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SYNTHESIS OF *CIS* OR *TRANS* 4-HETEROAROMATIC SUBSTITUTED FURANO AND PYRANO[3,2-*c*]TETRAHYDROQUINOLINES BY ONE-POT IMINO DIELS-ALDER REACTIONS

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Abstract –A mild and an efficient method for the synthesis of substituted furano and pyrano[3,2-*c*]tetrahydroquinoline derivatives was described, using the imino Diels-Alder reaction between 2-(4-aminophenyl)benzofuran, aromatic aldehyde, and cyclic enol ethers. Furthermore, 2-hydroxyalkyl-4-heteroaromatic substituted tetrahydrofurano[3,2-*c*]quinoline was synthesized with good yields through the same imino Diels-Alder reaction in the absence of aldehydes. The advantages of this procedure are mild reaction conditions, and good yields with high diastereoselectivity.

In the latest years, numerous efforts have been directed towards the discovery of 2-(4-aminophenyl)-benzothiazole because its analogues comprise a novel mechanistic class of antitumor agents.[1] This nucleus is derived from related structures such as polyhydroxylated 2-phenylbenzothiazoles, flavone quercetin, and the isoflavone genistein, which are tyrosine kinase inhibitors with potent antitumor activity.[2] Furthermore, some 2-phenylbenzofuran analogues have showed potent anticancer activities.

Meanwhile, it is a remarkable fact that tetrahydroquinoline moiety, as an important fragment of various natural products and pharmaceutical agents that have exhibited a broad range of biological characteristics.[3] In addition, tetrahydroquinoline derivatives are used as potent pharmaceuticals,[4] for example，a group containing a tricyclic tetrahydroquinoline nucleus have been developed and investigated

as the selective androgen receptor modulator or strong platelet inhibitors. Methods for tetrahydroquinoline derivative synthesis were developed, including the Lewis-acid catalyzed imino Diels–Alder reaction (Povarov reaction) of *N*-arylimines with dienophiles.[5] Tricyclic compounds (furano or pyranoquinoline derivatives) were obtained when cyclic enol ethers such as 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran were employed as dienophiles.[6]

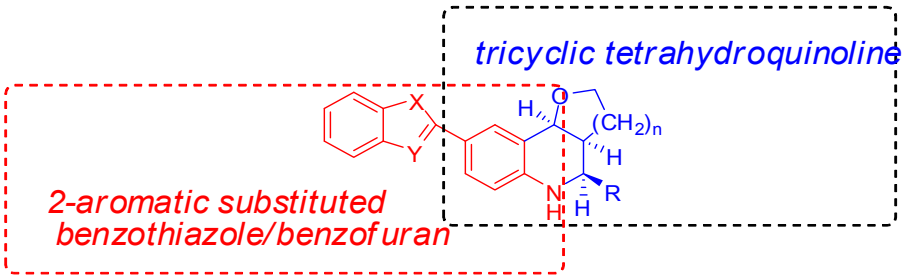


Figure 1. Chemical structure of 4-heteroaromatic substituted furano and pyrano[3,2-*c*]-tetrahydroquinoline derivatives

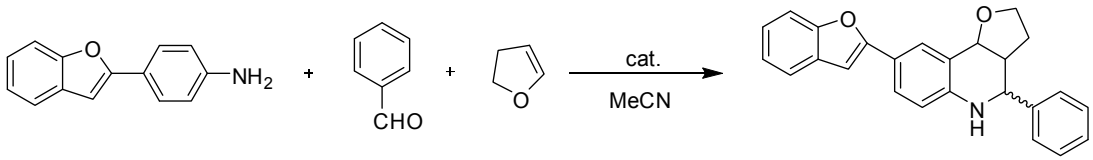
Although numerous methods for tetrahydroquinoline derivative synthesis have been reported in recent years, an efficient and highly diastereoselective method for the synthesis of novel tetrahydroquinoline scaffolds, an intriguing combination of two synthetically important pharmacophores, is still in demand.

To the best of our knowledge, the synthesis of 4-heteroaromatic substitute furano and pyrano[3,2-*c*]tetrahydroquinoline derivatives have never been reported. Such methodical variations may contribute to the bioactivity differences and enrich the tetrahydroquinoline library for biomedical screening. This report focuses on the synthesis of 4-heteroaromatic substitute furano and pyrano[3,2-*c*]tetrahydroquinoline derivatives through the reaction of aromatic aldehyde, 2-(4-aminophenyl)benzofuran, and 2,3-dihydrofuran (or 2,3-dihydropyran) catalyzed by indium chloride as a continuation of our previous research on new methods for the heterocyclic compound preparation by multi-component reactions.[7]

In this study, imino Diels-Alder reaction is a LUMO-diene controlled Diels-Alder reaction between an electron-deficient 2-azadiene (formed in situ from **7** with an aromatic aldehyde) and electron-rich dienophiles, such as cyclic enol ethers.[6] This imino Diels-Alder reaction was first optimized using 2-(4-aminophenyl)benzofuran, benzaldehyde, and 3,4-dihydro-2*H*-furan (DHF). In the presence of 20 mol% indium chloride ($InCl_3$) at room temperature, the corresponding 4-(2-benzofuranyl)-furano[3,2-*c*]tetrahydroquinoline derivatives are derived with good yields. Obviously, these results are better than those reactions catalyzed by BF_3, $AlCl_3$, *p*-toluenesulfonic acid (*p*-TsOH), trifluoroacetic acid (TFA), or iodine using simple aromatic amines as reactants at similar conditions (Table 1, entries 1–4). Thereafter, the same imino Diels-Alder reaction of 2-(4-aminophenyl)benzofuran with benzaldehyde in

the presence of 2,3-dihydrofuran (DHF) was performed, using $InCl_3$ as catalyst and acetonitrile as solvent at different conditions (Table 1, entries 5–9). Notably, reactions run faster at room temperatures, and 20 mol% is the optimal catalyst amount.

Table 1. Varying catalysts for reaction and of **7** with benzaldehyde and dihydrofuran (DHF)

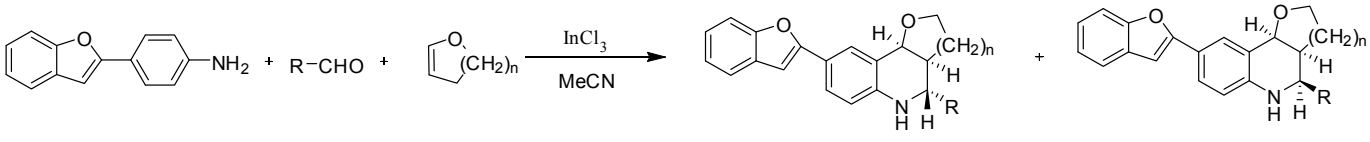


7 **8a** **9a** **10a+11a**

Entry	Catalyst	Catalyst %	Solvent	Temp.	Reaction Time	Yield (%)[a]
1	I_2	20 mol%	MeCN	rt	20 min	65
2	$InCl_3$	20 mol%	MeCN	rt	20 min	72
3	*p*-TsOH	20 mol%	MeCN	rt	2 h	60
4	TFA	20 mol%	MeCN	rt	2 h	45
5	$InCl_3$	10 mol%	MeCN	rt	20 min	61
6	$InCl_3$	30 mol%	MeCN	rt	20 min	69
7	$InCl_3$	20 mol%	MeCN	0 °C	>3 h	N.R.[b]
8	$InCl_3$	20 mol%	MeCN	50 °C	0.5 h	51
9	$InCl_3$	20 mol%	MeCN	reflux	0.5 h	32

[a] Yields refer to isolated products. [b] No reaction.

Under optimized conditions, various aromatic aldehydes **8** are then subjected to react with **7** and 2,3-dihydrofuran (**9a**) to generate a library of 4-(2-benzofuranyl)furano[3,2-*c*]tetrahydroquinoline derivatives (Table 3). For aldehyde **8**, the products were not sensitive to the aromatic ring's electronic properties in the presence of electron-withdrawing groups (such as halide) or electron-donating groups (such as alkoxy group) (Table 2). The corresponding products were observed in the reaction system solution monitored by TLC.



7 **8a-j** **9a n=1** **9b n=2** **10a-h n=1** **12a-j n=2** **11a-h n=1** **13a-j n=2**

Scheme 1. One-pot imino Diels-Alder reactions catalyzed by $InCl_3$ at room temperature

Table2. Imino Diels-Alder reactions catalyzed by $InCl_3$ for the Synthesis of furano[3,2-*c*]quinolines **10a–h** and **11a–h**[a]

Entry	R	Product	Reaction Time	Catalyst %	Yield (%)[b]	*dr*[c]
1	phenyl	**10a+11a**	20 min	20 mol%	72	33:67
2	3-hydroxyphenyl	**10b+11b**	30 min	20 mol%	65	65:35
3	4-bromo-2-thiophenyl	**10c+11c**	30 min	20 mol%	66	50:50
4	4-*t*Bu-phenyl	**11d**	30 min	20 mol%	58	<1:20
5	2,4-dichlorophenyl	**10e+11e**	30 min	20 mol%	62	13:87
6	4-acetylamidophenyl	**10f+11f**	30 min	20 mol%	64	43:57
7	3-chlorophenyl	**10g+11g**	25 min	20 mol%	64	37:63
8	3-methoxyphenyl	**10h+11h**	1.5 h	20 mol%	63	33:67

[a] Reaction temperature is 25 °C. [b] Yields refer to isolated products. [c] Diastereomeric ratios (*dr*) were determined by means of ^{1}H NMR analysis.

Table 3. Imino Diels-Alder reactions catalyzed by $InCl_3$ for the synthesis of pyrano[3,2-*c*]quinolines **12a–i** and **13a–i**[a]

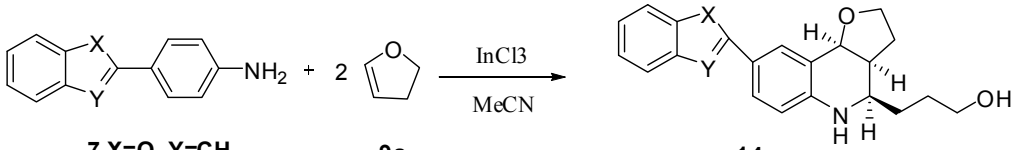
Entry	R	Product	Reaction Time	Catalyst %	Yield (%)[b]	*dr*[c]
1	phenyl	**13a**	40 min	20 mol%	60	<1:20
2	3-hydroxyphenyl	**12b+13b**	20 min	20 mol%	71	30:70
3	4-bromo-2-thiophenyl	**12c+13c**	20 min	20 mol%	69	15:85
4	4-bromo-2-chlorophenyl	**12d+13d**	20 min	20 mol%	71	12:88
5	4-*t*Bu-phenyl	**12e+13e**	40 min	20 mol%	62	20:80
6	2,4-dichlorophenyl	**13f**	20 min	20 mol%	68	<1:20
7	4-acetylamidophenyl	**12g+13g**	1.5 h	20 mol%	49	87:13
8	3-chlorophenyl	**12h+13h**	20 min	20 mol%	73	45:55
9	3-methoxyphenyl	**13i**	20 min	20 mol%	70	<1:20

[a] Reaction temperature is 25 °C. [b] Yields refer to isolated products. [c] Diastereomeric ratios (*dr*) were determined by means of ^{1}H NMR analysis.

Subsequently the product was separated by filtration before crystallization, and was also confirmed by ^{1}H NMR as the isomer type.[5,9] As expected, the 2,3-dihydrofuran substrates were extended to 3,4-dihydro-2*H*-pyran, which is also chosen to react with the aromatic aldehyde, 2-(4-aminophenyl) benzofuran, and were found to generate the corresponding 4-(2-benzofuranyl)pyrano[3,2-*c*]-

tetrahydroquinoline derivatives (**12a-i**, **13a-i**). The results are summarized in Table 3. The structure of **13f** was also confirmed by COSY, HMBC, and NOE experiments.

Table 4. Imino Diels-Alder reaction of **7** with 2.0 equiv of cyclic enol ether DHF[a]



7 X=O, Y=CH
8 X=O, Y=N
9 X=S, Y=N

9a

14a-c

Entry	Product	X	Y	Reaction Time	Catalyst %	Yield (%)[a]	*dr*[b]
1	**14a**	O	C	25 min	20 mol%	80	<1:20
2	**14b**	O	N	25 min	20 mol%	75	<1:20
3	**14c**	S	N	30 min	20 mol%	73	<1:20

[a] Reaction temperature is 25 °C. [b] Yields refer to isolated products. [c] Diastereomeric ratios (*dr*) were determined by means of ^{1}H NMR analysis.

In addition, the imino Diels-Alder procedure was performed without adding the aldehyde.[6,8] The 2-alkoxy-4-heteroaromatic-substituted furano[3,2-*c*]tetrahydroquinolines **14** preparation is shown in Table 4. Using 2.0 equiv enol ether, DHF, and $InCl_3$ catalyst provided good yields. In these reactions, only *cis* isomers were observed. Relative isomer configurations were obtained from ^{1}H NMR spectral data, and assigned by comparison with NMR literature.[8]

In conclusion, a mild and efficient procedure for the synthesis of 4-heteroaromatic substituted furano and pyrano[3,2-*c*]tetrahydroquinolines, using the one pot imino Diels-Alder approach was reported. Different catalysts and reaction conditions were examined, and the best results were obtained with $InCl_3$ catalyst at room temperature. The isomer types (*trans/cis*) were assigned by ^{1}H NMR spectra analysis. These tetrahydroquinoline derivatives were obtained in moderate to good yields with electron-withdrawing and electron-donating aromatic aldehydes. Without the addition of aldehyde, the imino Diels-Alder reaction using electron-rich olefins results in 2-alkoxy-4-heteroaromatic-substituted tetrahydroquinoline formation.

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9. The relative configuration of **10-13** was assigned by comparing the coupling constants for proton with other analogues, see references 13, 17 and 18, for more detailed information, see the supporting information.