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DESIGN AND SYNTHESIS OF A NEW CLASS OF *N*-ARYLSULFONYLAMINATED PYRIDONES

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A novel synthesis of *N*-arylsulfonylamino-2-pyridones via reaction of arylmethylene-malononitriles with cyanoacetyl-*N*-arylsulfonylhydrazides is reported and the synthetic potential of the method is demonstrated.

Keywords: *N*-Sulfonylaminated pyridones; arylmethylidenemalononitriles; Michael addition

This is a part of our program for the development of new simple and efficient procedures for the synthesis of antimetabolites.^{1,7} Recently, arylsulfonylhydrazones of pyridines have been shown to cause inhibition of thymidine and uridine incorporation into DNA and RNA, thus they have useful properties as antimetabolites in biochemical reactions.^{8,9} Since these sulfonylhydrazones appear to constitute a new class of compounds with potent antineoplastic properties, it was of interest to evaluate synthetic methods for the preparation of their analogues. To this end, the present investigation reports the synthesis of novel *N*-arylsulfonylamino derivatives of pyridones. As far as we know this is the first class of this type to be reported for pyridones. 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. Compound **2a** possesses the molecular formula C₉H₉N₃O₃S (M⁺239). Its ¹H NMR spectrum contains signals at δ = 3.63 ppm assignable to a CH₂

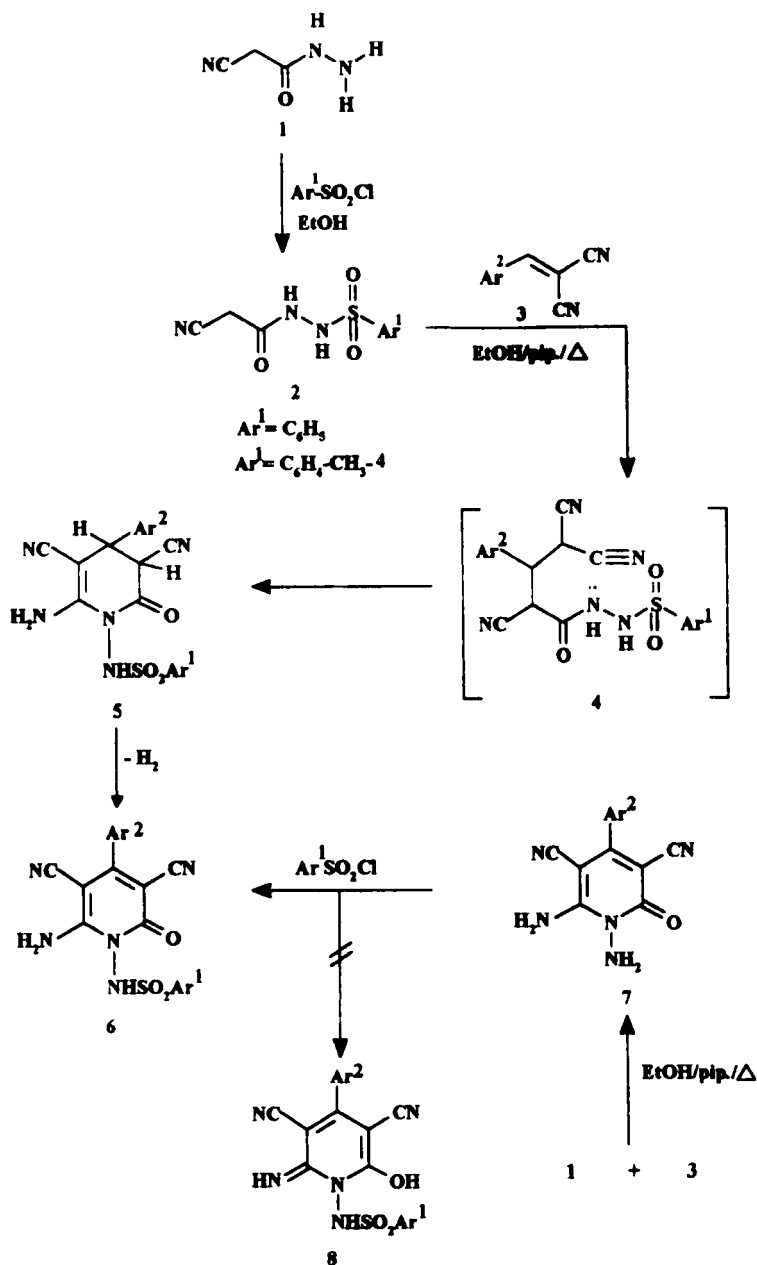
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group, a multiplet at $\delta = 7.56\text{--}7.86$ ppm assigned for aromatic protons and two broad singlets at $\delta = 10.11$ and 10.40 ppm assignable for two NH groups. Compounds **2** reacted with arylmethylenemalononitriles **3** in refluxing ethanol containing catalytic amounts of piperidine to give the corresponding *N*-arylsulfonylamino-2-pyridones **6** or **8** in good yields. The structures **8** were excluded due to the absence of imine and hydroxy functions from their ^1H NMR spectra. Structure **6a** is supported by its mass spectrum which showed a molecular ion corresponding to the formula $\text{C}_{19}\text{H}_{13}\text{N}_5\text{O}_3\text{S}$ (M^+ 391). The ^1H NMR spectrum contained a multiplet at $\delta = 7.40\text{--}7.93$ ppm assigned to the aromatic protons, a broad band at $\delta = 8.78$ ppm assigned to an amino function, and a singlet at $\delta = 11.62$ ppm assigned to the NH group. The ^{13}C NMR spectra were characterized by a signal at $\delta = 164.80$ ppm corresponding the carbonyl carbon atom. The formation of **6** from **2** and **3** 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 dihydropyridine derivatives **5**, which is oxidised under the reaction conditions to the novel *N*-arylsulfonylamino-2-pyridone derivatives **6**. The reaction of cyanoaceto-hydrazide **1** with **3** and piperidine in ethanol leads to the reported *N*-amino-2-pyridones **7**.¹⁰ When **7** was left to react with arenesulfonyl chlorides in ethanol containing catalytic amounts of piperidine at room temperature for 24 h, the corresponding *N*-arylsulfonylamino-2-pyridones **6** were obtained in good yield.

This result indicates that the reaction of cyanoacetyl-*N*-arylsulfonyl-hydrazides with α,β -unsaturated nitriles can be utilized as an excellent route for the synthesis of several *N*-sulfonated aminopyridine derivatives, which are otherwise accessible only with difficulty. The obtained compounds are now under 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.



6	Ar¹	Ar²	6	Ar¹	Ar²
a	C₆H₅	C₆H₅	g	C₆H₄-CH₃-4	C₆H₅
b	C₆H₅	C₆H₄-Cl-4	h	C₆H₄-CH₃-4	C₆H₄-Cl-4
c	C₆H₅	C₆H₄-CH₃-4	i	C₆H₄-CH₃-4	C₆H₄-CH₃-4
d	C₆H₅	C₆H₄-OCH₃-4	j	C₆H₄-CH₃-4	C₆H₄-OCH₃-4
e	C₆H₅	C₆H₄-NO₂-4	k	C₆H₄-CH₃-4	C₆H₄-NO₂-4
f	C₆H₅	2-furyl	l	C₆H₄-CH₃-4	2-furyl

Compounds **3** were prepared through a Knoevenagel condensation of aromatic aldehydes with malononitrile and compounds **7** were prepared following literature procedures¹⁰.

Arylsulphonylcianoacetohydrazide **2a,b**

A mixture of cyanoaceto-hydrazide **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** (80% yield): mp 170°C; IR (KBr) 3407, 3284 (NH, NH), 2215 (CN), and 1672 cm⁻¹(CO); ¹H NMR δ 3.63 (s, 2H, CH₂), 7.56–7.86 (m, 5H, C₆H₅), 10.11 (s, br, 1H, NH), and 10.40 (s, br, 1H, NH); MS: M⁺ 239. Found: C, 45.0; H, 3.5; N, 17.3%; Calcd for C₉H₉N₃O₃S: C, 45.2; H, 3.8; N, 17.6%.

2b (85% yield): mp 180°C. Found: C, 47.0; H, 4.1; N, 16.3%. Calcd for C₁₀H₁₁N₃O₃S: C, 47.4; H, 4.3; N, 16.6%.

N-Arylsulfonylamino-2-pyridone derivatives **6a-l**

Method a

A mixture of compounds **2a,b** (0.01 mol) and arylmethylenemalononitriles **3a-l** (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 **7** (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 (65% yield): mp 225°C; from EtOH, IR (KBr) 3461, 3300, 3219 (NH, NH₂), 2220 (CN), and 1692 cm⁻¹ (CO); ¹H NMR δ 7.40–7.93 (m, 10 H, 2 C₆H₅), 8.78 (s, br, 2H, NH₂), 11.62 (s, br, 1H, NH). ¹³C NMR δ 110.62 (CN), 114.23 (CN), 118.67 (C-5), 124.06 (C-3), 128.07–133.82 (Ar-C), 150.60 (C-4), 151.61 (C-6), 164.80 (C-2). MS: M⁺ 339 Found: C, 58.5; H, 3.0; N, 18.0%;. Calcd for C₁₉H₁₃N₅O₃S: C, 58.3; H, 3.3; N, 17.9%.

6b (55% yield); mp 215°C; from EtOH-DMF, IR (KBr) 3453, 3396, 3258 (NH, NH₂), 2259 (CN), 2220 (CN), and 1673 cm⁻¹ (CO). ¹H NMR δ 7.18–7.89 (m, 9H, C₆H₅, C₆H₄), 8.28 (s, br, 2H, NH₂), 11.28 (s, br, 1H, NH). Found: C, 53.1; H, 3.1; N, 16.2%. Calcd for C₁₉H₁₂ClN₅O₃S: C, 53.6; H, 2.8; N, 16.5%.

6c (52% yield): mp >300°C; from EtOH-DMF, IR (KBr) 3364, 3277 (NH, NH₂), 2213 (CN), and 1647 cm⁻¹ (CO). Found: C, 59.5; H, 3.3; N, 17.0%. Calcd for C₂₀H₁₅N₅O₃S: C, 59.3; H, 3.7; N, 17.3%.

6d (62% yield): mp 250°C; from EtOH-DMF, IR (KBr) 3315 (NH, NH₂), 2213 (CN), and 1650 cm⁻¹ (CO). ¹H NMR δ 3.88 (s, 3H, OCH₃), 7.09–7.77 (m, 9H, C₆H₅, C₆H₄), 8.56 (s, br, 2H, NH₂), 11.52 (s, br, 1H, NH). Found: C, 56.5; H, 3.2; N, 16.9%. Calcd for C₂₀H₁₅N₅O₄S: C, 57.0; H, 3.6; N, 16.6%.

6e (45% yield): mp 290°C; from EtOH-DMF, IR (KBr) 3471, 3352 (NH, NH₂), 2218 (CN), and 1682 cm⁻¹ (CO). Found: C, 52.5; H, 2.5; N, 19.0%. Calcd for C₁₉H₁₂N₆O₅S: C, 52.2; H, 2.8; N, 19.3%.

6f (44% yield): mp 210°C; from EtOH-DMF, IR (KBr) 3318, 3248 (NH, NH₂), 2217 (CN), and 1667 cm⁻¹ (CO). Found: C, 53.0; H, 2.7; N, 18.6%. Calcd for C₁₇H₁₁N₅O₄S: C, 53.5; H, 2.9; N, 18.4%.

6g (60% yield): mp 280°C; from EtOH, IR (KBr) 3470, 3392, 3353, 3218 (NH, NH₂), 2209 (CN), and 1665 cm⁻¹ (CO). ¹H NMR δ 2.59 (s, 3H, CH₃), 7.21–7.88 (m, 9H, C₆H₅, C₆H₄), 8.18 (s, br, 2H, NH₂), 11.92 (s,

br, 1H, NH). ^{13}C NMR δ 18.86 (CH_3), 111.28 (CN), 113.92 (CN), 121.23 (C-5), 126.24 (C-3), 129.21–138.32 (Ar-C), 149.23 (C-4), 154.23 (C-6), 168.21 (C-2). Found: C, 59.0; H, 3.5; N, 17.5%. Calcd for $\text{C}_{20}\text{H}_{15}\text{N}_5\text{O}_3\text{S}$: C, 59.3; H, 3.7; N, 17.3%.

6h (72% yield): mp 240°C; from EtOH, IR (KBr) 3434, 3297, 3233 (NH, NH_2), 2221 (CN), and 1733 cm^{-1} (CO); ^1H NMR δ 2.41 (s, 3H, CH_3), 7.39–7.55 (m, 8H, $2\text{C}_6\text{H}_4$), 8.94 (s, br, 2H, NH_2), and 11.58 (s, br, 1H, NH). Found: C, 55.0; H, 3.4; N, 15.6%. Calcd for $\text{C}_{20}\text{H}_{14}\text{ClN}_5\text{O}_3\text{S}$: C, 54.6; H, 3.2; N, 15.9%.

6i (62% yield) mp 227°C; from MeOH, IR (KBr) 3334, 3204 (NH, NH_2), 2221 (CN), and 1733 cm^{-1} (CO). Found: C, 59.5; H, 3.8; N, 17.1%; Calcd for $\text{C}_{21}\text{H}_{17}\text{N}_5\text{O}_3\text{S}$: C, 60; H, 4.0; N, 16.9%.

6j (66% yield): mp 260°C; from EtOH, IR (KBr) 3338, 3206 (NH, NH_2), 2214 (CN), and 1608 cm^{-1} (CO). Found: C, 58.1; H, 3.8; N, 16.7%. Calcd for $\text{C}_{21}\text{H}_{17}\text{N}_5\text{O}_4\text{S}$: C, 57.9; H, 3.9; N, 16.9%.

6k (62% yield): mp 262°C; from EtOH-DMF, IR (KBr) 3427, 3343, 3281 (NH, NH_2), 2219 (CN), and 1633 cm^{-1} (CO); ^1H NMR δ 2.45 (s, 3H, CH_3), 7.21 (s, br, 2H, NH_2), 7.80–8.40 (m, 8H, $2\text{C}_6\text{H}_4$), 11.82 (s, br, 1H, NH). Found: C, 53.5; H, 2.9; N, 18.5%. Calcd for $\text{C}_{20}\text{H}_{14}\text{N}_6\text{O}_5\text{S}$: C, 53.3; H, 3.1; N, 18.7%.

6l (47% yield): mp 255°C; from MeOH, IR (KBr) 3597, 3465, 3287 (NH, NH_2), 2216 (CN), and 1685 cm^{-1} (CO). Found: C, 54.2; H, 3.5; N, 17.5%. Calcd for $\text{C}_{18}\text{H}_{13}\text{N}_5\text{O}_4\text{S}$: C, 54.7; H, 3.3; N, 17.7%.

N-Amino-2-pyridones 7a-l

A mixture of **1** and **3** (0.01 mol) in ethanol (30 ml) containing piperidine (0.5 ml) is refluxed for 15 min. The resulting product is collected by filtration and crystallized from the appropriate solvent.

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