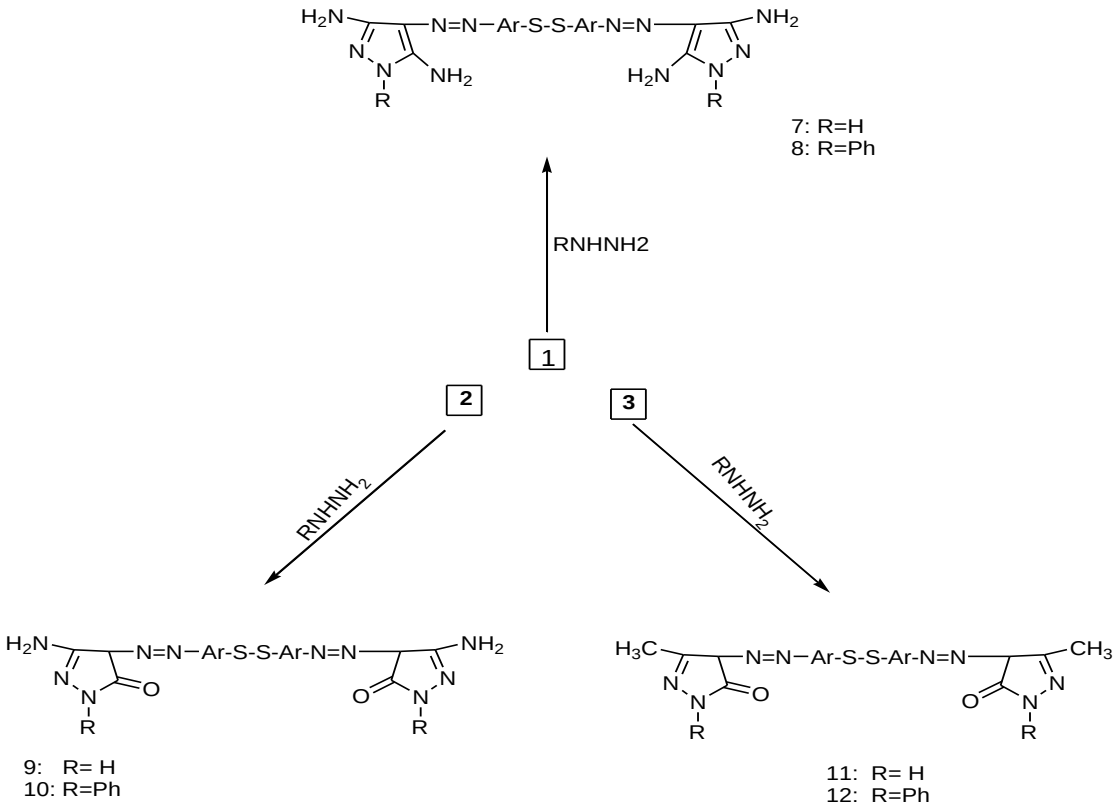
On the other side , reaction of (6) with urea ,thiourea was produced derivatives(15,16) ,respectively. The FT.IR spectra of(15,16) were showed the disappearance of the C N

group and showed absorptions bands at (3260, 3411) , (3330, 3420) cm-1 for NH2 groups respectively, and another band at 3630 attributed to stretching vibration of OH group which substitution on pyrimidine ring in compound(15) . Behind that, FT.IR spectrum of (16) was appeared new band at 2250 cm-1 due to SH group .

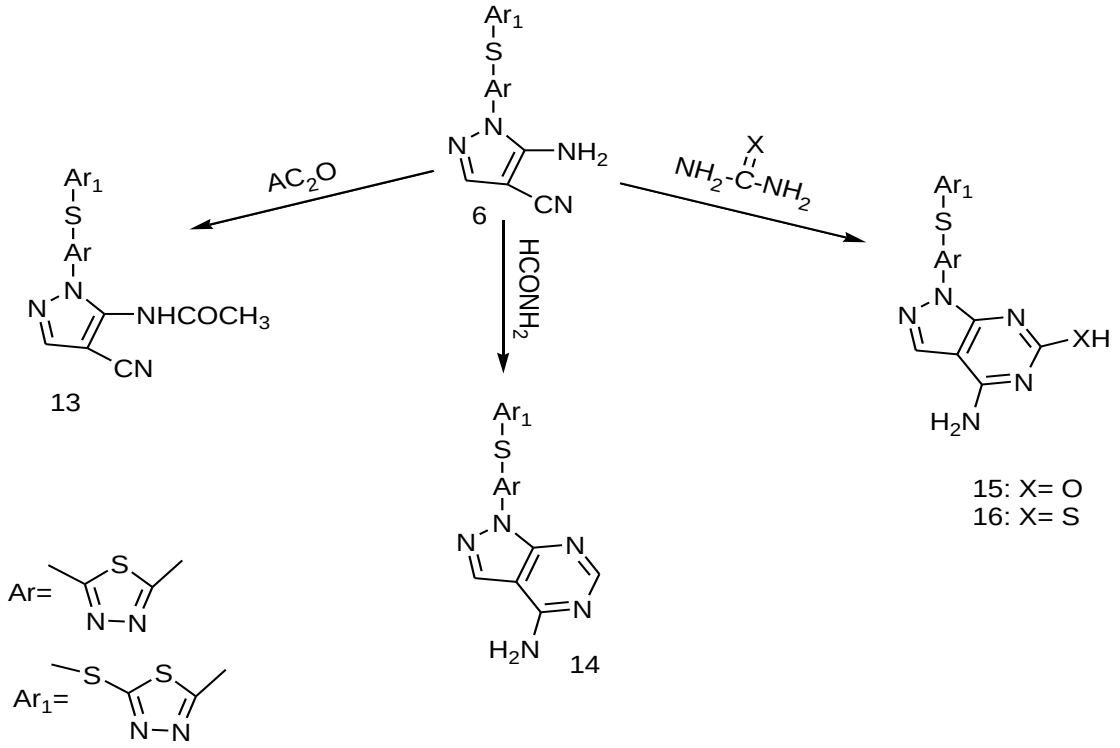
Finally, 1H-NMR spectra of derivatives (15,16) were appeared the following data in ppm: 4(S,4H,2NH2), 5(S,2H OH) and 4(S,4H,2NH2) , 3(S,2H,2SH) respectively.While 13CNMR spectra were given the following signals for (15, 16) : (105,, 133, 145, 163, 174.5), (105,, 133, 145, 168, 187) respectively.



Scheme (1)



Scheme (2)



Scheme (3)

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