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Summary of Lecture Transcripts

Process Development for the Sulfonamide Herbicide Pyroxsulam

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Abstract:

The development of a manufacturing process for the initial commercial production of pyroxsulam sulfonamide herbicide is described. The process encompasses seven reaction steps, and includes a new route to 4-(trifluoromethyl)pyridines, a scaleable method of lithiating a pyridine intermediate, and a sulfilimine-catalyzed formation of a sulfonamide.

Introduction

Pyroxsulam, shown in Figure 1, will be the latest in a series of triazolopyrimidine sulfonamide herbicides to be commercialized by Dow AgroSciences LLC. [1] These herbicides act via inhibition of acetolactase synthase enzyme, preventing the biosynthesis of key amino acids, and have a variety of applications within crop protection.[2] Typical attributes of this class of herbicides include low rates of application and superior toxicology and environmental profiles. Pyroxsulam is being developed for control of key weeds in cereal crops such as wheat, and is expected to enter the commercial market in 2008. Initial production was needed in 2007 to supply the launch.

In addition to the goals of developing a safe, reliable, and low-cost process, the project was required to fit the process as much as possible into the existing sulfonamides herbicide manufacturing complex to minimize capital expenses. This sometimes led to selection of processing operations based on a best fit to the available manufacturing environment and precluded investigation of areas that were considered to be incompatible with the available equipment. The desire to maintain sufficient similarity of the impurity profile with that of the material used in toxicology studies to avoid additional toxicology testing also precluded some technologies.

Results and Discussion

The formation of the sulfonamide unit from the corresponding amine **2** and sulfonyl chloride **3** as the final reaction to produce pyroxsulam allows a convergent synthesis in addition to leveraging technology of the existing commercial sulfonamides. For these reasons, this approach was an obvious choice for development although some alternatives were also investigated.[3] As the amine **2** was expected to be sourced from specialty chemical suppliers, the larger decision with respect to route selection was whether to approach the sulfonyl chloride **3** from γ-picoline and install the fluorines subsequently or to begin with a trifluoromethylated building block and implement a pyridine cyclization strategy (Scheme 1).

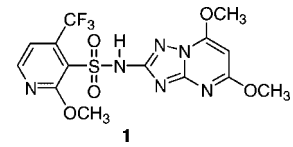

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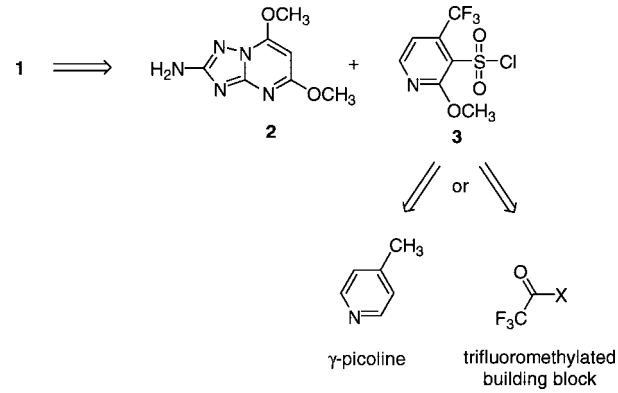
Figure 1. **Pyroxsulam herbicide.**

Scheme 1. **Retrosynthesis of Pyroxsulam**



The coupling reaction of **2** and **3** may appear to be trivial but, in fact, is rather complicated. Little or no reaction occurs under typical conditions (e.g., treatment with various bases and solvents), and both reactants require some form of activation (Scheme 2). For **3**, activation can be achieved by the use of pyridine-type compounds as the base. 3,5-Lutidine is remarkably effective for this purpose, apparently containing the optimum combination of basicity and steric nature as it is much more effective than pyridine itself or the α-substituted pyridines such as 2-picoline or 2,6-lutidine.[4] This presumably forms the corresponding sulfonylpyridinium chloride **4** as a reactive species although this has not been detected analytically.[5] For **2**, activation occurs by *in situ* formation of its dimethylsulfilimine **5** via the reaction of DMSO with **2** and **3**.[6] The sulfilimine

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(1) Johnson, T. C.; Vanheertum, J. C.; Ouse, D. G.; Pobanz, M. A.; Arndt, K. E.; Walker, D. K. PCT Int. Appl. WO 2002/036595, 2002.
(2) Kramer, W., Schirmer, U., Eds. *Modern Crop Protection Compounds*; Wiley-VCH: Weinheim, 2007; pp 93–112..
(3) Bell, B. M.; Fanwick, P. E.; Graupner, P. R.; Roth, G. A. *Org. Process Res. Dev.* **2006**, *10*, 1167–1171.
(4) Hamilton, C. T. U.S. Patent Appl. Publ. U.S. 20050215570, 2005.
(5) Rogne, O. *J. Chem. Soc. B* **1970**, *4*, 727–730.
(6) Ringer, J. W.; Pearson, D. L.; Scott, C. A.; Wallin, A. P. PCT Int. Appl. WO 1998/21178, 1998.

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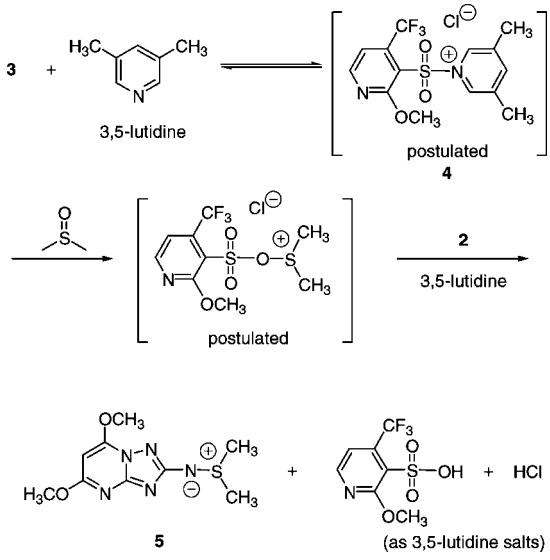
Scheme 2. **Proposed roles of DMSO and 3,5-lutidine in the pyroxsulam coupling reaction**



5 thus formed is proposed to act as the nucleophilic agent and engage in a catalytic cycle with the activated form of **3** to produce the pyroxsulam molecule (Scheme 3). Consistent with the proposed mechanism, the sulfilimine **5** can be prepared externally as its azasulfonium salt **6** from the reaction of **2** with methyl sulfide and *N*-chlorosuccinimide[4,7,8] as shown in Scheme 4 and used in place of the DMSO to give a similar coupling reaction result. Effective activation of the coupling reaction is observed using DMSO in amounts around 5–10 mol %. Via this protocol, the reaction conversion (based on sulfonyl chloride) is in the low 80%'s, and the isolated yield is typically in the mid 70%'s using materials with quality typical of that expected in the production setting.

The formation of sulfilimine **5** using DMSO is very convenient, but does involve the sacrifice of sulfonyl chloride **3** equimolar to the DMSO amount according to the proposed mechanism. Of course it would be preferential to avoid this sacrifice, and alternative methods for generation of the sulfilimine, such as using dimethyl sulfide and chlorine[4,6] may be implemented in future production.

Aminotriazolopyrimidine **2** is described in several publications[3,9] and was obtained via purchase from a specialty chemicals vendor. It can be prepared from either 2-amino-4,6-dimethoxypyrimidine or 2-chloro-4,6-dimethoxypyrimidine.

Sulfonyl chloride **3** was envisioned to come from the corresponding pyridine **7** via a sequence of lithiation, thiolation, and chloroxidation. The route shown in Scheme 5 was developed for this transformation. For the lithiation and thiolation, the pyridine **7** and elemental sulfur are combined in THF and treated with a solution of LDA. In addition to an excellent yield (>90%), this avoids the accumulation of the potentially energetic lithio(trifluoromethyl)pyridine intermediate and operates well at ambient temperatures (15–20 °C). After addition of water, the thiolate salt **8** partitions cleanly into the aqueous phase. This is decanted, concentrated slightly to remove residual organics, and forwarded on as an aqueous solution (~24 wt%) to the next step. Another significant benefit of this procedure is that the aqueous thiolate salt solution is much less malodorous than its corresponding free thiol, which was considered to be too noxious for handling in our facilities.

The treatment of the aqueous solution of thiolate **8** with chlorine and water (chloroxidation) in the presence of dichloromethane as cosolvent provides sulfonyl chloride **3** in excellent yield (~95%). To minimize potential for reaction of thiolate **8** with dichloromethane, enough HCl is added to the water layer to acidify the thiolate prior to the addition of the chlorine. Instead of attempting to isolate **3** as a solid, the organic layer is decanted, and the dichloromethane is removed by distillation (most of which is suitable for recycling) and replaced with the higher-boiling acetonitrile. This affords a dry solution of **3** for use in the coupling reaction.

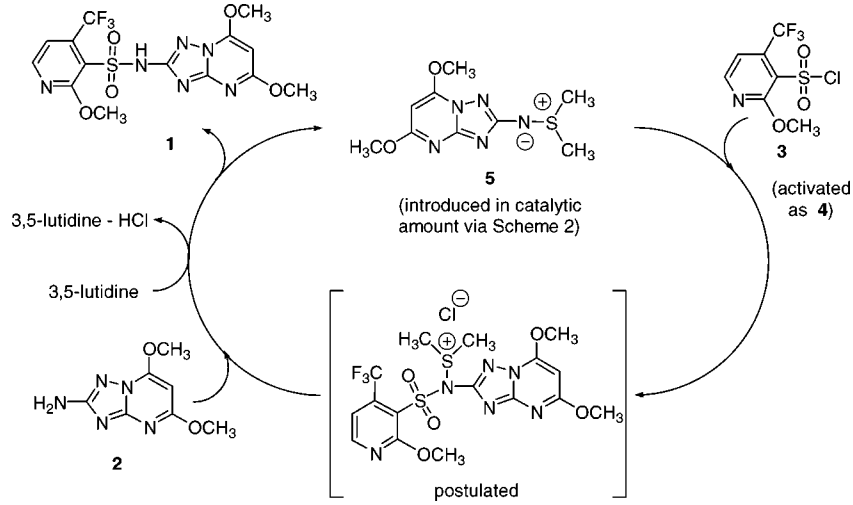
The thiolation precursor, pyridine **7**, was initially expected to come from chlorination and fluorination of γ-picoline. This route would employ relatively inexpensive raw materials (γ-picoline, HF, Cl_2) and would utilize core technologies of Dow AgroSciences LLC. However, the existing assets for this type of service were of much larger scale than required, and even a few equipment modifications were predicted to result in very high capital costs due to the requirement for highly specialized metals to handle the corrosivity of this process.

Efforts were then directed at development of a method that began with a starting material containing the trifluoromethyl group and used cyclization to form the pyridine ring. The trifluorobutenone **9** was identified as having the correct oxidation state for elaboration to **7** and was commercially available with reasonable physical properties for use in production. The challenge was in directing a carbon nucleophile to a condensation with the carbonyl group to obtain a 4-(trifluoromethyl)pyridine as opposed to Michael addition to the olefin leading to 2-(trifluoromethyl)pyridines. Some precedent did exist in the literature for using **9** to access 4-(trifluoromethyl)pyridines,[10] including a route to 2-chloro-4-(trifluoromethyl)pyridine using a Reformatsky-type reaction of **9** with chloroacetonitrile in the presence of zinc and TMS-Cl[11], but it was perceived by us that it would be difficult to develop this reaction into a scaleable process.

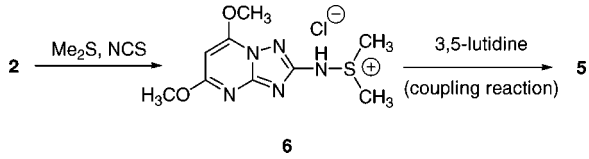
The desired selectivity was achieved by the use of trialkyl phosphonate anions in the Horner−Wadsworth−Emmons reaction with **9**.[12] The method can work with a variety of alkyl phosphonate esters and solvents, but the use of the trimethyl ester **10** with sodium methoxide and methanol in the presence of a catalytic amount of triethylamine afforded the best yield

(7) Taylor, E. C.; Tseng, C.-P.; Rampal, J. B. *J. Org. Chem.* **1982**, *47*, 552.
(8) Gilchrist, T. L.; Moody, C. J. *Chem. Rev.* **1977**, *77*, 409.
(9) (a) Bee, M. A.; Rose, F. *J. Chem. Soc. C.* **1966**, 2031. (b) Vercek, B.; Ogoreve, B.; Stanovnik, B.; Tisler, M. *Monatsh. Chem.* **1983**, *114*, 789. (c) 2-Amino-5,7-dimethoxy[1,2,4]triazolo[1,5-*a*]pyrimidine starting with 2-chloro-4,6-dimethoxypyrimidine. Anon. U.S.A. *IP.com J.* **2004**, *4*(6), 11. Publisher: IP.com, Inc., CODEN: IJPOBX; ISSN: 1533-0001. Patent written in English: *Chem. Abs.* **2005**, *143*, 115495.
(10) (a) Tetsuo, K.; Koyanagi, T.; Kanamor, F.; Kanbayashi, S.; Tanimura, T.; Horiuchi, N. Eur. Pat. Appl. 1996-107614, 1996. (b) Pazenok, S. PCT Intl. Appl. WO 2003/099791, 2003. (c) Volle, J.; Schlosser, M. *Eur. J. Org. Chem.* **2002**, 1490.
(11) Jiang, B.; Xiong, W.; Zhang, X.; Zhang, F. *Org. Process Res. Dev.* **2001**, *5*, 531.
(12) (a) Gebhardt, J.; Gotz, N.; Jaedicke, H.; Mayer, G.; Rack, M. PCT Int. Appl. WO 2005/063780, 2005. (b) Hamilton, C. T.; Gullo, M. F.; Gonzalez, M. A.; Roth, G. A.; Gorman, D. B. U.S. Pat. Appl. U.S. 2005288511, 2005.

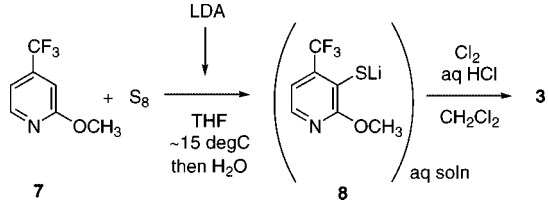
Scheme 3. **Pyroxsulam coupling reaction via proposed sulfilimine catalytic cycle**



Scheme 4. **Preparation of Azasulfonium Salt 6 and Conversion to Sulfilimine 5**



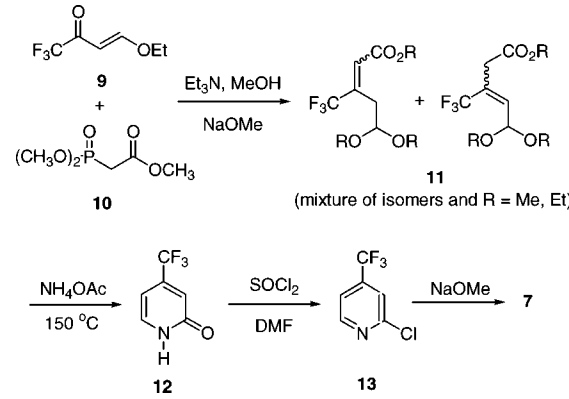
Scheme 5. **thiolation and chloroxidation of 2-methoxy-4-(trifluoromethyl)pyridine**



as well as the lowest raw material costs. The condensation gives a mixture of adducts, generally represented by structures **11**, which are isolated in ~85% yield as an oil after water quench, extraction, and solvent evaporation. The mixture **11** is cyclized by treatment with an ammonia source to provide the pyridinone **12**. Specifically, the use of ammonium acetate in formamide at ~150 °C provides **12** in ~80% yield after isolation of the product solid by filtration. The pyridinone **12** can be converted to the desired pyridine **7** via established methods. The overall route is shown in Scheme 6.

For the chlorination of **12**, applying the standard technology of heating the pyridinone in excess thionyl chloride with catalytic DMF resulted in a reaction that went through a thick slurry stage, was prone to stalling, had high levels of impurities and side-products such as the 5-chloro isomer of **13**, and formation of significant amounts of dimethylcarbamoyl chloride, a known carcinogen. Revising the process to use stoichiometric amounts of DMF and $SOCl_2$ (~1.1 equiv of each relative to **12**) alleviated all of these problems, as well as eliminated the

Scheme 6. **Horner–Wadsworth–Emmons route to 2-methoxy-4-(trifluoromethyl)pyridine (7)**



need to do a $SOCl_2$ quench or recycle. The methoxylation reaction of **13** was straightforward, providing the desired pyridine **7** in good purity. The yield of both of these reactions was high in the laboratory (>90%), and both reactions were successfully demonstrated at the production scale.

Conclusion

A process for the manufacture of the herbicide pyroxsulam was developed and implemented. It comprises seven steps with only one solid intermediate isolation. The process was successfully demonstrated at production scales in 2006–2007 to obtain the first manufacturing supply of pyroxsulam herbicide active ingredient for use in its commercial launch.

Acknowledgment

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