Synthesis of Heterocyclic Compounds; XL. Regioselective Synthesis of 4-Substituted 2-Amino-5-cyano-6-methoxy-3-benzenesulfonylpyridines

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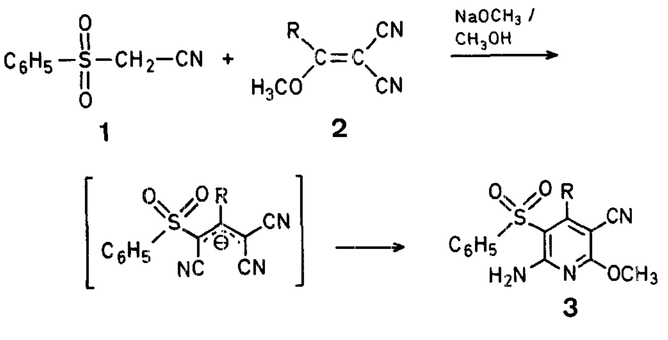
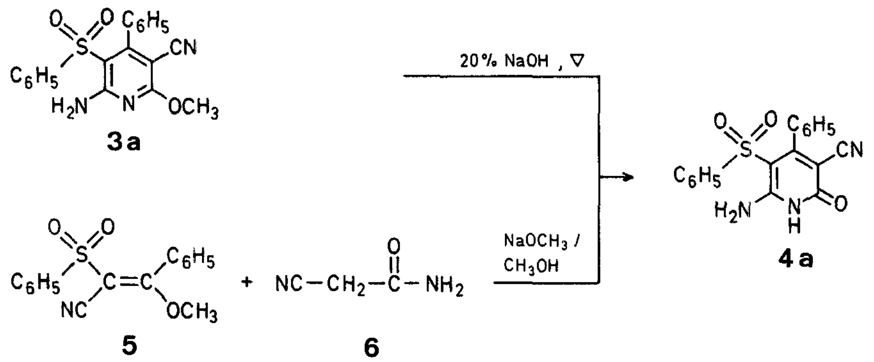
A versatile method for the synthesis of 2-amino substituted pyridines[1,2] and pyrimidines[3] consists in the reaction of substituted 3-alkoxypropenenitriles with active cyano compounds in the presence of an alcohol/alkoxide system. The pyridines and pyrimidines prepared in this way incorporate the amino and alkoxy groups at the 2 and 6 positions, locating, in all cases, a cyano and the alkoxy groups at *vic*-positions. In an extension of our studies about this regioselective synthesis, we report here on the preparation of the hitherto unknown 4-substituted 2-amino-5-cyano-6-methoxy-3-benzenesulfonylpyridines **3** by reaction of 2-ethoxy-1,1-propenedicarbonitrile (**2f**) and a series of α-cyano-β-methoxycinnamonitriles **2a–e** with benzenesulfonylacetonitrile (**1**) and sodium methoxide in methanol (Scheme A, Table).



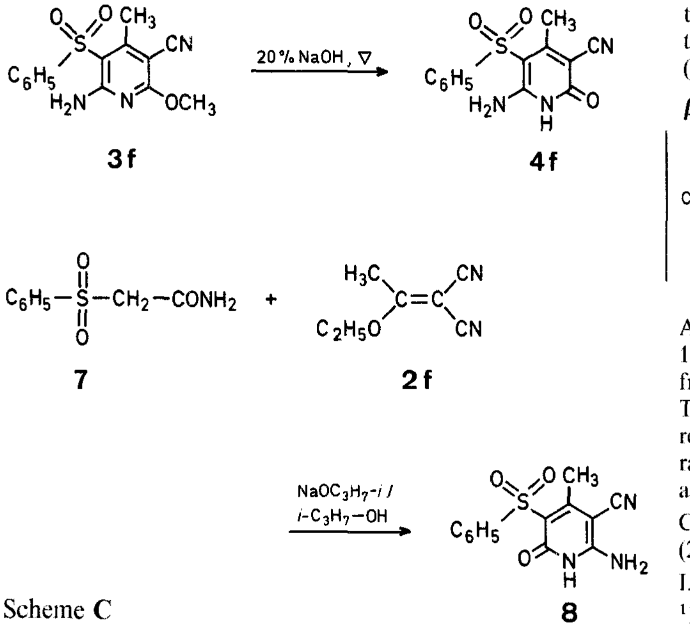
Scheme A

The products were identified on the basis of their spectral data and relevent transformation reactions. Thus, the assignment of the amino and methoxy groups at the 2 and 6 positions in pyridines **3a–e** was made by hydrolysing, for example, **3a** to the pyridone **4a** with aqueous sodium hydroxide. The pyridone **4a** was unambiguously synthesized by the condensation of β-methoxy-α-benzenesulfonylcinnamonitrile (**5**) with cyanoacetamide (**6**) (Scheme B)



Scheme **B**

In a similar way, the pyridine **3f** gave the 3-methyl substituted pyridone **4f**. It is structurally compared with the isomeric pyridone **8**, synthesized independently from the easily accessible benzenesulfonylacetamide (**7**)[4] and 2-ethoxy-1,1-propenedicarbonitrile (**2f**)[5] (Scheme C)

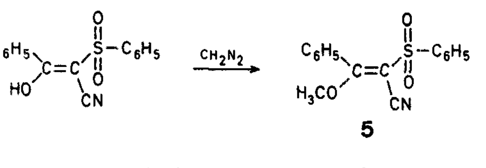


Scheme C

4-Substituted 2-Amino-5-cyano-6-methoxy-3-benzenesulfonylpyridines 3; General Procedure:

To a solution of sodium methoxide (0.54 g, 10 mmol) in dry methanol (40 ml), benzenesulfonylacetonitrile (**1**; 0.905 g, 5 mmol) and the appropriate α-cyano-β-methoxycinnamonitrile **2a–e** (5 mmol) or 2-ethoxy-1,1-propenedicarbonitrile (**2f**; 0.68 g, 5 mmol) are added. The mixture is heated under reflux with stirring for 24 h and then allowed to stand overnight at room temperature. The precipitate formed is collected and recrystallized to yield pyridines **3** (Table).

β-Methoxy-α-benzenesulfonylcinnamonitrile (5):



A solution of β-hydroxy-α-benzenesulfonylcinnamonitrile[6] (2.85 g, 10 mmol) in dry ether (100 ml) is treated with diazomethane liberated from N-methyl-N-nitroso-p-toluenesulfonamide[7] (3.2 g, 15 mmol). The mixture is stirred for 3 h at 0 °C, after which time the solvent is removed under reduced pressure and the solid residue chromatographed on a silica gel column using hexane as eluent. Recrystallization from methanol gives **5**; yield: 1.37 g (46 %); m.p. 154–155 °C.

$C_{16}H_{13}NO_3S$	calc.	C 64.19	H 4.38	N 4.68	S 10.71
(299.3)	found	64.28	4.67	4.30	10.98

I.R. (KBr): ν = 2210, 1580, 1545, 1445, 1340–1300, 1145 cm^{-1}.
^{1}H-N.M.R. (DMSO-d_6): δ = 3.59 (OCH$_3$); 7.2–8.2 ppm (H$_{arom}$).

Table. 4-Substituted 2-Amino-5-cyano-6-methoxy-3-benzenesulfonylpyridines **3** prepared

Product No.	R	Yield [%]	m.p. [°C][a]	Molecular formula[b]	I.R. (KBr) ν[cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6) δ[ppm]
3a	C_6H_5	58	250–251°	$C_{19}H_{15}N_3O_3S$ (365.4)	3445, 3300, 3200, 2210, 1615, 1570, 1525	3.95 (s, 3H); 6.6–7.7 (m, 10H); 8.0 (br. s, 2H)
3b	4-Cl—C_6H_4	51	230–231°	$C_{19}H_{14}ClN_3O_3S$ (399.8)	3440, 3320, 3200, 2210, 1605, 1565, 1525	3.86 (s, 3H); 6.81, 7.15 (A_2B_2, J = 8 Hz, 4H); 7.3 (s, 5H); 7.8 (br.s, 2H)
3c	4-H_3C—C_6H_4	48	163–164°	$C_{20}H_{17}N_3O_3S$ (379.4)	3440, 3320, 2210, 1600, 1565, 1525	2.30 (s, 3H); 3.90 (s, 3H); 6.63, 6.89 (A_2B_2, J = 8 Hz, 4H); 7.26 (s, 5H); 7.7 (br.s, 2H)
3d	3-Cl—C_6H_4	55	246–247°	$C_{19}H_{14}ClN_3O_3S$ (399.8)	3440, 3320, 3210, 2220 1620, 1570, 1530	3.96 (s, 3H); 6.7–7.8 (m, 9H); 8.0 (br.s, 2H)
3e	4-H_3CO—C_6H_4	56	181–182°	$C_{20}H_{17}N_3O_4S$ (395.4)	3450, 3320, 2220, 1605, 1570, 1535, 1510	3.77 (s, 3H); 3.95 (s, 3H); 6.78 (s, 4H); 7.38 (s, 5H); 8.0 (br.s, 2H)
3f	CH_3	40	194–195°	$C_{14}H_{13}N_3O_3S$ (303.3)	3415, 3310, 3200, 2220, 1610, 1580, 1535	2.50 (s, 3H); 3.93 (s, 3H); 7.1–8.5 (m, 7H)

[a] Compounds **3** are recrystallized from methanol except **3e** (ethanol).
[b] Satisfactory microanalyses obtained: C ±0.43, H ±0.19, N ±0.46, Cl ±0.42, S ±0.40.

6-Amino-3-cyano-4-phenyl-5-benzenesulfonyl-2-pyridone (4a):
Method A: To ethanol (5 ml) containing 20 % aqueous sodium hydroxide (2 ml) is added **3a** (183 mg, 0.5 mmol). The mixture is heated under reflux with stirring for 1 h. The solution is poured over ice/water (50 ml) weakly acidified by hydrochloric acid. The precipitate formed is collected and recrystallized from methanol; yield: 156 mg (89 %); m.p. 309–313 °C (dec).

Method B: A solution of sodium methoxide (108 mg, 2 mmol), β-methoxy-α-benzenesulfonylcinnamonitrile (**5**; 0.6 g, 2 mmol) and cyanoacetamide (**6**; 168 mg, 2 mmol) in methanol (15 ml) is heated under reflux for 12 h, after which time the mixture is poured over ice/water (50 ml) acidified by hydrochloric acid. The precipitate thus formed is collected and recrystallized from methanol; yield: 370 mg (53 %); m.p. 309–313 °C (dec.).

$C_{18}H_{13}N_3O_3S$	calc.	C 61.53	H 3.73	N 11.96	S 9.12
(351.4)	found	61.63	3.30	12.05	9.02

I.R. (KBr): ν = 3390, 3290, 2210 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ = 6.3–8.2 (H_{arom} + NH_2); 11.70 ppm (NH).

6-Amino-3-cyano-4-methyl-5-benzenesulfonyl-2-pyridone (4f):
The hydrolysis of **3f** (303 mg, 1 mmol) is carried out as described under Method A for **4a** to give **4f**; yield: 242 mg (84 %); m.p. 302–305 °C (dec).

$C_{13}H_{11}N_3O_3S$	calc.	C 53.97	H 3.83	N 14.52	S 11.08
(289.3)	found	53.61	4.06	14.54	11.34

I.R. (KBr); ν = 3400, 3290, 3180, 2210 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ = 2.33 (CH_3); 6.9–8.2 (H_{arom} + NH_2); 11.54 ppm (NH).

6-Amino-5-cyano-4-methyl-3-benzenesulfonyl-2-pyridone (8):
To a solution of benzenesulfonylacetamide[4] (**7**; 2 g, 10 mmol) and sodium 2-propoxide (0.82 g, 10 mmol) in 2-propanol (25 ml), 2-ethoxy-1,1-propenedicarbonitrile (**2f**; 1.36 g, 10 mmol) is added. The mixture is stirred under reflux for 24 h. After cooling, the precipitated solid (1.6 g) is separated by filtration and warm water (100 ml) is added to the solid, which is stirred until complete dissolution. The solution is acidified with hydrochloric acid and the resultant solid product is filtered and recrystallized from dimethylformamide; yield: 0.8 g (28 %); m.p. 319–322 °C (dec).

$C_{13}H_{11}N_3O_3S$	calc.	53.97	H 3.83	N 14.52	S 11.08
(289.3)	found	54.16	3.36	14.52	11.11

I.R. (KBr): ν = 3365, 3270, 3200, 2215 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ = 2,29 (—CH_3); 7.1–8.6 (H_{arom} + NH_2); 11.8 ppm (NH).

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