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Electrophilic fluorination: the aminopyridine dilemma

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ABSTRACT

An unusually high yielding fluorination of aminopyralid (**3**) using F-TEDA (SELECTFLUOR™) in warm water, followed by kinetic resolution (via iterative esterification/saponification) of the crude fluorination product with dry HCl in methanol produced pure ring-fluorinated pyridine **2** in an overall yield of 31% for the two steps.

1. Introduction

The recent discovery of the commercially active ingredient aminopyralid (**3**),[1] a potent broad spectrum auxinic picolinate herbicide, prompted us to revisit the structure–activity relationships of this historical class of pyridine herbicides.[2] Through an activity optimization effort, we discovered that replacement of the 6-Cl on the pyridine ring of **2** with aryl groups produced **1** which showed unexpectedly high levels of herbicidal activity under a controlled environment (glasshouse testing).[3] To validate this discovery, we decided to test a representative of **1** in the field, which mandated the synthesis of kilogram quantities of the material. The electrolysis (**4**→**3**) and the arylation (**2**→**1**) reactions were known to proceed in high yield.[3,4] However, initial attempts at the electrophilic fluorination step (**3**→**2**) were extremely poor. Thus, in order for us to prepare a kilogram field sample of **1** utilizing our commodity starting material **4**, we required a dependable, scaleable electrophilic fluorination method to convert **3**→**2** (see Scheme 1).

Fluorination of electron-rich aromatic ring systems generally can be accomplished by reaction with electrophilic fluorinating agents.[5] However, electron-rich pyridines tend to favor ring N-fluorination. While such pyridine N-fluorination has been used to advantage, for instance, to rearrange to 2-C–F pyridines[6] or to facilitate nucleophilic substitution at the 2- and/or 4-position on the pyridine ring,[7] for that same reason, it proves detrimental for electrophilic ring fluorination.[8] In fact, a survey of some of the widely used electrophilic fluorinating agents for neutral aromatics, such as $CsOSO_2OF$,[9] CF_3SO_3F,[10] NOF,[11] NO_3F,[12] CF_3OF,[13] and AcOF,[14] revealed that these materials are better N-fluorinating reagents than C-fluorinating agents when it comes to pyridines. Elemental fluorine (F_2) and xenon difluoride (XeF_2), the most potent reagents in this class, are known to react with little selectivity as both an N- and a C-fluorinating agent depending on the reaction conditions and the electronics of the pyridines.[15] In addition, toxicity and special handling requirements associated with F_2 make alternative fluorinating reagents preferable whenever possible. Use of the other common route to C-fluorinated pyridines via fluorination of metalated aromatic rings with reagents such as N–F pyridinium salts,[16] NFSi reagents,[5] N–F sultams,[17] N–F sulfonamides[18], and N–F sulfonimides,[19] is precluded by the acidic NH_2 protons present in substrate **3**. Thus, F-TEDA[20] was identified as our reagent of choice for effecting the transformation of **3**→**2** as it had been reported as one of the most powerful electrophilic fluorinating agents for neutral electron-rich aromatic systems (just behind $(CF_3SO_2)_2NF$ and F_2 itself),[21] while still being safe and easy to handle.[22]

We initiated our studies of F-TEDA using acetonitrile as it appeared in the literature to be a preferred solvent.[23] Under standard reaction conditions we observed the following problems: (1) *Production of undesirable picloram* (**4**). Competing chlorination during F-TEDA reaction had indeed been previously reported though it is unclear what the chlorinating species is or how it is generated.[24,25] (2) *Low mass recovery*. The strong oxidizing power of F-TEDA, as measured by its one-electron reduction potential,[26] could easily account for the destruction of UV-active (presumed) pyridyl products. (3) *Poor conversion*. While the heterogeneity of the reaction could be suspected, competing N-fluorination of the pyridine ring by F-TEDA along with unproductive complexation of F-TEDA with F-TEDA's desfluoro byproduct[27] more adequately explain our incomplete fluorination and recovery of starting material.

In our case, competitive N-fluorination of both the product **2** and the starting material **3** would consume F-TEDA reagent as well

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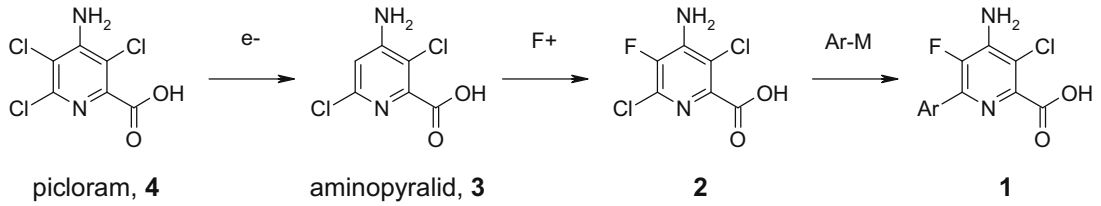


Scheme 1. Schematic synthesis of field candidate **1**.

as render **3** less electron rich and incapable of ring fluorination. The putative N-fluorinated adducts, which would not survive workup and/or chromatography, would then create the appearance of incomplete reaction after reverting back to the parent pyridines (or worse, as our mass balance was only ~50%).[28]

Despite these initial issues, F-TEDA was investigated further to optimize the yield and minimize the aforementioned problems. After surveying different solvents,[29] catalysts, co-reagents, and reaction temperatures, we attempted an aqueous reaction to improve the solubility (cf. reaction heterogeneity mentioned in note 3 above) of F-TEDA even though it is reported to be sensitive to hydroxylic solvents.[30] To our delight, the reaction proceeded smoothly with much shorter reaction time and was eventually optimized in *deionized water* at 65 °C, with respect to both yield and product purity.

Unfortunately, even with excess F-TEDA and extended reaction times, the fluorination reactions never exceeded 50% yield of **2** (as monitored by HPLC), with most of the mass balance attributed to 'unreacted' **3**. Attempts to drive the reaction further only led to higher levels of picloram (**4**)[31] at the expense of recoverable desired **2** and/or starting material **3**. Therefore, the reactions were stopped when analysis by HPLC typically indicated a composition of 40% **2**, 55% **3**, and <4% **4**. Workup with 6 N HCl followed by cooling precipitated the pyridine mixture.

Attempts to separate **2** from **3** and **4** via reversed-phase chromatography or recrystallization were not successful. Furthermore, we also demonstrated that it was difficult to remove the 5-H and 5-Cl by-products via chromatography at subsequent stages. Thus, a reliable large-scale method to purify **2** at this point was critical. One approach was to convert the mixture of acids to their methyl esters, then attempt separation using normal-phase chromatography. During this process, we observed that **2** esterified much more rapidly than either **3** or **4** in dry HCl in methanol. The enhanced reactivity of **2** is possibly due to fluorine's ability to be a pi-donor[32] when a full positive charge can be stabilized through hyperconjugation, and the rates of acid-catalyzed esterification of benzoic acids have also been shown to increase as electron density increases toward the carboxyl group.[33]

To take advantage of this fortuitous discovery, an iterative kinetic purification process was executed. Upon completion of the esterification of crude **2** (CH_3OH, HCl, 40 °C), the reaction mixture was neutralized by addition of aqueous $NaHCO_3$. This coincidentally precipitated the ester products (enriched in ester **5**), enabling separation from the unreacted picolinic acids (mostly **3** and **4,** as their sodium salts) via suction filtration. Subsequent saponification of the ester product mixture back to the corresponding acids, fortified in **2**, and then repeating the esterification/saponification sequence one more time afforded **2** in >90% purity, by HPLC. The development of this procedure to purify **2** was critical for the preparation of the kilogram field sample of **1** (see Scheme 2).

The overall route thus became fluorination of **3** with F-TEDA in warm water, followed by iterative esterification/saponification of the crude with dry HCl in methanol, to yield **2** in an overall yield of 31% for the two steps: an especially efficient outcome for a pyridine.

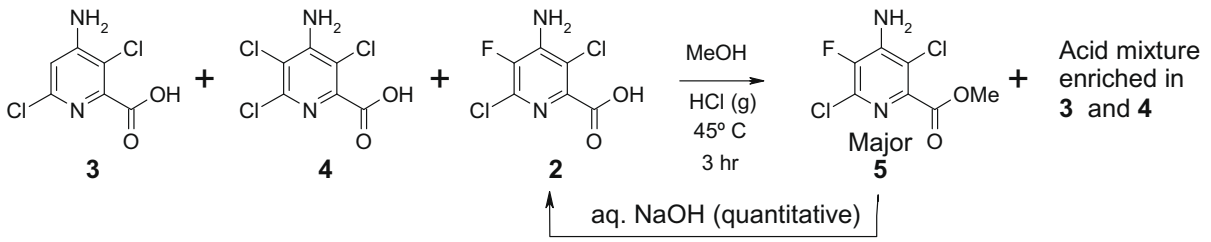
2. Experimental

2.1. General

All solvents and reagents were of reagent grade or higher. All reactants were purchased from Aldrich unless otherwise noted. HPLC data were collected on a Beckman System Gold version 1.6 (solvent delivery Module 126, diode array detector Module 168, Varian's Microsorb C_{18} column), eluting via gradient (0–100% CH_3CN). Purity was established via ^1H NMR or HPLC. 300 MHz ^1H NMR and 75 MHz ^{13}C NMR data were collected in $CDCl_3$ with TMS as internal standard.

2.2. 4-Amino-3,6-dichloro-5-fluoropyridine-2-carboxylic acid (2)

A 1 l three neck round-bottomed flask equipped with a mechanical stirrer and a reflux condenser was charged with **3** (22.1 g, 108.3 mmol) and H_2O (110 mL). While stirring at 25 °C, solid F-TEDA (Air Products; 42.0 g, 118.6 mmol) was added in portions. The resulting heterogeneous mixture was warmed to 65 °C and progress was monitored periodically via HPLC. After 6 h, the reaction was allowed to cool and made acidic with 6 N HCl. Stirring was continued for 10 min and then the precipitate was collected with suction filtration and rinsed several times with additional 6 N HCl. It was allowed to air dry overnight. Analysis of this crude product via HPLC showed ~ 40% **2**, 55% **3**, and 4.5% **4**. The filtrate was extracted several times with 10% THF/CH_2Cl_2 and a small



Scheme 2. Iterative esterification/saponification purification sequence.

amount of crude product (~1.2 g) was recovered. Scaling this reaction up to 250 g provided 196 g of crude **2**, used in the next step without further purification.

2.3. Purification of 2 via esterification/saponification

Crude **2** (196 g; 55% **2**, 40% **3**, and 4% **4**) was dissolved in methanol (700 mL) saturated with anhydrous HCl. The solution was heated to 40–45 °C for 3 h, then cooled to 25 °C, and poured into an equivolume of saturated aqueous $NaHCO_3$ solution. The precipitate was collected by vacuum filtration, washed with water (300 mL), and air dried giving 120 g of **5** in 85% purity by HPLC. The solid product was dissolved in methanol (500 mL), the pH brought to >12 with 2 N NaOH (320 mL, 1.2 equiv), and then stirred at 25 °C for 2 h. The methanol was evaporated in vacuo, and the residual aqueous solution acidified with 6 N HCl to pH <1. The resulting precipitate was collected by vacuum filtration, washed with water (300 mL), and air dried on the filter to give 110 g of **2** in 85% purity by HPLC. The sample of **2** was subjected to the esterification/saponification sequence as described above to provide 98 g **2** in 91.5% purity. The overall yield from **3** was 31%. Analytical sample: ^{1}H NMR (DMSO-d_6) **3**: 13.83 (br s, 1H); 7.22 (s, 2H); ^{19}F NMR: −137.36 ppm. Anal. Calcd. for $C_6H_3N_2O_2Cl_2F$ (224): C, 32.04; H, 1.34; N, 12.50. Found: C, 31.91; H, 1.32; N, 12.33.

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