Novel and Efficient Lewis Acids as Catalysts for Single-step Synthesis of Pyrano- and Furoquinolines[1]

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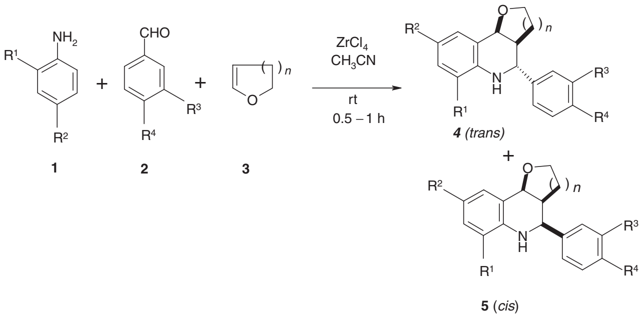
Some Lewis acids such as $ZrCl_4$, $SnCl_4$, $TiCl_4$, and $PtCl_4$ have been found to be novel and highly efficient catalysts for one-pot coupling of the three components, anilines, aldehydes, and 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran to produce the corresponding pyrano- or furoqinolines in high yields and high diastereoselectivity.

Pyranoquinolines have been found to possess different important pharmacological activities such as anti-inflammatory, antiallergic, and estrogenic properties.[2] Various bioactive natural alkaloids are pyranoquinoline derivatives.[3] The synthesis of such compounds is thus quite necessary. Pyranoquinolines are generally prepared by the aza-Diels–Alder reaction of imines (derived from aromatic amines and benzaldehydes) with 3,4-dihydro-2*H*-pyran.[4] Various Lewis acids are used[4,5] to catalyze this reaction. However, many of these Lewis acids are expensive or not easily available, require longer times to complete the reactions and form the mixture of products. Several imines are also unstable, hygroscopic, and difficult for purification and thus the preparation of these compounds in pure form followed by coupling with dihydropyran in steps is not advantageous. However, a number of Lewis acids cannot be applicable for one-pot coupling of anilines, aldehydes, and dihydropyran or furan as they will be decomposed or deactivated by amines and water formed in the intermediate imine formation stage. Thus there are a limited number of reported methods[6] for single-step coupling of these three components though different processes for multi step coupling are well known.

In continuation of our work[7] on the development of novel synthetic methodologies, we have recently discovered that $ZrCl_4$ is a highly effective catalyst for the preparation of pyrano- or furanoquinolines by coupling of anilines (**1**), benzaldehydes (**2**), and 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran (**3**) (Scheme 1).

A series of pyrano- and furoquinolines were prepared[8] by following the above method. The products (**4** and **5**) were the mixture of *trans*- and *cis*-isomers which could be separated by column chromatography over silica gel. The *trans*-isomer was the major and *cis*-isomer minor in each conversion. The reaction thus proceeded with high yield and high diastereoselectivity. The ratio of the isomers formed in a reaction was determined by ^{1}H NMR spectrum of the crude product and the structures of the products were established from the spectral (^{1}H NMR and MS) data of the pure compounds.[8]



Scheme 1.

To examine the catalytic activity of different Lewis acids such as $AlCl_3$, $FeCl_3$, $SnCl_4$, $TiCl_4$, $ZrCl_4$, $HfCl_4$, $PtCl_4$, and WCl_6 each catalyst (0.1 equiv.) was added separately to a solution of aniline (1 mmol), benzaldehyde (1 mmol) and 3,4-dihydro-2*H*-pyran (1.1 mmol, 0.1 mL) in CH_3CN (10 mL) at room temparature for 0.5 h. $ZrCl_4$ was found to be the most effective catalyst under the present experimental conditions in term of the yield of pyranoquinoline (86%). The activity of $SnCl_4$, $TiCl_4$, and $PtCl_4$ was comparable forming the pyranoquinoline with yields of 82, 78, and 76%, respectively. However, the activity of $HfCl_4$ and WCl_6 was somewhat low and the former formed the pyranoquinoline with a yield of 67% while the latter with a yield of 61%. The reaction with other lewis acids, $AlCl_3$ and $FeCl_3$ produced the pyranoquinoline with yields of 47 and 43%, respectively.

In the present process the imines generated in situ by condensation of anilines and benzaldehydes act as heterodienes which undergo the aza-Diels–Alder reaction with the electron rich dienophile, 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran in the presence of $ZrCl_4$ to produce the corresponding pyrano- or furoquinolines. The conversion could not be achieved in absence

Table 1. Preparation of pyrano- and furoquinolines using $ZrCl_4$[a]

Entry	Aniline (1)		Benzaldehyde (2)		Olefin (3)	Time /min	Isolated Yield /%	Product Ratio[b] **(4:5)**
	R^1	R^2	R^3	R^4	n			
a	H	H	H	H	2	35	88	87:13
b	H	H	H	OMe	2	45	91	90:10
c	H	H	H	Cl	2	30	93	94:6
d	H	H	OCH_2O		2	45	90	88:12
e	H	H	Cl	Cl	2	35	94	92:8
f	H	Me	H	Cl	2	40	91	86:14
g	H	OMe	H	H	2	45	90	85:15
h	Me	H	H	H	2	50	80	78:22
i	H	H	H	H	1	45	85	89:11
j	H	H	H	OMe	1	50	88	90:10
k	H	H	H	Cl	1	40	90	92:8
l	H	H	Cl	Cl	1	55	92	89:11
m	H	OMe	H	H	1	50	86	82:18
n	Me	H	H	H	1	60	75	80:20

[a]All the products were characterized from their spectral data.
[b]Product ratio was determined from the ^{1}H NMR spectrum of the crude product.

of the catalyst. However, the imines (prepared separately) when treated with the dihydropyran or furan using ZrCl$_4$ formed the desired quinolines in high yields.

ZrCl$_4$, as well as some catalysts examined here, is easily available and less costly. Industrially its catalytic applications are recently steadily increasing.[9] Multicomponent reactions are also of growing importance in current organic synthesis owing to their speed, diversity, and efficiency. ZrCl$_4$ is thus a very suitable catalyst for single-step synthesis of pyrano- or furanoquinolines from the three components, anilines, benzaldehydes and 3,4-dihydro-2*H*-pyran- or 2,3-dihydrofuran.

In conclusion, we have applied novel and highly efficient catalysts for simple one-pot synthesis of pyrano- and furoquinolines in high yields and high diastereoselectivity. The present process may be a useful attractive alternative to the existing methods for the synthesis of quinoline derivatives.

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References and Notes

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8 General experimental procedure for the preparation of pyrano- and furoquinolines: To a solution of an aniline (1 mmol), a benzaldehyde (1 mmol) and 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran (0.1 mL) in CH$_3$CN (10 mL) was added ZrCl$_4$ (0.1 equiv., 0.1 mmol). The mixture was stirred at room temperature and the reaction was monitored by TLC. After completion the mixture was filtered and the filtrate was concentrated to a viscous mass. This was subjected to column chromatography on silica gel and the column was eluted with hexane-EtOAc (20:1) to produce the pyrano- or furoquinolines. The spectral data of some representative pyrano- and furoquinolines are given here: **4b:** mp 145–146 °C; ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.32 (2H, d, $J = 8.0$ Hz), 7.18 (2H, d, $J = 8.0$ Hz), 7.04 (1H, t, $J = 8.0$ Hz), 6.84 (2H, d, $J = 8.0$ Hz), 6.64 (1H, t, $J = 8.0$ Hz), 6.45 (1H, d, $J = 8.0$ Hz), 4.64 (1H, d, $J = 10.0$ Hz), 4.36 (1H, d, $J = 2.5$ Hz), 4.06 (1H, m), 3.97 (1H, d, $J = 3.0$ Hz), 3.82 (3H,s), 3.63 (1H, t, $J = 10.0$ Hz), 2.02 (1H, m), 1.82 (1H, m), 1.64 (1H, m), 1.44 (1H, m), 1.28 (1H, m); FABMS: m/z 296 ($M^+ + 1$). **5b:** mp 154–155 °C; ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.38 (1H, d, $J = 8.0$ Hz), 7.30 (2H, d, $J = 8.0$ Hz), 7.00 (1H, m), 6.82 (2H, d, $J = 8.0$ Hz), 6.77 (1H, t, $J = 8.0$ Hz), 6.50 (1H, d, $J = 8.0$ Hz), 5.26 (1H, d, $J = 3.0$ Hz), 4.60 (1H, d, $J = 3.0$ Hz), 3.84 (1H, m), 3.82 (3H, s), 3.58 (1H, m), 3.22 (1H, m), 2.04 (1H, m), 1.58–1.30 (4H, m); FABMS: m/z 296 ($M^+ + 1$). **4d:** mp 152–153 °C; ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.18 (1H, d, $J = 8.0$ Hz), 7.04 (1H, t, $J = 8.0$ Hz), 6.92 (1H, d, $J = 2.5$ Hz), 6.84–6.62 (3H, m), 6.46 (1H, d, $J = 8.0$ Hz), 5.96 (2H, s), 4.62 (1H, d, $J = 10.0$ Hz), 4.36 (1H, d, $J = 3.5$ Hz), 4.10 (1H, m), 3.98 (1H, brs), 3.70 (1H, m), 2.02 (1H, m), 1.85–1.22 (4H, m); FABMS: m/z 310 ($M^+ + 1$). **5d:** mp 159–160 °C; ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.38 (1H, d, $J = 8.0$ Hz), 7.04 (1H, t, $J = 8.0$ Hz), 6.92–6.76 (4H, m), 6.56 (1H, d, $J = 8.0$ Hz), 5.96 (2H, s), 5.24 (1H, d, $J = 6.0$ Hz), 4.60 (1H, d, $J = 3.0$ Hz), 3.78 (1H, brs), 3.60–3.38 (2H, m), 2.05 (1H, m), 1.60–1.38 (4H, m); FABMS: m/z 310 ($M^+ + 1$). **4k:** mp 148–149 °C; ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.35 (4H,s), 7.14 (1H, d, $J = 8.0$ Hz), 7.05 (1H, t, $J = 8.0$ Hz), 6.64 (1H, d, $J = 8.0$ Hz), 6.42 (1H, d, $J = 8.0$ Hz), 4.58 (1H, d, $J = 5.0$ Hz), 4.08 (1H, m), 3.85–3.42 (2H, m), 2.45 (1H, m), 2.00 (1H, m), 1.72 (1H, m); FABMS: m/z 286 ($M^+ + 1$). **5k:** mp 152–153 °C; ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.40 (1H, d, $J = 8.0$ Hz), 7.36 (4H, s), 7.05 (1H, t, $J = 8.0$ Hz), 6.68 (1H, t, $J = 8.0$ Hz), 6.41 (1H, d, $J = 8.0$ Hz), 5.25 (1H, d, $J = 8.0$ Hz), 4.65 (1H, d, $J = 3.0$ Hz), 3.78 (1H, brs), 3.62–3.40 (2H, m), 2.18 (1H, m), 1.62–1.50 (2H, m); FABMS: m/z 286 ($M^+ + 1$).

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