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Research Paper

A mild and efficient method for the synthesis of unusual heteroaryl sulfonyl chlorides

Kamlesh Chavan, Santanu Medhi, Rajiv Sharma and Nabajyoti Deka*

Department of Medicinal Chemistry, Piramal Life Sciences Limited, 1 Nirlon Complex, Goregaon East, Mumbai 400 063, India

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Abstract: A variety of unusual heteroaryl sulfonyl chlorides were prepared from their respective amines by using sulfur dioxide and acetic acid in presence of copper chloride at 0-5 ºC via the formation of diazonium salts in quantitative yield.

Introduction

Sulfonyl chlorides are important intermediates in organic synthesis[1,2] and are widely used for the preparation of sulfonamides and esters including industrial and agricultural chemicals.[3] They are used in the production of herbicides, detergents, dyes, elastomers, ion exchange resins, and pharmaceuticals.[4] The most conventional method for the preparation of sulfonyl chlorides is the reaction of corresponding sulfonic acids with thionyl chloride in dimethylformamide.[5] Sulfonyl chlorides are also prepared by reacting mercaptans,[6] sulfides,[7] disulfides,[8] sulfoxides, or other precursors with chlorine gas in aqueous acidic solutions. However, these processes suffer from disadvantages like formation of complex with DMF, chloroxidation of certain aryl sulfur precursors and poor solubility in aqueous solution. Other methods include the reaction of sulfonic acids with phosphoryl chloride or phosphorous pentachloride, both of which require harsh conditions, such as heating for many hours at high temperature. In addition, there are disadvantages that these methods necessitate an excess of chlorinating reagent which yielded highly toxic and corrosive byproducts. Sulfonyl chlorides have also been prepared from the direct reaction of the corresponding diazonium salt with thionyl chloride.[9] In this report we describe a very convenient method for the synthesis of 5,6-disubstituted pyridine-3-sulfonyl chloride from their respective amino compounds.

Corresponding Author*
Email: nabajyotid.deka@piramal.com

Discussion

As part of an ongoing medicinal chemistry program in metabolic disorder it was imperative to synthesize a series with

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sulfonamides and reverse sulfonamides.[10] As evident from the retrosynthetic analysis (**Scheme-1**), the reverse sulfonamide series requires 5,6-disubstituted pyridine-3-sulfonyl chlorides as key intermediates which can be prepared from their corresponding amines via diazotization. Though this is not such a well established and extensively used reaction but it has been reported as early as in 1969 by Meerwin et al. on simple aromatic amines. We decided to extend this methodology on more complex heterocyclic systems to generate sulfonyl chlorides in good yields. In brief, 2,3-disubstituted 5-aminopyridine were treated with $NaNO_2$/HCl and chlorosulfonation of the diazonium salts were carried out by using SO_2 gas in acetic acid and copper chloride as catalyst to get the corresponding pyridine-3-sulfonyl chlorides.

Conversion of 2,3-disubstituted 5-aminopyridine to corresponding sulfonyl chlorides via their diazonium salts is an efficient and mild method and also generates quantitative yields. Treatment of the hydrochloride salt of 2,3-disubstituted 5-aminopyridine with sodium nitrite in a mixture of glacial acetic acid and aqueous hydrochloric acid afforded the corresponding diazonium salt. The chlorosulfonylation was conducted in both copper(I) or copper(II) salts though copper(I) required shorter reaction time. The yield of the chloro- sulfonation product mostly increased with increase in concentration of SO_2. The gas was introduced by passing gaseous SO_2 directly into the reaction. It was also observed that excess water in the reaction mixture lead to reduction in the product yield. Upon optimization of the reaction conditions it was examined the efficacy of the reaction on a variety of substituted heterocycles. Yield of sulfonyl chloride also depends on the formation of diazonium salt.

Different corresponding amines were synthesized from 2-chloro-5-nitropyridines (1) with quantitative yield (**Scheme-2**) and subsequently converted to corresponding sulfonyl chlorides.

Reduction of the nitro compounds (**2**) to the precursor of corresponding sulfonyl chlorides was carried out by using $SnCl_2.2H_2O$ in ethyl acetate at room temperature. Reduction with Fe/HCl or Zn-dust/NH_4Cl also worked well but it was observed that isolation and yield of the aminopyridines was comparatively better in $SnCl_2.2H_2O$ ethyl acetate method. Purified amines were treated with $NaNO_2$/HCl at 0 ^oC followed by SO_2 in acetic acid in presence of copper chloride. In each case, corresponding sulfonyl chloride was isolated in high yield and purified after filtration of the crude reaction mixtures.

In some cases it was observed that due to the presence of an ortho-hydroxy to the amino group, formation of diazonium intermediates and their respective sulfonyl chlorides did not take place. For example, synthesis of 2-hydroxypyridine-3-sulfonyl chloride from 3-aminopyridin-2-ol was not possible. Trace amount of Sandmeyer product was formed on treatment of the diazonium salt with copper cyanide.

Conclusion

In conclusion we report an efficient method for the synthesis of hetero aryl sulfonyl chlorides from corresponding amines via the formation of diazonium intermediate in good yield.

Experimental

All reagents and solvents were obtained

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from commercial sources and used as received.

1H-NMR spectra were obtained on a 'Bruker 300 MHz' instrument equipped with a 5 mm 1H/13C/X (BBO) probe and the solvent indicated with tetramethylsilane as an internal standard. For all 1D experiments viz., 1H, 13C pulse program used was employed from the pulse program library of Bruker. The data obtained so, were processed and analyzed by using Bruker software, XWIN NMR version 3.5.

Analytical HPLC was run using a Zorbax Eclipse XDB-C8 3.5 µm 4.6x75 mm column eluting with a mixture of acetonitrile and water containing 0.1% trifluoroacetic acid with a 5 minute gradient of 10-100%. MS results were obtained on 'ESI-QTOF' instruments of Bruker Daltonics (model MicrotofQ). 10 µl of each sample (fraction) was injected. The sample was ionized using Electron Spray Ionisation technique and analyzed using Quadruple Time of Flight. The mobile phase used was Acetonitrile and of 0.1 % formic acid (50:50) with a flow rate of 0.2 ml/min. The samples were analyzed both in the positive mode and negative mode by Direct Injection Mode. Liquid chromatography/ mass spectroscopy studies have been carried out using 'Agilent 1100 Series/ esquire 4000' instrument of Bruker Daltonics. Same analytical HPLC method was used with 'Phenomenex Luna C18' column. 0.1% Formic Acid and Acetonitrile (80:20) were used as mobile phase. Automated column chromatography was performed on a CombiFlash Rf 200 (Teledyne Isco Inc.). Melting points were taken on a Mel-Temp apparatus and are uncorrected.

General procedure for synthesis of heteroayl sulfonyl chlorides: 2,3-disubstituted-5-aminopyridine (10 mmol) was added portionwise with stirring to concentrated hydrochloric acid (10 ml) at 0 °C. A solution of sodium nitrite (15 mmol) in water (5 ml) was added dropwise at such a rate that the temperature did not exceed 0ºC. After complete addition of sodium nitrite solution, the mixture was stirred for 45 min. The temperature was maintained at 0ºC. 10 ml of glacial acetic acid was saturated with sulfur dioxide and catalytic amount of cuprous chloride (3 mmol) was added. The mixture was then placed in an ice bath and cooled with stirring. The diazotization reaction mixture was added slowly to the sulfur dioxide-glacial acetic acid solution at 5 ºC. After completion of the addition of diazonium salt, stirring was continued for 45 minutes and the reaction mixture was poured into ice water. The precipitate obtained was filtered off and washed with water and dried under high vacuum over calcium chloride.

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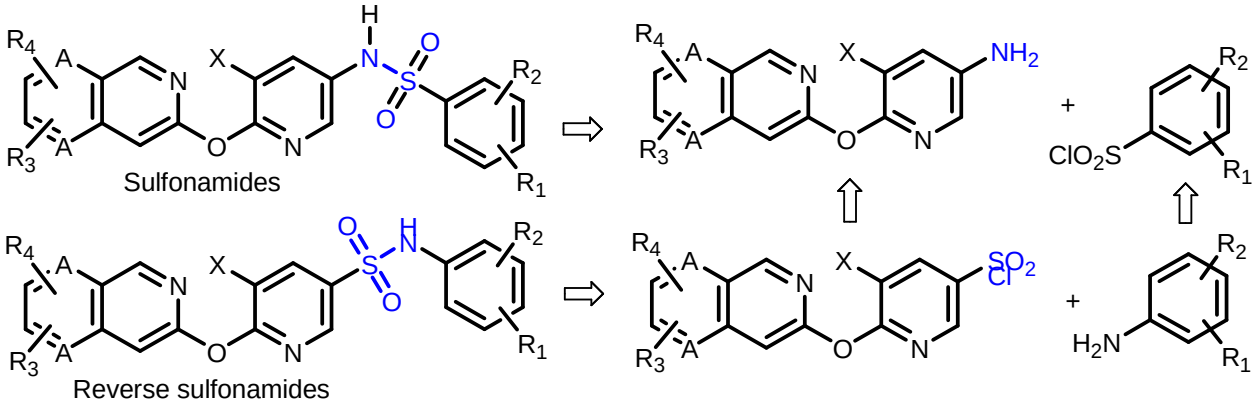
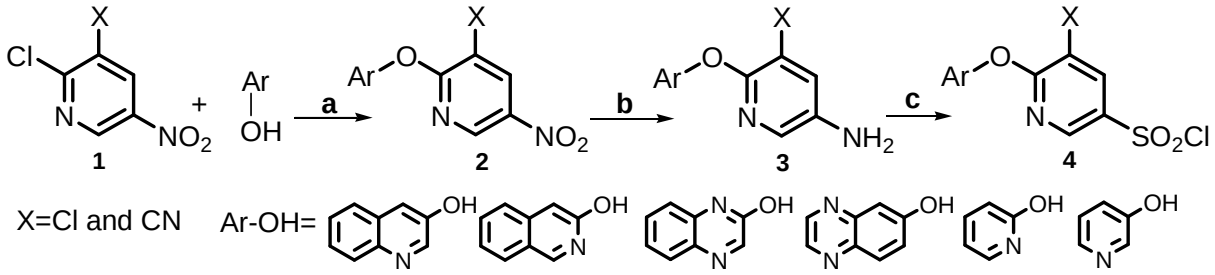
Scheme-1: Retrosynthesis of 5,6-disubstituted pyridine-3-sulfonyl chlorides



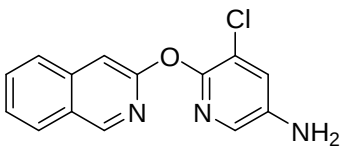
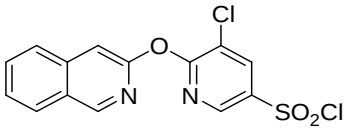
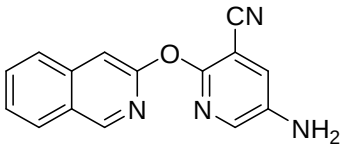
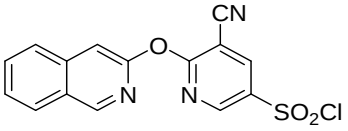
Scheme-2: Synthesis of 5,6-disubstituted pyridine-3-sulfonyl chlorides.



a. Cs_2CO_3, DMF, heating at 70-80 ^oC, 2-4 hrs **b**. $SnCl_2.H_2O$, Ethylacetate, r.t, 15 hrs

c. $NaNO_2$, HCl, H_2O, 0 ^oC; SO_2, CuCl, HOAc, HCl

Table-1: Synthesis of heteroaryl sulfonyl chlorides

S. No	Amines	Sulfonyl Chloride	Yield (%)
a			82
b			82

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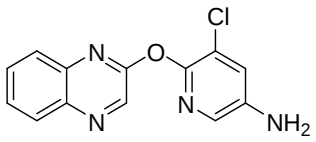
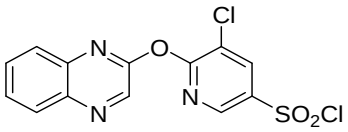
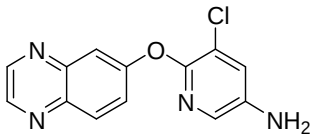
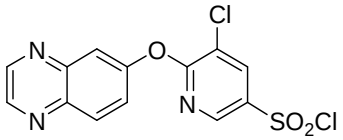
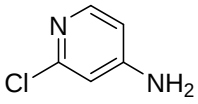
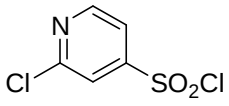
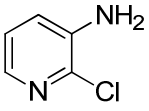
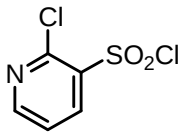
c			82
d			82
e			73
f			80

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