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Benign and highly efficient synthesis of quinolines from 2-aminoarylketone or 2-aminoarylaldehyde and carbonyl compounds mediated by hydrochloric acid in water

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Abstract—An environmentally friendly and highly efficient procedure for the preparation of substituted quinoline derivatives was developed by a simple Friedländer reaction of 2-aminoarylketone or 2-aminoarylaldehyde with carbonyl compounds in the presence of hydrochloric acid utilizing water as the solvent.

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 synthetic building blocks.[1b] Many synthetic methods such as Skraup, Doebner–von Miller, Friedländer, Combes reactions have been developed for the preparation of quinolines,[3] but due to their great importance, the development of novel synthetic 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 an aldehyde or ketone with an α-methylene functionality. Friedländer reaction can occur under base-,[2c,d,3d,5] Brønsted acids-,[3d,5a,6] Lewis acid-,[7] inorganic salt-,[8] or ionic liquid-catalyzed[9] conditions. Generally, better product yields were achieved for the acid-catalyzed Friedländer reaction.[5a] Most of the reported protocols for the synthesis of quinolines suffered from the usage 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.

In recent years, organic reactions in aqueous media[10] have acquired tremendous interest in organic synthesis because the use of water as a reaction medium has a number of advantages such as the cheapest solvent available on earth, being non-hazardous and non-toxic to the environment, easy product isolation by simple phase separation. These aqueous reactions are more sophisticated and also more environmentally benign if they can be carried out in the absence of any metal catalysts. Although Brønsted acids such as sulfuric acid,[5a,6c,d] hydrochloric acid,[5a] and *p*-toluenesulfonic acid[6a] have been employed for the Friedländer reaction, there are some drawbacks associated with these systems. For example, the sulfuric acid protocol[5a,6c,d] involved the utilization of excessive refluxing acetic acid as the solvent, while the hydrochloric acid method[5a] required a reaction temperature as high as 200 °C. To the best of our knowledge, there has been no report on the Brønsted acid-catalyzed Friedländer reaction in pure water. In the continuation of our interest in organic reactions in water,[11] herein we report a simple, highly efficient and ecofriendly process for the preparation of the biologically important quinolines through the

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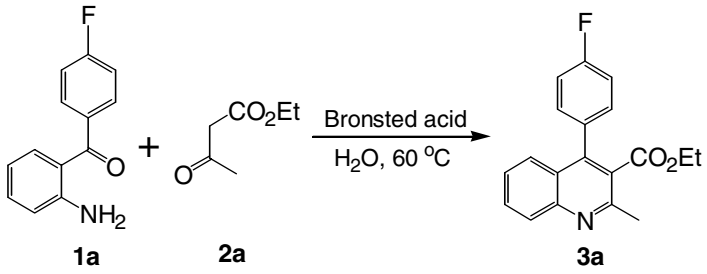


Scheme 1.

Friedländer reaction in the presence of a Brønsted acid using pure water as the reaction media.

2-Amino-4′-fluoro-benzophenone (**1a**) has been used as the starting material to synthesize quinoline derivatives, which can functionalize as HMG-CoA reductase inhibitors.[6a,d] We therefore first chose **1a** and searched for the best Brønsted acid for its reaction with ethyl acetoacetate (**2a**) to afford quinoline **3a** in water at 60 °C (Scheme 1).

Typically, to a mixture of **1a** (1.0 mmol) and **2a** (1.2 mmol) was added 1 mL of water and the desired amount of acid. The reaction mixture was stirred at 60 °C for a designated time. After completion of the reaction, the resulting suspension was neutralized with 1 mL of 1 N NaOH. Usual work-up afforded product **3a**. The yields, reaction times and amounts of the used Brønsted acid for the Friedländer reaction of **1a** with **2a** were listed in Table 1.

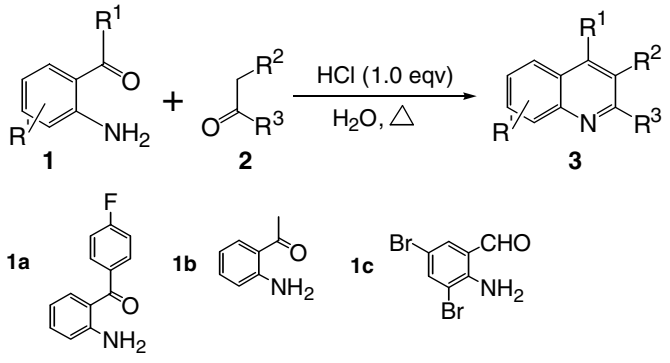
Table 1. The reaction conditions and yields for the synthesis of quinoline **3a** with different Brønsted acid[a]

Entry	Brønsted acid	Equivalent	Time (h)	Yield (%)
1	None	—	6	Trace
2	HCl	0.1	6	12
3	HCl	0.2	6	22
4	HCl	0.3	6	38
5	HCl	0.4	6	62
6	HCl	0.5	6	78
7	HCl	0.8	0.5	86
8	HCl	1.0	0.5	96
9	H_2SO_4	1.0	0.5	93
10	H_3PO_4	1.0	3	36
11	H_3PO_4	1.0	12	90
12	CF_3CO_2H	1.0	0.5	91
13	CH_3CO_2H	1.0	6	16
14	*p*-TsOH	1.0	6	62

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol) and H_2O (1 mL); reaction temperature: 60 °C.

From Table 1 it can be seen that all the employed Brønsted acids can promote the reaction to a certain extent, however, the reaction hardly proceeded in the absence of Brønsted acids even after long reaction time. In our study, the effect of the amount of the utilized Brønsted acid on the yield of product **3a** was first examined. Take hydrochloric acid as an example, we found that the increase of the amount of the catalyst afforded higher yield of product **3a** (entries 1–8). When 1.0 equiv of hydrochloric acid was used, the reaction proceeded smoothly and efficiently with almost quantitative yield (entry 8). Among the investigated acids, hydrochloric acid appeared to be the best catalyst for this reaction, showing the fastest reaction rate and the highest yield. Although sulfuric acid (entry 9) and trifluoroacetic acid (entry 12) exhibited similar catalytic activity when compared with hydrochloric acid, the latter was preferred because of its higher safety, more environmental friendliness and lower price. The above results prompted us to select 1.0 equiv of hydrochloric acid as the catalyst for further study.

Reagents **1a** and **2a** were then extended to other structurally varied substrates to examine the scope and generality of the HCl-catalyzed Friedländer reaction. To our delight, we found that **1a** could be replaced by 2-aminoacetophenone (**1b**) or 2-amino-3,5-dibromobenzaldehyde (**1c**), and α-methylene ketones could be extended from ethyl acetoacetate (**2a**) to other β-keto-

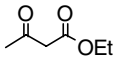
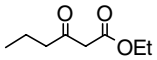
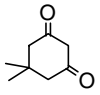
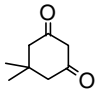
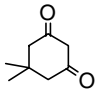


Scheme 2.

ester such as ethyl butyrylacetate (**2b**), simple cyclic ketones such as cyclopentanone (**2d**) and cyclohexanone (**2e**), acyclic 1,3-diketone such as 2,4-pentanedione (**2c**), and cyclic 1,3-diketones such as 1,3-cyclohexanedione (**2f**) and 5,5-dimethyl-1,3-cyclohexanedione (**2g**). A library synthesis of quinoline **3** was successfully obtained in very high yields through Friedländer condensation of **1a–c** with various carbonyl compounds **2a–g** in the presence of hydrochloric acid in pure water (Scheme 2).

The experimental procedure was very simple.[12] In most cases, the products were isolated by simple filtration in practically pure form. The current method was fairly

Table 2. Reaction times, yields and melting points of quinolines **3** by the HCl-catalyzed Friedländer reaction in water[a]

Entry	Substrate **1**	Substrate **2**	Quinoline **3**	Reaction time (h)	Yield (%)[b]	Mp (Lit.) (°C)
1	**1a**	 **2a**	**3a**	0.5	96	118–120 (120–121)[13]
2	**1a**	 **2b**	**3b**	1.5	92	Oil (oil)[13]
3	**1a**	 **2c**	**3c**	0.5	94 (95)	140–142
4	**1a**	 **2d**	**3d**	1	91	139–141
5	**1a**	 **2e**	**3e**	1	91 (93)	172–174
6	**1a**	 **2f**	**3f**	0.5	93 (95)	170–172
7	**1a**	 **2g**	**3g**	0.5	95 (97)	211–213
8	**1b**	 **2c**	**3h**	1	92	Oil (oil)[9]
9	**1b**	 **2d**	**3i**[c]	5	85	58–60 (60)[9]
10	**1b**	 **2e**	**3j**[c]	2	92	75–77 (78)[9]
11	**1b**	 **2f**	**3k**	0.5	94	65–66 (68)[14]
12	**1b**	 **2g**	**3l**	0.5	95 (98)	105–106
13	**1c**	 **2c**	**3m**[c]	1.5	92 (96)	162–164
14	**1c**	 **2e**	**3n**[c]	6	90	106–108 (105–106)[15]
15	**1c**	 **2f**	**3o**[c]	2	94 (98)	176–178
16	**1c**	 **2g**	**3p**[c]	2	95 (96)	164–166

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.2 mmol), HCl (1.0 mmol) and H_2O (1 mL); reactions conducted at 60 °C unless where noted. All products were fully characterized by IR, ^1H NMR, ^{13}C NMR and HRMS spectral data.

[b] Isolated yields, and those in the parentheses refer to reactions at 10 mmol scale.

[c] Reactions conducted at 90 °C.

general, clean, rapid, and efficient, providing an expeditious access to the preparation of various quinolines.

The reaction times, yields and melting points of quinolines **3** for the aqueous reaction of 2-aminoarylketone or 2-aminoarylaldehyde **1** with α-methylene ketone **2** in a molar ratio of 1:1.2 in the presence of 1.0 equiv of hydrochloric acid were collected in Table 2.

As seen from Table 2, the current protocol can be applied to 2-aminoarylketones (**1a**,**b**) or 2-aminoarylaldehyde (**1c**) and a wide range of α-methylene ketones such as β-ketoester, cyclic ketones, acyclic and cyclic 1,3-diketones, and tolerate the presence of halogen, ketone and ester groups. Interestingly, cyclic ketones (**2d**–**g**) afforded the corresponding tricyclic quinolines.

In conclusion, we have demonstrated that a straightforward, highly efficient and cost-effective synthesis of biologically active quinolines can be achieved by HCl-catalyzed Friedländer reaction in pure water. The current method presents a very appealing synthetic process for quinolines because of the following advantages: (1) use of water as environmentally benign reaction media, (2) use of very cheap and readily available hydrochloric acid, (3) very high yield and short reaction time, (4) straightforward and easy work-up procedure and (5) no use of any metal catalyst or phase-transfer catalyst or surfactant.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.12.053.

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12. Typical procedure for the synthesis of quinoline **3**: To a mixture of 2-aminoarylketone or 2-aminoarylaldehyde **1** (1.0 mmol) and α-methylene ketone **2** (1.2 mmol), 1 mL of 1 N HCl aqueous solution was added. The reaction mixture was stirred at 60 °C (or 90 °C) for a designated time. After completion of the reaction (monitored by TLC), the resulting suspension was neutralized with 1 mL of 1 N NaOH. The solid was collected by Büchner filtration, washed with water (6 mL × 3), air-dried to give the product as white or slightly yellow powder. The solid product was further purified by recrystallization when necessary. For the oil or low-melting-point products, the purification procedure was different. The neutralized mixture was extracted with ethyl acetate (5 mL × 2). The organic layer was separated out and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded the crude product as slightly yellow oil, which was further purified by column chromatography on silica gel.
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