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Oxalic Acid: An Efficient and Cost-Effective Organic Catalyst for the *Friedländer* Quinoline Synthesis under Solvent-Free Conditions

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Summary. Oxalic acid is used as an efficient catalyst in the condensation of 2-aminoaryl ketones with carbonyl compounds leading to the formation of quinolines in excellent yields under solvent-free conditions. This methodology offers significant improvements for the synthesis of quinolines with regard to the yield of products, simplicity in operation, inexpensive reagents, and green aspects by avoiding toxic catalysts and solvents.

Keywords. Heterocycle; *Friedländer* synthesis; Quinoline; Solvent-free.

Introduction

Quinolines and their derivatives are very important compounds because of their wide occurrence in natural products [1] and biologically active compounds [2]. A large variety of quinolines have displayed interesting physiological activities and found attractive applications as pharmaceuticals and agrochemicals, as well as being general synthesis building blocks [1b]. Many synthesis methods such as *Skraup*, *Doebner–von Miller*, *Friedländer*, and *Combes* reactions have been developed for the preparation of quinolines [3], but due to their great importance, the development of novel synthesis approaches remains an active research area [4]. Amongst various methodologies reported for the preparation of quinolines, *Friedländer* annulation is one of the simplest and most straightforward protocols. *Friedländer* synthesis involves a condensation followed by a cyclodehydration between an aromatic 2-aminoaldehyde or ketone and a carbonyl compound containing an activated α-CH acid functionality. The *Friedländer* reaction can occur under base [2c, d, 3d, 5], *Brønsted* acid [3d, 5a, 6], *Lewis* acid [7], inorganic salt [8], or ionic liquid-catalyzed [9] conditions. Generally, better product yields have been achieved for the acid-catalyzed *Friedländer* reaction [5a]. Most of the reported protocols for the synthesis of quinolines suffered from the use of harmful organic solvents, high reaction temperatures, prolonged reaction times, low product yields, and complicated work-up procedures. Thus, the development of simple, convenient, and environmentally friendly approaches for the synthesis of quinolines is still demanding.

As part of a continuing effort in our laboratory toward the development of new methods for the expeditious synthesis of biologically relevant heterocyclic compounds [10], we became interested in the possibility of developing an efficient method to construct the quinoline scaffold.

Results and Discussion

Initial study was performed by treatment of 2-aminobenzophenone with ethyl acetoacetate under solvent-free conditions in the presence of a catalytic amount of oxalic acid (10 mol%) at 80°C. To our delight, we observed the formation of ethyl 2-methyl-4-phenylquinoline-3-carboxylate. Complete conversion and 91% isolated yield was obtained after

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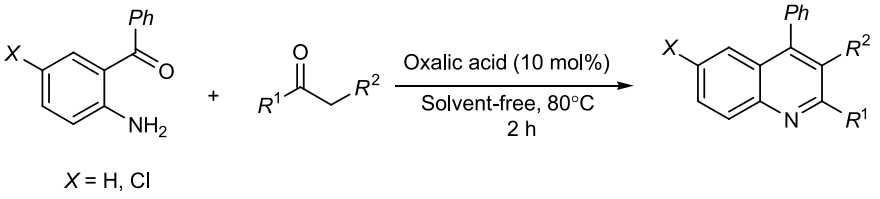
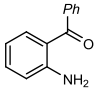
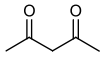
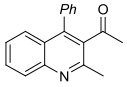
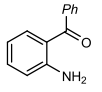
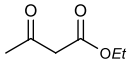
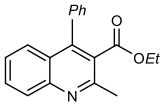
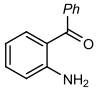
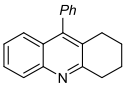
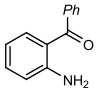
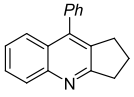
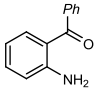
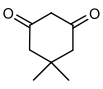
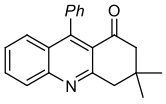
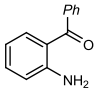
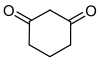
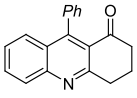
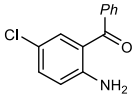
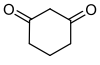
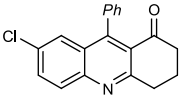
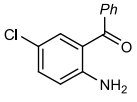
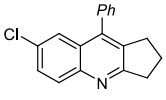
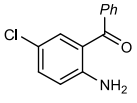
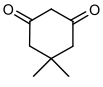
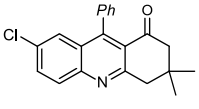
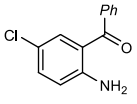
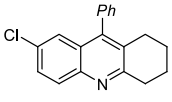
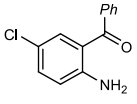
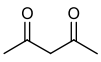
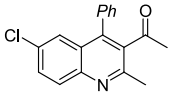


Scheme 1

Table 1. *Friedländer* synthesis of quinolines in the presence of oxalic acid under solvent-free condition at 80°C for 2 h

Entry	2-Aminoaryl ketone	CH-acid	Product	Yield/%[a]	Mp/°C	Ref.[b]
1				90	111–112	[6g]
2				91	100–101	[6g]
3				94	156–157	[6f]
4				90	130–132	[6f]
5				89	190–192	[6f]
6				92	155–156	[6f]
7				89	185–186	[9]
8				88	106–107	[9]
9				92	208–209	[6g]
10				95	164–165	[6g]
11				91	150–151	[9]

[a] Isolated yield

[b] The products were characterized by comparison of their spectroscopic and physical data with authentic samples synthesized by the procedures given in the references

2 h. Among the conditions (*Et*OH, *THF*, H_2O, *Me*CN, toluene, and solvent-free) screened, solvent-free was demonstrated as the best condition. Further studies showed that 1–5 mol% of catalyst were also efficient in this reaction at the expense of reaction time (5 mol%: 5 h, 90% yield; 1 mol%, 1 d, 88% yield). To demonstrate the generality of this method, we next investigated the scope of this reaction (Scheme 1) and the results are summarized in Table 1.

As shown in Table 1, this method is equally effective for both cyclic and acyclic ketones. Substituted 2-aminoaryl ketones, such as 2-aminobenzophenone and 2-amino-5-chlorobenzophenone reacted smoothly with methylene ketones to produce a range of quinoline derivatives. Complete conversion and good to excellent isolated yields were observed for all substrates employed. This reaction is very clean and free from side reactions such as self-condensation of ketones, which is normally observed under basic conditions. In the absence of catalyst, the reaction did not yield any product even after long reaction times. Interestingly, cyclic ketones, such as cyclopentanone, cyclohexanone, dimedone, and 1,3-cyclohexadione also underwent smooth condensation with 2-aminoaryl ketones to afford the respective tricyclic quinolines (Table 1, entries 3–10).

In conclusion, we describe an efficient route for the synthesis of quinolines and polycyclic quinolines utilizing oxalic acid as an organic catalyst *via Friedländer* annulation. This method not only provides an excellent complement to quinoline synthesis *via Friedländer* annulation, but also avoids the use of hazardous acids or bases and harsh reaction conditions. The advantages of this method include good substrate generality, the use of inexpensive reagents and catalyst under mild conditions, and experimental operational ease. Reactions employing oxalic acid as a catalyst for other organic transformations are currently under investigation in our research group, and will be reported in due course.

Experimental

Melting points were obtained in open capillary tubes and were measured on an electrothermal 9200 apparatus. Mass spectra were recorded on a Shimadzu QP 1100 BX mass spectrometer. IR spectra were recorded on KBr pellets on a Shimadzu IR-470 spectrophotometer. ^1H and ^{13}C NMR spectra were determined on a Bruker 300 DRX Avance instrument at 300 and 75 MHz.

General Procedure for the Synthesis of Quinolines

A mixture of 1.0 mmol 2-aminoaryl ketone, 1.1 mmol α-CH acid, and 0.013 g oxalic acid (0.1 mmol) was heated under solvent-free conditions with stirring at 80°C for 2 h. After completion of the reaction as indicated by TLC (eluent: *n*-hexane/ethyl acetate = 2/1) the reaction mixture was washed with $2 \times 10\,cm^3$ H_2O, and filtered. The crude solid product was recrystallised from ethanol.

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