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AN EFFICIENT PROTOCOL FOR THE FRIEDLÄNDER QUINOLINE SYNTHESIS USING THE LEWIS ACIDIC IONIC LIQUID CHOLINE CHLORIDE · $2ZnCl_2$

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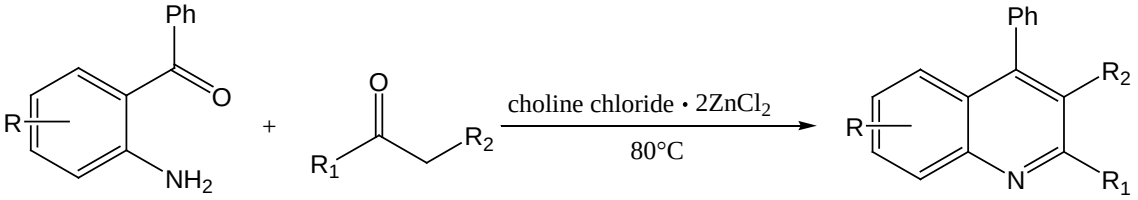
Abstract - Lewis acidic ionic liquid choline chloride · $2ZnCl_2$ is shown to be for the first time an excellent solvent and efficient catalyst for the synthesis of quinolines *via* Friedländer annulation under mild conditions.

Quinoline derivatives have been well known not only in medicinal chemistry, because of their wide occurrence in natural products[1] and[2] drugs, but also in polymer chemistry, electronics and optoelectronics for their excellent mechanical properties.[3] Versatile methods for the synthesis of the quinoline ring system have been developed.[4]

Friedländer annulation is one of the most simple and straightforward approaches for the synthesis of quinoline derivatives. Friedländer synthesis can be catalysed by strong acids or bases, and may take place without a catalyst at higher temperature. Brønsted acids like hydrochloric acid, sulfuric acid, *p*-toluenesulfonic acid and phosphoric acid were widely used as catalysts. However, many of these methods require harsh reaction condition and lead to several side reactions. Recently, Lewis acids such as $ZnCl_2$, $SnCl_2$, $Bi(OTf)_3$, $Sc(OTf)_3$, silver phosphotungstate, sodium fluoride, and $AuCl_3$ have been reported to be effective for the synthesis of quinolines.[5] However, many of these procedures suffered from harsh reaction conditions, low yields, difficulties in work up, and the use of stoichiometric and/or relatively expensive reagents. Since quinoline derivatives are increasingly useful and important in pharmaceuticals and industry, the development of simple, eco-benign, low cost protocol is still desirable.

Room temperature ionic liquids (RTILs) have gained popularity such as “green” alternative to conventional solvents, due to several interesting properties[6] like negligible vapor pressure and wide

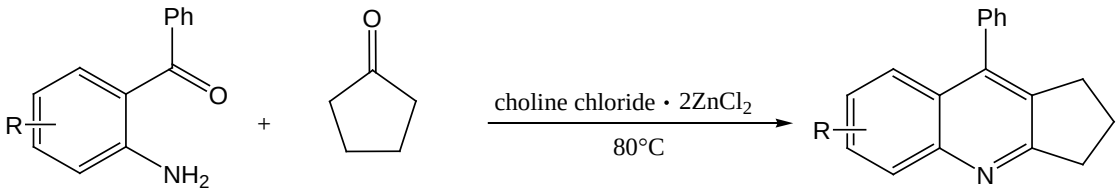
liquid range. Recently, the alkylimidazolium-aluminium chloride mixtures have been studied extensively for use in acid catalysed reactions, particularly in Friedel-Crafts reactions[7] However, for practical utilization, these imidazolium-based ionic liquids still suffer from the relatively expensive cost. In the case of chloroaluminate ionic liquid, their poor stability to moisture can lead to undesired side reactions. More recently, a series of inexpensive and moisture-stable Lewis acidic ionic liquids have been prepared from choline chloride and $ZnCl_2$,[8] and used in Diels–Alder[9] and Fischer indole[10] reactions. In this paper, we report the use of choline chloride・$2ZnCl_2$ as solvent and catalyst for the synthesis of quinolines *via* Friedländer annulation under mild conditions.



1 **2** **3**

Scheme 1

Treatment of *o*-aminoaryl ketones (**1**) with dicarbonyl compounds or ketones (**2**) in ionic liquid choline chloride・$2ZnCl_2$ at 80℃ for 1 h caused cyclodehydration to give quinolines (**3**) in good to excellent yields (Scheme 1). The results are given in Table 1. *o*-Aminobenzophenone (**1a**) react with acetylacetone and ethyl acetoactate to give the corresponding quinolines (**3a, 3b**) in 88 % and 90 % yield, respectively. Cyclic ketone such as cyclopentanone (**2e**) also underwent smooth condensation with *o*-aminoaryl ketones (**1**) to afford the respective tricyclic quinolines (**3e**, **3j**) in 89 % and 93 % yields (Scheme 2).

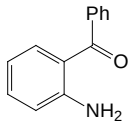
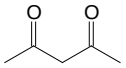
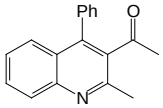
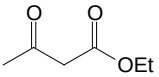
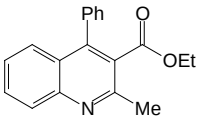
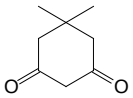
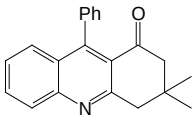
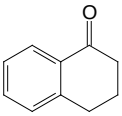
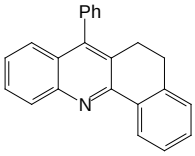
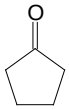
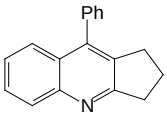
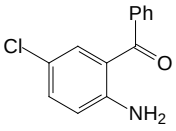
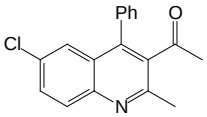
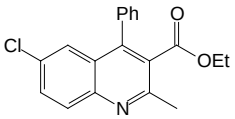
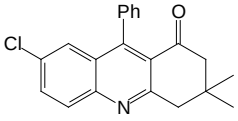
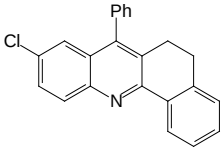
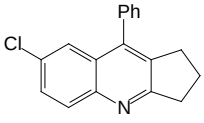


1 **2e** **(3e, 3j)**

Scheme 2

In conclusion, we describe a mild and efficient route for the synthesis of quinolines and polycylic quinolines utilizing choline chloride・$2ZnCl_2$ as solvent and catalyst *via* Friedländer annulation under mild conditions. This ionic liquid is cheap, moisture-stable and easy to prepare compared to imidazolium based ionic liquids.

Table 1. Choline Chloride・$2ZnCl_2$ Catalyzed Friedländer Synthesis of Quinolines.

Entry	Substrate **1**	Ketone **2**	Quinoline **3**	Yield/%
1	 **1a**	 **2a**	 **3a**	88
2	**1a**	 **2b**	 **3b**	90
3	**1a**	 **2c**	 **3c**	87
4	**1a**	 **2d**	 **3d**	82
5	**1a**	 **2e**	 **3e**	89
6	 **1b**	**2a**	 **3f**	85
7	**1b**	**2b**	 **3g**	92
8	**1b**	**2c**	 **3h**	89
9	**1b**	**2d**	 **3i**	84
10	**1b**	**2e**	 **3j**	93

ACKNOWLEDGEMENT

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EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded on a Shimadzu IR-27 G spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Unity Plus 400 MHz. Chemical shifts (δ) were measured in ppm with respect to TMS. MS were obtained on a JEOL JMS D-300 instrument.

General procedure for the preparation quinoline (3)

A mixture of *o*-aminoaryl kone (1 mmol) and ketone (2 mmol) in choline chloride·2$ZnCl_2$ (0.5 mL) ionic liquid was stirred for 1 h at 80 ℃. The reaction mixture was extracted with EtOAc. The remaining ionic liquid was reused after drying in vacuum. The extract was dried ($MgSO_4$) and concentrated under reduced pressure and the residue was purified by chromatography on a silica gel column with hexane-EtOAc (3 : 1) to give quinoline (**3**).

1-(2-Methyl-4-phenylquinolin-3-yl)ethanone (3a)

Mp 114-115 ℃ (Lit.,[11] 111-112℃). IR (KBr) ν : 3062, 2907, 1696 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ : 1.95 (s, 3H), 2.66 (s, 3H), 7.30-7.32 (m, 2H), 7.30-7.39 (m, 1H), 7.44-7.48 (m, 3H), 7.57 (dd, *J* = 0.8, 8.4 Hz, 1H), 7.63-7.68 (m, 1H), 8.03 (d, *J* = 8.4Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 23.7, 31.7, 124.8, 125.9, 126.3, 128.5, 128.6, 128.8, 129.8, 129.9, 134.6, 135.0, 143.7, 147.3, 153.3, 205.5; EI-MS *m/z* : 261 (M^+), 246, 218, 176.

2-Methyl-4-phenyl-quinoline-3-carboxylic acid ethyl ester (3b)

Mp 99-100°C. (Lit.,[11] mp 99-100°C). IR (KBr) ν : 3060, 2927, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ : 0.91 (t, *J* = 7.3 Hz, 3H), 2.76 (s, 3H), 4.00-4.10 (m, 2H), 7.31-7.46 (m, 6H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.67 (t, *J* = 8.4 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 13.4, 23.6, 61.1, 124.9, 126.2, 128.0, 128.3, 128.6, 129.2, 130.1, 135.5, 146.1, 147.5, 154.4, 168.2; EI-MS *m/z* : 291 (M^+), 246, 245, 218.

3,3-Dimethyl-9-phenyl-3,4-dihydro-2*H*-acridin-1-one (3c)

Mp 191°C. (Lit.,[11] mp 195°C). IR (KBr) ν : 3065, 2868, 1682 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ : 1.15 (s, 6H), 2.55 (s, 2H), 3.26 (s, 2H), 7.16-7.19 (m, 2H), 7.36-7.39 (m, 1H), 7.44-7.51 (m, 4H), 7.71-7.75 (m, 1H), 8.06 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 28,2, 32.1, 48.2, 54.0, 122.5, 126.3, 127.2, 127.3, 127.9, 128.0, 128.1, 128.3, 131.5, 137.4, 148.8, 150.8, 160.9, 197.7; EI-MS *m/z*: 301 (M^+), 300, 272, 245, 217, 189.

5,6-Dihydro-7-phenylbenzo[*c*]acridine (3d)

Mp 143-145°C. (Lit.,[12] mp 148-149°C). IR (KBr) ν : 3057, 2924, 1574, 14484, 696 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ : 2.86-2.89 (m, 4H), 7.11-7.72 (m, 11H), 8.20 (d, *J* = 8.4Hz, 1H), 8.63 (dd, *J* = 1.2, 7.6Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 26.4, 28.2, 125.9, 126.0, 126.3, 127.2, 127.4, 127.8, 128.0, 128.4, 128.5, 128.9, 129.5, 129.6, 130.2, 135.0, 136.9, 137.5, 139.2, 147.1, 153.0; EI-MS *m/z*: 307 (M^+), 306, 305, 230, 152.

2,3-Dihydro-9-phenyl-1*H*-cyclopenta[*b*]quinoline (3e)

Mp 1313-132°C. (Lit.,[13] mp 130°C). IR (KBr) ν : 3058, 2923, 1569, 1485, 831 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ : 2.15-2.19 (m, 2H), 2.91 (t, *J* = 7.2Hz, 2H), 3.24 (t, *J* = 7.6Hz, 2H), 7.35-7.41 (m, 3H), 7.47-7.54 (m, 3H), 7.60-7.64 (m, 2H), 8.06-8.08 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 23.5, 30.3, 35.1, 125.4, 125.6, 126.2, 128.2, 128.4, 129.2, 133.6, 136.7, 142.6, 147.9, 167.4; EI-MS *m/z*: 245 (M^+), 244, 217, 168.

1-(6-Chloro-2-methyl-4-phenylquinolin-3-yl)ethanone (3f)

Mp 155-156°C (Lit.,[11] mp 154°C). IR (KBr) ν : 3049, 2925, 1699 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ : 1.97 (s, 3H), 2.65 (s, 3H), 7.29-7.31 (m, 2H), 7.48-7.54 (m, 4H), 7.59-7.62 (m, 1H), 7.97 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 23.7, 31.7, 124.8, 125.7, 128.8, 129.1, 129.8, 130.4, 130.8, 132.3, 134.3, 135.4, 142.9, 145.7, 153.8, 205.1; EI-MS *m/z*: 297 (M^++2), 295 (M^+), 280, 217, 176.

6-Chloro-2-methyl-4-phenylquinoline-3-carboxylic acid ethyl ester (3g)

Mp 102-105°C. (Lit.,[11] mp 108°C). IR (KBr) ν : 3075,2926, 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ : 0.85 (t, *J*=7.2 Hz, 3H), 2.69 (s, 3H), 3.98 (q, *J* = 7.2 Hz, 2H), 7.25-7.45 (m, 6H), 7.51 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.88 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 13.3, 23.4, 61.1, 124.8, 125.5, 128.1, 128.3, 128.4, 129.0, 130.2, 130.7, 132.0, 134.7, 145.0, 145.7, 154.6, 167.7; EI-MS *m/z*: 327 (M^++2), 325 (M^+), 280, 217, 216.

7-Chloro-3,3-dimethyl-9-phenyl-3,4-dihydro-2*H*-acridin-1-one (3h)

Mp 209-211°C. (Lit.,[11] mp 209-211°C). IR (KBr) ν : 3071, 2946, 1693 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ : 1.15(s, 6H), 2.57(s, 2H), 3.25(s, 2H), 7.14-7.17(m, 2H), 7.28(d, *J* = 2.4 Hz, 1H), 7.42-7.55 (m, 3H), 7.69 (dd, *J* = 2.4, 9.0 Hz, 1H), 8.00 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 28.3, 32.2, 48.2, 54.1, 123.2, 126.7, 127.8, 127.9, 128.2, 128.3, 130.1, 132.4, 132.5, 136.7, 147.3, 150.1, 161.4, 197.6; EI-MS *m/z*: 337 (M^++2), 335 (M^+), 334, 306, 279, 216 189.

9-Chloro-5,6-dihydro-7-phenylbenzo[*c*]acridine (3i)

Mp 134-136°C. (Lit.,[14] mp 130°C). IR (KBr) ν : 3052, 2935, 1600, 1479, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ : 2.81-2.90 (m, 4H), 7.24-7.59 (m, 10H), 8.11 (d, *J* = 8.8 Hz, 1H), 8.59 (dd, *J* = 1.2, 7.6 Hz,1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 26.5, 28.1, 124.8, 126.3, 127.3, 127.7, 127.9, 128.2, 128.7, 129.0, 128.3, 129.4, 129.8, 131.1, 131.6, 134.7, 136.1, 139.2, 144.5, 145.5, 153.3; EI-MS *m/z*: 343

(M^++2), 341 (M^+), 304, 152.

7-Chloro-2,3-dihydro-9-phenyl-1*H*-cyclopenta[*b*]quinoline (3j)

Mp 103-104°C. (Lit.,[14] mp 105°C). IR (KBr) ν : 3038, 2923, 1601, 1483, 828 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ : 2.17 (m, 2H), 2.89 (t, *J* = 7.6 Hz, 2H), 3.22 (t, *J* = 7.6 Hz, 2H), 7.32-7.35 (m, 2H), 7.46-7.58 (m, 5H), 7.99 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ : 23.4, 30.3, 35.1, 124.5, 127.0, 128.2, 128.7, 128.9, 129.1, 130.3, 131.2, 1134.6, 136.0, 141.8, 146.3, 167.8; EI-MS *m/z*: 281 (M^++2), 279 (M^+), 246, 244.

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