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Note

$MgCl_2 \cdot 6H_2O$/*p*-TSA catalyzed simple and efficient synthesis of some known and novel quinolines

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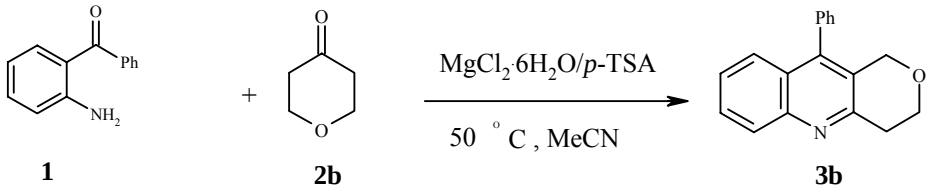
A simple and efficient method has been developed for the synthesis of some important fused quinolines from *o*-aminoaryl ketones and α-methylene ketones in the presence of catalytic amounts of $MgCl_2 \cdot 6H_2O$/*p*-TSA in high yield. The reaction works at ambient temperature to give the products within 40 min.

Keywords: Quinoline, *o*-aminoaryl ketones, α-methylene ketones, Friedlander heteroannulation

The fused polycyclic quinoline moiety is a ubiquitous subunit in many natural products with remarkable pharmacological activity such as antimalarial, anti-inflammatory, antiasthmatic, antibacterial and antihypertensive activities[1,2]. Tyrosine kinase PDGF-RTK inhibiting properties[3] continues to spur synthetic efforts regarding their acquisition[4]. In addition, quinolines are valuable synthons for the preparation of nano-meso structures and polymers that combine enhanced electronic, optoelectronic or non-linear optical properties with excellent mechanical properties[5]. A number of catalysts have been developed for the synthesis of quinolines such as $AuCl_3 \cdot 3H_2O$, $FeCl_3$, $ZnCl_2$, $Mg(ClO_4)_2$, $SnCl_2$, $Bi(OTf)_3$, $Sc(OTf)_3$, $Y(OTf)_3$, $NaAuCl_4 \cdot 2H_2O$, silver phosphotungstate[6], diphosgene/acetonitrile[7] and $ZnCl_2$/triethylamine[8] have been used for Friedlander reaction. Ruthenium, palladium, and iron complexes have been shown to affect the formation of 2,3-disubstiuted quinolines from nitrobenzene and aldehydes or alcohols in the presence of CO (ref. 9). Aniline was shown to undergo *N*-heterocyclization to generate quinolines with aliphatic aldehydes in the presence of transition-metal complexes[10]. The synthesis of polyhydroquinoline is also carried out under microwave irradiation[10f]. Friedlander reaction is also effected in the absence of catalysts by refluxing an aqueous or alcoholic solution at temperature ranging from 150−220˚C (ref.11). Many of these methods have significant drawbacks such as involving expensive reagents, strongly acidic conditions, longer reaction duration, high temperature, difficulties in work-up, stoichiometric quantities of reagents, incompatible with other functional groups, cumbersome product isolation, environmental pollution and unsatisfactory yields.

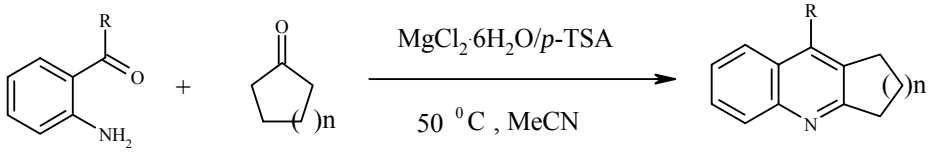
In the past reports[12,13], the synthesis of biologically active compounds using metal chlorides and *p*-TSA[13b,c] using different methodologies have been described. Herein the use of an economical reagent $MgCl_2 \cdot 6H_2O$ and catalytic amount of *p*-TSA, for the facile synthesis of some known and novel quinolines is reported. Accordingly, a mixture of 2-amino-benzophenone **1**, tetrahydro-4*H*-pyran-4-one **2**, $MgCl_2 \cdot 6H_2O$ and catalytic amount of *p*-TSA in acetonitrile was stirred at 50ºC to get 10-phenyl-3,4-dihydro-1*H*-pyrano[4,3-*b*] quinoline **3b** in 94% yield (**Scheme I**). Five novel quinolines have been synthesized from different heterocyclic ketones like tetrahydro-4*H*-pyran-4-one, *N*-methyl-4-pyperidone, indane-1,3-dione and benzylacetoacetate, and it has been found that, these ketones smoothly react with *o*-aminobenzophenone to give corresponding products in excellent yields.

Other cyclic ketones such a cyclopentanone and cyclohexanone also underwent smooth condensation with *o*-aminoaryl ketones (**Scheme II**). The method is equally effective for both cyclic and acyclic ketones (**Table I**), thus is very useful for the preparation of quinolines from both *o*-aminobenzophenones and *o*-aminoacetophenones. Acetonitrile was found to be the superior solvent giving the bests results (**Table II)**. The efficacy of other combination of metal chlorides was studied for this reaction and the results are presented in **Table III**. Among the catalysts used, $MgCl_2 \cdot 6H_2O$ and catalytic amount of *p*-TSA was found to be superior in terms of conversion and reaction rates. However, in the absence of metal chloride or *p*-TSA, the reaction is incomplete even after 5 hr. All the products were characterized by spectral analysis and by comparison with authentic samples.



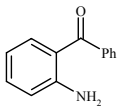
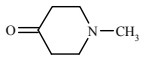
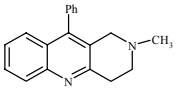
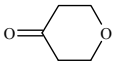
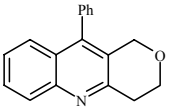
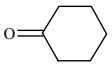
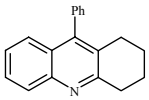
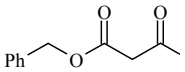
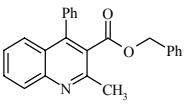
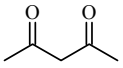
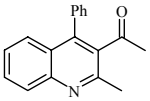
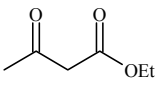
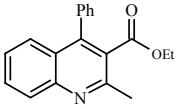
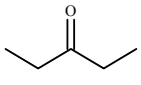
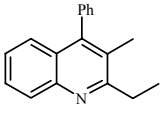
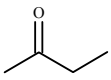
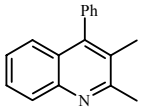
1 **2b** **3b**

Scheme I



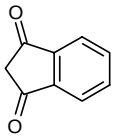
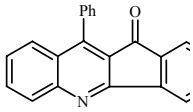
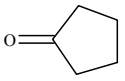
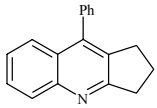
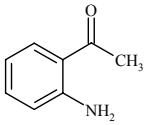
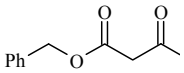
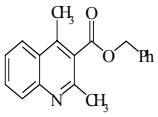
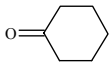
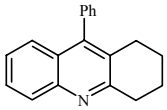
Scheme II

Table I — $MgCl_2 \cdot 6H_2O$/*p*-TSA-catalyzed synthesis of 2,3,4-trisubstituted quinolines

Entry	*o*-Aminoketone **1**	Ketone **2**	Quinoline[a] **3**	Time (min)	Yield[b] (%)	m.p.(Lit.)(ºC)
a				40	92	98-100[†]
b				40	94	135-136[†]
c				45	90	140(138)[c]
d				50	95	82[†]
e				40	88	115(115)[c]
f				40	90	98(99-100)[c]
g				40	94	95-96(96)[c]
h				40	82	144(147)[c]

—Contd

Table I — $MgCl_2·6H_2O$/*p*-TSA-catalyzed synthesis of 2,3,4-trisubstituted quinolines—*Contd*

Entry	*o*-Aminoketone **1**	Ketone **2**	Quinoline[a] **3**	Time (min)	Yield[b] (%)	m.p.(Lit.)(ºC)
i				50	95	172[†]
j				45	92	132(132-134)[c]
k				45	94	89[†]
l				45	92	132(131)[c]

[†] Novel compounds **a, b, d, i** and **k** are characterized by IR, ^{1}H NMR and LC-mass spectral analysis. [a] Products **c, e, f, g, h, j** and **l** are known and compared with the authentic samples (reference 9f). [b] Isolated yields. [c] Reported melting points

Experimental Section

Melting points were determined on a Büchi melting point apparatus and are uncorrected. IR, ^{1}H NMR, ^{13}C NMR and LC-MS were recorded on Nicolet 400DFT-IR spectrophotometer, 400 MHz Brucker-spectrometer and Agilent LC-MS respectively. *o*-Aminoaryl ketone, Ketones and metal chlorides were all commercial products and were used without further purification.

General procedure for the preparation of quinolines. A mixture of the *o*-aminoaryl ketone (**1**, 0.5 mmole), ketone (**2**, 1.2 equiv.), $MgCl_2·6H_2O$ (25 mole%) and *p*-TSA (1 mole%) in MeCN (1.0 mL) was stirred at 50ºC. After completion of the reaction (TLC), the reaction-mixture was filtered to separate $MgCl_2$ ($MgCl_2$ thus separated was washed with MeCN, dried and kept aside for reuse), mother liquor was concentrated and taken into EtOAc (2 × 10 mL), washed with 10% aqueous $NaHCO_3$ and brine, evaporation of the solvent gave the crude product; recrystallization from hexane or by purification on silica gel column afforded pure quinoline.

Spectral data for novel compounds

2-Methyl-10-phenyl-1,2,3,4-tetrahydrobenzo[*b*]1,6-napthhydrine 3a

IR (KBr): 3059, 2950, 2841, 2764, 1584, 1491, 1409, 1362, 1264, 1171, 948, 768 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H), 2.87−2.90 (t, *J* = 4.0 Hz, 2H), 3.35−3.38 (t, *J* = 4.0 Hz, 2H), 3.48 (s, 2H), 7.25−7.27(m, 2H), 7.34−7.35(d, *J* = 4.0 Hz, 2H), 7.53−7.57(m, 3H), 7.6−7.65 (m, 1H), 8.03−8.05 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 33.69, 46.07, 52.87, 56.65, 125.9, 125.69, 125.82, 126.4, 128.1, 128.4, 128.7, 128.81, 128.95,135.93, 145.06, 146.7, 155.72; MS: (*m/z*) 275 (M^+)

10-Phenyl-3,4-dihydro-1*H*-pyrano[4,3-*b*]quinoline 3b

IR (KBr): 3053, 2976, 2940, 2872, 1590, 1491, 1403, 1238,1109, 772 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.3−3.4 (t, *J* = 6.0 Hz, 2H), 4.15−4.18 (t, *J* = 6.0 Hz, 2H), 4.63 (s, 2H), 7.2−7.41 (m, 2H), 7.4−7.49 (m, 2H), 7.52−7.66 (m, 3H), 7.66−7.7 (t, *J* = 2.0 Hz, 2H), 8.10 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR

Table II — Comparative study of use of various organic solvents for the synthesis of 10-Phenyl-3,4-dihydro-1*H*-pyrano [4,3-*b*] quinoline **3b** in the presence of $MgCl_2 \cdot 6H_2O$/*p*-TSA

Entry	Solvent	Temperature (˚C)	Time (hr)	Yield (%)
1	MeOH	60–65	5	70
2	EtOH	60–65	5	75
3	THF	60–65	5	60
4	CH_2Cl_2	60–65	5	35
5	$CHCl_3$	60–65	5	32
6	C_6H_6	60–65	5	60
7	$C_6H_5CH_3$	60–65	5	64
8	MeCN	60–65	1	85
9	MeCN	55–60	0.83	88
10	MeCN	50	0.67	92

[a] Isolated and unoptimized yields

Table III — Comparative study of various metal chloride with $MgCl_2$ /*p*-TSA in the synthesis 10-Phenyl-3,4-dihydro-1*H*-pyrano [4,3-*b*] quinoline **3b** in the presence of MeCN

Entry	Catalysts	Temperature (˚C)	Time (hr)	Yield [a] (%)
1	$ZnCl_2$ /*p*-TSA	60–65	2	55<
2	$CuCl_2$ /*p*-TSA	60–65	2	50<
3	$FeCl_2$ /*p*-TSA	60–65	2	50<
4	$CoCl_2$ /*p*-TSA	60–65	2	55<
5	$NiCl_2$ /*p*-TSA	60–65	2	55<
6	$CdCl_2$ /*p*-TSA	60–65	2	60<
7	$CaCl_2$ /*p*-TSA	60–65	2	40<
8	$MgCl_2$	60–65	5	30<
9	p-TSA	60–65	5	45
10	$MgCl_2$ /*p*-TSA	50	0.67	94[a]

[a] Isolated and unoptimized yields

(400 MHz, $CDCl_3$): δ 33.67, 46.00, 52.87, 56.65, 125.9, 125.69, 125.82, 126.4, 128.2, 128.5, 128.8, 129.83, 128.87, 135.91, 146.08, 147.2, 156.5; MS: (*m/z*) 261.9 (M^+).

Benzyl-2-methyl-4-phenylquinoline-3-carboxylate 3d

IR (KBr): 3064, 3022, 2955, 1724, 1574, 1486, 1414, 1300, 1238, 1176, 1083, 767 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.83 (s, 3H), 5.04 (s, 2H), 7.06−7.08 (t, *J* = 4.0 Hz 1H),7.27−7.30 (t, *J* = 8.0 Hz, 3H), 7.31−7.32 (dd, *J* = 8.0 Hz, 2H), 7.4 (m, 4H), 7.61−7.63 (d, *J* = 8.0 Hz, 1H), 7.75−7.79 (t, *J* = 8.0 Hz, 1H), 8.23 (s,1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 23.62, 67.47, 125.15, 126.54, 126.60, 127.16, 128.07, 128.35, 128.38, 128.48,128.61, 129.11, 129.33, 130.51, 134.78, 135.40, 146.64, 147.35, 154.54, 168.22, 170.34; MS: (*m/z*) 354.1 (M^+).

6-phenyl-7*H*-indeno[1,2-*b*]pyridine-7-one 3i

IR (KBr): 3074, 2929, 1621, 1455, 1326, 964, 778, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46 (t, *J* = 8.0 Hz, 2H), 7.5−7.6 (m, 4H), 7.6−7.7 (t, *J* = 8.0 Hz, 3H), 7.8−7.84 (t, *J* = 8.0 Hz, 1H), 8.5 (s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 29.69, 122.82, 123.89, 127.23, 127.82, 128.17, 128.65, 129.04, 129.40, 131.79, 131.93, 132.76, 135.35, 137.58, 162.00; MS: (*m/z*) 307.9 (M^+).

Benzyl-2,4-dimethylquinoline-3-carboxylate 3k

IR (KBr): 3069, 2960, 1724, 1569, 1409, 1300, 1238, 1078, 767 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.25 (s, 3H), 2.69 (s, 3H), 5.49 (s, 2H), 7.27−7.37 (m, 4H), 7.4−7.5 (m, 2H), 7.5−7.58 (t, *J* = 8.0 Hz, 1H), 7.75−7.8 (t, *J* = 8.0 Hz, 1H), 8.0−8.1 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 15.83, 67.66, 124.03, 125.81, 126.68, 126.97, 128.55, 128.75, 128.83, 135.05, 154.05; MS: (*m/z*) 291.9 (M^+).

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References

1 a) Larsen R D, Corley E G, King A O, Carrol J D, Davis P, Verhoeven T R, Reider P J, Labelle M, Gauthier J Y, Xiang Y B & Zamboni R J, *J Org Chem*, 61, **1996**, 3398; b) Chen Y L, Fang K C, Sheu J Y, Hsu S L & Tzeng C C, *J Med Chem*, 44, **2001**, 2374; c) Roma G, Braccio M D, Grossi G, Mattioli F & Ghia M, *Eur J Med Chem*, 51, **2000**, 1021.

2 a) Doube D, Bloun M, Brideau C, Chan C, Desmarais S, Eithier D, Falgueyeret J P, Friesen R W, Girad M, Girad Y, Guay J, Tagari P & Yong R N, *Bioorg Med Chem Lett*, 8, **1998**, 1255; b) Maguire M P, Sheets K R, Mcvety A P, Spada & Zilberstein A, *J Med Chem*, 37, **1994**, 2129; c) Bilker O, Lindo V, Panico M, Etiene A E, Paxton T, Dell A, Rogers M, Sinden R E & Morris H R, *Nature*, **1998**, 289.

3 a) Ko T C, Hour M J, Lien J C, Teng C M, Lee K H, Kuo S C & Huang L J, *Bioorg Med Chem Lett*, 11, **2001**, 279; b) Ferrarini P L, Mori C, Badwneh M, Manera C, Martinelli A, Miceli M, Ramagnoli F & Saccomanni G, *J Heterocycl Chem*, 34, **1997**, 1501; c) Maguire M P, Sheets K R, McVety K, Spada A P & Zilberstein A, *J Med Chem*, 37, **1994**, 2129.

4 a) Nakatani K, Sando S, & Saito I, *Bioorg Med Chem*, 9, **2001**, 2381; b) He C & Lippard S J, *J Am Chem Soc*, 40, **2001**, 1414.

5 a) Agarwal A K & Jenekhe S A, *Macromolecules*, 24, **1991**, 6806; b) Zhang X, Shetty A S & Jenekhe S A, *Macromolecules*, 32, **1999**, 7422; c) Zhang X, Shetty A S & Jenekhe S A. *Macromolecules*, 33, **2000**, 2069; d) Jenekhe S A, Lu L & Alam M M, *Macromolecules*, 34, **2001**, 7315.

6 a) Strekowski L & Czamy L, *J Fluorine Chem*, 104, **2000**, 281; b) Hu Y Z, Zang G & Thummel R P, *Org Lett*, 5, **2003**, 2251; c) Arcadi A, Chiarini M, Di S, Giuseppe & Marinelli F, *Synlett*, **2003**, 203; d) McNaughton B R & Miller B L, *Org Lett*, 5, **2003**, 4257; e)Yadav J S, Reddy B V S & Premlatha K, *Synlett*, **2004**, 963; f) Yadav J S, Reddy B V S, Sreedhar P, Rao R S & Nagaiah K, *Synthesis*, **2004**, 2381; g) Mogilaih K & Reddy C S, *Synth Commun*, **2003**, 3131; h) Walser A, Flyll T & Fryer R I, *J Heterocycl Chem*, 12, **1975**, 737; i) De S K & Gibbs R A, *Tetrahedron Lett*, 46, **2005**, 1647; j) Arumugam P, Karthikeyan G, Atchudan R, Muralidharan D & Perumal P T, *Chem Lett*, 34, **2005**, 314; k) Wu J, Zhang L & Diao T N, *Synlett*, **2005**, 2653.

7 Lee B S, Lee J H & Chi D Y, *J Org Chem*, **2002**, *67*, 7884.

8 Jiang B & Si YG, *J Org Chem*, 67, **2002**, 9449.

9 Hegedus L S, *Angew Chem Int Ed Engl,* 27, **1988**, 1113; b) Watanabe Y, Tsuji Y & Ohsugi Y, *Tetrahedron Lett*, 22, **1981**, 2667; c) Watanabe Y, Suzuki N, Tsuji Y, Shim S C & Mitsudo T, *Bull Chem Soc Japan*, 55, **1982**, 1116; d) Watanabe Y, Tsuji Y & Shida, *J Bull Chem Soc Jpn*, 57, **1984**, 435; e) Watanabe Y, Takatsuki K, Shim S C, Mitsudo T & Takegami Y, *Bull Chem Soc Japan*, 51, **1978**, 3397.

10 a) Watanabe Y, Tsuji Y, Ohsugi Y & Shida J, *Bull Chem Soc Japan*, 56, **1983**, 2452; b) Watanabe Y, Shim S C & Mitsudo T, *Bull Chem Soc Japan*, 54, **1981**, 3460; c) Larock R C, Hightower T R, Hasvold L A & Peterson K P, *J Org Chem*, 61, **1996**, 3584; d) Larock R C & Kuo M Y, *Tetrahedron Lett*, 32, **1991**, 569; e) Beller M, Thiel O R, Trauthwein H & Hartung C G, *Chem Eur J*, 6, **2000**, 2513; f) Song S J, Cho S J, Park D K, Kwan T W & Jenekhe S A, *Tetrahedron Lett*, 44, **2003**, 255.

11 a) Cheng C C & Yan S J, *Org React*, 28, **1982**, 37; b) Thummel R P, *Synlett*, **1992**, 1; c) Eckert H, *Angew Chem Int Ed Engl*, 20, **1981**, 208; d) Glaldiali S, Chelucci G, Mudadu M S, Gastaut M A & Thummel R P, *J Org Chem*, 66, **2001**, 400; e) Fehnel E A, *J Heterocycl Chem*, 4, **1967,** 565; f) Wang G W, Jia C S & Dong Y W, *Tetrahedron Lett*, 47, **2006**,1059 and references cited therein. g) Sliskovic D R, Picard J A, Roark W H, Roth B D, Ferguson E, Krause B R, Newton R S, Sekerke C & Shaw M K, *J Med Chem*, 34, **1991**, 367; f) Fehnel E A, *J Org Chem*, 31, **1966**, 2899; g) Strekowski L, Czarny A & Lee H, *J Fluor Chem*, 104, **2000**, 281; h) Suzuki M, Iwasaki H, Fujikawa Y, Kitahara M, Sakashita M & Sakoda R, *Bioorg Med Chem*, 9, **2001**, 2727.

12 a) Pasha M A & Jayashankara V P, *Synthetic Commun*, 36, **2006**, 1787; b) Pasha M A & Jayashankara V P, *Heterocycles*, 68, **2006**, 1017; c) Manjula K, Jayashankara V P & Pasha M A, *J Chem Res* (*S*), 5, **2006**, 333; d) Pasha M A, Manjula K & Jayashankara V P, *Synth React Inorg Metal Org Nano-Metal Chem*, 36, **2006**, 321; e) Pasha M A & Jayashankara V P, *Ultrasonics Sonochem*, 13, **2006**, 42.

13 a) Pasha M A & Jayashankara V P, *Heterocyclic Commun*, 12, **2006**, 61; b) Pasha M A & Jayashankara V P, *J Pharma Toxicology*, 1(6), **2006**, 573; c) Pasha M A & Jayashankara V P, *J Pharma Toxicology*, 1(6), **2006**, 585; d) Pasha M A & Jayashankara V P, *Bioorg Med Chem Lett*, 17, **2007**, 621.