VCl_3-Catalyzed aza-Diels-Alder reaction: one-pot synthesis of pyrano[3,2-*c*]quinolines and furo[3,2-*c*]quinolines

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Dedicated to Professor Bartoli on the occasion of his 65th birthday

Abstract
Vanadium(III) chloride was found to be an efficient catalyst for the aza-Diels–Alder reactions of aldimines with dihydropyran or dihydrofuran to afford the corresponding pyrano- and furo[3,2-*c*]quinolines in high yields with high diastereoselectivity in a short period of time.

Keywords: Aza-Diels–Alder reactions, vanadium(III) chloride, pyrano- and furo-quinolines

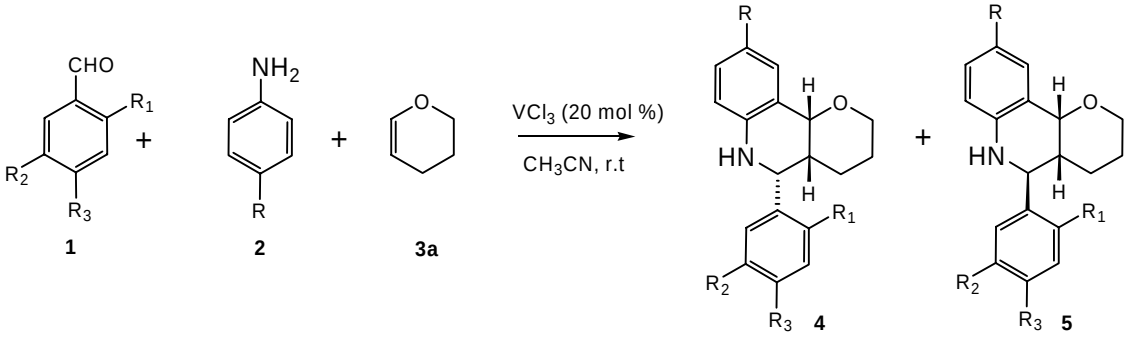
Introduction

Aza-Diels–Alder reactions rank among the most powerful methodologies for the construction of nitrogen-containing six-membered ring compounds.[1] Pyranoquinolines are known to exhibit various biological properties[2] such as psychotropic, antiallergic, anti-inflammatory and estrogenic activities.[3–6] In addition to this they are used as pharmaceuticals.[7] Furoquinolines function as antagonists [8] of 5-hydroxytryptamine receptors in animals and have been found to be most potent anti-inflammatory agents.[9] Some alkaloids possess the furoquinoline skeleton.[10] Generally these compounds are prepared by aza-Diels–Alder reactions of imines derived from aldehydes and amines with dihydropyran or dihydrofuran. Transition-metal complexes such as $Co_2(CO)_8$, $Ni(CO)_4$[11] and $InCl_3$[12] find their use for this reaction, although $BF_3.OEt_2$ has been the most commonly used catalyst.[13] Various methods[14] are reported in the literature which include the use of $GdCl_3$, $ZrCl_4$, $LiClO_4$, $LiBF_4$, I_2 and montmorillonite clay to promote this reaction. Many Lewis acids cannot be utilized for the single-step coupling of aldehydes, amines and enol ethers because they will be decomposed or deactivated by the amines and water formed in the intermediate imine- formation step. Most imines are hygroscopic, unstable at high temperature, and difficult to purify, so a one-pot three- component coupling protocol is highly desirable. Owing to the potential biological activities of pyrano- and furo-quinolines, mild and more

efficient one-pot protocol for the synthesis of these compounds are still in great demand in organic synthesis.

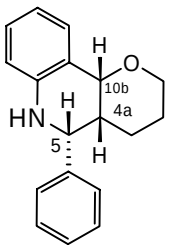
Results and Discussion

In continuation of our work on the development of novel methodologies utilizing VCl_3,[15] we now report our observations on the synthesis of pyrano- and furo-quinolines by a one-pot three-component coupling of benzaldehydes (**1**), anilines (**2**) and 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran (**3a, b**) catalyzed by VCl_3 (Scheme 1). In a typical procedure, benzaldehyde and aniline were reacted with 3,4-dihydro-2*H*-pyran in the presence of a catalytic amount of VCl_3 (20 mol. %) in acetonitrile at room temperature. The reaction was found to proceed smoothly to afford the corresponding pyrano[3,2-c]quinoline as a mixture of *cis*- and *trans*- isomers (**4a** and **5a)** in a ratio of 20:80, in an overall yield of 90%. These isomers were separated by column chromatography over silica gel.

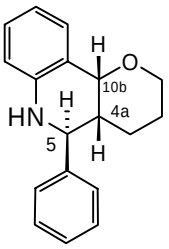


Scheme 1

Their structures were established based on ^{1}H NMR data. Similarly, various benzaldehydes and anilines were reacted with dihydropyran, with the results listed in Table 1. In all cases, the imines generated *in situ* from aromatic aldehydes and anilines react immediately with dihydropyran, and the three-component one-pot reaction proceeded to give the corresponding pyranoquinolines in high yields and with high diastereoselectivity. The ratio of the isomers obtained in each reaction was determined from the ^{1}H NMR spectrum of the crude product, and the structures of the products were established on the basis of spectroscopic (IR, ^{1}H NMR, ^{13}C NMR and MS) data of the pure compounds.



4, cis

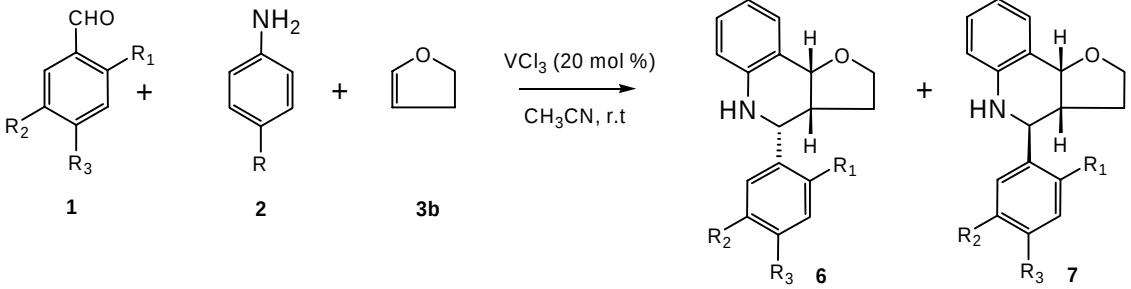


5, trans

In the isomer **4**, the coupling constant ($J_{4a,\ 5}$) = 5.2 Hz is small and typical for a gauche conformation of the protons, consistent with an all *cis*- configuration of the hydrogen atoms **4a**, **5**, and **10b**. In the isomer **5**, the value of ($J_{4a,\ 5}$) = 10.5 Hz is indicative of the anti- orientation of protons H-4a and H-5, corresponding to their mutual *trans*-configuration.

The coupling constant ($J_{4a,10b}$) in all products (2.2–2.9 Hz) indicates the *cis*- fusion of the pyran- and quinoline rings.

Further, we have exploited the reactivity of dihydrofuran with benzaldehydes and anilines catalyzed by VCl_3. The reaction proceeded in a short period of time and afforded the corresponding furo[3,2-c]quinolines as *cis/trans* mixtures, which could be separated by column chromatography over silica gel (Scheme 2) and the results are listed in Table 1. The structures of compounds were characterized by IR, ^{1}H NMR and MS spectral data, and were also compared with the data of compounds reported in the literature.[14a] The products could not be isolated in the absence of VCl_3.



1 **2** **3b** **6** **7**

Scheme 2

In conclusion, we have demonstrated that VCl_3 is an effective catalyst for the aza- Diels–Alder reaction, to afford pyrano- and furo-quinolines in good yields, under mild reaction conditions, with high diastereoselectivity.

Table 1. VCl_3 –Catalyzed synthesis of pyrano- and furoquinolines

entry	aniline(**2**) R	benzaldehyde(**1**) R1	R2	R3	olefin **3**	Time (h)	Yield (%)	Product ratio[a] **4:5** or **6:7**
a	H	H	H	H	 **3a**	2.5	90	20:80[14a]
b	H	H	H	Cl		3	88	25:75[14d]
c	H	F	NO_2	H		4	85	30:70
d	H	H	H	OMe		2.5	90	15:85[14f]
e	H	H	NO_2	H		4	88	40:60[14f]
f	F	H	H	Cl		4	87	35:65
g	Br	H	H	H		3	82	25:75[14e]
h	CH_3	H	H	H		2.5	92	20:80[14e]
i	H	H	H	H	 **3b**	2	88	15:85[14e]
j	H	H	H	Br		3	84	40:60
k	F	H	H	Cl		3.5	85	30:70
l	OMe	H	H	Cl		2.5	90	30:70
m	H	Cl	NO_2	H		4	88	20:80

[a] isomer ratios were calculated based on ^{1}H NMR spectra of the crude products.

Experimental Section

General Procedures. Reagents and solvents were of analytical grade or were purified by standard procedures prior to use; petroleum refers to the fraction b.p. 60–80 °C. ^{1}H NMR spectra

were recorded on Varian FT-200 MHz (Gemini) and Bruker UXNMR FT-300 MHz (Avance) instruments, in $CDCl_3$. Chemicals shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.0) as internal standard. Mass spectra were recorded under electron impact at 70eV on a Finnigan Mat 1020B mass spectrometer. Melting points were recorded on a Büchi 535 and are uncorrected. Column chromatography was performed on silica gel (100–200 mesh) supplied by Acme Chemical Co. (India). Thin-layer chromatography was performed on Merck 60 F-254 silica gel plates.

General experimental procedure. To a stirred solution of the benzaldehyde (1 mmol), the aniline (1 mmol), and 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran (1 mmol) in acetonitrile (10 ml), vanadium(III) chloride (0.2 mmol) was added and the mixture stirred at room temperature for the specified time (see Table 1). After completion (followed by TLC), the solvent was removed under reduced pressure using a rotary evaporator. The crude material was subjected to column chromatography over silica gel eluting with hexane–EtOAc (2-10%) to afford the pure pyrano- or furoquinolines.

The known compounds were identified by comparison of spectral data and mp with those reported. The mp and spectral data of the new compounds are presented below.

Spectroscopic data for selected compounds

(4a*R,5*R**,10b*R**)-5-(2-Fluoro-5-nitrophenyl)-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-*c*]-quinoline (4c).** Solid, mp 148–152 °C (n-hexane); IR (KBr): ν 3325, 2925, 2857, 1606, 1527, 1486 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.17 (d, 1H, *J* = 8.3 Hz), 7.75 (d, 1H, *J* = 7.4 Hz), 7.55 (t, 1H, *J* = 7.4 Hz), 7.38 (d, 1H, *J* = 7.4 Hz), 7.07 (t, 1H, *J* = 8.3 Hz), 6.80 (t, 1H, *J* = 6.5 Hz), 6.60 (d, 1H, *J* = 8.3 Hz), 5.30 (d, 1H, *J* = 5.5 Hz), 4.80 (1H, brs), 3.85 (1H, s), 3.63–3.30 (m, 2H), 2.20–2.05 (m, 1H) 1.67–1.40 (m, 2H), 1.24–1.14 (m, 1H). EIMS *m/z* (%): 328 (M^+).

(4a*R, 5*S**, 10b*R**)-5-(2-Fluoro-5-nitrophenyl)-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-*c*]-quinoline(5c).** Semi-solid; IR (neat): ν 3370, 2938, 1610, 1529, 1488 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.56–8.47 (m, 1H), 8.26–8.14 (m, 1H), 7.30–7.15 (m, 2H), 7.10 (t, 1H, *J* = 7.6 Hz), 6.74 (t, 1H, *J* = 7.6 Hz), 6.55 (d, 1H, *J* = 7.6 Hz), 5.17 (d, 1H, *J* = 10.1 Hz), 4.37 (d, 1H, *J* = 2.5 Hz), 4.13–3.94 (m, 1H), 3.69 (t, 1H, *J* = 11.0 Hz), 2.0–1.6 (m, 1H), 1.47–1.20 (m, 4H). EIMS *m/z* (%): 328 (M^+).

(4a*R,5*R**,10b*R**)-5-(4-Chlorophenyl)-9-fluoro-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-*c*]-quinoline (4g).** Solid, mp 158–160 °C (n-hexane); IR (KBr): ν 3382, 2931, 1607, 1504 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.25–7.42 (m, 3H), 7.14 (dd, 1H, *J* = 2.2, 9.6 Hz), 6.75–6.95 (m, 2H), 6.48–6.56 (m, 2H), 5.25 (d, 1H, *J* = 5.2 Hz), 4.64 (d, 1H, *J* = 2.2 Hz), 4.28 (s, 1H), 3.56–3.74 (m, 2H), 3.33–3.48 (m, 1H), 2.05–2.21 (m, 1H), 1.41–1.67 (m, 2H). EIMS *m/z* (%): 316 (M^+-1).

(4a*R,5*S**,10b*R**)-5-(4-Chlorophenyl)-9-fluoro-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-*c*]quinoline (5g).** Solid, mp 128 °C (n-hexane); IR (KBr): ν 3350, 2923, 2852, 1509 cm^{-1}; ^1H

NMR (300 MHz, $CDCl_3$): δ 7.32 (s, 4H), 6.90 (dd, 1H, *J* = 3.0, 9.0 Hz), 6.80 (dt, 1H, *J* = 3.0, 8.3 Hz), 6.43 (dd, 1H, *J* = 4.5, 9.0 Hz), 4.61 (d, 1H, *J* = 10.5 Hz), 4.30 (d, 1H, *J* = 3.0 Hz), 4.09–3.99 (m, 1H), 3.90 (s, 1H), 3.67 (dt, 1H, *J* = 2.2, 11.3 Hz), 2.02–1.94 (m, 1H), 1.81–1.56 (m, 2H), 1.51–1.21 (m, 2H). EIMS *m/z* (%): 317 (M^+).

(3a*R,4*R**,9b*R**)-4-(4-Bromophenyl)-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline (6k).** Solid, mp 210–215 °C (n-hexane); IR (neat): ν 3416, 1617, 1485, 1353 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.53–7.42 (m, 2H), 7.36–7.26 (m, 3H), 7.03 (dt, 1H, *J* = 1.3, 8.4 Hz), 6.77 (t, 1H, *J* = 7.5 Hz), 6.52 (d, 1H, *J* = 7.9 Hz), 5.2 (d, 1H, *J* = 7.7 Hz), 4.65 (d, 1H, *J* = 2.6 Hz), 3.81–3.51 (m, 1H), 2.75–2.65 (m, 1H), 2.23–2.07 (m, 1H). 1.50 (m, 1H) EIMS *m/z* (%): 329 (M^+).

(3a*R,4*S**,9b*R**)-4-(4-Bromophenyl)-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline (7k).** solid, mp 142-147 °C (n-hexane); IR (neat): ν 3417,1617, 1352 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.51–7.46 (m, 2H), 7.35–7.30 (m, 3H), 7.08 (dt, 1H, *J* = 1.5, 9.0 Hz), 6.77 (t, 1H, *J* = 7.5 Hz), 6.57 (d, 1H, *J* = 7.5 Hz), 4.53 (d, 1H, *J* = 5.2 Hz), 4.03–3.95 (m, 2H), 3.84–3.71 (m, 2H), 2.42–2.30 (m, 1H), 2.06–1.93 (m, 1H), 1.71–1.60 (m, 1H). EIMS *m/z* (%): 328 (M^+-1).

(3a*R,4*R**,9b*R**)-4-(4-Chlorophenyl)-8-fluoro-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline (6l).** Solid, mp 219 °C (n-hexane); IR (KBr): ν 3335, 2886, 1653, 1496 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.42–7.18 (m, 4H), 7.02 (dd, 1H, *J* = 2.9, 8.8 Hz), 6.77 (dt, 1H, *J* = 2.9, 5.8 Hz), 6.49 (q, 1H, *J* = 4.4, 8.8 Hz), 5.17 (d, 1H, *J* = 8.0 Hz), 4.64 (d, 1H, *J* = 2.9 Hz), 3.81–3.63 (m, 1H), 2.78–2.61 (m, 1H), 2.04–1.96 (m, 1H), 1.60–1.39 (m, 2H). EIMS *m/z* (%): 302 (M^+-1).

(3a*R,4*S**,9b*R**)-4-(4-Chlorophenyl)-8-fluoro-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline (7l).** Solid, mp 146 °C (n-hexane); IR (KBr): ν 3384, 2932, 1625, 1498 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35 (s, 4H), 7.08 (dd, 1H, *J* = 3.0, 9.0 Hz), 6.83 (dt, 1H, *J* = 3.0, 9.0 Hz), 6.53 (dd, 1H, *J* = 4.5, 9.0 Hz), 4.51 (d, 1H, *J* = 5.2 Hz), 4.03–3.90 (m, 2H), 3.83–3.67 (m, 2H), 2.44–2.30 (m, 1H), 2.0–1.90 (m, 1H), 1.71–1.60 (m, 1H). EIMS *m/z* (%): 302 (M^+-1).

(3a*R,4*R**,9b*R**)-4-(4-Chlorophenyl)-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinolin-8-yl methyl ether(6m).** Solid, mp 190 °C (n-hexane); IR (neat): ν 3443, 2924, 1622, 1497 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.42–7.30 (dd, 4H, *J* = 9.0, 13.5 Hz), 6.90 (d, 1H, *J* = 3.0 Hz), 6.69 (dd, 1H, *J* = 9 Hz), 6.52 (d, 1H, *J* = 6.3 Hz), 4.52 (d, 1H, *J* = 5.2 Hz), 4.02–3.94 (m, 1H), 3.81–3.70 (m, 2H), 3.72(s, 3H), 2.43–2.35 (m, 1H), 2.04–1.92 (m, 1H), 1.61–1.59 (m, 1H). EIMS *m/z* (%): 314 (M^+-1).

(3a*R,4*S**,9b*R**)-4-(4-Chlorophenyl)-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinolin-8-yl methyl ether(7m).** Solid, mp 128 °C (n-hexane); IR (KBr): ν 3319, 2858, 1505, 1409 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.37–7.30 (m, 4H), 6.90 (d, 1H, *J* = 3.0 Hz,), 6.70 (dd, 1H, *J* = 2.2, 8.3 Hz), 6.52 (d, 1H, *J* = 8.3 Hz), 4.52 (d, 1H, *J* = 5.2 Hz), 4.03–3.93 (m, 1H), 3.76 (s, 3H), 3.68 (d, 1H, *J* = 11.3 Hz), 2.44–2.34 (m, 1H), 2.04–1.92 (m, 1H), 1.79–1.59 (m, 1H). EIMS *m/z* (%): 314 (M^+-1).

(3a*R,4*R**,9b*R**)-4-(2-Chloro-5-nitrophenyl)-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline (6n).** Solid, mp 208 °C (n-hexane); IR (neat): ν 3415, 3284, 2887, 1613, 1514, 1484 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.64 (d, 1H, *J* = 2.6 Hz), 8.12 (dd, 1H, *J* = 2.6, 8.6 Hz), 7.56 (d, 1H, *J* = 8.6 Hz), 7.32 (d, 1H, *J* = 7.1 Hz), 7.10–7.03 (m, 1H), 6.86–6.79 (m, 1H), 6.61 (d, 1H, *J* = 7.9

Hz), 6.45 (s, 1H), 5.26 (d, 1H, *J* = 7.7 Hz), 5.10 (d, 1H, *J* = 2.8 Hz), 3.83–3.63 (m, 1H), 3.02–2.90 (m, 1H). EIMS *m/z* (%): 329 (M^+-1).

(3a*R,4*S**,9b*R**)-4-(2-Chloro-5-nitrophenyl)-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline (7n).** Solid, mp 176 °C (n-hexane); IR (neat): ν 3422, 1622, 1349 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.55 (d, 1H, *J* = 3.0 Hz), 8.13 (dd, 1H, *J* = 3.9 Hz), 7.60 (d, 1H, *J* = 9.0 Hz), 7.35 (d, 1H, *J* = 8.3 Hz), 7.12 (dt, 1H, *J* = 1.5, 7.5 Hz), 6.83 (t, 1H, *J* = 8.3 Hz), 6.62 (d, 1H, *J* = 8.3 Hz), 4.60 (d, 1H, *J* = 4.5 Hz), 4.57 (s, 1H), 4.12–4.00 (m, 2H), 2.57–2.47 (m, 1H), 2.16–2.02 (m, 1H), 1.76–1.65 (m, 1H). EIMS *m/z* (%): 329 (M^+-1).

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