A Novel Preparation of 4-Phenylquinoline Derivatives in Ionic Liquids

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A novel preparation of 4-phenylquinoline derivatives through acid-catalyzed Friedländer reaction in ionic liquid ([bmim][BF_4]) is described. The preparative procedure presented in this paper is operationally simple and environmentally benign. The reaction media and the catalyst used can be recovered and reused for at least four times without loss in the catalytic activity.

Keywords: Friedländer reaction; Ionic liquid; Quinoline derivatives.

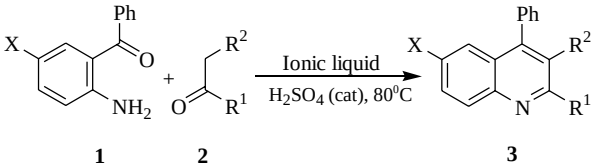
INTRODUCTION

The synthesis of quinoline and its derivatives has been of considerable interest to organic and medicinal chemistry for many years since a large number of natural products[1] and drugs[2] contain this heterocyclic nucleus. For instance, a quinoline subunit is present in a new class of peptidoleukotriene LTD_4 antagonists developed as antiasthmatic therapeutics,[3] in a series of potent 5-lipoxigenase inhibitors and also in some new anti-inflamatory derivatives.[4] Due to their importance, many methods have already been developed for the synthesis of quinolines. 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 pathways to quinoline derivatives, the Friedländer synthesis is an acid or base catalyzed condensation followed by a cyclodehydration between an aromatic 2-aminoaldehyde or ketone with the carbonyl compounds containing a reactive α-methlene group.[5] For instance, it has been reported that drops of concentrated sulfuric acid or 6 N hydrochloric acid can be used as efficient catalysts in the Friedländer condensation procedure.[6] With this method, various structurally varied substrates can give the corresponding quinoline products in moderate to high yields. Unfortunately, this method involves the utilization of excessive glacial acetic acid as solvent or necessitates a metal bath to maintain the reaction temperature at as high as 200 °C, thus making this method unsuitable for an up-scaling process.

Room temperature ionic liquids, especially those based on 1,3-dialkylimidazolium cation is attracting increasing interest as alternative environmentally benign reaction media. These solvents are non-volatile, recyclable, non-explosive, thermally stable, and easy to handle. They have been applied in various non-catalytic and catalytic reactions,[7] as well as extraction procedures.[8] In addition, catalysts with a polar or ionic character can be immobilized in these ionic media, thus permitting a practical method of recycling of the catalyst together with the solvent by simple extraction of products from the ionic reaction media.[9] In line with our research programme in using ionic liquid as novel reaction media in organic reactions,[10] herein we wish to report a novel and efficient procedure for the preparation of 4-arylquinolines catalyzed by sulfuric acid in ionic liquid (shown in Scheme I).

Scheme I



1 **2** **3**

RESULTS AND DISCUSSION

The effectiveness of ionic liquid as solvent for the Friedländer reaction was examined in the preparation of polysubstituted quinoline derivatives (**3**, Scheme I) from 2-aminobenzophenones (**1**, Scheme I) and ketones containing a reactive α-methlene group (**2**, Scheme I). We set out to examine the reaction in one of the most widely used ionic liquids, 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]), using drops of concentrated sulfuric acid as catalyst

and 2-aminobenzophenone and acetophenone as the starting materials (entry **a**, Table 1). The reaction was carried out by dissolving 0.20 g (1 mmol) of 2-aminobenzophenone in 2 mL [bmim][BF_4] and followed by addition of 0.12 g (1 mmol) of acetophenone and 2 drops of concentrated sulfuric acid, then stirring and heating the reaction mixture at 80 °C. The product was obtained by simple extraction with diethyl ether of the reaction mixture and subsequent purification through a silica gel column as a light yellow solid. The yield of the product was found to be higher than in the case where a conventional solvent, glacial acetic acid,[6] was used (entry **a**, Table 1).

The process was then extended to other structurally varied substrates and the results are listed in Table 1. We can see from this table that in a similar fashion, a wide range of ketones containing a reactive α-methlene group underwent smooth condensation with 2-aminobenzophenones to give substituted quinolines with short reaction times and in reasonably high yields. It is worth noting that both aliphatic and aromatic-aliphatic ketones gave the corresponding quinoline products in almost equally fair yields. In addition, higher yields were obtained with 4-nitroacetophone (entries **c** and **i**, Table 1), showing that the yields of quinolines are to some extent affected by the nature of the substituents attached to the aromatic ring of ketones.

Our attention was then directed toward the possibility of recycling the reaction media since recovery and reuse of the catalyst and solvent are highly preferable for a greener process. In this work, the catalyst could be immobilized in [bmim][BF_4] at the end of the condensation reaction. 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. Investigations by using 2-aminobenzophenone and acetophenone as model substrates showed that even in the fourth round, reuse of the ionic liquid and the catalyst recovered from the third round still gave the corresponding product with fairly good yields (Table 2, entry **4**).

In summary, this paper describes a modification of the classical Friedländer reaction and presents a novel and efficient method for the preparation of 4-phenylquinoline derivatives by using ionic liquid as solvent and sulfuric acid as catalyst. The simple experimental procedure combined with the ease of recovery and reuse of the catalyst together with the environmentally benign reaction media is expected to contribute to the development of a greener and waste free chemical process for the preparation of quinoline derivatives with potential biological activities. Further studies to develop other new uses of ionic liquid in the preparation of heterocyclic compounds are now in progress in our laboratory.

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

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

[a] Isolated yields. [b] Yield reported in Ref. 6. [c] Reaction temperature is 40 °C.

Table 2. Reusability of [bmim][BF_4] together with the catalyst

Round	Yield (%)	Ionic liquid recovered (%)
1	77	99
2	78	98
3	75	95
4	70	94

EXPERIMENTAL

Melting points were measured by a Kofler micro-melting point apparatus and were uncorrected. Infrared spectra were recorded on a Bruker Vector 22 spectrometer in KBr with absorption in cm^{-1}. ^1H NMR spectra were determined on a Bruker AC 400 spectrometer as $CDCl_3$ solutions. Chemical shifts (δ) were expressed in ppm downfield from the internal standard tetramethylsilane and coupling constants *J* were given in Hz. Mass spectra were recorded on a HP5989B mass spectrometer. Elemental analyses were performed on an EA-1110 instrument.

Typical procedure for the preparation of 2,4-diphenylquinoline

2-Aminobenzophenone (1 mmol), acetophenone (1 mmol) and 2 drops of concentrated sulfuric acid were added to a 10 mL round-bottomed flask containing 2 mL [bmim][BF_4]. Then the mixture was stirred at 80 °C for 5 h. After completion, the reaction mixture was extracted with diethyl

ether (3 × 10 mL). The combined ether extractions were concentrated under reduced pressure and the resulting product was charged on silica gel column and eluted with a mixture of ethyl acetate/n-hexane (1:8) to afford pure 2,4-diphenylquinoline. The rest of the viscous ionic liquid together with the catalyst was dried at 80 °C under reduced pressure to retain its activity for subsequent use. Other quinoline products can be obtained in a similar fashion.

2,4-Diphenylquinoline (3a)

M.p. 110-111 °C (lit. 112-113 °C[11]); IR ν 3045, 1615, 1590 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, 1H, *J* = 8.4 Hz), 8.19-8.22 (m, 2H), 7.91 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.2 Hz), 7.83 (s, 1H), 7.72-7.76 (m, 1H), 7.47-7.59 (m, 9H); MS *m/z* (%): 281 (M^+, 70), 280 (M^+ - 1, 100), 202 (9), 139 (8).

2-(4-Bromophenyl)-4-phenylquinoline (3b)

M.p. 128-129.5 °C; IR ν 3050, 1610, 1590 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, 1H, *J* = 8.0 Hz), 8.08-8.11 (m, 2H), 7.90 (d, 1H, *J* = 8.0 Hz), 7.72-7.78 (m, 2H), 7.64-7.67 (m, 2H), 7.47-7.59 (m, 6H); MS *m/z* (%): 361 (M^+ + 2, 89), 360 (M^+ + 1, 100), 359 (M^+, 89), 358 (M^+ - 1, 95), 278 (40), 202 (17), 139 (25). Anal. Calcd for $C_{21}H_{14}BrN$: C 70.01, H 3.92, N 3.89; Found: C 69.85, H 3.88, N 3.73.

2-(4-Nitrophenyl)-4-phenylquinoline (3c)

M.p. 162-163 °C; IR ν 3061, 1620, 1595 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37-8.42 (m, 4H), 8.31 (d, 1H, *J* = 8.0 Hz), 7.96 (d, 1H, *J* = 8.0 Hz), 7.87 (s, 1H), 7.80 (t, 1H, *J* = 8.0 Hz), 7.54-7.59 (m, 6H); MS *m/z* (%): 326 (M^+, 100), 202 (23). Anal. Calcd for $C_{21}H_{14}N_2O_2$: C 77.29, H 4.32, N 8.58; Found: C 77.15, H 4.48, N 8.63.

2-Methyl-4-phenylquinoline (3d)

M.p. 93-95 °C; IR ν 3057, 2971, 1617, 1485 m^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, 1H, *J* = 8.4 Hz), 7.85 (dd, 1H, J_1 = 8.4 Hz, J_2 = 0.8 Hz), 7.66-7.70 (m, 1H), 7.45-7.55 (m, 5H), 7.40-7.45 (m, 1H), 7.22 (s, 1H), 2.77 (s, 3H); MS *m/z* (%): 219 (M^+, 100), 218 (M^+ - 1, 48), 204 (14), 176 (10). Anal. Calcd for $C_{16}H_{13}N$: C 87.64, H 5.98, N 6.39; Found: C 87.48, H 6.12, N 6.46.

6-Chloro-2,4-diphenylquinoline (3e)

M.p. 130-132 °C; IR ν 3050, 1610, 1589 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11-8.15 (m, 3H), 7.82 (d, 1H, *J* = 2.2 Hz), 7.76 (s, 1H), 7.59-7.60 (m, 2H), 7.45-7.50 (m, 7H); MS *m/z* (%): 317 (M^+ + 2, 33.9), 315 (M^+, 100), 280 (32.0). Anal. Calcd for $C_{21}H_{14}ClN$: C 79.87, H 4.47, N 4.44; Found: C 79.95, H 4.43, N 4.35.

6-Chloro-2-(4-methylphenyl)-4-phenylquinoline (3f)

M.p. 132-134 °C; IR ν 3048, 1600, 1580 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, 1H, *J* = 8.4 Hz), 8.09 (d, 2H, *J* = 8.0 Hz), 7.85 (d, 1H, *J* = 3.5 Hz), 7.82 (s, 1H), 7.67-7.64 (m, 1H), 7.57-7.52 (m, 5H), 7.33 (d, 2H, *J* = 8.0 Hz), 2.43 (s, 3H); MS *m/z* (%): 331 (M^+ + 2, 33.5), 329 (M^+, 100), 294 (23). Anal. Calcd for $C_{22}H_{16}ClN$: C 80.11, H 4.89, N 4.25; Found: C 80.25, H 4.78, N 4.33.

6-Chloro-2-(4-chlorophenyl)-4-phenylquinoline (3g)

M.p. 164-166 °C; IR ν 3058, 1605, 1587 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, 1H, *J* = 8.4 Hz), 8.15 (d, 2H, *J* = 8 Hz), 7.87 (d, 1H, *J* = 2.2 Hz), 7.80 (s, 1H), 7.68-7.71 (m, 1H), 7.50-7.59 (m, 7H); MS *m/z* (%): 353 (M^+ + 4, 11.7), 351 (M^+ + 2, 64.9), 349 (M^+, 100), 314 (33.8). Anal. Calcd for $C_{21}H_{13}Cl_2N$: C 72.02, H 3.74, N 4.00; Found: C 72.07, H 3.71, N 4.03.

6-Chloro-2-(4-bromophenyl)-4-phenylquinoline (3h)

M.p. 174-176 °C; IR ν 3061, 1600, 1590 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, 1H, *J* = 8.8 Hz), 8.07 (d, 2H, *J* = 8.8 Hz), 7.85 (d, 1H, *J* = 2.2 Hz), 7.79 (s, 1H), 7.64-7.68 (m, 3H), 7.54-7.58 (m, 5H); MS *m/z* (%): 397 (M^+ + 4, 25.8), 395 (M^+ + 2, 100), 393 (M^+, 79.0), 358 (17.5). Anal. Calcd for $C_{21}H_{13}BrClN$: C 63.90, H 3.32, N 3.55; Found: C 63.85, H 3.21, N 3.53.

6-Chloro-2-(4-nitrophenyl)-4-phenylquinoline (3i)

M.p. 218-220 °C; IR ν 3038, 1610, 1525 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.34-8.38 (m, 4H), 8.20 (d, 1H, *J* = 8.0 Hz), 7.90 (d, 1H, *J* = 2.4 Hz), 7.88 (s, 1H), 7.54-7.60 (m, 5H), 7.23 (dd, 1H, J_1 = 9.2 Hz, J_2 = 2.4 Hz); MS *m/z* (%): 362 (M^+ + 2, 34), 360 (M^+, 100), 314 (40), 278 (32), 139 (20). Anal. Calcd for $C_{21}H_{13}ClN_2O_2$: C 69.91, H 3.63, N 7.76; Found: C 69.94, H 3.68, N 7.59.

6-Chloro-2-methyl-4-phenylquinoline (3j)

M.p. 88-90 °C; IR ν 3050, 2978, 1610, 1496 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, 1H, *J* = 9.2 Hz), 7.82 (d, 1H, *J* = 2.4 Hz), 7.62 (dd, 1H, J_1 = 9.2 Hz, J_2 = 2.4 Hz), 7.46-7.57 (m, 5H), 7.26 (s, 1H), 2.77 (s, 3H); MS *m/z* (%): 255 (M^+ + 2, 32), 253 (M^+, 100), 218 (40), 176 (11). Anal. Calcd for $C_{16}H_{12}ClN$: C 75.74, H 4.77, N 5.52; Found: C 75.88, H 4.62, N 5.63.

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