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# Quinoline- and 1,8-naphthyridine-3-carboxylic acids using a self-catalyzed Friedländer approach

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ABSTRACT

One-step syntheses of 2-alkyl- and 2,4-dialkyl-substituted quinoline-3-carboxylic acids and 1,8-naphthyridine-3-carboxylic acids are reported using a catalyst-free Friedländer reaction. The reaction is carried out in one step by simple heating of 2-aminobenzaldehyde, 2-amino-5-chlorobenzaldehyde, 2-aminonicotinaldehyde, or 2-aminoacetophenone with a β-ketoester in toluene or xylene for 24 h. Under these conditions, the carboxylic acid product is isolated directly from the reaction mixture without need for further purification. The observation that the reaction starts slowly and accelerates as it proceeds suggests that the transformation is self-catalyzed. This hypothesis is also supported by the finding that attempts to extend the current reaction to diketones, which cannot hydrolyze to an acid, were generally unsuccessful.



The Friedländer synthesis of quinolines has generated considerable interest among researchers throughout the world. The reaction most often involves condensation of a 2-aminoaryl-aldehyde or ketone with a carbonyl compound containing an active methylene group.[1] The reaction is generally performed with a catalyst present and has been promoted by acids, Lewis acids, and bases. Several reports have also appeared where the transformation was performed without catalyst, but the reaction required high temperatures (150–220 °C). Very recently, a paper describing the synthesis of quinolines without added catalyst in water at 70 °C was reported,[2] but we have been unable to repeat this work as published.

Quinolines display a wide range of biological activities and are also present in various biologically active natural products such as 20-(*S*)-camptothecin and luotonin A and F.[3] More specifically, derivatives of 2-alkylquinoline-3-carboxylic acids are currently under investigation as drugs to treat cancer,[4] HIV,[5] and malaria[6] as well as additives for helioprotective ointments.[7] Finally, the patent literature is replete with reports of quinoline-3-carboxylic acid derivatives as drugs for CNS disorders[8] and as herbicides,[9] while the corresponding naphthyridine derivatives have attracted interest as potential anti-HIV agents,[10] antibacterials,[11] antiasthmatics,[12] contrast agents for imaging myocardial perfusion[13] and herbicides.[14]

We have recently reported a synthesis of α-aminonitriles as well as benzo-fused, five-membered heterocycles using a green approach without expensive or corrosive catalysts.[15] In a continuation of our work in this area, we have undertaken the study of a catalyst-free Friedländer reaction. An initial reaction of 2-aminobenzaldehyde (**1a**) with methyl acetoacetate (**2a**) was performed in benzene and the reaction was refluxed for a period of 12 h. A tan solid appeared during the reaction and TLC indicated the complete consumption of starting material with the formation of two products. Analysis of the mixture revealed these products to be quinoline-3-carboxylic acid (**3a**) and its corresponding methyl ester **4a** (Scheme 1). This observation piqued our curiosity, and we decided to investigate the reaction in more detail. The same transformation was repeated at a higher temperature in refluxing toluene (or xylene) for 24 h and showed exclusive formation of acid **3a** in high yield with none of the corresponding ester. To the best of our knowledge, acids have not previously been observed directly from this reaction.[16] Ethyl acetoacetate showed similar reactivity.

Beyond these aromatic solvents, water, acetonitrile, and several cyclic ethers were evaluated as media for the reaction and the results are summarized in Figure 1. Of the solvents examined, toluene and xylene furnished product **3a** in the highest yield and purity. The product, obtained after cooling and filtration, was chromatographically and spectroscopically clean, and further purification was unnecessary.

The results of our study are summarized in Schemes 2–4. Aminobenzaldehydes **1a**[17] and **1b** were reacted with a series of β-ketoesters **2a–f**[18] in toluene at 110 °C for 24 h to give

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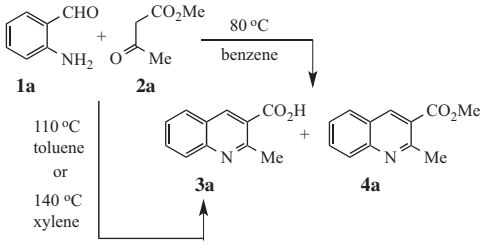



**Scheme 1.** Quinoline formation in aromatic solvents at reflux.

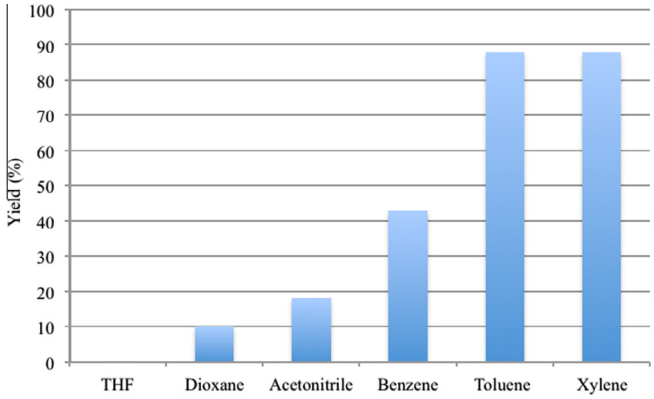
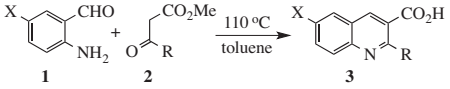



**Figure 1.** Effect of solvent on the yield of product **3a** (the reaction was performed at the reflux temperature of each solvent).

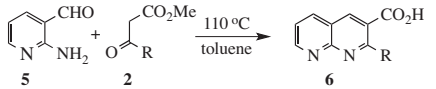



| 1 | 2[a] | 3[a] | Yield (%) of 3 |
|---|---|---|---|
| **a** (X = H) | **a** (R = Me) | **a** (X = H, R = Me) | 88 |
| | **b** (R = Et) | **b** (X = H R = Et) | 94 |
| | **c** (R = *n*-Pr) | **c** (X = H, R = *n*-Pr) | 86 |
| | **d** (R = *i*-Pr) | **d** (X = H, R = *i*-Pr) | 90 |
| | **e** (R = $C_4H_7$) | **e** (X = H, R = $C_4H_7$) | 89 |
| | **f** (R = $CH_2OPh$) | **f** (X = H, R = $CH_2OPh$) | 85 |
| **b** (X = Cl) | **a** (R = Me) | **g** (X = H, R = Me) | 87 |
| | **b** (R = Et) | **h** (X = H R = Et) | 85 |
| | **c** (R = *n*-Pr) | **i** (X = H, R = *n*-Pr) | 90 |
| | **d** (R = *i*-Pr) | **j** (X = H, R = *i*-Pr) | 86 |
| | **e** (R = $C_4H_7$) | **k** (X = H, R = $C_4H_7$) | 90 |

[a] $C_4H_7$ = 3-butenyl

**Scheme 2.** Quinoline-3-carboxylic acids from aldehydes using the Friedländer reaction in refluxing toluene.

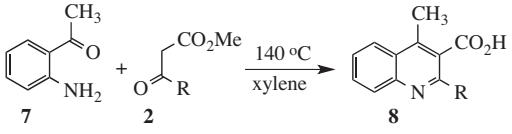
2-alkylquinoline-3-carboxylic acids **3a**–**k** (Scheme 2). The reaction was also applied to 2-aminonicotinaldehyde (**5**) to yield 2-alkyl-1,8-naphthyridine-3-carboxylic acids **6a**–**e** (Scheme 3). During the course of the reaction most of the acid product precipitated from the mixture. When the reaction was complete, the mixture was cooled, concentrated to one-half its volume, and filtered to give the crude product. The isolated solid was washed with 1:1




| 2[a] | Yield (%) of 6 |
|---|---|
| **a** (R = Me) | 87 |
| **b** (R = Et) | 90 |
| **c** (R = *n*-Pr) | 98 |
| **d** (R = *i*-Pr) | 92 |
| **e** (R = $C_4H_7$) | 88 |

[a] $C_4H_7$ = 3-butenyl

**Scheme 3.** 1,8-Naphthyridine-3-carboxylic acids from 2-aminonicotinaldehyde using the Friedländer reaction in refluxing toluene.




| 2[a] | Yield (%) of 8 |
|---|---|
| **a** (R = Me) | 83 |
| **b** (R = Et) | 82 |
| **c** (R = *n*-Pr) | 90 |
| **d** (R = *i*-Pr) | 11 |
| **e** (R = $C_4H_7$) | 78 |
| **f** (R = $CH_2OPh$) | 73 |

[a] $C_4H_7$ = 3-butenyl

**Scheme 4.** Quinoline-3-carboxylic acids from ketones using the Friedländer reaction in refluxing xylene.

ether/hexane and dried to give the final product in pure form. Previous routes to these compounds utilized a Friedländer modification promoted by piperidine in boiling ethanol to prepare the ester, followed by saponification using aqueous NaOH and neutralization with acid.[19] Thus, the resulting products were likely contaminated with base, or the carboxylate or quinolinium salt of the product. For example, compound **6a**, prepared by this sequence,[19] gave a melting point nearly 100 °C lower than that recorded in the current study, strongly suggesting the presence of impurities. The reactions reported in this work were performed in one step, without exogenous catalyst, and delivered the products with no residual contaminants. Compounds prepared by the earlier route[19] were not subjected to NMR analysis to establish their purity. The products reported herein were characterized by $^1H$ and $^{13}C$ NMR (at 90 °C due to low solubility), which verified both their structures and purities.

The current variant of the Friedländer reaction has been further extended to include reactions between 2-aminoacetophenone (**7**) and β-ketoesters (Scheme 4). In these cases, the cyclizations were sluggish in refluxing toluene at 110 °C, and often failed to proceed to completion. Therefore, the conditions were modified to use refluxing xylene at 140 °C where the reaction occurred more efficiently. Most products were isolated in high yields with the exception of **8d** (R = *i*-Pr), indicating that the reaction is subject to steric limitations. To date, there appear to be relatively few direct syntheses of 2,4-dialkylquinoline-3-carboxylic acids.[16,20]

Attempts to expand the scope of this reaction to other active methylene substrates were generally not successful without added

catalyst.[21] Thus, we believe that the current reaction is self-catalyzed by the carboxylic acid product. This hypothesis was supported by the observation that the reaction was slow to start but gradually accelerated to completion over the 24 h reaction period. At toluene reflux temperature, the reaction likely proceeds to initially form the quinoline-3-carboxylic ester. At this temperature, a small amount of the ester is hydrolyzed by water produced during the condensation, which could be initially catalyzed by traces of acid in the β-ketoesters.[22] The product acid is only sparingly soluble in aromatic hydrocarbon solvents. Thus, the concentration in solution remains low, but is sufficient to catalyze further hydrolysis of the initial ester product. Since the methanol produced is volatile and present in low concentration, no re-esterification is observed. Finally, due to the high temperature of the reaction and the volatility of the reactants, the mass balance of reactions involving low molecular weight substrates suffers some loss unless precautions are taken to cool the reaction before removing aliquots for TLC and other analyses.

In summary, we have demonstrated that the Friedländer reaction of 2-aminoaryl- aldehydes and ketones with β-ketoesters can be performed in the absence of exogenous catalyst to give high yields of 2-alkylquinoline-, 2-alkyl-1,8-naphthyridine-, and 2,4-dialkylquinoline-3-carboxylic acids. The method is highly reliable and avoids the use of additives, which can contaminate the final products. The products, prepared as described here, are isolated directly from the reaction mixture and require no further purification.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.04.010.

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