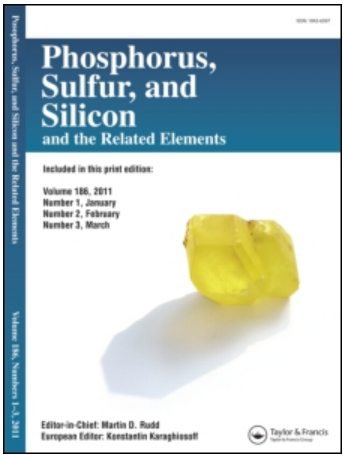

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Synthesis of Some Novel Sulfonamide Derivatives

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Synthesis of Some Novel Sulfonamide Derivatives

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*Sulfapyridine (**1**) was selected as the starting material for the synthesis of some novel thiazolidine, thiosemicarbazide, and quinazoline derivatives. The structures of synthesized compounds were elucidated by elemental analyses and spectral data.*

Keywords Quinazoline and sulfonamide derivatives; thiazolidine

INTRODUCTION

Substituted thiazolidines have been demonstrated to possess antibacterial,[1] antifungal,[2] anticonvulsant,[3] anticancer,[4] and antituberculosis[5] activities. Also, thiazolidines have been reported as novel inhibitors of the bacterial enzyme Mur B, which was the precursor acting during the biosynthesis of peptidoglycan.[6] Furthermore, antibacterial,[7] antifungal,[8] insulin releasing,[9] carbonic anhydrase inhibitory,[10] antiinflammatory,[11] and antitumor[12] properties of sulfamoyl moiety were described. As a continuation of our research program[13–15] on the synthesis of heterocyclic compounds, in this article we report the synthesis of some novel thiazolidine and quinazoline derivatives containing sulfamoyl moiety from the readily available sulfapyridine **(1)**.

RESULTS AND DISCUSSION

The non-isolable intermediate **2** was prepared by treatment of sulfapyridine **(1)** with carbon disulfide in dimethylformamide in the presence of potassium hydroxide at room temperature (Scheme 1). The non-isolable intermediate **2** was selected as starting material

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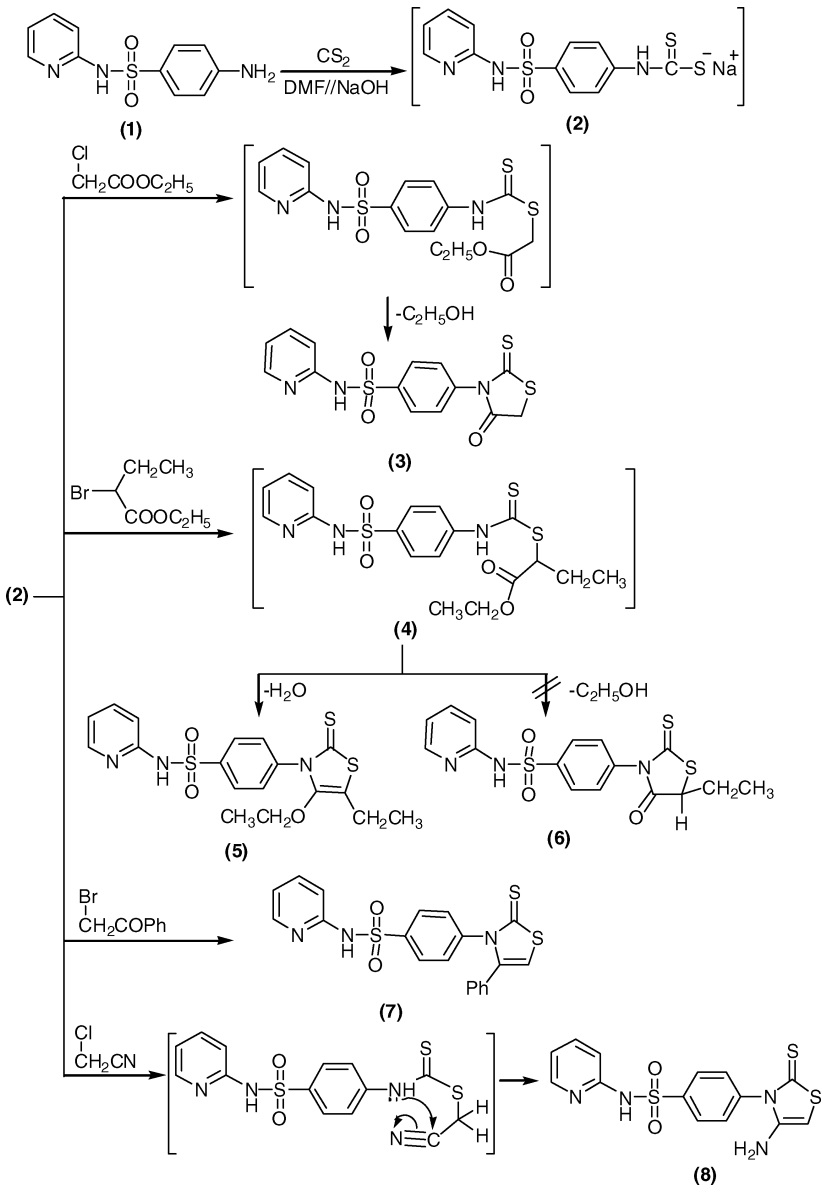
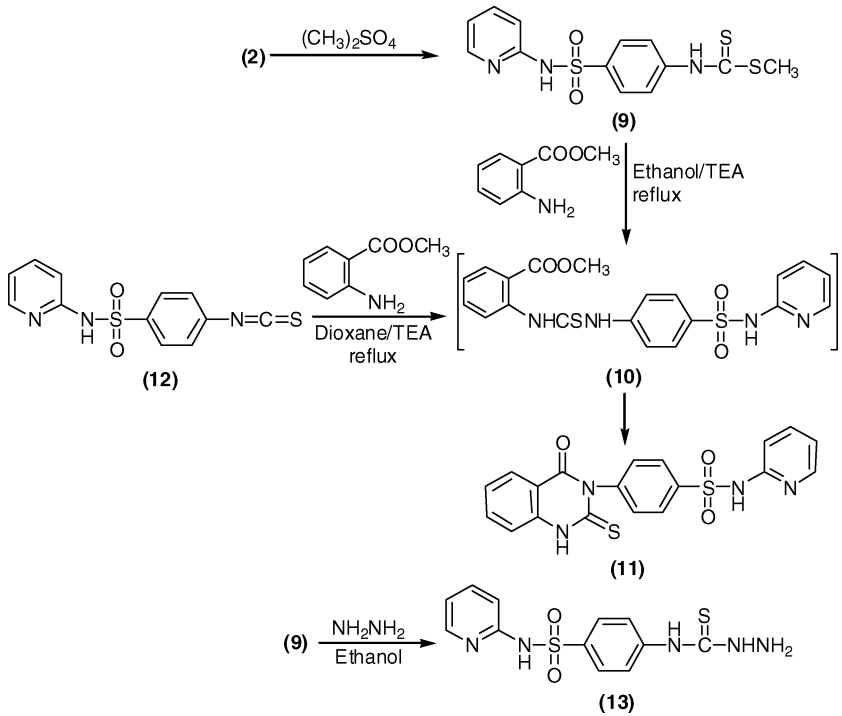


SCHEME 1

for the synthesis of some novel thiazolidine and quinazoline derivatives. Thus, the reaction of the non-isolable intermediate **2** with some halo compounds was investigated. The cycloconden-sation of the non-isolable intermediate **2** with ethyl chloroacetate at room temperature

afforded 4-thiazolidinone derivative **3** (Scheme 1). The structure of 4-thiazolidinone **3** was confirmed by elemental and spectral data. Its infrared spectrum showed characteristic absorption bands for NH, CH-arom., C=O, C=N, and SO_2 functional groups. Also, its ^{1}HNMR (DMSO-d_6) displayed a signal at $\delta = 4.20$ ppm assigned to CH_2 in addition to NH and aromatic protons. The formation of **3** is assumed to proceed via the initial alkylation by loss of sodium chloride followed by intramolecular cyclization through ethanol elimination. Treatment of the non-isolated intermediate **2** with α-bromobutyrate furnished thiazolidine derivatives **5** and structure **6** was ruled out on the basis of analytical and spectral data. The infrared spectrum of **5** exhibited absorption band at 3210 cm^{-1} due to NH group and 1634 cm^{-1} due to the C=N group. The ^{1}HNMR of (**5**; DMSO-d_6) revealed two ethyl groups in addition to NH and aromatic protons. The formation of **5** is assumed to proceed via the initial formation of intermediate **4** followed by elimination of water (Scheme 1). The non-isolable intermediate **2** was reacted with phenacyl bromide to yield the thiazolidine derivative **7** on the basis of analytical and spectral data. Its infrared spectrum showed absorption band at 3200 cm^{-1} due to NH and no absorption band between 1600–1680 cm^{-1} due to the absence of C=O group. The ^{1}HNMR spectrum of (**7**; DMSO-d_6) displayed the absence of methylene moiety, in addition to the presence of thiazolidine-H, NH, and aromatic protons. The reaction involves an initial alkylation by loss of sodium chloride followed by dehydration. Cyclization of the non-isolable intermediate **2** with the appropriate chloroacetonitrile produced 4-aminothiazolidine derivative **8**. The structure of thiazolidine **8** was elucidated by elemental analysis and spectral data. Its infrared spectrum showed absorption bands at 3450, 3410 cm^{-1} due to NH_2 group, and no absorption band was observed in the spectrum characteristic for C≡N group. The formation of **8** is assumed to proceed via initial alkylation followed by nucleophilic addition of secondary amino group to the cyano group and tautomerization (Scheme 1).

Alkylation of the non-isolable intermediate **2** with dimethyl sulfate afforded [4-(pyridin-2-ylsulfamoyl)-phenyl]-dithiocarbamic acid methyl ester **(9)** (Scheme 2). The structure of **9** was established on the basis of its elemental analysis and spectral data. The ^{1}HNMR spectrum of (**9**; DMSO-d_6) revealed a singlet at $\delta = 2.94$ ppm assigned to SCH_3 in addition to NH and aromatic protons. Reaction of compound **9** with methyl anthranilate in ethanol in the presence of triethylamine under reflux gave quinazoline derivative **11**. The structure of **11** was confirmed on the basis of elemental analysis, spectral data and alternative synthesis. Its infrared spectrum showed absorption band at 3222 cm^{-1} due to NH group in addition to the presence of C=O (quinazolinone) at 1662 cm^{-1}.



SCHEME 2

Also, its ^{1}H NMR spectrum (DMSO-d_6) revealed the absence of SCH_3 in addition to the presence of NH and aromatic protons. The formation of **11** is assumed to proceed via the initial formation of the intermediate **10** by loss of methyl mercaptan followed by intramolecular cyclization through methanol elimination. Also, quinazoline derivative **11** was obtained via another synthetic route by cyclization of anthranilate with isothiocyanate derivative **12**[16] in dioxane under reflux in the presence of triethylamine. The novel thiosemicarbazide derivative **13** was achieved by treatment of compound **9** with hydrazine hydrate in ethanol at room temperature. Mass spectrum of **13** revealed a molecular ion peak at m/z = 323 (4.5%), and the base peak was found in the spectrum at m/z = 55.

The reaction of sulfapyridine **(1)** with chloroacetyl chloride in acetone containing 10% caustic soda at room temperature afforded the starting material N^4-chloroacetylsulfanilamide derivative **14**[17] (Scheme 2). Refluxing of compound **14** with potassium thiocyanate in dimethylformamide furnished the novel 4-thiazolidinone derivative **16** in high

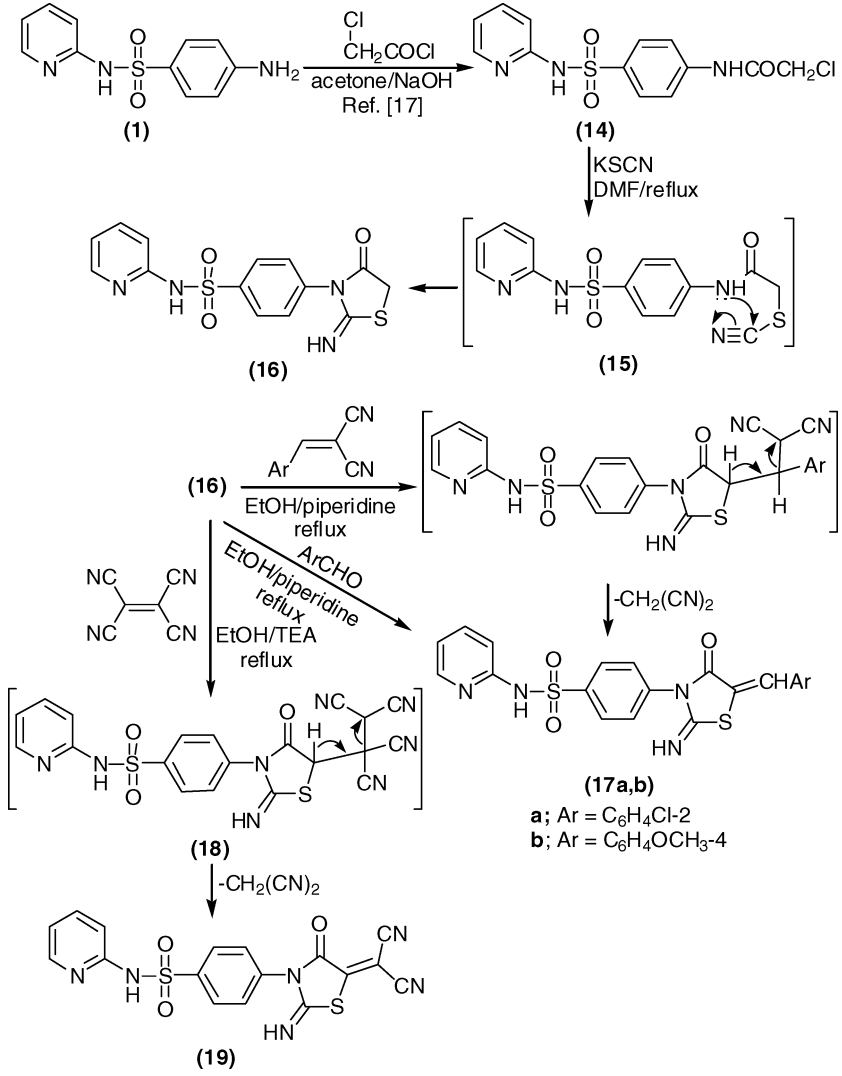
yield. The structure of **16** was established on the basis of analytical and spectral data. Its infrared spectrum revealed the absence of thiocyanate functional group in addition to the presence of NH and C=O functional groups. Also, mass spectrum showed a molecular ion peak at m/z = 283 [M-64 (SO_2); 100%], which is the base peak in the spectrum. The formation of **16** is assumed to proceed via the formation of intermediate **15** followed by intramolecular cyclization of amino group to the thiocyanate group (Scheme 2). The reactivity of 4-thiazolidinone **16** towards some electrophilic reagents was studied. Condensation of compo-und **16** with benzylidene-malononitriles (1:1 molar ratio) in ethanol in the presence of piperidine under reflux yielded the novel 4-thiazolidinone derivatives **17a**,**b**. The structures of compounds **17a**,**b** were confirmed on the basis of their elemental analysis, spectral data and alternative synthesis. Infrared spectra of compounds **17a**,**b** showed the absence of absorption band for the cyano group. Mass spectrum of compound **17a** displayed a molecular ion peak at m/z 410 [M-59 (HSCN); 2.71%], and the base peak was observed in the spectrum at m/z 405. The formation of **17** is assumed to proceed via Michael addition of the active methylene functional group to the activated ethylenic bond followed by the elimination of malononitrile[18] to yield **17**. Also, 4-thiazolidinone derivatives **17a**,**b** were achieved by treatment of thiazolidine **16** with aromatic aldehyde in refluxing ethanol in the presence of piperidine. In a similar manner, condensation of **16** with tetracyanoethylene under reflux in ethanol in the presence of triethylamine afforded the corresponding cyanomethylene derivative **19**. The structure of **19** was established on the basis of analytical and spectral data. Its infrared spectra showed the presence of cyano and NH functional groups. The formation of **19** is assumed to proceed via the formation of intermediate **18** followed by elimination of malononitrile[18] to give **19** (Scheme 3).

CONCLUSION

The non-isolable intermediate **2** was used as starting material for the synthesis of some novel thiazole derivatives **3**,**5**,**7**, and **8** through its reaction, with α-halo compounds. Dithiocarbamic acid **9** was converted into the quinazoline derivative **11** by treatment with methyl anthranilate. The reaction of 4-thiazolidinone **16** with some electrophilic reagents was investigated.

EXPERIMENTAL

All melting points are uncorrected. IR spectra (KBr) were measured on Shimadzu 440 spectrometer, ^{1}H-NMR spectra were determined in



SCHEME 3

DMSO-d_6 on a Varian Gemini 200 MHz spectrometer using TMS as internal standard. Chemical shifts are expressed as δ ppm units. Mass spectra were obtained on GCMS 1000 Ex mass spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University. The characteristics data for prepared compounds are given in Table 1.

TABLE I Characteristic Data for the Synthesized Compounds

Compd. no.	Yield (%)	Solvent cryst.	M.p. (°C)	Mol. formula (mol. wt.)	Elemental analyses calcd./found %			
					C%	H%	N%	S%
3	78	Acetic acid	145–46	$C_{14}H_{11}N_3O_3S_3$	46.01	3.03	11.50	26.32
				(365.45)	46.00	3.00	11.40	26.20
5	67	Dioxane	154-56	$C_{18}H_{19}N_3O_3S_3$	51.28	4.54	9.97	22.82
				(421.56)	51.00	4.50	9.90	22.80
7	65	Acetic acid	160–62	$C_{20}H_{15}N_3O_2S_3$	56.45	3.55	9.87	22.61
				(425.55)	56.30	3.50	9.70	22.50
8	60	Ethanol	170–72	$C_{14}H_{12}N_4O_2S_3$	46.14	3.32	15.37	26.39
				(364.47)	46.00	3.20	15.30	26.30
9	64	Dioxane	140–41	$C_{13}H_{13}N_3O_2S_3$	46.00	3.86	12.38	28.34
				(339.46)	45.90	3.90	12.30	28.30
11	55	DMF	285–87	$C_{19}H_{14}N_4O_3S_2$	55.60	3.44	13.65	15.62
				(410.47)	55.50	3.40	13.50	15.50
13	57	Dioxane	195–97	$C_{12}H_{13}N_5O_2S_2$	44.57	4.05	21.66	19.83
				(323.39)	44.50	4.10	21.60	19.80
16	63	Dioxane	240–42	$C_{14}H_{12}N_4O_3S_2$	48.26	3.47	16.08	18.41
				(348.40)	48.20	3.40	16.00	18.30
17a	70	Acetic Acid	290–92	$C_{21}H_{15}ClN_4O_3S_2$	53.56	3.21	11.90	13.62
				(470.95)	53.50	3.10	11.80	13.50
17b	72	Acetic Acid	>300	$C_{22}H_{18}N_4O_4S_2$	56.64	3.89	12.01	13.75
				(466.53)	56.60	3.70	11.90	13.70
19	52	Dioxane	150—51	$C_{17}H_{10}N_6O_3S_2$	49.75	2.46	20.48	15.63
				(410.43)	49.70	2.40	20.40	15.50

DMF = dimethylformamide.

Reaction of 1 with Ethyl Chloroacetate, α-Bromobutyrate, Phenacyl Bromide or Chloroacetonitrile Formation of Compounds 4-(4-Oxo-2-thioxo-thiazolidin-3-yl)-N-pyri-din-2-yl-benzenesulfonamide (3), 4-(4-Ethoxy-5-ethyl-2-thioxo-thiazol-3-yl)-N-pyridin-2-ylbenzenesulfonamide (5), 4-(4-Phenyl-2-thioxo-thia-zol-3-yl)-N-pyridin-2-yl-benzenesulfonamide (7) and 4-(4-Amino-2-thioxo-thiazol-3-yl)-N-pyridin-2-yl-benzenesulfonamide (8) (General Procedure)

To a suspension of finely powdered sodium hydroxide (0.04 g, 0.01 mol) in dry dimethylformamide (10 ml) at 0°C, the carbon disulfide (0.76 g, 0.01 mol) and sulfapyridine **(1)** (2.49 g, 0.01 mole) were added in portions. The reaction mixture was stirred at room temperature for 3 h and then treated with α-halo compound (0.01 mol) and left at room temperature for 24 h; then, it was poured into ice/water and acidified with 0.1 N HCl at pH 3–4. The resulting precipitate was filtered off,

TABLE II Spectral Data of the Synthesized Compounds.

Compd. no.	IR/ν_{max} (cm^{-1})	^1H NMR (DMSO-d_6) (δ / ppm)
3	3210 (NH), 2932 (CH-aliph), 1634 (C═N), 1366, 1140 (SO_2)	4.20 (s, 2H, CH_2), 6.85–8.02 (m, 8H, Ar─H), and 10.3 (s, 1H, NH)
5	3210 (NH), 2932 (CH-aliph), 1634 (C═N), 1366, 1140 (SO_2)	1.02 (t, 3H, CH_3), 1.99 (t, 3H, CH_3), 3.41 (q, 2H, CH_2), 4.5 (q, 2H, CH_2), 6.56–7.99 (m, 8H, Ar─H), and 10.42 (s, 1H, NH)
7	3200 (NH), 1558 (C═N), 1362, 1136 (SO_2)	4.59 (s, 1H, NH), 6.3 (s, 1H, thiazolidine-H) and 6.63–7.78 (m, 13H, Ar─H)
8	3450, 3410 (NH_2), 2926 (CH-aliph.), 1634 (C═N), 1390, 1138 (SO_2)	—
9	3264 (NH), 3050 (CH-arom.), 2922 (CH-aliph.)	2.94 (s, 3H, CH_3), 6.54-8.11 (m, 8H, Ar─H), 9.32, 11.9 (2s, 2H, 2NH)
11	3222 (NH), 3036 (CH-arom.), 1662 (C═O; quinazolinone), 1610 (C═N), 1328, 1140 (SO_2)	6.89–7.99 (m, 14H, Ar─H + NH), 13.14 (s, 1H, NH)
13	3458, 3330 (NH/NH_2), 3060 (CH-arom.), 1338,1150 (SO_2)	—
16	3252, 3190 (2NH), 1686 (C═O), 1628 (C═N), 1388, 1136 (SO_2)	4.01 (s, 2H, CH_2), 6.84–8.01 (m, 8H, Ar─H), 10.3, 11.9 (2s, 2H, 2NH)
17a	3280, 3200 (2NH), 1680 (C═O), 1608 (C═N), 1364, 1140 (SO_2)	
17b	3320 (NH), 2930 (CH-aliph.), 1602 (C═N), 1382, 1138 (SO_2)	3.6 (s, 3H, OCH_3), 6.67–7.78 (m, 15H, Ar-H + benzylidene-H + 2NH)
19	3250 (NH), 2110 (C≡N), 1682 (C═O), 1624 (C═N), 1384, 1128 (SO_2)	4.3 (s, 1H, NH), 6.8–7.9 (m, 9H, Ar─H + NH)

dried, and recrystallized from the proper solvent to yield **3**, **5**, **7**, and **8**, respectively.

Synthesis of Compound [4-(Pyridin-2-ylsulfamoyl)-phenyl]-dithiocar-bamic Acid Methyl Ester (9)

The experimental procedure for **3** was carried out except for the use of dimethylsulfate instead of the halo compound.

Synthesis of Compound 4-(4-Oxo-2-thioxo-1,4-dihydro-2H-quinazolin-3-yl)-*N*-pyridin-2-yl-benzenesulfonamide (11)

Method A

A mixture of compound **9** (3.39 g, 0.01 mol), methyl anthranilate (1.51 g, 0.01 mol), and triethylamine (1.01 g, 0.01 mol) in ethanol (20

ml) was heated under reflux for 12 h. The solid product which produced on heating was collected and recrystallized from the proper solvent.

Method B

A mixture of compound **12** (2.91 g, 0.01 mol), methyl anthranilate (1.51 g, 0.01 mol), and triethylamine (1.01 g, 0.01 mol) in ethanol (20 ml) was heated under reflux for 1h. The solid product which produced on heating was collected and recrystallized to give **11**.

Synthesis of Thiosemicarbazide Derivative (13)

To a suspension of compound **9** (3.39 g, 0.01 mol) in ethanol (30 ml), the appropriate hydrazine hydrate (0.5 g, 0.01 mol) was added in portions with stirring. The reaction mixture was stirred at room temperature for 30 min; the solid that separated out was filtered off and recrystallized from the proper solvent to give **13**.

Synthesis of 4-(2-Imino-4-oxo-thiazolidin-3-yl)-*N*-pyridin-2-yl-benzene-sulfonamide (16)

A suspension of compound **14** (3.25 g, 0.01 mol) and potassium thiocyanate (0.96 g, 0.01 mol) in dimethylformamide (10 ml) is heated under reflux for 1 h. After cooling the reaction mixture is poured into water (100 ml), the precipitate is separated by filtration and washed with water to give **16**.

Synthesis of 4-[5-(2-Chlorobenzylidene)-2-imino-4-oxo-thiazolidin-3-yl]-*N*-pyridin-2-yl-benzenesulfonamide (17a) and 4-[5-(4-Methoxy-benzylidene)-2-imino-4-oxo-thiazolidin-3-yl]-*N*-pyridin-2-yl-benzene-sulfonamide (17b)

Method A

A mixture of compound **16** (3.48 g, 0.01 mol), benzylidenemalononitrile (0.01), and piperidine (0.85 g, 0.01 mol) in ethanol (20 ml) was heated under reflux for 3h. The solid product which produced on heating was collected and recrystallized from the proper solvent to give **17**.

Method B

A mixture of compound **16** (3.48 g, 0.01 mol), aromatic aldehyde (0.01 mol), and piperidine (0.85 g, 0.01 mol) in ethanol (20 ml) was heated under reflux for 1 h. The solid product was collected and recrystallized to give **17**.

Synthesis of 4-(5-Dicyanomethylene-2-imino-4-oxo-thiazolidin-3-yl)-*N*-pyridin-2-yl-benzenesulfonamide (19)

A mixture of compound **16** (3.48 g, 0.01 mol), tetracyanoethylene (1.28 g, 0.01 mol), and triethylamine (1.01 g, 0.01 mol) in ethanol (20 ml) was heated under reflux for 0.5h. The solid product which produced on heating was collected and recrystallized to give **19**.

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