A Mild, Efficient and Improved Protocol for the Friedländer Synthesis of Quinolines using Lewis acidic Ionic Liquid

Ganesan Karthikeyan and Paramasivan T. Perumal*

Organic Chemistry Division,
Central Leather Research Institute, Adyar, Chennai-600 020, INDIA
E-mail: ptperumal@hotmail.com; Fax: 91-44-24911589
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Lewis acidic ionic liquid is shown to be for the first time an excellent medium and efficient catalyst for the synthesis of quinolines at room temperature from *o*-amino aromatic carbonyls and ketones containing active methylene group.

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Introduction.

The Friedländer condensation is still considered as the most popular method, which provides rapid access to quinolines and related aza aromatic compounds [1]. The quinoline derivatives display wide range of biological properties such as antiasthamatic [2], antiinflamatory [3], and tyrosine kinase PDGF-RTF inhibiting properties [4]. The potent biological properties have naturally received much attention of the synthetic community and several reports on the synthesis of quinolines and substituted quinolines have been described [5].

Friedländer synthesis can be catalysed by strong acids or bases or may take place without a catalyst at higher temperature. The acidic catalysts used are conc. hydrochloric acid, conc. sulfuric acid, *p*-toluenesulfonic acid and phosphoric acid and $ZnCl_2$ [1b]. Uncatalysed Friedländer synthesis usually requires more drastic reaction condition with temperature in the range 150-220 °C. The synthetic scope of this reaction however is reduced as a result of the harsh reaction conditions and the use of strong acid or base catalyst, which are incompatible with either acid or base sensitive groups. Arcadi *et al*. [6a] reported a green approach for the Friedländer synthesis using $NaAuCl_4$ as a catalyst and Levacher *et al*., [6b] described a novel traceless solid-phase Friedländer synthesis. Recently, Palimkar *et al*. [6c] have reported the synthesis of quinolines using ionic liquid at higher temperature.

Room temperature ionic liquids (RTILs) have gained popularity such as "green" alternative to conventional solvents, due to several interesting properties [7] like negligible vapour pressure and wide liquid range. Chloroaluminate ionic liquid has been reported as both solvent and Lewis acid catalyst for Friedel-Crafts reaction [8] and Diels- Alder reaction [9]. Similar to the EMIC-$AlCl_3$ system, the combination of anhydrous $ZnCl_2$ and EMIC have reported [10] to produce a low temperature Lewis acidic molten salts. Recently, Davies and co-workers [11a] synthesized Lewis acidic ionic liquids by mixing appropriate molar ratio of MCl_2 (M = Zn, Sn) with quaternary ammonium salts and employed it as a catalyst for the Diels- Alder reaction [11b].

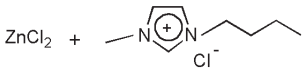


Figure 1

The Lewis acidity of the Zinc chloride-1-butyl-3-methyl imidazolium chloride molten melt ($ZnCl_2$-bmimCl) can be adjusted by varying the molar ratio of $ZnCl_2$ to bmimCl in the melts. Melts containing more than 33 mol% of $ZnCl_2$ are considered to be acidic because there are not enough chloride ions to fully co-ordinate with Zn(II) and, thus the Zinc (II) species that are present in the melts might be the coordinate unsaturated species like $ZnCl_3^-$, $Zn_2Cl_7^-$ and $(ZnCl_2)_n$ which are chloride ion acceptors. In continuation [12] of our interest in the application of room temperature ionic liquids (RTILs) in organic synthesis, we reinvestigated the Friedländer synthesis of quinolines by using bmimCl:$ZnCl_2$ melt (1:2 molar ratio) that can act both as a solvent and catalyst on account of its high polarity and Lewis acidity.

Scheme 1

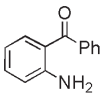
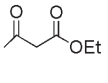
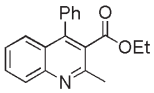
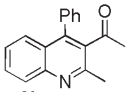
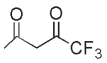
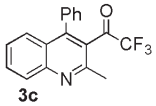
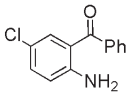
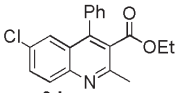
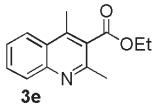
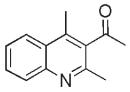
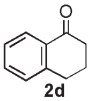
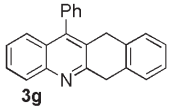
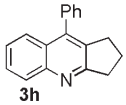
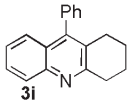
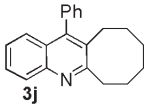
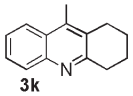
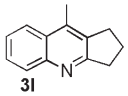
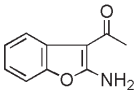
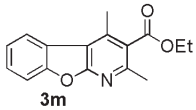
1a **2a** **3a**

Results and Discussion.

o-Amino substituted aromatic ketones and 1,3 dicarbonyls (Scheme 1) were taken in bmimCl:$ZnCl_2$ melt and stirred at room temperature for 24 hr. to get quinolines (**3a** -**3m**) [13] in good to excellent yields. The results are presented in Table-I. The reaction path suggested for the Friedländer synthesis may involve sequential formation of *N*-(*o*-acyl–phenyl)-β-enaminones/cyclodehydration reaction. *o*-Aminobenzophenones react with ethyl acetoacetate and acetyl acetone to give the corresponding quinolines (**3a**, **3b**) in 92% and 89 % yields. In the case of

Table 1

Friedländer Synthesis of Quinolines using Lewis Acidic Ionic Liquid (bmimCl:$ZnCl_2$)

Entry	Substrate	Reagent	Product [a]	Yield (%) [b]
1	 **1a**	 **2a**	 **3a**	92
2	**1a**	 **2b**	 **3b**	89
3	**1a**	 **2c**	 **3c**	55 [c]
4	 **1b**	**2a**	 **3d**	90
5	 **1c**	**2a**	 **3e**	88
6	**1c**	**2b**	 **3f**	86
7	**1a**	 **2d**	 **3g**	68
8	**1a**	 **2e**	 **3h**	88
9	**1a**	 **2f**	 **3i**	80
10	**1a**	 **2g**	 **3j**	70
11	**1b**	**2f**	 **3k**	60
12	**1b**	**2e**	 **3l**	65
13	 **1d**	**2a**	 **3m**	55 [c, d]

a. All the products were identified by IR, NMR and MS. b. Isolated yield after column chromatography. c. Reactions were carried out at 80° C. d. Reaction done with 0.57 mmol of 1d.

o-aminoacetophenones, the corresponding quinoline were synthesized in excellent yield (**3e**-88%, **3f**-86%) which is better in comparison with reported procedures [6a,6d]. When cyclic ketones were used as a carbonyl substrate the reaction proceeded at room temperature giving the corresponding qinolines in good yield. It is of interest to note that the same reaction reported by Arcadi *et al*. required 60 ºC heating. Finally, this protocol was extended for the reaction of 2-amino, 3-acyl benzofuran with ethyl acetoacetate giving the corresponding quinolines in 55% yield.

The reusability of bmimCl:$ZnCl_2$ ionic liquid was studied and a marginal progressive loss in activity of ionic liquid was found. The second and third run produce **3a** in 89 and 86% yields.

Conclusion.

In conclusion, we have developed a simple and efficient protocol for the effective synthesis of quinolines under mild reaction conditions. This procedure neither requires harsh reaction conditions nor the use of hazardous acids or bases. We hope that this methodology will further widen the use of Friedländer quinolines synthesis.

EXPERIMENTAL

General Experimental Procedure.

To bmimCl:$ZnCl_2$ melt (0.35 g:0.55 g, heated at 90 ºC for 3 hr under Ar atmosphere) was added acetyl acetone (0.2 g, 2 mmol) and *o*-aminobenzophenone (0.197 g, 1 mmol) and stirred at room temperature under Ar atmosphere for 24 hr. The reaction mixture was extracted with diethyl ether (3 × 20 mL). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The ionic liquid that remained after ether extraction was dried under reduced pressure and reused. The crude **3b** thus obtained was purified by column chromatography (ethyl acetate/petroleum ether, 5:95) to yield 1-(2-methyl-4-phenylquinolin-3-yl)ethanone (**3b**): 0.234 g (88 %); IR (Perkin Elmer, KBr): 1691 cm^{-1}; ^1H NMR (JOEL,500 MHz, $CDCl_3$): δ 1.98 (s, 3H, CH_3), 2.68 (s, 3H, COCH_3), 7.32-7.35 (m, 1H), 7.40 (m, 1H), 7.47 – 7.50 (m, 4H). 7.59 (d, 1H, *J* = 8.0 Hz), 7.68 (m, 1H), 8.05 (d, 1H, *J* = 8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.9, 32.0, 121.1, 126.2, 128.8, 128.9, 129.0, 130.1, 130.2, 134.9, 135.2, 144.0, 147.6, 153.6, 205.8; MS(JOEL DX-303): *m/z* (relative intensity) 261 (47) [M^+], 246 (100).

Spectral data for **3c**, **3i**, **3m**: **3c**: IR (KBr): 1726 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.69 (s, 3H, CH_3), 7.31-7.33 (m, 2H), 7.47-7.50 (m, 4H), 7.66(d, 1H, *J* = 8 Hz), 7.71 (m, 1H), 8.10 (d, 1H, *J* = 8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.9, 116.2 (q, *J* = 300 Hz), 124.5, 126.4, 127.2, 127.6, 128.7, 129.1, 129.5, 130.4, 131.4, 133.8, 147.5, 148.4, 153.4, 189.6 (q, *J* = 38 Hz); MS: *m/z* (relative intensity) 315 (34) [M^+], 246 (77), 218 (26), 70 (100). **3i**: IR (KBr): 3060, 2944, 1604 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.77 (m, 2H), 1.95 (m, 2H), 2.59 (t, 2H, *J* = 6.9 Hz), 3.20 (t, 2H, *J* = 6.85 Hz), 7.21 (d, 2H, *J* = 5.75 Hz), 7.28 – 7.32 (m, 2H), 7.43 – 7.47 (m, 1H), 7.49 – 7.52 (t, 2H, *J* = 7.45 Hz), 7.57 – 7.62 (m, 1H), 8.01 (d, 1H, *J* = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.9, 23.1, 34.2, 125.5, 125.8, 126.7, 127.8,

128.3, 128.5, 128.7, 129.1, 137.1, 146.2, 146.7, 159.1; MS: *m/z* (relative intensity) 259 (44) [M^+], 207 (43), 55(100). **3m**: mp. 52° C IR (neat): 1728 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.40 (t, 3H, *J* = 6.85 Hz CH2CH3), 2.53 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 4.44 (q, 2H, *J* = 6.85 Hz), 7.33–7.34 (t, 1H, *J* = 8.0 Hz), 7.44-7.53 (m, 2H), 8.17 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.7, 14.3, 23.2, 61.7, 112.0, 121.5, 123.2, 123.5, 127.3, 128.6, 142.9, 147.3, 151.2, 157.8, 168.4. MS: *m/z* (relative intensity) 269 (100) [M^+]; *Anal*. Calcd for $C_{16}H_{15}NO_3$ (269): C, 71.36; H, 5.48; N, 5.85. Found: C, 71.40; H, 5.45; N, 5.90.

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[13] All compounds except **3m** are known and exhibited spectroscopic properties that agree with literature data according to reference 6.