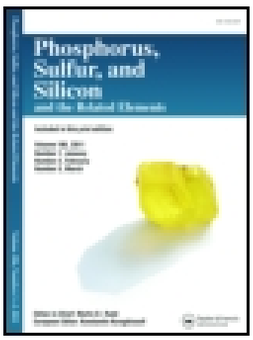

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SYNTHESIS OF SOME NEW 2-SUBSTITUTED-4-SULFAMOYLPHENYLAZO-THIOPHENE AND/OR THIAZOLE DERIVATIVES AS ANTIBACTERIAL AGENTS

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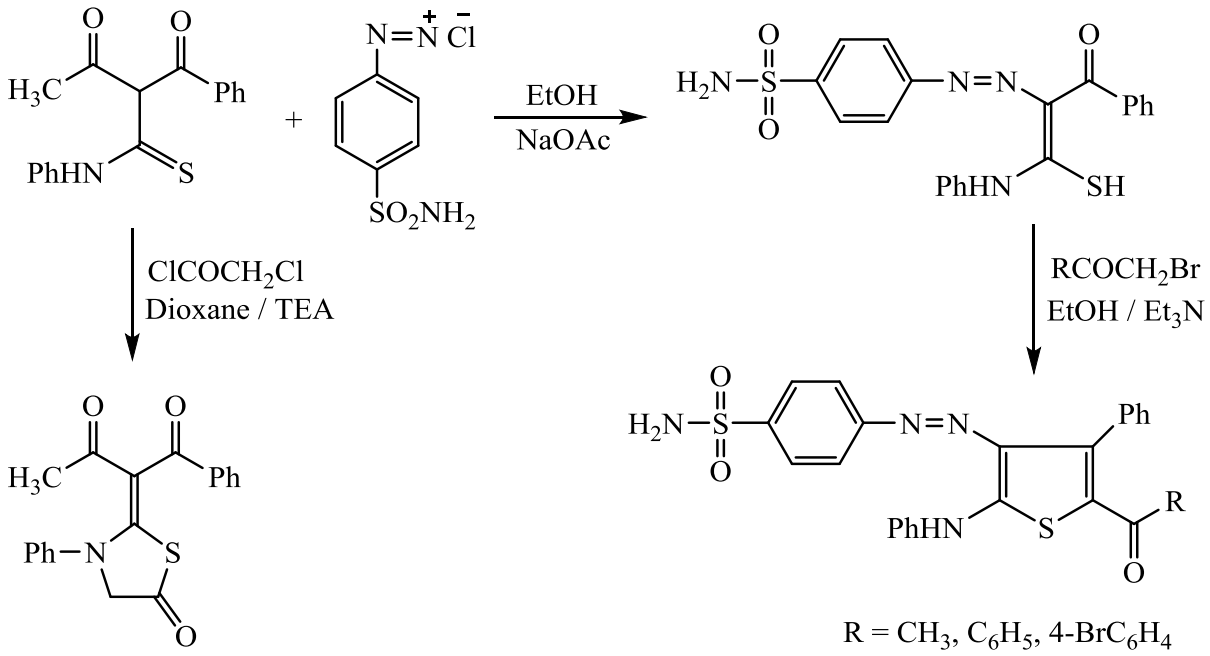
Abstract

Benzoylacetone has been reacted with phenyl isothiocyanate to afford two different thiocarbamoyl derivatives (α-phenylthiocarbamoyl benzoylacetone and benzoyl thioacetanilide) depending upon the base used to perform the reaction. Several new 2-substituted-4-sulfamoylphenylazo-thiophene and/or thiazole derivatives were synthesized by heterocyclization of the thiocarbamoyl derivatives with various halogenated reagents. The synthesized compounds were screened for their antibacterial activities; they showed accepted activities with respect to the control drugs.



Keywords

Benzoylacetone; sulfanilamide; thiocarbamoyl; thiophene; thiazolodin-5-one; antibacterial activities

INTRODUCTION

Apart from commercialized applications as antibacterial/antibiotic agents, various sulfonamides are known to inhibit several enzymes such as carbonic anhydrase, cysteine protease, HIV protease and cyclooxygenase [1]. Moreover, the widespread potential value of sulfonamides, have led to the discovery of various other therapeutic applications, in cancer chemotherapy, diuretics, hypoglycemia and the anti-impotence agent Viagra [2].

In addition, five membered heterocyclic compounds containing sulfur are essentially utilized in medicine for the treatment of different kinds of fungal and bacterial infections and gastric ulcers and cancer [3]. Among the antimicrobial and antifungal agents, thiophene containing heterocycles are known to have a promising activity [4]. Thiazole derivatives have considerable interest from therapeutic point of view because of their utility as antibacterial and antifungal [5,6], anti-inflammatory [7], anti-tubercular [8], potent central nervous system (CNS) [9], anti-HIV [10] and antimalarial agents [11]. A growing number of semi-synthetic penicillin analogues and other antibiotics known to have the chemical structure of classic antimicrobial drugs (such as sulfanilamides), as well as an increasingly pressing problem of bacterial resistance urged us to investigate new sulfanilamide derivatives.

The aim of our work was to study the influence of sulfanilamides on the antibacterial activity of thiophene and/or thiazole derivatives. Therefore, it is of therapeutic interest to design and produce compounds containing sulfonamide and thiophene or thiazole pharmacophores in one molecule.

RESULTS AND DISCUSSION

The base-prompted reaction of benzoylacetone, which is an acidic methylene compound, with phenyl isothiocyanate in dry DMF containing KOH at room temperature led to the formation of the non-isolable intermediate **1** which gave α-phenylthiocarbamoyl benzoylacetone **(2)** upon treatment with dilute HCl [12] (Scheme 1). On the other hand, heating of benzoyl acetone with phenyl isothiocyanate in ethanolic sodium ethoxide solution (EtOH/NaOEt) affects the acetyl cleavage with the formation of benzoyl thioacetanilide **(3)**.

Diazotization of sulfanilamide by a reaction with nitrous acid (HCl/ $NaNO_2$) at 0-5°C yielded the corresponding diazonium chloride **4** which underwent a coupling reaction with α-phenylthiocarbamoyl benzoylacetone **(2)** in ethanol containing sodium acetate affected one group (acetyl or benzoyl) cleavage through the intermediate **5** to form the corresponding benzoyl derivative **7**. The formation of 2-benzoyl-2-[(4-sulfamoyl-phenyl)-hydrazono]-thioacetanilide **(7)** through an acetyl cleavage finds support from the literature, Japp-Klingemann reaction type [13,14], and spectral data rather than the benzoyl cleavage which lead to the non-isolated product **6** (Scheme 2).

Heterocyclization of compound **7** with different α-bromoketone compounds such as bromoacetone, phenacyl bromide and *p*-bromophenacyl bromide furnished the corresponding thiophene derivatives **9a**, **9b** and **9c**; the reaction proceeded in good yields by refluxing the reactants in ethanol containing drops of triethylamine as a catalyst (Scheme 3). The formation of thiophene derivatives **9** from the reaction of **7** with the appropriate alkylating agent (such as bromoacetone, phenacyl bromide and *p*-bromophenacyl bromide) starts through nucleophilic attack of the thiolate group to form the non-isolable S-alkylated intermediate **8** which via nucleophilic addition and intramolecular cyclocondensation by water elimination [12] gave the

corresponding 5-anilino-3-phenyl-2-substituted-4-[(4-sulfamoyl-phenyl)-azo]-thiophene derivatives **9a-c**.

In a similar manner, treatment of 2-benzoyl-2-[(4-sulfamoyl-phenyl)-hydrazono]-thioacetanilide **(7)** with ethyl bromoacetate by reflux in ethanol containing drops of triethylamine led to the formation of the corresponding thiophene derivative, 5-anilino-2-ethoxycarbonyl-3-phenyl-4-[(4-sulfamoyl-phenyl)-azo]-thiophene **(10)** (Scheme 3). In addition, 5-anilino-2-cyano-3-phenyl-4-[(4-sulfamoyl-phenyl)-azo]-thiophene **(11)** was prepared by the reaction of thioacetanilide derivative **7** with chloroacetonitrile by reflux in ethanol containing a catalytic amount of triethylamine. The structure of thiophene compound **11** was verified by elemental analysis and by spectroscopic methods.

Heterocyclization of compound **7** with chloroacetanilide to give the corresponding thiophene **13** and/or thiazole **14** did not proceed under the conditions of hot ethanol catalyzed by triethylamine. The reaction proceeded only in ethanolic sodium ethoxide solution under reflux to afford the corresponding thiophene derivatives **13** through nucleophilic attack of the thiolate group followed by ring closure and water elimination (Scheme 4). Based on its elemental analysis and spectral data, the product was assigned as the thiophene structure **13** not the thiazole structure **14**. Thus, the IR spectrum showed three absorption bands at 3397, 3317, 3246 due to NH_2 and NH) functions besides one carbonyl absorption band at 1647 cm^{-1}. The ^1H NMR spectrum revealed multiplet signal in the region δ 7.14-7.82 corresponding to the protons of phenyl and amino groups, in addition to two singlet signals at δ 11.16 and 13.62 due to the protons of two NH groups. Stirring of 2-benzoyl-2-[(4-sulfamoyl-phenyl)-hydrazono]-thioacetanilide **(7)** with chloroacetyl chloride in dioxane containing drops of triethylamine as a

catalyst at room temperature afforded the corresponding arylazo-thiazole derivative **16** through heterocyclization of the non-isolable intermediate **15**. The product **16** that analyzed for $C_{23}H_{18}N_4O_4S_2$ was isolated in moderate yield. Its ^{1}H NMR spectrum showed singlet signal at 4.16 of the cyclic methylene protons and multiplet signal in the region 7.05-7.80 due to the aromatic and amino protons.

Heterocyclization of the thiocarbamoyl derivatives **2** and/or **3** with chloroacetyl chloride in dioxane containing drops of triethylamine furnished the corresponding thiazolidin-5-one derivatives **17** and/or **18** respectively (Scheme 5). The reactivity of the methylene group of these thiazolidin-5-one derivatives was tested towards the electrophilic coupling reaction. Thus, diazo-coupling of **17** and/or **18** with diazotized sulfanilamide proceeds in ethanol containing sodium acetate to afford the corresponding 4-arylazo-thiazolidin-5-one derivatives **19** and/or **20** respectively (Scheme 5). The chemical structures of the synthesized thiazolidin-5-one derivatives **17-20** were elucidated based on their elemental analyses and spectral data (experimental section).

Diazo-coupling reaction of the diazotized sulfanilamide **4** with phenacyl bromide proceeds in pyridine at 0-5 °C to give the corresponding hydrazonoyl bromide compound **21** (Scheme 6). Refluxing of **21** with thiosemicarbazone derivative in ethanol containing drops of triethylamine as a basic catalyst afforded the corresponding 5-arylazothiazole derivative **22**. The chemical structures of compounds **21** and **22** were secured by correct elemental analyses and spectral data.

Antibacterial Screening

The synthesized compounds **7-11**, **13**, **16-20** and **22** were screened for their antibacterial activities at 100 μg/mL concentration against two *Gram positive bacteria* (*Bacillus subtilis*

ATCC6633; Staphylococcus aureus ATCC 29213), two *Gram negative bacteria* (*Pseudomonas aeruginosa* ATCC 27953; *Escherichia coli ATCC 25922*). Ampicillin was used as standard antibacterial reference. The results of antibacterial activities were shown in Table S 1 (Supplemental Materials).

EXPERIMENTAL

All melting points (uncorrected) were determined on an electrothermal Gallenkamp melting point apparatus. The IR spectra were recorded in KBr disks on a Thermo Scientific Nicolet iS 50 FT-IR spectrometer (not all frequencies are reported). The NMR spectra were acquired using a Bruker WP 300 spectrometer at 300 MHz using *TMS* as an internal standard and DMSO-d_6 or CF_3COOD as solvent. The mass spectra were performed using a Varian MAT 311 mass spectrometer at 70 eV. The progress of the reactions was monitored by TLC using aluminum silica gel plates 60 F245. Elemental analyses were carried out at the Micro Analytical Center, Cairo University, Giza, Egypt; the results were in satisfactory agreement with the calculated values. Antimicrobial tests were carried out by the agar well diffusion method [15] at the Micro Analytical Center, Cairo University, Giza, Egypt. The synthesized compounds were individually tested against a panel of gram positive and gram negative bacterial pathogens. The Supplemental Materials contains sample ^{1}H and ^{13}C NMR spectra for selected products (Figures S 1 – S 14).

Synthesis of α-phenyl thiocarbamoyl-benzoylacetone (2):

To a cold suspension of potassium hydroxide (0.56 g, 0.01 mol) in DMF (20 mL), benzoylacetone (1.62 g, 0.01 mol) and phenyl isothiocyanate (1.2 mL, 0.01 mol) were added. The mixture was stirred overnight at room temperature and then poured onto ice-cold water (95-

100 mL). Acidification using dilute HCl until the medium becomes acidic gave the solid product **2** which was filtered off, washed with water, dried and crystallized from ethanol.

Yellow crystals, m.p. = 139-140°C, lit. m. p. = 140°C [12], yield = 91%. IR (ν / cm^{-1}): 3229 (NH), 1665 (broad, C=O). Analysis for $C_{17}H_{15}NO_2S$ (297.08): Calcd.: C, 68.66; H, 5.08; N, 4.71%; Found: C, 68.58; H, 5.10; N, 4.76%.

Synthesis of benzoyl thioacetanilide (3):

A mixture of benzoylacetone (1.62 g, 0.01 mol) and phenyl isothiocyanate (1.2 mL, 0.01 mol) in NaOEt solution (prepared from 0.23 g Na metal and 20 mL absolute ethanol) was refluxed for 2 h. The reaction mixture was allowed to cool at room temperature, and then poured onto ice-cold water (75-80 mL). The solid precipitate, which formed upon neutralization with dilute HCl, was filtered off, washed with water, dried and recrystallized from ethanol to give benzoyl thioacetanilide **(3)**.

Yellow crystals, m.p. = 110-111°C, yield = 72%. IR ($\bar{\nu}$ /cm^{-1}): 3190 (NH), 1677 (C=O), 1278 (C=S). ^{1}H NMR (DMSO-d_6): δ/ppm = 4.65 (s, 2H, CH_2), 7.25-8.05 (m. 10H, Ar-H), 12.13 (s, 1H, NH). ^{13}C NMR ($CDCl_3$/CF_3COOD): δ/ppm = 37.40, 123.63 (2C), 126.33, 129.50 (2C), 129.66 (4C), 132.06, 133.18, 138.74, 173.78, 195.53. Analysis for $C_{15}H_{13}NOS$ (255.07): Calcd.: C, 70.56; H, 5.13; N, 5.49%; Found: C, 70.67; H, 5.08; N, 5.56%.

Synthesis of 2-benzoyl-2-[(4-sufamoyl-phenyl)-hydrazo]-thioacetanilide (7):

A well stirred solution of sulfanilamide (1.72 g, 0.01 mol) in concentrated HCl (3 mL) was cooled in an ice bath and diazotized with a solution of sodium nitrite (0.7 g, 0.01 mol) in water (10 mL). The freshly prepared cold diazonium solution was added dropwise to a well stirred cold solution of **2** (2.97 g, 0.01 mol) in ethanol (25 mL) containing 3 g sodium acetate.

The reaction mixture was stirred for 2 h at 0-5ºC. The crude product **7** was filtered off, dried well and recrystallized from ethanol.

Orange crystals, m.p. = 165-166°C, yield = 68%. IR ($\bar{\nu}$/cm^{-1}): 3335, 3254 (NH_2), 1631 (conjugated C=O), 1592 (C=N), 1520 (N=N), 1269 (C=S). ^{1}H NMR (DMSO-d_6): δ/ppm = 7.18 (s, 2H, NH_2), 7.25-8.16 (m. 14H, Ar-H), 10.91 (s, 1H, =NNH), 12.34 (s, 1H, NH). ^{13}C NMR (CF_3COOD): δ/ppm = 110.42, 121.54, 121.77 (2C), 128.68 (4C), 130.88 (4C), 131.39, 131.52, 132.50. 133.60, 143.13, 144.37, 152.84, 157.52, 159.78. MS (EI): m/z (%) = 438 (molecular ion peak, 28), 105 (base peak, 100). Analysis for $C_{21}H_{18}N_4O_3S_2$ (438.08): Calcd.: C, 57.52; H, 4.14; N, 12.78%; Found: C, 57.64; H, 4.09; N, 12.71%.

Synthesis of 5-anilino-2-substituted-3-phenyl-4-[(4-sulfamoyl-phenyl)azo]-thiophene derivatives 9-11:

General procedure: A mixture of thiocarbamoyl compound **7** (0.876 g, 0.002 mol) and different α-halogenated compounds (namely; bromoacetone, phenacyl bromide, *p*-bromophenacyl bromide, ethyl bromoacetate and chloroacetonitrile) (0.002 mol) was refluxed for 4 h in absolute ethanol (20 ml) and catalytic amount of triethylamine (5 drops). The reaction mixture was allowed to cool and the solid product that formed was filtered off, dried and recrystallized from ethanol to give the corresponding thiophene derivatives **9a-c**, **10** and/or **11**, respectively.

2-Acetyl -5-anilino-3-phenyl-4-[(4-sulfamoyl-phenyl)azo]-thiophene (9a):

Orange crystals, m.p. = 216-217°C, yield = 88%. IR ($\bar{\nu}$/cm^{-1}): 3305, 3234 (NH_2 and NH), 1641 (C=O), 1541 (N=N). ^{1}H NMR (DMSO-d_6): δ/ppm = 1.89 (s, 3H, CH_3), 7.31 (s, 2H, NH_2), 7.48-7.80 (m, 14H, Ar-H), 13.97 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ/ppm = 21.40, 119.93 (2C), 122.51

(2C), 124.49 (2C), 128.31 (2C), 129.32 (2C), 129.50 (2C), 129.74 (2C), 130.24 (2C), 133.86, 138.83, 140.01, 141.11, 150.85, 152.89, 165.52. MS (EI): m/z (%) = 476 (molecular ion peak, 5), 77 (base peak, 100). Analysis for $C_{24}H_{20}N_4O_3S_2$ (476.10): Calcd.: C, 60.49; H, 4.23; N, 11.76%; Found: C, 60.67; H, 4.16; N, 11.84%.

5-Anilino-2-benzoyl- 3-phenyl-4-[(4-sulfamoyl-phenyl)azo]-thiophene (9b):

Red crystals, m.p. = 235-236°C, yield = 80%. IR (ν / cm^{-1}): 3446, 3297, 3230 (NH_2 and NH), 1596 (broad, conjugated C=O and C=C), 1544 (N=N). ^{1}H NMR (DMSO-d_6): δ/ppm = 7.13-7.83 (m, 21H, Ar-H and NH_2), 14.23 (s, 1H, NH). Analysis for $C_{29}H_{22}N_4O_3S_2$ (538.11): Calcd.: C, 64.66; H, 4.12; N, 10.40%; Found: C, 64.84; H, 4.03; N, 10.51%.

5-Anilino-2-(4-bromobenzoyl)-3-phenyl-4-[(4-sulfamoyl-phenyl)azo]-thiophene (9c):

Red crystals, m.p. = 272-273°C, yield = 77%. IR ($\bar{\nu}$ /cm^{-1}): 3372, 3242 (NH_2 and NH), 1608 (conjugated C=O), 1590 (C=C), 1557 (N=N). MS (EI): m/z (%) = 616 (20.77), 618 (22.42) (molecular ion peaks), 183 (100), 185 (96.87) (base peaks). Analysis for $C_{29}H_{21}BrN_4O_3S_2$ (616.02): Calcd.: C, 56.40; H, 3.43; N, 9.07%; Found: C, 56.18; H, 3.33; N, 9.18%.

5-Anilino-2-ethoxycarbonyl-3-phenyl-4-[(4-sulfamoyl-phenyl)-azo]-thiophene (10):

Orange crystals, 167-169°C, yield = 88%. IR ($\bar{\nu}$ /cm^{-1}): 3340, 3243, 3105 (NH_2 and NH), 1669 (C=O), 1595 (C=C), 1545 (N=N). ^{1}H NMR (DMSO-d_6): δ/ppm = 1.21 (t, 3H, CH_3), 4.08 (q, 2H, CH_2), 7.22-7.78 (m, 16H, Ar-H and NH_2), 14.13 (s, 1H, NH). MS (EI): m/z (%) = 506 (molecular ion peak and base peak, 100). Analysis for $C_{25}H_{22}N_4O_4S_2$ (506.11): Calcd.: C, 59.27; H, 4.38; N, 11.06%; Found: C, 59.11; H, 4.44; N, 11.14%.

5-Anilino-2-cyano-3-phenyl-4-[(4-sulfamoyl-phenyl)-azo]-thiophene (11):

Reddish brown crystals, m.p. = 268-270°C, yield = 82%. IR ($\bar{\nu}$ /cm^{-1}): 3328, 3248 (NH_2 and

NH), 2202 (C≡N), 1594 (C=C), 1546 (N=N). ^{1}H NMR (DMSO-d_6): δ/ppm = 7.17-7.84 (m, 16H, Ar-H and NH_2), 13.96 (s, 1H, NH). MS (EI): m/z (%) = 459 (molecular ion peak, 69.05), 77 (base peak, 100). Analysis for $C_{23}H_{17}N_5O_2S_2$ (459.08): Calcd.: C, 60.11; H, 3.73; N, 15.24%; Found: C, 60.22; H, 3.70; N, 15.29%.

Synthesis of 5-anilino-3-phenyl-2-phenylcarbamoyl-4-[(4-sulfamoyl-phenyl)-azo]-thiophene (13):

A mixture of thiocarbamoyl compound **7** (0.88 g, 0.002 mol) and chloroacetanilide (0.34 g, 0.002 mol) in 0.003 mol NaOEt solution (prepared from 0.07 g Na metal and 15 mL absolute ethanol) was refluxed for 2 h. The reaction mixture was allowed to cool at room temperature, poured onto ice-cold water (45-50 mL) and neutralized by dilute HCl. The solid product that formed was filtered off, washed with water, dried and recrystallized from ethanol to give the thiophene compound **13**.

Orange crystals, m.p. = 135-136°C, yield = 68%. IR ($\bar{\nu}$ /cm^{-1}): 3397, 3317, 3246 (NH_2 and NH), 1647 (C=O), 1596 (C=C), 1523 (N=N). ^{1}H NMR (DMSO-d_6): δ/ppm = 7.14-7.82 (m, 21H, Ar-H and NH_2), 11.16 (s, 1H, NH), 13.62 (s, 1H, NH). MS (EI): m/z (%) = 553 (molecular ion peak, 41.47), 77 (base peak, 100). Analysis for $C_{29}H_{23}N_5O_3S_2$ (553.12): Calcd.: C, 62.91; H, 4.19; N, 12.65%; Found: C, 62.75; H, 4.27; N, 12.54%.

Synthesis of 2-[benzoyl-(4-sulfamoyl-phenylazo)methylene]-3-phenyl-1,3-thiazolidin-5-one (16):

To a solution of **7** (2.19 g, 0.005 mol) in dioxane (20 mL) containing drops of triethylamine, chloroacetyl chloride (0.8 mL, 0.01 mol) was added dropwise with stirring at 0-5°C. After complete addition, the reaction mixture was stirred for 2 h and then poured into ice-

cooled water (45-50 mL). The solid product that formed was collected by filtration and recrystallized from ethanol.

Red crystals, m.p. = 175-177 °C, yield = 66%. IR ($\bar{\nu}$/cm^{-1}): 3377, 3261 (NH_2), 1711 (C=O, ring), 1663 (C=O), 1594 (C=C), 1510 (N=N). ^{1}H NMR ($CDCl_3$): δ/ppm = 4.16 (s, 2H, CH_2), 7.05-7.80 (m, 16H, Ar-H and NH_2). ^{13}C NMR ($CDCl_3$/CF_3COOD): δ/ppm = 33.73, 95.59, 122.28 (2C), 123.02 (2C), 128.60 (2C), 129.55, 129.73 (2C), 130.66 (2C), 130.73 (2C), 132.28, 132.38, 135.55, 136.56, 149.00, 149.45, 159.60, 168.74. Analysis for $C_{23}H_{18}N_4O_4S_2$ (478.08): Calcd.: C, 57.73; H, 3.79; N, 11.71%; Found: C, 57.91; H, 3.87; N, 11.59%.

Synthesis of 3-phenyl-2-substituted-thiazolidin-5-ones 17 and 18:

To a solution of thiocarbamoyl derivatives **2** and/or **3** (0.005 mol) in dioxane (20 mL) containing drops of triethylamine, chloroacetyl chloride (0.8 mL, 0.01 mol) was added dropwise with stirring at 0-5°C. After complete addition, the reaction mixture was stirred for 2 h and then poured onto ice-cooled water (75-80 mL). The solid product that formed was collected by filtration and recrystallized from ethanol to give **17** and/or **18**.

2-(1,3-Dioxo-1-phenylbutan-2-ylidene)-3-phenylthiazolidin-5-one (17):

Yellow crystals, m.p. = 152-153°C, yield = 72%. IR ($\bar{\nu}$/cm^{-1}): 1729 (C=O, broad), 1638 (C=O), 1593 (C=C). ^{1}H NMR (DMSO-d_6): δ/ppm = 2.00 (s, 3H, CH_3), 4.00 (s, 2H, CH_2), 6.95-7.55 (m, 10H, Ar-H). Analysis for $C_{19}H_{15}NO_3S$ (337.08): Calcd.: C, 67.64; H, 4.48; N, 4.15%; Found: C, 67.72; H, 4.50; N, 4.10%.

2-[Benzoyl-methylene]-3-phenyl-thiazolidin-5-one (18):

Yellow crystals, m.p. = 224-225°C, yield = 58%. IR ($\bar{\nu}$/cm^{-1}): 1758 (C=O, ring), 1674 (C=O, benzoyl), 1591 (C=C). ^{1}H NMR (DMSO-d_6): δ/ppm = 4.31 (s, 2H, CH_2), 7.29-7.60 (m, 11H, Ar-

H and olefinic CH=C). Analysis for $C_{17}H_{13}NO_2S$ (295.07): Calcd.: C, 69.13; H, 4.44; N, 4.74%; Found: C, 69.02; H, 4.50; N, 4.81%.

Synthesis of 2-[benzoyl-methylene]-3-phenyl-4-(4-sulfamoyl-phenylazo)-1,3-thiazolidin-5-one 19 and 20:

A well-stirred solution of sulfanilamide (0.86 g, 0.005 mol) in concentrated HCl (1.5 mL) was cooled in an ice bath and diazotized with a solution of sodium nitrite (0.35 g, 0.005 mol) in water (10 mL). The freshly prepared cold diazonium solution was added dropwise to a well stirred cold solution (0-5°C) of the thiazolidin-5-one derivatives **17** and/or **18** (0.005 mol) in pyridine (20 mL). The reaction mixture was stirred for 2 h at 0-5°C. The crude products **19** and/or **20** were filtered off, dried well and recrystallized from ethanol.

2-(1,3-Dioxo-1-phenylbutan-2-ylidene)-3-phenyl-4-(4-sulfamoyl-phenyl-hydrazono)-thiazolidin-5-one (19):

Yellow crystals, m.p. = 234-235°C, yield = 58%. IR ($\bar{\nu}$/cm^{-1}): 3442, 3335 (NH_2 and NH), 1731 (C=O, ring), 1639 (C=O). ^{1}H NMR (DMSO-d_6): δ/ppm = 1.80 (s, 3H, CH_3), 6.75 (s, 2H, NH_2), 6.95-7.60 (m, 14H, Ar-H), 11.15 (s, 1H, NH). ^{13}C NMR ($CDCl_3$/DMSO): δ/ppm = 26.57, 109.53, 124.31 (2C), 127.12 (2C), 128.31, 130.32 (2C), 132.33, 134.26 (2C), 134.43 (2C), 134.91 (2C), 140.33, 144.43, 145.43, 145.77, 153.16, 156.06, 159.94, 168.42, 169.87. Analysis for $C_{25}H_{20}N_4O_5S_2$ (520.09): Calcd.: C, 57.68; H, 3.87; N, 10.76%; Found: C, 57.77; H, 3.90; N, 10.71%.

2-[Benzoyl-methylene]-3-phenyl-4-(4-sulfamoyl-phenylhydrazono)-thiazolidin-5-one (20):

Yellow crystals, m.p. = 256-258°C, yield = 64%. IR ($\bar{\nu}$/cm^{-1}): 3420, 3342 (NH_2 and NH), 1713 (C=O, ring), 1628 (C=O, conjugated). ^{1}H NMR (DMSO-d_6): δ/ppm = 6.85 (s, 2H, NH_2), 7.25-

7.80 (m, 15H, Ar-H and olefinic CH=C), 11.35 (s, 1H, NH). MS (EI): m/z (%) = 478 (molecular ion peak, 20.0), 77 (base peak, 100). Analysis for $C_{23}H_{18}N_4O_4S_2$ (478.08): Calcd.: C, 57.73; H, 3.79; N, 11.71%; Found: C, 57.58; H, 3.71; N, 11.64%.

Synthesis of (4-sulfamoyl-phenylhydrazono) phenacyl bromide (21):

A well-stirred solution of sulfanilamide (0.86 g, 0.005 mol) in concentrated HCl (1.5 mL) was cooled in an ice bath and diazotized with a solution of sodium nitrite (0.35 g, 0.005 mol) in water (10 mL). The freshly prepared cold diazonium solution was added dropwise to a well stirred cold solution (0-5°C) of phenacyl bromide (1.0 g, 0.005 mol) in pyridine (20 mL). The reaction mixture was stirred for 2 h at 0-5°C. The solid product was filtered off, dried well and recrystallized from ethanol to give orange crystals of **21**.

Orange crystals, m.p. = 190-191°C, yield = 78%. IR ($\bar{\nu}$/cm^{-1}): 3307, 3236 (NH_2 and NH), 1674 (C=O). ^{1}H NMR (DMSO-d_6): δ/ppm = 7.10 (s, 2H, NH_2), 7.40-7.80 (m, 9H, Ar-H), 12.25 (s, 1H, NH). Analysis for $C_{14}H_{12}BrN_3O_3S$ (380.98): Calcd.: C, 43.99; H, 3.16; N, 10.99%; Found: C, 43.82; H, 3.23; N, 11.12%.

Synthesis of 2-(benzylidenehydrazino)-4-phenyl-5-(4-sulfamoyl-phenylazo)-thiazole derivatives 22:

A mixture of hydrazonoyl bromide **21** (0.76 g, 002 mol) and the appropriate thiosemicarbazone derivative (0.002 mol) in absolute ethanol (20 mL) and triethylamine (0.2 mL) was refluxed for 2 h. The precipitate formed on cooling was filtered off, dried, and finally recrystallized from EtOH/DMF mixture (2:1) to afford the corresponding thiazole **22**.

2-(Benzylidenehydrazino)-4-phenyl-5-(4-sulfamoyl-phenylazo)-thiazole (22a):

Reddish brown crystals, m.p. = 241-242°C, yield = 72%. IR ($\bar{\nu}$/cm^{-1}): 3323, 3224 (NH_2 and

NH), 1658 (C=N), 1554 (N=N). ^{1}H NMR (DMSO-d_6): δ/ppm = 7.20 (s, 2H, NH_2), 7.35-7.80 (m, 14H, Ar-H), 8.10 (s, 1H, CH=N), 11.65 (s, 1H, NH). ^{13}C NMR ($CDCl_3$/CF_3COOD): δ/ppm = 123.76 (2C), 126.39, 128.67 (2C), 129.45 (2C), 129.53 (3C), 129.57 (4C), 131.87, 133.09, 135.08, 139.79, 142.34, 151.47, 163.14, 166.53. Analysis for $C_{22}H_{18}N_6O_2S_2$ (462.55): Calcd.: C, 57.13; H, 3.92; N, 18.17%; Found: C, 57.27; H, 3.85; N, 18.25%.

2-(4-Methylbenzylidenehydrazino)-4-phenyl-5-(4-sulfamoyl-phenylazo)-thiazole (22b):

Brown crystals, m.p. = 255-256°C, yield = 82%. IR ($\bar{\nu}$/cm^{-1}): 3315, 3214 (NH_2 and NH), 1655 (C=N), 1548 (N=N). ^{1}H NMR (DMSO-d_6): δ/ppm = 2.40 (s, 3H, CH_3), 7.15 (s, 2H, NH_2), 7.30-7.80 (m, 13H, Ar-H), 8.15 (s, 1H, CH=N), 11.55 (s, 1H, NH). MS (EI): m/z (%) = 281 (molecular ion peak – C_6H_5, – 4-MeC_6H_4CH=N, 100). Analysis for $C_{23}H_{20}N_6O_2S_2$ (476.11): Calcd.: C, 57.97; H, 4.23; N, 17.63%; Found: C, 57.85; H, 4.27; N, 17.71%.

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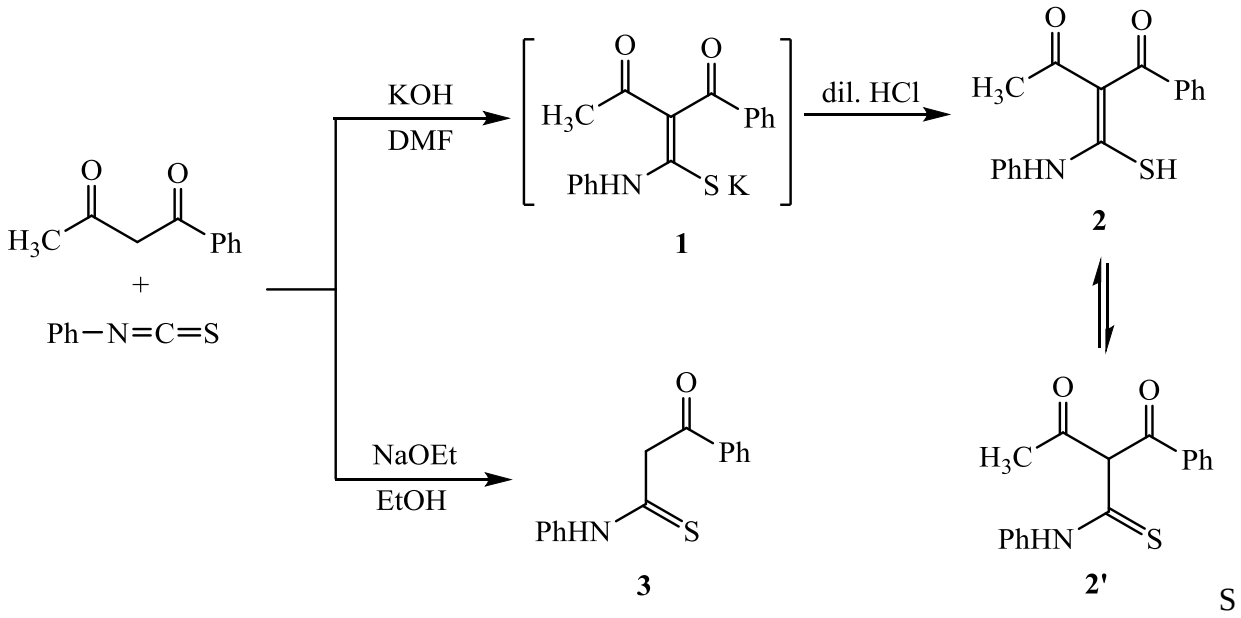
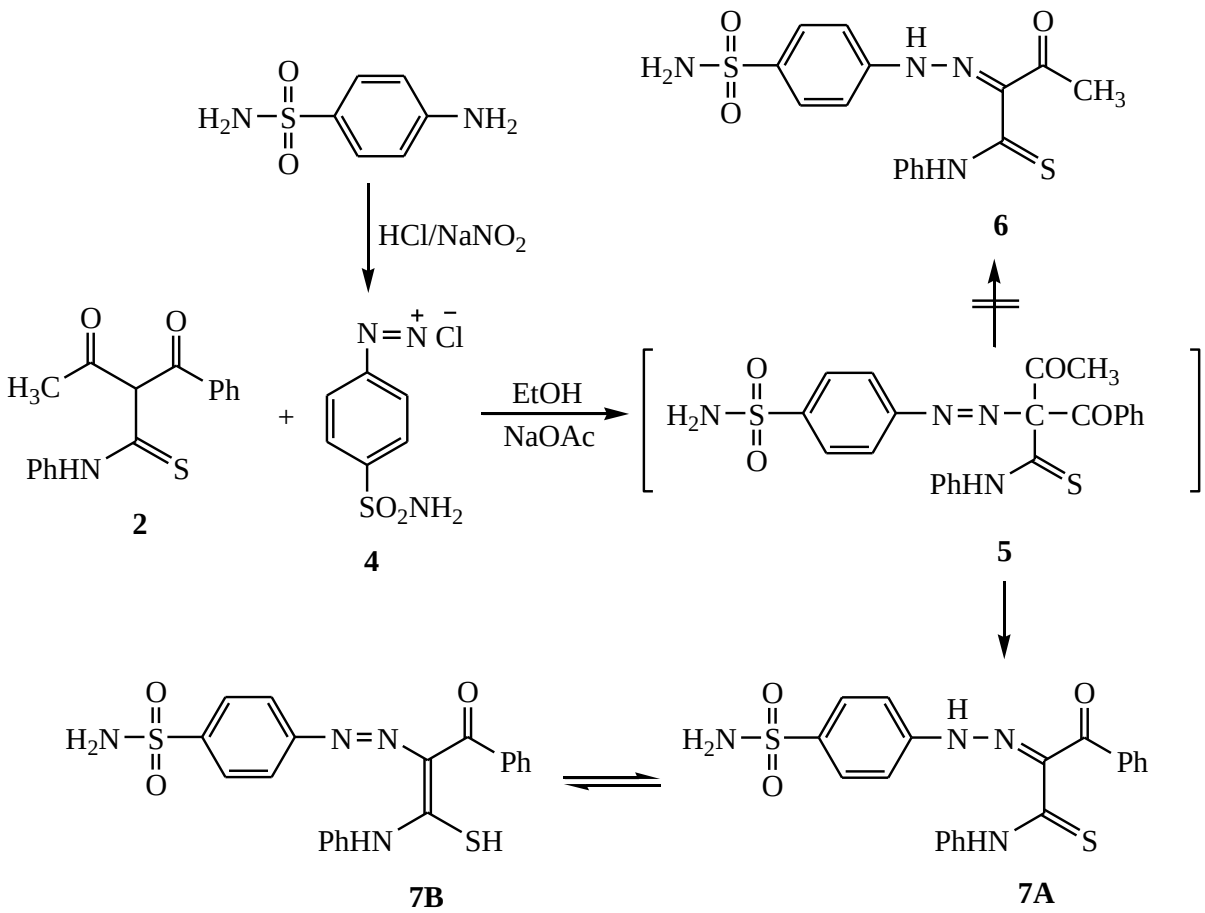


S

cheme 1:



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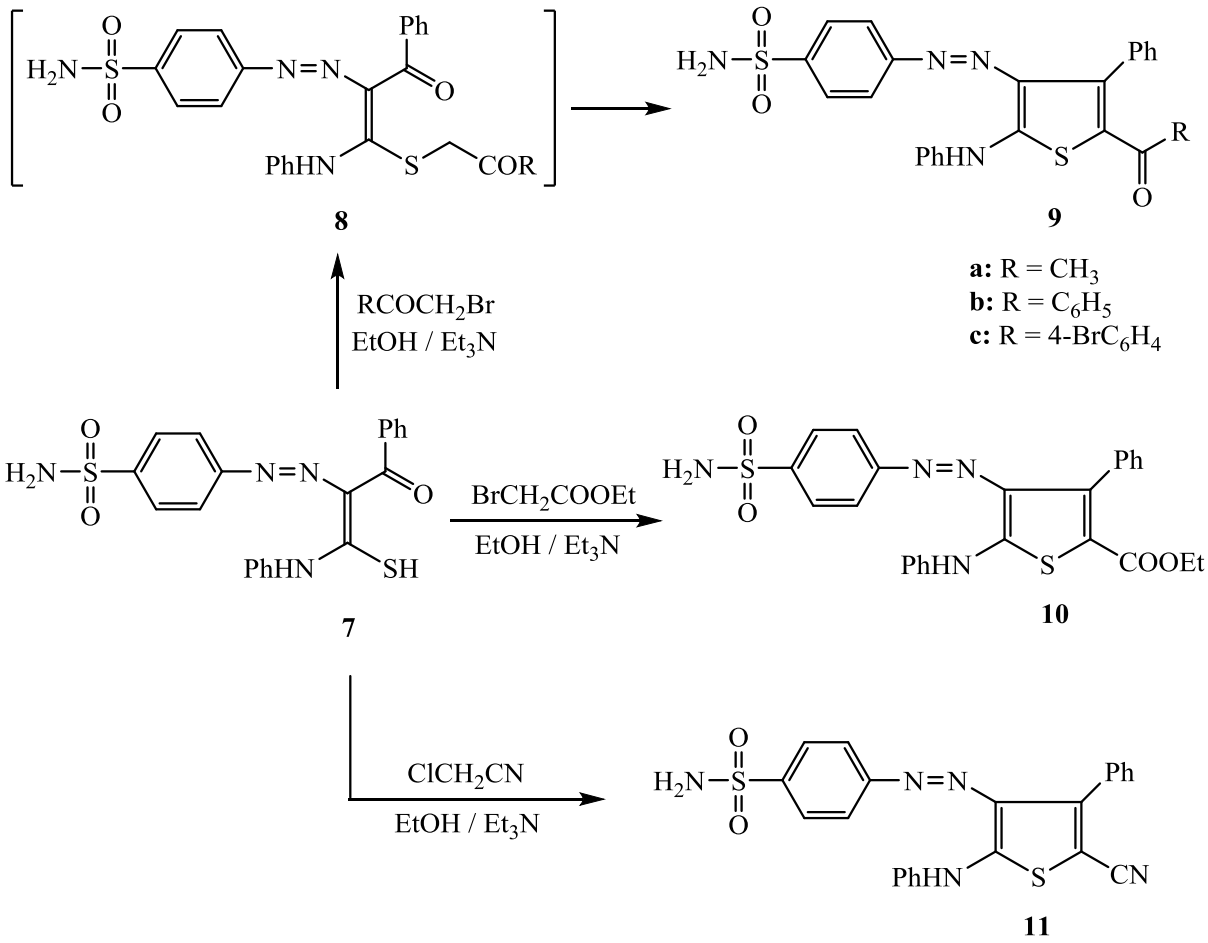

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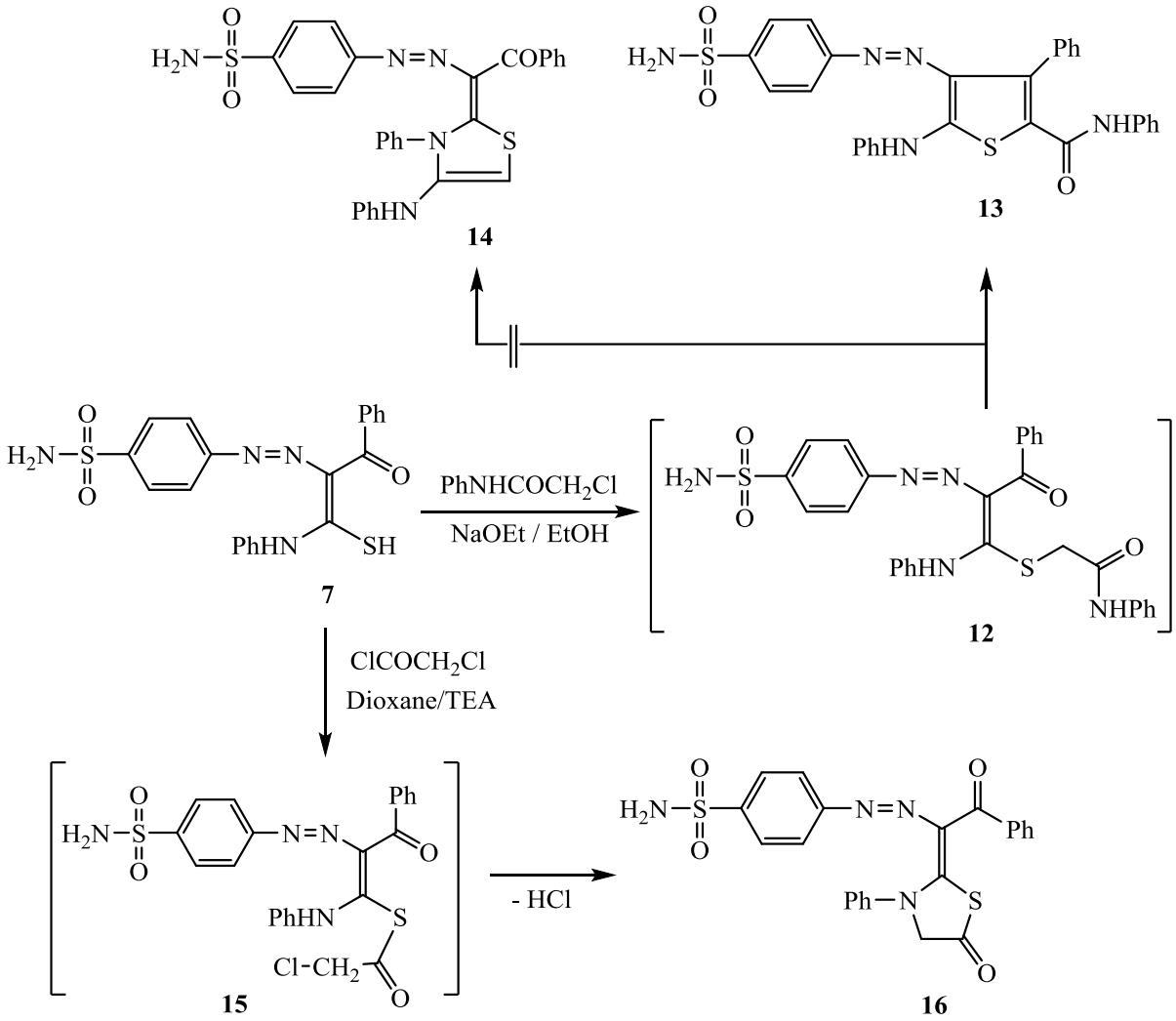

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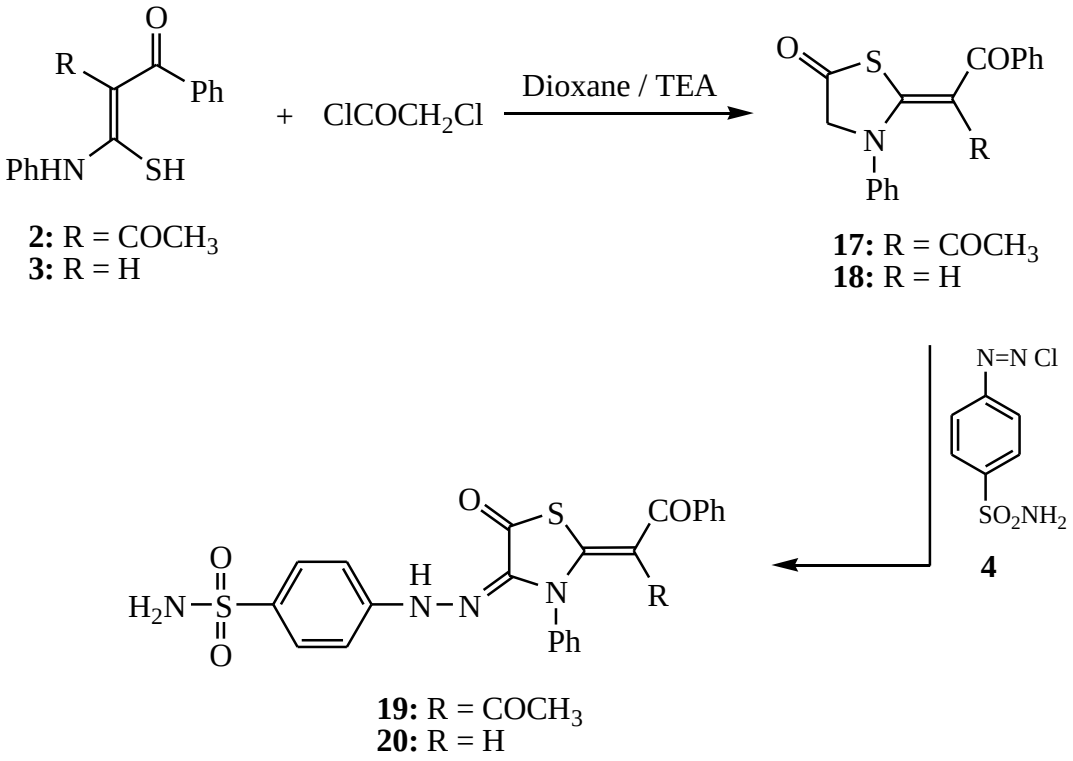
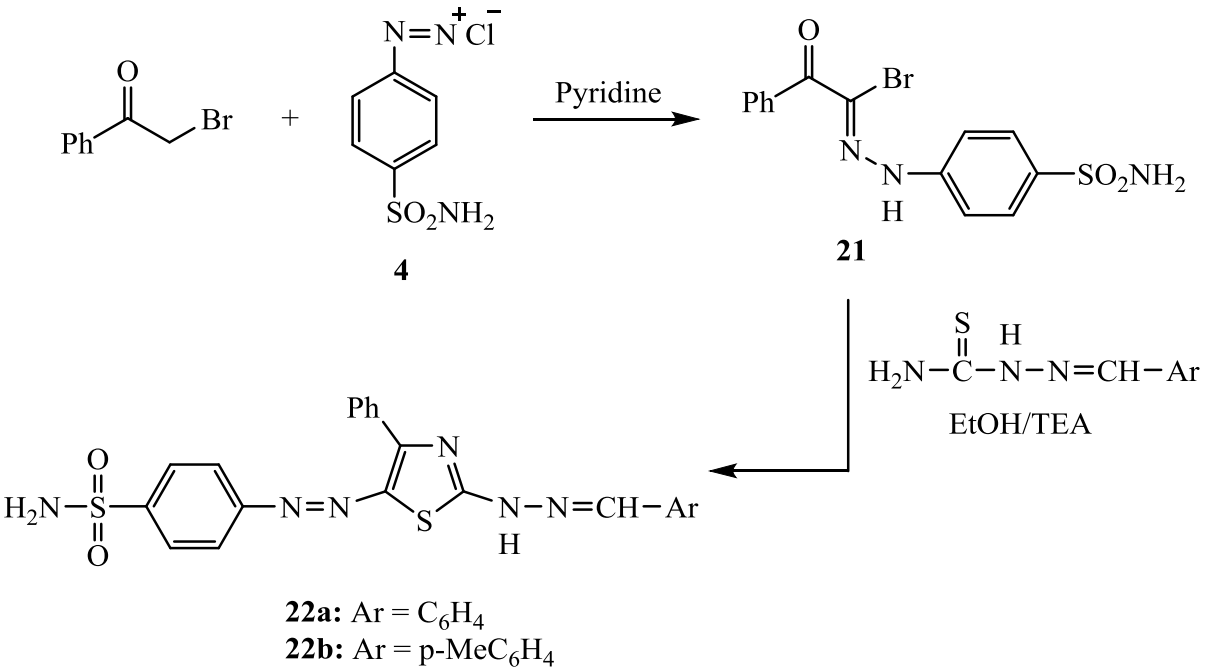


2: R = $COCH_3$
3: R = H

17: R = $COCH_3$
18: R = H

19: R = $COCH_3$
20: R = H

Scheme 5:



Scheme 6: