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Simple and practical synthesis of pyrano- and furano[3,2-*c*]-quinoline derivatives under non-Lewis acid catalysis

Rui Huan Liu [a], Xin Yu [b], Liang Hu [a], Nie Fang Yu [a,*]

[a] *School of Pharmaceutical Sciences, Central South University, Changsha 410013, China*
[b] *School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 51006, China*

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Abstract

One-pot synthesis of substituted pyrano- and furano[3,2-*c*]quinoline derivatives from appropriately substituted anilines, substituted benzaldehydes and dienophiles *via* Povarov reaction catalyzed by HCl–ethanol were reported. Good to excellent yields with high diastereoselectivity were obtained in all entries tested.

Keywords: Non-Lewis acid; Catalysis; HCl–ethanol; Diastereoselectivity; Povarov reaction

The 1,2,3,4-tetrahydroquinoline skeleton is presented as an important subunit in many biological active alkaloids including those that target NMDA receptor [1], CETP [2], G-protein coupled receptor [3] and HIV-1 RT [4]. Thus, the construction of this skeleton has attracted a great deal of attentions. Diverse methods for the synthesis of tetrahydroquinoline derivatives have been developed so far [5,6]. Among them, the *aza*-Diels–Alder reaction between *N*-aryl imines and nucleophilic olefins was frequently applied for this synthesis purpose in the presence of suitable catalyst. To date, a number of Lewis acids have been explored as catalysts for the preparation of these compounds, including $BF_3{\cdot}OEt_2$ [7], $Yb(OTf)_3$ [8], VCl_3 [9], and others [10–16]. However, the efficiency and/or readily accessibility of the catalysts remain occasionally concerned issues in this aza-Diels–Alder reaction.

Herein, we describe a practical procedure for synthesis of substituted pyrano- and furano[3,2-*c*]quinolines v*ia* Povarov reaction in the presence of HCl–ethanol, an inexpensive and readily accessible reagent compared with most of Lewis acids. This synthetic procedure involves treating a mixture of 3,4-dihydro-2*H*-pyran and benzaldehyde with an acetonitrile solution of aniline and HCl–ethanol (Scheme 1), to give the corresponding tetrahydroquinolines **3a** and **4a** in 90% yield.

In the initial attempt, HCl–ethanol with different concentrations were prepared and applied in the model reaction of aniline (0.93 g, 10 mmol), benzaldehyde (1.07 g, 10 mmol) with 3,4-dihydro-2*H*-pyran (0.84 g, 10 mmol) in acetonitrile (25 mL) at ambient temperature (Scheme 1). As a result, the reaction rate appeared more reasonable in the

* Corresponding author.
E-mail address: niefang_yu@126.com (N.F. Yu).

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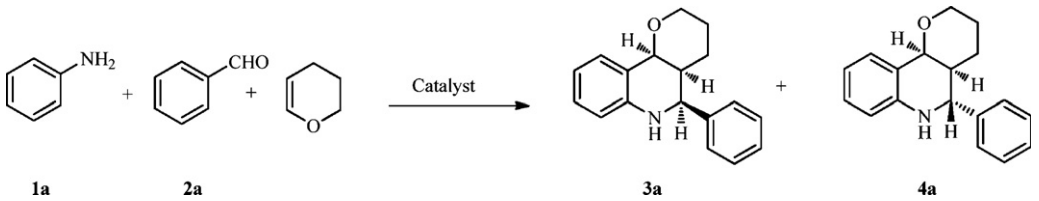


Scheme 1.

Table 1
Effect of solvents and concentrations of HCl (in ethanol) on the reaction.

Round	Solvent	Concentration[a,b] (wt%)	Volume of solvents (mL)	Time (h)	Conversion rate[c] (%)
1	CH_3CN	0	25	2	0
2	CH_3CN	5	25	2	32
3	CH_3CN	10	25	1.5	95
4	CH_3CN	15	25	2	93
5	CH_3CN	20	25	2	92
6	CH_3OH	10	25	2	89
7	CH_3CH_2OH	10	25	2	85
8	CH_2Cl_2	10	25	2	47

[a] Concentration of HCl in ethanol.
[b] HCl–ethanol solutions with different concentrations were prepared by diluting 22.7% HCl–ethanol (fresh prepared) with ethanol.
[c] The conversion rates were determined by LC/MS.

presence of 10% (wt) HCl–ethanol, while no significant changes were found when higher concentrated HCl–ethanol were applied instead. Based on these findings, the effect of solvents on the reaction catalyzed by 10% (wt) HCl–ethanol was studied, and acetonitrile was proved to be the better solvent than other solvents examined (Table 1).

We also assayed the ability of other seven common acids functioning as catalysts for the cycloaddition in this reaction (Scheme 1). Our results indicated that HCl–ethanol was a more suitable catalyst, offering acceptable yield and high diastereoselectivity. And the efficiency of HCl–ethanol could be also observed from the comparison between our results and literature data of some other reported catalysts (Table 2).

To explore the scope of this protocol, the reactions of various substituted anilines and substituted benzaldehydes with 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran were carried out under the optimized conditions [17], and the results were summarized in Table 3. In all cases, the reactions went smoothly to give the corresponding products in moderate

Table 2
The catalytic efficiency of HCl–ethanol and some other catalysts.

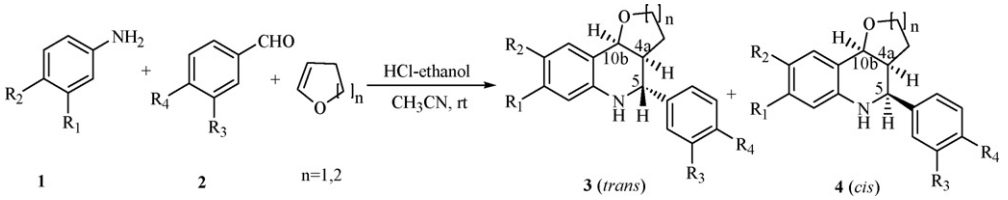
Round	Catalyst	Amount	Reaction time (h)	Yield[a] (%)	Ratio[b] (**3a**:**4a**)
1	HCOOH[c]	1 mL	12	48	68:32
2	AcOH[c]	1 mL	12	25	55:45
3	HNO_3 (35%)[c]	1 mL	24	10	85:15
4	H_2SO_4[c]	1 mL	24	5	83:17
5	HCl (36%)[c]	1 mL	2	9	55:45
6	HBr (40%)[c]	1 mL	2	60	80:20
7	HI (45%)[c]	1 mL	2	55	78:22
8	HCl–ethanol (10%)	1 mL	1.5	90	90:10 [17]
9	Proline triflate	5 mol%	5	85	75:25 [10]
10	$GdCl_3$	20 mol%	0.5	86	67:33 [11]
11	$InCl_3$	20 mol%	0.5	80	41:59 [13]
12	I_2	30 mol%	3	84	77:23 [16]

[a] Isolated yields of **3a** and **4a**.
[b] The product ratios were determined by LC/MS.
[c] Similar reaction conditions as entry 8.

Table 3
Synthesis of pyrano- and furano[3,2-*c*]quinoline derivatives under HCl–ethanol catalysis.

Entry	R_1	R_2	R_3	R_4	*n*	Time [h]	Yield[a] [%]	Ratio[b] (**3**:**4**)	Ref
a	H	H	H	H	2	1.5	77 (**3a**)	90:10	[18]
b	H	CH_3	H	H	2	2.5	65 (**3b**)	72:18	[18]
c	H	Cl	H	H	2	2.5	70 (**3c**)	95:5	[18]
d	H	OCH_3	H	H	2	1.5	55 (**3d**)	85:15	[19]
e	H	H	H	OH	2	2.5	63 (**3e**)	80:20	
f	H	H	H	NO_2	2	1.0	78 (**3f**)	95:5	[18]
g	H	H	H	CH_3	2	2.5	65 (**3g**)	86:14	[20]
h	H	H	Br	H	2	1.5	73 (**3h**)	85:15	[10]
i	H	H	H	OCH_3	2	2.5	70 (**3i**)	87:13	[19]
j	H	H	H	H	1	1.5	75 (**4j**)	9:91	[18]
k	H	CH_3	H	H	1	1.5	58 (**4k**)	35:65	
l	H	Cl	H	H	1	2.5	70 (**4l**)	5:95	[18]
m	H	CH_3	H	OH	1	3.5	58 (**4m**)	20:80	
n	H	OCH_3	H	H	1	2.0	68 (**4n**)	25:75	[11]
o	H	H	H	OH	1	2.5	67 (**4o**)	25:75	
p	H	H	H	NO_2	1	1.0	80 (**4p**)	0:100	[18]
q	H	H	H	CH_3	1	2.5	62 (**4q**)	30:70	[18]
r	H	H	Br	H	1	1.5	83 (**4r**)	30:70	

[a] Isolated yields.
[b] The product ratios were determined by LC/MS.



Scheme 2.

to good yields. The major products were isolated and characterized by ^{1}H NMR, ^{13}C NMR and HRMS, and the stereochemistry of the isolated products was assessed on the basis of the coupling constant values between H-C_{4a} and H-C_5 ($J_{4a,5}$) and comparison with literature data. The data acquired in this investigation suggested a close correlation between the product diastereoselectivities and the dienophile used. Dihydropyran provided a great opportunity for the generation of *trans* diastereosimers, while *cis* diastereoisomers were favored in cases of dihydrofuran. Adducts **3a–i**, exhibited higher coupling constants $J_{4a,5}$ (8.1–11.1 Hz), typical for a *trans* conformation in which the pyran ring and phenyl ring are on opposite sides of the quinoline ring. In adducts **4j–r**, smaller coupling constants $J_{4a,5}$ (4.6–5.6 Hz) were observed indicating a *cis* conformation that the furan ring and phenyl group are on the same side (Scheme 2).

In conclusion, we have demonstrated that HCl, a readily available non-Lewis acid, can be used as catalyst for construction of pyrano- and furano[3,2-*c*]quinolines. In comparison with the other acids examined (*e.g.*, AcOH) and some other reported catalysts (*e.g.*, $GdCl_3$), HCl–ethanol is more effective and affords better yields with high diastereoselectivity according to our experimental results. Furthermore, our novel procedure possesses some other advantages including chemistry more accessible and cleaner reaction mixture. These features make our procedure a useful approach for the synthesis of fused-ring quinolines of biological importance.

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[17] A typical procedure. In a 100 mL round bottomed flask, HCl–ethanol (10 wt%, fresh prepared, 1 mL) was mixed with a solution of anilines (0.93 g, 10.0 mmol) in acetonitrile (10 mL) and left to stand for 10 min at ambient temperature. A solution of benzaldehyde (1.07 g, 10.0 mmol) in acetonitrile (10 mL) was added under stirring, followed by the 3,4-dihydro-2H-pyran (0.84 g, 10.0 mmol) in acetonitrile (5 mL). The resulting mixture was stirred, as evident by TLC. After completion of reaction, the reaction mixture was diluted with saturated $NaHCO_3$ solution (40 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was dried with anhydrous Na_2SO_4. The solvent was removed in vacuo. The desired products were isolated by flash chromatography over silica gel (EtOAc-hexanes, 5:95) and characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS. 3a: IR (KBr): 3382, 2942, 2855, 1699, 1666, 1201 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.45–7.37 (m, 4H), 7.34–7.30 (m, 1H), 7.05 (dd, 1 H, J = 1.4 Hz, 7.5 Hz), 6.99 (td, 1H, J = 1.6 Hz, 8.2 Hz), 6.61 (dd, 1H, J = 0.7 Hz, 7.4 Hz), 6.51 (td, 1 H, J = 1.0 Hz, 7.3 Hz), 4.53 (d, 1H, J = 10.4 Hz), 4.28 (d, 1H, J = 2.8 Hz), 3.90 (m, 1H), 3.60 (td, 1 H, J = 1.8 Hz, 11.0 Hz), 1.94–1.91 (m, 1H), 1.77–1.71 (m, 1 H), 1.64–1.58 (m, 1 H), 1.28–1.26 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 145.9, 143.2, 130.9, 129.1, 128.8, 128.2, 127.9, 120.3, 115.9, 114.3, 74.1, 67.7, 54.4, 24.1, 22.1. HRMS (ESI): m/z [M+H]$^+$ calcd. for $C_{18}H_{20}NO$: 266.1536; found: 266.1539.
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