JOC Note

Cascade Synthesis of 3-Quinolinecarboxylic Ester via Benzylation/ Propargylation−Cyclization

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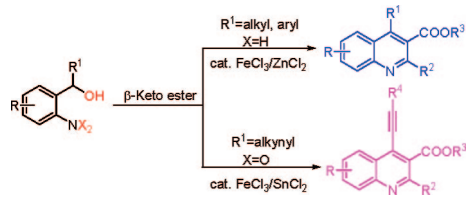

Reactions of 2-amino-aryl alcohols with β-ketoesters catalyzed by a catalytic amout of $FeCl_3$ via tandem benzylation−cyclization produce the corresponding 3-quinolinecarboxylic esters in good to high yields. Extending this methodology to propargylation−cyclization, 2-nitrophenyl propargyl alcohols with β-ketoesters catalyzed by $FeCl_3$ and $SnCl_2$ also produce the 4-alkyne-3-quinolinecarboxylic esters. The mechanistic details of this benzylation/propargylation and cyclization cascade process are also discussed.

Quinolines and their derivatives occur widely in natural products and have attracted considerable attention due to their wide spectrum of biological activities, functioning as antimalarial, anti-bacterial, anti-asthmatic, anti-hypertensive, anti-inflammatory, anti-platelet activity and tyro-kinase PDGF-RTK inhibiting agents, as well as being general synthetic building blocks.[1] The classical methods for the synthesis of quinolines, such as the Skraup, Doebner−von Miller, Doebner, Combes, Pfitzinger quinoline syntheses,[2] require harsh reaction conditions and the yields are unsatisfactory in most cases. The Friedländer annulation[3] is the simplest, most straightforward synthetic method for the synthesis of quinoline derivatives, especially for the highly substituted 3-quinolinecarboxylic esters.[4−7] This method usually involves acid- or base-catalyzed or thermal (up to 250 °C) condensation between a 2-aminoaryl ketone or aldehyde and a second carbonyl compound possessing a reactive α-methylene group, followed by cyclodehydration. However, most of the synthetic approaches reported so far have suffered from the need of high temperatures and the use of hazardous and expensive catalysts,[8] Therefore, the development of a general, efficient, and conventional method for highly substituted 3-quinolinecarboxylic esters is highly desirable.

In recent years, benzylic alcohols and their derivatives have received considerable attention as carbon electrophiles capable of reacting with various carbon, oxygen, and sulfur nucleophiles.[9,10]

Herein, we present a novel approach to synthesize highly substituted 3-quinolinecarboxylic acid with a readily available

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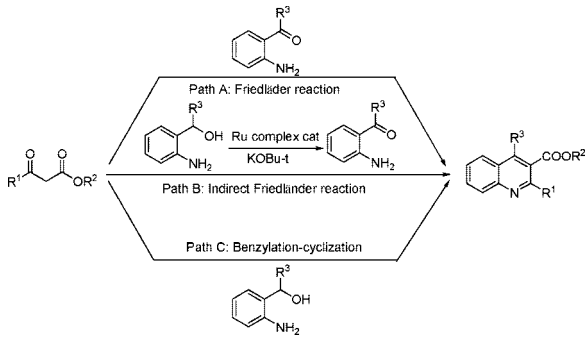
SCHEME 1. Direct and Indirect Friedländer Annulation versus Benzylation−Cyclization

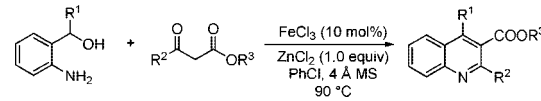


catalyst, $FeCl_3$ (Scheme 1, path C). This novel methodology is entirely distinct from the Friedländer annulation (Scheme 1, path A) and the modified Friedländer annulation (Scheme 1, path B).[11] To the best of our knowledge, the synthetic method we propose here (Scheme 1, path C) is the first example a highly substituted 3-quinolinecarboxylic ester system formed by a cascade reaction of benzylation and cyclization. The mechanistic details of this benzylation and cyclization cascade process are also discussed.

Having established the optimal reaction conditions (see Supporting Information), we then examined a spectrum of 2-aminoarylmethyl alcohols and β-ketoesters to explore the generality of this new method (Table 1). In general, a range of differently substituted 2-aminoarylmethyl alcohols with electron-donating or electron-withdrawing groups and various β-ketoesters were tolerated and gave good to excellent yields of the corresponding products. Initially, when the 2-aminobenzyl alcohol was used as a substrate, only a moderate yield was observed due to the low stability of the carbocation intermediate (Table 1, entry 1). Secondary alcohols which may produce a more stable carbocation intermediate gave much higher yields of the desired products (Table 1, entries 2−17). The presence of an electron-withdrawing substituent on the 2-aminoarylalcohol appeared to be unfavorable (Table 1, entries 10−12). However, a strong electron-donating substituent on the 2-aminoarymethyl lalcohol also retarded the reaction and a relatively low reaction temperature was suitable for this substrate (Table 1, entry 13). On the other hand, no significant influence of various β-ketoesters was observed except for methyl 4-methyl-3-oxopentanoate (Table 1, entry 9) probably due to its powerful hindrance. Heteroaromatic substituents were also readily introduced into the quinoline skeleton at the 4-position in this method (Table 1, entries 15 and 16). To our surprise, strong electron-deficient substrate, (2-aminopyridin-3-yl)(phenyl)-methanol gave the 1,4-dihydro-1,8-naphthyridine product in only moderate yield (Table 1, entry 17).

Next, to explore the utility of the $FeCl_3$-catalyzed alkylation cyclization reaction, we sought to extend this methodology to propargylation[12]−cyclization. First, we endeavored to synthesize *o*-anilinopropargyl alcohol by the reduction of *o*-nitrophenyl propargyl alcohol with $SnCl_2 \cdot 2H_2O$[13] and we obtained 2-phenyl quinoline in 72% yield unexpectedly. Shifting the reductant to Ni_2B,[14] we also detected that 2-phenyl quinoline was the main product (59% yield) (Table 2, entry 1). In this case, we used *o*-nitrophenyl propargyl alcohols as substrates to react with β-ketoesters in a one-pot protocol (Table 2, entries 2−10). In all cases, moderate to good yields were obtained. For the *o*-nitrophenyl propargyl alcohols, aromatic alkyne substrates proved to be of greater benefit (Table 2, entries 2−6 and 9)

TABLE 1. Synthesis of 3-Quinolinecarboxylic Esters[a]



Entry	Arylalcohol	β-ketoester	Product		Yield(%)[b]
1	1a	2a		3a	65
2	1a	2a	R^1=Me R^2=Et	3b	85
3	1b	2b	R^1=Me R^2=Me	3c	87
4	1b	2c	R^1=Ph R^2=Et	3d	90
5	1c	2a	R^1=Me R^2=Et	3e	90
6	1c	2b	R^1=Me R^2=Me	3f	92
7	1c	2c	R^1=Ph R^2=Et	3g	84
8	1c	2d	R^1=n-Pr R^2=Et	3h	82
9	1c	2e	R^1=i-Pr R^2=Me	3i	66
10	1d	2a	R^1=Me R^2=Et	3j	87
11	1d	2b	R^1=Me R^2=Me	3k	85
12	1d	2c	R^1=Ph R^2=Et	3l	80
13	1e	2a		3m	25(77[c])
14	1f	2a		3n	94
15	1g	2a		3o	92
16	1h	2a		3p	87
17	1i	2a		3q	59

[a] Reaction conditions: 2-aminoarylalcohol (0.5 mmol), β-ketoester (2 mmol), $FeCl_3$ (10 mol %), $ZnCl_2$ (100 mol %), PhCl (1.5 mL), 0.5 g of 4 Å MS, 90 °C, 12 h. [b] Yield of isolated product. [c] The yield in the parenthesis was obtained when the reaction was performed at 25 °C.

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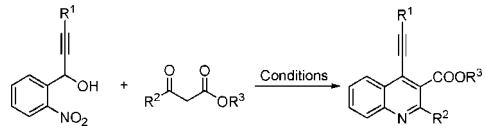
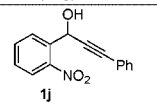
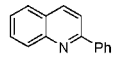
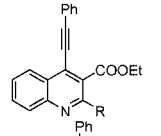
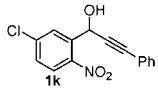
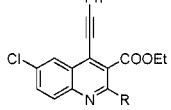
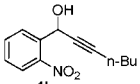
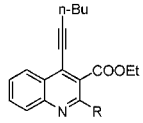
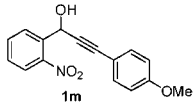
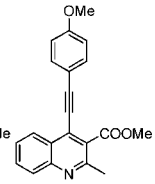
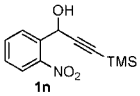
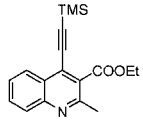
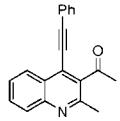
TABLE 2. Synthesis of 4-Alkyne-3-quinolinecarboxylic Esters[a]



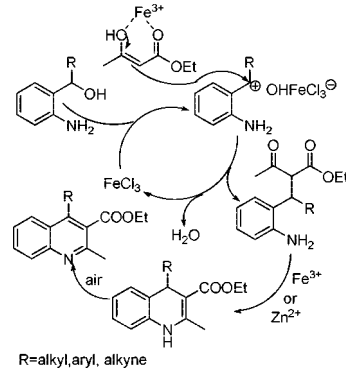
Entry	Propargyl alcohol	Product			Yield(%)[b]
1[c]				5a	72[d]
	1j				59[e]
2			R=Me	4a	69
3	1j		R=Ph	4b	56
4			R=n-Pr	4c	66[f]
5			R=Me	4d	63
6	1k		R=Ph	4e	72[f]
7			R=Me	4f	62
8	1l		R=Ph	4g	54
9				4h	66
	1m				
10				4i	44
	1n				
11	1j			4j	80

[a] Reaction conditions: *o*-nitrophenyl propargyl alcohol (0.5 mmol), β-ketoester (2 mmol), $FeCl_3$ (10 mol %), PhCl (1.5 mL), 0.5 g of 4 Å MS, 70 °C, after 4 h, $SnCl_2 \cdot 2H_2O$ (1.5 mmol) was added, 70 °C, 8 h. [b] Yield of isolated product. [c] *o*-Nitrophenyl propargyl alcohol (0.5 mmol), PhCl (1.5 mL), reductant, in the absence of β-ketoester. [d] $SnCl_2 \cdot 2H_2O$ (1.5 mmol) was used as reductant, 70 °C, 6 h. [e] $NaBH_4$ (5 mmol) and $NiCl_2 \cdot 2H_2O$ (0.5 mmol) was used as reductant, 0 °C, 3 h. [f] $FeCl_3$ (20 mol%).

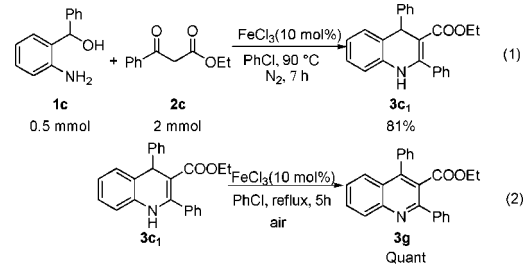
than the aliphatic ones (Table 2, entries 7−8 and 10). No obvious electronic effect was observed with **1k**, which bears an electron-withdrawing *p*-chloro group. A low yield was obtained when trimethylsilyl-substituted *o*-nitrophenyl propargyl alcohol was used (Table 2,entry 10), probably because of the electronic effect of the trimethylsilyl substituent. Similar to the benzylation−cyclization reaction, no significant influence of various β-ketoesters was observed. When β-diketone was used as the nucleophilic partner, such as pentane-2,4-dione, a much higher yield was obtained (Table 2, entry 11).

Based on the isolation of 1,4-dihydro-1,8-naphthyridine (Table 1, entry 17), a tentative mechanism is proposed in Scheme 2: (1) formation of a carbocation intermediate from 2-aminoarylmethyl alcohol by $FeCl_3$ and coordination of β-ketoester onto $FeCl_3$ to form an activated enol, (2) nucleophilic attack of the enol, (3) cyclization of amido and carbonyl to form a 1,4-dihydro-3-quinolinecarboxylic ester, and (4) oxidation by air to give a 3-quinolinecarboxylic ester.

SCHEME 2. Tentative Mechanism for the Synthesis of 3-Quinolinecarboxylic Ester via Benzylation/ Propargylation−Cyclization



In order to validate the last step, the oxidation of 1,4-dihydro-3-quinolinecarboxylic ester by air to give a 3-quinolinecarboxylic ester, we performed the reaction in the presence of N_2 atmosphere (eq a). Subjecting the reaction mixture after 7 h to flash chromatography immediately, we obtained ethyl 2,4-diphenyl-1,4-dihydroquinoline-3-carboxylate (**3c$_1$**) in 81% yield. Subsequently, **3c$_1$** was oxidized by air in PhCl in the presence of $FeCl_3$ under refluxing conditions, giving ethyl 2,4-diphenylquinoline-3-carboxylate (**3g**) in quantitative yield (eq 2)].



In summary, we have developed a novel $FeCl_3$-catalyzed benzylation/propargylation−cyclization reaction for synthesizing highly substituted 3-quinolinecarboxylic esters and 4-alkyne 3-quinolinecarboxylic esters. In particular, the 4-alkyne 3-quinolinecarboxylic esters are commonly synthesized by the Sonogashira reaction. This study has achieved a Lewis acid catalyzed casade construction of the quinoline skeleton. Future work will address the further exploitation of this principle in other highly substituted heterocyclic natural product skeletons.

Experimental Section

General Procedure A for Benzylation and Cyclization. $FeCl_3$ (8.1 mg, 0.05 mmol), anhydrous $ZnCl_2$ (68.0 mg, 0.50 mmol), and 0.50 g of 4 Å MS were added to a solution of 1-(2-aminophenyl)ethanol **1b** (68.5 mg, 0.5 mmol) and ethyl 3-oxobutanoate **2a** (260.0 mg, 2.0 mmol) in freshly distilled PhCl (1.5 mL). The resulting mixture was stirred at 90 °C for 12 h in the atmosphere of air. The reaction mixture was then cooled to room temperature and quenched with saturated $NaHCO_3$, and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with water and saturated brine, dried over Na_2SO_4 and filtered. Solvents were evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel to give **3b** (97.3 mg, 85%).

Ethyl 2,4-Dimethylquinoline-3-carboxylate (3b). ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 8.03−7.97 (m, 2 H), 7.73−7.68 (m, 1 H), 7.56−7.51 (m, 1 H), 4.48 (q, J = 7.2 Hz, 2 H), 2.70 (s, 3 H), 2.65 (s, 3 H), 1.45−1.41 (t, J = 7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$,

75 MHz, ppm): δ 169.3, 154.5, 147.1, 141.7, 130.2, 129.3, 128.1, 126.5, 126.0, 124.1, 61.8, 23.8, 15.8, 14.4. IR (liquid film, cm^{-1}): υ 3068, 2959, 1951, 1726, 1614, 1589, 1566, 1498, 1446, 1403, 1337, 1341, 1287, 1233, 1162, 1129, 1081, 1056, 852, 758, 645. HRMS calcd $C_{14}H_{15}NO_2$ (M^+): 229.1103, found 229.1114.

General Procedure B for Propargylation and Cyclization. $FeCl_3$ (8.1 mg, 0.05 mmol) and 0.50 g of 4 Å MS were added to a solution of 1-(2-nitrophenyl)-3-phenylprop-2-yn-1-ol **1j** (126.5 mg, 0.5 mmol) and ethyl 3-oxobutanoate **2a** (260.0 mg, 2.0 mmol) in freshly distilled PhCl (1.5 mL). The mixture was stirred at 70 °C for 4 h. Then $SnCl_2 \cdot 2H_2O$ (337.5 mg, 1.50 mmol) was added and the result mixture was stirred at 70 °C for another 8 h. After cooled to room temperature, the system was rendered basic (pH 8) with 10% aqueous $NaHCO_3$, then transferred to a separatory funnel, and extracted with ethyl acetate. The combined organic extracts were washed with water and saturated brine, dried over Na_2SO_4 and filtered. Solvents were evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel to give **4a** (108.7 mg, 69%).

Ethyl 2-Methyl-4-(phenylethynyl)quinoline-3-carboxylate (4a). ^1H NMR ($CDCl_3$, 300 MHz, ppm): δ 8.34 (d, J = 8.4 Hz, 1 H), 8.04 (d, J = 8.1 Hz, 1 H), 7.78−7.76 (m, 1 H), 7.63−7.61 (m, 3 H), 7.55−7.30 (m, 3 H), 4.53 (q, J = 7.2 Hz, 2 H), 2.78 (s, 3 H), 1.44 (t, J = 7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): δ 167.98, 154.8, 147.5, 132.1, 130.3, 129.7, 129.4, 129.1, 128.7, 128.1, 127.2, 126.4, 125.5, 122.2, 102.3, 83.2, 62.0, 23.9, 14.4. IR (liquid film, cm^{-1}): υ 3062, 2981, 2209, 1727, 1567, 1496, 1432, 1405, 1299, 1229, 1153, 1128, 1074, 1033, 865, 760, 690. HRMS calcd $C_{21}H_{17}NO_2$ (M^+): 315.1259, found 315.1267.

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Supporting Information Available: Typical procedure for the reaction, preparation of starting materials, optimization of the reaction conditions and characterization data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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