Organic Process Research & Development **2009,** *13,* 875–879

Aqueous Process Chemistry: The Preparation of Aryl Sulfonyl Chlorides

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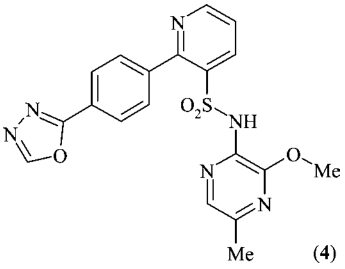
Abstract:

The use of aqueous acidic conditions for the preparation of arylsulfonyl chlorides from diazonium salts in the presence of copper salts, preferably CuCl, together with thionyl chloride as the sulfur dioxide source, has considerable advantages over recommended literature procedures, whereby reactions are carried out in acetic acid with minimisation of water content of the solvent. The method has been shown to be successful for a wide range of electron-deficient and electron-neutral aryl substrates. The sulfonyl chlorides are protected from hydrolysis by their low solubility in water, which results in their direct precipitation from the reaction mixture in good yields (>70%) and high strength (>98% w/w). The aqueous process, which is additionally safer and more robust, can be readily scaled up and has significant environmental benefits.

Introduction

Reaction rates in liquid−liquid and solid−liquid two-phase systems are proportional to the reactant solubility in the reacting phase.[1] One consequence of this is that substrates highly susceptible to hydrolysis may be stable in the presence of water, provided that their aqueous solubility is sufficiently low. We wish to show that this can be used to advantage in the development of a manufacturing process for aryl sulfonyl chlorides, in particular, 2-chloropyridine-3-sulfonyl chloride, **1**, used to form sulfonamide **3**, isobutyl [(2-chloropyridin-3-yl)sulfonyl](5-methylpyrazin-2-yl)carbamate, via reaction with isobutyl (5-methylpyrazin-2-yl)carbamate, **2**, in the presence of sodium hydride, Scheme 1.

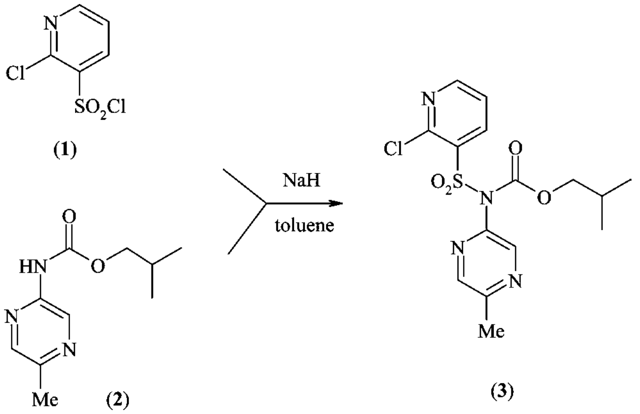
The sulfonamide, **3**, is a common intermediate in the preparation of a series of endothelium antagonists, such as *N*-(3-methylpyrazin-2-yl)-2-[4-(1,3,4-oxadiazol-2-yl)phenyl]pyridine-3-sulfonamide, **4**.[2]



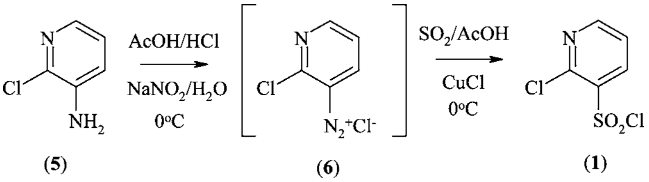
(4)

The most convenient way of producing aryl sulfonyl chlorides, such as **1**, is by a modified Sandmeyer reaction, introduced by Meerwein[3a], involving reaction of the appropriate diazonium salt with sulfur dioxide in the presence of copper salts. This is illustrated in Scheme 2, which includes recommended literature conditions for the transformation. These include the use of acetic acid as solvent, concentrated aq HCl with NaNO$_2$ to effect diazotisation, and addition of the diazonium salt, **6**, to sulfur dioxide in acetic acid in the presence of an appropriate copper salt to generate the desired sulfonyl chloride.[4−7] An important additional factor is the *minimisation of the water content of the system*.

Scheme 1. **Formation of sulfonamide 3**



Scheme 2. **Formation of sulfonyl chloride 1**



In preliminary work, we found it is necessary to avoid temperatures above 5 °C in order to prevent uncontrolled decomposition of the intermediate diazonium salt, **6**, and that the use of copper(I) chloride, in preference to commonly used copper(II) chloride, enabled a considerable reduction in copper usage (0.02 equiv compared with typically 0.25 equiv of CuCl$_2$).

In practice, reaction according to Scheme 2 proceeded well, with nonisolated yields of over 70%, the major impurities being the Sandmeyer product, 2,3-dichloropyridine (**7**), the hydrolysis

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(1) Atherton, J. H.; Carpenter, K. J. *Process Development: Physicochemical Concepts*; Oxford University Press: New York, 1994; Chapter 8.

(2) Bradbury, R. Hugh; Butlin, R. J.; James, R. (Zeneca Limited, UK). PCT Int. Appl. 9640681, 1996.

(3) Meerwein, H; Dittmar, G.; Gollner, R.; Hafner, K; Mensch, F; Steiner, O. *Chem. Ber.* **1957**, *90*, 841.

(4) Gilbert, E. E. *Synthesis* **1969**, *1*, 3.

(5) Saunders, K. H.; Allen, R. L. M. *Aromatic Diazo Compounds*, 3rd ed.; Edward Arnold: London, 1985.

(6) Krishnan, L; Wilk, B. K.; Varriano, J. P. (Wyeth). PCT Int. Appl. US02/34900, 2001.

(7) Lebegue, N.; Gallet, S.; Flouquent, N.; Carato, P.; Pfeiffer, B.; Renard, P.; Léonce, S.; Pierré, A.; Chavatte, P.; Berthelot, P. *J. Med. Chem.* **2005**, *48*, 7363–7373.

10.1021/op9000862 CCC: $40.75 © 2009 American Chemical Society
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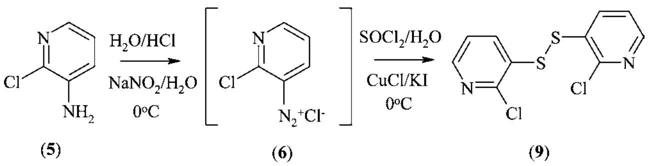
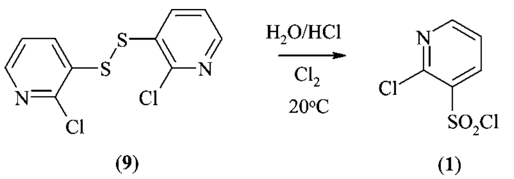
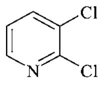
Scheme 3. **Formation of disulfide 9**



Scheme 4. **Conversion of disulfide 9 to sulfonyl chloride 1**



product, 2-chloropyridine-3-sulfonic acid (**8**), the disulfide, 3,3′-dithiobis(2-chloropyridine (**9**), and the sulfone, 3,3′sulfonylbis(2-chloropyridine (**10**).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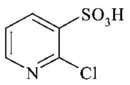
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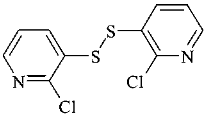
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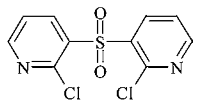

(10)

The requirement of an acid-free sulfonyl chloride in the subsequent reaction stage (Scheme 1), however, necessitated an aqueous drown-out, followed by neutralisation of the acid, and extraction and crystallisation of the product. Two major issues arose: (1) losses due to hydrolysis during isolation were considerable, with the result that isolated yields at large scale were typically around 45% and showed considerable variability, and (2) the effluent load was very high. The product losses could be reduced by cold and rapid neutralisation, but this becomes increasingly difficult on scale-up. Additionally, SO_2 dissolution via headspace saturation took a significant time (>10 h) at larger scales.

In view of these difficulties we decided to explore alternative reaction workup conditions and reaction schemes, as described below.

Results and Discussion

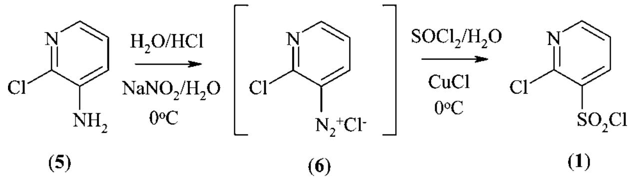
Attempted variations in the workup and changes to the sulfonation stage to include acetic acid/dichloromethane mixtures, from which a product-rich dichloromethane phase separated, did not give significant benefits to either yield or effluent generation. An alternative pathway, based on the oxidation of disulfide, **9**, was then investigated. It was prepared in 45% isolated yield using an all-aqueous process, Scheme 3, in which thionyl chloride was used as the SO_2 source.

The reaction was not optimised, but the major byproduct was the sulfone, **10**.

Oxidation of the disulfide with Cl_2 in aq 36% HCl gave the desired sulfonyl pyridine, **1**, Scheme 4.

Remarkably, the product crystallised from the aqueous reaction mixture in a very pure state (~100% w/w) and in a yield of 84%. The overall yield (equivalent to 34% from 3-amino-2-chloropyridine) was unsatisfactory, but the observation that **1** separates from the aqueous mixture in high purity and with minimum hydrolysis suggested the possibility of using an all-aqueous process based in Scheme 2 for the manufacture of **1**.

Scheme 5. **Aqueous process for the formation of sulfonyl chloride 1**



Scheme 6. **Mechanism of sulfonyl chloride formation**

$$ArN_2^+ + e \xrightarrow{(Cu^+ \rightarrow Cu^{2+})} Ar\cdot + N_2$$

$$Ar\cdot + SO_2 \longrightarrow ArSO_2\cdot$$

$$ArSO_2\cdot + Cl^- \xrightarrow{(Cu^{2+} \rightarrow Cu^+)} ArSO_2Cl + e$$

The process developed is illustrated in Scheme 5. As expected, the product precipitated from the reaction mixture (>98% w/w), thus being protected from hydrolysis, with an overall yield of 72%. It could be isolated as the solid or extracted into toluene and used directly in the subsequent stage (Scheme 1). Furthermore, additional benefits arose from the increased thermal stability of the aqueous diazonium solution, compared with that in acetic acid as solvent, and the avoidance of the need in the earlier process to neutralise the acetic acid and organic extracts with aqueous base. The latter enabled a considerable reduction in the effluent load of the process.

The in situ reaction of thionyl chloride with water to generate SO_2 for the second stage of this aqueous process, rather than saturated aq SO_2, was found to be very beneficial; the latter gave only a 10% yield of a low-purity product (32% w/w). The successful use of thionyl chloride suggests that the accompanying high levels of chloride generated by the hydrolysis of thionyl chloride to SO_2 are needed for efficient generation of **1** under aqueous conditions. The proposed reaction mechanism, Scheme 6,[3,8] necessarily includes reaction with chloride, but we note that reactions of the diazonium ions with SO_2 in acetic acid do not require HCl additional to that produced during diazonium formation.[3−7] In practice, the use of thionyl chloride rather than SO_2 is also operationally more convenient, and this point was not explored further.

The method illustrated in Scheme 5 has been extended to several other substrates, and the outcomes are listed in Table 1.

Quantitative studies of the reactivity of the various substrates were not carried out, but it was apparent from the rate of gas evolution during the preparations that the reaction times decreased directly as the electron-withdrawing power of the aryl system increased. The conversion of the diazonium ions to sulfonyl chloride became increasingly slow as the aromatic system became more electron neutral, and for electron-rich rings, such as aniline and 4-aminotoluene, product formation was almost completely inhibited. This is in contrast to reactions carried out under standard literature conditions involving reaction of the diazonium ion with SO_2 in acetic acid.[3−7] We have not explored this further and are unsure of the reason for the difference; it may reflect a different mechanism for daizonium conversion under aqueous conditions.

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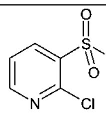
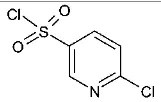
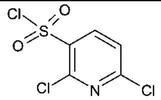
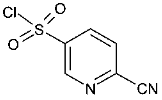
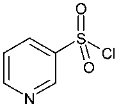
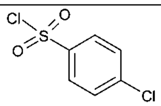
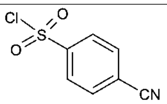
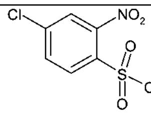
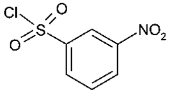
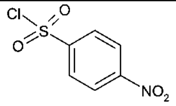
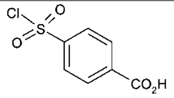
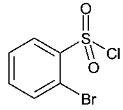
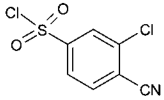
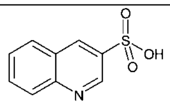
(8) Waters, W. A. *J. Chem. Soc.* **1942**, 266.

Table 1. Preparation of aryl sulfonyl chlorides

Product	Structure	Yield	m.p. (°C)	^{1}H NMR δ ($CDCl_3$)
2-chloro-3-pyridinesulfonyl chloride[a]		70.3	42-43	7.50-7.60 (m, 1H); 8.45-8.50 (m, 1H); 8.72-8.75 (m, 1H)
2-chloro-5-pyridinesulfonyl chloride[a]		77.3	49-50	7.60 (d,1H); 8.30 (dd ,1H); 9.03 (d, 1H).
2,6-dichloro-3-pyridinesulphonyl chloride		87.7		7.32 (d, 1H) 8.39 (d, 1H)
2-cyano-5-pyridinesulfonyl chloride		61.1		7.98 (dd, 1H) 8.49 (dd, 1H) 9.33 (dd, 1H)
3-pyridinesufonyl chloride[a,b]		38.4		7.62 (bt, 1H); 8.20 (d, 1H,); 8.21 (bs, 1H); 9.30 (bs,1H)
4-chlorobenzene sulfonyl chloride[c,d,e,f]		67.2	49-50 50-52[g]	7.60 (d, 2H); 7.99 (d, 2H,)
4-cyanobenzene sulfonyl chloride[c,d,h]		72.9	107-108 108-110[g]	7.97 (d, 2H); 8.20 (d, 2H)
4-chloro-2-nitrobenzene sulfonyl chloride		69.0	75-78	7.65 (dd, 1H) 7.83 (d, 1H) 7.84 (d, 1H)
3-nitrobenzene sulfonyl chloride[c,f,h]		79.8	41-45 63-65[g]	7.90 (t, 1H); 8.37-8.40 (m, 1H); 8.60-8.62 (m, 1H); 8.89-8.91 (m, 1H)
4-nitrobenzene sulfonyl chloride[c,f]		81.7	74-75 66-70[g]	8.27 (d, 2H); 8.48 (d, 2H)
4-(chlorosulfonyl) benzoic acid[c,e,f]		81.1	228-232 233-235[g]	8.30 (d, 2H); 8.40 (d, 2H,)
2-bromobenzene sulfonyl chloride[c,d,e,f]		76.5	45-48 51-52[g]	7.53-7.60 (m, 2H); 7.84-7.91 (m, 1H); 8.18-8.25 (m, 1H)
2-chloro-4-(chlorosulfonyl) benzonitrile[a,c]		78.0	51-54	7.98-8.10 (m, 2H);8.20 (d, 1H)
3-quinolinesulfonic acid[c,i]		60.9	196-197 (dec.)	5.10 (s, 1H); 7.15 (d, 1H,); 7.30 (t, 1H,); 7.40 (t, 1H); 7.60 (d, 1H); 8.90 (s, 1H); 12.44 (bs, 1H)[j]

[a] Structure confirmed by mass spectral analysis. [b] 3-Pyridinesufonyl chloride is an oil which is soluble in the reaction mixture and was obtained after extraction into dichloromethane. [c] In the benzene series the amine hydrochlorides were precipitated as solids during the addition of the amine to the aqueous hydrochloric acid. To ensure complete salt formation the mixture was heated at 30 to 50 °C for up to 60 min prior to cooling and addition of the aqueous sodium nitrite solution (diazonium reagent formation). [d] The products were obtained in two crops, the second crop being precipitated from the combined aqueous mother liquor and wash filtrates. [e] 4-Chlorobenzenesulfonyl chloride, 4-(chlorosulfonyl)benzoic acid, and 2-bromobenzenesulfonyl chloride were precipitated from their reaction mixtures after allowing them to warm to 20 °C and stirring at that temperature for 65, 17, and 27 h respectively. [f] ^{1}H and ^{13}C NMR spectra of the products are consistent with those of the commercially available compounds. [g] Mp of standard commercial sample. [h] 3-Nitrobenzenesulfonyl chloride separated from the reaction mixture as an oil which crystallised during the agitation hold period prior to filtration. [i] The soluble 3-quinolinesulfonyl chloride product was initially formed but hydrolysed in solution and precipitated as the corresponding sulfonic acid; [j] DMSO-d_6.

For very strongly electron-deficient systems, such as 4-aminopyrine, 2-amino-3-nitropyridine, and 2-amino-5-chloropyridine, the diazonium ions were insufficiently stable to allow successful reactions.

The manufacture of 2-chloropyridine-3-sulfonyl chloride, **1**, has been successfully carried out in-house on the multikilogram scale. We note that the HCl/salt-rich reaction mixtures and process liquors are highly corrosive to mild and stainless steel, and therefore the use of glass-, plastic-, or rubber-lined vessels is required. Hastelloy C-276 metal, although not corroded, is coated with an insoluble black material on contact with the reaction mixtures or process liquors, and this can be difficult to remove. Details of the hazard evaluation of these reactions are given below.

Wang et. al[9] describe a successful alternative multikilogram-scale process for the preparation of aryl sulfonyl chlorides, based on the chlorine gas oxidation of aryl propyl sulfides in formic acid. Product isolation was achieved by quenching with cold water and cooling to below 5 °C, resulting in product precipitation with a purity of ~97%.

Hazard Evaluation of Diazonium Salt Formation and Reaction. *Addition of Hydrochloric Acid.* The heat of reaction was determined, and thermal stability tests were carried out. The reaction mixture after addition was shown to be stable to well above processing temperatures. Similarly the exotherm associated with the heat of reaction was shown to be insufficient to generate any hazard.

Addition of Sodium Nitrite: Batch Thermal Stability. Screening and adiabatic thermal stability testing were carried out on the diazonium solutions. The results showed that if cooling were to be lost, then the batch would self-heat. The maximum batch temperature attained, however, was only 44 °C, which is below the boiling point of the batch and the temperatures from which further exothermic decomposition could be accessed. Therefore

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(9) Wang, C; Hamilton, C; Meister, P; Menning, C. *Org. Process Res. Dev.* **2007**, *11*, 52.

the system was not hazardous, provided that the gas could be safely vented (see below).

Addition of Sodium Nitrite: Heat of Reaction. The addition was shown to be exothermic, such that uncontrolled addition would result in decomposition of the diazonium ion. Decomposition could be avoided by carrying out the addition in a controlled manner, with agitation, and balanced against the available cooling.

Gas Evolution. It was shown that no significant gas was evolved at the proposed reaction temperature. Should cooling be lost, however, gas would be generated; adiabatic experiments were carried out to determine the maximum gas rate. The vent system was such that it could cope with the maximum gas rate (including a safety factor of 2).

Stability of Diazo in the Presence of Hastelloy C-276 and Stainless Steel 316. Formation of diazonium ion was tested in the presence of Hastelloy C-276. No gas was observed during the reaction or during a subsequent hold period at 0 °C. Loss of cooling, in the presence of Hastelloy, was investigated using adiabatic calorimetry. The associated temperature rise and gas rates were measured and shown to be slightly higher than in the absence of Hastelloy, but not sufficient to generate any hazard.

Similar work to the above, but with stainless steel 316 led to the conclusion that the presence of large amounts of stainless steel (e.g., in transfer lines) would result in the diazotised batch evolving gas. It was recommended that stainless steel should not be used for transfer lines. Work did, however, confirm that trace amounts of stainless steel would not have any significant effect on the stability of the diazotised batch.

General Hazards of Aqueous Diazotisation. Diazonium salt solutions/slurries gas slowly even at low temperatures. Therefore, transfer lines should not be sealed when containing diazonium salt solutions, and pressure buildup between a pump and a closed valve should not be possible.

Some diazonium salts when dry are capable of decomposing explosively and may be friction-, shock-, and heat sensitive. Therefore the diazonium salt solution should not be allowed to dry out. After transfer of the diazonium salt solution, the reactor and transfer lines etc. should be washed thoroughly. Contact of diazonium salts with copper or nickel can result in reduced stability and should be avoided.

Sodium nitrite can form explosive mixtures with amines, sulphamates, and ammonium salts. Inadvertent mixing of sodium nitrite with other chemicals should therefore be avoided.

Finally, we note that aqueous aromatic diazonium ions, typically prepared by the action of mineral acids and sodium nitrite on aromatic amines, are used extensively in the manufacture of azo dyes, to the extent of thousands of tons per annum.[10] They can, therefore, be handled safely, provided that precautions such as those described above are taken.

Summary

The use of totally aqueous acidic conditions for generation and reaction of the diazonium ion intermediates, combined with use of thionyl chloride as the sulfur dioxide source, has been found to be advantageous for the preparation of a range of electron-deficient or electron-neutral arylsulfonyl chlorides.[11] The product arylsulfonyl chlorides precipitate directly from the reaction mixture in good yield and high quality. The omission of acetic acid as cosolvent (which solubilises the product) eliminates the need for extensive neutralisation of the reaction mixtures prior to isolation, which can cause significant product hydrolysis and yield loss.

Experimental Section

Materials. Inorganic chemicals and starting aryl amines were high-purity commercial reagents and were used without further purification.

Preparation of 2-Chloropyridine-3-sulfonyl Chloride, 1, (Scheme 4). Hydrochloric acid (36% w/w, 20 mL) was added, with agitation, to 3,3′-dithiobis(2-chloropyridine) (2.0 g) at 20 °C to give a pale-yellow solution. Water (5 mL) was added, and chlorine gas bubbled through the solution for 1 h, maintaining the temperature of the mixture at 20−23 °C. Water (25 mL) was added dropwise to the reaction mixture, maintaining the temperature at 20−29 °C. A white solid precipitated during this addition, and after cooling the mixture to 20 °C the suspended solid was collected by vacuum filtration, washed with water (3 × 25 mL), and dried under vacuum at below 35 °C to give 2-chloropyridine-3-sulfonyl chloride (2.47 g; 83.6% yield); mp 51 °C.

^{1}H NMR ($CDCl_3$, 270 MHz, 300 K): δ 7.54−7.58 (m, 1H), 8.45−8.50 (m, 1H), 8.75−8.77 (m, 1H).[6] ^{13}C NMR ($CDCl_3$, 270 MHz, 300 K): δ 123.0, 138.8, 139.1, 148.2, 154.8. Mass Spec EI^+ 211 (M^+), 176 (M − Cl), 112 (M − SO_2Cl), 76 (112 − HCl).

Preparation of 2-Chloropyridine-3-sulfonyl Chloride, 1, (Scheme 5). (a) Thionyl chloride (42 mL) was added dropwise over 60 min to water (250 mL), cooled to 0 °C, maintaining the temperature of the mixture 0−7 °C. The solution was allowed to warm to 18 °C over 17 h. Copper(I) chloride (0.151 g) was added to the mixture, and the resultant yellow-green solution was cooled to −3 °C using an acetone/ice bath

(b) Hydrochloric acid (36% w/w, 135 mL) was added, with agitation, to 3-amino-2-chloropyridine (17.3 g), maintaining the temperature of the mixture below 30 °C with ice cooling. The reaction mixture was cooled to −5 °C using an ice/acetone bath and a solution of sodium nitrite (10.0 g) in water (40 mL) was added dropwise over 45 min, maintaining the temperature of the reaction mixture between −5 to 0 °C, the resultant slurry was cooled to −2 °C and stirred for 10 min.

(c) The slurry from step b was cooled to −5 °C and added to the solution obtained from step a over 95 min, maintaining the temperature of the reaction mixture between −3 to 0 °C (the slurry from step b was maintained at −5 °C throughout the addition). As the reaction proceeded, a solid began to precipitate. When the addition was complete, the reaction mixture was agitated at 0 °C for 75 min. The suspended solid was collected by vacuum filtration, washed with water (2 × 125 mL), and dried under vacuum at below 35 °C to give 2-chloropyridine-3-sulfonyl chloride (19.6 g; 70% yield.); mp 42 °C.

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^{1}H NMR ($CDCl_3$, 270 MHz, 300 K): δ 7.50−7.60 (m, 1H), 8.45−8.50 (m, 1H), 8.72−8.75 (m, 1H).[6] ^{13}C NMR ($CDCl_3$, 270 MHz, 300 K): δ 123.5, 139.5, 140.0, 149.0, 155.0. Mass Spec EI$^+$ 211 (M^+), 176 (M − Cl), 112 (M − SO_2Cl), 76 (112 − HCl).

Preparation of 3,3′-Dithiobis(2-chloropyridine), 9. (a) Thionyl chloride (42 mL) was added dropwise over 30 min to water (250 mL) cooled to 0 °C, maintaining the temperature of the mixture 0−7 °C. The solution was allowed to warm to 15 °C over 17 h. Copper(I) chloride (1.33 g) was added to the mixture to give a yellow-green solution and KI (1.42 g) added, precipitating a beige solid. The resultant mixture was cooled to −3 °C using an acetone/ice bath.

(b) Hydrochloric acid (36% w/w, 135 mL) was added, with agitation, to 3-amino-2-chloropyridine (17.3 g), maintaining the temperature of the mixture below 30 °C with ice cooling. The reaction mixture was cooled to −3 °C using an ice/acetone bath, and a solution of sodium nitrite (10.0 g) in water (40 mL) was added dropwise over 40 min, maintaining the temperature of the reaction mixture between −3 to 0 °C; the resultant slurry was cooled to −2 °C and stirred for 10 min.

(c) The slurry from step b was cooled to −3 °C and added to the solution obtained from step a over 55 min, maintaining the temperature of the reaction mixture between −3 to 3 °C (the slurry from step b was maintained at −5 °C throughout the addition). When the addition was complete, the reaction mixture was agitated at 0 °C for 150 min, during which time a solid began to precipitate. The suspended solid was collected by vacuum filtration, washed with water (2 × 100 mL), and dried under vacuum at below 35 °C to give crude byproduct, 3,3′-bis(2-chloropyridine)sulphone (5.0 g), which after dissolution in dichloromethane, washing with aqueous sodium hydroxide, filtration to remove precipitated inorganics, separation and evaporation of the lower organic filtrate phase, and recrystallisation from aqueous acetonitrile gave a white solid byproduct 3,3′-bis(2-chloropyridine)sulfone (3.60 g, 18.9% yield).

^{1}H NMR (CD_3CN, 270 MHz, 300 K): δ 7.66−7.71 (m, 2H), 8.69 (dd, 2H), 8.79 (dd, 2H). ^{13}C NMR (CD_3CN, 270 MHz, 300 K): δ 124.8, 134.9, 143.5, 148.6, 155.8. Mass Spec EI$^+$ 288 (M^+), 189 [M − (SO_2 + Cl)], 160, 112, 76 (112 − HCl).

The product was then obtained in two solid crops as follows: the filtrates and water washes from above were diluted with water (800 mL), and the mixture was stirred at 20 °C for 120 min during which time a white solid was precipitated. The suspended solid was collected by vacuum filtration, washed with water (2 × 100 mL), and dried under vacuum at below 35 °C (first crude solid yield, 5.52 g). Again the filtrates and water washes from above were diluted with water (100 mL), and the mixture was stirred at 20 °C for several days during which time a second crop of solid precipitated. The suspended solid was collected by vacuum filtration, washed with water (2 × 100 mL), and dried under vacuum at below 35 °C (crude second crop yield, 3.72 g). The combined crude solid product crops were dissolved in acetontrile (250 mL) at reflux, hot filtered to remove unwanted insoluble material, and then cooled to 20 °C for 17 h. The recrystallised suspended white solid was collected by vacuum filtration, washed with acetonitrile (20 mL), and dried under vacuum at below 35 °C to give the 3,3′-dithiobis(2-chloropyridine) (7.77 g; 40.9% yield.); mp 215−216 °C.

^{1}H NMR ($CDCl_3$, 270 MHz, 300 K): δ 7.15−7.20 (m, 2H), 7.78 (dd, 2H), 8.19 (dd, 2H). Mass Spec ES$^+$ 291 (MH^+), 289 (M^+), 250, 214 (250 − HCl).

Acknowledgment

We thank Stephen Hallam for hazard evaluation and advice relating to the work described above.

Received for review April 7, 2009.

OP9000862