A Novel and Efficient Method for the Synthesis of *N*-Arylsulfonylamino-2-pyridones

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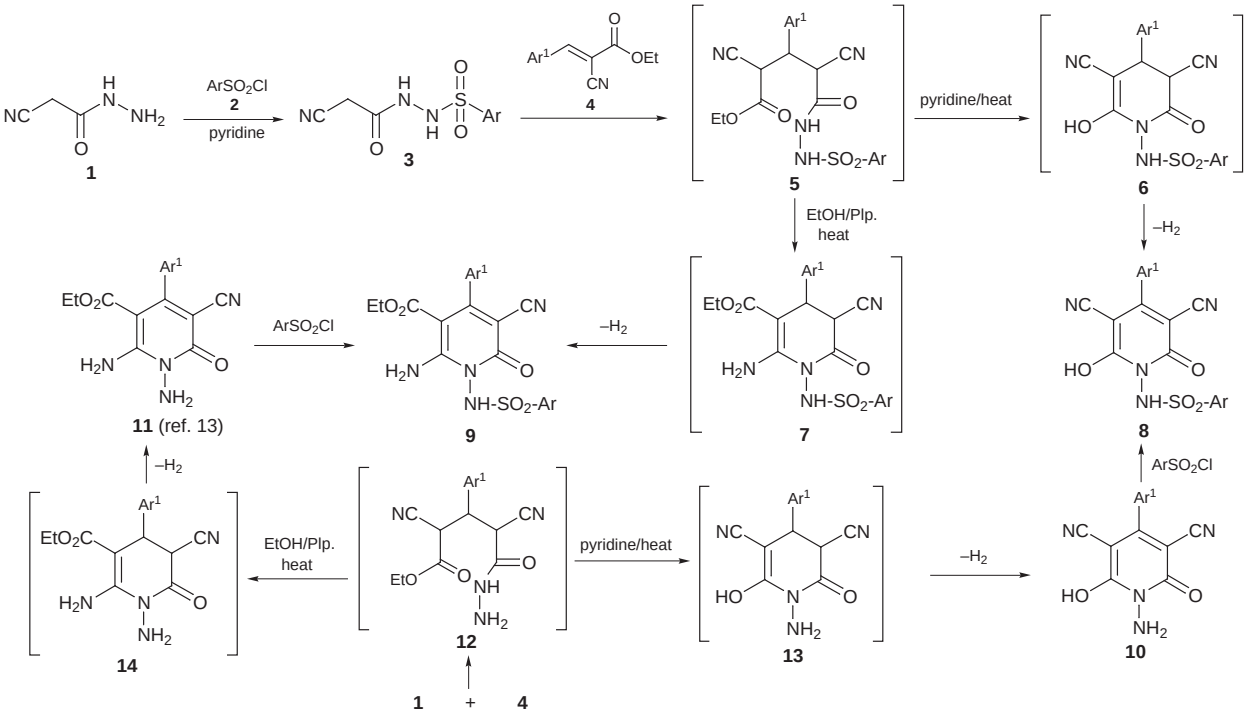
A novel and efficient method for the synthesis of *N*-arylsulfonylamino-2-pyridones, *via* the reaction of *N*-cyanoacetohydrazides with ethyl arylidenecyanoacetate derivatives, is investigated; *N*-sulfonated aminopyridines are also prepared from the reaction of *N*-amino-2-pyridones with arylsulfonyl chlorides.

We report here a new, one-step synthesis of *N*-sulfonated aminopyridine derivatives from the reaction of *N*-cyanoacetoarylsulfonyl hydrazides with ethylarylidenecyanoactate derivatives; the scope and limitation of our procedure for the synthesis of *N*-alkylated amino-2-pyridone derivatives is also discussed.

Recently, *N*-amino-2-pyridones have proved to be useful synthetic intermediates but there are very few synthetic procedures for the preparation of such compounds.[1]

Recent reports from our laboratory have demonstrated the effectiveness of a variety of *N*-substituted amino derivatives of pyridines and other antimetabolites are antineoplastic agents in a number of experimental murine tumour systems.[2–4] Since these compounds have been shown to inhibit the incorporation of thymidine and uridine into DNA and RNA and appear to constitute a new class of antimetabolites, it was of interest to evaluate the effects of various structural modifications on biological activity. To this end, here we report the synthesis of novel *N*-sulfonylamino derivatives of 2-pyridones. Thus, it has been found that cyanoacetohydrazide **1** reacts with arylsulfonyl chloride **2** in pyridine to afford the corresponding *N*-cyanoacetoarylsulfonylhydrazides **3** in good yields (Chart 1). Compounds **3** reacted with ethyl arylidenecyanoacetate in refluxing pyridine (6 h) to yield the *N*-arylsulfonylamino-2-pyridones **8**. Each structure of **8** was established on the basis of elemental analysis and spectral data. Thus, the mass spectrum of **8c** was compatible with the molecular formula $C_{20}H_{14}N_4O_4S$ (M^+ 406), and ^1H NMR spectrum contained two broad singlets at δ 3.9 and 8.6, assignable to OH and NH groups, respectively. The formation of **8** from **3** and **4** is assumed to proceed *via* addition of the active



2	Ar
a	Ph
b	4-H_3C-C_6H_4

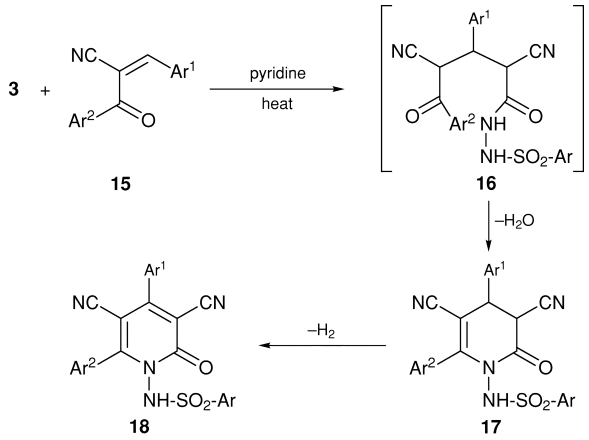
10,11	Ar^1
a	Ph
b	4-Cl-C_6H_4
c	4-H_3CO-C_6H_4
d	4-NO_2-C_6H_4

8,9	Ar	Ar^1
a	Ph	Ph
b	Ph	4-Cl-C_6H_4
c	Ph	4-H_3C-C_6H_4
d	Ph	4-H_3CO-C_6H_4
e	Ph	4-$(H_3C)_2N$-C_6H_4
f	Ph	4-NO_2-C_6H_4

8,9	Ar	Ar^1
g	4-H_3C-C_6H_4	Ph
h	4-H_3C-C_6H_4	4-Cl-C_6H_4
i	4-H_3C-C_6H_4	4-H_3C-C_6H_4
j	4-H_3C-C_6H_4	4-H_3CO-C_6H_4
k	4-H_3C-C_6H_4	4-$(H_3C)_2N$-C_6H_4
l	4-H_3C-C_6H_4	4-NO_2-C_6H_4

Chart 1

*To receive any correspondence.



18	Ar	Ar^1	Ar^2
a	Ph	Ph	Ph
b	4-H_3C-C_6H_4	Ph	Ph
c	Ph	4-Cl-C_6H_4	Ph
d	4-H_3C-C_6H_4	4-Cl-C_6H_4	Ph
e	Ph	4-NO_2-C_6H_4	Ph
f	4-H_3C-C_6H_4	4-NO_2-C_6H_4	Ph
g	Ph	4-H_3CO-C_6H_4	Ph
h	4-H_3C-C_6H_4	4-H_3CO-C_6H_4	Ph
i	Ph	4-H_3C-C_6H_4	Ph
j	4-H_3C-C_6H_4	4-H_3C-C_6H_4	Ph
k	Ph	4-$(H_3C)_2N$-C_6H_4	Ph
l	4-H_3C-C_6H_4	4-$(H_3C)_2N$-C_6H_4	Ph

Chart 2

methylene group of **3** to the double bond of **4** to give the intermediate acyclic adduct **5**. The Michael adduct **5** was cyclized *via* ethanol elimination to give the intermediate dihydropyridine derivatives **6**, which are oxidized under the reaction conditions to yield the novel *N*-arylsulfonylamino-2-pyridone derivatives **8**. The course of the reaction between the *N*-cyanoacetylarylsulfonylhydrazides **3** and **4** prompted us to investigate this reaction between cyanoacetohydrazide **1** and **4** under the same conditions. The products obtained were shown to be formed by the same mechanism as that between **3** and **4** to give the *N*-amino-2-pyridones **10**.[5] The structures of compounds **10** were established on the basis of elemental analysis and spectral data. When **10** was stirred with arylsulfonyl chlorides in pyridine at room temperature for 24 h, it gave the corresponding *N*-sulfonated pyridine **8**. To investigate the scope of this reaction further we studied the reaction of **3** and **4** under other basic conditions. In contrast, it has been found that **3** reacted with **4**, in refluxing ethanol that contains catalytic amounts of piperidine, to yield the corresponding 5-ethoxycarbonyl-*N*-arylsulfonylamino-2-pyridone derivatives **9** in good yields. The structures of **9** were established and confirmed for the reaction products on the basis of their elemental analysis and spectral data (MS, IR, and ^{1}H NMR). The analytical data for **9g** revealed a molecular formula $C_{22}H_{20}N_4O_5S$, (M^+ 452); ^{1}H NMR spectroscopy was used to confirm this structure for the product. Thus, ^{1}H NMR revealed a triplet at δ 0.612, assigned to a methyl ester group, a quartet at δ 3.79, assigned to a CH_2 ester group, and a broad singlet at δ 9.2, assignable to an NH group. The mechanism of the reaction of **3** and **4** under these conditions is assumed to proceed through the formation of the initial acyclic adduct **5**, which cyclises to the intermediate **7** and hence to the product **9**. The reaction of cyanoacetohydrazide **1** and **4** and piperidine in refluxing ethanol led to the reported ethyl *N*-amino-2-pyridone-5-carboxylate **11**.[5] When **11** was left to react with arylsulfonyl chlorides in pyridine at room temperature for 24 h, the corresponding *N*-arylsulfonylamino-2-pyridones **9** was obtained in good yields. Similar to the behaviour of **3** towards **4**, compounds **3** reacted with arylidene derivatives of benzoylacetonitrile (**15**) in refluxing pyridine to yield the *N*-sulfonated pyridines **18** (Chart 2). The structures of **18** were established on the basis of their elemental analysis and spectral data. Thus, structure **18i** is supported by its mass spectrum which showed a molecular formula $C_{26}H_{18}N_4O_3S$ (M^+ 466). ^{1}H NMR spectroscopy was used to confirm this structure for the products. Thus, ^{1}H NMR revealed a multiplet at δ 7.35–8.65, assigned to the aromatic protons and a broad singlet at δ 11.55, assigned to the NH proton. In summary, we have achieved a regiospecific synthesis of interesting *N*-sulfonated aminopyridines by the reaction of cyanosulfonylhydrazides with α,β-unsaturated nitriles.

Techniques used: IR, ^{1}H NMR and mass spectrometry

References: 13

Charts: 2

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References cited in this synopsis

1 A. Hadi, N. Martin, C. Seoane and L. J. Soto, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1045.
2 G. E. H. Elgemei, A. M. Attia, O. S. Farag and S. M. Sherif, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1285.
3 G. E. H. Elgemeie and B. A. W. Hussain, *Tetrahedron*, 1994, **50**, 199.
4 G. E. H. Elgemeie, A. M. Attia and N. M. Fathy, *Liebigs Ann. Chem.*, 1994, 955.
5 M. R. H. El Moghayar, A. A. El-Agamay, N. M. Abed and M. K. A. Ibrahim, *An. Quim.*, 1983, **81**, 286.