Friedländer Synthesis of Poly-Substituted Quinolines in the Presence of Triethylammonium Hydrogen Sulfate $[Et_3NH][HSO_4]$ as a Highly Efficient, and Cost Effective Acidic Ionic Liquid Catalyst

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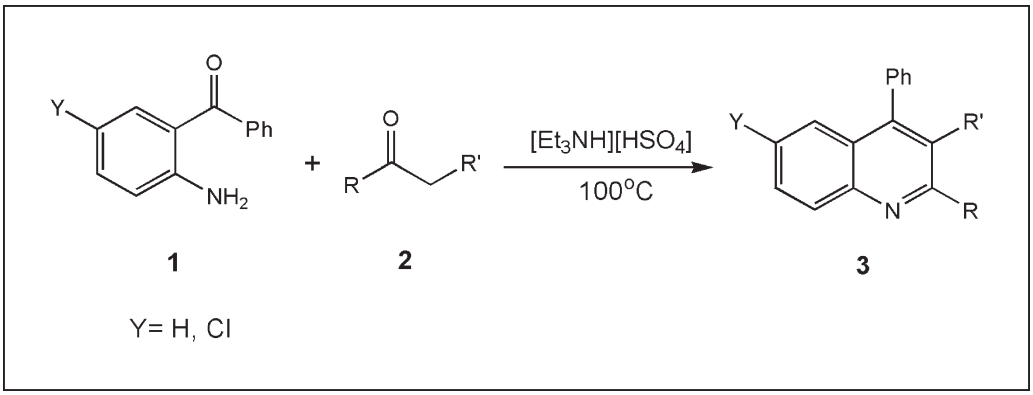

A rapid and an efficient method for the preparation of a variety of substituted quinolines has been developed through the reactions of *o*-aminoarylketones with carbonyl compounds containing a reactive α-methylene moiety in the presence of molten $[Et_3NH][HSO_4]$ under solvent-free conditions in high yields.

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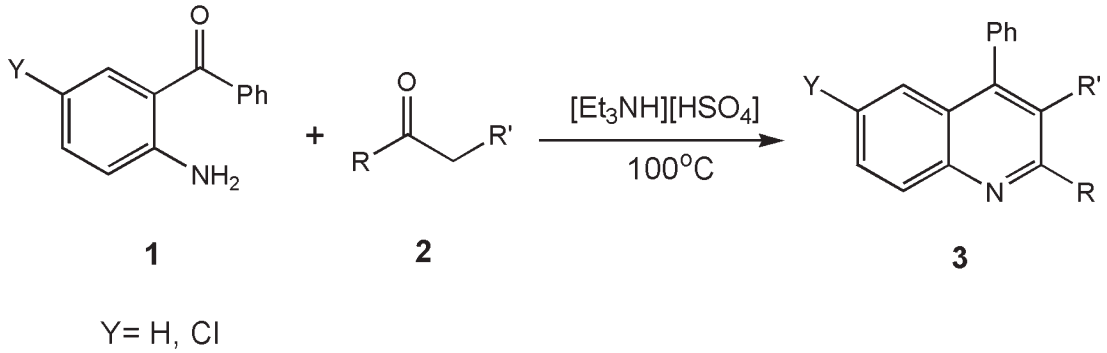
INTRODUCTION

The majority of chemical transformations are done in solution to more efficiently control the heat flow of exothermic and endothermic reactions. In addition, polar reactions that proceed *via* polar or ionic intermediates or transition states are promoted by polar solvents due to a strong stabilization by solvation. The organic reactions that can be performed in the solid state [1] or solvent-free are limited. Several solvents used for reactions in the laboratory and industry belong to the group of volatile organic compounds. Solvents like chlorinated hydrocarbons derived from methane, ethane, and propane are volatile and chemically relatively stable; they are harmful to the environment. Because of their persistence, they accumulate in the atmosphere and contribute to ozone depletion and to smog in urban areas [2]. To overcome this concern of synthetic organic chemistry, new ''green solvents'' have been developed, which are slowly finding their way into chemical laboratories and industries. The new ''green'' solvents include supercritical carbon dioxide, ionic liquids, water, and fluorous biphasic mixtures [3].

Ionic liquids have attracted considerable interest as environmentally friendly or ''green'' alternates to conventional molecular organic solvents they have very low vapor pressure and are nonexplosive and thermally stable in a wide temperature range [4]. Furthermore, they are often immiscible with organic solvents because of their polar nature and may therefore be used in biphasic systems. Now ionic liquids have been used as environmentally benign solvents or catalysts for a number of chemical processes [5], such as separations [6], reactions [7], homogeneous two phase catalysis [8], and polymerizations [9]. The current emphasis on alternate reaction media is motivated by the need for efficient methods for replacing toxic or hazardous solvents and catalysts. The use of ionic liquids as alternate reaction media may offer a convenient solution to both the solvent emission and the catalyst recycling problem [10].

Notwithstanding the unique advantages of ionic liquids as reaction media and catalysts, currently they have not been widely applied in industry. The reason for this is probably related to the high cost of ionic liquids, the difficulty in separation or recycling, the paucity of data with regard to their toxicity and biodegradability, and so on. Recently, some new ionic liquids have been prepared *via* a simple and atomeconomic acid–base neutralization reaction. For example, Noda et al. [11] reported the preparation and application of the Brønsted acid–base ionic liquids from imidazole and bis(trifluoromethanesulfonyl) amide. Han and coworkers

Scheme 1. $[Et_3NH][HSO_4]$-Catalyzed Friedländer synthesis of quinolines.



[12] prepared new ionic liquids by neutralization of 1, 1, 3, 3- tetramethylguanidine with different acids. However, the preparation of simple ammonium ionic liquid *via* acid–base neutralization from cheap amine and acid is absence in the literature.

Quinolines and their derivatives are very important biological compounds that occur widely in natural products. Some members of this family have displayed interesting physiological activities and found attractive applications in medicinal chemistry, being used as antimalarial [13], antibacterial [14], anti-inflammatory [15], antihypertensive [16], antiplatelet agents, and as tyrosine kinase inhibiting agents [17]. In addition, quinolines are valuable synthons used in a variety of nanostructures and mesostructures with enhanced electronic and photonic functions [18]. Also, quinolines have been used in the study of bioorganic and bioorganometallic processes [19]. There has been tremendous interest in developing efficient methods for quinoline synthesis [20]. Among these methods, the Friedländer annulation is still one of the most simple and straightforward procedures for the synthesis of poly-substituted quinolines.

The Friedländer quinoline synthesis involves a condensation reaction between an aromatic ortho-aminoaryl ketone or aldehyde with an aldehyde or ketone containing an α-methylene group, and then a cyclodehydration. This reaction is generally carried out by refluxing either an aqueous or an alcoholic solution of reactants in the presence of a base at high temperature, 150–220°C, in the absence of a catalyst. However, under basic or thermal-catalysis conditions, *ortho*-aminobenzophenone does not react with simple ketones, such as cyclohexanone and β-keto esters. Brönsted acid catalysts such as hydrochloric acid, sulfuric acid, *p*-toluenesulfonic acid, and polyphosphoric acid have been widely used [21]. Also, modified methods, using Lewis acid [22] and inorganic salt catalysts [21], ionic liquids [23], microwave conditions [24], and molecular iodine [25] have been reported for this reaction. Many of these procedures have significant drawbacks such as low yields of the products, long reaction times, and harsh reaction conditions. Moreover, this reaction is usually carried out in polar and in aprotic solvents such as acetonitrile, tetrahydrofuran (THF), dimethyl sulfoxide (DMSO), and dimethylformamide (DMF) leading to tedious work-up procedures. Thus, the development of simple, convenient, and environmentally benign methods for the synthesis of quinolines is still required. To overcome these problems, herein, we describe the utility of $[Et_3NH][HSO_4]$ in molten state (Scheme 1), which is a mild acidic, nonvolatile, and noncorrosive ionic liquid, as an efficient Brönsted acid catalyst in solvent-free conditions for the Friedländer reaction.

RESULTS AND DISCUSSION

Initial study was performed by treatment of 2-amino-5-chlorobenzophenone with ethyl acetoacetate under solvent-free conditions in the presence of $[Et_3NH][HSO_4]$. Best results were obtained with molar ratio 1:1.1:2 for 2-amino-5-chlorobenzophenone, ethyl acetoacetate, and $[Et_3NH][HSO_4]$ at 100°C. To demonstrate the generality of this method, we next investigated the scope of this reaction, and the results are summarized in Table 1.

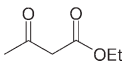
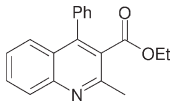
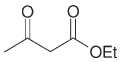
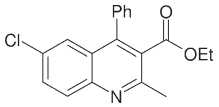
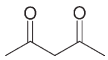
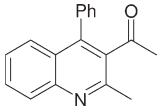
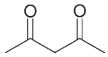
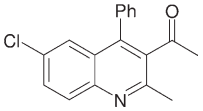
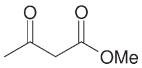
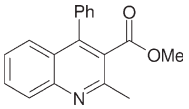
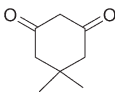
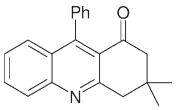
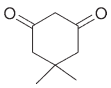
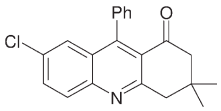
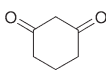
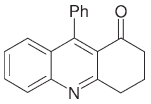
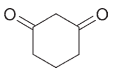
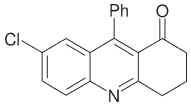
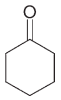
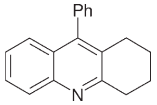
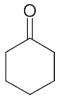
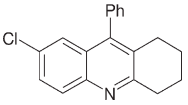
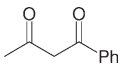
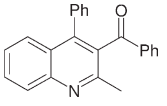
As shown in Table 1, this method is equally effective for both cyclic and acyclic ketones. Substituted 2-aminoaryl ketones, such as 2-aminobenzophenone and 2-amino-5-chlorobenzophenone reacted smoothly with methylene ketones to produce a range of quinoline derivatives. This reaction is very clean and free from side reactions such as self-condensation of ketones, which is normally observed under basic conditions. Also, simple experimental procedure and easy workup is another advantage of this method. A reasonable pathway for the reaction of 2-amino arylketone with carbonyl compounds conducted in the presence of $[Et_3NH][HSO_4]$ is presented by Scheme 2.

EXPERIMENTAL

All chemicals were purchased from Merck chemical company and were used without further purification. All products are known and were identified by comparison of their spectral data and physical properties with those of the authentic

Table 1

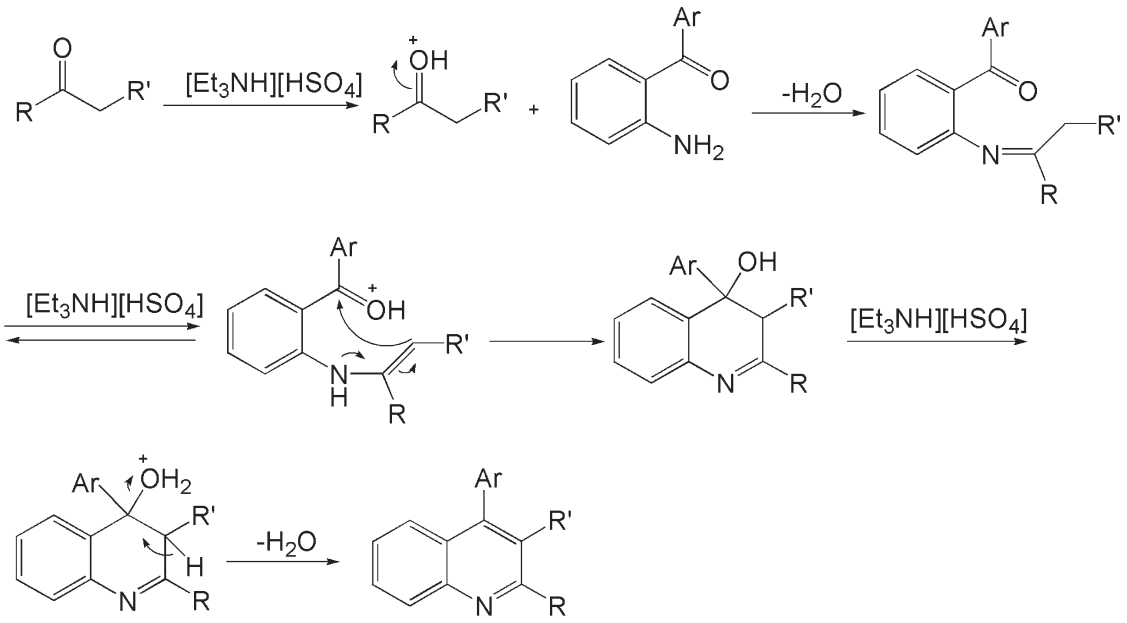
$[Et_3NH][HSO_4]$-Catalyzed Fridedländer synthesis of quinolines under solvent-free conditions at 100°C.

Entry	Y	Ketone **2**	Product **3**	Time (min)	Yield (%)
3a	H			40	93
3b	Cl			20	88
3c	H			25	92
3d	Cl			30	85
3e	H			47	93
3f	H			25	80
3g	Cl			20	80
3h	H			25	89
3i	Cl			15	94
3j	H			45	81
3k	Cl			30	93
3l	H			70	65

samples. Melting points were obtained in open capillary tubes and were measured on a Gallenkamp apparatus. IR spectra were recorded using KBr pellets on a Bruker IR spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were determined on a Bruker 500-DRX Avance instrument at 500 and 125 MHz.

General procedure for preparation of substituted quinolines. 2-Amino aryl ketone **1** (1 mmol) was added to 1.1 mmol ketone **2** and 2.0 mmol $[Et_3NH][HSO_4]$. The reaction mixture was stirred at 100°C for appropriate time. After completion of the reaction (monitored by thin layer chromatography (TLC)),

Scheme 2. A reasonable mechanism for the reaction of 2-amino arylketones with carbonyl compounds.



10 mL of ethanol was added. The mixture was poured into cold water, and resulting precipitate was recrystalyzed from ethanol to give pure product **3**.

Ethyl-6-chloro-2-methyl-4-phenylquinoline-3-carboxylate (3b). Mp (°C): 90; IR (KBr): 3078, 2977, 1720 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ (ppm) 0.98 (t, J = 7.0 Hz, 3H, CH_3), 2.81 (s, 3H, CH_3), 4.10 (q, J = 7.0 Hz, 2H, CH_2), 7.37 (m, 2H, Ar-H), 7.52 (m, 3H, Ar-H), 7.57 (s, 1H, Ar-H), 7.68 (d, J = 8.8 Hz, 1H, Ar-H), 8.05 (d, J = 8.8 Hz, 1H, Ar-H). ^{13}C-NMR ($CDCl_3$): δ (ppm) 14.0, 24.1, 61.9, 125.7, 126.4, 128.6, 128.9, 129.2, 129.7, 130.9, 131.6, 132.8, 135.4, 146.0, 147.0, 155.4, 168.5.

1-(6-Chloro-2-methyl-4-phenylquinoline-3-yl)ethanone (3d). Mp (°C): 150; IR (KBr): 3051, 2927, 1700 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ (ppm) 2.02 (s, 3H, CH_3), 2.71 (s, 3H, CH_3), 7.36 (d, J = 2.3Hz, 1H, Ar-H), 7.37 (d, J = 3.5 Hz, 1H, Ar-H), 7.54–7.56 (m, 3H, Ar-H), 7.60 (d, J = 2.2 Hz, 1H, Ar-H), 7.67 (dd, J = 2.3 Hz, J = 8.9 Hz, 1H, Ar-H), 8.04 (d, J = 8.9 Hz, 1H, Ar-H). ^{13}C-NMR ($CDCl_3$): δ (ppm) 24.2, 32.2, 125.3, 126.3, 129.4, 129.7, 130.4, 130.9, 131.4, 132.9, 134.9, 135.9, 143.6, 146.3, 154.4, 205.6.

3, 4-Dihydro-3, 3-dimethyl-9-phenylacridine-1(2H)-one (3f). Mp (°C): 184; IR (KBr): 3066, 2938, 16870 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ (ppm) 1.19 (s, 6H, $2CH_3$), 2.60 (s, 2H, CH_2), 3.31 (s, 2H, CH_2), 7.21–7.22 (m, 2H, Ar-H), 7.44 (t, J = 8.2 Hz, 1H, Ar-H), 7.50–7.55 (m, 4H, Ar-H), 7.80 (t, J = 6.8 Hz, 1H, Ar-H), 8.11 (d, J = 8.4 Hz, 1H, Ar-H). ^{13}C-NMR ($CDCl_3$): δ (ppm) 28.8, 32.7, 48.8, 54.7, 123.2, 126.9, 127.8, 127.9, 128.5, 128.5, 128.7, 128.9, 132.1, 138.0, 149.4, 151.0, 161.5, 198.3.

CONCLUSION

In conclusion, we have reported an efficient procedure for the synthesis of quinoline derivatives using $[Et_3NH][HSO_4]$ as nontoxic, noncorrosive, and homogeneous catalyst in molten state. The method offers advantages such as clean reaction, high yields of products, short reaction times, and use of various substrates, which make it a useful and an attractive strategy for the synthesis of quinoline derivatives.

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