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Imino Diels–Alder reactions: One-pot synthesis of tetrahydroquinolines

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Abstract

An efficient synthesis of tetrahydroquinoline derivatives is reported via three component coupling reactions of aldehydes and anilines with various dienophiles in the presence of a catalytic amount of perchloric acid adsorbed on silica gel ($HClO_4$ –SiO₂) under mild reaction conditions.

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The aza-Diels–Alder reaction is one of the most important synthetic routes for the construction of six-membered heterocycles containing a N-atom [1,2]. Tetrahydroquinolines constitute an important class of compounds with profound interest to medicinal chemist since the tetrahydroquinoline moiety exhibits diverse biological properties such as anti-allergic [3], anti-inflammatory [4], estrogenic [5], and psychotropic activity [6], and have potential pharmaceutical applications [7]. Moreover, pyranoquinoline is an important core structure of many bio-active alkaloids [8].

The classical methods that have been reported for the synthesis of tetrahydroquinolines involve the reaction of imines (derived from aromatic amines and benzaldehydes) with dienophiles [1,2] (for Lewis acid catalyzed reactions see [9–14]). However, these methods involve one or more disadvantages like extended reaction times, low chemical yields, and drastic reaction conditions. Moreover, several imines are hygroscopic, unstable, and difficult to purify, and thus the preparation of these compounds in pure form followed by coupling with dienophiles in steps is not advantageous. Tetrahydroquinolines can also be successfully obtained by one-pot coupling reactions of aldehydes and anilines with dienophiles employing catalysts like GdCl₃ [15], ZrCl₄ [16], Fe³⁺-K-10 clay or HY-Zeolite [17], Bi(OTf)₃-[Bmim]PF₆ [18], SbCl₃ [19], SbCl₃-HAP [20], KHSO₄ [21], TMSCl [22], and fluorinated alcohols [23], Mg(ClO₄)₂ [24], BiCl₃ [25], silica chloride or amberlyst-15 [26], SmI₂ [27], and I₂ [28]. Unfortunately, most of these

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catalysts are required in large amounts as they are decomposed or deactivated by amines. Therefore, based on multicomponent strategies, the development of convenient, high yielding, a cost effective and clean approach is highly desirable.

1. Experimental

All chemicals were of analytical grade. IR spectra were recorded on Bomem MB FT-IR spectrometer. ¹H NMR spectra were recorded on AC 300 F spectrometer (200 MHz). Mass spectra were recorded with a Bruker ion trap spectrometer. CHN analyses were recorded on a Vario EL analyzer. Most of the products are known and were determined using comparison of their physical and spectral data with those reported in the literature.

1.1. Typical experimental procedure

A mixture of benzaldehyde (5 mmol), aniline (5 mmol), 3,4-dihydro-2H-pyran (7 mmol), was stirred at room temperature in the presence of a catalytic amount of $HClO_4$ -SiO₂ (0.25 mmol, 5 mol%) for an appropriate time (Table 2). After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with MeCN (10 mL), filtered through a plug of cotton to separate the catalyst, and the cotton plug was washed with MeCN (2× 5 mL). The combined MeCN layer concentrated under reduced pressure to afford crude product which was purified by column chromatography on silica gel (Merk, 100–200 mesh, ethyl acetate:hexane 1:9 to afford pure pyranoquinoline (95%)).

The recovered catalyst was activated by heating at 80 °C under vacuum for 2 h and reused for fresh lot of benzaldehyde (5 mmol) affording 92% yield of pyranoquinoline after 20 min. The recovered catalyst, after activation, was reused for two more consecutive reactions of benzaldehyde (5 mmol) affording 90%, 87% yields, respectively, in 25 and 35 min.

4a: IR: 3375 cm⁻¹; ¹H NMR (δ): 1.25–1.63 (m, 4H), 2.18–2.22 (m, 1H), 3.40–3.62 (m, 2H), 3.82 (s, 1H), 4.70 (d, 1H, J = 2.8 Hz), 5.32 (d, 1H, J = 5.8 Hz), 6.57 (d, 1H, J = 7.8 Hz), 6.82 (t, 1H, J = 7.8 Hz), 7.05 (t, 1H, J = 7.8 Hz), 7.22–7.42 (m, 6H), MS: m/z = 266 [M⁺+1].

5a: IR: 3375 cm⁻¹; ¹H NMR (δ): 1.25–1.90 (m, 4H), 2.2–2.3 (m, 1H), 3.75 (dt, 1H, J = 2.5, 11.6 Hz), 3.92–4.15 (m, 2H), 4.42 (d, 1H, J = 2.8 Hz), 4.72 (d, 1H, J = 10.8 Hz), 6.52 (d, 1H, J = 7.2 Hz), 6.72 (t, 1H, J = 7.2 Hz), 7.06 (dt, 1H, J = 7.2 Hz), 7.20 (d, 1H, J = 7.2 Hz), 7.25–7.40 (m, 5H); MS: m/z = 266 [M⁺+1].

2. Results and discussion

In recent years, the organic reactions on solid supported reagents [29–45] have received considerable importance in organic synthesis because of their ease of handling, enhanced reaction rates, greater selectivity, simple work-up and recoverability of catalysts. In view of recent surge in the use of heterogeneous catalysts, herein we wish to report a simple, convenient and efficient method for the one-pot synthesis of tetrahydroquinolines from the reactions of aldehydes and anilines with dienophiles using silica supported perchloric acid as an inexpensive catalyst which was prepared by following the pioneering work on the discovery of silica supported perchloric acid [32] (Scheme 1).

The three component coupling reactions of aldehydes, anilines and dienophiles in the presence of 5 mol% of $HClO_4$ -SiO₂ in MeCN at room temperature were conducted and the results are summarized in Table 1. A variety of aldehydes and anilines in the presence of $HClO_4$ -SiO₂ (5 mol%) in MeCN was treated with 3,4-dihydro-2*H*-pyran or



Scheme 1.

Table 1 HClO₄–SiO₂ catalyzed preparation of tetrahydroquinolines.

Entry	Aniline		Aldehyde		Olefin (3a , <i>n</i> = 2; 3b , <i>n</i> = 1)	Time	Yield ^a	Product	Refs.
	R ₁	R ₂	R ₃	R ₄	n	(min)	(%)	ratio ^b (4:5)	
a	Н	Н	Н	Н	2	15	95	89:11	[14]
b	Н	Cl	Н	Н	2	25	91	87:13	[14]
c	Н	Me	Н	Н	2	25	88	87:13	[14]
d	Н	OMe	Н	Н	2	35	90	85:15	[14]
e	Н	Br	Н	Н	2	30	89	86:14	[14]
f	Н	Н	OCH ₂ O	-	2	35	90	87:13	[17]
g	Н	F	Н	Н	2	35	87	90:10	[14]
h	Н	NO_2	Н	Н	2	40	86	82:18	[24]
i	Me	Н	Н	Н	2	25	90	87:13	[13]
j	Н	Н	Н	Cl	2	40	88	84:16	[14]
k	Н	Н	Н	NO_2	2	35	87	90:10	[14]
1	Н	Н	Н	Br	2	30	87	83:17	[26]
m	Н	Н	Н	OMe	2	45	84	86:14	[13]
n	Н	Н	Н	Me	2	30	88	83:17	[27]
0	Н	Н	Н	Н	1	20	89	84:16	[14]
р	Н	Н	Н	NO_2	1	35	83	86:14	[24]
q	Н	Н	Н	Me	1	25	90	85:15	[13]
r	Н	Н	Н	OMe	1	25	90	80:20	[13]
S	Н	Н	Н	Cl	1	35	85	84:16	[14]
t	Н	Cl	Н	Н	1	40	84	83:17	[15]
u	Н	OMe	Н	Н	1	25	87	85:15	[15]
v	Н	Br	Н	Н	1	25	85	83:17	[15]

^a All the isolated products were characterized from there spectral data.

^b Product ratio was determined from the ¹H NMR spectrum of the crude product.

2,3-dihydrofuran to give the corresponding pyrano- or furanoquinoline derivatives in good to excellent yields with high diastereoselectivity. The yields are, in general, high regardless of the structural variations in aromatic anilines and aldehydes. The products were obtained as a mixture of *trans* and *cis* isomers, favoring the *trans* diastereomer. The product ratios were determined from the ¹H NMR spectra of the crude products. The stereochemistry of the products was assigned on the basis of coupling constants. The coupling constants of H-5 proton ($J_{4a, 5}$) in products **4a–n** (10.1–10.9 Hz) and **5a–n** (5.1–5.8 Hz) are in accordance with the *exo* and *endo* configurations, respectively. Besides, the coupling constant ($J_{4a, 10b}$) in all products (2.7–3.0 Hz) indicates the *cis* junction between pyran and quinoline rings.

While comparing the effect of catalysts for the reaction of benzaldehyde, aniline, with 3,4-dihydro-2*H*-pyran in MeCN, we found that $HClO_4$ -SiO₂ was more effective than recently reported catalysts in terms of the amount of catalyst used, yields and reaction times (Table 2).

Comparison of the catalytic efficiency of HClO₄-SiO₂ against other reported catalysts for the one-pot reaction of benzaldehyde (1 mmol), aniline with 3,4-dihydro-2*H*-pyran.

Catalyst	Catalyst (mol%)	Temp. (°C)	Solvent	Time min/[h]	Yield ^a (%)
GdCl ₃	20	r.t.	MeCN	30	86[15]
ZrCl ₄	10	r.t.	MeCN	35	88[16]
Fe ³⁺ -K-10/	100 mg	r.t.	MeCN	[3.5]	88[17]
HY-Zeolite	100 mg	Reflux	MeCN	[5]	82[17]
Bi (OTf) ₃	10	r.t.	[Bmim]PF ₆	[2]	90[18]
SbCl ₃	10	r.t.	MeCN	40	90[19]
KHSO ₄	40	r.t.	MeCN	60	64[21]
TMSCl	20	r.t.	MeCN	40	95[22]
Fluorinated alcohols	3 mL	r.t.	Fluorinated alcohols	[4]	91[23]
HClO ₄ -SiO ₂	5	r.t.	MeCN	15	95

^a Yields refer to pure isolated product.

Table 2

In conclusion, we have described herein $HClO_4$ -SiO₂ as an extremely efficient catalyst for the preparation of tetrahydroquinolines. The important features of the present method are: (i) room temperature conditions, (ii) use of a cheap and easy to handle catalyst, (iii) short reaction times, (iv) non-aqueous work-up, (v) high yields, (vi) use of low amount of catalyst, and (vii) reuse of catalyst.

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