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An Efficient and Convenient Synthesis of Certain 2-Thioxothiazole,2-oxo-1,2-dihydropridine, 2-Oxo-2*H*-pyran,2,4-diaminothiophene and Pyrazolo[5,1-c][1,2,4]triazine Derivatives Containing Antipyrine Moiety

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ABSTRACT

2-Thioxothiazole derivatives **5a-c** were prepared by reacting a mixture of **1a-c**, CS_2/KOH and 4-(2-chloroacetyl)-1, 5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one (**3**). Reacting 2-cyano-*N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)acetamide (**5c)** with mercaptoacetic acid, arylidenemalononitriles **8** and (*E*)-3-(dimethylamino)-1-(furan-2-yl)prop-2-en-1-one (**12**) give 4-oxo-4,5-dihydrothiazole **6**, 2-oxo-1,2-dihydropyridine **10** and 2-oxo-2*H*-pyran **15** respectively. Heating a mixture of **5c**, malononitrile and elemental sulfur yield 2,4-diaminothiophene **19**. Coupling of **5c** with the diazotized aminopyrazole **20** and aryldiazonium salts **23** give pyrazolo[5,1-c][1,2,4] triazines **22** and arylhydrazones **25** respectively.

Keywords: Thioxothiazoles; Pyridine; Thiophene; Pyrazolotriazines

1. Introduction

Diverse pharmacological properties have been associated with thiazole derivatives [1-3]. These pharmacological activities have been attracted special attention to prepare a new class of thiazole derivatives carrying antipyrinyl moiety because of their applications in the field of pharmaceuticals [4-6] and antibacterials [7-9]. The present work reports the synthesis of certain thiazole derivatives containing antipyrine moiety using readily available starting materials.

2. Experimental

All melting points are uncorrected and have been measured on a Griffin & George MBF010T (London) apparatus. Recorded yields correspond to the pure products. IR (KBr) spectra were recorded on a Perkin Elmer SP-880 spectrometer and from samples of sufficient solubility. ^{1}H-NMR spectra were measured on a Varian 270 MHz spectrometer on DMSO-d_6 as solvent and TMS as an internal standard. Chemical shifts are reported in δ units (ppm). Microanalyses were performed on a LECO CHN-932 elemental analyzer and carried out in the Microanalytical Data Units at Cairo and Mansoura Universities.

***General procedure for preparation of* 4,4'-(2-*thioxothiazole*-3,4-(2*H*)-*diyl*)*bis*(1,5-*dimethyl*-2-*phenyl*-1*H*-*pyrazol*-3(2*H*)-*one*)(5a),2-(4-*chlorophenoxy*)-*N*-(-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-2-*thioxothiazol*-3(2*H*)-*yl*)*acetamide*(5b) *and* 2-*cyano*-*N*-(4-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-2-*thioxothiazol*-3(2*H*)-*yl*)*acetamide*(5c)**

A solution of 4-amino-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one (**1a**) or 2-(chlorophenoxy)acetohydrazide (**1b**) or 2-cyanoacetohydrazide (**1c**) (0.01 mol) in dimethylformamide (30 mL) containing potassium hydroxide (0.01 mol) and (0.01 mol) of carbon disulfide was stirred at room temperature for 6 h. To this solution (0.01 mol) of 4-(2-chloroacetyl)-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3 (2*H*)-one (**2**) was added, then the solution was stirred again overnight, poured on ice and neutralized with dilute hydrochloric acid. The precipitates formed were collected by filtration and crystallized from ethanol to give **5a-c** respectively.

4,4'-(2-*Thioxothiazole*-3,4-(2*H*)-*diyl*)*bis*(1,5-*dimethyl*

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-2-*phenyl*-1*H*-*pyrazol*-3(2*H*)-*one*)(5a)

Colorless crystals, m.p. 265˚C - 267°C, yield 70%. -IR(γ/cm^{-1}): 1660 (antipyrinyl C=O), 1240(C=S). -^{1}H-NMR (DMSO-d$_6$, δ/ppm): 2.16, 2.21 (2s, 6H, 2CH$_3$), 3.02, 3.35 (2s, 6H, 2N-CH$_3$), 7.07 (s, 1H, thiazole H-5), 7.16 - 7.50 (m, 10H, aryl H). -$C_{25}H_{23}N_5S_2O_2$ (489.62) Calcd. C 61.33, H 4.74, N 14.30. Found C 61.43, H 5.2, N 14.12.

2-(4-*Chlorophenoxy*)-*N*-(-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-2-*thioxothiazol*-3(2*H*)-*yl*) *acetamide*(5b)

Colorless crystals, m.p. 215˚C - 217˚C, yield 70%. -IR(γ/cm^{-1}): 3480 (NH), (C=O), 1660 (antipyrinyl C=O). -^{1}H-NMR(DMSO-d$_6$, δ/ppm): 2.94 (s, 3H, CH$_3$), 3.32 (s, 3H, N-CH$_3$), 4.73 (s, 2H, CH$_2$), 6.91 - 7.79 (m, aryl H), 10.34 (s, 1H, NH). -$C_{22}H_{19}N_4ClS_2O_3$(486.59) Calcd. C 54.31, H 3.94, N 11.50. Found C 54.16, H 4.05, N 11.43.

2-*Cyano*-*N*-(4-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-2-*thioxothiazol*-3(2*H*)-*yl*)*acetamide*(5c) was prepared according to the literature procedure [4].

***Preparation of N*-(4-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-2-*thioxothiazol*-3(2*H*)-2-(4-*oxo*-4,5-*dihydrothiazol*-2-*yl*)*acetamide*(6)**

A solution of 2-cyano-*N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)acetamide (**5c)** (0.01 mol) and mercaptoacetic acid (0.01 mol) in dry pyridine (30 mL) was refluxed for 6 h. The solvent was removed in *vacuo*. The product was collected by filtration, crystallized from ethanol/DMF, to give **6** as brown crystals, no melt ν/300˚C, yield 60%. -IR(γ/cm^{-1}): 3450, 3420 (NH, OH), 1685 (C=O), 1670 (antipyrinyl C=O). -^{1}H-NMR(DMSO-d$_6$, δ/ppm): 2.52 (s, 3H, CH$_3$), 3.11 (s, 3H, N-CH3), 4.77 (s, 2H, CH$_2$), 7.42 - 7.56 (m, 7H, aryl H), 8.9, 10.40 (2s, 2H, 1H, OH and 1H, NH). -$C_{19}H_{17}N_5S_3O_3$ (459.57) Calcd. C 49.66, H 3.73, N 15.24. Found C 49.63, H 4.03, N 14.75.

***Preparation of* (*E*)-3-*aryl*-2-*cyano*-*N*-(4-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-2-*thioxothiazol*-3(2*H*)-*yl*)*acrylamides*(7a, b)**

A solution of 2-cyano-*N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)acetamide (**5c**) (0.01 mol) in ethanol (50 mL) was treated with the appropriate aromatic aldehydes (0.01 mol) and few drops of piperidine. The reaction mixture was refluxed for 2 h and then the solvent was concentrated to its half volume. The solid products were collected by filtration, crystallized from ethanol and identified as (**7a**, **b**).

(*E*)-2-*Cyano*-*N*-(4-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-2-*thioxothiazol*-3-(2*H*)-*yl*)-3-(4-*hydroxyphenyl*) *acrylamide*(7a)

Colorless crystals, m.p. 236˚C - 238˚C, yield 65%. -IR (γ/cm^{-1}): 3450, 3383 (OH, NH), 2212 (conjugated CN), 1670 (amidic C=O), 1658 (antipyrinyl C=O). -$C_{24}H_{19}N_5S_2O_3$ (489.58) Calcd. C 58.88, H 3.91, N 14.3; Found C 59.04, H 3.82, N 14.10.

(*E*) 3-(3-*Chlorophenyl*)-2-*cyano*-*N*-(4-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-2-*thioxothiazol*-3-(2*H*)-*yl*)*acrylamide*(7b)

Pale yellow, m.p. 200˚C - 202˚C, yield 63%. -IR(γ/cm^{-1}): 3560, 3441, 3389 (NH), 2206 (conjugated CN), 1676 (C=O), 1651 (antipyrinyl C=O). -^{1}H-NMR(DMSO-d$_6$, δ/ppm): 2.41 (s, 3H, CH$_3$), 3.27 (s, 3H, N-CH$_3$), 7.41-7.54 (m, 7H, 6H, aryl H + 1H, NH), 8.31 (s, 1H, ylidenic H). -$C_{24}H_{18}ClN_5S_2O_2$ (508.02) Calcd. C 56.74, H 3.57, N 13.79; Found C 56.82, H 3.48, N 13.67.

***Synthesis of* 6-*amino*-4-*aryl*-1-(4-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-2-*thioxothiazol*-3(2*H*)-*yl*-2-*oxo*-1,2-*dihydro pyridine*-3,5-*dicarbonitriles*(10b)**

***Method A*:**

A solution of 2-cyano-*N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)acetamide (**5c**) (0.01 mol) in ethanol (50 mL) containing (0.1 mL) of piperidine, was treated with (0.01 mol) of arylidenemalononitriles **8**. The reaction mixture was refluxed for 3 h, then left to cool. The solid products formed were collected by filtration and crystallized from ethanol to give (**10a**, **b**).

***Method B*:**

6-*Amino*-4-*aryl*-1-(4-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-2-*thioxothiazol*-3(2*H*)-*yl*-2-*oxo*-1,2-*dihydropyridine*-3,5-*dicarbonitriles*(10b) were also prepared by reacting (E)-3-aryl-2-cyano-*N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)acrylamides (**7a**, **b**) with malononitrile in ethanolic-piperidine.

6-*Amino*-1-(4-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-2-*thioxothiazol*-3(2*H*)-*yl*-4-(4-*hydroxy phenyl*)-2-*oxo*-1,2-*dihydropyridine*-3,5-*dicarbonitrile*(10a)

Faint brown crystals, m.p. 254˚C - 256˚C, yield 63%. -IR(γ/cm^{-1}): 3500, 3380(OH, NH$_2$), 2223(conjugated CN), 1700 (C=O), 1652 (antipyrinyl C=O). -$C_{27}H_{19}N_7S_2O_3$ (553.62) Calcd. C 58.58, H 3.46, N 17.78; Found C 58.64, H 3.38, N 18.03.

6-*Amino*-4-(3-*chlorophenyl*)-1-(4-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-2-*thioxothiazol*-3(2*H*)-*yl*)-2-*oxo*-1,2-*dihydropyridine*-3,5-*dicarbonitrile* (10b)

Brown cryctals, m.p. 230˚C - 232˚C, yield 60%. –IR (γ/cm^{-1}): 3448, 3387 (NH$_2$), 2206 (conjugated CN), 1740 (C=O), 1672 (C=O antipyrinyl). -^{1}H-NMR (DMSO-d$_6$, δ/ppm): 2.34 (s, 3H, CH$_3$), 3.30 (s, 3H, N-CH$_3$), 7.11 - 7.74 (m, 10Haryl H), 8.10 (s, 2H, NH$_2$).
-$C_{27}H_{18}ClN_7S_2O_2$ (572.06) Calcd. C 56.69, H 3.17, N 17.17; Found C 56.83, H 3.34, N 17.32.

***N*-(4-(1,5-*Dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-2-*thioxothiazol*-3(2*H*)-*yl*)-6-(*furan*-2-*yl*)-2-*oxo*-2*H*-*pyran*-3-*carboxamide*(15)**

A solution of 2-cyano-*N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)acetamide (**5c**) (0.01 mol) and (0.01 mol) of (*E*)-3-(dimethylamino)-1-(furan-2-yl)prop-2-en-1-one (**12**) in ethanol (50 mL) was treated with acetic acid (1 mL) was refluxed for 3 h and then left to cool. The solid formed was collected by filtration and crystallized from ethanol to give **15** as faint brown crystals, m.p. 170˚C - 172˚C, yield 60%. -IR(γ/cm^{-1}): 3450 (NH), 1743 (C=O amidic), 1652 (antipyrinyl C=O). -^{1}H-NMR(DMSO-d$_6$, δ/ppm): 2.35 (s, 3H, CH_3), 3.33 (s, 3H, N-CH_3), 6.70 (s, 1H, thiazoleH-5), 6.90 (d, J = 8 Hz, 1H, pyroneH-5), 7.21 - 8.0 (m, 8H, aryl H), 8.20 (d, J = 8 Hz, 1*H*, pyroneH-4), 9.6 (s, 1H, NH). -$C_{24}H_{18}N_4S_2O_5$ (505.55) Calcd. C 56.91, H 3.58, N 11.06; Found C 57.01, H 3.48, N 11.35.

***Preparation of* 2,4-*diamino*-5-*cyano*-*N*-(4-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-2-*thioxothiazol*-3(2*H*)-*yl*)*thiophene*-3-*carboxamide*(19)**

A solution of 2-cyano-*N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)acetamide (**5c)** (0.01 mol) and (0.01 mol) of malononitrile and elemental sulfur (0.01 mol) in ethanol (50 mL) containing (0.1 mL) of triethylamine was refluxed for 2 h and then left to cool to room temperature. The precipitate formed was collected by filtration, crystallized from ethanol to give **19** as faint brown crystals, m.p. 220˚C - 222˚C, yield 65%. -IR(γ/cm^{-1}): 3527, 3380 (NH_2), 2223 (conjugated CN), 1702 (C=O amidic),1654 (antipyrinyl C=O). -^{1}H-NMR (DMSO-d$_6$, δ/ppm): 2.29 (s, 3H, CH_3), 3.03 (s, 3H, N-CH_3), 7.22 - 7.782 (m, 10H, 5H, arylH, 5H, 2NH_2 + 1H, NH). -$C_{20}H_{17}N_7S_3O_2$ (483.59) Calcd. C 49.67, H 3.54, N 20.27; Found C 49.75, H 3.63, N 20.35.

***Genaral method for synthesis of* 4-*amino*-*N*-(4-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-2-*thioxothiazol*-3(2*H*)-*yl*)-7-*substituted pyrazolo*[5,1-*c*][1,2,4]*trazine*-3-*carboxamides* (22*a,b*) *and* 2-(*arylhydrazono*)-*N*-(4-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihyd o*-1*H*-*pyrazol*-4-*yl*)-2-*thioxothiazol*-3(2*H*)-*yl*)-2-(4-*oxo*-4,5-*dihydrothiazol*-*yl*)*acetamides*(24a-c)**

To a cold solution of 2-cyano-*N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothia zol-3(2*H*)-yl)acetamide (**5c**) (0.01 mol) in water-ethanol mixture (1:1) containing saturated solution of sodium acetate (10 mL), the diazotized 4-(5-amino-1H-pyrazol-3-yl)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one (**20**) (prepared from 4-(5-amino-1H-pyrazol-3-yl)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one hydrochloride (0.01 mol) and (0.01 mol) of sodium nitrite) or the aryldiazonium salts **23** (prepared from primary aromatic amine hydrochloride) (0.01 mol) and the equivalent amount of sodium nitrite was added dropwise with stirring. The reaction mixture was left in the refrigerator overnight. The resulting solids were collected by filtration and crystallized from the proper solvents to give (**22a**, **b**) and (**24a-c**) repectively.

4-*Amino*-7-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-*N*-(4-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-2-*thioxothiazol*-3(2*H*)-*yl*)*pyrazolo*[5,1-*c*][1,2,4]*triazine*-3-*carboxamide*(22a)

Brown crystals, from ethanol/DMF, m.p. 220˚C - 222˚C, yield 75%. -IR(γ/cm^{-1}): 3500 - 3370 (NH_2, NH), 1705 (amidic C=O), 1670 (antipyrinyl C=O). -$C_{31}H_{27}N_{11}S_2O_3$ (665.75) Calcd. C 55. 93, H 4.09.46, N 23.14; Found C 56.03, H 4.11, N 23.34.

4-*Amino*-*N*-(4-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-2-*thioxothiazol*-3(2*H*)-*yl*)-7-*phenylpyrazolo*[5,1-*c*][1,2,4]*trazine*-3-*carboxamide*(22b)

Brown crystals, from ethanol, m.p. 180˚C - 182˚C, yield 80%. -IR(γ/cm^{-1}): 3507 - 3385 (NH_2, NH), 1703 (C=O amidic), 1675 (antipyrinyl C=O). -^{1}H-NMR (DMSO-d$_6$, δ/ppm): 2.33 (s, 3H, CH_3), 3.30 (s, 3H, N-CH_3), 6.2 (s, 1H, pyrazoleH-4), 6.65 (s, 1H, thiazole H-5), 7.31 - 7.90 (m, 12H, 10H, aryl H + 2H, NH_2). -$C_{26}H_{21}N_9S_2O_2$ (555.64) Calcd. C 56.20, H 3. 81, N 22.69; Found C 56.42, H 3.61, N 22.41.

2-(4-(1,5-*Dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-2-*thioxothiazol*-3(2*H*)-*ylamino*)-2-*oxo*-*N*$^-$-*p*-*tolylacetohydrazonoyl cyanide*(24a)

Red crystals, from ethanol, m.p.160˚C - 162˚C, yield 75%. -IR(γ/cm^{-1}): 3455 (NH), 2210 (conjugated CN), 1700 (C=O amidic), 1660 (antipyrinyl C=O), 1630 (C=N), 1590 (N=N). -^{1}H-NMR (DMSO-d$_6$, δ/ppm) :2.33 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 3.32(s, 3H, N-CH_3) 6.65 (s, 1H, thiazole H-5), 7.14 - 7.56 (m, 10H, aryl H), 9.25, 10.17 (2S, 2H, 2NH). -$C_{24}H_{21}N_7S_2O_2$ (503.61) Calcd. C 57. 24, H 4. 20, N 19.47; Found C 57.28, H 4.34, N 19.56.

***N*$^-$-(4-*Chlorophenyl*)-2-(4-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-2-*thioxothiazol*-3(2*H*)-*ylamino*)-2-*oxoacetohydra-zonoyl cyanide*(24b)**

Reddish brown crystals, from ethanol, m.p. 180˚C - 182˚C, yield 75%. -IR(γ/cm^{-1}): 3449 (NH), 2214 (conjugated CN), 1741 (C=O amidic), 1677, m.p. 170˚C - 172˚C, yield 60%. -IR(γ/cm^{-1}): 3450 (NH), 1743 (C=O amidic), 1652 (antipyrinyl C=O). -^{1}H-NMR(DMSO-d$_6$, δ/ppm): 2.35 (s, 3H, CH_3), 3.33 (s, 3H, N-CH_3), 6.70 (s, 1H, thiazoleH-5), 6.90 (d, J = 8 Hz, 1H, pyroneH-5), 7.21 - 8.0 (m,8H, aryl H), 8.20(d, J = 8 Hz, 1*H*, pyroneH-4), 9.6 (s, 1H, NH). -$C_{24}H_{18}N_4S_2O_5$ (505.55) Calcd. C 56. 91, H 3.58, N 11.06; Found C 57.01, H 3.48, N 11.35.

***N*$^-$-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-2-(4-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-2-*thioxothiazol*-3(2*H*)-*ylamino*)-2-*oxoacetohydrazonoyl cyanide*(24c)**

Brown crystals, from ethanol, m.p. 175˚C - 1177˚C, yield 65%. -IR(γ/cm^{-1}): 3500 (NH), 2210 (conjugated CN), 1700 (C=O amidic), 1665 (antipyrinyl C=O), 1630 (C=N), 1600 (N=N). -$C_{28}H_{25}N_9S_2O_2$ (599.69) Calcd.C 56.08, H 4.20, N 21.02; Found C 56.13, H 4.34, N 21.33.

***Preparation of N-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-thioxothiazol-3(2H)-yl)-2-(4-oxo-4,5-dihydrothiazol-2-yl)-2-(2-p-tolylhydrazono)acetamide*(25)**

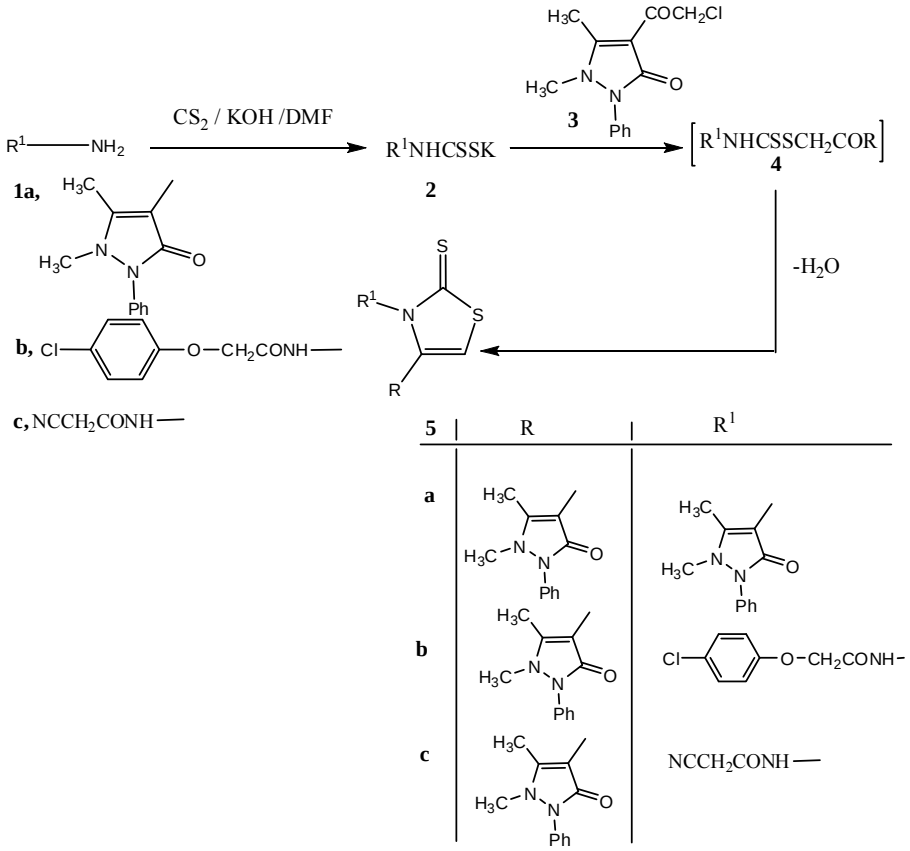
A solution of 2-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-ylamino) -2-oxo-*N*¯-*p*-tolylacetohydrazonoyl cyanide (**24a**) (0.01 mol) and (0.01 mol) of mercatoacetic acid in dry pyridine (30 mL) was refluxed for 6 h. The solvent evaporated under reduced pressure, then triturated with ethanol. The solid product was collected by filtration, crystallized from ethanol/1,4-dioxan,to give **25**. The same product also prepared by reacting *N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)-2-(4-oxo-4,5-dihydrothiazol-2-yl)acetamide (**6**) with aryl diazonium salt (**23a**).

Dark brown crystals, m.p. 245˚C - 247˚C, yield 60%. -IR(γ/cm^{-1}): 3450 (NH), 1705 (C=O amidic), 1665 (antipyrinyl C=O), 1630 (C=N), 1600 (N=N). -$C_{26}H_{23}N_7S_3O_2$ (577.71) Calcd. C 54.06, H 4.01, N 16.97; Found C 54.13, H 4.23, N 17.04.

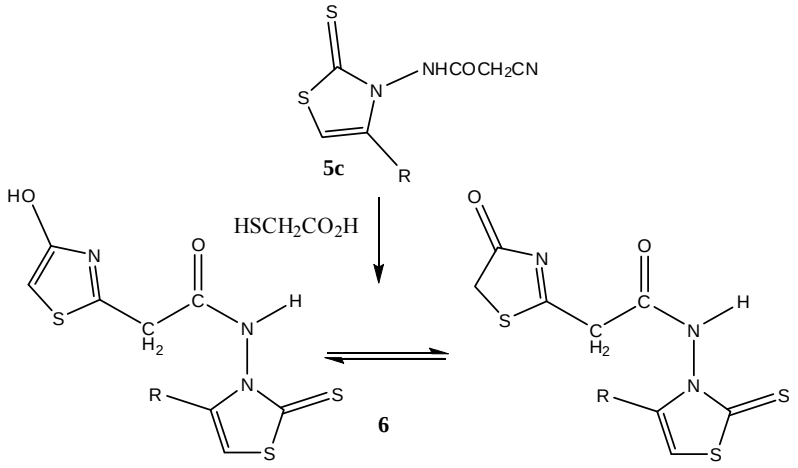
3. Results and Discussion

It has been found that, treatment of 4-amino-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one (**1a**) or 2-(chlorophenoxy) acetohydrazide (**1b**) or 2-cyanoacetohydrazide (**1c**) with carbon disulfide in dimethylformamide containing equivalent amount of potassium hydroxide give the non-isolable potassium salts **2a-c**. The latter were alkylated with 4-(2-chloroacetyl)-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one (**2**) to yield products with water elimination. 2-Thioxothiazole structures **5a-c** were assigned as reaction products based on their analytical and spectral data. The 2-thioxothiazole derivatives **5a-c** were presumably formed through the intermediacy of **4** (*cf*. **Scheme 1**).

The chemical reactivity of 2-cyano-*N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)acetamide (**5c**) [4] towards different reagents was studied. Thus, compound **5c** reacted with mercaptoacetic acid in dry pyridine to afford *N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)-2-(4-oxo-4,5-dihydrothiazol-2-yl)acetamide (**6**). IR specrum of **6** indicates the absence of signal due to cyano group. ^{1}H-NMR spectrum of **6** exhibits two signlets at δ = 8.9, 10.4 ppm for OH and NH in addition to aromatic protons. Thus, the *N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)-2-(4-oxo-4,5-dihydrothiazol-2-yl) acetamide structure **6** was established as reaction product (*cf*. **Scheme 2**).



Scheme 1. Formation of 2-thioxothiazoles 5.



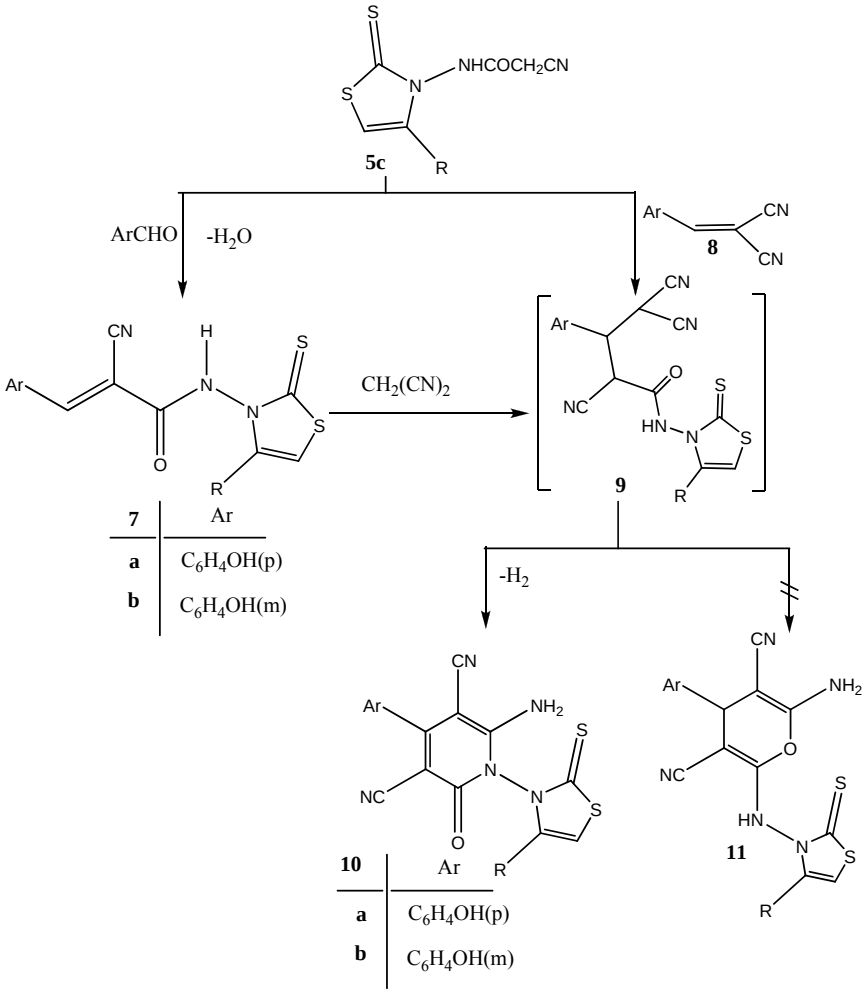
Scheme 2. Formation of 2-(4-oxo-4,5-dihydrothiazol-2-yl)acetamide 6.

Condensation of 2-cyano-*N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)acetamide (**5c**) with aromatic aldehydes in ethanol and in presence of piperidine as catalyst to afford (*E*)-3-aryl-2-cyano-*N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)acrylamides (**7a**, **b**).

Refluxing of 2-cyano-*N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)acetamide (**5c**) with the arylidenemalononitriles **8** in ethanol containing catalytic amount of piperidine resulted in the formation of the 6-amino-4-aryl-1-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles (**10a**, **b**) or 2-amino-4-aryl-6-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl-2-thioxothiazol-3(2*H*)-ylamino)-4H-pyran-3,5-dicarbonitriles (**11a**, **b**). The pyridine structures **10a**, **b** were suggested as reaction products based on their elemental analysis and spectral data. If the reaction products were 2-amino-4-aryl-6-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl-2-thioxothiazol-3(2*H*)-ylamino)-4*H*-pyran-3,5-dicarbonitriles (**11a**, **b**), one would expect 4*H*-pyran signals at δ = 4.5 - 5.0 ppm. In addition, 6-amino-4-aryl-1-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles(**10a**, **b**) were also prepared *via* reacting (*E*)-3-aryl-2-cyano-*N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)acrylamides (**7a**, **b**) with malononitrile in ethanolic-piperidine. 6-Amino-4-aryl-1-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles (**10a**, **b**) were proposed to be formed through Michael type addition of the active methylene group in the 2-cyano-*N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)acetamide (**5c**) to the pideficient center in (*E*)-3-aryl-2-cyano-*N*-(4-(1,5-dime-thyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl) acrylamides (**7a**, **b**) to give Michael adduct **9** which cyclized and readily eliminate one molecule of hydrogen to yield 6-amino-4-aryl-1-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxthiazol-3(2*H*)-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles (**10a**, **b**) (*cf*. **Scheme 3**).

The reactivity of 2-cyano-*N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)acetamide (**5c)** towards enaminones were also studied. Thus, 2-cyano-*N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)acetamide (**5c)** was reacted with (*E*)-3-(dimethylamino)-1-(furan-2-yl)prop-2-en-1-one (**12**) in ethanol catalysed by aceticacid to afford *N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-6-(furan-2-yl)-2-oxo-2*H*-pyran-3-carboxamide (**15**) or 1-(4-(1,5-dihydro-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3-(2*H*)-6-(furan-2-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (**16**). Structure **15** was preferred over possible **16** by IR specrum which clearly indicates the presence of cyano group. Compound **15** was assumed to be obtained by first addition of the active methylene group in **5c** to the activated double bond to give the adduct **13** which readily eliminate dimethylamine to give the intermediate **14**. The latter cyclized to **15**.

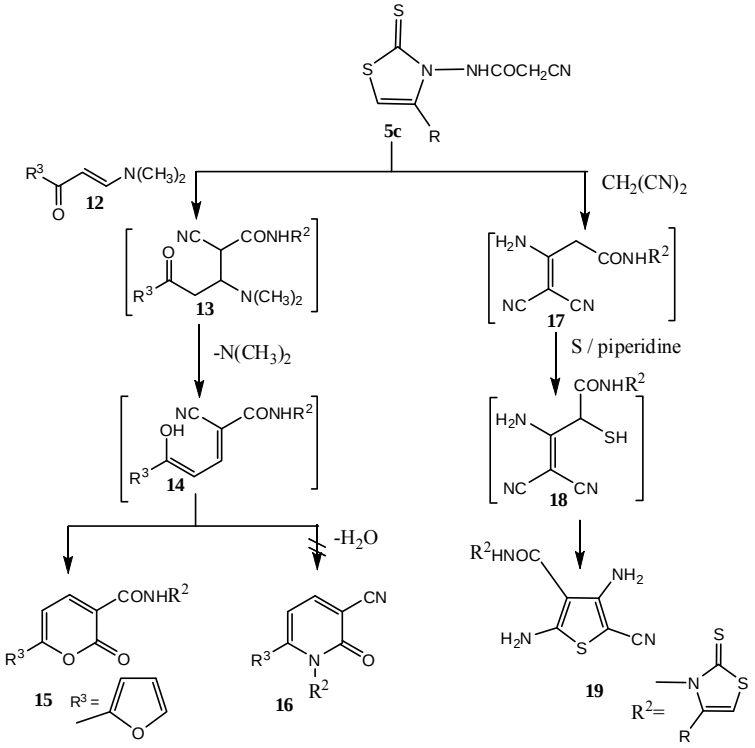
On the other hand, compound 2-cyano-*N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl) acetamide **5c** was reacted with a mixture of reacted with a mixture of malononitrile and elemental sulfur to afford 2,4-diamino-5-cyano-*N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3-(2*H*)-yl)thiophene-3-carboxamide (**19**) Compound **19** is proposed to be formed by adding the active methylene group in malononitrile to the cyano



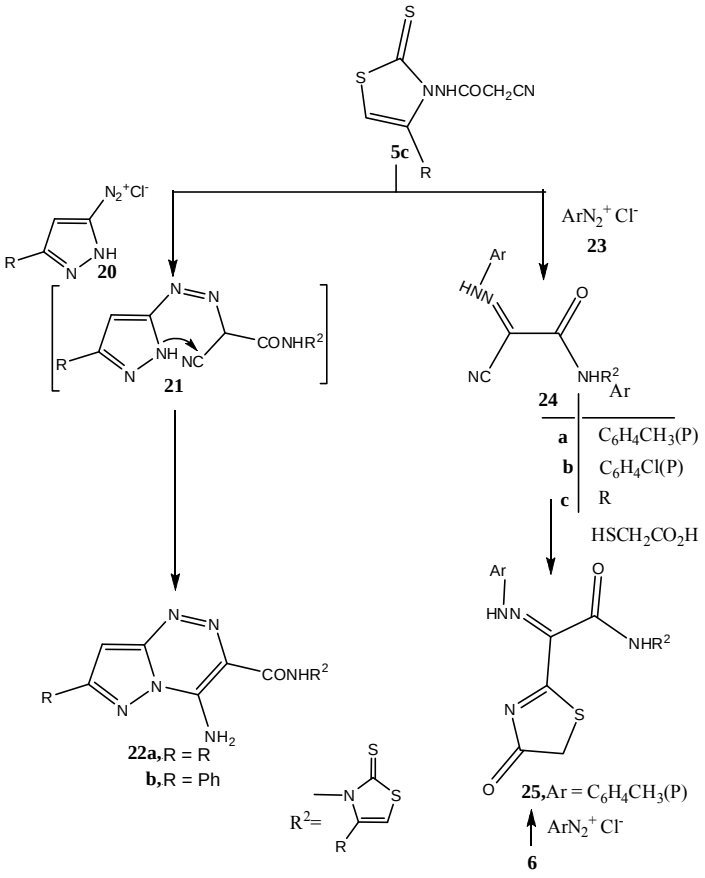
Scheme 3. Reaction of 2-thioxothiazole 5c with arylidenemalononitriles.

group in 2-cyano-*N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2, 3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl) acetamide **5c** to give the intermediate **17**, which reacted with elemental sulfur and then cyclized to yield **19** (*cf*. **Scheme 4**).

In recent puplications , it has been reported that [5,10], diazotized aminopyrazoles or arene diazonium salts were used as starting materials for synthesis of pyrazolotriazines [5,10]. In the present work, diazotized 4-(5-amino-1*H*-pyrazol-3-yl)-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one (**20**) [11,12] coupled with the thiazole 2-cyano-*N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)acetamide (**5c**) in aqueous ethanolic-sodium acetate to afford 4-amino-7-(1, 5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl) -*N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl) pyrazolo[5,1-c][1,2,4] triazine-3-carboxamide (**22a**) and 4-amino-*N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)-7-phenyl pyrazolo [5,1-c][1,2,4] trazine-3-carboxamide (**22b**). IR spectra of **22a**, **b** showed no signals attributable to cyano group. 4-Amino-7-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-*N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl) pyrazolo[5,1-c][1,2,4] triazine-3-carboxamide (**22a**) and 4-amino-*N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)-7-phenyl pyrazolo [5,1-c] [1,2,4]trazine-3-carboxamide (**22b**) were suggested to be formed *via* reacting the diazonium salt **20** with the active methylene group in 2-cyano-*N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3 (2*H*)-yl)acetamide (**5c)** to give the intermediates **21** which cyclized *via* addition of highly nucleophilic pyrazole NH to the cyano group to affod 4-Amino-7-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-*N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)pyrazolo[5,1-c][1,2,4] triazine-3-carboxamide (**22a**) and 4-amino-*N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)-7-phenyl pyrazolo [5,1-c][1,2, 4]trazine-3-carboxamide (**22b**) respectively. Coupling of



Scheme 4. Formation of 2-oxo-3*H*-pyran 15 and 2,4-diaminothiophne 19.



Scheme 5. Formation of pyrazolotriazines 22a, b; arylhydrazones 24 and 25.

2-cyano-*N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)acetamide (**5c)** with aryl diazonium salts **23** yield 2-(arylhydrazono)-*N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)-2-(4-oxo-4,5-dihydrothiazol-2-yl)acetamides (**24a-c**).

2-(4-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-ylamino)-2-oxo-*N*¯*p*-tolylacetohydrazonoyl cyanide (**24a**) reacted with mercaptoaceticacid to give *N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)-2-(4-oxo-4,5-dihydrothiazol-2-yl)-2-(2-*p*-tolylhydrazono) acetamide (**25**). The same product was prepared from reaction of *N*-(4-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-2-thioxothiazol-3(2*H*)-yl)-2-(4-oxo-4,5-dihydrothiazol-2-yl)acetamide (**6**) with *p*-tolyldiazonium chloride (*cf*. **Scheme 5**).

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