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Iron(III) Chloride–Promoted, Solvent-Free, Facile, and Efficient Friedländer Synthesis of Quinolines

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Abstract: A mild, efficient, and solvent-free version of Friedländer annulation of 2-amino ketones and α-methylene carbonyl compounds for the synthesis of polysubstituted quinolines using a catalytic amount of commercially available iron(III) chloride at room temperature in excellent yields is described.

Keywords: 2-amino ketones, Friedländer synthesis, iron(III) chloride, α-methylene carbonyl compounds, quinolines

Quinolines and their derivatives are of unique significance because they are ubiquitous in nature[1] and have wide-ranging biological activities. The broad spectrum of activities includes antimalarial, anti-inflammatory, antihypertensive, antibacterial, and tyrosine kinase-inhibiting properties.[2] New quinoline derivatives continue to unfold further biological activities, such as the histamine H_3 receptor antagonist.[3] Apart from these pharmaceutical activities, quinolines are important synthetic materials for the preparation of nano- and mesostrutures.[4] The industrial, biological, and synthetic significance places this scaffold at a prestigious position. For the synthesis of these quinolines, well-known reactions such as Skraup, Doebner–von Miller, and Friedländer are available to chemists.[5] The Friedländer reaction[6] appears to be simple and continues to attract the considerable

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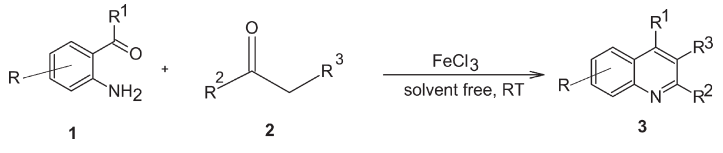
attention of the scientific community.[7] The typical Friedländer procedure involves refluxing aqueous or alcoholic solution of amino ketones and suitably substituted carbonyl compound. The refluxing time ranged up to several hours, and high temperatures on the order of 150–220°C were used. In a few reports, the reaction mixture was heated for more than 24 h using 5–10 equivalents of an acidic catalyst such as diphenylphosphate (DPP) in highly toxic m-cresol solvent.[4,8] Even then, reaction was not fairly general in scope; it failed in the case of acetoacetic ester[9] and several other ketones such as cyclohexanone and deoxybenzion. These failures prompted a search for fairly general catalytic system that followed reports of use of inorganic bases,[5,10,11] strong Brønsted acid catalysts such as HCl, H_2SO_4, and sulfuric acid derivatives; and phosphoric acids.[12,13] Even classical catalysis required harsh conditions and long reaction times. To overcome these problems, Lewis acids such as $ZnCl_2$, $AuCl_3$, and inorganic salts and microwave- and ionic liquid–catalysed conditions were used,[14] including a few metal triflates such as $Y(OTf)_3$. But these are accompanied by one or another drawback, such as environmental toxicity or expense, and the use of microwaves is not practical for large-scale production. In view of foregoing industrial, pharmacological, and commercial importance of quinolines, we feel a further simple, convenient, and environmentally benign protocol in still timely.

In recent years, iron(III) chloride has emerged as efficient catalyst for various prominent reactions of organic chemistry such as Michael reaction,[15] Biginelli and Biginelli-like reactions,[16] and several others.[17] Recently, Christoffers et al. have systematically investigated and established the superiority of this catalyst over other transition-metal Lewis acids[15,18] in Michael and other related reactions. Prompted by these recent reports of the superiority of iron(III) chloride in literature, we employed this catalyst in the Friendländer reaction for the synthesis of quiniolines, which is fairly cheap and commercially available as a shelf chemical (Scheme 1).

In the course of optimizating the reaction condition, 10 mol% of $FeCl_3$ was found to be the optimum amount. Use of a higher amount of catalyst did not improve the yield while a decrease in the amount of catalyst decreases the yield. In the absence of $FeCl_3$, the reaction did not proceed even after a long reaction time (18–20 h). Increase in reaction time did not prove fruitful. To see the scope of this protocol, several examples were



Scheme 1.

studied. Various substituted 2-aminoketones such as 2-aminobenzophenone and 2-amino-5,2′-dichlorobenzophenone reacted effectively with α-methylene carbonyl compound such as acetyl acetone, ethyl acetoacetate, 1,3-cyclohexanedione, 5,5-dimethyl cychohexanedione, and cyclohexanone (Table 1). The reaction proceeds smoothly without the formation of any side products.

In summary, we describe a simple, facile, one-pot, solvent-free, and efficient version of Friedländer annulation for the synthesis of quinolines using a commercially available bench chemical, $FeCl_3$. The operational simplicity, lack of harsh reaction conditions, and use of an inexpensive catalyst are other merits of this protocol.

EXPERIMENTAL

Melting points were determined on a Buchi melting-point apparatus and are uncorrected. IR spectra were recorded by using KBr disc on a Perkin-Elmer 240c analyzer. ^{1}H NMR spectra were obtained on Brucker AC 300 spectrometers (chemical shifts in δ, ppm) using tetramethylsilane as internal standard. All the solvents were distilled before use. The progress of the reaction was monitored by thin-layer chromatography (TLC) using silica gel G (Merck), and spots were exposed in iodine vapor. Chromatographic purification was performed with silica gel (100–200 mesh, Merck). $FeCl_3$ is used as procured from Merck.

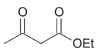
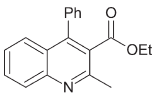
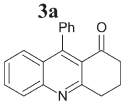
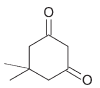
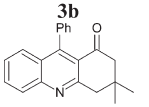
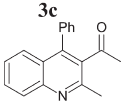
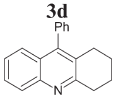
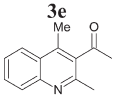
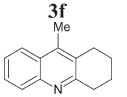
General Procedure for the Synthesis of Quinolines (3a–l)

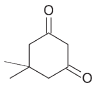
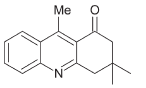
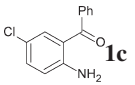
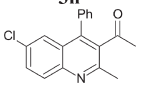
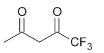
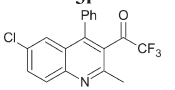
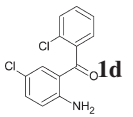
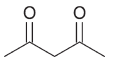
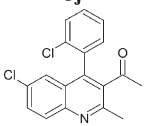
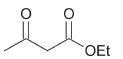
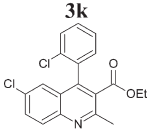
An equimolar solution of 2-amino ketone, α-methylene carbonyl compound, and $FeCl_3$ (0.1 equiv.) were stirred at room temperature for a specified time. After the completion of reaction (vide TLC), water (20 mL) was added to reaction mixture and extracted with ethyl acetate (3 × 15 mL). The product was dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The solid, thus obtained, was purified chromatographically to give pure quinolines.

Spectral Data of Some Selected Compounds

Ethyl-2-methyl-4-phenylquinoline-3-carboxylate (**3a**): mp 99–100°C, IR (KBr): 3061, 2975, 1724, 1610 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.97$ (t, $J = 6.8$ Hz, 3H), 2.75 (s, 3H), 4.02 (q, $J = 6.8$ Hz, 2H), 7.28–7.50 (m, 7H), 7.65–7.73 (m, 2H), 8.05 (d, $J = 8.1$ Hz, 1H). ^{13}C NMR: (75 MHz, $CDCl_3$): $\delta = 13.5$, 23.1, 60.8, 96.3, 125.2, 126.1, 126.4, 127.7, 128.2, 129.2, 129.7, 135.7, 145.8, 147.6, 153.9, 167.5. EIMS: m/z

Table 1. $FeCl_3$-mediated Friedländer synthesis of quinolines **3a–l**

Entry	2-Aminoketone	α-Methylene carbonyl	Quinoline[a]	Yield (%)[b]	Time (min)	Mp (°C)[c]
1	 **1a**		 **3a**	89	40	99–100 (99–100)
2	**1a**		 **3b**	90	45	155–156 (156–157)
3	**1a**		 **3c**	88	55	190–191 (190–192)
4	**1a**		 **3d**	91	45	114–115 (115)
5	**1a**		 **3e**	78[d]	60	139–141 (140–142)
6	 **1b**		 **3f**	84	45	Liquid
7	**1b**		 **3g**	78[d]	60	76–79 (78–79)

8	**1b**		 **3h**	86	50	106–107 (105–106)
9	 **1c**		 **3i**	81	45	150–152 (151–152)
10	**1c**		 **3j**	89	40	80–81 (80–81)
11	 **1d**		 **3k**	84	50	137–138 (138)
12	**1d**		 **3k**	82	50	110–112 (112)

[a]All products were characterized by mp, IR, and ^{1}H NMR.
[b]Yields refer to pure isolated product.
[c]Literature melting points given in parentheses.
[d]0.2 Equivqlents of catalyst were used.

(%) = 291 (85) [M^+], 263 (10), 246 (100), 218 (60), 176 (40), 150 (20). Anal. calcd. for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.31; H, 5.84; N, 4.78.

9-Phenyl-3,4-dihydroacridin-1(2*H*)-one (**3b**): mp 155–156°C, IR (KBr): 3060, 2951, 1712, 1610, 1575, 1204 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 2.25–2.30$ (m, 2H), 2.70 (t, $J = 6.6$ Hz, 2H), 3.36 (t, $J = 6.4$ Hz, 2H), 7.15–7.18 (m, 2H), 7.45–7.50 (m, 6H), 8.12 (d, $J = 8.7$ Hz, 1H). Anal. calcd. for $C_{19}H_{15}NO$: C, 83.49; H, 5.53; N, 5.12. Found: C, 83.56; H, 5.49; N, 5.135.37.

3,3-Dimethyl-9-phenyl-3,4-dihydroacridin-1(2*H*)-one (**3c**): mp 190–191°C, IR (KBr): 3065, 2954, 1718, 1605, 1570, 1210 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.20$ (s, 6H), 2.60 (s, 2H), 3.35 (s, 2H), 7.15–7.25 (m, 2H), 7.40–7.50 (m, 5H), 7.80 (t, $J = 7.9$ Hz, 1H), 8.10 (d, $J = 8.1$ Hz, 1H). EIMS: m/z (%) = 301 (100) [M^+], 272 (72), 246 (60), 218 (50), 190 (10). Anal. calcd. for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.79; H, 6.51; N, 4.66.

1-(2-Methyl-4-phenylquinolin-3-yl)ethanone (**3d**): mp 114–115°C, IR (KBr): 3050, 2970, 1701, 1620 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 2.01$ (s, 3H), 2.61 (s, 3H), 7.32–7.75 (m, 8H), 8.03 (d, $J = 8.0$ Hz, 1H). EIMS: m/z (%) = 261 (75) [M^+], 246 (100), 218 (80), 176 (50), 150 (20), 43 (30). Anal. calcd. for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.81; H, 5.81; N, 5.37.

9-Phenyl-1,2,3,4-tetrahydroacridine (**3e**): mp 139–141°C, IR (KBr): 3055, 2940, 1612 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.70–1.82$ (m, 2H), 1.98–2.04 (m, 2H), 2.59 (t, $J = 7.0$ Hz, 2H), 3.18 (t, $J = 7.2$ Hz), 7.19–7.30 (m, 3H), 7.38–7.58 (m, 5H), 8.1 (d. $J = 8.1$ Hz, 1H). ^{13}C NMR: (75 MHz, $CDCl_3$): $\delta = 22.8$, 23.1, 27.6, 34.2, 96.2, 125.2, 126.3, 126.7, 127.6, 128.1, 128.6, 129.2, 137.7, 145.9, 146.6, 158.9. Anal. calcd. for $C_{19}H_{17}N$: C, 87.99; H, 6.61; N, 5.40. Found: C, 88.06; H, 6.58; N, 5.36.

3,3,9-Trimethyl-3,4-dihydroacridin-1(2*H*)-one (**3h**): mp 106–107°C, IR (KBr): 2949, 2965, 1685, 1557, 1498, 1370, 1280, 1222 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.10$ (s, 6H), 2.63 (s, 2H), 3.10 (s, 3H), 7.53–7.57 (m, 1H), 7.76–7.79 (m, 1H), 8.06 (d, $J = 8.4$, 1H), 8.25 (d, $J = 8.4$ Hz, 1H). Anal. calcd. for $C_{18}H_{14}ClNO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.41; H, 7.12; N, 5.84.

1-(6-Chloro-2-methyl-4-phenylquinolin-3-yl)-2,2,2-trifluoroethanone (**3j**): mp 80–81°C, IR (KBr): 3030, 1745, 1624 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 2.51$ (s, 3H), 7.33–7.72 (m, 8H), 8.05 (d, $J = 8.03$ Hz, 1H).

Anal. calcd. for $C_{18}H_{13}ClFNO$: C, 61.82; H, 3.17; N, 4.00. Found: C, 61.88; H, 3.18; N, 3.97.

1-[6-Chloro-4-(2-chlorophenyl)-2-methylquinolin-3-yl]ethanone (**3k**): mp 137–138°C, IR (KBr): 3058, 2962, 1695, 1626 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.01–1.05$ (m, 3H), 2.81 (s, 3H), 4.06–4.10 (m, 2H), 7.25–7.48 (m, 6H), 8.06 (d, $J = 9.1$ Hz, 1H). Anal. calcd. for $C_{18}H_{13}Cl_2NO$: C, 65.47; H, 3.97; N, 4.24. Found: C, 65.46; H, 3.92; N, 4.18.

Ethyl 6-chloro-4-(2-chlorophenyl)-2-methylquinoline-3-carboxylate (**3l**): mp 110–112°C, IR (KBr): 3071, 2962, 1715, 1605, 1248 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 2.18$ (s, 3H), 2.65 (s, 3H), 7.25–7.30 (m, 2H), 7.40–7.58 (m, 4H), 8.08 (d, $J = 9.0$ Hz, 1H). Anal. calcd. for $C_{19}H_{15}Cl_2NO_2$: C, 63.35; H, 4.20; N, 3.89. Found: C, 63.48; H, 4.14; N, 3.82.

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