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GREEN APPROACH FOR THE EFFICIENT SYNTHESIS OF QUINOLINES PROMOTED BY CITRIC ACID

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Abstract – Citric acid promoted Friedlander synthesis of a mini-library of poly substituted quinolines (30 examples) at 100 ^{o}C under solvent-free conditions was achieved in moderate to excellent yields (54-99%). The method is simple, cost-effective and environmentally benign.

INTRODUCTION

Quinolines are privileged scaffolds possessing wide applications in medicinal chemistry,[1] being used as antimalarial, anti-inflammatory, anti-asthametic, antibacterial, antihypertensive and tyrosine kinase PDGF-RTK inhibiting agents.[2] In addition, quinolines are valuable synthons, used for the nano and mesostructures with enhanced electronic and photonic properties.[3] Although other methods such as Skraup, Doebner von Miller, and Combes procedures have been reported[4] for the preparation of quinolines, the Friedlander annulation is one of the most simple and straightforward methods for the synthesis of substituted quinolines.

The Friedlander synthesis is an acid or base catalyzed condensation followed by a cyclodehydration between 2-aminoaryl ketone and a second carbonyl compound containing a reactive α-methylene group. Generally, this reaction is carried out by refluxing an aqueous or alcoholic solution of reactants in the presence of base at high temperature.[5] Under thermal or base catalysis conditions, *o*-aminobenzophenone

fails to react with simple ketones such as cyclohexanone and β-keto esters.[6] Recently, notable Bronsted and Lewis acids[7] such as H_2SO_4, HCl, $ZnCl_2$, $NaAuCl_4{\cdot}2H_2O$, $Y(OTf)_3$, $SnCl_2{\cdot}2H_2O$, $FeCl_3$, ionic liquids, molecular iodine, $Nd(NO_3)_3{\cdot}6H_2O$, *p*-TsOH, TCT (2,4,6-trichloro-1,3,5-triazine or cyanuric chloride), $CeCl_3{\cdot}7H_2O$, $[Sc(O_3SOC_{12}H_{25})_3]$, silver phosphotungstate, zirconium tetra(dodecyl sulfate) ($Zr(DS)_4$), amberlyst-15, and sulfonated cellulose and starch have been shown to be effective for the synthesis of quinolines. However, most of the methods have significant drawbacks such as low yields of the products, harsh reaction conditions, difficulties in work-up and often use of expensive acid and base catalysts.

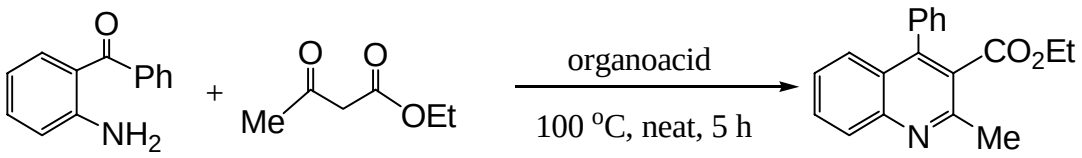
Furthermore, the synthesis of quinolines in general have been carried out in polar solvents such as acetonitrile, THF, DMF, and DMSO leading to complex isolation and recovery procedures. Since quinoline derivatives are increasingly useful and important in drugs and pharmaceuticals, the development of a simple, efficient and environmentally benign protocol is still desirable.

Another promising synthetic approach to environmentally friendly chemistry is to minimize or eliminate the use of harmful organic solvents. Organic reactions under solvent-free conditions are advantageous because of their enhanced selectivity and efficiency, ease of manipulation, cleaner product formation, and toxic or often volatile solvents are avoided.[8] In recent years, a lot of attention has been paid to organocatalysts owing to their eco-friendliness and can proceed under aerobic atmosphere, other notable advantages are: usually less expensive and commercially available.[9]

RESULTS AND DISCUSSION

Based on our recent expertise and following related literature reports on utilization of organoacids as promoters in construction of various heterocycles,[10] and also our continued efforts in developing novel synthetic routes for carbon-carbon, carbon-heterobond formations,[11] we at first began our study for the model reaction using 2-aminobenzophenone (1 mmol) and ethyl acetoacetate (EAA, 1.1 mmol) at 100 ^oC for a period of 5 h under neat conditions promoted by 4-nitrobenzoic acid (1 equiv.). As we expected, the corresponding quinoline was isolated in good yield (entry 2, Table 1).

Table 1. Model reaction 2-aminobenzophenone with EAA



Entry	Organoacid	Isolated Yield (%)
1	malonic acid	78
2	4 -nitrobenzoic acid	88
3	*p*-anisic acid	69
4	tartaric acid	80
5	*p*-TsOH	90
6	anthranilic acid	58
7	citric acid	94
8	benzoic acid	79
9	cinnamic acid	65
10	proline	70
11	mandelic acid	74
12	2-picric acid	86
13	no catalyst	42

Inspired by this result, we surveyed the efficacy of various organoacids chosen (Table 1) under the above reaction conditions for the model reaction. Among the catalysts screened, citric acid (entry 7, Table 1) showed the best result with a 94% isolated yield. Citric acid is a tricarboxylic weak organoacid which serves as an environmentally benign cleaning agent,[12] relatively inexpensive reagent. In the absence of any catalyst, 42% of the isolated yield was observed (entry 13, Table 1).

The optimum yields of the product were obtained when a ratio of substrate to EAA (1:1.1). Further, 0.5 equiv. of promoter was sufficient to give the optimum yield whereas the reaction was sluggish when carried out decreasing the amount of catalyst loadings further. The desired product could not be obtained in the same yield (94%) at the temperature lower than 100 ^{o}C. To the best of our knowledge, there are no earlier reports on the preparation of quinolines using citric acid as an organo promoter.

Then, we studied the effect of various solvents on the model reaction and the results are summarized in Table 2. As can be seen from Table 2, good yield was obtained using water (entry 1, Table 2) as reaction medium, thus opening the scope for green chemistry as well. Compared to the organic solvents tested (entries 2-4 and 6-7, Table 2), solvent free conditions afforded excellent isolated yields (94%, entry 5, Table 2) under the optimized conditions.

Table 2. Effect of solvents on the model reaction

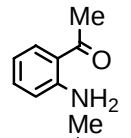
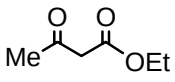
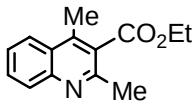
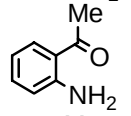
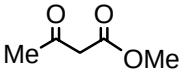
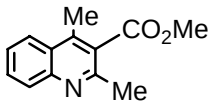
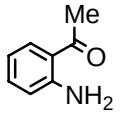
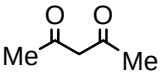
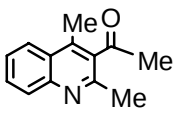
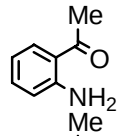
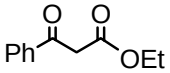
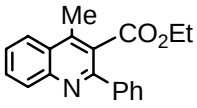
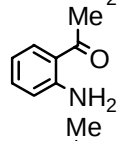
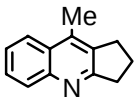
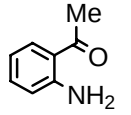
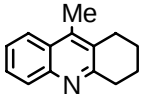
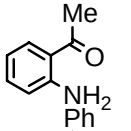
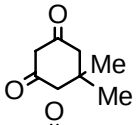
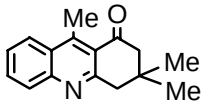
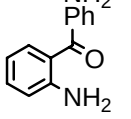
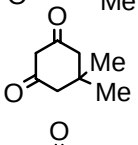
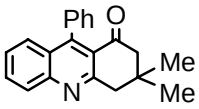
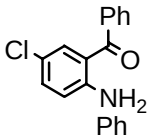
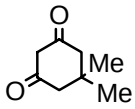
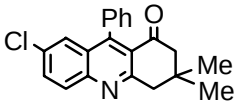
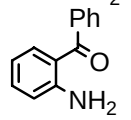
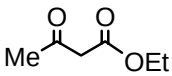
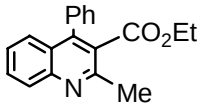
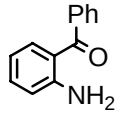
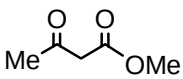
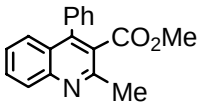
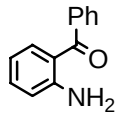
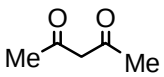
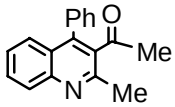
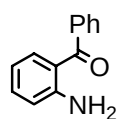
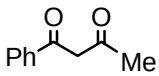
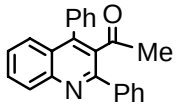
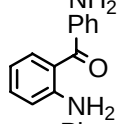
Entry	Solvent	Yield (%)[a]
1	H_2O	76
2	THF	73
3	$CHCl_3$	80
4	MeCN	58
5	neat	94
6	toluene	21
7	DMF	0

[a]Isolated yields.

To determine the scope of the methodology, the reaction was performed with model reaction on a 20 mmol scale using citric acid (0.5 equiv.). And to our utmost satisfaction, the reaction was complete in 5 h affording the corresponding product in 92% isolated yield, thus confirming the possibility of being scaled up.

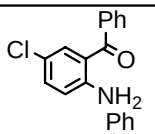
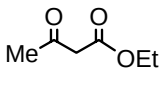
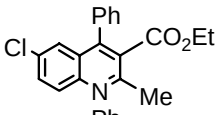
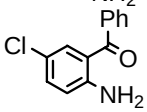
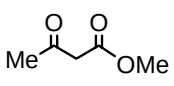
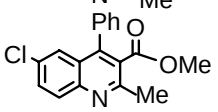
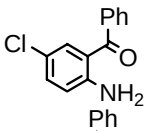
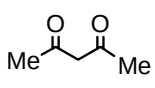
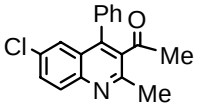
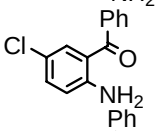
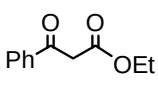
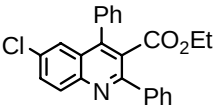
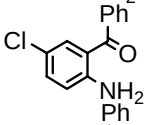
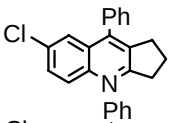
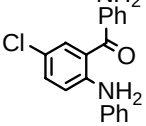
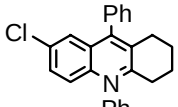
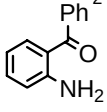
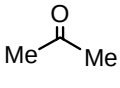
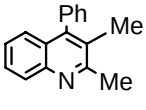
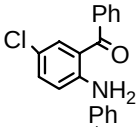
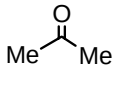
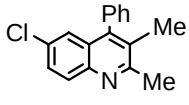
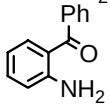
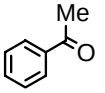
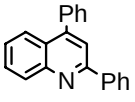
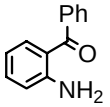
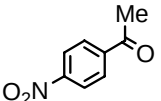
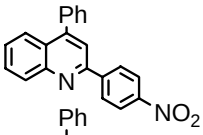
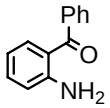
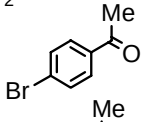
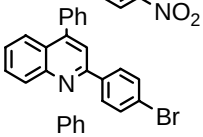
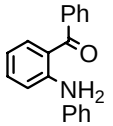
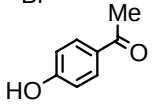
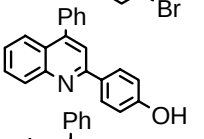
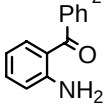
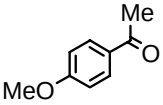
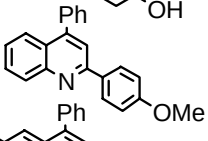
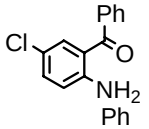
Intrigued by the results obtained under optimized conditions, we then examined various structurally divergent 2-aminoaryl ketones such as 2-aminobenzophenone, 2-aminoacetophenone, and 2-amino-5-chlorobenzophenone for the condensation to take place; and β-keto esters could also be extended to other α-methylene ketones such as cyclopentanone, cyclohexanone, 5,5-dimethylcyclohexanedione (dimedone) and the results are summarized in Table 3. The present protocol is equally effective for both cyclic and acyclic ketones. In all cases reactions were clean and devoid of self-condensation of ketones, which are normally observed under basic conditions. Furthermore, most of the products (solids) were isolated by simple filtration as described in experimental procedure.

Table 3. Synthesis of polysubstituted quinolines promoted by citric acid

Entry	α-aminoaryl ketone	α-methylene ketone	Product	Time (h)	Yield (%)[a]	Mp (°C) Lit.[ref.]	Mp (°C) Found
1				5	93	oil[7]	oil
2				5	95	oil[7]	oil
3				5	93	oil[7]	oil
4				5.5	82	oil[7]	oil
5				2	92	58-60[7]	60
6				4	86	75-77[7]	76
7				4	98	105-107[7]	108
8				5	69	65-66[7]	65
9				5	75	208-210[7]	210
10				5	94/92[b]	98-99[7]	100
11				5.5	83	99-100[7]	99
12				5	88	114-116[7]	114-116
13				5	78	105-107[7]	88
14				2	95	139-141[7]	140-141
15				4	99	140-142[7]	141-142

[a] Isolated yields. [b]Reaction on 20 mmol scale.

Table 3. Synthesis of polysubstituted quinolines promoted by citric acid

Entry	α-aminoaryl ketone	α-methylene ketone	Product	Time (h)	Yield (%)[a]	Mp (°C) Lit.[ref.]	Mp (°C) Found
16				5	84	108[7]	108
17				5	96	133-135[7]	135
18				5	92	149-150[7]	149
19				5	78	105-107[7]	106
20				5	87	104-105[7]	104
21				5	84	131-132[7]	131-132
22				3	93	98-99[7]	99
23				3	88	127[7]	127
24				6	79	105-107[7]	106
25				6	70	-	161
26				6	65	-	126
27				8	54	-	137
28				6	72	-	162-163
29				8	74	102[7]	101-103
30				8	58	195[7]	194-196

[a] Isolated yields. [b]Reaction on 20 mmol scale.

The proposed mechanism for the citric acid-promoted synthesis of substituted quinolines may tentatively be visualized to occur via a tandem sequence of reactions involving initially the formation of

amino-ketone condensation, thereafter activation of carbonyl oxygen of second carbonyl compound containing active methylene group by carboxylic hydrogen of citric acid through *intermolecular hydrogen bonding*, and subsequent cyclocondensation to produce a quinoline derivative.

The efficiency and generality of the present citric acid-promoted protocol can be realized at a glance by comparing our results for the chosen model substrate (entry 7, Table 1) with those of some recently reported procedures (as shown in Table 4). The reaction has been compared to with respect to the reaction times and isolated yields.

Table 4. Comparision of the catalytic efficiency of citric acid with some recently reported catalysts for the model reaction

Entry	Catalyst [ref]	Time (h)	Isolated yield (%)
1	$NaAuCl_4 \cdot 2H_2O$[7]	6	83
2	$Nd(NO_3)_3 \cdot 6H_2O$[7]	10	92
3[a]	bmimCl:$ZnCl_2$	24	92
4	I_2[7]	16	96
5	citric acid	5	94
6	$Y(OTf)_3$[7]	4	89
7	$Sc(O_3SOC_{l2}H_{25})_3$[7]	12	94
8	$Zr(DS)_4$[7]	3	72
9	Amberlyst-15[7]	2.5	89
10	$CeCl_3 \cdot 7H_2O$[7]	1.5	95

[a]bmim=1-butyl-3-methyl imidazolium chloride

In conclusion, we have demonstrated a mild and efficient eco-friendly Friedlander synthesis of quinolines, using citric acid as a novel organoacid green promoter, that uses neither harsh conditions nor the use of hazardous acids or bases. Notable advantages of our protocol includes: (a) operational simplicity, (b) good substrate scope, (c) the relatively non-toxic, inexpensive, water soluble organocatalyst (d) high yields of products (e) no transition metal contamination.

EXPERIMENTAL

Experimental protocols

Melting points were recorded a Buchi R-535 apparatus. IR spectra were determined on a Bruker Vector-22 spectrometer. ^{1}H NMR spectra of $CDCl_3$ solutions were recorded on Bruker Avance-300 spectrometer. The chemical shifts are reported as parts per million downfield from tetramethylsilane. ^{13}C NMR spectra (75.5 MHz) were recorded on a Bruker Avance-300 spectrometer with complete proton

decoupling; chemical shifts are reported in ppm relative to the solvent resonance as the internal solvent ($CDCl_3$, δ = 77.16). Mass spectra were recorded on a VG7070H micromass spectrometer. Elemental analysis was performed on a Vario EL analyzer. The purity of the compounds was checked by TLC on precoated SiO_2 gel (HF254, 100-200 mesh) aluminum plates (E. Merck) using *n*-hexane: EtOAc (9:1) as mobile phase and visualized by iodine vapors.

General procedure

A mixture of *o*-amino-aryl ketone (1.0 mmol), α-methylene ketone (1.1 mmol) and citric acid (0.5 mmol)**,** was stirred at 100 ^{0}C under solvent-free conditions for appropriate time (**Table 3**). After completion of the reaction as indicated by TLC, the reaction mixture was diluted with water (2 mL) and the solid quinoline product which separated out was filtered, washed with water and dried. The crude solid was then recrystallized from a mixture of Et_2O and hexane. For liquid quinolines, the reaction mixture was extracted in Et_2O (2×5 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product which was further purified either by a short column chromatography (silica gel, EtOAc-hexane, 1:9) to afford the corresponding pure quinoline derivative.

All the compounds were known and characterized by IR, NMR, mass spectrometry and also by comparing their physical characteristics with those in the literature.[4-7]

Please see supporting information for spectral data for selected compounds.

Spectral data for representative compounds:

Entry 3, Table 3: Oil; IR (NaCl): ν 3068, 2959, 1703, 1614, 1585, 1208, 758 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.57 (s, 3H), 2.58 (s, 3H), 2.62 (s, 3H), 7.53-8.01 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15, 23.3, 32.4, 123.5, 126.2, 129, 129.6, 135.6, 138.4, 146.7, 152.4, 206.3; MS (EI, 70 eV): *m*/*z*= 199 (M^+), 158, 125; Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.32; H, 6.51; N, 7.07. **Entry 5, Table 3**: Solid; mp 60 ^{o}C; IR (KBr): ν 3065, 2957, 1613, 908, 751 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.2 (m, 2H), 2.49 (s, 3H), 2.99 (t, *J* =7.55 Hz, 2H), 3.3 (t, *J* =6.9 Hz, 2H), 7.46-8.01 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.6, 22.7, 29.4, 34.8, 123.1, 125.0, 126.9, 127.8, 128.9, 133.7, 137.8, 147.2, 166.7; MS (EI, 70 eV): *m*/*z*= 183 (M^+), 168, 154, 140, 127, 115, 102, 90, 77, 63, 57; Anal. Calcd for $C_{13}H_{13}N$: C, 85.21; H, 7.15; N, 7.64. Found: C, 85.17; H, 7.07; N, 7.72. **Entry 9, Table 3**: Yellow solid; mp 210 ^{o}C; IR (KBr): ν 3074, 2952, 2866, 1696, 1554, 1477, 1384, 1297, 1198, 1079, 837, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (s, 6H), 2.56 (s, 2H), 3.25 (s, 2H), 7.14-7.17 (m, 2H), 7.43-7.97 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.3, 32.1, 48.3, 54.2, 123.3, 126.7, 127.8, 128.1, 128.3, 130.2, 132.4, 136.8, 147.4, 150.0, 161.4, 197.5; MS (EI, 70 eV): *m*/*z*= 335 (M^+); Anal. Calcd for $C_{21}H_{18}ClNO$: C, 75.11; H, 5.40; N, 4.17. Found: C, 75.07; H, 5.43; N, 4.21. **Entry 16, Table 3:** Yellow

solid; mp 108 ^{o}C; IR (KBr): ν 3064, 2983, 1725, 1605, 1224, 907, 732 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$):0.92-0.95 (t, J = Hz, 3H), 2.73 (s, 3H), 4.03-4.07 (q, J = 7 Hz 2H), 7.32-8 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.5, 23.6, 61.4, 125.1, 125.9, 128.4, 128.7, 129.2, 130.5, 131, 132.3, 135, 145.3, 146, 154, 168; MS (EI, 70 eV): m/z= 325 (M^+), 296, 280, 252, 217, 189, 176, 149, 123, 109, 88, 71, 57; Anal. Calcd for $C_{20}H_{19}ClNO_2$: C, 70.05; H, 4.95; N, 4.30. Found: C, 70.09; H, 4.90; N, 4.36. **Entry 21, Table 3**: Yellow solid; mp 165 ^{o}C; IR (KBr): ν 3059, 2945, 2858, 1599, 1570, 1477, 1440, 1349, 1266, 1165, 1075, 937, 831, 818, 757, 708, 617 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55 (m, 2H), 1.59 (m, 2H), 2.56 (t, J =6.5 Hz, 2H), 3.3 (t, J=7 Hz, 2H), 7.2-8.02 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23, 28.2, 34.3, 124.6, 127.5, 128.2, 128.9, 129.1, 129.3, 129.5, 130.2, 131.3, 136.5, 144.8, 145.8, 159.6; MS (EI, 70 eV): m/z= 293 (M^+), 278, 258, 242, 230, 201, 189, 176, 150, 89, 77. Anal. Calcd for $C_{19}H_{16}ClN$: C, 77.68; H, 5.49; N, 4.77. Found: C, 77.59; H, 5.34; N, 4.68. **Entry 29, Table 3:** Solid; mp 101-103 ^{o}C; IR (KBr): ν 3055, 1684, 1483, 907, 729 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.4-8.02 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 120, 124.4, 126.4, 127.5, 128.7, 128.8, 129.4, 130.4, 131.6, 132.7, 137.7, 139.1, 147.2, 148.4, 157; MS (EI, 70 eV): m/z= 316 (M^+), 288, 125; Anal. Calcd for $C_{21}H_{14}ClN$: C, 79.87; H, 4.47; N, 4.44. Found: C, 79.81; H, 4.52; N, 4.41.

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