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Imino Diels–Alder reactions: an efficient one-pot synthesis of pyrano and furanoquinoline derivatives catalyzed by $SbCl_3$

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Abstract—Antimony trichloride ($SbCl_3$) was found to be an efficient catalyst for the inverse electron demand imino Diels–Alder reactions of in situ generated *N*-benzylidenes with 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran to afford pyrano and furano[3,2-*c*]quinolines in excellent yields.

The products containing pyrano and furanoquinoline moieties are widely distributed in nature and found to be associated with a wide range of biological activities. Pyranotetrahydroquinolines are found in several alkaloids[1] such as veprisine, flinderesine and oricine. These alkaloids possess important biological activities such as *anti*-allergic,[2] psychrotopic,[3] *anti*-inflammatory[4] and estrogenic activities.[5] The alkaloids skimimianine and balflouridine which contain furanoquinoline moieties also show biological activity, which has led to the synthesis of pyrano and furanoquinoline derivatives over the years.[6] Therefore, it is not surprising that many synthetic methods have been developed for these types of compounds. Amongst them, the Lewis acid catalyzed aza-Diels–Alder reaction between *N*-benzylideneanilines and nucleophilic olefins is one of the most powerful synthetic tools for constructing nitrogen-containing six-membered heterocyclic compounds. However, an in situ generated diene is preferred over a preformed heterodiene, leading to a one-pot procedure, which is especially useful when the diene is unstable, sensitive to moisture and difficult to purify by column chromatography or distillation.[7] Since the pioneering work of Povarov,[8] these reactions have been extensively studied with protic acids[9] (TFA, *p*-TsOH), different Lewis acids such as $BF_3{\cdot}OEt_2$[10] and lanthanide triflates[11] including $Ln(OTf)_3$, $Sc(OTf)_3$, $Yb(OTf)_3$ and $InCl_3$.[12] Lanthanide chloride[13] ($GdCl_3$), $LiClO_4$ in diethyl ether,[14] $LiBF_4$,[15] $ZrCl_4$,[16] Montmorillonite[17] and fluorinated alcohols[18] have also been used as efficient catalysts for the synthesis of tetrahydroquinolines. Very recently, $KHSO_4$[19] and iodine[20] have also been used as efficient catalysts for the one-pot synthesis of the pyranoquinoline moiety. However, most of these methods involve expensive reagents and more than stoichiometric amounts of Lewis acid catalysts are needed due to strong co-ordination with the heterodiene, coupled with longer reaction times and strongly acidic conditions. Hence, a milder and better method is desirable.

In this letter, we report the synthesis of substituted pyrano and furanoquinolines via an imino Diels–Alder reaction using antimony trichloride ($SbCl_3$) as a catalyst. To the best of our knowledge, there is no report of the use of $SbCl_3$ as a mild and inexpensive catalyst for these types of reactions. $SbCl_3$ is easier to handle than other metal halides such as $InCl_3$, $GdCl_3$ and $TiCl_4$. Thus, the reaction[21] of an aldehyde (2.0 mmol), an aromatic amine (2.0 mmol) and a dihydropyran or dihydrofuran (2.2 mmol) in the presence of anhydrous Na_2SO_4 (100 mg) and $SbCl_3$ (10 mol %) in acetonitrile at room temperature furnished the corresponding pyrano or furanoquinolines **4** and **5** in good to excellent yield (Scheme 1). A series of tetrahydropyranoquinolines were prepared in good to excellent yields using this protocol as summarized in Table 1. Various solvents were used for this reaction and acetonitrile was found to give the best yield of product in comparison with dichloromethane (46%, in a cis:trans ratio of 31:69 with respect to C-4a

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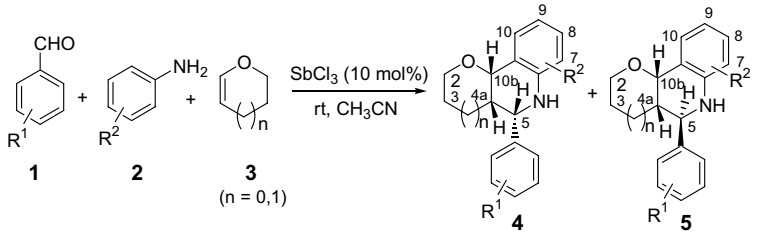


Scheme 1.

Table 1. One-pot synthesis of pyrano and furanoquinolines catalyzed by antimony trichloride ($SbCl_3$)[a]

Entry	R^1	R^2	*n*	Time (min)	Product ratio (4:5)[b]	Yield (%)	Ref.
1	H	H	1	40	28:72	90	13
2	H	4-Cl	1	40	31:69	75	13
3	H	3-Cl	1	15	—	73[c]	13
4	H	2-CH_3	1	90	26:74	78	13
5	H	4-CH_3	1	90	30:70	84	16a
6	H	4-OCH_3	1	50	33:67	84	13
7	H	4-Br	1	40	28:72	72	16a
8	4-Cl	H	1	45	32:68	80	16a
9	4-OCH_3	H	1	80	28:72	86	20
10	H	2-OH	1	120	31:69	86	13
11	H	H	0	15	52:48	92	13
12	H	4-OCH_3	0	20	54:46	83	13
13	H	4-CH_3	0	18	52:48	91	—
14	H	4-Cl	0	18	43:57	80	13
15	H	4-Br	0	15	48:52	86	—
16	4-Cl	H	0	25	57:43	84	16a
17	2-OCH_3	H	0	25	62:38	82	—
18	H	2-CH_3	0	20	33:67	85	13

[a] All reactions were conducted at room temperature using 10 mol % $SbCl_3$ in acetonitrile.
[b] Products were characterized by mp, IR and ^{1}H NMR. The product ratio was based on isolation by chromatography.
[c] Ratio (17:22:43:18) of four products characterized by ^{1}H NMR.

and C-5), diethyl ether (31%, cis:trans; 45:55), tetrahydrofuran (63%, cis:trans; 18:82) and toluene (44%, cis:trans; 68:32).

The pyran ring was cis-fused in the tetrahydroquinoline moiety and the stereochemistry of the products was established based on the coupling constants. The coupling constant of C_5–H ($J_{4a,5} = 4.6$–5.5 Hz) in **4** indicated the cis relationship between C-4a and C-5, whereas in **5** ($J_{4a,5} = 10.2$–11.10 Hz) the coupling was trans. In all cases, $J_{4a,10b}$ was found to be 2.6–2.9 Hz indicating a cis ring junction between the quinoline and pyran rings which is in accord with literature values.[16a] Similarly, a series of in situ generated *N*-arylbenzylidenes reacted with 2,3-dihydrofuran to give the corresponding tetrahydrofuranoquinolines in good to excellent yields (Table 1).

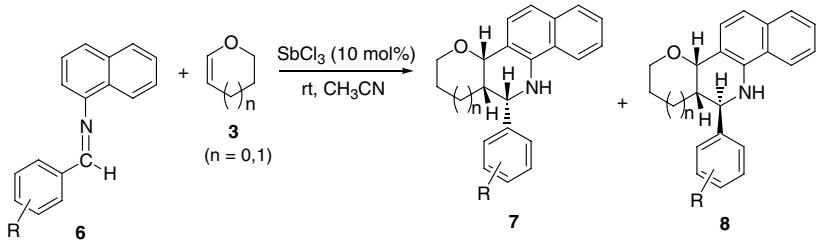
Phenanthridine skeletons[22] are present in lycorine, chelidonine and haemanthamine alkaloids. Antimony trichloride also catalyzed effectively the imino Diels–Alder reaction (Scheme 2) of in situ generated *N*-benzylidene-1-naphthylamine **6** with 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran to afford the phenanthridine derivatives **7** and **8** as a mixture of cis and trans isomers in good overall yields (54–62%) (Table 2).

In conclusion, we have developed a new and effective methodology for the synthesis of tetrahydropyranoquinolines and furanoquinolines in one-pot using a catalytic amount of antimony trichloride. Mild and neutral reaction conditions, high yields of products, the low cost of reagents, enhanced reactivity and selectivity, operational simplicity and ease of isolation of the products are the main advantages over existing procedures for the synthesis of pyrano and furanoquinoline derivatives.

Table 2. One-pot synthesis of pyrano and furanophenanthridines catalyzed by antimony trichloride ($SbCl_3$)[a]

Entry	R	*n*	Time (h)	Product ratio (7:8)[b]	Yield (%)
1	H	1	12	49:51	59
2	4-Cl	1	9	30:70	62
3	H	0	0.5	35:65	58
4	4-OCH_3	0	1	23:77	54

[a] All reactions were conducted at room temperature using 10 mol % $SbCl_3$ in acetonitrile.
[b] Products were characterized by mp, IR and ^{1}H NMR. The product ratio was based on isolation by chromatography.



Scheme 2.

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21. *Representative procedure*: To a suspension of $SbCl_3$ (46 mg, 0.2 mmol) and anhydrous Na_2SO_4 (200 mg) were added a solution of benzaldehyde (212 mg, 2.0 mmol) in acetonitrile (1.5 mL) and a solution of aniline (205 mg, 2.2 mmol) in acetonitrile (2 mL) at room temperature. The mixture was stirred for 10 min at room temperature. To this mixture, dihydropyran (218 mg, 2.6 mmol) was added and the reaction stirred for the period of time as mentioned in Table 1. After completion of the reaction (monitored by TLC), it was quenched with water and extracted with CH_2Cl_2 (3×20 mL). The organic layer was washed with water (2×10 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude residue obtained was purified by column chromatography over silica gel (5% ethyl acetate in petroleum ether) to give pure tetrahydropyranoquinolines **4** and **5** (475 mg, 90%).
Spectral data of tetrahydropyranoquinolines, Table 1, entry 9: Cis isomer: mp 159 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41–1.62 (m, 4H), 2.14–2.15 (m, 1H), 3.41 (dt, $J = 2.3$, 8.9 Hz, 1H), 3.60 (dd, $J = 3.2$, 11.9 Hz, 1H), 3.84 (s, 3H), 4.64 (d, $J = 2.0$ Hz, 1H), 5.29 (d, $J = 5.5$ Hz, 1H), 6.65 (d, $J = 7.9$ Hz, 1H), 6.86 (d, $J = 7.5$ Hz, 1H), 6.92 (d, $J = 8.4$ Hz, 2H), 7.09 (t, $J = 7.9$ Hz, 1H), 7.39 (d, $J = 8.3$ Hz, 2H), 7.45 (d, $J = 7.7$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.0, 25.4, 39.0, 55.3, 58.7, 60.6, 72.7, 113.7 (2), 114.3, 118.2, 119.8, 127.6, 127.8 (2), 128.0, 133.1, 145.2, 158.9; HRMS calcd for $[C_{19}H_{21}O_2N+H^+]$ 296.1550, found 296.1651.
Trans isomer: mp 132 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29–1.33 (m, 1H), 1.50–1.54 (m, 1H), 1.60–1.80 (m, 2H), 2.16–2.19 (m, 1H), 3.71 (dt, $J = 2.1$, 11.7 Hz, 1H), 3.84 (s, 3H), 4.09 (dd, $J = 2.1$, 3.9 Hz, 1H), 4.42 (d, $J = 2.2$ Hz, 1H), 4.72 (d, $J = 11.1$ Hz, 1H), 6.53 (d, $J = 8.1$ Hz, 1H), 6.81 (t, $J = 7.1$ Hz, 1H), 6.93 (d, $J = 8.4$ Hz, 2H), 7.09 (t, $J = 7.5$ Hz, 1H), 7.25 (d, $J = 7.5$ Hz, 1H), 7.41 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9, 24.1, 38.8, 54.1, 55.3, 68.8, 74.6, 113.9 (2), 114.3, 117.5, 120.8, 128.9 (2), 129.3, 130.9, 134.1, 144.6, 159.2; HRMS calcd for $[C_{19}H_{21}O_2N+H^+]$ 296.1550, found 296.1653.
Spectral data of tetrahydrofuranoquinolines, Table 1, entry 13: Cis isomer: mp 115 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55–1.64 (m, 1H), 2.35 (s, 3H), 2.84–2.88 (m, 1H), 3.74–3.82 (m, 2H), 3.88–3.95 (m, 1H), 4.72 (d, $J = 2.7$ Hz, 1H), 5.33 (d, $J = 8.0$ Hz, 1H), 6.61 (d, $J = 8.1$ Hz, 1H), 6.99 (d, $J = 7.9$ Hz, 1H), 7.26 (s, 1H), 7.39–7.56 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5, 24.7, 45.9, 57.8, 66.9, 76.1, 115.0, 122.7, 126.5 (2), 127.6, 128.4, 128.6 (2), 129.1, 130.3, 142.3, 142.7; HRMS calcd for $[C_{18}H_{19}ON+H^+]$ 266.1545, found 266.1577.
Trans isomer: mp 82 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.68–1.75 (m, 1H), 1.98–2.06 (m, 1H), 2.28 (s, 3H), 2.49–2.53 (m, 1H), 3.76–3.87 (m, 2H), 3.99–4.07 (m, 1H), 4.60 (d, $J = 5.1$ Hz, 1H), 6.58 (d, $J = 8.1$ Hz, 1H), 6.95 (d, $J = 8.1$ Hz, 1H) 7.23 (s, 1H), 7.35–7.47 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.4, 28.8, 43.5, 58.0, 65.2, 76.1, 114.7, 120.1, 127.6, 128.0, 128.2 (2), 128.5 (2), 129.6, 131.2, 141.7, 143.0; HRMS calcd for $[C_{18}H_{19}ON+H^+]$ 266.1545, found 266.1533.
Spectral data of tetrahydrofuranoquinolines, Table 1, entry 15: Cis isomer: mp 152 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.53–1.63 (m, 1H), 2.11–2.22 (m, 1H), 2.73–2.82 (m, 1H), 3.70–3.87 (m, 2H), 4.69 (d, $J = 2.6$ Hz, 1H), 5.21 (d, $J = 7.8$, 1H), 6.52 (d, $J = 8.6$ Hz, 1H), 7.17 (dd, $J = 2.3$, 8.8 Hz, 1H), 7.31–7.48 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.4, 45.3, 57.2, 66.9, 75.4, 110.7, 116.5, 124.6, 126.4 (2), 127.8, 128.7 (2), 131.1, 132.6, 141.7, 143.7; HRMS calcd for $[C_{17}H_{16}ONBr+H^+]$ 330.0593, found 330.0591.
Trans isomer: mp 104 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.66–1.76 (m, 1H), 1.96–2.08 (m, 1H), 2.45–2.50 (m, 1H), 3.75–3.87 (m, 2H), 3.98–4.06 (m, 1H), 4.56 (d, $J = 5.2$ Hz, 1H), 6.53 (d, $J = 8.6$ Hz, 1H), 7.20 (dd, $J = 2.0$, 8.6 Hz,

1H), 7.34–7.45 (m, 5H), 7.52 (d, $J = 1.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.7, 43.1, 57.7, 65.2, 75.6, 109.8, 116.3, 122.2, 128.2 (2), 128.3, 128.7 (2), 131.7, 133.6, 141.1, 144.3; HRMS calcd for [$C_{17}H_{16}ONBr+H^+$] 330.0593, found 330.0601.

Spectral data of phenanthridine derivatives, Table 2, entry 1: Cis isomer: light brown viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36–1.44 (m, 2H), 1.49–1.66 (m, 2H), 2.27–2.31 (m, 1H), 3.33–3.41 (m, 1H), 3.61–3.64 (m, 1H), 4.83 (d, $J = 1.7$ Hz, 1H), 5.52 (d, $J = 5.5$ Hz, 1H), 7.33–7.46 (m, 5H), 7.55–7.64 (m, 4H), 7.77–7.83 (m, 2H); HRMS calcd for [$C_{22}H_{21}ON+H^+$] 316.1701, found 316.1675.

Trans isomer: mp 128 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36–1.41 (m, 1H), 1.52–1.56 (m, 1H), 1.69–1.77 (m, 1H), 1.79–1.90 (m, 1H), 2.22–2.26 (m, 1H), 3.78 (dt, $J = 1.7$, 11.0 Hz, 1H), 4.11–4.15 (m, 1H), 4.53 (d, $J = 2.4$ Hz, 1H), 4.85 (d, $J = 10.9$ Hz, 1H), 7.25 (d, $J = 7.7$ Hz, 1H), 7.35–7.59 (m, 8H), 7.69–7.78 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.2, 24.1, 38.7, 55.2, 68.6, 74.7, 114.7, 117.3, 120.0, 122.6, 124.7, 125.9, 127.9, 128.0 (2), 128.5, 128.6, 128.7 (2), 134.4, 139.8, 142.3; HRMS calcd for [$C_{22}H_{21}ON+H^+$] 316.1701, found 316.1699.

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