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A One-Step Synthesis of 2,4-Unsubstituted Quinoline-3-carboxylic Acid Esters from *o*-Nitrobenzaldehydes

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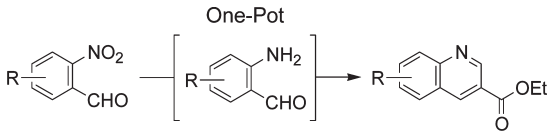
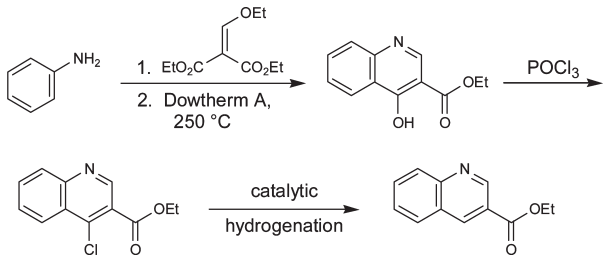


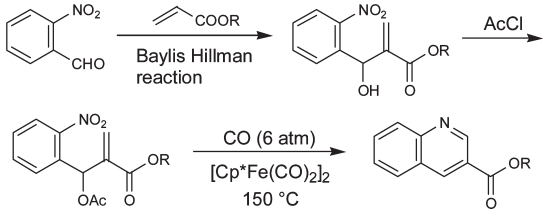
A straightforward and efficient one-step procedure for the synthesis of 2,4-unsubstituted quinoline-3-carboxylic acid ethyl esters is described. The simple reductive cyclization is carried out by treating various substituted *o*-nitrobenzaldehydes with inexpensive, commercially available 3,3-diethoxypropionic acid ethyl ester and $SnCl_2 \cdot 2H_2O$ in refluxing ethanol.

The quinoline ring system is a prevalent structural motif in natural products[1] as well as in numerous marketed drugs such as antibacterials, antimalarial agents, HIV-1 integrase inhibitors,[2] and other compounds of pharmaceutical interest.[3] As part of our ongoing drug discovery efforts, we required a rapid, efficient, and practical synthesis of substituted quinoline-3-carboxylic acids. Despite the existence of extensive literature for the synthesis of quinolines,[4] the routes available to specifically synthesize 2,4-unsubstituted 3-carbalkoxy quinolines were, to our surprise, limited. Most common procedures require multiple steps, long reaction times, elevated temperatures (and in one instance high pressure), and expensive reagents, resulting in unsatisfactorily low overall yields.[5]

SCHEME 1. Synthesis of Quinoline-3-carboxylic Acid Ester with the Gould−Jacobs Route



SCHEME 2. Transition Metal-Catalyzed Synthesis of Quinoline-3-carboxylic Acid Ester



Typically, substituted anilines can be converted to 4-hydroxyquinoline-3-carboxylate via the classical Gould−Jacobs reaction. A two-step deoxygenation procedure then furnishes the desired quinoline-3-carboxylate via conversion to the chloride followed by reduction of the chloride under catalytic hydrogenation conditions (Scheme 1).[5c] The route suffers from poorly controlled regioselectivities in the first step and requires elevated temperatures in the second step (250 °C). Furthermore, catalytic hydrogenation can lead to over-reduction of the quinoline ring and is incompatible with certain substituents such as the chloride or the bromide, which are versatile handles for further elaboration.

Recently, Nicholas and co-workers have reported a reductive cyclization of *o*-nitro-substituted Baylis−Hillman acetates by CO, catalyzed by $[Cp^*Fe(CO)_2]_2$ (Scheme 2).[5d] The key step in this three-step route requires heating to high temperature and pressure (150 °C at 6 atm of CO).

The routes described above require high temperatures and/or pressures, are lengthy, and result in low overall yields in most cases. This prompted us to investigate a more practical and efficient route. In our search for a simpler procedure for the synthesis of quinoline-3-carboxylates, we felt that we could use the well-known Friedlander synthesis to our advantage.[4,6] Several groups have investigated variations

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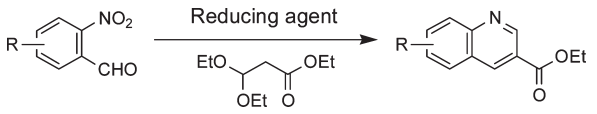
SCHEME 3. Proposed Synthesis of Quinoline-3-carboxylic Acid Ester

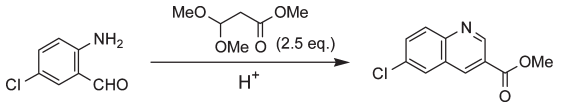


of the reaction using acidic as well as basic conditions.[7] However, to the best of our knowledge, only one synthesis of 2,4-unsubstituted quinoline-3-carboxylic acid utilizing the Friedlander reaction starting from a substituted 2-aminobenzaldehyde has been disclosed and is of limited practical value due to the low overall yield (13%).[8] Moreover, the aldehyde partner that is required to affect this transformation, 3-oxo-propionic acid ethyl ester, is not readily available commercially, although it can be synthesized in a single step.[9] In contrast, the corresponding ethyl acetal is both inexpensive and commercially available. This synthon shares the parent aldehyde's reactivity profile under the Friedlander conditions and we elected to investigate this reagent in the Friedlander reaction. Herein, we report a rapid, modified Friedlander synthesis of aryl-substituted quinoline-3-carboxylic acid esters from commercially available ethyl 3,3-diethoxypropionate and *o*-nitrobenzaldehydes (Scheme 3).

At first, we elected to test the viability of the cyclization reaction using 2-amino-5-chlorobenzaldehyde under a variety of acidic conditions (Table 1). We were pleased to find that treatment of 5-chloro-2-aminobenzaldehyde with 3,3-dimethoxy methyl propionate in the presence of 4 M HCl in dioxane at room temperature yielded the desired product, albeit in low yield (entry 1). Heating the reaction mixture to reflux did not improve the yield of the reaction (entry 2). However, heating the reaction mixture with AcOH resulted in good yield of the product (entry 3). Acids such as TFA, MsOH, and CSA led to considerable decomposition and moderate yields of product (entries 4, 5, and 6). The use of PPTS in THF led to moderate yields of the desired product (entry 7). We found that, performing the reaction in toluene or THF using *p*-TsOH under refluxing conditions provided the best yields of 6-chloroethyl quinoline-3-carboxylate (67% and 76% respectively, entries 9 and 10). We have performed the optimized procedure on a number of other amino benzaldehydes that were not commercially available (data not shown) and have consistently obtained good yields of the quinoline-3-carboxylates (> 70% typically).

Encouraged by the results, we wished to extend the utility of the reaction and explore the possibility of affecting a one-step reductive cyclization of *o*-nitrobenzaldehydes. Success in this more complex transformation would allow access to a much greater number of commercially available aromatic aldehyde starting materials.

TABLE 1. Synthesis of 6-Chloroquinoline-3-carboxylic Acid Methyl Ester from 2-Amino-5-chlorobenzaldehyde



entry	solvent	acid	temp (°C)	time (h)	yield (%)
1	dioxane	4 M HCl (anhydrous)	rt	21	30
2	dioxane	4 M HCl (anhydrous)	100	21	32
3	AcOH		100	23	60
4	TFA		100	22	41
5	THF	$MeSO_3H$	80	19	50
6	THF	CSA	80	19	40
7	THF	PPTS	80	19	44
8	dioxane	*p*-TsOH	110	17	63
9	toluene	*p*-TsOH	110	17	67
10	THF	*p*-TsOH	80	17	76

Two reagents that have been used extensively for the reduction of the nitro group are $Na_2S_2O_4$ and Fe/acid.[10] First, we attempted to perform the one-pot procedure using *o*-nitrobenzaldehyde, alkyl 3,3-dialkoxypropionate (methyl or ethyl), and $Na_2S_2O_4$ in refluxing acetic acid and obtained a low yield of the desired product (21% and 20% respectively, entries 1 and 2, Table 2). Additionally, we found that the reaction under these conditions was capricious and irreproducible. The use of $Na_2S_2O_4$ and TsOH in toluene did not yield any of the desired product (entry 3). Similarly, the use of iron and HCl or iron and *p*-TsOH in EtOH and toluene, respectively, did not yield any product (entries 4 and 5). The nitro group underwent reduction smoothly under these reaction conditions but failed to cyclize.

$SnCl_2$ can function as a chemoselective reducing agent[11] as well as a mild Lewis acid and was therefore an attractive reagent for carrying out this reductive cyclization. Using $SnCl_2 \cdot 2H_2O$ in refluxing EtOH we consistently obtained good yields of the desired product (entry 6, 82% average over 2 runs). The reaction was further optimized by varying the time and the number of equivalents of $SnCl_2 \cdot 2H_2O$ required for the transformation. We found that 4 equiv of $SnCl_2 \cdot 2H_2O$ were necessary to give optimal yields of product. Depending on the substrate, the reaction time generally varied between 1.5 and 4 h. The reaction is operationally very simple: all reagents are mixed in EtOH and refluxed until the reaction is complete, prior to aqueous workup and isolation by flash column chromatography.

Having established the optimal conditions for the reaction, we then examined a variety of substituted *o*-nitrobenzaldehydes to explore the scope and limitations of the reaction (Table 3).

The reaction accommodates a range of functional groups, including electron-withdrawing as well as electron-releasing substituents on the nitrobenzaldehyde. Also, under these reaction conditions, it is worth noting that bromides, chlorides, ester, and methoxy groups as well as the *O*-benzyl group are tolerated (entries 2−5 and 7−10). Amine substitutions

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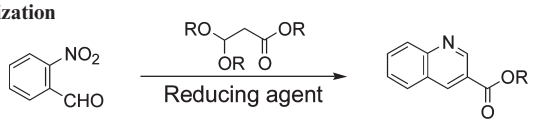
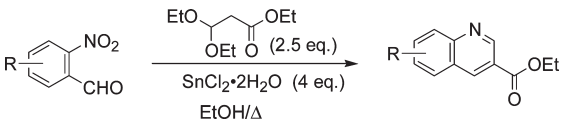
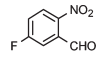
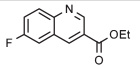
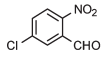
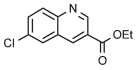
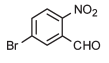
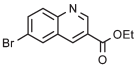
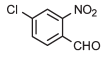
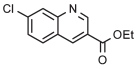
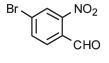
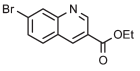
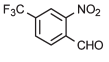
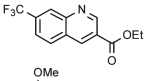
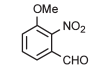
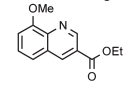
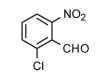
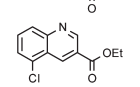
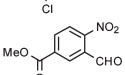
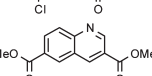
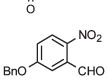
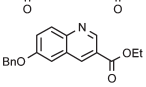
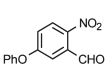
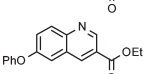
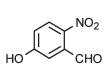
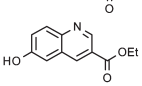
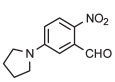
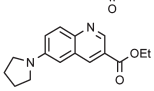
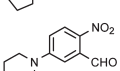
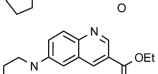
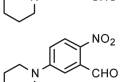
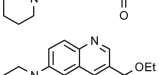
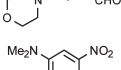
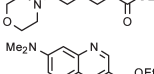
TABLE 2. Optimization of Reductive Cyclization



entry	R	acid	reducing agent	solvent	time/temp	yield (%)
1	Me	AcOH	$Na_2S_2O_4$	AcOH	3 h at 65 °C and 3 h at 110 °C	21
2	Et	AcOH	$Na_2S_2O_4$	AcOH	3 h at 65 °C and 3 h at 100 °C	20
3	Me	TsOH	$Na_2S_2O_4$	toluene	3 h at 65 °C and 18 h at 110 °C	0
4	Et	HCl	Fe	EtOH	18 h at 95 °C	0
5	Me	TsOH	Fe	toluene	18 h at 100 °C	0
6	Et	$SnCl_2$	$SnCl_2$	EtOH	3 h at 90 °C	82

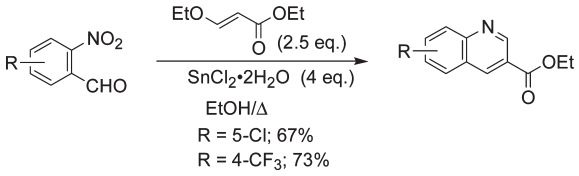
TABLE 3. Scope of One-Step Modified Friedlander Reaction



entry	substate	product	yield (%)
1			68
2			72
3			74
4			73
5			85
6			86
7			70
8			67
9			58[a]
10			49
11			51
12			46
13			53
14			55
15			68
16			31

[a]3,3-dimethoxy methyl propionate in refluxing methanol was used.

SCHEME 4. 3-Ethoxy Ethyl Acrylate Mediated Synthesis of Quinoline-3-carboxylic Acid Ethyl Ester



such as pyrrolidine, piperidine, and dimethylamine provide more modest yields relative to other substrates (entries 13, 14, and 16). It seemed reasonable to hypothesize that the reaction proceeds through the intermediacy of 3-alkoxy acrylate and we tested this hypothesis by performing the reaction using commercially available 3-ethoxy ethyl acrylate (Scheme 4). The use of this reagent in the reductive Friedlander reaction provided yields of desired product comparable to those observed from ethyl 3,3-diethoxypropionate (67% for 5-chloro-2-nitrobenzaldehyde and 73% for 4-trifluoromethyl-2-nitrobenzaldehyde).

In summary we have developed a simple procedure for the synthesis of 2,4-unsubstituted quinoline-3-carboxylic acid esters from *o*-nitrobenzaldehydes in good yield using an inexpensive, commercially available synthon. The efficient methodology described here represents the shortest route available to access a variety of 2,4-unsubstituted 3-carboxyquinolines, tolerates a range of functional groups, is operationally simple, and provides a significant improvement over existing routes for the preparation of this class of molecules.

Experimental Section

General Procedure for Acid-Catalyzed Cyclization: 6-Chloroquinoline-3-carboxylic Acid Ethyl Ester (Table 1, entry 9). 3,3-Dimethoxypropionic acid methyl ester (0.71 mL, 5.0 mmol) was added to a solution of 5-chloro-2-aminobenzaldehyde (0.311 g, 2.00 mmol) and toluene (5 mL), followed by *p*-TsOH (38 mg, 0.20 mmol). The reaction mixture was heated to 110 °C for 18 h. Saturated aqueous $NaHCO_3$ was then added and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (SiO_2, 0−25% EtOAc/hexanes) to yield a pale yellow crystalline solid (0.264 g, 67%): mp 168.6−169.5 °C (lit. mp 174−176 °C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.43 (d, J = 2.1 Hz, 1H), 8.75 (d, J = 1.9 Hz, 1H), 8.10 (d, J = 9.0 Hz, 1H), 7.91 (d, J = 2.3 Hz, 1H), 7.76 (dd, J = 9.0, 2.3 Hz, 1H), 4.03 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.5, 150.2, 148.2, 137.7, 133.3, 132.7, 131.1, 127.6, 127.5, 123.8, 52.7. Anal. Calcd for $C_{11}H_8ClNO_2$: C, 59.61; H, 3.64; N, 6.32. Found: C, 59.70; H, 4.00; N, 6.35.

General Procedure for Tin(II) Chloride-Mediated Reductive Cyclization: Quinoline-3-carboxylic Acid Ethyl Ester (Table 2, entry 6). Tin(II) chloride dihydrate (1.81 g, 8.00 mmol) was added to a solution of 2-nitrobenzaldehyde (0.302 g, 2.00 mmol) and EtOH (10 mL) followed by 3,3-diethoxypropionic acid ethyl ester (0.97 mL, 5.0 mmol). The reaction mixture was heated to 90 °C for 4 h. Upon cooling, the reaction mixture was concentrated and the residue was dissolved in EtOAc and quenched with saturated aq $NaHCO_3$. The resulting emulsion was filtered through a pad of Celite, and rinsed well with EtOAc. The remaining aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (SiO_2, 10−30% EtOAc/hexanes) to yield an off-white solid (0.331 g, 82%): mp 67.4−67.9 °C (lit. mp 69−69.5 °C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.46 (d, J = 2.1 Hz, 1H), 8.85 (d, J = 1.7 Hz, 1H), 8.17 (d, J = 8.5 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.84 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.66−7.60 (m, 1H), 4.49 (q, J = 7.1 Hz, 2H), 1.47 (t, J = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.4, 150.1, 149.8, 138.7, 131.8, 129.5, 129.1, 127.4, 126.9, 123.3, 61.5, 14.4. Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.31; H, 5.66; N, 6.72.

Acknowledgment. We warmly thank Victor Phuong and Alice Lee-Dutra for kindly providing 4-bromo-2-nitrobenzaldehyde and 2-nitro-5-phenoxybenzaldehyde, respectively.

Supporting Information Available: ^{1}H and ^{13}C NMR, melting points, and copies of spectra for all prepared compounds. This material is available free of charge via the Internet at http://pubs.acs.org.