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A Novel Green Synthesis of Quinolines through Acid-catalyzed Friedlander Reaction in Ionic Liquids

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Abstract: Quinoline derivatives were efficiently prepared through acid-catalyzed Friedlander reaction in ionic liquid ([bmim][BF_4]). It is shown that the proposed method is operationally simple and environmentally benign in that the reaction media and the catalyst can be recovered and be reused effectively for at least four times.

Keywords: Quinoline derivatives, Friedlander synthesis, ionic liquid.

The quinoline ring system is an important structural unit in naturally occurring quinoline alkaloids, therapeutics, and synthetic analogues with interesting biological activities[1]. Therefore, the development of new and efficient synthetic routes to the quinoline ring system is of interest in both synthetic organic and medicinal chemistry. Versatile methods for the synthesis of the quinoline ring system have been developed[2]. However, most of these methods are not fully satisfactory with regard to yield, reaction conditions, generality and operational simplicity. Thus, a simple, general and efficient procedure is still in demand for the synthesis of this important heterocycle.

As one of the most frequently used pathway to quinoline derivatives, the Friedlander synthesis is an acid or base catalyzed condensation followed by a cyclodehydration between an aromatic 2-aminoaldehyde or ketone with the carbonyl compound containing a reactive α-methlene group[3]. It has been reported that drops of concentrated sulfuric acid or 6 mol/L hydrochloric acid can be used as efficient catalysts in the Friedlander condensation procedure[4]. With this method, various structurally varied substrates can give the corresponding quinoline products in moderate to high yields. Unfortunately, this method involved the utilization of excessive glacial acetic acid as solvent or necessitated a metal bath to maintain the reaction temperature at as high as 200°C, thus making this method unsuitable for an up-scaling process.

Ionic liquids have recently been found to be excellent environmentally benign solvents for a variety of reactions[5]. These liquids offer an attractive alternative to conventional organic solvents in that they are non-volatile, non-flammable, non-explosive,

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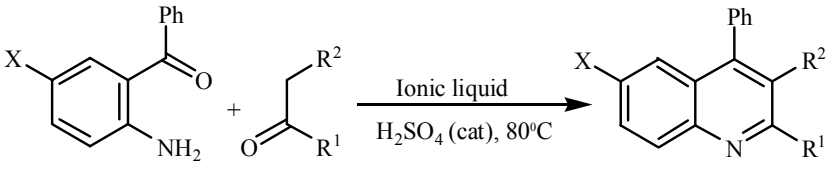
Scheme 1



1 **2** **3**

Table 1 Synthesis of quinoline derivatives through Friedlander reaction in ionic liquid.

Entry	X	R^1	R^2	Reaction time (h)	Products	Yield (%)[a]
1	H	C_6H_5	H	5	**3a**	77, 67[b]
2	H	4-BrC_6H_4	H	5	**3b**	82
3	H	4-$NO_2C_6H_4$	H	4	**3c**	86
4	H	CH_3	H	8	**3d**	72[c]
5	Cl	C_6H_5	H	5	**3e**	75
6	Cl	4-$CH_3C_6H_4$	H	5	**3f**	72
7	Cl	4-ClC_6H_4	H	5	**3g**	78
8	Cl	4-BrC_6H_4	H	5	**3h**	80
9	Cl	4-$NO_2C_6H_4$	H	4	**3i**	88
10	Cl	CH_3	H	8	**3j**	73[c]

a) Isolated yields; b) yield reported in ref. **4**; c) reaction temperature is 40°C.

and can be recycled. In line with our research programme in using ionic liquid as novel reaction media in organic reactions[6], herein we report a novel and efficient procedure for the preparation of quinolines catalyzed by sulfuric acid in ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) (showed in **Scheme 1**).

In a typical experimental procedure, a solution of 2-aminobenzophenone (1 mmol) and acetophenone (1 mmol) in [bmim][BF_4] (2 mL) was heated at 80°C in the presence of 2 drops of concentrated sulfuric acid for a certain period of time as required to complete the reaction (monitored by TLC). Then, the product was obtained by simple extraction with diethyl ether and subsequent purification through a silica gel column. The yield of the product was found to be higher than in the case where glacial acetic acid was used as the solvent[4] (entry 1, **Table 1**).

From **Table 1**, we can see that a wide range of ketones including aliphatic and aromatic-aliphatic ketones which contain a reactive α-methylene group can undergo smooth condensation with 2-aminobenzophenones to give substituted quinolines in short reaction time and with reasonably high yields. The products were characterized by ^1H NMR, IR and MS. In addition, after extraction of the product with diethyl ether, the solvent [bmim][BF_4] and the catalyst could be recovered easily by drying at 80°C under reduced pressure for several hours and could be reused for at least four times without obvious decrease of yield.

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