Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926081

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To cite this Article Abu-Shanab, Fathi A.(2006) 'Synthesis of polyfunctionally substituted pyridine-2-(1*H*)-thiones containing a sulfone moiety', Journal of Sulfur Chemistry, 27: 5, 433 — 440
To link to this Article: DOI: 10.1080/17415990600875327
URL: http://dx.doi.org/10.1080/17415990600875327

Journal of Sulfur Chemistry
Vol. 27, No. 5, October 2006, 433–440

Taylor & Francis
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RESEARCH ARTICLE

Synthesis of polyfunctionally substituted pyridine-2-(1*H*)-thiones containing a sulfone moiety

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(Received 13 May 2006; in final form 16 June 2006)

1-Phenyl-2-(phenylsulfonyl)ethanone (**1**) reacts with DMFDMA to give enamine **2**, which upon treatment with cyanothioacetamide affords 3-cyano-5-benzenesulfonyl-4-phenylpyridine-2(1*H*)-thione (**4**), a compound that can also be obtained by the reaction of 1-benzenesulfonyl-1-benzoyl-2-ethoxyethene (**3**) with cyanothioacetamide. The reaction of 2-thiocarbamoylacetamide (**8a**) and N-phenyl-2-thiocarbamoylacetamide (**8b**) with 3-aryl-2-benzenesulfonylacrylonitrile (**9a–c**) affords **10a–f**. The methylation of **10d–f** with methyl iodide results in the formation of S-methyl derivatives (**12a–c**). Compound **12c** can be obtained by the reaction of **13** with **9c**.

Keywords: Dimethylformamide dimethyl acetal; Triethylorthoformate; Pyridine-2(1*H*)-thione; 1-phenyl-2-(phenylsulfonyl)ethanone; Dioxane

1. Introduction

Our efforts directed toward the preparation of polyfunctional pyridine-2-(1*H*)-thiones [1–6] are related to their use as versatile precursors in the preparation of dyes, herbicides, bactericides and other biologically active compounds [7–9]. The considerable activity of polyfunctional pyridines [10–12] as calcium channel blockers and as antiviral agents has stimulated considerable interest in the synthesis of pyridine derivatives [13]. Also sulfones have proven to be valuable for the preparation of a wide variety of biologically active heterocyclic systems [14, 15]. Hence, it was felt the presence of the sulfone moiety in the pyridinethione ring may increase its biological activity.

2. Results and discusion

The reaction of 1-phenyl-2-(phenylsulfonyl)ethanone (**1**) with N,N-dimethylformamide dimethyl acetal (DMFDMA) in dry dioxane at room temperature overnight followed by reflux

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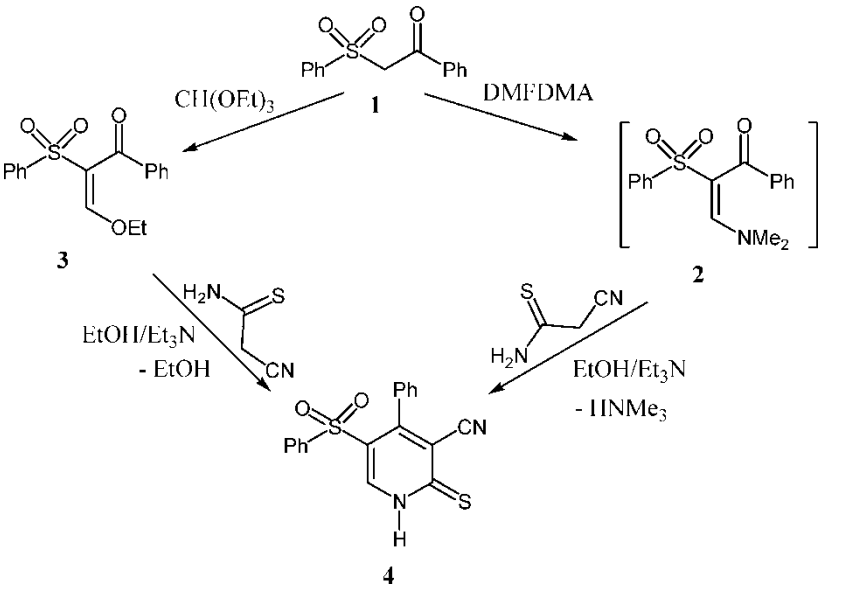
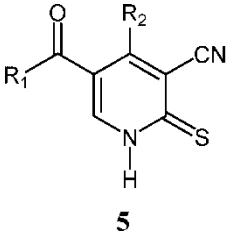
Journal of Sulfur Chemistry
ISSN 1741-5993 print/ISSN 1741-6000 online
http://www.tandf.co.uk/journals
DOI: 10.1080/17415990600875327



SCHEME 1

for about 2 h. gave the corresponding enamine **2**. This intermediate need not be isolated but can be reacted directly with cyanothioacetamide in a convenient process to give 3-cyano-5-benzenesulfonyl-4-phenyl-pyridine-2(1*H*)-thione (**4**) (scheme 1). Pyridine-2(1*H*)-thione **4** was also obtained by the reaction of **1** with triethyl orthoformate in acetic anhydride to give 1-benzoyl-1-benzenesulfonyl-2-ethoxyethene **3** after treatment with cyanothioacetamide. This outcome was confirmed by the elemental and spectroscopic analysis as well as mixed melting point. The reaction proceeds via condensation of the active methylene with the carbonyl group followed by cyclization and releasing of dimethylamine or ethanol to afford the target product (**4**).

The IR spectrum of compound **4** shows the presence of a cyano group at ν_{max} 2216 cm^{-1} and an NH at 3315 cm^{-1} and the ^1H NMR spectrum shows singlet signal at δ_H 4.25 ppm for one proton and multiplet for 11 protons at δ_H 6.78–7.8 ppm. However, the expected position for the ring proton is at about δ_H 8.5 ppm and the NH at about δ_H 13 ppm [2, 3, 17]. Moreover, the chemical shift of the ring proton for tetrasubstituted pyridines **5** and **6** predicts the chemical shift of the ring proton should appear between 8.75 to 9.38 ppm. Finally, the chemical shift of pyridine-2(1*H*)-thione, the parent compound, shows H-4 proton at δ_H 7.3 ppm and H-6 at δ_H 7.23 ppm [16].



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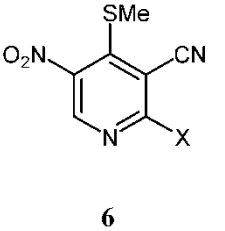

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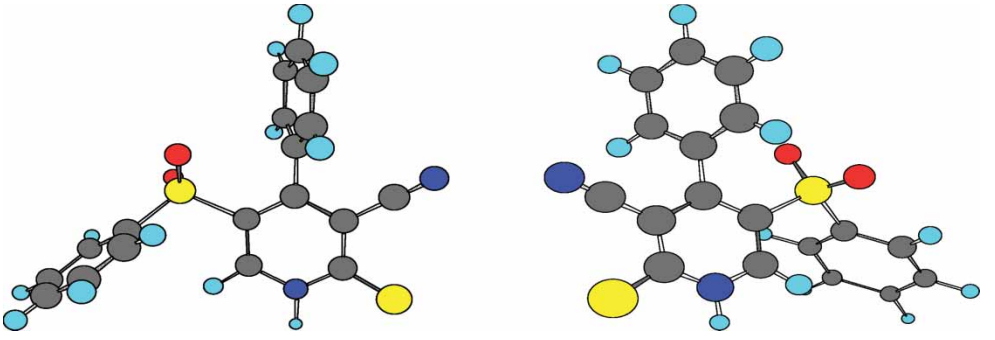
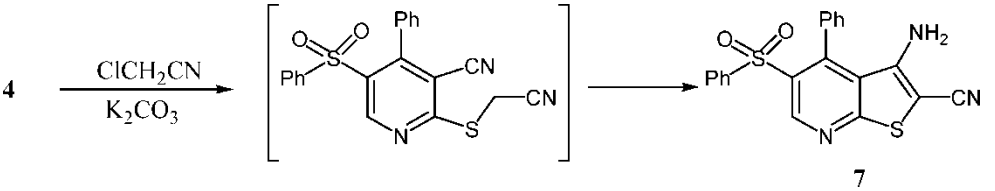


Figure 1. Molecular modeling minimization of 3-cyano-5-benzenesulfonyl-4-phenylpyridine-2(1*H*)-thione (**3**) shows that the ring-H6 and NH protons located in the positive cone of the phenyl ring of sulfonyl moiety.

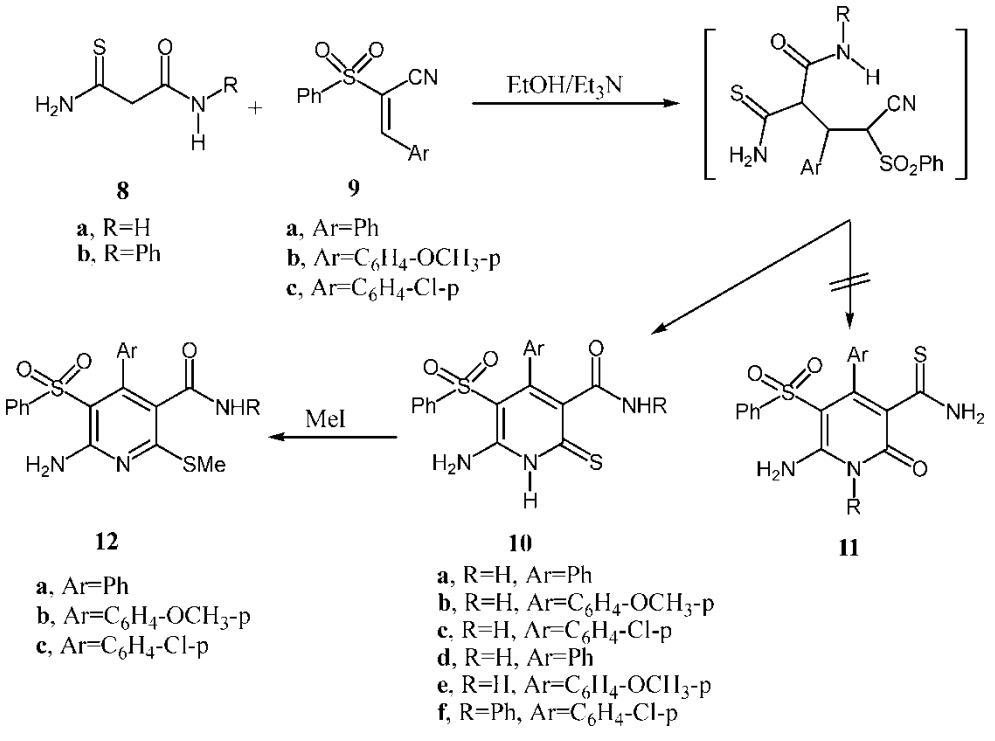
In our data, the ring proton is shifted upfield and appears at 4.25 ppm whereas the NH proton appear with aromatic protons at 7.6 ppm. Analysis of the pyridine-2(1*H*)-thione **4** by molecular modelling, (figure 1), shows that the ring-6 proton is located in the shielding region (positive cone) of the benzene ring of the sulfonyl moiety explaining why the proton appears more upfield than expected. Also the NH proton is affected by the shielding region (positive cone) of the benzene ring of the sulfonyl moiety and also appears upfield compared to prediction.

Pyridinethione **4** reacted with α-chloroacetonitrile in ethanol in the presence of potassium carbonate to afford 3-amino-5-benzenesulfonyl-4-phenyltheino[2,3-b]pyridine-2-carbonitrile (**7**). The reaction proceeds through S-alkylation followed by cyclization to give the target product **7**.



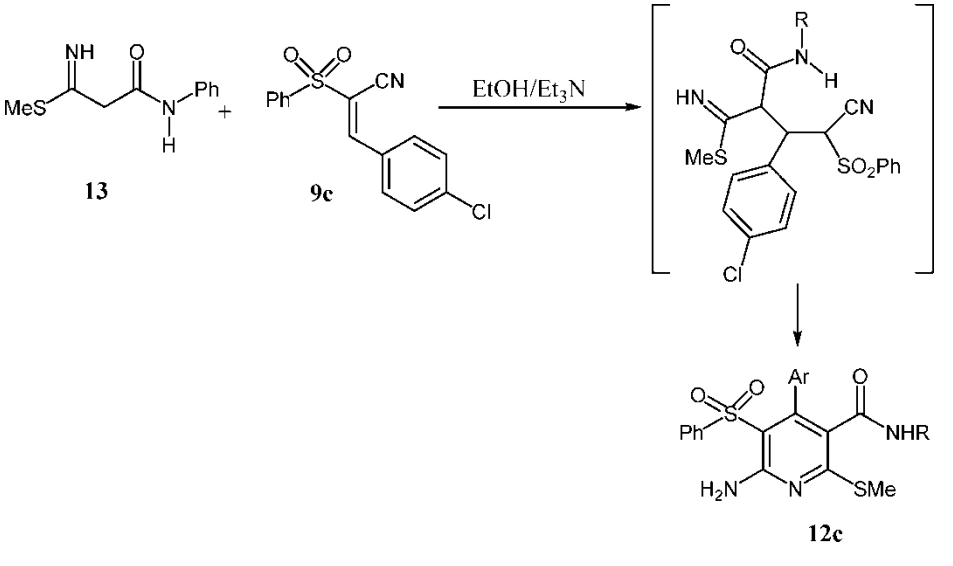
7

The reactions of 2-thiocarbamoylacetamide (**8a**) or N-phenyl-2-thiocarbamoylacetamide (**8b**) with 3-aryl-2-benzenesulfonyl-acrylonitrile (**9a–c**) in ethanolic triethylamine solution each afforded a single product in very good yield. The structure was surmised to be either **10** or **11**, but was eventually decided to be **10** on the basis of spectral data. In particular, the ^{1}H NMR spectra of the isolated products showed three types of exchangeable protons in accordance with structure **10** and the chemical shift values of the NH_2 groups in **10** are consistent with those of compounds with a somewhat similar structure [17]. Also structure **10** was further confirmed chemically based on its behavior towards different chemical reagents. Accordingly, methylation of **10d–f** with methyl iodide in methanolic potassium carbonate resulting in the formation of S-methyl derivatives **12a–c** (scheme 2). The ^{1}H NMR spectra of these compounds (**12a–c**) show the exchange of singlet at about 6.5 ppm for NHCS proton for compounds **10a–f** upon treatment with D_2O.



SCHEME 2

For further confirmation of structure, compound **12c** can also be obtained by the reaction of 2-phenylcarbamoylthioacetimidic acid methyl ester (**13**) [17] with **9c** in boiling ethanolic triethylamine. This was confirmed by spectral data as well as mixed melting point.



3. Experimental

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 1710 FTIR spectrometer as KBr disks. NMR spectra were recorded on Bruker AC300 spectrometer at 200 MHz for solutions of DMSO-d_6 or $CDCl_3$ with tetramethylsilane (TMS) as an internal standard unless otherwise recorded. Mass spectra were obtained on Finnigan 4500 (low resolution) spectrometer using electron impact (EI). The starting materials **8a, b, 9a–c** and **13** were prepared by literature procedure [17]. Also cyanothioacetamide was prepared by literature procedure [18] and DMFDMA is commercially obtained from Aldrich.

3.1 *1-Benzoyl-1-phenylsulfonyl-2-ethoxyethene 3*

A solution of phenacyl sulfone **1** (2.6 g, 0.01 mol) and triethyl orthoformate (1.4 g, 0.01 mol) in acetic anhydride (20 ml) was left under reflux for 30 min. The solid obtained was collected by filtration after the vaporization of excess acetic anhydride recrystallized from ethanol as yellow crystals; yield 2.7 g (65%), mp 145–147 °C. IR: (υ_{max}/cm^{-1}): 1715 (CO), 1620 (C=C). NMR ^{1}H, $CDCl_3$, δ (ppm): 0.9 (t, 3H, CH_3, J = 6.9 Hz), 3.82 (q, 2H, CH_2, J = 6.9 Hz), 6.21 (s, 1 H, olefinic proton), 6.81–7.80 (m, 10H, Ar) EI-MS: m/z = 316 (M^+). Anal. Calcd (%) for $C_{17}H_{16}O_4S$: C, 64.54; H, 5.10; S, 10.14. Found: C, 64.3; H, 4.8; S, 9.9%.

3.2 *5-Benzensulfonyl-3-cyano-4-phenylpyridine-2(1H)-thione 4*

3.2.1 Method A. A solution of unsaturated sulfone **1** (2.6 g, 0.01 mol) in dry dioxane is treated with DMFDMA (1.19 g, 0.01 mol) and left stirring over night followed by reflux for about 2 h. The mixture was treated with cyanothioacetamide [18] (1.0 g, 0.01 mol) in ethanol and catalytic amount of triethylamine, left under reflux for 4 h. and poured on to ice/water. The solid obtained was recovered by filteration and recrystallized from ethanol as brown crystals. Yield 2 g, (62%), mp 195–197 °C. IR: (υ_{max}/cm^{-1}) 3320 (NH), 2218 (CN), 1620 (C=C). NMR ^{1}H, DMSO-d_6, δ (ppm): 4.25 (s, 1H, ring proton), 6.78–7.80 (m, 11H, Ar and NH) EI-MS: m/z = 352 (M^+). Anal. Calcd (%) for $C_{18}H_{12}N_2O_2S_2$: C, 61.34; H, 3.43; N, 7.95; S, 18.20. Found: C, 61.1; H, 3.2; N, 7.8; S, 18.0%.

3.2.2 Method B. To a solution of **3** (3.1 g, 0.01 mol) in ethanol (40 ml), cyanothioacetamide (1.0 g, 0.01 mol) and a catalytic amount of triethylamine were added. The reaction mixture was left under reflux for 4 h and poured on to ice/water. The solid obtained was recovered by filtration and recrystallized from ethanol to give 2.1 g (57%) of compound **4** (mp and mixed mp is the same) 195–197 °C.

3.3 *3-Amino-5-benzenesulfonyl-2-cyano-4-phenylthieno[2,3-b]pyridine 7*

A solution of pyridine-2(1*H*)-thione **3** (3.2 g, 0.01 mol) in ethanol (40 ml), 2-chloroacetonitrile (0.75 g, 0.01 mol) and potassium carbonate (0.05 g) were added. The reaction mixture was left under reflux for 3 h. After cooling the reaction mixture was diluted with water and the solid obtained was recrystallized from ethanol as orange crystals. Yield 1.9 g (54%); mp 176–178 °C. IR: (υ_{max}/cm^{-1}) 3450, 3320 (NH_2), 2216 (CN), 1615 (C=C). NMR ^{1}H, DMSO-d_6, δ (ppm); 4.3 (s, 1H, ring-H), 4.43 (exch., 2H, NH_2), 6.72–7.82 (m, 10H, Ar). EI-MS: m/z = 391 (M^+).

Anal. Calcd (%) for $C_{20}H_{13}N_3O_2S_2$: C, 61.36; H, 3.35; N, 10.73; S, 16. Found: C, 61.1; H, 3.2; N, 10.6; S, 15.8%.

3.4 *6-Amino-4-aryl-5-benzenesulfonyl-3-carboxamidopyridine-2(1H)-thione (10a–f)*

3.4.1 General procedure. To a solution of anilide (**8a, b**) (0.01 mol) in ethanol (50 ml), 3-aryl-2-benzenesulfonyl-acrylonitrile (**9a–c**) and a catalytic amount of triethylamine were added. The reaction mixture was left under reflux for 3 h. and poured on to ice/water the solid obtained was collected by filtration and recrystallized from ethanol.

3.4.2 6-Amino-5-benzenesulfonyl-3-carboxamido-4-phenylpridine-2(1H)-thione (10a). Yellow crystals; yield 59%; mp 212–214 °C. IR: (υ_{max}/cm^{-1}) 3400–3320 (NH, NH_2), 1670 (C=O), NMR ^{1}H, DMSO-d_6, δ_H (ppm); 4.25 (exch. br, 2H, NH_2), 4.46 (exch. br, 2H, NH_2), 6.50 (exch. s, 1H, NH), 6.75–7.92 (m, 9H, Ar) EI-MS: m/z = 385 (M^+). Anal. Calcd (%) for $C_{18}H_{15}N_3O_3S_2$: C, 56.09; H, 3.92; N, 10.90; S, 16.64. Found: C, 55.8; H, 3.8; N, 10.6; S, 16.4%.

3.4.3 6-Amino-5-benzenesulfonyl-3-carboxamido-4-(4-methoxyphenyl)-pridine-2(1H)-thione (10b). Yellow crystals; yield 60%; mp 220–222 °C. IR: (υ_{max}/cm^{-1}) 3450–3320 (NH, NH_2), 1675 (C=O), NMR ^{1}H, DMSO-d_6, δ (ppm); 2.93 (s, 3H, OCH_3), 4.23 (exch. br, 2H, NH_2), 4.45 (exch. br, 2H, NH_2), 6.20 (exch. s, 1H, NH), 6.8–7.8 (m, 9H, Ar). EI-MS: m/z = 415 (M^+). Anal. Calcd (%) for $C_{19}H_{17}N_3O_4S_2$: C, 54.92; H, 4.12; N, 10.11; S, 15.44. Found: C, 54.8; H, 3.8; N, 10.0; S, 15.2%.

3.4.4 6-Amino-5-benzenesulfonyl-3-carboxamido-4-(4-chlorophenyl)-pridine-2(1H)-thione (10c). Yellow crystals; yield 65%; mp 190–192 °C. IR: (υ_{max}/cm^{-1}) 3450–3320 (NH, NH_2), 1675 (C=O), NMR ^{1}H, DMSO-d_6, δ (ppm); 4.21 (exch. br, 2H, NH_2), 4.45 (exch. br, 2H, NH_2), 6.60 (exch. s, 1H, NH), 6.68–7.81 (m, 9H, Ar) EI-MS: m/z = 419 (M^+). Anal. Calcd (%) for $C_{18}H_{14}ClN_3O_3S_2$: C, 51.49; H, 3.36; N, 10.01; S, 15.27. Found: C, 51.2; H, 3.1; N, 9.8; S, 15.0%.

3.4.5 6-Amino-5-benzenesulfonyl-4phenyl-3-(N-phenylcarboxamido)-pridine-2(1H)-thione (10d). Yellow crystals; yield 70%; mp 250–252 °C. IR: (υ_{max}/cm^{-1}) 3450–3320 (NH, NH_2), 1670 (C=O), NMR ^{1}H, DMSO-d_6, δ (ppm); 4.25 (exch. br, 2H, NH_2), 6.50 (exch. s, 1H, NH), 6.72–7.81 (m, 15H, Ar) 12.23 (exch. s, 1H, NH) EI-MS: m/z = 461 (M^+). Anal. Calcd (%) for $C_{24}H_{19}N_3O_3S_2$: C, 62.45; H, 4.15; N, 9.10; S, 13.89. Found: C, 62.1; H, 3.9; N, 9.8; S, 13.6%.

3.4.6 6-Amino-5-benzenesulfonyl-4-(4-methoxyphenyl)-3-(N-phenylcarboxamido)-pridine-2(1H)-thione (10e). Yellow crystals; yield 80%; mp 200–202 °C. IR: (υ_{max}/cm^{-1}) 3440–3320 (NH, NH_2), 1670 (C=O). NMR ^{1}H, DMSO-d_6, δ (ppm); 4.25 (exch. br, 2H, NH_2), 6.52 (exch. s, 1H, NH), 6.7–7.8 (m, 14H, Ar), 12.22 (exch. s, 1H, NH). EI-MS: m/z = 491 (M^+). Anal. Calcd (%) for $C_{25}H_{21}N_3O_4S_2$: C, 61.08; H, 4.31; N, 8.55; S, 13.05. Found: C, 60.8; H, 4.1; N, 8.3; S, 12.8%.

3.4.7 6-Amino-5-benzenesulfonyl-4-(4-chlorophenyl)-3-(N-phenylcarboxamido)-pridine-2(1H)-thione (10f). Yellow crystals; yield 70%; mp 230–232 °C. IR: (υ_{max}/cm^{-1}) 3450–3320 (NH, NH_2), 1670 (C=O). NMR ^{1}H, DMSO-d_6, δ (ppm); 4.27 (exch. br, 2H, NH_2), 6.60 (exch. s, 1H, NH), 6.7–7.8 (m, 14H, Ar), 12.23 (exch. s, 1H, NH). EI-MS: m/z = 495 (M^+). Anal. Calcd (%) for $C_{24}H_{18}ClN_3O_3S_2$: C, 58.12; H, 3.66; N, 8.47; S, 12.93. Found: C, 57.8; H, 3.4; N, 8.2; S, 12.7%.

3.5 *6-Amino-5-arylsulfonyl-2-methylsulfanyl-4,N-diphenyl-nicotinamide (12a–c)*

3.5.1 General procedure: Method A. To a solution of 6-amino-4-aryl-5-benzenesulfonyl-3-carboxamidopyridine-2(1*H*)-thione **10d–f** (0.01 mol) in methanol (30 ml) methyl iodide (0.01 mol) and potassium carbonate were added. The reaction mixture was left under reflux for 2 h. followed by filtration and the filtrate was diluted by water. The solid obtained was recovered by filtration and recrystallized from ethanol.

3.5.2 Method B. Equimolar amounts of **13** (0.01 mol) and 2-benzenesulfonyl-3-(4-chlorophenyl)acrylonitrile **9c** (0.01 mol) in absolute ethanol in the presence of catalytic amount of triethylamine was left under reflux for 3 h. The reaction mixture was diluted with water and the solid obtained was collected by filtration to give **12c**.

3.5.3 6-Amino-5-benzenesulfonyl-2-methylsulfenyl-4,N-diphenylnicotinmide (12a). Yellow crystals; yield 55%; mp 180–182 °C. IR: (υ_{max}/cm^{-1}) 3450–3320 (NH, NH_2), 1670 (C=O). NMR ^{1}H, DMSO-d_6, δ (ppm); 2.93 (s, 3H, CH_3), 4.42 (exch. br, 2H, NH_2), 6.75–7.81 (m, 15H, Ar), 12.41 (exch. s, 1H, NH). EI-MS: m/z = 475 (M^+). Anal. Calcd (%) for $C_{25}H_{21}N_3O_3S_2$: C, 63.14; H, 4.45; N, 8.84; S, 13.48. Found: C, 62.9; H, 4.2; N, 8.6; S, 13.2%.

3.5.4 6-Amino-5-benzenesulfonyl-4-(4-methoxy-phenyl)-2-methylsulfenyl-N-phenyl-nicotinamide (12b). Yellow crystals; yield 70%; mp 210–212 °C. IR: (υ_{max}/cm^{-1}) 3440–3320 (NH, NH_2), 1675 (C=O). NMR ^{1}H, DMSO-d_6, δ (ppm); 2.93 (s, 3H, CH_3), 2.95 (s, 3H, CH_3), 4.40 (exch. br, 2H, NH_2), 6.7–7.79 (m, 14H, Ar), 12.22 (exch. s, 1H, NH). EI-MS: m/z = 505 (M^+). Anal. Calcd (%) for $C_{26}H_{23}N_3O_4S_2$: C, 61.76; H, 4.59; N, 8.31; S, 12.68. Found: C, 61.5; H, 4.3; N, 8.1; S, 12.4%.

3.5.5 6-Amino-5-benzenesulfonyl-4-(4-chloro-phenyl)-2-methylsulfenyl-N-phenyl-nicotinamide (12c). Orange crystals; yield 60%; mp 190–192 °C. IR: (υ_{max}/cm^{-1}) 3450–3320 (NH, NH_2), 1670 (C=O). NMR ^{1}H, DMSO-d_6, δ (ppm); 2.89 (s, 3H, CH_3), 4.40 (exch. br, 2H, NH_2), 6.71–7.79 (m, 14H, Ar), 12.23 (exch. s, 1H, NH). EI-MS: m/z = 510 (M^+). Anal. Calcd (%) for $C_{25}H_{20}ClN_3O_3S_2$: C, 58.87; H, 3.95; N, 8.24; S, 12.57. Found: C, 58.6; H, 3.7; N, 8.0; S, 12.3%.

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