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Heterocyclic Sulfonesiv: A Novel Synthesis of Pyrrole and Fused Heterocyclic Sulfones

Fivian F. Mahmoud^a, Nadia R. Mohamed^b, Sherif M. Sherif^c & Ayman W. Erian^c

^a Department of Chemistry , Faculty of Science, Al-Azhar University

^b Department of Photochemistry, National Research Center, Dokki

^c Department of Chemistry, Faculty of Science , Cairo University , Giza Published online: 03 Jan 2007.

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HETEROCYCLIC SULFONES IV:¹⁻³ A NOVEL SYNTHESIS OF PYRROLE AND FUSED HETEROCYCLIC SULFONES

FIVIAN F. MAHMOUD^a, NADIA R. MOHAMED^b, SHERIF M. SHERIF^c and AYMAN W. ERIAN^{c*}

"Department of Chemistry, Faculty of Science, Al-Azhar University, ^bDepartment of Photochemistry, National Research Center, Dokki and ^cDepartment of Chemistry, Faculty of Science, Cairo University, Giza

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The applicability and synthetic potency of the reagent diethyl 2-aryl-3-phenylsulfonylpropen-1,1-dicarboxylate 3 is reported. Compound 3 proved to be a key precursor in heterocyclic sulfones synthesis. Chemical and spectroscopic evidences for the structure of the newly synthesized compounds are described.

Keywords: Sulfones; pyrrole; benzoates; heterocycles

In view of the diverse biological and physiological activities of sulfones.¹⁻⁷ and in connection with our previous efforts directed towards the facile synthesis of heterocyclic ring systems, $^{8-12}$ we designed a simple program aimed at the development of convenient synthetic approches to heterocyclic sulfone systems of expected potential bioresponses utilizing the reagent **3** as a unique, key procursor. The newly synthesized sulfone derivatives appear to be promising for further chemical transformations as well as biological evaluations.

Diethyl 2-aryl-3-bromopropen-1,1,-dicarboxylate 2, prepared in our laboratories from 1^3 reacted with equimolar amounts of sodium benzenesulfinate in ethanolic solution to produce the corresponding reagent 3 (Scheme 1).

Compound 3 proved to be highly reactive towards various reagents forming a wide range of heterocyclic sulfone systems. Thus, compound 3

^{*} Corresponding Author.



could be brominated when equimolar amounts of **3a,b** and bromine in dry benzene were boiled under reflux to afford the corresponding diethyl 2-aryl-3-bromo-3-phenylsulfonylpropen-1,1-dicarboxylate 4. Treatment of 4 with the appropriate primary aromatic amine in ethanolic/triethylamine solutions afforded the corresponding phenylsulfonylpyrrole derivatives 5. The latter reaction yielded the corresponding ethyl 2-aryl-5-oxo-1-phenylsulfonylpyrrolo[2,1-b]-benzo-[d][1,3]oxazine-3-carboxylate 8 in a one-pot reaction if anthranilonitrile 6 was used. Similarly. the DYrrolo[2,1-b]thieno[2,3-d][1,3]oxazines 10 were obtained on treatment of 4a with the appropriate ethyl 2-aminothiophene-3-carboxylate 9 (Scheme 2).

Compound **3a** reacted with arylidenemalononitrile **11** to yield the corresponding ethyl 4-aryl-3-cyano-2-hydroxy-6-phenyl-5-phenylsulfonyl-benzoates **13**. Compound **13** was assumed to be formed via addition of **3a** to the activated double bond in **11** to yield the Michael adducts **12** which intramolecularly cyclized and aromatized, via loss of HCN, to give the final isolable ethyl benzoate derivative **13**. Compound **13a** could be prepared via an independent route involving the condensation of **3a** with benzaldehyde and subsequent addition of malononitrile to the so-formed benzylidene derivative **14** (Scheme **3**).

Compound **3a** readily coupled with equimolar amounts of aryldiazonium chloride to yield coupling products which may be formulated as hydrazone form **15** or its cyclic pyridazine form **18**. The hydrazone form **15** is preferred on the basis of its ¹H-NMR spectra which revealed the presence of multiplet signals corresponding for two ester groups. Further-





more, on boiling the hydrazone 15 in ethanolic sodium acetate solutions, the pyridazines 16 could be obtained.

The phenysulfonylpyridine derivative 17 was obtained in a good yield from the reaction of **3a** with benzoyl isothiocyanate in boiling dry dioxane. Compound 17 reacted with each of chloroacetonitrile or ethyl chloroacetate in the presence of K_2CO_3 to yield the corresponding ethyl thiazolo[2,3-*a*]pyridine-6-carboxylate derivatives 18.





Compound 3 reacted with equimolar amounts of trichloroacetonitrile in ethanolic/NaOAc solutions to produce exclusively the corresponding pyridine derivatives 19. The trichloromethyl group in 19 proved to be highly reactive towards nucleophilic reagents. Thus, compound 19 reacted readily with equimolar amounts of hydrazine hydrate in ethanol under reflux to give the corresponding ethyl 6-hydrazinopyridine-3-carboxylate derivatives 20. Compound 20a could be successfully cyclized into the corresponding ethyl 5-oxo-7-phenyl-8-phenylsulfonyltetrazolo[1,5-a]pyridine-6-carboxylate (21) upon treatment with equimolar proportion of NaNO₂ in

glacial acetic acid (Scheme 4). Treatment of 19 with $9a^{13}$ in absolute ethanol solution containing glacial acetic acid, under reflux, furnished the coresponding ethyl 8-aryl-4,6-dioxo-9-phenylsulfonyl-10*H*-pyrido[1,2-*a*] -thieno[2,3-*d*]pyrimidine-7-carboxylates 22. Similarly, ethyl pyrido[2,1-*b*] quinazoline-8-carboxylates 23 could be obtained upon treatment of 19 with anthranilonitrile 6.



SCHEME 4

EXPERIMENTAL

All melting points were uncorrected. IR spectra were recorded (KBr) on a Pye Unicam SP-1000 spectrometer. ¹H-NMR spectra were obtained on a Varian Gemini 200 MHz spectrometer using TMS as an internal reference. Chemical shifts are expresed as δ (ppm). Mass spectra were recorded on a GCMS-QP 1000 EX mass spectrometer operating at 70 eV. Microanalytical data were performed by the Microanalytical Unit, Cairo University. Compounds **2a,b** have been prepared according to our previously reported methodology.³

Diethyl 2-Aryl-3-phenylsulfonylpropen-1,1-dicarboxylate (3a,b; General Procedure

To a solution of **2a,b** (0.02 mol) in ethanol (50 ml) was added sodium benzenesulfinate (0.02 mol). The reaction mixture was refluxed for 3 h, and the solvent was triturated with cold H_2O (20 ml), whereby the solid product formed was collected by filtration, washed thoroughly with H_2O , dried, and crystallized from the appropriate solvent.

Diethyl 2-Phenyl-3-phenylsulfonylpropen-1,1-dicarboxylate (3a)

Yield (5.2 g, 65%), m.p. 110 °C (ethanol); IR: 3000–2950 (CH₂), 1715, 1700 (2 C=O) cm⁻¹; ¹H-NMR (DMSO- d_6) δ 1.08–1.30 (m, 6H, 2 CH₃), 3.80–4.28 (m, 4H, 2 CH₂), 4.66 (s, 2H, CH₂), 6.90–7.85 (m, 10H, aromatic protons); MS m/z: 402 (M⁺, 18%). Anal. calcd. for C₂₁H₂₂O₆S (402.46): C 62, 67, H 5.51, S 7.96. Found C 62.50, H 5.40, S 7.90.

Diethyl 2-(p-Chlorophenyl)-3-phenylsulfonylpropen-1,1dicarboxylate (3b)

Yield (5.9 g, 68%), m.p. 117 °C (ethanol); IR: 3000–2960 (CH₂), 1712, 1700, (2C=O) cm⁻¹; ¹H-NMR (DMSO- d_6) δ 1.05–1.25 (m, 6H, 2 CH₃), 3.70–4.22 (m, 4H, 2 CH₂), 4.65 (s, 2H, CH₂), 6.95–7.74 (m, 9H, aromatic protons); Anal. Calcd. for C₂₁H₂₁ClO₆S (436.90): C 57.73, H 4.84, Cl 8.11, S 7.33. Found C 57.80, H 4.70, Cl 8.00, S 7.50.

Diethyl 2-Aryl-3-bromo-3-phenylsulfonylpropen-1,1-dicarboxylate (4a,b; General Procedure)

To a solution of 3a,b (0.02 mol) in dry benzene (50 ml), was added dropwise bromine (0.02 mol). The reaction mixture was refluxed for 3 h, and the solvent was then evaporated in vacuo. The residue was triturated with ethanol, whereby the solid product formed was collected by filtration. dried, and crystallized from the appropriate solvent.

Diethyl 3-Bromo-2-phenyl-3-phenylsulfonylpropen-1,1-dicarboxylate (4a)

Yield (5.6 g, 59%), m.p. 146 °C (ethanol); IR: 1718, 1705 (2 C=O) cm⁻¹; ¹H-NMR (DMSO- d_6) δ 1.05–1.33 (m, 6H, 2 CH₃), 3.85–4.45 (m, 4H,

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 2 CH_2), 5.61 (s, 1H, CH), 6.95–7.90 (m, 10H, aromatic protons); Anal. calcd. for $C_{21}H_{21}BrO_6S$ (481.36): C 52.39, H 4.40, Br 16.60, S 6.66. Found C 52.30, H 4.20, Br 16.50, S 6.40.

Diethyl 3-Bromo-2-(p-chlorophenyl)-3-phenylsulfonylpropen-1,1-dicarboxylate (4b)

Yield (6.2 g, 60%), m.p. 151 °C (ethanol); IR: 1715, 1705 (2 C=O) cm⁻¹; ¹H-NMR (DMSO- d_6) δ 0.95–1.30 (m, 6H, 2 CH₃), 3.90–4.32 (m, 4H, 2 CH₂), 5.59 (s, 1H, CH), 6.85–7.90 (m, 9H, aromatic protons); Anal. calcd. for C₂₁H₂₀BrClO₆S (515.80): C 48.90, H 3.91, Br 15.49, Cl 6.87, S 6.22. Found C 48.80, H 3.90, Br 15.40, Cl 6.70, S 6.20.

Ethyl 1,4-Diaryl-2-hydroxy-5-phenylsulfonylpyrrole-3-carboxylates (5a-c, General Procedure)

To a warm solution of 4 (0.003 mol) in absolute ethanol (25 ml) containing anhydrous Et_3N (0.5 ml), was added the appropriate primary amine (0.003 mol). The reaction mixture was refluxed for 2 h, poured into cold water, then neutralized with dilute HCl. The solid product formed was collected by filtration, washed with water, dried and crystallized from the appropriate solvent.

Ethyl 1-(p-Chlorophenyl)-2-hydroxy-4-phenyl-5phenylsulfonylpyrrole-3-carboxylate (5a)

Yield (0.79 g, 55%), m.p. 160 °C (ethanol); IR: 3500–3330 (OH), 1690 (C=O) cm⁻¹; ¹H-NMR (DMSO- d_6) δ 1.22 (t, 3H, J = 8.2 Hz, CH₃), 4.13 (q, 2H, J = 8.2 Hz, CH₂), 6.90–7.83 (m, 14H, aromatic protons), 13.15 (s, 1H, OH); MS m/z: 481 (M⁺, 22%). Anal. calcd. for C₂₅H₂₀CINO₅S (481.95): C 62.30, H 4.18, Cl 7.35, N 2.91, S 6.5. Found C 62.30, H 4.00, Cl 7.30, N 2.70, S 6.50.

Ethyl 1-(p-Bromophenyl)-2-hydroxy-4-phenyl-5phenylsulfonylpyrrole-3-carboxylate (5b)

Yield (0.82 g, 52%), m.p. 171 °C (ethanol); IR: 3495–3335 (OH), 1690 (C=O) cm⁻¹: ¹H-NMR (DMSO- d_6) δ 1.25 (t, 3H, J = 8.2 Hz, CH₃), 4.18

(q, 2H, J = 8.2 Hz, CH₂), 6.81-7.79 (m, 14H, aromatic protons), 13.19 (s, 1H, OH); Anal. calcd. for C₂₅H₂₀BrNO₅S (526.40): C 57.04, H 3.83, Br 15.18, N 2.66, S 6.09. Found C 56.90, H 3.80, Br 15.10, N 2.40, S 6.00.

Ethyl 1,4-Di-(p-Chlorophenyl)-2-hydroxy--5phenylsulfonylpyrrole-3-carboxylate (5c)

Yield (0.86 g, 56%), m.p. 176 °C (ethanol); IR: 3500–3325 (OH), 1690 (C=O) cm⁻¹; ¹H-NMR (DMSO- d_6) δ 1.28 (t, 3H, J = 8.2 Hz, CH₃), 4.51 (q, 2H, J = 8.2 Hz, CH₂), 6.95–7.80 (m, 13H, aromatic protons), 13.10 (s, 1H, OH); Anal. calcd. for C₂₅H₁₉Cl₂NO₅S (516.39): C 58.14, H 3.71, Cl 13.73, N 2.71, S 6.21. Found C 58.10, H 3.60, Cl 13.70, N 2.60, S 6.00.

Ethyl 2-Aryl-5-oxo-1-phenylsulfonylpyrrolo[2,1-b]benzo[d][1,3]oxazine-3-carboxylates (8a,b; General Procedure)

A mixture of 4 (0.003 mol) and anthranilonitrile (6) (0.003 mol) in dry dioxane (30 ml) containing anhydrous Et_3N (1.0 ml) was refluxed for 3h. The reaction mixture was left aside at room temperature overnight, poured into an ice/water mixture and neutralized with dilute HCl. The solid so-formed was filtered off, washed with water, dried and crystallized from the appropriate solvent.

Ethyl 5-Oxo-2-phenyl-1-phenylsulfonylpyrrolo[2,1-b]benzo[d][1,3]oxazine-3-carboxylate (8a)

Yield (0.64 g, 45%), m.p. 182 °C (dioxane); IR: 1715, 1708 (C=O) cm⁻¹; ¹H-NMR (DMSO- d_6) δ 1.24 (t, 3H, J = 8.2 Hz, CH₃), 4.55 (q, 2H, J = 8.2 Hz, CH₂), 6.88–7.92 (m, 14H, aromatic protons); MS m/z: 312 (M⁺, 16%); Anal. calcd. for C₂₆H₁₉NO₆S (473.50): C 65.95, H 4.04, N 2.95, S 6.77. Found C 65.90, H 3.80, N 2.90, S 6.60.

Ethyl 2-(p-Chlorophenyl)-5-oxo-1-phenylsulfonylpyrrolo[2,1-b] benzo[d][1,3]oxazine-3-carboxylate (8b)

Yield (0.77 g, 51%), m.p. 189 °C (dioxane); IR: 1718, 1710 (C=O) cm⁻¹; ¹H-NMR (DMSO- d_6) δ 1.28 (t, 3H, J = 8.2 Hz, CH₃), 4.28 (q, 2H, J = 8.2 Hz, CH₂), 6.90–7.82 (m, 13H, aromatic protons); Anal. calcd. for C₂₆H₁₈ClNO₆S (507.94): C 61.48, H 3.57, Cl 6.98, N 2.75, S 6.31. Found C 61.40, H 3.40, Cl 6.90, N 2.50, S 6.20.

Ethyl 2-Aryl-5-oxo-1-phenylsulfonylpyrrolo[2,1-b]thieno[2,3-b][1,3]oxazine-3-carboxylates (10a,b; General Procedure)

A mixture of **4a** (0.003 mol) and the appropriate ethyl 2-aminothiophene-3-carboxylate **9** (0.003 mol) in dry dioxane (30 ml) containing Et_3N (1.0 ml) was refluxed for 3 h. The reaction mixture was poured onto cold water and neutralized with dilute HCl. The resulting precipitate was collected by filtation, dried and crystallized from the appropriate solvent.

Ethyl 6-Cyano-7-methyl-5-oxo-2-phenyl-1-phenylsulfonylpyrrolo[2,1-b]thieno[2,3-d]-[1,3]oxazine-3-carboxylate (10a)

Yield (0.65 g, 42%), m.p. 220 °C (dioxane); IR: 2218 (CN), 1720, 1712 (2 C=O) cm⁻¹; ¹H-NMR (DMSO- d_6) δ 1.15 (s, 3H, CH₃), 1.22 (t, 3H, J = 8.2 Hz, CH₃), 4.15 (q, 2H, J = 8.2 Hz, CH₂), 6.85–7.96 (m, 10H, aromatic protons); MS m/z: 518 (M⁺, 14%); Anal. calcd. for C₂₆H₁₈N₂O₆S₂ (518.56): C 60.22, H 3.49, N 5.40, S 12.36. Found C 60.10, H 3.40, N 5.40, S 12.20.

Diethyl 7-Methyl-5-oxo-2-phenyl-1-phenylsulfonylpyrrolo[2,1-b] thieno-[2,3-b][1,3]-oxazine-3,6-dicarboxylate (10b)

Yield (0.66 g, 39%), m.p. 192 °C (dioxane); IR: 1722, 1718, 1710 (3 C=O) cm⁻¹; ¹H-NMR (DMSO- d_6) δ 1.15 (s, 3H, CH₃), 1.05–1.29 (m, 6H, 2 CH₃), 3.85–4.28 (m, 4H, 2 CH₂), 6.91–7.88 (m, 10H, aromatic protons); Anal. calcd. for C₂₈H₂₃NO₈S₂(565.61): C 59.45, H 4.09, N 2.47, S 11.33. Found C 59.40, H 3.80, N 2.40, S 11.20.

Ethyl 4-Aryl-3-cyano-2-hydroxy-6-phenyl-5-phenylsulfonylbenzoates (13a-c; General Procedure)

Method A

A mixture of 3a (0.002 mol) and the appropriate arylidenemalono-nitrile 11 (0.002 mol) in ethanol (25 ml) containing Et_3N (0.5 ml) was heated

under reflux for 3h. The reaction mixture was evaporated in vacuo, triturated with cold water and neutralized with dilute HCl. The solid product was collected by filtration, dried and crystallized from the appropriate solvent.

Ethyl 3-Cyano-4,6-diphenyl-2-hydroxy-5-phenylsulfonylbenzoate (13a)

Yield (0.66 g, 69%), m.p. 220 °C (ethanol); IR: 3615 (OH), 2216 (CN), 1710 (C=O) cm⁻¹; ¹H-NMR (DMSO- d_6) δ 0.96 (t, 3H, J = 8.3 Hz, CH₃), 4.10 (q, 2H, J = 8.3 Hz, CH₂), 5.96 (s, 1H, OH), 6.82–7.91 (m, 15H, aromatic protons); MS m/z: 483 (M⁺, 15%); Anal. calcd. for C₂₈H₂₁NO₅S (483.53): C 69.55, H 4.37, N 2.89, S 6.63. Found C 69.50, H 4.30, N 2.80, S 6.50.

Ethyl 4-(p-Chlorophenyl)-3-cyano-2-hydroxy-6-phenyl-5phenylsulfonylbenzoate (13b)

Yield (0.68 g, 66%), m.p. 229 °C (dioxane); IR: 3620 (OH), 2218 (CN), 1710 (C=O) cm⁻¹; ¹H-NMR (DMSO- d_6) δ 0.92 (t, 3H, J = 8.3 Hz, CH₃), 4.23 (q, 2H, J = 8.3 Hz, CH₂), 5.94 (s, 1H, OH), 6.90–7.83 (m, 15H, aromatic protons); Anal. calcd. for C₂₈H₂₀ClNO₅S (517.98): C 64.92, H 3.89, CI 6.84, N 2.70, S 6.19. Found C 64.90, H 3.80, CI 6.70, N 2.60, S 6.00.

Ethyl 3-Cyano-2-hydroxy-6-phenyl-5-phenylsulfonyl-4-(p-tolyl)benzoate (13c)

Yield (0.60 g, 60%), m.p. 206 °C (dioxane); IR: 3615 (OH), 3025 (CH₃), 2218 (CN), 1710 (C=O) cm⁻¹; ¹H-NMR (DMSO- d_6) δ 0.95 (t, 3H, J = 8.2 Hz, CH₃), 2.21 (s, 3H, CH₃), 4.28 (q, 2H, J = 8.2 Hz, CH₂), 5.96 (s, 1H, OH), 6.93–7.91 (m, 14H, aromatic protons); Anal. calcd. for C₂₉H₂₃NO₅S (497.56): C 70.00, H 4.65, N 2.81, S 6.44. Found C 69.90, H 4.60, N 2.70, S 6.40.

Method B

A mixture of 14 (0.002 mol) and malononitrile (0.002 mol) in ethanol (25 ml) containing Et_3N (0.5 ml) was refluxed for 3 h. The reaction mixture

was poured into cold water and nuteralized with dilute HCl. The solid product formed was collected by filtration, dried, crystallized from ethanol, and found to be identical in all aspects (m.p., mixed m.p. and IR spectrum) with an authentic sample of **13a** prepared according to Method A.

Diethyl 2,4-Diphenyl-3-phenylsulfonylbut-1,3-diene-1,1-dicarboxylate (14)

A mixture of **3a** (0.003 mol) and benzaldehyde (0.003 mol) in absolute ethanol (30 ml) containing Et₃N (0.5 ml) was refluxed for 3 h. The reaction mixture was left to cool at room temperature, poured into cold water and neutralized with dilute HCl. The solid product formed was filtered off, dried and crystallized from ethanol. Yield (1.0 g, 69%), m.p. 173°C (ethanol); IR: 1715, 1700 (2 C=O), 1650 (C=C) cm⁻¹; ¹H-NMR (DMSO- d_6) δ 0.95–1.35 (m, 6H, 2 CH₃), 3.92–4.25 (m, 4H, 2 CH₂), 6.75–7.83 (m, 16H, aromatic protons and arylidene-CH); Anal. calcd. for C₂₈H₂₆O₆S (490.57): C 68.55, H 5.34, S 6.53. Found C 68.50, H 5.20, S 6.40.

Diethyl 3-Arylhydrazono-2-phenyl-3-phenylsulfonylpropen-1,1dicarboxylates (15a,b, General Procedure)

The appropriate aryldiazonium chloride (0.003 mol) [prepared by adding $NaNO_2$ (0.003 mol) to the appropriate primary aromatic amine (0.003 mol) in concentrated HCl (2 ml) at 0-5 °C and stirring] was added to a stirred solution of **3a** (0.003 mol) in ethanol (50 ml) containing NaOAc (2.0 g) dropwise while cooling at 0-5 °C and stirring. The reaction mixture was left aside at room temperature for 3 h, whereby the solid product formed was collected by filteration, dried and crystallized from the appropriate solvent.

Diethyl 3-(p-Chlorophenylhydrazono)-2-phenyl-3phenylsulfonylpropen-1,1-dicarboxylate (15a)

Yield (1.0 g, 65%), m.p. 165 °C (ethanol); IR: 3350–3320 (NH), 1718, 1700 (2 C=O) cm⁻¹; ¹H-NMR (DMSO- d_6) δ 0.96–1.25 (m, 6H, 2 CH₃), 3.95–4.05 (m, 4H, 2 CH₂), 6.73–7.56 (m, 14H, aromatic protons), 11.28 (br s, 1H, NH); MS m/z: 541 (M⁺, 18%); Anal. calcd. for C₂₇H₂₅CIN₂O₆S

(541.02): C 59.94, H 4.65, Cl 6.55, N 5.17, S 5.92. Found C 59.90, H 4.50, Cl 6.40, N 5.00, S 5.80.

Diethyl 3-(p-Bromophenylhydrazono)-2-phenyl-3phenylsulfonylpropen-1,1-dicarboxylate (15b)

Yield (1.07 g, 61%), m.p. 171 °C (dioxane); IR: 3350–3318 (NH), 1715, 1705 (2 C=O) cm⁻¹; ¹H-NMR (DMSO- d_6) δ 1.02–1.28 (m, 6H, 2 CH₃), 3.95–4.12 (m, 4H, 2 CH₂), 6.81–7.63 (m, 14H, aromatic protons), 11.54 (br s, 1H, NH); Anal. calcd. for C₂₇H₂₅BrN₂O₆S (585.47): C 55.39, H 4.30, Br 13.65, N 4.78, S 5.47. Found C 55.20, H 4.30, Br 13.50, N 4.60, S 5.40.

Ethyl 2-Aryl-2,3-dihydro-3-oxo-5-phenyl-6phenylsulfonylpyridazine-4-carboxylates (16a,b, General Procedure)

A solution of 15 (0.002 mol) in ethanol (30 ml) containing NaOAc (1.0 g) was refluxed for 3 h. The reaction mixture was poured into cold water and neutralized with dilute HCl. The resulting precipitated solid was filtered off, dried and crystallized from the appropriate solvent.

Ethyl 2-(p-Chlorophenyl)-2,3-dihydro-3-oxo-5-phenyl-6phenylsulfonyl-pyridazine-4-carboxylate (16a)

Yield (0.54 g, 55%), m.p. 195 °C (AcOH); IR: 1718, 1695 (2 C=O) cm⁻¹; ¹H-NMR (DMSO- d_6) δ 1.21 (t, 3H, J = 8.2 Hz, CH₃), 4.25 (q, 2H, J = 8.2 Hz, CH₂), 6.91–7.43 (m, 14H, aromatic protons); MS m/z 494 (M⁺, 14%): Anal. calcd. for C₂₅H₁₉ClN₂O₅S (494.94): C 60.66, H 3.86, Cl 7.16, N 5.66, S 6.47. Found C 60.50 H 3.80, Cl 7.00, N 5.50, S 6.40.

Ethyl 2-(p-Bromophenyl)-2,3-dihydro-3-oxo-5-phenyl-6phenylsulfonyl-pyridazine-4-carboxylate (16b)

Yield (0.62 g, 58%), m.p. 206 °C (AcOH); IR: 1718, 1700 (2 C=O) cm⁻¹; ¹H-NMR (DMSO- d_6) δ 1.21 (t, 3H, J = 8.2 Hz, CH₃), 4.09 (q, 2H, J = 8.2 Hz, CH₂), 6.85–7.40 (m, 14H, aromatic protons); Anal. calcd. for C₂₅H₁₉BrN₂O₅S (539.40): C 55.66, H 3.55, Br 14.81, N 5.19, S 5.94. Found C 55.60, H 3.40, Br 14.70, N 5.00, S 5.90.

Ethyl 1-Benzoyl-1,2-dihydro-2-oxo-6-mercapto-4-phenyl-5phenylsulfonyl-pyridine-3-carboxylate (17)

To a suspension of NH₄SCN (0.005 mol) in dioxane (50 ml), was added benzoyl chloride (0.005 mol). The reaction mixture was refluxed for 2 min., then treated with **3a** (0.005 mol). The reaction mixture was refluxed for 2 h, poured into ice/water, whereby the solid product formed was filtered and crystallized from dioxane. Yield (1.90 g, 66%), m.p. 210 °C; IR: 2250 (SH), 1718, 1705, 1684 (3 C=O) cm⁻¹; ¹H-NMR (DMSO-*d*₆) δ 1.20 (t, 3H, J = 8.2 Hz, CH₃), 3.24 (s, 1H, SH). 4.25 (q, 2H, J = 8.2 Hz, CH₂), 6.90–7.68 (m, 15H, aromatic protons); MS m/z: 573 (M⁺, 12%); Anal. calcd. for C₂₇H₂₁NO₆S₂ (519.58): C 62.41, H 4.07, N 2.69, S 12.13. Found C 62.40, H 4.00, N 2.80, S 12.40.

Ethyl 3,7-Dihydro-5-oxo-8-phenylsulfonylthiazolo[3,2-a]pyridine-6carboxylate derivatives (18a,b, General Procedure)

To a suspension of 17 (0.002 mol) in ethanol (30 ml), was added aqueous solution K_2CO_3 (0.004 mol in 20 ml H_2O), and the appropriate α -chloro compound (0.002 mol). The reaction mixture was refluxed for 2 h, left to cool at room temperature and poured into cold water. The solid product formed was filtered off and crystallized from the appropriate solvent.

Ethyl 2-Cyano-3,7-diphenyl-5-oxo-8-phenylsulfonylthiazolo[3,2-a]pyridine-6-carboxylate (18a)

Yield (0.67 g, 62%), m.p. > 250°C (dioxane); IR: 2218 (CN), 1715, 1700 (2 C=O) cm⁻¹; ¹H-NMR (DMSO- d_6) δ 1.15 (t, 3H, J = 8.2 Hz, CH₃), 4.12 (q, 2H, J = 8.2 Hz, CH₂), 6.93–7.55 (m, 15H, aromatic protons); MS m/z: 540 (M⁺, 16%); Anal. calcd. for C₂₉H₂₀N₂O₀S₂(540.61): C 64.43, H 3.72, N 5.18, S 11.86. Found C 64.30, H 3.70. N 5.00, S 11.80.

Diethyl 3,7-Diphenyl-5-oxo-8-phenylsulfonylthiazolo[3,2-a]pyridine-2,6-carboxylate (18b)

Yield (0.65 g, 56%), m.p. 212 °C (dioxane); IR: 1718, 1705, 1692 (3 C=O) cm⁻¹; ¹H-NMR (DMSO- d_6) δ 0.95–1.32 (m, 6H, 2 CH₃), 3.83–4.22 (m, 4H, 2 CH₂), 6.85–7.64 (m, 16H, aromatic protons). Anal. calcd. for

C₃₁H₂₅NO₇S₂ (587.66): C 63.35, H 4.28, N 2.38, S 10.91. Found C 63.20, H 4.20, N 2.20, S 10.90.

Ethyl 4-Aryl-1,2-dihydro-2-oxo-5-phenylsulfonyl-6-trichloromethylpyridine-3-carboxylates (19a,b, General Procedure)

To a suspension of 3a,b (0.005 mol) in ethanol (30 ml) containing NaOAc (0.5 g), was added trichloroacetonitrile (0.005 mol). The reaction mixture was heated under reflux for 2 h and left aside at room temperature overnight. The mixture was poured into an ice/water mixture, neutralized with dilute HCl, filtered off, washed with water, dried and crystallized from the appropriate solvent.

Ethyl 1,2-Dihydro-2-oxo-4-phenyl-5-phenylsulfonyl-6trichloromethyl-pyridine-3-carboxylate (19a)

Yield (1.53 g, 61%), m.p. 135 °C (ethanol); IR: 3370 (NH), 1715 (C=O) cm⁻¹; ¹H-NMR (DMSO- d_6) δ 1.12 (t, 3H, J = 8.2 Hz, CH₂), 6.70–7.82 (m, 10H, aromatic protons), 9.98 (br s, 1H, NH); MS m/z: 500 (M⁺, 12%). Anal. calcd. for C₂₁H₁₆Cl₃NO₅S (500.78): C 50.36, H 3.22, Cl 21.23, N 2.79, S 6.40. Found C 50.20, H 3.00, Cl 21.20, N 2.70, S 6.20.

Ethyl 4-(p-Chlorophenyl)-1,2-dihydro-2-oxo--phenylsulfonyl-6 -trichloro-methylpyridine-3-carboxylate (19b)

Yield (1.74 g, 65%), m.p. 142 °C (ethanol); IR: 3362 (NH), 1720, 1704 (2 C=O) cm⁻¹; ¹H-NMR (DMSO- d_6) δ 1.05 (t, 3H, J = 8.2 Hz, CH₃), 4.05 (q, 2H, J = 8.2 Hz, CH₂), 6.84–7.72 (m, 9H, aromatic protons), 10.52 (br s, 1H, NH); Anal. calcd. for C₂₁H₁₅Cl₄NO₅S (535.22): C 47.12, H 2.82, Cl 26.49, N 2.61, S 5.99. Found C 47.00, H 2.80, Cl 26.30, N 2.60, S 5.80.

Ethyl 4-Aryl-1,2-dihydro-6-hydrazino-2-oxo-5phenylsulfonylpyridine-3-carboxylates (20a,b, General Procedure)

A mixture of 19a,b (0.003 mol) and hydrazine hydrate (0.003 mol) in ethanol (30 ml) was refluxed for 30 min. and then left at room temperature overnight. The mixture was poured into cold water, whereby the solid product so-formed was filtered off and crystallized from the appropriate solvent.

Ethyl 4-(p-Chlorophenyl)-1,2-dihydro-6-hydrazino-2-oxo-5phenyl-sulfonylpyridine-3-carboxylate (20a)

Yield (0.80 g, 65%), m.p. 146°C (ethanol); IR: 3420–3380 (NH₂, NH), 1712, 1700 (2 C=O) cm⁻¹; ¹H-NMR (DMSO- d_6) δ 1.10 (t, 3H, J = 8.2 Hz, CH₃), 3.25 (br s, 2H, NH2), 4.14 (q, 2H, J = 8.2 Hz, CH₂), 6.29 (br s, 1H, NH), 6.89–7.48 (m, 10H, aromatic protons), 8.35 (br s, 1H, NH); Anal. calcd. for C₂₀H₁₉N₃O₅S (413.44): C 58.10, H 4.63, N 10.16, S 7.75. Found C 58.00, H 4.60, N 10.10, S 7.70.

Ethyl 1,2-Dihydro-6-hydrazino-2-oxo-4-phenyl-5-phenylsulfonylpyridine-3-carboxylate (20b)

Yield (0.83 g, 62%), m.p. 158 °C (ethanol); IR: 3428–3365 (NH₂, NH), 1715, 1708 (2 C=O) cm⁻¹; ¹H-NMR (DMSO- d_6) δ 1.12 (t, 3H, J = 8.2 Hz, CH₃). 3.61 (br s, 2H, NH₂), 4.23 (q, 2H, J = 8.2 Hz, CH₂), 6.35 (br s, 1H, NH), 6.92–7.51 (m, 9H, aromatic protons), 9.12 (br s, 1H, NH); Anal. calcd. for C₂₀H₁₈ClN₃O₅S (447.89): C 53.63, H 4.05, Cl 7.91, N 9.38, S 7.15. Found C 53.50, H 4.00, Cl 7.80, N 9.20, S 7.10.

Ethyl 5-Oxo-7-phenyl-8-phenylsulfonyltetraazolo[1,5-a]pyridine-6-carboxylate (21)

A solution of **20a** (0.002 mol) in glacial acetic acid (25 ml) was treated with NaNO₂ (0.004 mol) portionwise while stirring at room temperature. The reaction mixture was stirred for additional 1 h, whereby the solid product separated was filtered off, washed with water and crystallized from acetic acid. Yield (0.52 g, 61%), m.p. > 270 °C (ethanol); IR: 3450– 3415 (NH), 1715, 1705 (2 C=O) cm⁻¹; ¹H-NMR (DMSO-*d*₆) δ 0.95 (t, 3H, J = 8.2 Hz, CH₃), 4.00 (q, 2H, J = 8.2 Hz, CH₂), 6.85–7.55 (m, 10H, aromatic protons), 9.65 (br s, 1H, NH); Anal. calcd. for C₂₀H₁₆N₄O₅S (424.43): C 56.59, H 3.79, N 13.19, S 7.55. Found C 56.50, H 3.70, N 13.00, S 7.40.

Ethyl 8-Aryl-4,6-dioxo-9-phenylsulfonyl-10H-pyrido[1,2-a]thieno [2,3-d]-pyrimidine-7-carboxylates (22a,b, General Procedure)

To a solution of **19a,b** (0.002 mol) in absolute ethanol (30 ml) containing glacial acetic acid (1 ml), was added ethyl 2-amino-4-cyano-5-methylthiophene-3-carboxylate (**9a**)¹³ (0.002 mol). The reaction mixture was refluxed for 2 h., left aside to cool at room temperature and then poured into cold water. The solid product precipitated was filtered off, washed thoroughly with water and crystallized from the appropriate solvent.

Ethyl 3-Cyano-4,6-dioxo-8-phenyl-9-phenylsulfonyl-10H-pyrido [1,2-a]-thieno[2,3-d]-pyrimidine-7-carboxylate (22a)

Yield (0.70 g, 64%), m.p. 240 °C (DMF); IR: 3450–3420 (NH), 2220 (CN), 1718, 1710, 1705 (3 C=O) cm⁻¹; ¹H-NMR (DMSO-d₆) δ 1.12 (s. 3H, J = 8.2 Hz, CH₃), 2.15 (s, 3H, CH₃), 4.17 (q, 2H, J = 8.2 Hz, CH₂), 6.88–7.56 (m, 10H, aromatic protons), 9.61 (br s, 1H, NH); MS m/z: 545 (M⁺, 18%); Anal. calcd. for C₂₇H₁₉N₃O₆S₂(545.58): C 59.44, H 3.51, N 7.70, S 11.75. Found C 59.40, H 3.40, N 7.70, S 11.60.

Ethyl 8-(p-Chlorophenyl)-3-cyano-4,6-dioxo-9-phenylsulfonyl-10H-pyrido-[1,2-a]-thieno[2,3-d]-pyrimidine-7-carboxylate (22b)

Yield (0.70 g, 61%), m.p. > 250 °C (DMF); IR: 3456–3435 (NH), 2216 (CN). 1720, 1712, 1695 (3 C=O) cm⁻¹; ¹H-NMR (DMSO- d_6) δ 0.96 (s, 3H, J = 8.2 Hz, CH₃), 2.12 (s, 3H, CH₃), 4.05 (q, 2H, J = 8.2 Hz, CH₂), 6.73–7.51 (m, 9H, aromatic protons), 9.42 (br s, 1H, NH); Anal. calcd. for C₂₇H₁₈ClN₃O₆S₂ (580.03): C 55.91, H 3.12, Cl 6.11, N 7.24, S 11.05. Found C 55.80, H 3.00, Cl 6.10, N 7.00, S 11.00.

Ethyl 7-Aryl-9,11-dioxo-6-phenylsulfonylpyrido[2,1-b]quinazoline-8carboxylates (23a,b, General Procedure)

To a solution of 19a,b (0.002 mol) in absolute ethanol (30 ml) containing glacial acetic acid (1.0 ml) was added anthranilonitrile (6) (0.002 mol). The reaction mixture was refluxed for 2 h., left aside at room temperature overnight and then poured into cold water. The solid product precipitated was filtered off, dried and crystallized from the appropriate solvent.

Ethyl 9,11-Dioxo-7-phenyl-6-phenylsulfonylpyrido[2,1-b] quinazoline-8-carboxylate (23a)

Yield (2.95 g, 59%), m.p. 180 °C (ethanol); IR: 3445–3400 (NH), 1720, 1712, 1705 (3 C=O) cm⁻¹; ¹H-NMR (DMSO- d_6) δ 0.98 (s, 3H, J = 8.2 Hz, CH₃), 4.12 (q, 2H, J = 8.2 Hz, CH₂), 6.95–7.81 (m, 14H, aromatic protons), 9.73 (br s, 1H, NH); Anal. calcd. for C₂₇H₂₀N₂O₆S (500.52): C 64.79, H 4.03, N 5.59, S 6.40. Found C 64.60, H 4.00, N 5.60, S 6.50.

Ethyl 9,11-Dioxo-7-phenyl-6-phenylsulfonylpyrido[2,1-b] quinazoline-8-carboxylate (23a)

Yield (2.94 g, 55%), m.p. 192 °C (ethanol); IR: 3450–3415 (NH), 1718, 1710, 1700 (3 C=O) cm⁻¹; ¹H-NMR (DMSO- d_6) δ 0.95 (s, 3H, J = 8.2 Hz, CH₃), 4.00 (q, 2H, J = 8.2 Hz, CH₂), 6.80–7.75 (m, 13H, aromatic protons), 9.55 (br s, 1H, NH); Anal. calcd. for C₂₇H₁₉ClN₂O₆S (534.97): C 60.62, H 3.57, Cl 6.62, N 5.23, S 6.00. Found C 60.620, H 3.40, Cl 6.60, N 5.10, S 6.00.

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