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Efficient and Scalable Synthesis of Ethyl 2,6-Dichloro-5-Fluoronicotinoyl Acetate Using the Blaise Reaction as a Key Step[1]

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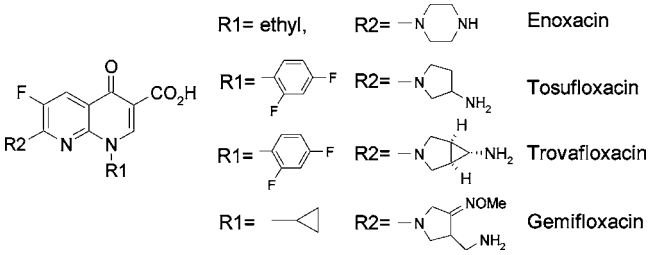
Abstract:

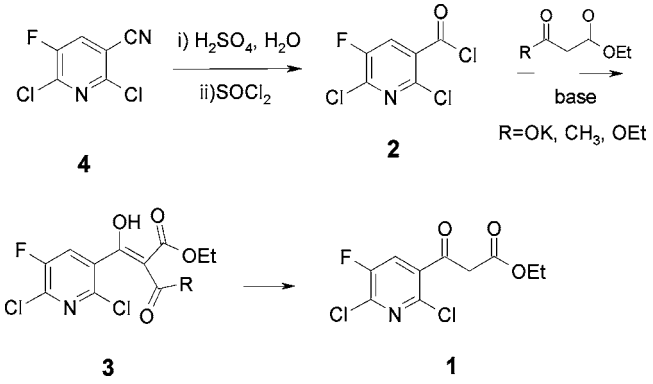
An efficient synthesis of 2,6-dichloro-5-fluoronicotinoyl acetate (1) has been accomplished in a single step using the Blaise reaction of ethyl bromoacetate with 3-cyano-2,6-dichloro-5-fluoropyridine (4). Use of methanesulfonic acid as an in situ activator of zinc removed the induction period of the Blaise reaction to render it safe and viable for a large-scale operation.

A naphthyridine ring is embedded as a key structural unit of many potent quinolone antibiotics such as enoxacin,[2] tosufloxacin,[3] trovafloxacin,[4] and gemifloxacin (Scheme 1).[5] To construct this structural segment, most of the reported syntheses employed ethyl 2,6-dichloro-5-fluoronicotinoyl acetate (**1**) as a key starting material that was prepared from a common synthetic route, the reaction of an acetate enolate equivalent with 2,6-dichloro-5-fluoronicotinoyl chloride (**2**) (Scheme 2). The reaction of magnesium enolate of diethyl malonate with the nicotinoyl chloride **2** proceeded well to give the diester intermediate **3** (R = OEt), which was partially hydrolyzed and decarboxylated to give **1**.[6] However, this process is complicated with the selective partial hydrolysis of the diester intermediate **3**: the formation of the methyl ketone impurity[7] via double decarboxylations was observed as a side product. A more advanced synthesis is the use of malonate monoester,[8] which clearly removed the problems of the selective hydrolysis of the diester intermediate. The last version employed the magnesium enolate of ethyl acetoacetate as an acetate enolate equivalent, and subsequent deacetylation of the formed intermediate **3** (R = CH_3) afforded **1**.[9]

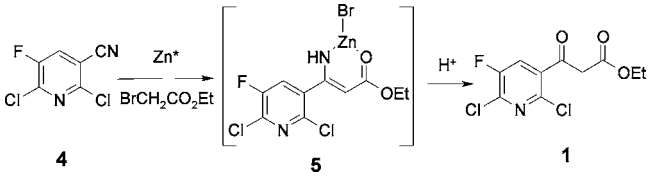
Scheme 1



Scheme 2



Scheme 3



Although the current syntheses are well established and scalable, we describe here an alternative, single-step transformation of the nitrile group of the early intermediate **4** into the β-keto ester functionality of **1**, employing the Blaise reaction (Scheme 3).[10]

As expected, slow addition of ethyl bromoacetate to a mixture of the 3-cyanopyridine **4** and activated zinc[11] in THF

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(6) The reported yield of **1** from the acid chloride **2** is 74%. See: (a) Bouzard, D.; Di Cesare, P.; Essiz, M.; Jacquet, J. P.; Ledoussal, B.; Remuzon, P.; Kessler, R. E.; Fung-Tomc, J. *J. Med. Chem.* **1992**, *35*, 518. (b) Miyamoto, T.; Matsumoto, J.-I. *Chem. Pharm. Bull.* **1990**, *38*, 3211.

(7) In an acid-catalyzed decarboxylation of **3** (R = OEt), ca. 10% (area % by HPLC) of the methyl ketone impurity was usually formed in the reaction mixture. The analysis of the isolated **1** showed ca. 2% contamination of the methyl ketone impurity. ^{1}H NMR data of the methyl ketone impurity: (300 MHz) δ 7.57 (d, 1H, J = 7.3 Hz), 2.71 (s, 3H).

(8) The reported yield of **1** from the acid chloride **2** is 96%. See: (a) Refer to ref 2. (b) O'Neill, B. T.; Busch, F. R.; Lehner, R. S. EP 449445, 1991. (c) Clay, R. J.; Collom, T. A.; Karrick, G. L.; Wemple, J. *Synthesis* **1993**, 290.

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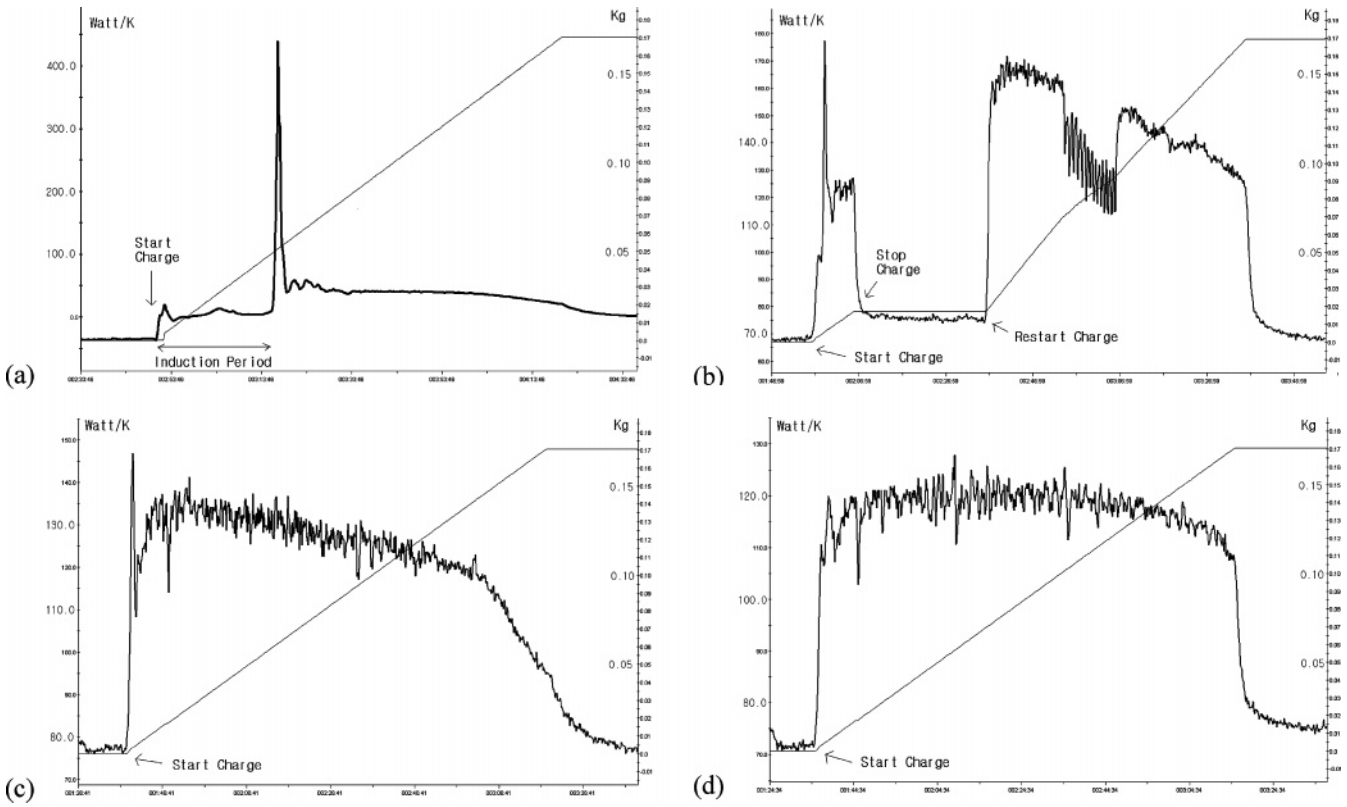

Figure 1. **Influence of the amount of MsOH and the particle size of zinc on the induction period of the Blaise reaction where ethyl bromoacetate was added slowly to a mixture of MsOH-activated zinc and 4. (a) Aldrich zinc (<10 μm) with 1 mol % MsOH. (b) Daejung zinc (150 μm) with 1 mol % MsOH. (c) Aldrich zinc (<10 μm) with 5 mol % MsOH. (d) Daejung zinc (150 μm) with 5 mol % MsOH.**

under reflux led to the formation of the β-aminoacrylate intermediate **5**, which was hydrolyzed by aqueous HCl solution to give **1**. Quick optimization of the reaction conditions disclosed that 1.5 equiv of activated zinc and 1.3 equiv of ethyl bromoacetate are sufficient for the completion of the reaction. Moreover, a very efficient isolation of the product **1** was accomplished. At the end of the Blaise reaction, the mixture was cooled to room temperature, and aqueous HCl solution was added[12] for the hydrolysis of the β-aminoacrylate group of **5**. After the completion of the hydrolysis, the mixture was cooled to 5 °C, giving a slow precipitation of the product **1**, which was filtered to provide **1** in 70−75% yield.[13] The purity of **1** was generally greater than 99% by HPLC assay. However, two problems were recognized for a large-scale application of this transformation. The first is the cumbersome preparation of activated zinc by aqueous HCl solution, and the second is the unpredictable induction period, thus making control of the reaction difficult.

In this regard, we devised a simple in situ activation of zinc by treatment with a catalytic amount of an organic acid.[14] By heating the suspension of zinc in THF in the presence of 1 mol % of methanesulfonic acid (MsOH) for ca. 10 min, consistent activation of zinc was accomplished with very reproducible outcomes. For the second problem, to the best of our knowledge, there is no report on the control or eradication of the induction period of the Reformatsky reagent-related reactions. Only one report clearly described the issues associated with the induction period in the generation of the Reformatsky reagent when 1,2-dibromoethane was used for the in situ activation of zinc.[15]

Taking advantage of the established in situ activation protocol by MsOH, we tested the influence of the amount of MsOH and the particle size of zinc on the induction period. When 1 mol % of MsOH was used for the activation of zinc (Aldrich, <10 μm), the Blaise reaction started in ca. 20 min induction period after the addition of ethyl bromoacetate to result in ejection of the reaction mixture due to uncontrollable exotherm (Figure 1a). Increase of the particle size of zinc (Daejung, Korea, 150 μm) showed a marginal effect on the reduction of the induction period. It was also observed that, after the initiation of the reaction, stopping and restarting the addition of ethyl bromoacetate did not show any sign of delayed reaction (Figure 1b). Quite interestingly, the use of 5 mol % of MsOH initiated the reaction right after the addition of ethyl bromoacetate irrespective of the source and the particle size of zinc (Figure 1c and d).[16] As far as we know, this is the first example demonstrating the removal of the induction period of the Blaise reaction, which will

(12) Evolution of hydrogen should be noticed.
(13) Isolation of **1** through extractive workup with ethyl acetate and subsequent column chromatography of the residue showed 85−90% yield.
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(16) The thermokinetic data of the Blaise reaction of **4** using 5 mol % MsOH (Figure 1d) are as follows: Cp initial [J/kg/K] = 2167, Cp final [J/kg/K] = 2640, total heat [kJ] = 271 (for 0.15 kg of **4**), molar heat [kJ/mol] = 266, adiabatic temp rise [°C] = 164.

certainly make the reaction more controllable and viable for a large-scale operation. By using the established conditions, the pilot-scale runs of the Blaise reaction of **4** (2 and 10 kg, respectively) with ethyl bromoacetate were performed successfully with complete reproducibility.

In conclusion, we describe very efficient and environmentally more benign synthesis[17] of **1** using the Blaise reaction as a key step. Moreover, the removal of the induction period of the Blaise reaction using MsOH as an in situ activator of zinc enhanced its safety aspect to a great extent.

Experimental Section

Solvents and reagents were obtained from commercial sources and used without further purification. NMR spectra were obtained on a Bruker 400 MHz and a JEOL 500 MHz spectrometer. HPLC analyses were carried out on a Hewlett-Packard 1100 system and a Waters 490E detector and 616 pump system. Mass spectra were collected using a Finnigan LCQ mass spectrometer system and a JEOL JMX-700 mass spectrometer.

Ethyl 2,6-Dichloro-5-fluoronicotinoyl Acetate (1). To a stirred suspension of zinc dust (Aldrich, $<10\ \mu$m, 5.1 kg, 78.5 mol) and 3-cyano-2,6-dichloro-5-fluoropyridine (**4**, 10.0 kg, 52.4 mol) in tetrahydrofuran (50 L) was added methanesulfonic acid (250.0 g, 2.6 mol), and the mixture was heated at reflux for 10 min. To the mixture was added dropwise ethyl bromoacetate (11.5 kg, 68.1 mol) over 2.5 h, maintaining reflux. After a further 0.5 h, the mixture was cooled to 0−5 °C, and 6 N HCl solution (25 L) and water (5 L) were added. The mixture was warmed to room temperature, and stirring was continued for 1 h. The mixture was cooled to 5 °C, and the formed solid was filtered, washed with cold ethanol−water (7:3, v/v, 30 L), and dried by nitrogen purge to afford the product **1** (10.6 kg, 72%). Spectral data of **4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4 (d, $J = 260$ Hz), 146.6, 142.9 (d, $J = 20$ Hz), 129.9 (d, $J = 20$ Hz), 112.9, 110.3. Physical and spectral data of **1**: mp 68−70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (enol form, 86%) 12.57 (s, 1H), 7.83 (d, $J = 7.6$ Hz, 1H), 5.83 (s, 1H), 4.30 (q, $J = 7.2$ Hz, 2H), 1.34 (t, $J = 7.2$ Hz, 3H); (keto form, 14%) 7.83 (d, $J = 7.6$ Hz, 1H), 4.20 (q, $J = 7.2$ Hz, 2H), 4.09 (s, 2H), 1.26 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (enol form) 172.4, 165.1, 154.0 (d, $J = 270$ Hz), 141.6, 138.7 (d, $J = 20$ Hz), 130.3, 126.9 (d, $J = 20$ Hz), 95.0, 61.2, 14.1; MS (APCl, *m*/*z*): 284 (M + 4), 282 (M + 2), 280 (M^+).

(17) The percentage of atom economy of the process is 66.1% compared to 41.1% of the diethyl malonate route of ref 6. However, the disposal of zinc waste should be accounted for further scale-up.

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