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Regioselective Synthesis of 2-Chloro-3-Pyridinecarboxylates[a]

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Abstract: 2-Chlorocyanoacetate was found to undergo base-catalyzed Michael addition to α,β-unsaturated ketones or aldehydes to afford 5-oxopentenenitrile derivatives. In the presence of anhydrous HCl, these compounds cyclize to yield 2-chloro-3-pyridinecarboxylates. The process is highly regiospecific and useful in the synthesis of 2,3-disubstituted pyridines.

The importance of 2-chloronicotinic acid (1) and derivatives as agricultural and pharmaceutical intermediates has been well established. Owing to the activity of its 2-position toward nucleophilic substitution and the maneuverability of the carboxylic group, a wide variety of 2,3-disubstituted pyridines can be synthesized from this versatile compound. Amongst them are the herbicides nicosulfuron (2)[1] and diflufenican (3)[2], the fungicide BC 60723 (4)[3], and the anti-inflammatory drug niflumic acid (5)[4]. Also worth noting is the potent HIV-reverse transcriptase inhibitor 6 which has been synthesized from two such 2,3-disubstituted-pyridine building blocks.[5]
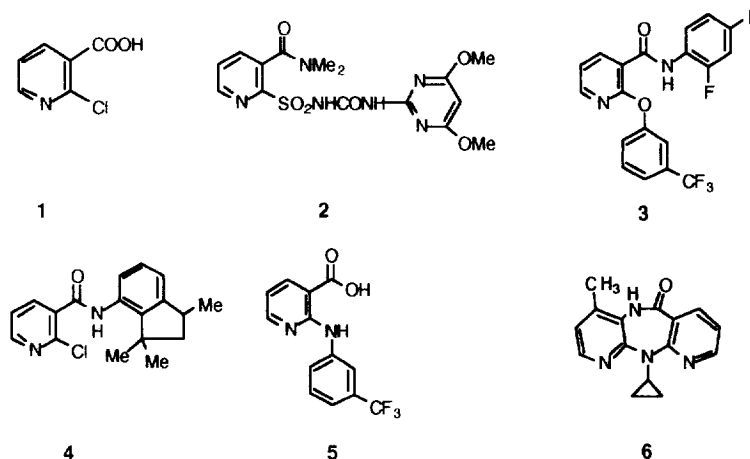

Figure 1

Synthesis of this valuable chemical intermediate (1) has received considerable research effort both in and

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a: Dedicated to Professor H. Suschitzky on the occasion of his 80th birthday.
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out of these laboratories. Most of the existing methods for the preparation of **1** have focused on the use of pyridine feed stocks. They include chlorination of the N-oxide of nicotinic acid derivatives by phosphorus oxychloride (POCl₃)[6], chlorination of 3-cyanopyridine[7], hydrolysis of 2-chloro-3-trichloromethylpyridine[8], and oxidation of 2-chloropicoline.[9] In practice, concomitant formation of regioisomers (mainly 6-chloro isomer), high cost of starting materials, and operational difficulties have limited the successful use of these routes in commercial production.

Preparation of **1** and its derivatives from acyclic precursors through ring synthesis approaches has also been investigated.[1,10] This type of synthesis offers the advantage of excellent regioselectivity and, thus, high product purity. However, the use of a key intermediate, tetramethoxypropane (**8**), rendered this process not cost effective from a point of atom economy as more than 75% of the molecular weight of **8** was not incorporated in **1** (Scheme 1).
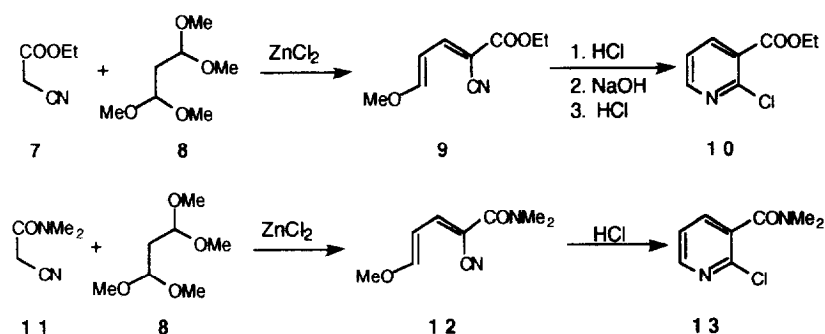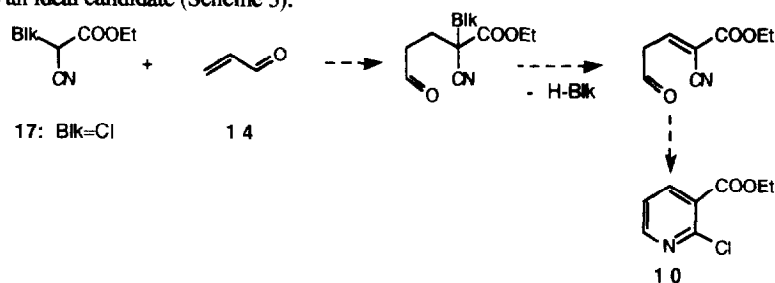

Scheme 1

At the outset of our study we explored briefly the use of readily available ethyl cyanoacetate (**7**) and acrolein (**14**) as key building blocks for **1** (Scheme 2). However, attempts to effect a Michael addition selectively between the two components have been impeded either by inactivity under mild conditions or side reactions, mainly double Michael additions to give **16** and polymerization under more forceful conditions, indicating greater acidity of 2-H in **15** than that of **7**.
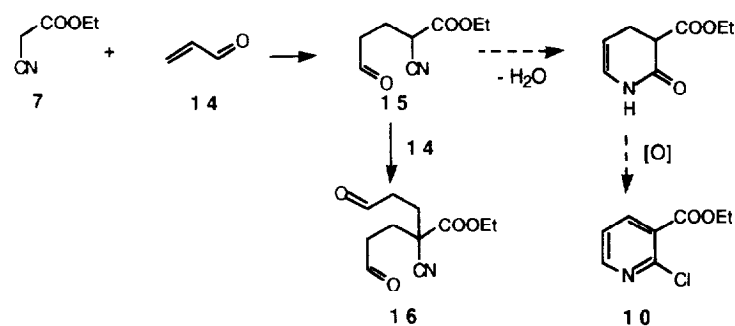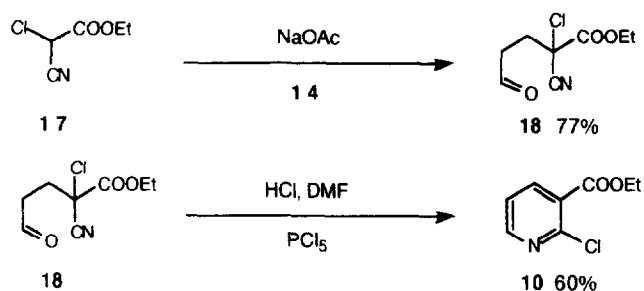

Scheme 2

It was soon recognized that in order to utilize acrolein as an efficient three-carbon building block, introduction of a blocking group on the 2-position of **7** was necessary. This blocking group must be removable in the later stage of the reaction sequence, and preferably an electronegative leaving group which would play the triple role by inhibiting double Michael addition, by increasing the acidity of 2-C-H, thus facilitating the

conjugate addition, and by providing the proper oxidation state for the final cycloaromatization. Compound 17[11] appeared to be an ideal candidate (Scheme 3).
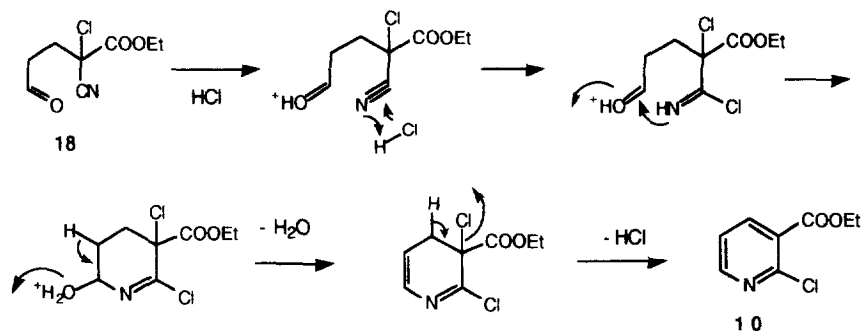

Scheme 3

Just as expected, 17 was found to undergo Michael addition to acrolein to give compound 18 in good yield under potassium carbonate (K_2CO_3) or sodium acetate (NaOAc) catalysis (Scheme 4). When 18 was treated with a solution of PCl_5 in dimethylformamide (DMF) saturated with anhydrous hydrogen chloride (HCl), 10 was isolated in 60% yield (unoptimized) as the sole product after a simple distillation[12]. The mechanism of this cyclization is believed to involve an intramolecular Ritter-type cyclocondensation of the nitrile-derived imidoyl chloride with the aldehyde followed by dehydrochlorination-aromatization, with phosphorus pentachloride (PCl_5) acting as a dehydrating agent (Scheme 5).
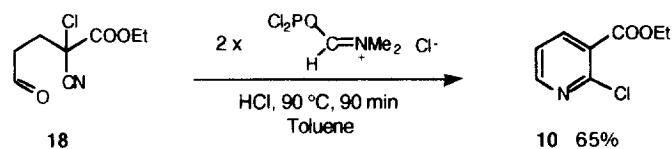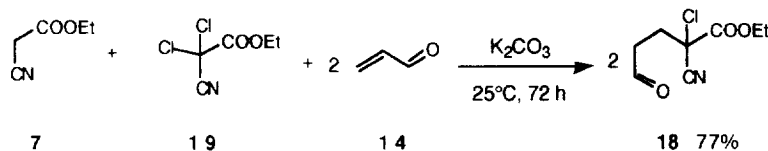

Scheme 4

Scheme 5

As an improvement, the hygroscopic solid PCl_5 could be replaced with liquid phosphorus trichloride (PCl_3) which is much cheaper and easier to handle. The reaction proceeded well using two equivalents of DMF/PCl_3 in a solution of toluene. The necessity of DMF is indicative of its possible role as an HCl carrier in the form of a Vilsmeier reagent to promote the cyclodehydration (Scheme 6).
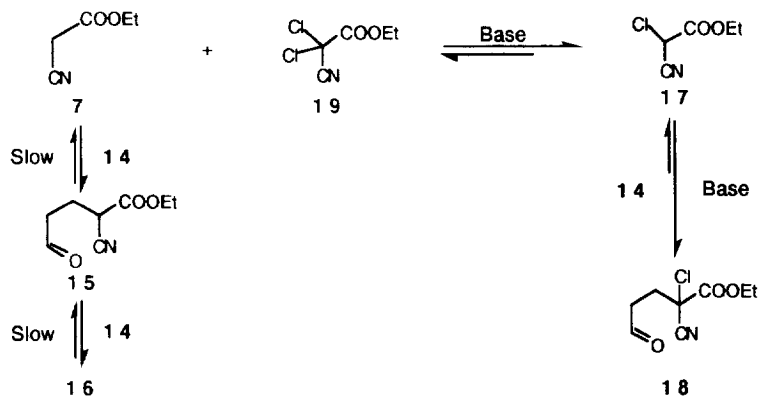

Scheme 6

An *in situ* generation of 17[13] from 7 and 19 was later developed which allows an efficient one-step synthesis of 18 (Scheme 7).

Scheme 7

The overall transformation is illustrated (Scheme 8). Since the rate of Michael addition of 17 to 14 is considerably faster than that of 7, the equilibrium among 17, 14, and 18 drives the conversion of 7 and 19 to 17 into completion, as 17 is being consumed by Michael addition to give 18. Rapid equilibrium among 7, 19, and 17 makes this "sinking" mechanism possible.

Scheme 8

Compound 19[14] was best prepared by chlorinating 7 with two equivalents of Cl_2. The HCl generated could potentially be used in the cyclization step (Scheme 9).
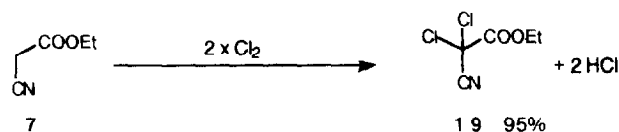
Scheme 9

The scope of this reaction was briefly investigated. Use of methyl vinyl ketone in lieu of acrolein afforded 6-methyl-2-chloronicotinate (20) in 36% overall yield (unoptimized) from ethyl cyanoacetate (Scheme 10).
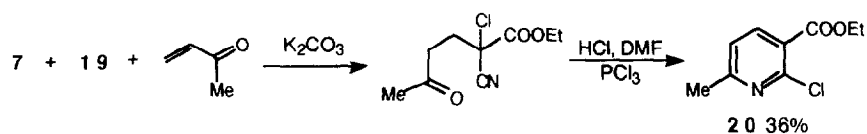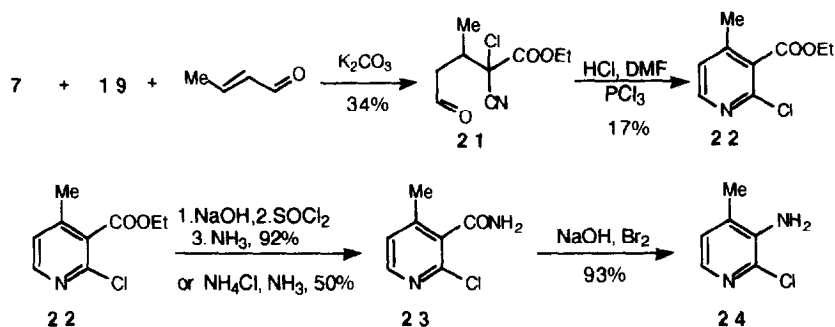

Scheme 10

Without optimization, the Michael addition with crotonaldehyde proved very slow (34%) and subsequent cyclization appears low yielding. Nonetheless, the resulting compound 22 was successfully transformed into 2-chloro-4-methyl-3-aminopyridine (24, Scheme 11), a key intermediate in the synthesis of the Nevirapine (6).

Scheme 11

Compound 10 was also converted to 3-amino-2-chloropyridine (26) in high yield by the same protocol (Scheme 12).
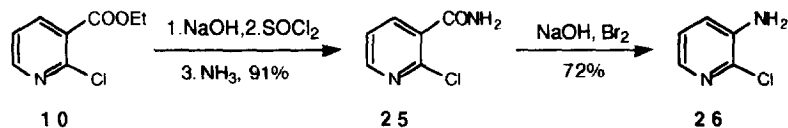
Scheme 12

In summary, a general cyclization approach to 2-chloronicotinic acid and derivatives has been developed. A few features of this process are noteworthy. First, it is highly regioselective, as the regiochemistry of the product is controlled by the starting material structure. Secondly, it has very good atom economy, every carbon

and nitrogen atom in the starting materials has been incorporated in the product. Last it uses inexpensive and readily available starting materials.

We are currently in the process of expanding the scope of this process to encompass the selective synthesis of other 2-chloro-3-substituted-pyridines.

EXPERIMENTAL

Ethyl Chlorocyanoacetate (17).

The literature procedure[11] was modified as follows. To a suspension of NaH in 400 mL of dimethylsulfoxide at 20 °C was added dropwise 79.1 g (700 mmol) of ethyl cyanoacetate. The solution was stirred for 1 h at 20 °C until no more hydrogen evolved from the reaction system. CCl_4 (156 mL, 1.5 mol) was added cautiously. Occasional cooling was applied so as to maintain the temperature between 20-25 °C. The mixture was carefully quenched with acetic acid, extracted with CH_2Cl_2 dried over $MgSO_4$, concentrated, and distilled to give 85.2 g (577 mmol) of the title compound (82.5 %, Literature 40%), bp 60-62 °C at 2 mm Hg, ^1H nmr ($CDCl_3$, 60 MHz): ppm 1.3 (t, 3H), 4.3 (q, 2H), 4.9 (s, 1H).

Ethyl 2-chloro-2-cyano-5-oxopentanoate (18).

To a suspension of finely ground K_2CO_3 (4.26 g, 30 mmol) in 100 mL of ethyl acetate were added sequentially 5.65 g of ethyl cyanoacetate (50 mmol) and 9.1 g of ethyl dichlorocyanoacetate (50 mmol) at 0 °C. Acrolein (6.72g, 120 mmol) was added within a period of 1 h using a syringe pump. The resulting reaction was allowed to stir at 25 °C for 72 h, filtered through Celite with the aid of CH_2Cl_2, concentrated (25 °C, 25 mm Hg), and distilled to give 15.6 g (77 mmol) of the title compound (77%), bp 125 °C at 1 mm Hg, ^1H nmr ($CDCL_3$, 60 MHz): ppm 1.4 (t, 3H), 2.75 (m, 4H), 4.45 (q, 2H), 9.9 (s,1H).

Ethyl 2-chloro-3-pyridinecarboxylate (10).

To a solution of DMF (3.22 g, 44 mmol) in 30 mL of toluene was added 6.05 g of PCl_3 (44 mmol). Anhydrous HCl was introduced until saturated while keeping the temperature around 60 °C. Ethyl 2-chloro-2-cyano-5-oxopentanoate (4.5 g, 20 mmol) in 10 mL of toluene was added in 30 min. The resulting mixture was stirred for 1.5 h at 90 °C, cooled to room temperature, quenched with water, extracted with toluene, dried over $MgSO_4$, and concentrated. GLC analysis using an internal standard indicated the title compound was formed in 82% yield. Distillation afforded 2.4 g (13 mmol) of the title compound (65 % yield), bp 110-115 °C at 0.2 mm Hg, ^1H nmr ($CDCl_3$, 60 MHz): ppm 1.5 (t, 3H), 4.5 (q, 2H), 7.5 (dd, 1H), 8.4 (dd, 1H), 8.7(dd, 1H), ms: m/z 185 (mol. ion), 157 (base peak), ir ν CO 1730 cm^{-1}.

Ethyl 2-chloro-6-methyl-3-pyridinecarboxylate (20).

To a mixture of 20 mL of toluene, 0.5 g (5 mmol) of potassium acetate, 0.7 ml (5 mmol) of triethylamine, and 4.25 g (40 mmol) of ethyl cyanoacetate at 5 °C was added dropwise 7.28 g (40 mmol) of ethyl 2,2-dichlorocyanoacetate. The resulting mixture was stirred at 5 °C for 30 min, and methyl vinyl ketone (4.2 g, 60 mmol) was added via a syringe pump in 1 h. After stirring at room temperature for 6 h, 6.2 mL (80 mmol) of DMF was added, followed by slow addition of PCl_3 (11 g, 80 mmol). Anhydrous HCl gas was bubbled in for 10 min, while keeping the reaction temperature around 65 °C. After being heated at 80 °C for 1 h, the reaction mixture was cooled, quenched with aqueous ammonium hydroxide, extracted with toluene, washed with 5 % $NaHCO_3$, and dried over $MgSO_4$. Distillation afforded 5.83 g (29 mmol)of the title compound. (36% yield, bp 112-115 °C at 0.2 mm Hg).

Ethyl 2-chloro-2-cyano-3-methyl-5-oxopentanoate (21).

Following the procedure for the preparation of 18, 37.6 g (332 mmol) of ethyl cyanoacetate, 60.5 g (332 mmol) of ethyl dichlorocyanoacetate, 350 mL of ethyl acetate, 1.7 g (12 mmol) of K_2CO_3, and 56 mL (47g, 680 mmol) of crotonaldehyde were allowed to react for an extended period of time. The title compound was obtained in 34%

yield after workup and distillation (b.p. 115 °C at 1.0 mm Hg). ^{1}H nmr (CDCl$_3$, 60MHz): ppm 1.4 (m), 2.5 (m), 4.4 (m), 9.35 (s), 9.45 (s), 9.8 (s).

Ethyl 2-chloro-4-methyl-3-pyridinecarboxylate (22).

The title compound was prepared in a similar fashion to that described for 10, with an exception that ethyl 2-chloro-2-cyano-3-methyl-5-oxopentanoate (38.52 g, 177 mmol) was added at 85°C instead. Distillation gave 6.12 g (31 mmol) of the title compound (b.p. 95-97 °C at 1.0 mm Hg). ^{1}H nmr (CDCl$_3$, 60MHz): ppm 1.4 (t, 3H), 2.35 (s, 3H), 4.45 (q, 2H), 7.15 (d, 1H), 8.3 (d, 1H), ms, m/z 199 (mol. ion), m/z 154 (base peak).

2-Chloro-4-methyl-3-pyridinecarboxamide (23).

Ethyl 2-chloro-4-methyl-3-pyridinecarboxylate (22), 7.48 g (38 mmol), was saponified with 3 g (75 mmol) of NaOH in 15 mL of H$_2$O and 13 mL of methanol at 75 °C. The solid obtained after acidification with 50 % H$_2$SO$_4$ was washed with cold water and dried to give 5.8 g (34 mmol) of 2-chloro-4-methyl-3-pyridinecarboxylic acid (90%, m.p.>155 °C, decomposed). ^{1}H nmr (DMSO-d$_6$, 60MHz): ppm 2.35 (s, 3H), 7.4 (d, 1H), 8.4 (d, 1H), ir ν CO 1725 cm^{-1}.To a mixture of 2-chloro-4-methyl-3-pyridinecarboxylic acid (24.7 g, 144 mmol) and 75 mL of toluene was added 75 mL of SOCl$_2$ (22.6 g, 190 mmol) at 70°C within a period of 1 h. The reaction mixture was heated at reflux for 4 h and the resulting solution was cooled to room temperature. Dry NH$_3$ gas was introduced at such a rate so as to maintain the internal temperature below 30 °C. After removing toluene, the solid residue was washed successively with cold water and methanol, and dried to yield 22.72 g (133 mmol) of the title compound (92%, m.p. 168-170°C, uncorrected). ^{1}H nmr (DMSO-d$_6$, 300MHz): ppm 2.35 (s, 3H), 7.35 (d, 1H), 8.3 (d, 1H), ms, m/z 170 (mol. ion, base peak), ir ν CO 1675 cm^{-1}.

2-Chloro-3-amino-4-methylpyridine (24).

To a solution of 2.28 g (57 mmol) NaOH in 25 mL of water was added 3.1 g (19 mmol) of Br$_2$ at 5 °C. The mixture was stirred for 10 min and 2.57 g (15 mmol) of 2-chloro-4-methyl-3-pyridinecarboxamide was added at once. After stirring at 5 °C for 15 min, the resulting clear solution was heated at 75 °C for 90 min, cooled to room temperature, extracted with CH$_2$Cl$_2$, and dried. Concentration gave 2.0 g (14 mmol) of the title compound (93%, mp 63-66 °C, uncorrected), ^{1}H nmr (CDCl$_3$, 300MHz): ppm 7.6 (d, 1H), 6.8 (d, 1H), 4.0 (2H, NH$_2$), 2.1 (s, 3H), ms, m/z 142 (mol. ion & base peak), ir ν NH 3420, 3300 cm^{-1}.

2-Chloro-3-aminopyridine (26).

In a manner similar to that described for 2-chloro-3-amino-4-methylpyridine (24), the title compound was prepared in 72% yield (m.p. 76-77.5 °C, uncorrected) from 10 g (64 mmol) of 2-chloro-3-pyridinecarboxamide (25), 9.8 g (250 mmol) of NaOH, and 12.5 g (78 mmol) of Br$_2$. ^{1}H nmr (CDCl$_3$, 60 MHz): ppm 7.0-7.2 (br, 2H), 7.7-7.9 (br, 1H), ms, m/z 128 (mol. ion & base peak), ir ν NH 3460, 3300 cm^{-1}.

ACKNOWLEDGEMENT

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