Note

A Facile Synthesis of 2,2,4-Trisubstituted-1,2-dihydroquinolines Catalyzed by Zinc Triflate under Solvent-free Conditions

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An efficient process has been developed for the synthesis of 2,2,4-trisubstituted-1,2-dihydroquinolines in good yields through a simple one-pot condensation between anilines and ketones in the presence of zinc triflate as a catalyst at room temperature under solvent-free conditions.

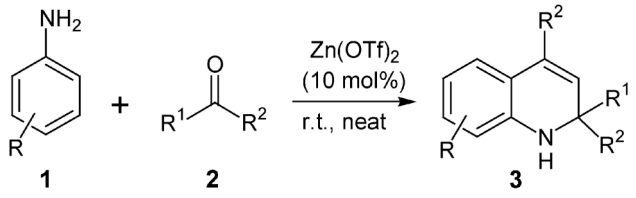
Keywords: Zinc triflate; Dihydroquinolines; Skraup-Doebner-Von Miller reaction; Solvent-free; Condensation.

INTRODUCTION

Owing to the widespread occurrence in nature, as well as the breadth of biological activity, the synthesis of dihyroquinolines and their derivatives have been the subject of continued interest among organic and medicinal chemists for many years.[1] Several derivatives of 2,2,4-trisubstituted-1,2-dihydroquinolines are known to exhibit a wide range of pharmacological properties such as bactericidal,[2] antidiabetic,[3] anti-inflammatory,[4] antimalarial,[5] lipid peroxidation inhibitors,[6] HMG-CoA reductase inhibitors,[7] ileal bile acid transporter inhibitors,[8] progesterone agonists[9] and antagonists.[10] Among the most general approaches for this ring formation is Skraup cyclization which involves the heating a mixture of nitroethane, aniline, and glycerol with concentrated sulfuric acid.[11] Doebner and Von Miller modified this procedure by using an α,β-unsaturated ketone with an aromatic amine by heating in the presence of acid catalyst or iodine.[12]

Over the last century, a number of other methods have been made to improve the yields and reproducibility of Skraup cyclization involving a variety of catalysts.[13,14] However, in spite of the potential utility, some of these methods suffer from drawbacks including the use of non-available and costly reagents, higher temperature, longer reaction times, lower yields and the use of hazardous solvents. Another important issue is that most of these procedures involve either conventional heating or microwave-irradiation. Thus, there are still scopes for renovation towards simple one-pot synthesis of dihydroquinolines and their derivatives under mild conditions at room temperature in cost-effective way. As a part of our program to study solvent-free reactions,[15,16] we would like to present here a zinc(II)-catalyzed one-pot procedure for the synthesis of 2,2,4-trisubstituted-1,2-dihydroquinolines at room temperature under solvent-free conditions (Scheme I).

Scheme I $Zn(OTf)_2$-catalyzed synthesis of 1,2-dihydroquinolines



RESULTS AND DISCUSSION

Representative results of the screening of the Zn-catalyst and the reaction conditions as studied for the condensation between aniline and acetone to synthesize dihydroquinolines are summarized in Table 1.

In the course of the optimization study we found that $Zn(OTf)_2$ was the optimal catalyst in terms of conversion and yields at room temperature under solvent-free conditions among other Zn-catalysts (entries 5, 9 and 10). Although CH_2Cl_2 was better solvent than other common solvents such as THF, CH_3COOEt, CH_3CN but overall yield was lower than solvent-free conditions (entries 1-5). Use of

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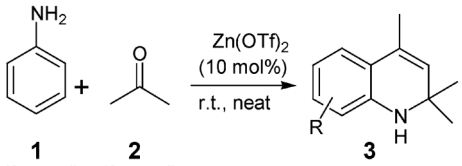
Table 1. Effect of catalyst and solvent on reaction between aniline and acetone

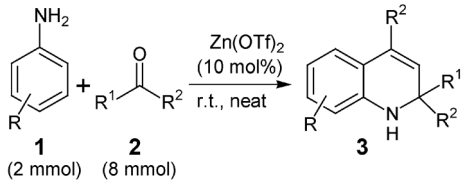


1 (2 mmol) 2 (8 mmol) 3

Entry	Zn-cat.	Conditions temp, time, solvent	Yield[a] (%)
1	$Zn(OTf)_2$, 10 mol%	r.t., 22 h, THF	20
2	$Zn(OTf)_2$, 10 mol%	r.t., 22 h, CH_3CN	22
3	$Zn(OTf)_2$, 10 mol%	r.t., 22 h, DCM	53
4	$Zn(OTf)_2$, 10 mol%	r.t., 22 h, EtOAC	34
5	$Zn(OTf)_2$, 10 mol%	r.t., 22 h, neat	78
6	$Zn(OTf)_2$, 10 mol%	70 °C, 12 h, neat	74
7	$Zn(OTf)_2$, 20 mol%	r.t., 22 h, neat	80
8	$Zn(OTf)_2$, 5 mol%	r.t., 22 h, neat	72
9	$ZnCl_2$, 10 mol%	r.t., 22 h, neat	24
10	$Zn(ClO_4)_2$, 10 mol%	r.t., 22 h, neat	66

[a] Pure isolated yields.

Table 2. Synthesis of 2,2,4-trisubstituted 1,2-dihydroquinolines



1 (2 mmol) 2 (8 mmol) 3

Entry	Anilines R	R^1	R^2	Time (h)	Yield[a] (%)	Ref
a	H	Me	Me	22	78	15
b	2-Me	Me	Me	22	77	15
c	4-Me	Me	Me	22	80	15
d	2-OMe	Me	Me	24	74	15
e	4-OMe	Me	Me	24	76	17
f	3-Cl	Me	Me	26	78[b]	15
g	4-Cl	Me	Me	26	77	15
h	4-F	Me	Me	22	80	
i	4-CO_2Et	Me	Me	23	77	
j	2,3-dimethyl	Me	Me	21	80	
k	3,4-methylenedioxy	Me	Me	21	77[c]	13d
l	H	Me	Et	24	70	
m	Me	Me	Et	24	72	
n	4-CO_2Et	Me	Et	24	75	

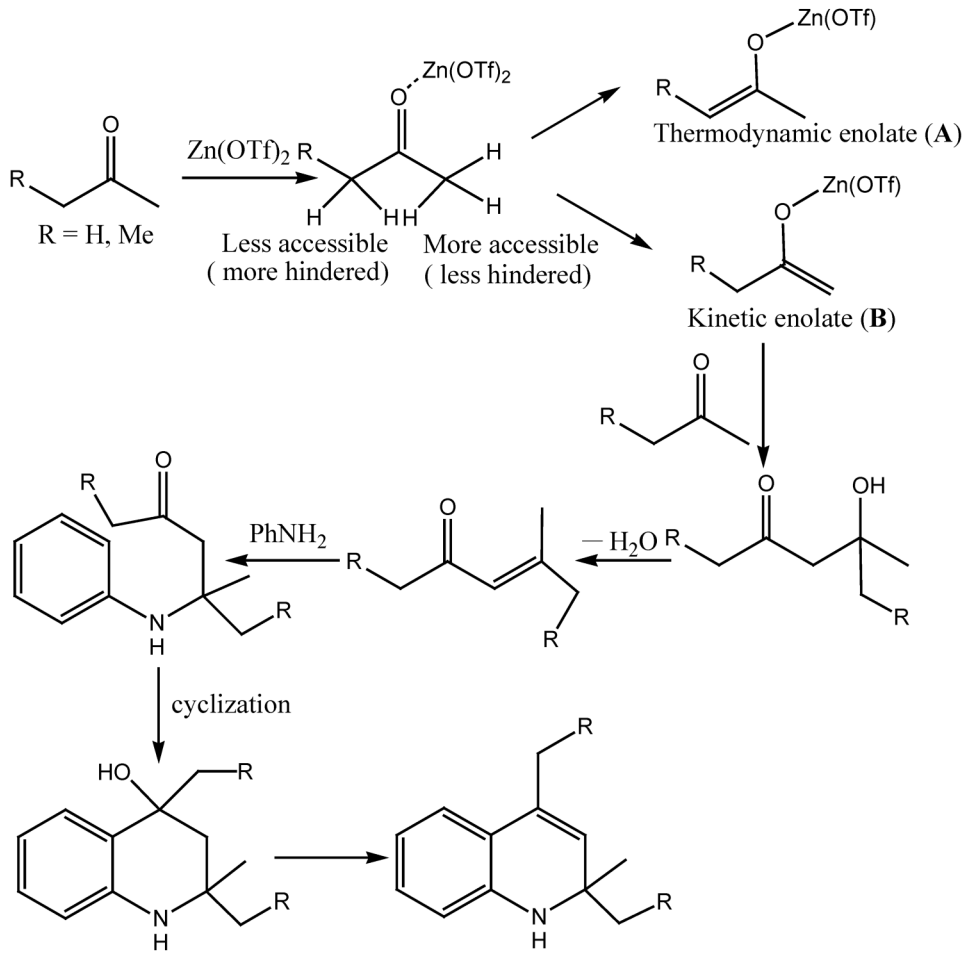
[a] Yields refer to pure isolated products, properly characterized by spectral and analytical data.
[b] *p*-Cyclization pdt.
[c] 6,7-Methylenedioxy-substituted dihydroquinoline as a major regioisomer.

just 10 mol% $Zn(OTf)_2$ was sufficient to push the reaction forward (entry 5). Elevated temperature did not improve the yields but the amount of undesired and unidentified products increased (entry 6). Higher amount of $Zn(OTf)_2$ did not improve the result (entry 7). Having identified the best conditions, we explored the scope of the reaction, and the results are summarized in Table 2.

In a typical experimental procedure, a mixture of aniline (2 mmol) and anhydrous acetone (8 mmol, 0.587 mL) was stirred at room temperature in the presence of catalytic amount of $Zn(OTf)_2$ (73 mg, 10 mol%) for a certain period of time as required for the completion (TLC). After completion of the reaction, the reaction mixture was diluted with diethyl ether and filtered through a plug of silica gel. After removal of solvent, purification with silica gel chromatography gave as a colorless liquid. All these reactions were carried out at room temperature under inert atmosphere and afforded the desire products in good yields. Several sensitive functionalities such as OMe (entries d and e), Cl (entries f and g), CO_2Et (entries i and n), methylenedioxy (entry k) were unaffected under the present reaction conditions. Fluoroaniline also reacted well to give the desired product in good yields (entry 8). In case of *m*-substituted aniline, major regioisomeric dihydroquinoline corresponding to *p*-cyclization was obtained (entry f). 3,4-Methylenedioxyaniline produced 6,7-methylenedioxy-substituted dihydroquinoline as a major regioisomer under the present reaction conditions (entry k). The cyclization between a variety of anilines with ethyl methyl ketone also proceeded very smoothly at room temperature to give the dihydroquinoline derivatives in good yields without difficulty. It was found that secondary anilines and aromatic ketones were failed to produce dihydroquinolines. 1-Naphtylamine also produced dihydrobenzoquinoline in good yields. Interestingly, the condensation between anilines and mesityl oxide also produced the similar kind of the dihyroquinoline derivatives under the present reaction conditions. More hindered ketone gave lower yields compare to acetone.

The mechanism in Scheme II is proposed for the coupling reactions between aniline and ketones. Though two regioisomers of the enolates (**A** & **B**) are possible, **B** formed faster as it is kinetic enolate. The sole product aldol is probably due to the reaction of the ketone with **B** only. Subsequently α,β-unsatured ketone formed after dehydration. The intermediate tertiary alcohol formed by Michael addition followed by cyclisation produced dihydroquinoline af-

Scheme II Plausible mechanism for the formation of dihydroquinoline



ter dehydration. During the specific aldol condensation process, the other possible thermodynamic enolate did not react. It may be due to the steric hinderence among the two methyl and ethyl groups of thermodynamic enolate and ketone.

In conclusion, the work presented here demonstrates a straightforward and mild procedure for the efficient synthesis of dihydroquinoline derivatives at room temperature under solvent-free conditions. The reaction possesses the following synthetic features: (a) mild conditions, (b) simple operation, (c) good yields, (d) nontoxic and cheap metal catalyst, and (e) the compatibility with various functional groups. The easy formation of substituted dihydroquinolines from inexpensive starting materials makes this an important synthetic procedure.

EXPERIMENTAL SECTION

NMR spectra were recorded on a Bruker DPX 300 instrument at 300 MHz for ^{1}H and at 75 MHz for ^{13}C NMR. IR spectra were measured on a FT 8400S Shimadzu spectrometer. Melting points are determined on a glass disk with an electric bath (Reichert, Austria) and are uncorrected. Elemental analyses were done by a Perkin-Elmer autoanalyzer. Column chromatography was performed on silica gel (60-120 mesh, SRL, India). Anilines and ketones were distilled before use. $Zn(OTf)_2$ was purchased from Aldrich.

General procedure for the synthesis of dihydroquinolines: representative procedure for 2,2,4-trimethyl-1,2-dihydroquinoline 3a

A mixture of aniline (186 mg, 2 mmol) and anhydrous acetone (8 mmol, 0.587 mL) was stirred at room temperature in the presence of catalytic amount of $Zn(OTf)_2$ (73 mg, 10 mol%) for 22 h (TLC). After completion of the reaction, the reaction mixture diluted with diethyl ether (20 mL) and filtered through a plug of silica gel. After removal

of solvent, purification with silica gel chromatography (hexane-Et_2O, 95:5) gave 2,2,4-trimethyl-1,2-dihydroquinoline as a colorless oil (270 mg, 78%) whose spectroscopic data (IR, ^1H NMR) are in good agreement with those reported.[15]

This procedure was followed for the synthesis of dihydroquinolines listed in Table 2. The spectral and elemental analyses of the compounds which are not readily found are provided here.

6-Fluoro-2,2,4-trimethyl-1,2-dihydroquinoline 3h

Colorless oil (80%); R_f 0.70 (hexane-Et_2O, 9:1); IR (neat): 3278, 1612, 1029 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 6.81-6.77 (m, 1H), 6.73-6.69 (m, 1H), 6.40-6.37 (m, 1H), 5.39 (s, 1H), 4.10 (board, 1H), 1.97 (d, *J* = 1.4 Hz, 3H), 1.27 (s, 6H); Anal. Cald for $C_{12}H_{14}FN$: C, 75.36; H, 7.38; N, 7.32. Found: C, 75.18; H, 7.12; N, 7.06.

6-Carboethoxy-2,2,4-trimethyl-1,2-dihydroquinoline 3i

Solid (77%); Mp 154-156 °C; R_f 0.63 (hexane-Et_2O, 9:1); IR (KBr): 3346, 2973, 1683, 16657, 1597, 1509, 1367 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.51 (s, 1H), 7.47 (d, *J* = 8.3 Hz, 1H), 6.17 (d, *J* = 8.3 Hz, 1H), 5.10 (s, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 1.80 (s, 3H), 1.14 (t, *J* = 7.1 Hz, 3H), 1.09 (s, 6H), N-H (not identified); Anal. Cald for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.12; H, 7.57; N, 5.54.

2,2,4,7,8-Pentamethyl-1,2-dihydroquinoline 3j

Colorless oil (80%); R_f 0.73 (hexane-Et_2O, 9:1); IR (neat): 3321, 1607, 1551 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 6.90 (d, *J* = 7.8 Hz, 1H), 6.51 (d, *J* = 7.8 Hz, 1H), 5.30 (s, 1H), 3.86 (broad, 1H), 2.26 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H), 1.30 (s, 6H); Anal. Cald for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.24; H, 9.37; N, 6.79.

2,4-Diethyl-2-methyl-1,2-dihydroquinoline 3l

Colorless oil (70%); R_f 0.63 (hexane-Et_2O, 9:1); IR (neat): 3321, 1611, 1528 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.10 (dd, *J* = 1.2 Hz, 7.7 Hz, 1H), 6.97 (t, *J* = 7.7 Hz, 1H), 6.62 (t, *J* = 6.4 Hz, 1H), 6.44 (dd, *J* = 0.9 Hz, 7.9 Hz, 1H), 5.22 (s, 1H), 3.82 (broad, 1H), 2.41 (q, *J* = 7.3 Hz, 2H), 1.52 (q, *J* = 7.3 Hz, 2H), 1.27 (s, 3H), 1.18 (t, *J* = 7.4 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H); Anal. Cald for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.29; H, 9.38; N, 6.67.

2,4-Diethyl-2,6-dimethyl-1,2-dihydroquinoline 3m

Colorless oil (72%); R_f 0.68 (hexane-Et_2O, 9:1); IR (neat): 3278, 1608, 1528 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 6.93 (s, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 6.39 (d, *J* = 7.9 Hz, 1H), 5.23 (s, 1H), 3.76 (broad, 1H), 2.41 (q, *J* = 7.4 Hz, 2H), 2.24 (s, 3H), 1.57-1.48 (m, 2H), 1.23 (s, 3H), 1.20-1.14 (m, 3H), 0.92 (t, *J* = 7.4 Hz, 3H); Anal. Cald for $C_{15}H_{21}N$: C, 83.67; H, 9.83; N, 6.50. Found: C, 83.32; H, 9.67; N, 6.34.

6-Carboethoxy-2,4-Diethyl-2-methyl-1,2-dihydroquinoline 3n

Solid (75%); Mp 105-106 °C; R_f 0.60 (hexane-Et_2O, 9:1); IR (KBr): 3349, 2970, 1688, 1652, 1591 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.68 (s, 1H), 7.58 (d, *J* = 8.3 Hz, 1H), 6.28 (d, *J* = 8.3 Hz, 1H), 5.08 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.01 (broad, 1H), 2.34 (q, *J* = 7.4 Hz, 2H), 1.42 (m, 2H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.17 (s, 3H), 1.09 (t, *J* = 7.4 Hz, 3H), 0.81 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 167.4, 148.6, 134.8, 130.9, 125.5, 124.9, 119.4, 118.1, 111.9, 60.5, 55.8, 37.7, 30.9, 24.7, 14.8, 13.0, 8.9; Anal. Cald for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.38; H, 8.31; N, 4.98.

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