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Discovery of the Decarboxylative Blaise Reaction and Its Application to the Efficient Synthesis of Ethyl 2,6-Dichloro-5-fluoronicotinoylacetate[1]

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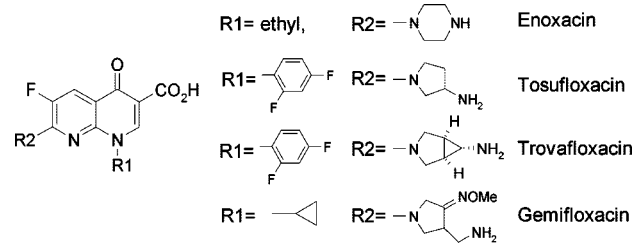
Abstract:

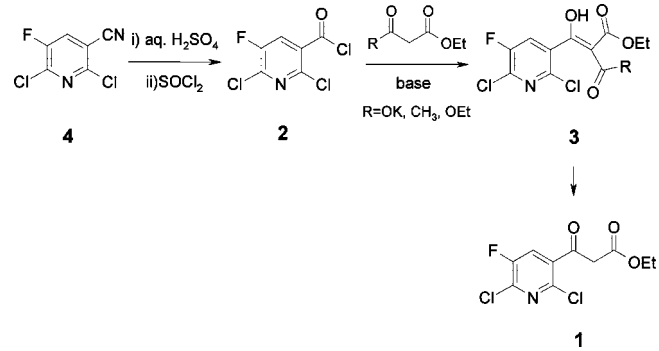
An efficient synthesis of 2,6-dichloro-5-fluoronicotinoylacetate (1) has been accomplished in a single step using the unprecedented decarboxylative Blaise reaction of 3-cyano-2,6-dichloro-5-fluoropyridine (4) with potassium ethyl malonate in the presence of zinc chloride.

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 as a key starting material ethyl 2,6-dichloro-5-fluoronicotinoylacetate (**1**), which 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 by the selective partial hydrolysis of the diester intermediate **3**: the formation of the methyl ketone impurity[7] via double decarboxylation was observed as a side product. To circumvent this drawback, malonate monoester[8] and ethyl acetoacetate[9] were used instead of diethyl malonate as an acetate enolate equivalent. As an alternative route, we have devised the one-pot Blaise reaction transformation[10] of nitrile **4** to **1** (Scheme 3). Although this process is more efficient than the current commercial process, its highly exothermic nature, use of excess materials, and use of lachrymatory ethyl bromoacetate leave room for further improvement for a large-scale operation.

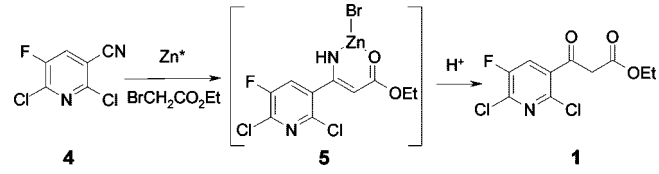
Scheme 1



Scheme 2



Scheme 3



On the basis that the copper(I) salt facilitated the decarboxylation of malonic acid,[11] we envisaged the decarboxylative Blaise reaction on the premise that zinc ethyl malonate species would undergo decarboxylation to form the Reformatsky

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(1) The content of the paper has been published as a part of patent. See: Shin, H.; Choi, B. S.; Lee, J. H. WO 2007064077, 2007.

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(6) (a) The reported yield of **1** from the acid chloride **2** is 74%. See: 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, J = 7.3Hz, 1H), 2.71 (s, 3H).

(8) (a) The reported yield of **1** from the acid chloride **2** is 96%. 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.

(9) The reported yield of **1** from the acid chloride **2** is 70%. See: Urban, F. J.; Moore, B. S.; Spargo, P. L. *Org. Prep. Proced. Int.* **1997**, *29*, 231.

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Scheme 4

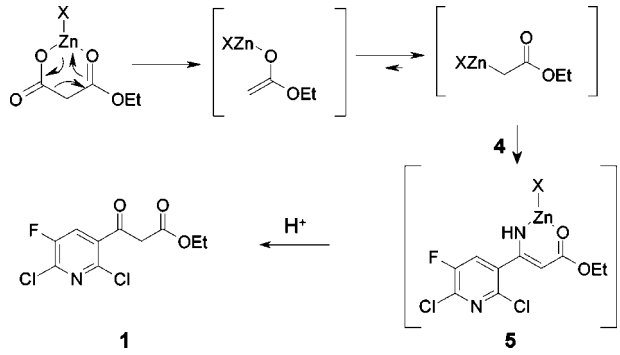
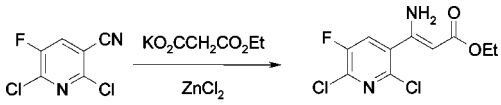


Table 1. **Solvent effect on the decarboxylative Blaise reaction of 4[a]**



entry	solvent	time (h)	conversion (%)[b]
1	NMP	2	100
2	DMF	2	100
3	DCE	3	100
4	$CHCl_3$	3	100
5	DME	15	9
6	dioxane	15	2
7	THF	15	trace
8	EtOH	15	5
9	toluene	15	22

[a] All reactions were run at 90 °C with 1.5 equiv of potassium ethyl malonate in the presence of 1.0 equiv of zinc chloride. [b] Sample was obtained by quenching the mixture with aqueous ammonium chloride solution, and the organic layer was checked by GC: HP-5MS column; injector 280 °C; initial time and temp 2 min and 70 °C; gradient 10 °C/min; final temp 300 °C; flow rate 1 mL/min. Compounds **4** and **6** were detected at 8.9 and 17.0 min, respectively.

reagent, which should react with nitrile **4** to form **5** (Scheme 4).

A clue for the possible success for the proposed decarboxylative Blaise reaction was secured by an early outcome: heating a mixture of potassium ethyl malonate, nitrile **4**, and zinc chloride in toluene to provide 22% conversion of the reaction (entry 9 in Table 1). Encouraged by this result, further screening of reaction solvents was performed to disclose a dramatic solvent effect. Polar aprotic solvents such as DMF and NMP (entries 1 and 2) showed complete conversion of the reaction. So did the chlorinated solvents such as 1,2-dichloroethane (DCE) and chloroform (entries 3 and 4). On the other hand, ethereal solvents such as DME, dioxane, and THF (entries 5–7) were poor media for this transformation, and ethanol (entry 8) showed minimal conversion.

Using DCE as the optimal medium for the reaction, the effect of metal salts on the reaction was investigated briefly, and the results are gathered in Table 2. Among zinc salts, zinc chloride (entry 1 in Table 2), bromide (entry 2), and triflate (entry 4) led to essentially complete conversion, whereas zinc iodide (entry 3) showed very low reactivity. Magnesium salts (entry 5) did not show any of the desired reactivity.

To check the catalytic turnover of the reaction towards zinc chloride, we tested the reaction with 0.5, 0.25, and 0.1 equiv

Table 2. **Metal salt effect on the decarboxylative Blaise reaction of 4 to 6[a]**

entry	Lewis acid	time (h)	conversion (%)[b]
1	$ZnCl_2$	3	100
2	$ZnBr_2$	3	99
3	ZnI_2	15	5
4	$Zn(OTf)_2$	3	95
5	MgX_2 (X = Cl, Br, I)	15	0

[a] All reactions were performed with 1.5 equiv of potassium ethyl malonate in the presence of 1.0 equiv of Lewis acid in DCE. [b] The analysis was performed as in the footnote b of Table 1.

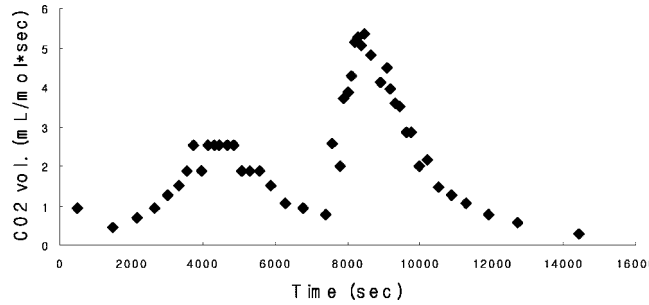


Figure 1. **Measure of CO_2 evolution. The reaction was started with 0.2 equiv of 4 in the presence of 1.5 equiv of potassium ethyl malonate and 0.5 equiv of zinc chloride. After the initial evolution of CO_2 was complete (at ca. 7000 s), the remaining 0.8 equiv of 4 was added.**

of zinc chloride. We found that reduction of the equivalency below 0.5 led to prolonged reaction time for the completion of the reaction: 0.5 equiv completed the reaction in 3 h, whereas 0.25 and 0.1 equiv required 2 d to reach 96% and 88% conversion, respectively. Although the turnover number is marginal, it clearly provided the feasibility to develop a more efficient catalytic reaction system.

In contrast to the classical Blaise reaction, the decarboxylative version is endothermic ($\Delta H = -6.5$ KJ/mol of **4**), rendering the reaction safer than the classical Blaise reaction. Moreover, the evolution of carbon dioxide was also readily controllable by portionwise addition of **4** to the mixture of potassium ethyl malonate and zinc chloride. Figure 1 shows how the evolution of carbon dioxide may be controlled in a dose-dependent manner.[12] With optimized conditions in hand, we successfully scaled up the reaction to the preparation of ca. 20 kg of **1** as described in Experimental Section.

In conclusion, we have discovered the decarboxylative Blaise reaction of **4** with potassium ethyl malonate in the presence of zinc chloride. This protocol is more environmentally benign in terms of reduced effluent discharge and avoids the use of a lachrymatory reagent. Moreover, successful scale-up to **1** in a one-pot manner using 20 kg of **4** clearly demonstrated its reproducibility. The general scope of the decarboxylative Blaise reaction will be published in due course.

(12) A simulated calculation using the experimentally measured CO_2 evolution data showed that a 2-in. diameter of ventilation tubing is sufficient to release CO_2 without any pressure build-up when a mixture of 100 kg of **4**, zinc chloride, and potassium ethyl malonate is heated at reflux.

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-fluoronicotinoylacetate (1). To a 250-L reactor containing 1,2-dichloroethane (100 L) were added 3-cyano-2,6-dichloro-5-fluoropyridine (**4**, 20.0 kg, 105 mol), zinc chloride (7.14 kg, 52.4 mol), and potassium ethyl malonate (21.4 kg, 126 mol) in sequence. The mixture was heated at reflux, leading to a gradual color change to red. After 3 h, 6 N HCl (150 L) was added slowly, and the mixture was heated at reflux for 30 min. The mixture was cooled down to ambient temperature, and the organic phase was separated and concentrated. To the residue was added EtOH/H_2O (5/1, 100 L), and the mixture was heated to 70 °C until all of the solid material was dissolved completely. The solution was cooled down slowly, and the pale yellowish solid started to precipitate at about 40 °C. The solution was further cooled down to 0 °C and stirred for another 1 h. The precipitate was filtered off and washed with EtOH/H_2O (5/1, 100 L) at ambient temperature to give **1** as a white solid (22.0 kg, 75.0%). 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^+).

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