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Studies toward an Improved Process for N^4,N^4-Disubstituted-2-cyano-N^1,N^1-dimethyl-1H-imidazole-1,4-disulfonamides

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Abstract:

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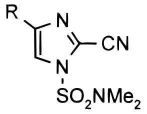
The development of a practical and cost-effective process for the manufacture of the title fungicidal compounds is described. In particular, substantial improvements in the chlorosulfonation of imidazole, studies on the stability of various cyanating agents, and a novel formylation/oximation/dehydration sequence to introduce the 2-cyano group are described.

Introduction

4-Substituted-2-cyano-1-sulfamoylimidazoles (**1**) have been of ongoing interest as fungicides.[1−5] One subclass of this type of chemistry offering a combination of good biological activity and tractable chemistry is exemplified by structures **2** and **3**. To further evaluate some of these compounds, large quantities were therefore required.



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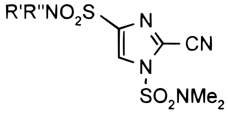


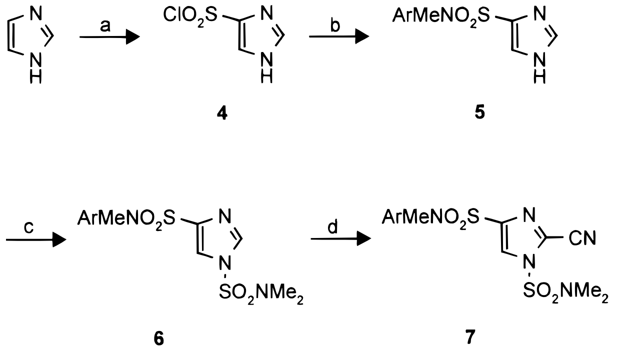
2 : R' = Aryl, R'' = Alkyl
3 : R' = Benzyl, R'' = Alkyl

Whilst these compounds are relatively easily synthesised in the laboratory (Scheme 1), the route used had several problems associated with it which made it unattractive from the point of view of both scale-up and cost. The major issues were multiple solids isolation, poor chlorosulfonation and cyanation yields, low temperatures not accessible in either our pilot plant or typical general purpose plants, and the preparation and handling of unstable cyanating agents. During work to address these issues, some novel chemistry and useful insights into the process emerged, and these are discussed in turn for each step in the synthesis of **7** (Scheme 1).

Chlorosulfonation of Imidazole

The initial procedure,[6] via the intermediate 4-sulfonic acid, had a number of drawbacks apart from the poor yield (53−61%). The addition of imidazole to chlorosulfonic acid (CSA) is strongly exothermic and difficult to operate on a large scale because the hydrogen chloride fumes tend to foul the addition device. Also, the reaction uses 3 equiv of CSA, two of which appear in a dilute aqueous waste stream. Finally, the product has to be isolated and dried quickly and efficiently to prevent its hydrolysis.

Scheme 1[a]



[a] Conditions: (a) CSA, 130 °C, then $SOCl_2$, 65 to 135 °C; (b) ArNHMe, pyridine, toluene, 85 °C; (c) Me_2NSO_2Cl, DMAP, K_2CO_3, acetone, 25 °C; (d) n-BuLi, THF, −78 °C, then PhOCN or TsCN at −20 to −10 °C.

Replacing CSA with sulfur trioxide[7] to give the 4-sulfonic acid was successful, but chlorination with phosphoryl or thionyl chloride in the absence of chlorosulfonic acid failed.

In addressing the drawbacks with CSA, the following observations were made:

(i) Formation of imidazole-4-sulfonic acid is rapid (0.5 h).

(ii) The optimum molar ratio of CSA to imidazole is 2.6−2.8:1. At lower ratios the reaction becomes too viscous, and above 3.0:1 yields are reduced.

(iii) The optimal chlorination temperature is 120−125 °C. Below 90 °C no reaction occurs, and above 150 °C a glass forms. This temperature could be maintained by controlling the rate of thionyl chloride addition (3 h) so that, despite operating 40−45 °C above the boiling point of thionyl chloride, no significant reflux was observed.

(iv) The yield is unaffected by the order of addition, enabling CSA to be added to molten imidazole.

(v) When sodium chloride is added to the CSA prior to addition to the molten imidazole, yields are dramatically improved (91−93%), being even better than those achieved (83−85%) with distilled reagents.

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† AgrEvo UK Ltd., Cambridgeshire.

‡ AgrEvo UK Ltd., Essex.

(1) Schering Agrochemicals Limited. EP 248277, 6 March 1988.

(2) Schering Agrochemicals Limited. EP 390506, 27 March 1990.

(3) Schering Agrochemicals Limited. EP 432892, 1 November 1990.

(4) Riordan, P. D.; Dudfield, P. J.; Briggs, G. G.; Ekwuru, C. T.; Osbourn, C. E.; Hamilton, K.; Simpson, D. J. *Synthesis and Chemistry of Agrochemicals IV*; ACS Symposium Series 584; American Chemical Society: Washington, DC, 1994; p 375.

(5) Ishihara Sangyo Kaisha Ltd. EP 337103, 11 March 1988.

(6) E. I. Du Pont de Nemours & Co. US 3,932,444, 13 January 1976.

(7) Bochkareva, T. P.; Passet, B. V.; Popov, K. R.; Platonova, N. V.; Koval'chuk, T. I. *Geterotsikl. Soedin* **1987**, *10*, 1353.

10.1021/op9800717 CCC: $18.00

This final, dramatic advance arose from speculation that chloride ion concentration might be important, but we have no convincing explanation for the effect. An important consequence of this yield enhancement was a 4−5-fold reduction in the organic effluent load.

To avoid the problems associated with isolating and drying the product, extraction into an organic solvent was investigated and shown to be feasible, although requiring of further optimisation, on a laboratory scale. Thus, controlled addition of the reaction mixture to cold brine and extraction with ethyl benzene/THF afforded, after concentration, a dry slurry of the sulfonyl chloride (**4**) in ethyl benzene ready for the next stage and a wet mixture of ethyl benzene and THF which can be used for the next extraction. Final extraction of the aqueous phase with ethyl benzene ensured that only low levels of THF remained in the aqueous phase. (This unusual choice of solvents was dictated by the need to use LDA/THF later in the process and the fact that styrene is used as a hydrogen acceptor in LDA manufacture so that ethyl benzene is present in LDA solutions. With an objective to use as few solvents as possible, we aimed to use only ethyl benzene, THF, and water. However, the sulfonyl chloride (**4**) was not sufficiently soluble in ethyl benzene alone.)

The remaining issue for this step was the acidic aqueous effluent. This could not be avoided because pre-recovery of the excess chlorosulfonic acid resulted in a reaction mixture that was too viscous to handle. However, it was envisaged that the acidic brine could be used to recover the diisopropylamine generated later in the process.

Conversion of Sulfonyl Chloride (4) to Sulfonamide (5)

In the laboratory route, this was carried out in a variety of solvents in the presence of pyridine at 60−85 °C. At the end of the reaction, the product was separated from a small amount of unreacted aniline and other impurities by extraction into aqueous caustic soda and was then precipitated in very pure form upon addition of hydrochloric acid.

In seeking to streamline this step, our aim was to eliminate the use of pyridine and carry the caustic soda solution of the product through to the next step.

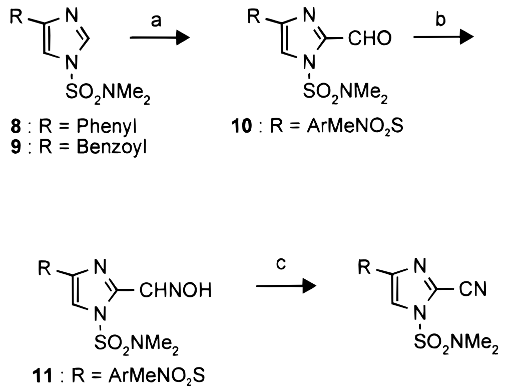
In the event, the condensation was smoothly achieved using a slight excess (3 mol %) of the aniline in refluxing ethyl benzene, giving the product in 98.5% yield; the hydrogen chloride produced was trapped in a caustic scrubber. The mixture was then cooled, the product extracted into aqueous caustic soda, and the solution fed forward to the next stage. The small aniline excess remained in the ethyl benzene and was recycled.

Conversion of Sulfonamide (5) to the Sulfamoylated Imidazole (6)

The sodium hydride initially used as the base in the original laboratory procedure was replaced with DMAP/K_2CO_3/acetone for the initial pilot plant work. However, the availability of **5** as its sodium salt gave us the opportunity to avoid adding base altogether.

The reaction of *N*,*N*-dimethylsulfamoyl chloride (DMSC) with an aqueous solution of **5** was hampered by the fact that the excess caustic soda required to keep **5** in solution is able to react with DMSC or the product. This could be suppressed, however by operating in a two-phase system, so that treating a mixture of the aqueous caustic soda solution of **5** and an equal volume of ethyl benzene with DMSC (1.1 equiv) in the presence of catalytic benzyltriethylammonium chloride (BTEAC) afforded 92% conversion to **6**, which dissolves in the organic layer with 8% starting material (**5**) crystallising at the interface. Although addition of fresh DMSC and caustic soda results in further conversion, significantly increased and, therefore, uneconomic quantities of DMSC are required to bring the reaction close to completion. The starting material **5** was more economically recycled by removing the bulk of the aqueous phase as waste, followed by addition of fresh water and sufficient caustic soda to dissolve the interfacial solid. This second aqueous phase could then be separated and recycled whilst the organic phase could be forwarded to the final cyanation step.

Scheme 2[a]



[a] Conditions: (a) n-BuLi, toluene, −78 to −35 °C, then MeOCHO; (b) $NH_2OH·HCl$, EtOH/THF 2:1, reflux; (c) TFAA, 1,4-dioxane/pyridine 1.7:1, −10 °C, or $(Me_2N{=}CHCl)^+·Cl^-$, Et_3N, 0 °C, DCM.

Direct Cyanation of the Sulfamoylated Imidazole (6)

The method originally used to introduce the nitrile group into 4-substituted-1-sulfamoyl-imidazoles was a three-step sequence via the 2-formylimidazole (Scheme 2).[4] For some substrates (e.g., **8**) this method worked well, with overall yields of ∼85%, but in other cases (e.g., **9**) yields were very poor. Direct cyanation[8] of the imidazoyl anion using phenyl cyanate or tosyl cyanide gave yields of only about 70% but was more convenient in the laboratory and more consistent across different substrates than the three-step process. It was therefore adopted as the normal laboratory method. Its essential features were that anion formation above −35 °C gave reduced yields, the cyanating agent had to be added as rapidly as possible at −20 °C to −10 °C, the reaction was strongly exothermic (200−300 kJ mol^{-1}), and the reaction did not go to completion (even though D_2O equilibration experiments indicated complete anion formation).

For pilot plant operation, this route offered two immediate problems: the low temperatures required and the handling of unstable cyanating agents on a large scale. For the longer term, there were additional problems. Reaction was usually

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(8) Dudfield, P. J.; Ekwuru, C. T.; Hamilton, K.; Osbourn, C. E.; Simpson, D. J. *Synlett* **1990**, *5*, 227.

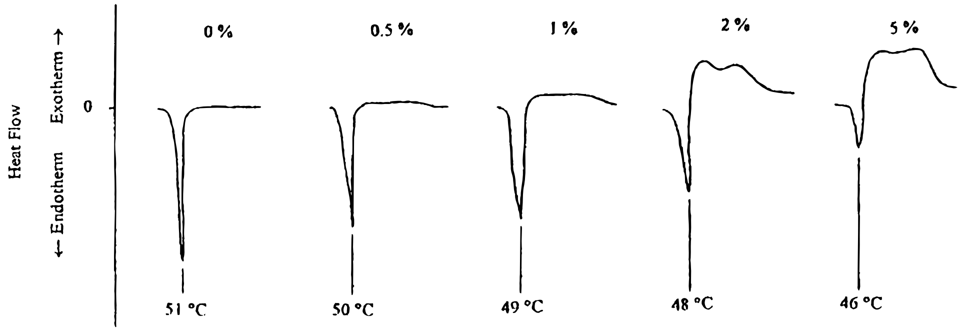


Figure 1. **Effect of added water on the low-temperature exothermicity of tosyl cyanide.**

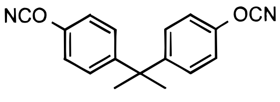
incomplete, and the need to add the cyanating agent rapidly, coupled with the strong exothermicity of the reaction, meant that only low concentrations of reactants could be used, which would clearly be inefficient. In addition, the cost and availability of cyanating agents was a concern.

These considerations led to work on alternative bases and cyanating agents, including studies on the stability of the latter.

Alternative Bases. Experiments with different bases (bis(trimethylsilyl)amides, alkoxides, and LDA) using phenyl cyanate as the cyanating agent showed that LDA gave good yields at temperatures accessible to our pilot plant (−10 to 0 °C). For imidazole-4-sulfonamides such as **6**, the relative stability of the anion at C-2 and C-5 of the imidazole is finely balanced. This is illustrated by previous findings with 4-aryl (**8**)- and 4-benzoyl (**9**)-substituted substrates, where the C-2 and C-5 anions are favoured, respectively.[4] In fact, the enhanced acidity of the C-5 position of the product and its subsequent equilibration with the starting anion might well be responsible, in part, for the failure of the cyanation reactions to go to completion.

Alternative Cyanating Agents. The cyanogen halides, mesyl cyanide, and 2,2-bis(4-cyanatophenyl)propane (BisCPP) were examined. The latter compound, which is, in fact, commercially available,[9] had not previously been used as a cyanating agent and was suggested during discussions with a supplier of the sulfonyl cyanides.

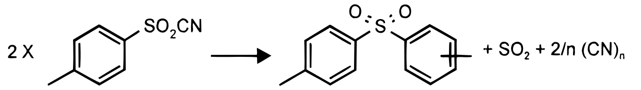
Although literature methods[10−12] using cyanogen halides failed to work with our substrates, mesyl cyanide and BisCPP both afforded the desired product.



BisCPP

Stability of the Cyanating Agents. Phenyl cyanate is easily prepared,[13] but its purification by distillation on a pilot plant scale was unattractive. Although the pure material is stable on heating to its boiling point (200 °C), in an impure state or in the presence of metal ions it decomposes exothermically at appreciably lower temperatures (predominantly to triphenyl *iso*-cyanurate).[7]

Scheme 3



Tosyl cyanide too is readily prepared, separating as a white solid from the aqueous reaction mixture.[14] However, drying other than small quantities of water-wet material is known to be hazardous (causing in one case the top of a desiccator to be blown off).[15] Accordingly, the material is usually extracted into a solvent from which it is isolated after drying, but even with this kind of procedure decompositions have occurred (private communication). For example, several kilograms of solvent-wet material self-reacted, resulting in a temperature rise from ambient temperature almost to ignition (the keg and residual contents were heavily charred).

Differential scanning calorimetry (DSC) on nominally dry samples of tosyl cyanide from several sources showed moderate exothermicity (∼500 J g^{-1}), with an onset temperature of about 190 °C. Crude samples of tosyl cyanide exhibited exothermicity just after melting (∼50 °C), and the overall exothermicity was increased in some cases to 800 J g^{-1}. DSC on samples of "dry" tosyl cyanide spiked with water (see Figure 1) suggested that the low-temperature exotherm is, at least initially, due to a hydrolytic reaction.

Decomposition of "dry" tosyl cyanide in miniautoclaves indicated the evolution of about 0.5 mol of a gas per mole of tosyl cyanide (consistent with Scheme 3, which is analogous to that proposed by Grewer[16] for sulfonyl chlorides), but rates of pressure rise (<50 bar s^{-1}) were well below those associated with unconfined explosion hazards.[17]

Samples of tosyl cyanide not exhibiting low-temperature exothermicity were also examined in the thermal activity monitor (TAM). Combining TAM and DSC results as recently proposed[18] indicated that even nominally dry tosyl cyanide might self-react in masses of 25 kg or so from about 50 °C.

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(9) Tonnage quantities are available from algroup lonza, Basel, Switzerland.

(10) Whitten, J. P.; Matthews, D. P.; McCarthy, J. R. *J. Org. Chem.* **1986**, *51*, 1891.

(11) McCarthy, J. R.; Matthews, D. P.; Whitten, J. P. *Tetrahedron Lett.* **1985**, 6273.

(12) Whitten, J. P.; Matthews, D. P.; McCarthy, J. R. *Synthesis* **1988**, 470.

(13) Murray, R. E.; Sweifel, G. *Synthesis* **1980**, 150.

(14) Cox, J. M.; Ghosh, R. *Tetrahedron Lett.* **1969**, 3351.

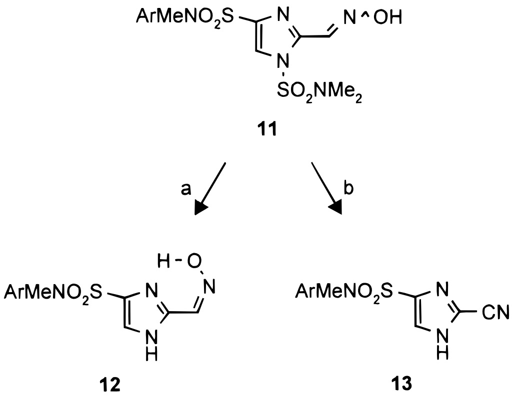
(15) Daluga, S.; Vince, R. J. *J. Org. Chem.* **1978**, *43*, 2311.

(16) Grewer, T. *Thermal hazards of chemical reactions*; Elsevier: Amsterdam, 1994; p 199.

(17) Whitmore, M. W.; Cutler, D. P.; Gladwell, J. P. *J. Loss Prev. Process Ind.* **1994**, *7 (10)*, 49.

(18) Whitmore, M. W. *Estimation of stability temperatures from differential thermal analysis and thermal activity monitor data in combination*; IChemE Symposium Series 134; IChemE: Rugby, UK, 1994; p 597.

Scheme 4[a]



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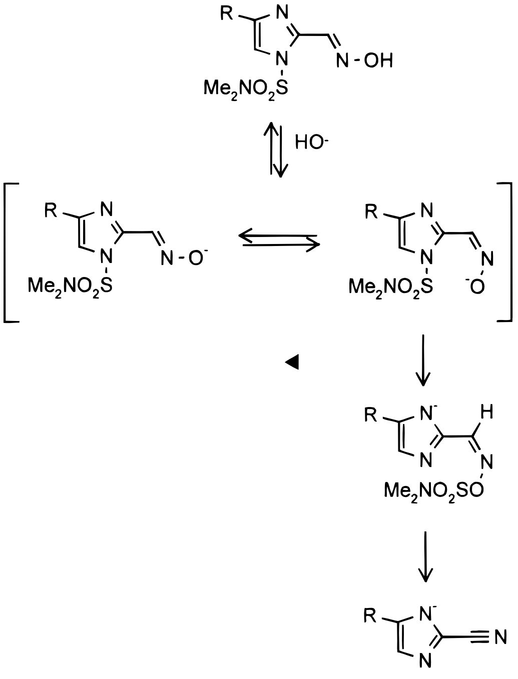
12 **13**

[a] Condition: (a) aq HCl, rt; (b) aq NaOH, rt.

Scheme 5



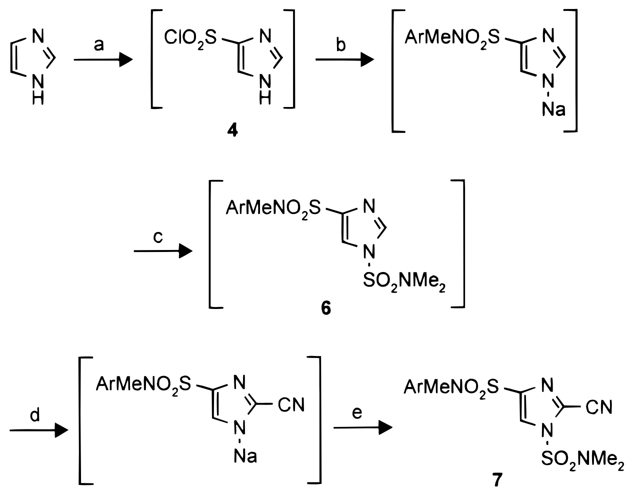
In view of these results, we decided that tosyl cyanide for pilot plant use should be supplied as a 50% solution in THF and its stability monitored.

Regarding the alternative cyanate, BisCPP, DSC showed it to be weakly exothermic (~300 J g^{-1}), with an onset temperature of about 170 °C. It was therefore considered suitable for large scale use.

Finally, previous studies had shown that mesyl cyanide was likely to be unstable at ambient temperature.[14,19] This was confirmed by some degradation of a sample in transit and DSC (onset 60 °C, exothermicity ~1500 J g^{-1}). Clearly, the material was too unstable for convenient large scale use.

Further Development of the Direct Cyanation. Pilot plant production of **7** by direct cyanation proved to be possible using LDA and either 50% tosyl cyanide solution or BisCPP, the latter being preferred for further scale-up. However, the problems of low concentration and incomplete reaction were not resolved. Although engineering the reaction differently, i.e., reverse addition or continuous cyanation, may have provided resolution of these issues, the cost of the cyanating agent was critical at this stage. Attention was therefore switched to the indirect route (Scheme 2), where the significantly higher concentrations (30% vs 5% w/w) that could be used ensured an overall cost savings.

Scheme 6[a]



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6

7

[a] Conditions: (a) CSA, NaCl, 80 to 125 °C, then SOCl$_2$, 120 to 130 °C; (b) ArNHMe, ethyl benzene, 135 °C, then NaOH, water, 20 °C; (c) Me$_2$NSO$_2$Cl, BnEt$_3$N$^+$Cl$^-$, ethyl benzene, 25 °C; (d) LDA, THF, −10 °C, then MeOCHO, −10 °C, added to NH$_2$OH·H$_2$SO$_4$, water, 20 °C, then aq NaOH, 20 °C; (e) Me$_2$NSO$_2$Cl, ethyl benzene, 25 °C.

Indirect Cyanation of the Sulfamoylated Imidazole (6) (Scheme 2)

Formylation. The formylation procedure used in the laboratory involved the sequential addition of n-BuLi and methyl formate to **6** in toluene at −35 °C to give **10** in ~60% yield. By varying the solvent, bearing in mind the preference for ethyl benzene (see above), we ultimately found that concentration of the ethyl benzene solution of **6** (which has the added benefit of ensuring that the solution is dry) from the previous step and addition of THF afforded a solution which could be readily formylated using LDA (at −10 °C) and methyl formate in 90% yield.

Oxime Formation. The product of the formylation reaction prior to acidification is a lithiated hemiacetal. Pleasingly, direct treatment of the formylation reaction mixture with a hydroxylamine salt liberated the aldehyde and hydroxylamine and resulted in oxime formation. Significant amounts of an impurity were also formed by this method, and its identification was to form the basis for a greatly improved process (see later).

As an alternative, adding the lithiated hemiacetal solution to aqueous hydroxylamine sulfate buffered with 2 equiv of acetic acid gave a 91% yield of the oxime (**11**) as a 10:1 mixture of *E*:*Z* isomers for the two steps from **6**.

Dehydration to 2-Cyanoimidazole. Although a number of procedures were developed as alternatives to those shown in Scheme 2 (e.g., POCl$_3$/DIPA, SiCl$_4$/Et$_3$N), no one method was ideal. However, whilst this was being addressed, information came to hand which was to resolve the issue satisfactorily (see below).

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(19) Vrijand, M. S. A. *Org. Synth.* **1977**, *57*, 88.

Modified Indirect Cyanation of the Sulfamoylated Imidazole (6)

The impurity formed in the oximation reaction was found to be the desulfamoylated nitrile (**13**) (Scheme 4). Further investigation of this rather surprising finding showed that, whilst treatment of **11** (10:1 *E*:*Z*) with aqueous acid gives desulfamoylated oxime (**12**) (as its *Z* isomer only), treatment with aqueous caustic soda results in the formation of **13** only. A reasonable mechanism for this transformation is shown in Scheme 5.

Application of this discovery allowed us to avoid many of the problems associated with the indirect cyanation route. Thus, adding the lithiated hemiacetal reaction mixture to aqueous hydroxylamine sulfate followed by the addition of caustic soda gave **13** in an unoptimised 76% yield (from **6**). Furthermore, **13** could be converted to final product **7** using a modified version of the earlier sulfamoylation procedure. In most cases, **7** precipitated from the reaction mixture so that filtration, followed by washing with ethyl benzene and then water, afforded the desired product in 95% yield and >99% purity (from **13**). Further process enhancements may be realised by replacing the *N*,*N*-dimethylsulfamoyl group in **6** with other sulfonyl derivatives (e.g., tosyl).

Conclusion

The final process is depicted in Scheme 6. Relative to the initial laboratory process, many improvements have been made: no solid intermediate handling is necessary before final product isolation; only two organic solvents are used; chlorosulfonation is excellent and cyanation yields are good; there is no use or handling of unstable or expensive cyanating agents; reactions can be done at temperatures available on normal, general purpose equipment; and costs are significantly lower.

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