Communication

Iodine-Catalyzed Friedlander Quinoline Synthesis under Solvent-Free Conditions

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Polyfunctional quinolines were synthesized using Friedlander method catalyzed by molecular iodine in high yields at 60 °C under solvent-free conditions.

Keywords: Quinolines; Molecular iodine; Friedlander synthesis; Solvent-free; Catalyst.

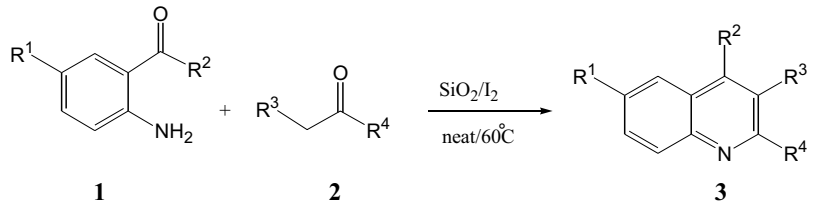
Quinolines occur in numerous natural compounds,[1] and have wide applications in medicinal chemistry such as anti-malarial, anti-inflammatory, anti-bacterial, anti-hypertensive activities and as tyrosine kinase inhibiting agents.[2] In addition, quinolines are valuable synthons used for the preparation of nano and mesostructures with enhanced electronic and photonic properties.[3] There are many reported methods for the synthesis of quinoline rings;[4] the Friedlander procedure[5] is still one of the most simple and straightforward methods for the synthesis of polyfunctional quinolines. Alternatively, this reaction was also investigated using different protic and Lewis acids such as $Bi(OTf)_3$,[6] $ZnCl_2$,[7] $FeCl_3$ and $Mg(ClO_4)_2$,[8] AcOH under microwave irradiation,[9] HCl,[10] sodium fluoride,[11] silvertungstophosphate,[12] $Y(OTf)_3$,[13] sulfamic acid,[14] ionic liquid,[15] and $NaAuCl_4$.[16]

However, most of the synthetic protocols reported so far suffer from high temperatures (150-200 °C), prolonged reaction times, low yields and the use of hazardous and often expensive catalysts. Moreover, the synthesis of these heterocyclic compounds have been usually carried out in harmful solvents such as acetonitrile, THF, DMF, and DMSO, leading to difficult product isolation and recovery procedures.

In recent years, molecular iodine has received considerable attention as an inexpensive, non-toxic, and readily available catalyst for various organic transformations under mild and convenient conditions.[17,18] Most of the reported reactions which have been promoted by molecular iodine produced the corresponding products with high yields and selectivity. Thus, to continue our investigation on developing new methodologies in organic chemistry,[19] synthesis of 1,4-dihydropyridines,[20] and quinolines,[21] and to explore the applicability of the molecular iodine in various reactions, we interested in I_2-promoted Friedlander synthesis of quinolines containing reactive functionalities. Firstly, we studied the synthesis of 6-chloro-3-(ethylformato)-2-methyl-4-phenylquinoline from 2-amino-5-chlorobenzophenone and ethyl acetoacetate in the presence of SiO_2/I_2 as catalyst.

We found that the above mentioned reaction was completed after 2 h at 60 °C under neat conditions, and the

Scheme I



1 **2** **3**

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desired quinoline was isolated in 80% yield. When I_2 was used alone, a sticky mixture was formed and the yield was low. For overcoming this limitation we used a small amount of SiO_2 together with molecular iodine. Then we applied the same conditions for the other substrates **1** and **2** (Scheme I, Table 1). The reactions proceeded with moderate to high yields. Surprisingly, under this new condition, 1,3-cyclohexanedione reacted faster than other diketones with **1a** and **1b** to produce the corresponding quinolines in high yields (Table 1, entries 1, 8). In addition, the results showed that the reaction of acetophenone with **1a** proceeded smoothly in moderate yield (Table 1, entry 12). Other β-dicarbonyl compounds also reacted satisfactorily with 2-aminobenzophenone and its 5-chloro derivative to produce the desired quinolines containing diverse reactive functional groups (Table 1).

In conclusion, we have successfully developed an easy and efficient method for the preparation of various quinolines from different ketones and diketones with 2-aminoarylketones in the presence of catalytic amounts of iodine and silica gel at 60 °C under solvent-free conditions. The catalytic activity of iodine is remarkable and the use of low cost and commercially available iodine as catalyst for the synthesis of quinolines in moderate to excellent yields is also significant under the aspect of environmentally benign processes.

EXPERIMENTAL SECTION

General

Chemicals were purchased from Fluka, Merck and Aldrich chemical companies. Yields refer to isolated pure products. The products were characterized by comparison of their spectral (IR, UV, ^{1}H-NMR and HRMS) and physical data with authentic samples. Silica gel mesh 70-230 was used.

Typical procedure

A mixture of 2-amino-5-chlorobenzophenone (0.233 g, 1 mmol), ethyl acetoacetate (0.195 g, 1.5 mmol), SiO_2 (0.1 g) and I_2 (0.050 g, 0.2 mmol) was stirred at 60 °C for 2 h. After completion of the reaction confirmed by TLC, $Na_2S_2O_3$ solution was added to the reaction mixture and filtered. The filtrate was washed with acetone (20 mL). After evaporation of the solvent, the product was recrystallized by ethanol. 6-Chloro-3-(ethylformato)-2-methyl-4-phenylquinoline as a yellow crystal was obtained in 80% yield (0.265 g).

Spectral data for some quinolines as typical

(**3a**): Yellow solid; mp 185 °C; FT-IR (KBr): υ 3024, 2956, 1684, 1551, 1476, 1075, 838, 697, cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ (ppm) 2.24 (q, 2H, J = 4.3, 7.7, 6.4), 2.71 (t, 2H, J = 6.4, 7.7), 3.36 (t, 2H, J = 4.3, 7.7), 7.20-7.95 (m, 8H). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ (ppm) 20.91, 34.16, 40.20, 124.15, 127.92, 128.28, 129.94, 132.00, 136.51, 146.66, 149.90, 162.17, 196.98. HRMS: *m/z* 306.

(**3b**): Yellow solid; mp 101 °C; FT-IR (KBr): υ 3076, 2977, 2930, 1719, 1602, 1564, 1479, 1381, 1308, 1216, 1162, 1069, 885, 797, 609 cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ (ppm) 0.95 (t, 3H, J = 6.4, 8.6), 2.78 (s, 3H), 4.03 (q, 2H, J = 6.4, 6.4, 8.6), 7.46-7.96 (m, 8H). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ (ppm) 13.42, 23.50, 61.11, 124.90, 125.70, 128.19, 128.51, 129.15, 130.41, 130.73, 132.09, 134.92, 145.03, 145.88, 154.74, 167.71, 195.83. HRMS: *m/z* 325.

(**3c**): White solid; mp 217 °C; FT-IR (KBr): υ 3390, 1672, 1569, 1480, 1226, 1022, 967, 831, 785, 699 cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ (ppm) 2.62 (s, 3H), 7.25-8.03 (m, 13H). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ (ppm) 23.95, 124.97, 126.12, 128.22, 128.51, 129.19, 129.93, 130.65, 130.91, 132.45, 133.62, 134.20, 136.99, 144.71, 148.28, 155.07, 197.24. HRMS: *m/z* 356.

(**3d**): Yellow solid; mp 211 °C; FT-IR (KBr): υ 3074, 2952, 2866, 1696, 1554, 1477, 1384, 1297, 1198, 1079, 837, 699 cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ (ppm) 1.15 (s, 6H), 2.56 (s, 2H), 3.25 (s, 2H), 7.21-7.95 (m, 8H). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ (ppm) 28.32, 32.16, 48.34, 54.18, 123.34, 126.73, 127.87, 128.07, 128.30, 130.26, 132.41, 136.82, 147.44, 150.03, 161.43, 197.49. HRMS: *m/z* 334.

(**3e**): Yellow solid; mp 135 °C; FT-IR (KBr): υ 3455, 3049, 2948, 1736, 1559, 1481, 1378, 1283, 1214, 1161, 1067, 828, 759, 712, 679 cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ (ppm) 2.76 (s, 3H), 3.58 (s, 3H), 7.47-7.96 (m, 9H). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ (ppm) 23.65, 52.07, 125.12, 125.79, 128.40, 128.71, 129.12, 130.54, 131.02, 132.32, 134.97, 145.39, 148.10, 154.84, 168.47. HRMS: *m/z* 311.

(**3f**): Yellow solid; mp 157 °C; FT-IR (KBr): υ 3076, 2977, 1720, 1561, 1479, 1380, 1219, 1068, 840, 711 cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ (ppm) 2.00 (s, 3H), 2.68 (s, 3H), 7.35-7.95 (m, 8H). HRMS: *m/z* 297.

(**3g**): Yellow solid; ^{1}H NMR (90 MHz, $CDCl_3$): δ (ppm) 2.64 (s, 3H), 7.23-8.11 (m, 14H).

Table 1. I_2 catalysed synthesis of quinolines under solvent-free conditions

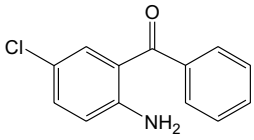
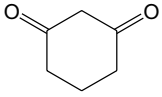
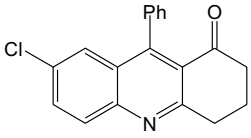
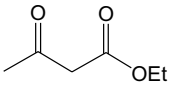
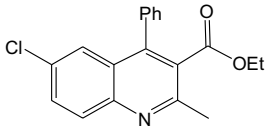
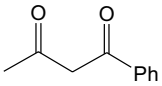
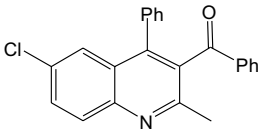
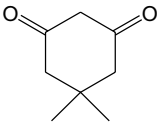
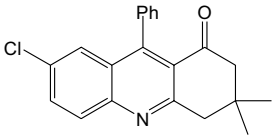
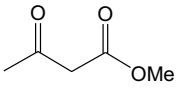
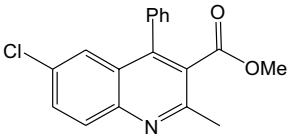
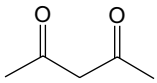
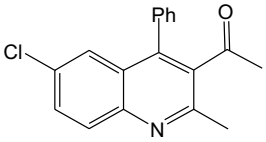
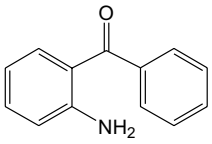
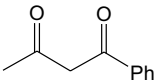
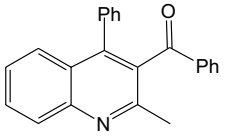
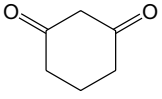
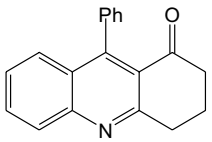
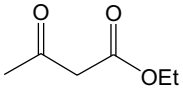
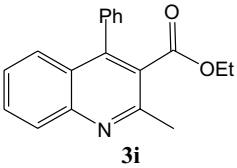
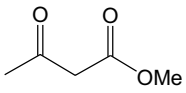
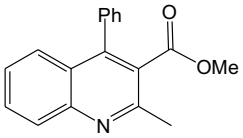
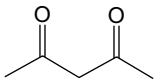
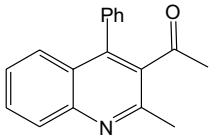
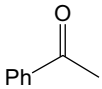
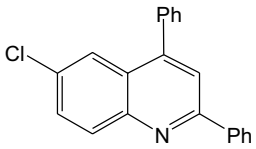
Entry	Substrate **1**	Ketone **2**	Quinoline **3**	Time (h)	Yield (%)[a]
1	 **1a**		 **3a**	1.5	97
2	**1a**		 **3b**	2	80
3	**1a**		 **3c**	3.5	72
4	**1a**		 **3d**	12	50
5	**1a**		 **3e**	1.5	77
6	**1a**		 **3f**	2.75	86
7	 **1b**		 **3g**	4	66
8	**1b**		 **3h**	1.75	80
9	**1b**		 **3i**	1.25	54

Table 1, continued

Entry	Substrate **1**	Ketone **2**	Quinoline **3**	Time (h)	Yield (%)[a]
10	**1b**		 **3j**	2.25	67
11	**1b**		 **3k**	3	80
12	**1a**		 **3l**	15	60

[a] Isolated yields.

(**3h**): Yellow solid; ^{1}H NMR (90 MHz, $CDCl_3$): δ (ppm) 2.21 (q, 2H, *J* = 5.8, 6.2, 5.8), 2.69 (t, 2H, *J* = 6.2, 6.4), 3.36 (t, 2H, *J* = 5.9, 5.9). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ (ppm) 20.86, 34.09, 40.09, 123.38, 125.90, 127.00, 127.67, 128.09, 131.11, 137.20, 148.21, 150.65, 161.73, 197.08.

(**3i**): Yellow solid; mp 99 °C; FT-IR (KBr): υ 3064, 2978, 2928, 1712, 1561, 1402, 1297, 1237, 1182, 1070, 872, 767 cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ (ppm) 0.86 (t, 3H, *J* = 7.7, 8.6), 2.71 (s, 3H), 3.93 (q, 2H, *J* = 7.7, 8.6, 7.7), 7.35-7.95 (m, 9H). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ (ppm) 13.48, 23.39, 61.19, 125.10, 126.44, 127.37, 128.40, 129.25, 130.33, 135.52, 146.61, 147.09, 154.45, 168.00. HRMS: *m/z* 291.

(**3j**): White solid; FT-IR (KBr): υ 3064, 2950, 2885, 1731, 1582, 1562, 1486, 1426, 1392, 1373, 1295, 1229, 1170, 1125, 1067, 1029, 967, 761, 700, 601 cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ (ppm) 2.78 (s, 3H), 3.55 (s, 3H), 7.41-8.03 (m, 9H). HRMS: *m/z* 277.

ACKNOWLEDGMENT

Financial support for this work by the Management and Programming Organization of I.R. Iran (special financial support due to selection by ESI as a top 1% researcher on the basis of paper citation) and Research Affairs, Bu-Ali Sina University, Hamadan, Iran, is gratefully acknowledged.

Received June 6, 2006.

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