

# 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*-cyanoaceto-hydrazides 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 ethyl arylidenecyanoacetate 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.<sup>1</sup>

Recent reports from our laboratory have demonstrated the effectiveness of a variety of *N*-substituted amino derivatives of pyridines and other antimetabolites are anti-neoplastic agents in a number of experimental murine tumour systems.<sup>2-4</sup> 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 cyanoaceto-hydrazide **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<sub>20</sub>H<sub>14</sub>N<sub>4</sub>O<sub>4</sub>S (M<sup>+</sup> 406), and <sup>1</sup>H 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

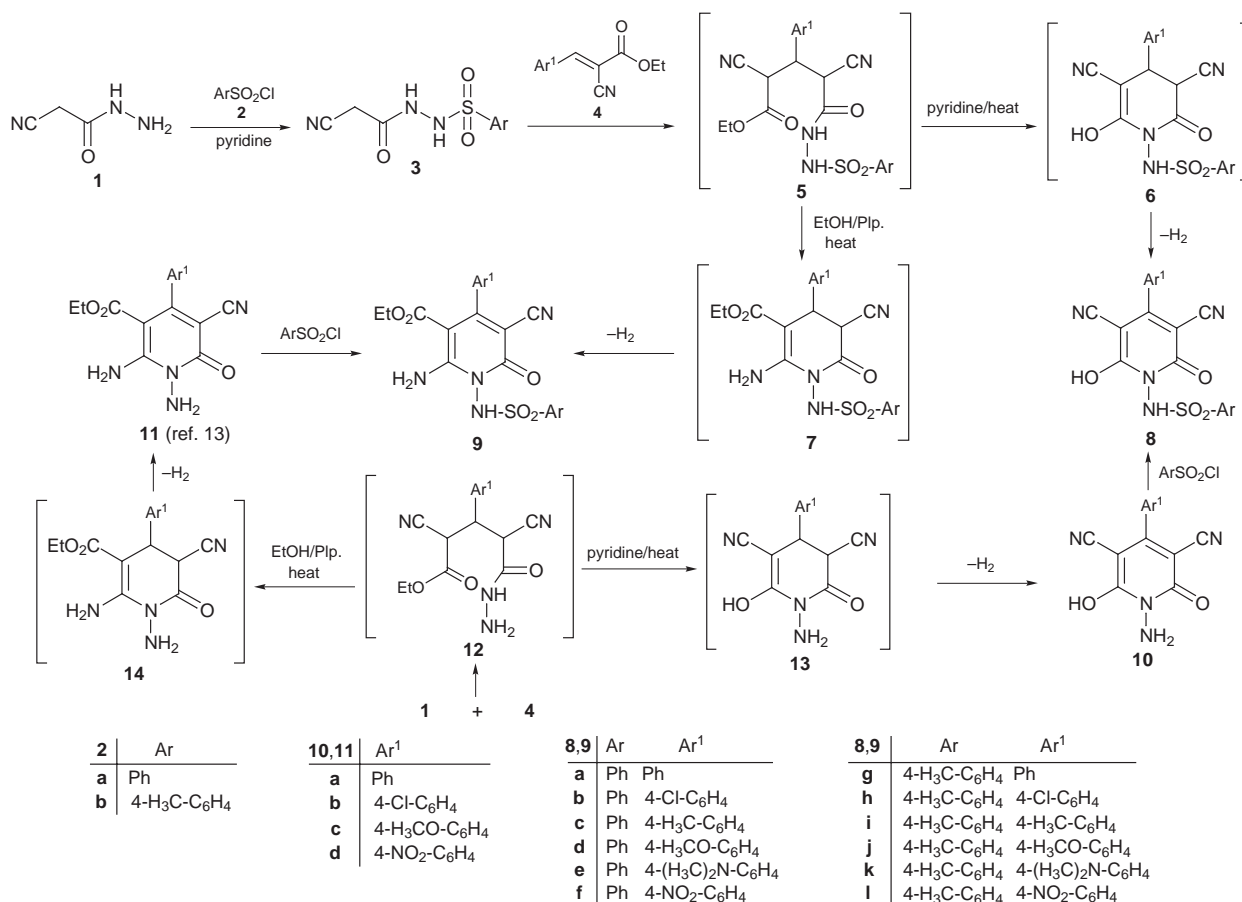


Chart 1

\*To receive any correspondence.

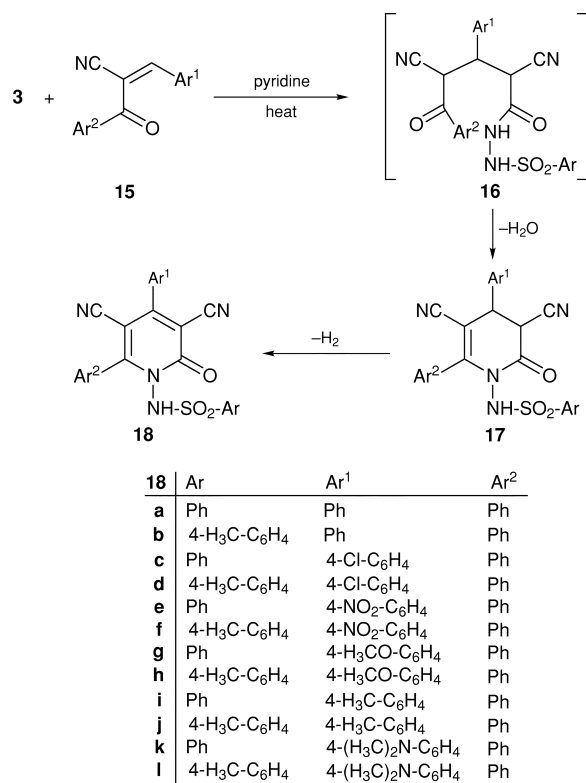


Chart 2

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**.<sup>5</sup> 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 struc-

tures of **9** were established and confirmed for the reaction products on the basis of their elemental analysis and spectral data (MS, IR, and <sup>1</sup>H NMR). The analytical data for **9g** revealed a molecular formula C<sub>22</sub>H<sub>20</sub>N<sub>4</sub>O<sub>5</sub>S, (M<sup>+</sup> 452); <sup>1</sup>H NMR spectroscopy was used to confirm this structure for the product. Thus, <sup>1</sup>H NMR revealed a triplet at δ 0.612, assigned to a methyl ester group, a quartet at δ 3.79, assignable to a CH<sub>2</sub> 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**.<sup>5</sup> 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<sub>26</sub>H<sub>18</sub>N<sub>4</sub>O<sub>3</sub>S (M<sup>+</sup> 466). <sup>1</sup>H NMR spectroscopy was used to confirm this structure for the products. Thus, <sup>1</sup>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, <sup>1</sup>H NMR and mass spectrometry

References: 13

Charts: 2

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