

REGIOSELECTIVE SYNTHESIS OF A NEW CLASS OF N-ARYLSULFONYLAMINATED BIHETEROCYCLES

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Abstract- A novel and efficient method for the synthesis of a new variety of novel N-arylsulfonylamino derivatives of biheterocycles by the reaction of N-cyanoaceto-arylsulphonylhydrazides with α,β -unsaturated nitriles. The synthetic potential of the method is demonstrated.

Recently, we have undertaken a comprehensive study of N-alkylated pyridines and related compounds and have reported the synthesis of new N-substitutedamino-2-pyridones¹⁻³. The synthetic applications of cyanoacetyl-N-arylsulfonylhydrazides **2** as reaction intermediate for the synthesis of a variety of interesting N-sulfonatedaminoheterocycles has aroused considerable interest from us during the last decade⁴⁻⁷. Since these compounds have been shown to constitute a new class of antimetabolites. It was of interest to evaluate synthetic methods for preparation of their analogues and demonstrate the effects of various structural modification on biological activity. To this end, the present investigation reports the synthesis of novel N-arylsulfonylamino derivatives of biheterocycles. As far as we know this is the first class of this type to be reported for N-substituted-aminopyridines. Thus, it has been found that cyanoaceto-hydrazide **1** reacts with arenesulfonyl chlorides in ethanol to afford the corresponding cyanoacetyl-N-arylsulfonylhydrazides **2** in good yields. Compounds **2** reacted with β -(2-furanyl)- and β -(2-thienyl)acrylonitrile derivatives **3a-d** in refluxing ethanol containing catalytic amounts of piperidine to give the corresponding N-arylsulfonylamino-2-pyridones **6a-h**. The structures of **6** were established on the basis of elemental analysis and spectral data (MS, IR, ¹H NMR). Thus, structure **6c** is supported by its mass spectrum which showed a molecular ion corresponding to the formula C₁₇H₁₁N₅S₂O₃ (M⁺ = 397). The ¹H NMR spectrum contained a multiplet at δ = 7.27-7.96 ppm assigned to the thiophene and aromatic protons, a broad band at δ = 8.5 ppm assigned to an amino function, and a broad singlet at δ = 8.84 ppm assigned to the NH group. The ¹³C NMR spectra were characterized by a signal at δ = 168.8 ppm corresponding to the carbonyl carbon atom. The formation of **6** from **2** and **3a-d** is assumed to proceed via addition of the active methylene group of **2** to the double bond of **3** to give the intermediates **4**. This Michael adduct then cyclizes to give the intermediate dihydropyridines **5**, which is oxidised under the reaction conditions to give the novel N-arylsulfonylamino-2-pyridone derivatives **6**. Compounds **6** could also be prepared by the reaction of the reported N-amino-2-pyridones **8**⁸ with arenesulfonyl chlorides in ethanol containing catalytic amounts of piperidine at room temperature for 24 h. The course of the reaction between the N-cyanoacetylarylsulphonylhydrazides **2** and **3** prompted us to investigate this reaction between **2** and **3** under other basic reaction conditions. In contrast, it has been found that compounds **3** reacted with ethyl furfurylidene- and thiophenylidenecyanoacetates **3c,d** in refluxing pyridine for 1 h to yield a product for which the N-arylsulphonylamino-6-hydroxy-2-pyridones **10a-d** were assigned. The each structure of compounds **10** was established on the basis of elemental analysis and spectral data. The formation of **10** from **2** and **3c,d** is assumed to proceed via addition of the active methylene

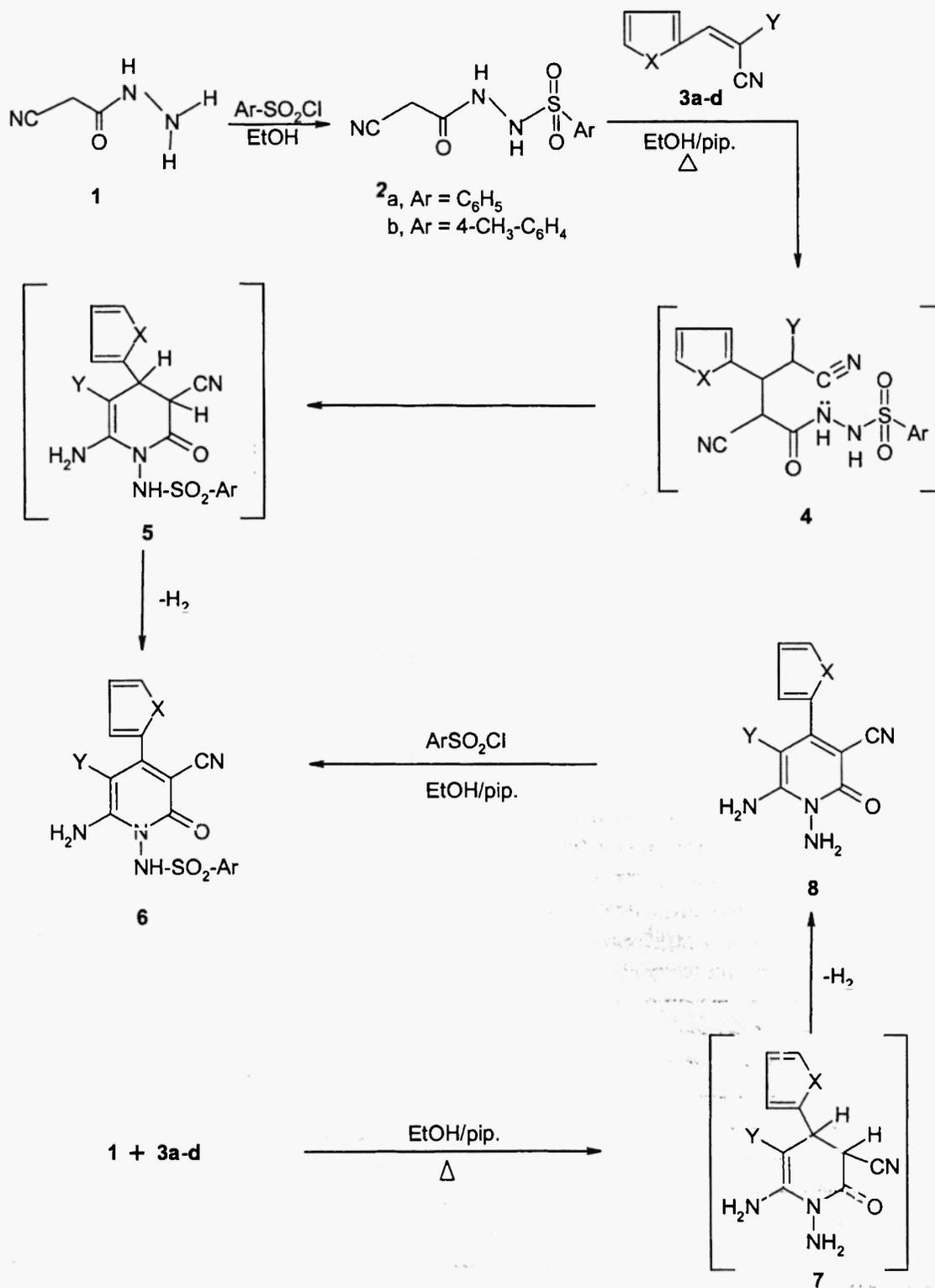
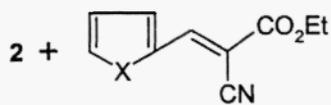
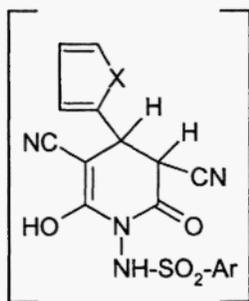
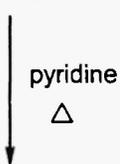


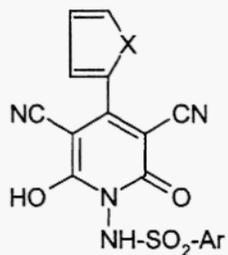
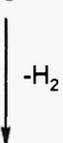
Chart (1)



3c,d



9



10

3	X	Y
a,	O	CN
b,	S	CN
c,	O	CO ₂ Et

6	X	Y	Ar
a,	O	CN	C ₆ H ₅
b,	O	CN	4-CH ₃ -C ₆ H ₄
c,	S	CN	C ₆ H ₅
d,	S	CN	4-CH ₃ -C ₆ H ₄

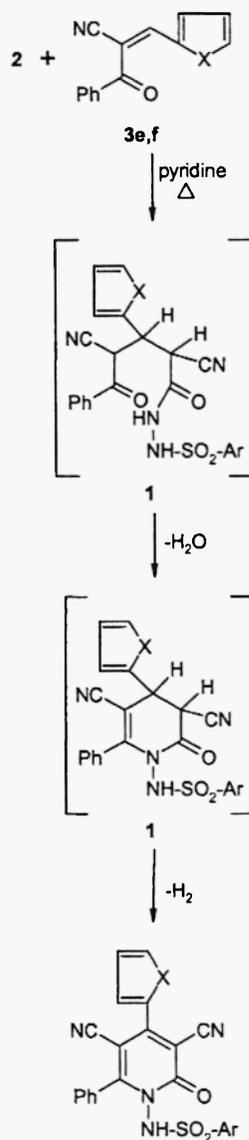
10	X	Ar
a,	O	C ₆ H ₅
b,	O	4-CH ₃ -C ₆ H ₄

3	X	Y
d,	S	CO ₂ Et
e,	O	COPh
f,	S	COPh

6	X	Y	Ar
e,	O	CO ₂ Et	C ₆ H ₅
f,	O	CO ₂ Et	4-CH ₃ -C ₆ H ₄
g,	S	CO ₂ Et	C ₆ H ₅
h,	S	CO ₂ Et	4-CH ₃ -C ₆ H ₄

10	X	Ar
c,	S	C ₆ H ₅
d,	S	4-CH ₃ -C ₆ H ₄

Chart (2)



13	X	Ar
a,	O	C ₆ H ₅
b,	O	4-CH ₃ -C ₆ H ₄
c,	S	C ₆ H ₅
d,	S	4-CH ₃ -C ₆ H ₄

Chart (3)

group of **2** to the double bond of **3** to give intermediate acyclic adducts, which were cyclized via ethanol elimination to give the intermediate dihydropyridines **9**. The later are oxidized under the reaction conditions to yield the novel *N*-arylsulfonylaminated-6-hydroxy-2-pyridone derivatives **10**. In order to investigate the scope of this reaction further we studied the reaction of **2** with furfurylidene- and thiophenylidene derivatives of ketonitriles. Thus, it has been found that compounds **2** reacted with furfurylidene- and thiophenylidene derivatives of benzoylacetonitrile **3e,f** in refluxing pyridine to yield the *N*-sulfonylaminated pyridones **13**. The structures of **13** were established on the basis of their elemental analysis and spectral data. Thus, structure **13a** is supported by its ¹H NMR spectroscopy which revealed a multiplet at $\delta = 7.00\text{--}7.80$ ppm assigned to the furan and aromatic protons and a broad singlet at $\delta = 11.90$ ppm assigned to the NH proton.

In summary, we have achieved a regiospecific synthesis of interesting N-sulfonated aminopyridines by the reaction of cyanosulphonylhydrazides with α,β -unsaturated nitriles. The compounds obtained seem promising for further chemical transformations and biological evaluation studies.

Experimental

All melting points are uncorrected. IR spectra were obtained (KBr disc) on a Pye Unicam instrument. ^1H NMR spectra were measured on a Varian 400 or Wilmad 270 MHz spectrometer for solutions in $(\text{CD}_3)_2\text{SO}$ using SiMe_4 as internal standard. Mass spectra were recorded on a Varian MAT 112 spectrometer. The analytical data were obtained from the Microanalytical Data Center at Cairo University. Compounds **3** were prepared through a Knoevenagel condensation of 2-furfuraldehyde or 2-thiophenylaldehyde with malononitrile, ethyl cyanoacetate or benzoylacetonitrile, respectively. Compounds **8** were prepared following literature procedures⁸.

Cyanoacetyl-N-arylsulfonylhydrazides **2a,b**

A mixture of cyanoacetoamide **1** (0.01 mol) and arenesulfonyl chloride (0.01 mol) in ethanol (30 ml) was stirred at room temperature for 24 h. The resulting solid product was collected by filtration and recrystallized from ethanol.

2a: white, mp 170 °C (from EtOH) yield (80%); IR (KBr disc) $\nu_{\text{max}} / \text{cm}^{-1}$ 3407, 3284 (NH, NH), 2215 (CN), and 1672 cm^{-1} (CO); ^1H NMR δ 3.63 (s, 2H, CH_2), 7.56-7.86 (m, 5H, C_6H_5), 10.11 (s, br, 1H, NH), and 10.40 (s, br, 1H, NH); $\text{C}_9\text{H}_9\text{N}_3\text{O}_3\text{S}$ (293) (M^+ = 239), Calcd: C, 45.2; H, 3.8; N, 17.6. Found: C, 45.0; H, 3.5; N, 17.3 %.

2b: white, mp 180 °C (from EtOH), yield (85%); $\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}_3\text{S}$, Calcd: C, 47.4; H, 4.3; N, 16.6. Found: C, 47.0; H, 4.1; N, 16.3%.

N-Arylsulfonylamino-2-pyridones **6a-h**

Method a: A mixture of compounds **2a,b** (0.01 mol) and β -(2-furanyl)- or β -(2-thienyl) acrylonitrile derivatives **3a-d** (0.01 mol) in ethanol (30 ml) containing a few drops of piperidine is refluxed for 3 h. The resulting product precipitates from the hot solution is collected by filtration and then recrystallized from the appropriate solvent.

Method b: To a mixture of **8** (0.01 mol) and an arenesulfonyl chloride (0.01 mol) in ethanol (50 ml) was added piperidine (0.05 ml). The reaction mixture was stirred at room temperature until the reaction was complete (TLC) and then set aside overnight. The resultant precipitate was filtered off and crystallized from the appropriate solvent.

6a: reddish brown, m.p 302-304 °C (from EtOH) yield (94%); IR (KBr disc) $\nu_{\text{max}} / \text{cm}^{-1}$ 3320, 3280 (NH, NH_2), 2214 (CN), 1690 (CO); ^1H NMR (DMSO) δ : 7.15-7.90 (m, 8H, furan H-3,4,5 and C_6H_5), 8.90 (s, br, 2H, NH_2), 11.50 (s, br, 1H, NH); $\text{C}_{17}\text{H}_{11}\text{N}_5\text{O}_4\text{S}$ (381), Calcd: C, 53.54; H, 2.88; N, 18.37. Found: C, 53.1; H, 2.1; N, 18.3%.

6b: red, m.p > 300 °C (from EtOH) yield (86 %); IR (KBr disc) $\nu_{\text{max}} / \text{cm}^{-1}$ 3320, 3300 (NH, NH_2); 2220 (CN), 1670 (CO); ^1H NMR (DMSO) δ , 2.51 (s, 3H, CH_3), 7.25-7.94 (m, 7H, furan H-3,4,5 and C_6H_4), 8.50 (s, br, 2H, NH_2), 11.80 (s, br, 1H, NH); $\text{C}_{18}\text{H}_{13}\text{N}_5\text{O}_4\text{S}$ (395), Calcd: C, 54.68; H, 3.29; N, 17.70. Found: C, 55.0; H, 3.3; N, 17.5%.

6c: white, m.p 240-242 °C (from EtOH) yield (90 %); IR (KBr disc) $\nu_{\text{max}} / \text{cm}^{-1}$ 3380, 3271 (NH, NH_2); 2259 (CN), 1680 (CO); ^1H NMR (DMSO) δ , 7.00-7.70 (m, 8H, thiophene H-3,4,5 and C_6H_5), 7.78 (s, br, 2H, NH_2), 11.77 (s, br, 1H, NH); $\text{C}_{17}\text{H}_{11}\text{N}_5\text{O}_3\text{S}_2$ (397) (M^+ =397), Calcd: C, 51.38; H, 2.77; N, 17.63. Found: C, 51.1; H, 3.0; N, 17.9%.

6d: white, m.p 158-160 °C (from EtOH) yield (95 %); IR (KBr disc) $\nu_{\text{max}} / \text{cm}^{-1}$ 3450, 3390, 3197 (NH, NH_2), 2214 (CN), 1690 (CO); ^1H NMR (DMSO) δ , 2.68 (s, 3H, CH_3), 7.18 (s, br, 2H, NH_2), 7.73-8.21 (m, 7H, thiophene H-3,4,5 and C_6H_4), 11.65 (s, br, 1H, NH), $\text{C}_{18}\text{H}_{13}\text{N}_5\text{O}_3\text{S}_2$ (411), Calcd: C, 52.55; H, 3.16; N, 17.93. Found: C, 53.0; H, 2.9; N, 16.8%.

6e: reddish brown, m.p > 300 °C (from EtOH) yield (85 %); IR (KBr disc) $\nu_{\text{max}} / \text{cm}^{-1}$ 3350, 3190 (NH_2), 1720 (CO), 1632 (CO); ^1H NMR (DMSO) δ , 0.99 (t, 3H, CH_3), 3.90 (q, 2H, CH_2), 7.12-7.88 (m, 8H, furan H-3,4,5 C_6H_5), 8.56 (s, br, 2H, NH_2), 10.3 (s, 1H, NH); $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_6\text{S}$ (428), Calcd: C, 53.27; H, 3.73; N, 13.08. Found: C, 52.9; H, 3.9; N, 13.9%.

6f: reddish brown, m.p > 300 °C (from EtOH) yield (95 %); IR (KBr disc) $\nu_{\text{max}} / \text{cm}^{-1}$ 3307 (NH, NH_2), 2225 (CN), 1737 (CO), 1680 (CO); ^1H NMR (DMSO) δ , 0.75 (t, 3H, CH_3), 2.42 (s, 3H, CH_3), 3.72 (q, 2H, CH_2), 7.25-7.8 (m, 7H, furan H-3,4,5 C_6H_4), 8.18 (s, br, 2H, NH_2), 9.20 (s, 1H, NH); $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}_6\text{S}$ (442), Calcd: C, 54.29; H, 4.07; N, 12.66. Found: C, 54.4; H, 3.8; N, 13.0 %.

6g: yellow, m.p over 300 °C (from EtOH) yield (89 %); IR (KBr disc) $\nu_{\text{max}} / \text{cm}^{-1}$ 3213 (NH, NH_2), 1722 (CO), 1670 (CO); ^1H NMR (DMSO) δ , 0.90 (t, 3H, CH_3), 4.00 (q, 2H, CH_2), 7.00-7.80 (m, 8H, thiophene H-3,4,5 C_6H_5), 9.50 (s, br, 2H, NH_2), 10.0 (s, 1H, NH); $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_5\text{S}_2$ (444), Calcd: C, 51.35; H, 3.60; N, 12.61. Found: C, 50.8; H, 3.5; N, 13.1%.

6h: yellow, m.p 182-184 °C (from EtOH) yield (87 %); IR (KBr disc) $\nu_{\text{max}} / \text{cm}^{-1}$ 3400, 3194 (NH, NH_2), 1621 (CO), 1720 (CO); ^1H NMR (DMSO) δ , 1.10 (t, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.98 (q, 2H, CH_2), 7.25-

7.8 (m, 7H, thiophene H-3,4,5 C₆H₄), 8.90 (s, br, 2H, NH₂), 9.55 (s, 1H, NH); C₂₀H₁₈N₄O₅S₂ (458), Calcd: C, 52.40; H, 3.93; N, 12.23. Found: C, 52.6; H, 4.2; N, 12.5%.

N-Arylsulphonylamino-3,5-dicyano-2-pyridones 10a-d

General procedure:

Method (1):

A mixture of ethyl 2-furfurylidene- (3c) or 2-thiophenylideneacyanoacetate (3d) (0.01 mol) and arylsulphonylcyanoacetohydrazide 2a,b (0.01 mol) was heated under reflux in pyridine (30 ml) for 1 h. The solution mixture was poured over an ice-water mixture and neutralized with dil. HCl to precipitate the solid product. The performed product isolated by suction and recrystallized from the appropriate solvent.

10a: white, m.p 260-262 °C (from EtOH) yield (78 %); IR (KBr disc) ν_{\max} / cm⁻¹ 3420, 3300 (OH, NH); 2220 (CN); 1690 (CO); ¹H NMR (DMSO) δ 7.00-7.80 (m, 8H, furan H-3,4,5 and C₆H₅); 7.99 (s, br, 1H, OH), 8.30 (s, br, 1H, NH); C₁₇H₁₀N₄O₅S (382), Calcd: C, 53.40; H, 2.62; N, 14.65. Found: C, 53.4; H, 2.4; N, 15.1%.

10b: white, m.p 218-220 °C (from EtOH) yield (75 %); IR (KBr disc) ν_{\max} / cm⁻¹ 3330, 3260 (OH, NH); 2220 (CN); 1680 (CO); ¹H NMR (DMSO) δ 2.21 (s, 3H, CH₃); 7.20-7.50 (m, 7H, furan H-3,4,5 and C₆H₄); 7.80 (s, br, 1H, OH), 8.22 (s, br, 1H, NH); C₁₈H₁₂N₄O₅S (396), Calcd: C, 54.54; H, 3.03; N, 14.14. Found: C, 54.6; H, 3.1; N, 14.3%.

10c: yellow, m.p 245-247 °C (from EtOH) yield (89 %); IR (KBr disc) ν_{\max} / cm⁻¹ 3340, 3300 (OH, NH); 2220 (CN); 1660 (CO); C₁₇H₁₀N₄O₄S₂ (398), Calcd: C, 51.26; H, 2.51; N, 14.70. Found: C, 50.3; H, 2.7; N, 14.7%.

10d: yellow, m.p > 300 °C (from EtOH) yield (81 %); IR (KBr disc) ν_{\max} / cm⁻¹ 3440-3250 (OH, NH); 2220 (CN); 1660 (CO); ¹H NMR (DMSO) δ 2.44 (s, 3H, CH₃); 7.15-7.58 (m, 7H, thiophene H-3,4,5 and C₆H₄); 7.99 (s, br, 1H, OH), 8.77 (s, br, 1H, NH); C₁₈H₁₂N₄O₄S₂ (412), Calcd: C, 52.42; H, 2.91; N, 13.59. Found: C, 52.3; H, 3.0; N, 13.8%.

N-Arylsulphonylamino-6-aryl-3,5-dicyano-2-pyridones 13

General procedure .

A mixture of 2-furfurylidene- (3e) or 2-thiophenylidene derivatives of benzoylacetone-nitrile (3f) (0.01 mol) and arylsulphonyl cyanoacetohydrazide 2a,b (0.01 mol) was heated under reflux in pyridine (30 ml) for 1 h. The solution mixture was poured over an ice-water mixture and neutralized with dil. HCl to precipitate the solid product. The performed product was isolated by suction and recrystallized from the appropriate solvent.

13a: white, m.p 271-273 °C (from EtOH) yield (72 %); ¹H NMR (DMSO) δ 7.52-7.99 (m, 13H, furan H-3,4,5 and 2C₆H₅), 12.55 (s, br, 1H, NH); C₂₃H₁₄N₄O₄S (442), Calcd: C, 62.44; H, 3.16; N, 12.66. Found: C, 62.3; H, 3.2; N, 12.8%.

13b: white, m.p 290-292 °C (from EtOH) yield (75 %); IR (KBr disc) ν_{\max} / cm⁻¹ 3350, 3250 (NH); 2220 (CN); 1690 (CO); ¹H NMR (DMSO) δ 2.25 (s, 3H, CH₃); 7.65-8.00 (m, 12H, furan H-3,4,5, C₆H₅, C₆H₄), 8.27 (s, br, 1H, NH); ¹³C NMR (DMSO) δ 21.22 (CH₃), 98.34 (CN), 101.15 (CN), 119.21-140.00 (furan and phenyl-C), 149.59 (C-3), 152.33 (C-5), 153.18 (C-4), 159.69 (C-6), 163.36 (C-2); C₂₄H₁₆N₄O₄S (456), Calcd: C, 63.15; H, 3.51; N, 12.28. Found: C, 62.9; H, 3.8; N, 12.6%.

13c: yellow, m.p 253-255 °C (from EtOH) yield (86 %); ¹H NMR (DMSO) δ 7.00-7.80 (m, 13H, thiophene H-3,4,5 and 2C₆H₅), 12.00 (s, br, 1H, NH); C₂₃H₁₄N₄O₃S₂ (458), Calcd: C, 60.26; H, 3.05; N, 12.22. Found: C, 60.3; H, 3.2; N, 12.6%.

13d: yellow, m.p 280-282 °C (from EtOH) yield (80 %); ¹H NMR (DMSO) δ 2.34 (s, 3H, CH₃); 7.22-8.04 (m, 12H, thiophene H-3,4,5, C₆H₅, C₆H₄), 8.55 (s, br, 1H, NH); C₂₄H₁₆N₄O₃S₂ (472), Calcd: C, 61.01; H, 3.38; N, 11.86. Found: C, 60.0; H, 3.3; N, 12.0%.

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