Achieving Positional Selectivity in Pyridine Synthesis

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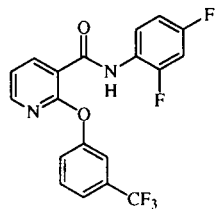
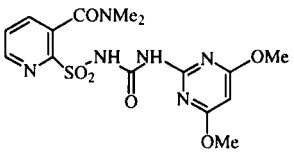
J. Heterocyclic Chem., **37**, 451 (2000).

The chemistry of pyridine and its derivatives has been studied widely because of its importance in the synthesis of agricultural chemicals, pharmaceuticals and performance products [1]. Bioactive pyridines frequently contain a 2,3- or 2,5-substitution pattern. For example, diflufenican (**1**) and nicosulfuron (**2**) (derived from 2-chloronicotinic acid) are herbicides and imidacloprid (3) (derived from 2-chloro-5-methylpyridine) is an insecticide. Usually these patterns are obtained by carrying out ring substitution reactions on a 3-substituted pyridine. Such reactions usually give a mixture of the 2,3- and 2,5-isomers. Therefore, much recent work, especially in industry, has focused on improving the regiospecificity of some well known reactions. However, separation of even a small amount of the unwanted isomer from the desired one can be very expensive on an industrial scale. The choice of synthetic approach is usually between a linear sequence of reactions originating from 3-methylpyridine, or a regiospecific convergent synthesis. This lecture articulates the basis for this choice by examining synthetic routes to two important intermediates: 2-chloro-5-methylpyridine and 2-chloronicotinic acid.

2,3-Disubstituted

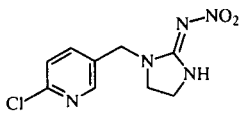


Diflufenican (**1**)



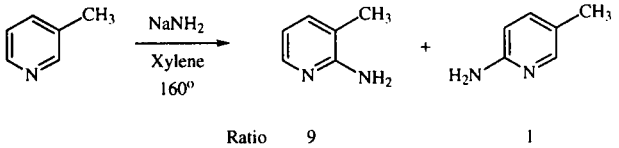
Nicosulfuron (**2**)

2,5-Disubstituted



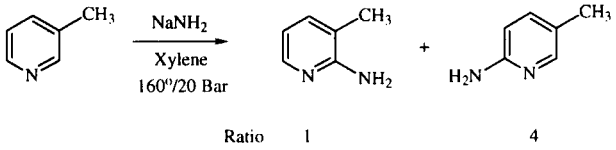
Imidacloprid (**3**)

Imidacloprid, for example, may be made from 2-chloro-5-chloromethylpyridine, which is derived from 2-chloro-5-methylpyridine. A potential high yield route to 2-chloro-5-methylpyridine may be achieved by chlorination of 2-amino-5-methylpyridine. Unfortunately, the amination of 3-methylpyridine favors 2-amino-3-methylpyridine over the other isomer by a factor of 9:1. We studied the effect of excess ammonia pressure on this reaction and found that at 20 bar the selectivity swings over to fourfold in favor of the 2,5-isomer [2]. We have not explained this remarkable change in orientation yet (Equation 1 and 2).



Ratio 9 1

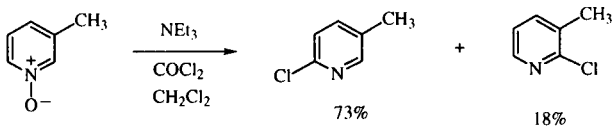
Equation 1.



Ratio 1 4

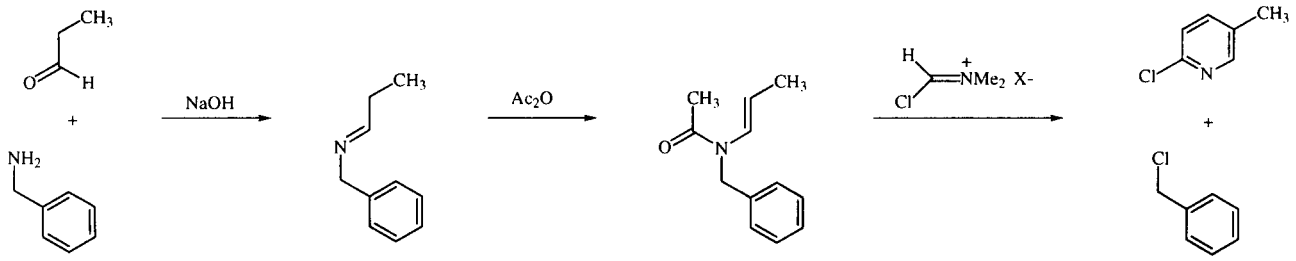
Equation 2.

Another high yield synthesis of 2-chloro-5-methylpyridine from 3-methylpyridine-1-oxide has been reported (Equation 3) [3]. A convergent high yield synthesis of 2-chloro-5-methylpyridine has been described (Equation 4) [4]. The ring closure step was achieved with a Vilsmeier reagent, by use of Meth-Cohn's procedure [5], to give a benzyl quaternary salt. This salt was debenzylated rapidly to afford the desired product and benzyl chloride.



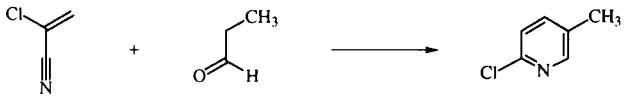
73% 18%

Equation 3.



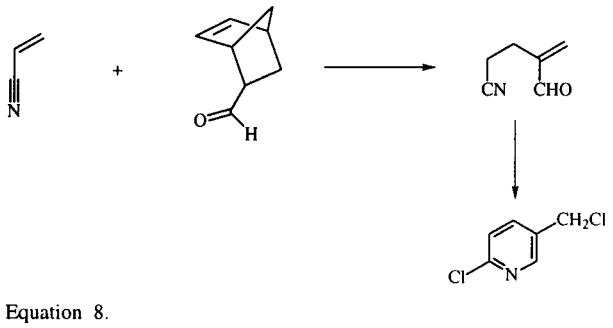
Equation 4.

Some earlier work by ICI [6] (Equation 5) led us to conceive that a Pinner reaction of acetonitrile with propionaldehyde should give us an imidoyl halide directly, obviating the use of benzylamine (Equation 6). We subsequently extended this idea to the direct formylation and ring closure of a pentene nitrile (Equation 7) [7]. Competitive formylation at the double bond gave us **4** as a by-product, but this was easily deformylated.



Equation 5.

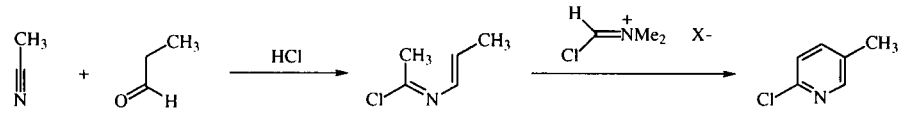
Further work to prepare directly 2-chloro-5-chloromethylpyridine by a ring synthetic approach makes use of a cyclopentadiene acrolein adduct, acrylonitrile and chlorine. The cyclopentadiene acrolein Diels-Alder adduct not only provides the double bond at a later step (by retro-Diels-Alder reaction) for chlorination (useful for providing the right unsaturation to form the pyridine derivative), but also controls the Michael addition of acrolein to acrylonitrile (Equation 8) [8].



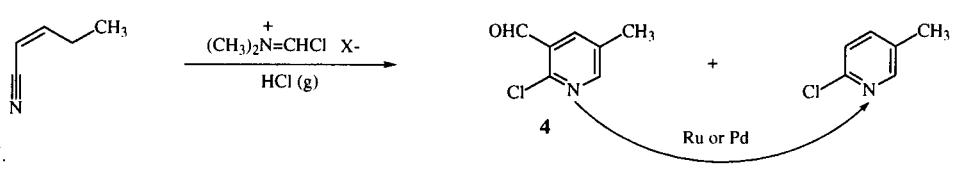
Equation 8.

The choice of elaboration of a 3-substituted pyridine versus convergent ring synthesis was examined for the synthesis of 2-chloronicotinic acid, a key intermediate for the production of the herbicides diflufenican (**1**) and nicosulfuron (**2**).

2-Chloronicotinic acid may be obtained by chlorination of nicotinic acid *N*-oxide (Equation 9) [9]. However a mixture of 2,3- and 2,5-isomers is formed. Separation of the unwanted isomer decreases the overall yield thus increasing the manufacturing cost. Therefore, we undertook a reexamination of ring synthesis approaches. The

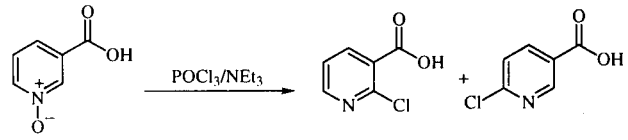


Equation 6.

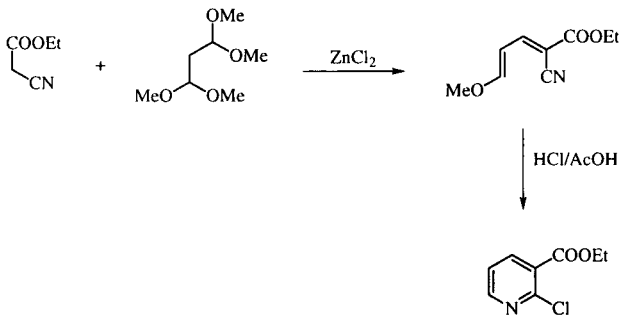


Equation 7.

synthesis of 2-chloronicotinic acid from acylic precursors has been reported in the literature. One of the approaches uses the reaction between ethyl cyanoacetate and 1,1,3,3-tetramethoxypropane in presence of the Lewis acid catalyst zinc chloride (Equation 10) [10]. The cyclization of the adduct obtained from the above step is done in acetic acid as solvent in the presence of hydrogen chloride to give specifically 2-chloronicotinic acid in good yield. The disadvantage of this process is the prohibitive cost of the tetramethoxypropane as a malondialdehyde equivalent.

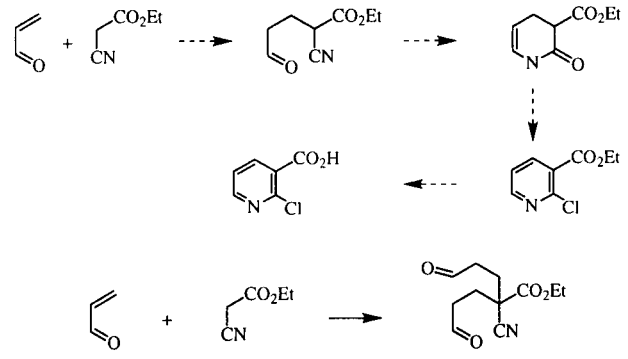


Equation 9.



Equation 10.

With cost and ease of operation in mind an alternative specific route to 2-chloronicotinic acid has been developed. The plan was to use ethyl cyanoacetate and acrolein as the raw materials (Equation 11). Instead of the desired outcome, the product of a double Michael addition **5** was obtained.

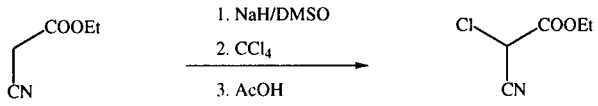


Equation 11.

5

Therefore, it was necessary to replace one hydrogen in the ethyl cyanoacetate with a leaving group, a chlorine atom was chosen. The presence of this chlorine atom prevents the second Michael addition with acrolein. It is also essential for hydrogen chloride elimination to give the right unsaturation to allow the formation of the aromatic pyridine ring. The hydrogen chloride gas generated further helps in the cyclization step by activating the cyano group.

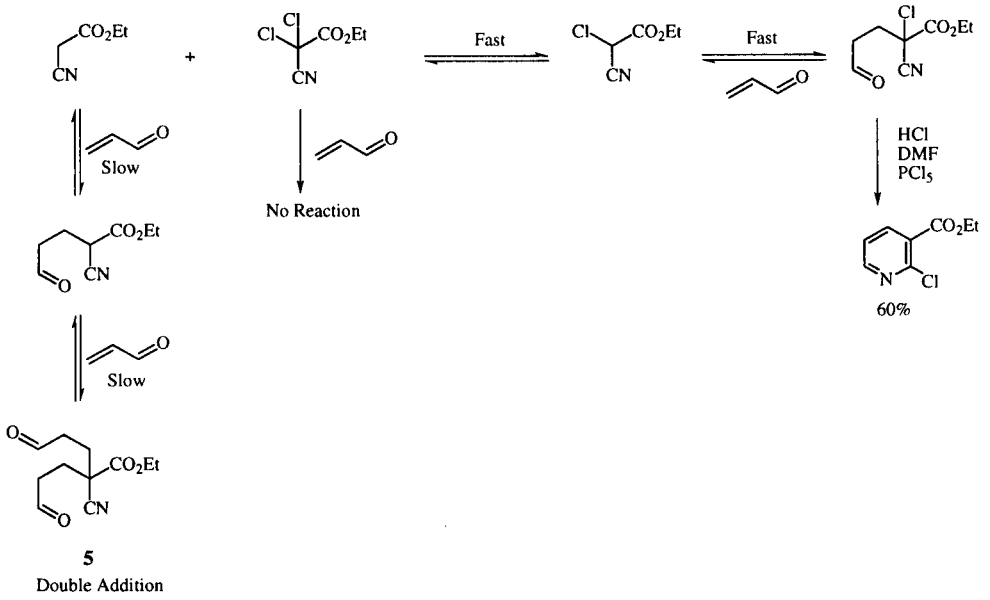
Preparation of the ethyl 2-chlorocyanoacetate is cumbersome (Equation 12). We found that ethyl 2-chlorocyanoacetate could be made easily by mixing an equimolar mixture of ethyl cyanoacetate and ethyl 2,2-dichlorocyanoacetate with a base. This base catalyzed halogen transfer occurs very rapidly to give an equilibrium concentration of ethyl 2-chlorocyanoacetate, which undergoes fast Michael addition with acrolein, therefore avoiding diversion to **5** (Equation 13). The cyclization of the Michael addition product obtained from the reaction between ethyl 2-chlorocyanoacetate and acrolein, is achieved by heating in dimethylformamide containing phosphorus trichloride in the presence of hydrogen chloride gas (Equation 13).



83%

Equation 12.

Selection of the best route for the synthesis of a 2,3- or 2,5-disubstituted pyridine regiospecifically is complex and depends upon a number of factors, such as raw material cost, chemical yields, ease of product separation and environmental concerns. When a target product is required in high purity (with less than 0.1% of an isomeric impurity) and it is three or more steps away from a cheaply available pyridine precursor (*e.g.*, 3-methylpyridine) it may well be made more cheaply by a convergent ring synthesis.



Equation 13.

REFERENCES AND NOTES

[1] E. F. V. Scriven, J. E. Toomey, Jr. and R. Murugan, in Kirk-Othmer Encyclopedia of Chemical Technology, Fourth Ed. Vol **20**, John Wiley & Sons, New York, NY, 1996, pp 641-679.

[2] C. K. McGill and A. Rappa, in Advances in Heterocyclic Chemistry, Vol **44**, A. R. Katritzky, ed, Academic Press, San Diego, 1988, pp 1-79.

[3] K. Jelich, D. Kaufmann, B. Gallenkamp and R. Lantzsch, German Offen. DE 4,020,053 (1991); *Chem. Abstr.*, **115**, 183122b (1991).

[4] R. Lantzsch, European Patent Appl., EP 546 418 (1993); *Chem. Abstr.*, **119**, 160133z (1993).

[5] O. Meth-Cohn and K. T. Westwood, *J. Chem. Soc. Perkin Trans. 1*, 1173 (1984).

[6] L. A. Hartmann and J. F. Stephen, European Patent Appl. EP 162,464 (1985); *Chem. Abstr.*, **104**, 186315a (1986).

[7] R. Murugan, E. F. V. Scriven and T. Y. Zhang, PCT Int. Appl. No 95 15, 313 (1995); *Chem. Abstr.*, **123**, 143654K (1995).

[8] T. Y. Zhang and E. F. V. Scriven, PCT Int. Appl. No 93 18,005 (1993); *Chem. Abstr.*, **120**, 106784v (1994); T. Y. Zhang, J. R. Stout, J. G. Keay, E. F. V. Scriven, J. E. Toomey and G. L. Goe, *Tetrahedron*, **51**, 13177 (1995).

[9] A. Said and W. Brig, German Offen. 2,713,316 (1977); *Chem. Abstr.*, **88**, 22654k (1978).

[10] G. C. S. Chiang, F. E. Granchelli and C. Wright, European Patent Appl. EP 323,881 (1989); *Chem Abstr.*, **112**, 35689q (1990).