HETEROCYCLES, Vol. 75, No. 10, 2008, pp. 2513 - 2521. © The Japan Institute of Heterocyclic Chemistry
Received, 16th May, 2008, Accepted, 9th June, 2008, Published online, 12th June, 2008. COM-08-11442

FRIEDLÄNDER QUINOLINE SYNTHESIS CATALYZED BY $M(HSO_4)_n$ (M=Al, Mg, Ca) UNDER SOLVENT-FREE CONDITIONS

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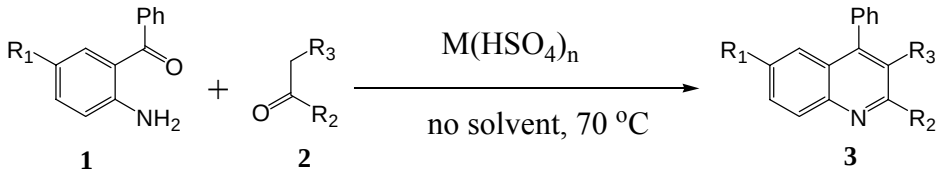
Abstract - Polysubstituted quinolines were synthesized from the 2-aminobenzophenone, ethylacetoacetate or ketones in the presence of metal hydrogen sulfates [$M(HSO_4)_n$] in good to high yields at 70 ˚C under solvent-free conditions.

Inorganic solid acidic salts such metal hydrogen sulfates play a prominent role in organic synthesis under heterogeneous conditions.[1-3] Along this line, using metal hydrogen sulfates especially; $Al(HSO_4)_3$,[4,5] $Mg(HSO_4)_2$,[6,7] $Ca(HSO_4)_2$,[8,9] which are low in toxicity, highly stable towards humidity, recyclable and air stable have found more attention. The importance of these solid acid catalysts is growing because of their safe and eco-friendly nature as attention is directed toward the development of clean and green technologies for important organic molecules to promote environmental safety.

Quinolines and their derivatives are very important compounds because of their wide occurrence in natural products[10] and biologically active compounds.[11,12] A large variety of quinolines have displayed interesting physiological activities and found attractive applications as pharmaceuticals and agrochemicals, as well as being general synthetic building blocks.[10] They show anti-malarial, anti-bacterial, anti-asthmatic, anti-hypertensive, antiinflammatory, anti-platelet and tyrokinase PDGF-RTK inhibiting properties.[13–17] Many synthetic methods such as Skraup, Döbner-von Miller, Friedländer, Combes reactions have been developed for the preparation of quinolines,[18-20] but due to their great importance, the development of novel synthetic approaches remains as active research area.[21-23] Amongst various methodologies reported for the preparation of quinolines, Friedländer annulation's is one of the simplest and most straightforward protocols. Friedländer synthesis involves a condensation followed by a cyclodehydration between an aromatic 2-aminoaldehyde or ketone and an aldehyde or ketone with a α-methylene functionality. Friedländer reaction can occur under base,[24] Brønsted acids,[25] Lewis acid,[26-29] inorganic salt,[30] iodine,[31] solid acid,[32] palladium,[33] nickel chloride,[34] potassium dodecatangestocobaltate

(25 mol %) (PDTC) in solvent-free conditions under microwave irradiation,[35] or ionic liquid-catalyzed,[36] conditions. Generally, better product yields were achieved for the acid-catalyzed Friedländer reactions.[24a] Most of the reported protocols for the synthesis of quinolines suffered from the usage of harmful organic solvents, high reaction temperatures, prolonged reaction times, low product yields, and complicated work-up procedures. Thus, the development of simple, convenient and environmentally friendly approaches for the synthesis of quinolines is still demanding. In connection with our recent reports on the use of metal hydrogen sulfates in organic synthesis[1-3] and in continuation of our studies on the synthesis of quinoline derivatives,[37] we were interested to design some new, cheap and powerful solid acidic salts for Friedländer method.

In this article we introduced a new method by mixing 2-aminobenzophenone, enolizable ketone and metal hydrogen sulfate at 70 ˚C under solvent-free conditions for specified times to give the corresponding quinoline derivatives in good to excellent yields (Scheme 1).



1 **2** **3**

$M(HSO_4)_n$: $Al(HSO_4)_3$, $Mg(HSO_4)_2$, $Ca(HSO_4)_2$

Scheme 1. Synthesis of polysubstituted quinolines catalyzed by $M(HSO_4)_n$

Typically, to a mixture of **1a** (1.0 mmol) and **2a** (1.0 mmol) was added the desired amount of acidic salts. The reaction mixture was heated at 70 ˚C under solvent-free conditions for a designated time. After completion of the reaction, the resulting suspension was neutralized with sodium bicarbonate. Usual work-up afforded product **3a**. The yields, reaction times and amounts of the used acid for the Friedländer reaction of **1a** with **2a** were listed in Table 1.

Table 1: The reaction conditions and yields for the synthesis of quinoline **3a** with different acidic salts[a]

Entry	Acidic salt	Equivalent	Time (h)	Yield (%)
1	None	-	24	Trace
2	$H_4SiW_{12}O_{40}.xH_2O$	0.3	24	<15
3	$KHSO_4$	2.0	24	<25
4	$Al(HSO_4)_3$	0.1	24	41
5	$Al(HSO_4)_3$	0.3	24	58
6	$Al(HSO_4)_3$	0.5	1	90
7	$Mg(HSO_4)_2$	0.5	2	86
8	$Ca(HSO_4)_2$	0.5	0.5	87

[a]Reaction conditions: 2-aminobenzophenone (**1a**) (1 mmol), ethyl acetoacetate (**2a**) (1 mmol); reaction temperature: 70 ˚C; under solvent-free conditions.

From Table 1, it can be seen that all the employed acidic salts can promote the reaction to a certain extent; however, the reaction hardly proceeded in the absence of acids even after long reaction time. In our study, the effect of the amount of the utilized acidic salt on the yield of **3a** was first examined. Take $Al(HSO_4)_3$ as an example, we found that the increase of the amount of the catalyst afforded higher yield of product **3a** (entries 4-6). When 0.5 equivalent of $Al(HSO_4)_3$ was used, the reaction proceeded smoothly and efficiently with almost quantitative yield (entry 6).

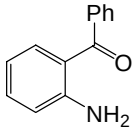
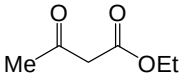
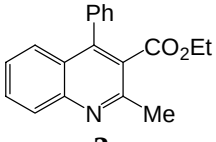
Also, the effect of various solvent on the yield and reaction times of the $Al(HSO_4)_3$ for the Friedländer reaction of **1a** with **2a** was investigated. As shown in Table 2, solvent-free was the best result with respect to reaction time and yield. Although, ethanol, acetonitrile, and ethyl acetate were good, we chose solvent-free for environmentally safety agreement.

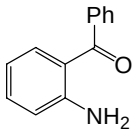
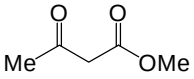
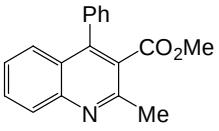
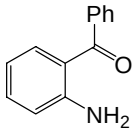
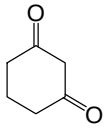
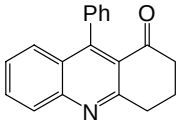
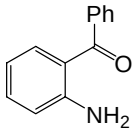
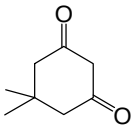
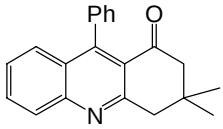
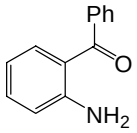
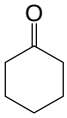
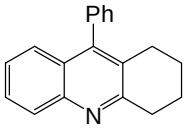
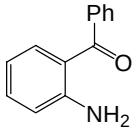
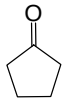
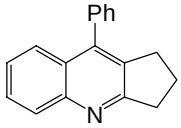
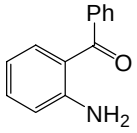
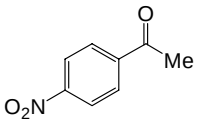
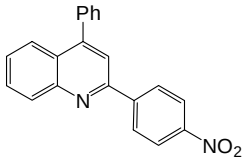
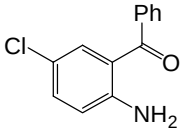
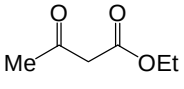
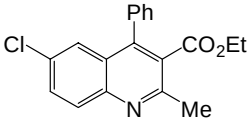
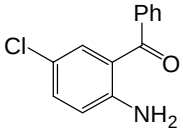
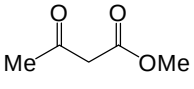
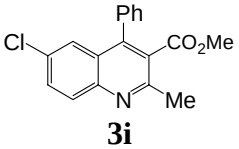
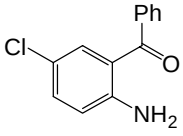
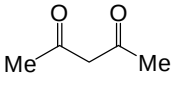
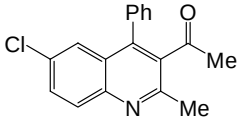
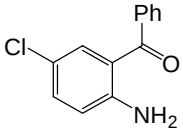
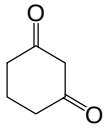
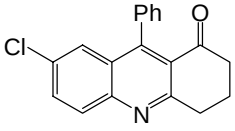
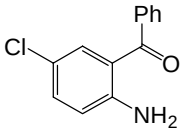
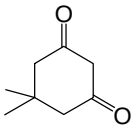
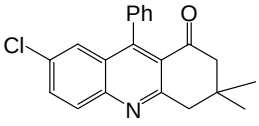
Table 2: The effect of various solvents on the yield and reaction times of 2-aminobenzophenone (1 mmol), ethyl acetoacetate (1 mmol), in the presence of $Al(HSO_4)_3$ (0.5 mmol) at 70 ˚C

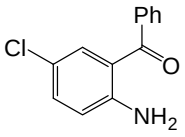
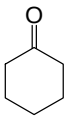
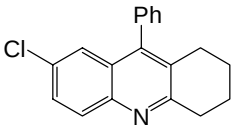
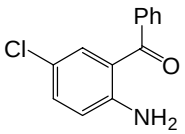
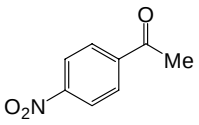
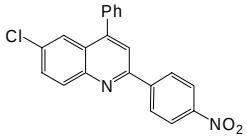
Entry	Solvent	Time (h)	Yield (%)
1	MeOH	14	91
2	EtOH	10	95
3	CH_2Cl_2	24	62
4	$MeCO_2Et$	10	78
5	MeCN	10	88
6	$CHCl_3$	15	67
7	H_2O	24	<15
8	THF	24	72
9	no solvent	1	90

Metal hydrogen sulfates were then extended to other structurally varied substrates to examine the scope and generality of the $M(HSO_4)_n$-catalyzed Friedländer reaction. The reaction times and yields of quinolines **3** for solvent-free reaction of 2-aminoarylketones **1** with α-methylene ketones **2** in a molar ratio of 1:1 in the presence of 0.5 equivalents of metal hydrogen sulfates were collected in Table 3.

Table 3: Preparation of quinoline derivatives by the reaction of 2-aminobenzophenone and carbonyl compounds in the presence of metal hydrogen sulfates [$Al(HSO_4)_3$ (**I**), $Mg(HSO_4)_2$ (**II**), $Ca(HSO_4)_2$ (**III**)][a] at 70 ˚C under solvent-free conditions.

Entry	Substrate	Carbonyl compound	Time (h) **I II III**	Product	Yield (%)[b] **I II III**	Ref.
1			1 2 0.5	 **3a**	90 86 87	28

2			1.5 2 1	 **3b**	88 81 89	31
3			8 12 2	 **3c**	78 89 80	39b
4			3 5 8	 **3d**	89 80 84	39b
5			2 10 7	 **3e**	89 85 86	28
6			5 48 28	 **3f**	82 75 71	39b
7			48 48 72	 **3g**	85 90 72	36b
8			1.5 2 2	 **3h**	90 91 89	31
9			1 4 8	 **3i**	90 81 81	31
10			3.5 4 12	 **3j**	82 83 72	39a
11			3.5 5 10	 **3k**	90 83 86	26
12			2.5 3.5 19	 **3l**	89 90 80	26

13			3 6 5	 **3m**	92 84 90	39b
14			24 72 72	 **3n**	89 85 81	36b

[a]The amount of catalysts was 0.5 mmol. [b]Isolated yield

As seen from Table 3, the current protocol can be applied to 2-aminoarylketones **1** and a wide range of α-methylene ketones such as β-ketoester, cyclic ketones, acyclic and cyclic 1,3-diketones, and tolerate the presence of halogen, ketone and ester groups. Interestingly, cyclic ketones afforded the corresponding tricyclic quinolines.

In comparison with the other reported metal hydrogen sulfates such as $Zr(HSO_4)_4$,[26] $KHSO_4$,[38] $NaHSO_4$-SiO_2,[39] which were done at 100 ˚C or at reflux conditions, we accomplished these reactions at 70 ˚C and mostly shorter reaction times under solvent-free conditions. We hoped that $Al(HSO_4)_3$ would be a superior to the other inorganic acidic metal hydrogen sulfates analogues due to a combination of Lewis and protic acidity.[1]

In conclusion, we have demonstrated that a straightforward, efficient and cost-effective synthesis of biologically active quinolines can be achieved by $M(HSO_4)_n$-catalyzed Friedländer reaction under solvent-free conditions. The notable advantageous of this method are mild reaction conditions, high yield, cheapness, safe, and eco-friendly of the metal hydrogen sulfates.

EXPERIMENTAL

General: Chemicals were purchased from Fluka, Merck and Aldrich chemical companies. IR spectra were run on a Shimadzu Infrared Spectroscopy IR-435. The ^{1}H NMR was run on Bruker Avance (DRX 500 MHz). With TLC using silica gel SILG/UV 254 plates the progress of reaction was followed. All the products are known compounds and were characterized by comparison of their spectral (IR, ^{1}H-NMR), TLC and physical data with the previously reported in the litrature.[26,28,31,36b,39]

General procedure:

A suspension of 2-aminobenzophenone (1 mmol), α-methylene ketones (1 mmol), and metal hydrogen sulfates (M= Mg, Al, Ca) (0.5 mmol) was heated in an oil bath at 70 ˚C under solvent-free conditions for specified time in Table 3. The progress of the reaction was monitored by TLC. After completion of the

reaction, the mixture was poured in ice-water (20 mL), and neutralized with saturated aqueous $NaHCO_3$. Then, the precipitates were filtered and recrystallized from n-hexane/ EtOAc to give corresponding quinoline derivatives.

(**3a**): ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.85 (t, 3H, J= 7.0 Hz), 2.66 (s, 3H), 4.01 (q, 2H, J= 7.0 Hz), 7.31-7.34 (m, 2H), 7.46-7.53 (m, 5H), 7.78 (t, 1H, J= 8.2 Hz), 8.03 (d, 1H, J= 8.3 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.84, 23.76, 61.48, 124.78, 126.44, 127.36, 128.80, 129.00, 129.09, 129.55, 130.98, 135.42, 145.91, 147.56, 154.30, 167.98.

(**3b**): ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.67 (s, 3H), 3.55 (s, 3H), 7.34-7.35 (m, 2H), 7.50-7.54 (m, 5H), 7.81 (t, 1H, J= 6.9 Hz), 8.05 (d, 1H, J= 8.2 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 24.19, 53.08, 125.15, 126.89, 127.75, 127.84, 129.30, 129.53, 129.56, 129.86, 131.48, 135.76, 146.39, 148.04, 154.70, 168.98.

(**3c**): ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.15 (p, 2H, J= 6.3 Hz), 2.65 (t, 2H, J= 6.5 Hz), 3.29 (t, 2H, J= 6.2 Hz), 7.19 (m, 2H), 7.33 (d, 1H, J= 8.3 Hz), 7.46-7.51 (m, 4H), 7.84 (t, 1H, J= 7.2 Hz), 8.03 (d, 1H, J= 8.3 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 21.68, 34.69, 40.90, 124.71, 127.50, 127.57, 128.14, 128.27, 128.77, 129.09, 129.19, 132.57, 138.28, 148.77, 150.80, 163.23, 198.30.

(**3d**): ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.07 (s, 6H), 2.55 (s, 2H), 3.22 (s, 2H), 7.16-7.18 (m, 2H), 7.30-7.33 (m, 1H), 7.46-7.54 (m, 5H), 7.80-7.85 (m, 1H), 8.02 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 28.31, 32.35, 47.85, 53.86, 127.15, 127.95, 128.38, 128.64, 128.79, 128.97, 131.33, 132.15, 134.69, 137.87, 148.77, 150.13, 161.62, 197.79.

(**3e**): ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.09 (m, 2H), 2.11 (m, 2H), 2.86 (t, 2H, J= 7.0 Hz), 3.23 (t, 2H, J= 7.20 Hz), 7.40-7.42 (m, 2H), 7.53-7.60 (m, 5H), 7.77 (t, 1H, J= 8.1 Hz), 8.05 (d, 1H, J= 8.1 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 22.76, 22.89, 27.96, 34.51, 126.39, 126.51, 126.77, 127.67, 129.56, 129.64, 129.88, 130.61, 135.67, 136.02, 144.78, 145.73, 167.20.

(**3f**): ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.08 (p, 2H, J= 7.4 Hz), 2.83 (t, 2H, J= 7.3 Hz), 3.11 (t, 2H, J= 7.6 Hz), 7.40-7.45 (m, 3H), 7.49-7.58 (m, 4H), 7.65 (t, 1H, J= 7.5 Hz), 7.98 (d, 1H, J= 8.3 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 23.84, 30.66, 35.27, 125.93, 126.33, 126.50, 128.99, 129.01, 129.50, 129.57, 130.01, 134.23, 136.90, 142.49, 148.41, 167.96.

(**3g**): ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.58-7.65 (m, 6H), 7.84 (t, 1H, J= 7.6 Hz), 7.88 (d, 1H, J= 8.3 Hz), 8.14 (s, 1H), 8.20 (d, 1H, J= 8.3 Hz), 8.34 (d, 2H, J= 8.9 Hz), 8.59 (d, 2H, J= 8.9 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 120.05, 124.73, 126.18, 126.33, 128.53, 129.39, 129.60, 130.40, 130.49, 130.83, 131.09, 138.09, 145.29, 148.86, 148.94, 149.98, 154.26.

(**3h**): ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.85 (t, 3H, J= 7.0 Hz), 2.64 (s, 3H), 4.02 (q, 2H, J= 7.0 Hz), 7.32-7.37 (m, 3H), 7.53-7.54 (m, 3H), 7.79 (d, 1H, J= 8.9 Hz), 8.03 (d, 1H, J= 8.9 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.83, 23.73, 61.66, 124.91, 125.70, 128.16, 128.99, 129.41, 129.52, 131.34, 131.46, 131.85, 134.67, 145.17, 145.96, 155.03, 167.60.

(**3i**): ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.67 (s, 3H), 3.56 (s, 3H), 7.35-7.37 (m, 2H), 7.41 (d, 1H, J= 2.2 Hz), 7.56-7.58 (m, 3H), 7.83 (dd, 1H, J_1= 8.9 Hz, J_2= 2.3 Hz), 8.06 (d, 1H, J= 8.9 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 24.16, 53.21, 125.39, 126.09, 128.55, 129.48, 129.83, 129.89, 131.81, 132.33, 135.05, 145.67, 146.48, 155.45, 168.60.

(**3j**): ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.05 (s, 3H), 2.60 (s, 3H), 7.36-7.40 (m, 3H), 7.58-7.59 (m, 3H), 7.80 (dd, 1H, J_1= 8.9 Hz, J_2= 2.0 Hz), 8.05 (d, 1H, J= 8.9 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 24.27, 32.59, 125.08, 126.32, 129.76, 130.14, 130.54, 131.55, 131.70, 132.19, 134.78, 136.19, 143.34, 146.13, 154.77, 205.59.

(**3k**): ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.15 (p, 2H, J= 6.5 Hz), 2.66 (t, 2H, J= 6.5 Hz), 3.28 (t, 2H, J= 6.5 Hz), 7.20-7.23 (m, 3H), 7.48-7.52 (m, 3H), 7.85 (dd, 1H, J_1= 8.9 Hz, J_2= 2.3 Hz), 8.06 (d, 1H, J= 8.9 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 21.53, 34.66, 40.82, 125.36, 126.54, 128.48, 128.97, 129.07, 131.53, 131.94, 132.92, 137.59, 147.25, 149.83, 163.93, 198.12.

(**3l**): ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.08 (s, 6H), 2.57 (s, 2H), 3.22 (s, 2H), 7.19-7.23 (m, 3H), 7.49-7.51 (m, 3H), 7.86 (d, 1H, J= 8.9 Hz), 8.06 (d, 1H, J= 8.9 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 28.71, 32.71, 48.19, 54.20, 124.08, 126.63, 128.46, 128.48, 128.97, 129.05, 131.52, 132.01, 132.93, 137.55, 147.62, 149.66, 162.70, 197.99.

(**3m**): ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.73 (m, 2H), 1.88 (m, 2H), 2.54 (t, 2H, J= 6.2 Hz), 3.08 (t, 2H, J= 6.2 Hz), 7.13 (s, 1H), 7.29 (d, 2H, J= 7.1 Hz), 7.53-7.66 (m, 4H), 7.96 (d, 1H, J= 8.8 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 23.00, 23.11, 28.41, 34.44, 124.58, 127.67, 129.11, 129.70, 129.75, 129.80, 130.21, 130.88, 131.44, 136.49, 145.08, 145.77, 160.41.

(**3n**): ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.63-7.71 (m, 5H), 7.83 (d, 1H, J= 2.2 Hz), 7.90 (dd, 1H, J_1= 8.9 Hz, J_2= 2.3 Hz), 8.25-8.28 (m, 2H), 8.40 (d, 2H, J= 8.9 Hz), 8.65 (d, 2H, J= 8.9 Hz). ^{13}C NMR (125 MHz, DMSO-d_6): δ 119.93, 124.13, 124.67, 126.90, 128.44, 129.01, 129.14, 129.41, 131.26, 131.67, 133.48, 137.15, 144.64, 146.87, 148.52, 149.52, 154.18.

ACKNOWLEGMENT

We are thankful to the Persian Gulf University Research Council for partial support of this work.

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