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$InCl_3$-catalyzed reaction of aromatic amines with cyclic hemiacetals in water: facile synthesis of 1,2,3,4-tetrahydroquinoline derivatives

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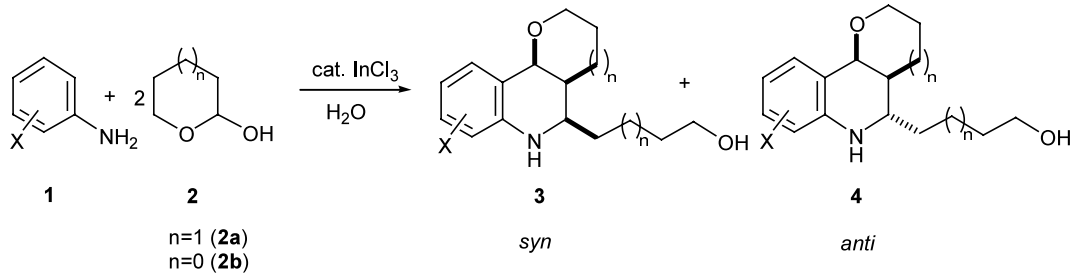
Abstract—By using a domino reaction of aromatic amines with various cyclic hemiacetals catalyzed by indium chloride in water, tetrahydroquinoline derivatives were synthesized efficiently.

Tetrahydroquinoline moiety is an important structural feature of various natural products and pharmaceutical agents that have exhibited a broad range of biological activities.[1] Continuous interest has been sustained to develop methods for the synthesis of tetrahydroquinoline derivatives.[2] Among the many efforts for their synthesis is the Lewis-acid catalyzed aza-Diels–Alder reaction of *N*-arylimines with dienophiles.[3] When cyclic enol ethers, such as 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran, are employed as the dienophiles, tricyclic compounds (furano or pyrano quinoline derivatives) are obtained.[4] A one-pot procedure for synthesizing such compounds, based on the three-components-reaction of substituted aniline, an aryl aldehyde, and an electron-rich olefin in the presence of Lewis acid catalysts has also been developed recently.[5] Batey and co-workers have developed a $Dy(OTf)_3$-catalyzed formation of hexahydrofuro[3,2-*c*]quinolines via 2:1 coupling of dihydrofuran with substituted anilines.[6]

Since the work of Loh,[7] indium(III) halide has been shown to be an effective Lewis acid for various reactions in aqueous medium.[8] Recently, we reported a synthesis of tetrahydroquinoline derivatives via a domino coupling of aniline derivatives with cyclic enol ethers catalyzed by indium(III) chloride in water.[9] As the availability of the cyclic enol ethers are rather limited, it is highly desirable to develop alternative methods for generating the same products. Herein, we wish to report a simple and general method for the synthesis of tetrahydroquinoline derivatives via the coupling of various cyclic hemiacetals and aniline derivatives catalyzed by $InCl_3$ in water (Scheme 1).

As a preliminary experiment, aniline **1a** was reacted with 2-hydroxy-tetrahydro-2*H*-pyran **2a** under several conditions in aqueous medium and $InCl_3$ was used as Lewis acid catalyst. While no desired tetrahydroquinoline product was observed in the absence of



Scheme 1.

Keywords: indium(III) chloride; aniline; tetrahydroquinoline; catalysis; aqueous.

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the $InCl_3$, in the presence of a catalytic amount (10 mol%) of $InCl_3$, a smooth reaction occurred to generate the desired product in combined 63% isolated yield of a pair of diastereomers **3a** and **4a**. Subsequently, the scope of the reaction was examined with a variety of aniline derivatives and cyclic hemiacetals. The results are listed in Table 1.

Various functional groups such as halogen, methoxy and cyano groups survived the reaction conditions. The rate of the reaction was strongly affected by the electronic nature of the substituents; the presence of an electron-withdrawing group (cyano) decreased the rate of the reaction considerably. Both five- and six-membered cyclic hemiacetals were effective for the reaction. In most cases, the anti-isomer was found to be the slightly major isomer, which was most likely due to a thermodynamic control. The reaction of 2-chromanol **5** and aniline produced smoothly [2-(*o*-hydroxyphenyl)]ethyl substituted tetrahydroquinoline **6a** and **6b** (Scheme 2).

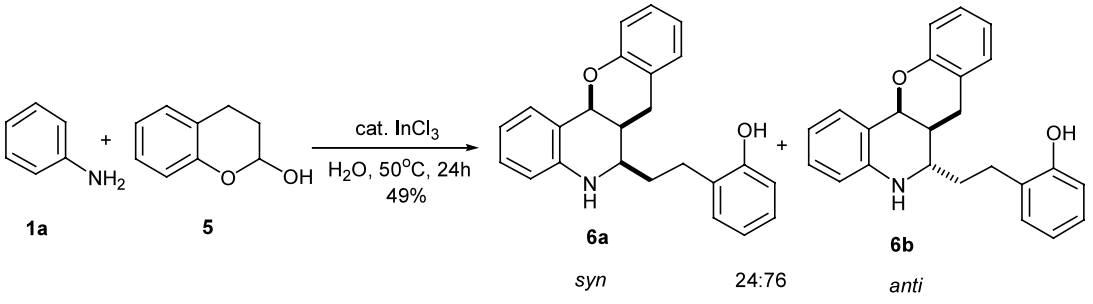
Interestingly, treatment of a 2-hydroxy cyclic ether analog, 2-deoxy-D-ribose **7**, with aniline in water catalyzed by $InCl_3$ afforded the novel tricyclic tetrahydroquinoline compounds **8** and **9** (Scheme 3). This example of reactivity towards 2-deoxy-D-ribose showed both the ability to tolerate hydroxyl groups as well as the scope of applications of the reaction in the field of carbohydrates.

The possible mechanism for the formation **8** and **9** was illustrated in Scheme 4. In the presence of $InCl_3$, 2-deoxy-D-ribose was in an equilibrium with its ring-opening form 3,4,5-trihydroxypentanal **10** in water. The α,β-unsaturated aldehyde **11** was then generated by the dehydration of **10**. Subsequently, conjugated addition of aniline to **11** (to generate **12**), followed by an aza-

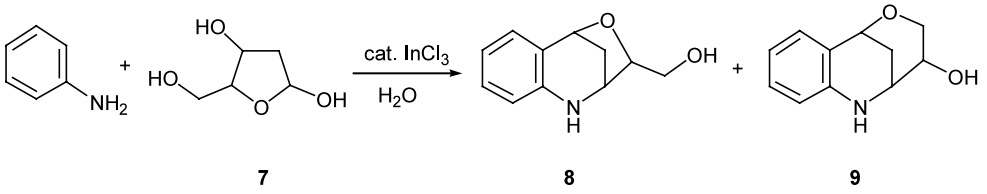
Table 1. Synthesis of tetrahydroquinolines by the reaction of aromatic amines with cyclic hemiacetals in water

Entry	Aniline	Hemiacetal	Conditions[a]	*syn*/*anti*	Total yield (%) (**3**+**4**)[b]
1	$PhNH_2$ (**1a**)	**2a**	Rt/24 h	32/68	63
2	4-$CH_3C_6H_4NH_2$ (**1b**)	**2a**	50°C/12 h	43/57	85
3	4-$CH_3OC_6H_4NH_2$ (**1c**)	**2a**	50°C/12 h	47/53	61
4	4-$ClC_6H_4NH_2$ (**1d**)	**2a**	50°C/12 h	45/55	47
5	4-$BrC_6H_4NH_2$ (**1e**)	**2a**	50°C/12 h	31/69	46
6	4-$FC_6H_4NH_2$ (**1f**)	**2a**	Rt/24 h	19/81	57
7	4-$CNC_6H_4NH_2$ (**1g**)	**2a**	50°C/24 h	–	Trace
8	$PhNH_2$ (**1a**)	**2b**	Rt/48 h	46/54	76
9	4-$CH_3C_6H_4NH_2$ (**1b**)	**2b**	Rt/12 h	48/52	66
10	4-$CH_3OC_6H_4NH_2$ (**1c**)	**2b**	50°C/12 h	42/58	71
11	4-$ClC_6H_4NH_2$ (**1d**)	**2b**	50°C/12 h	50/50	61
12	4-$BrC_6H_4NH_2$ (**1e**)	**2b**	50°C/12 h	39/61	44
13	4-$FC_6H_4NH_2$ (**1f**)	**2b**	Rt/24 h	52/47	66
14	4-$CNC_6H_4NH_2$ (**1g**)	**2b**	50°C/48 h	37/62	28

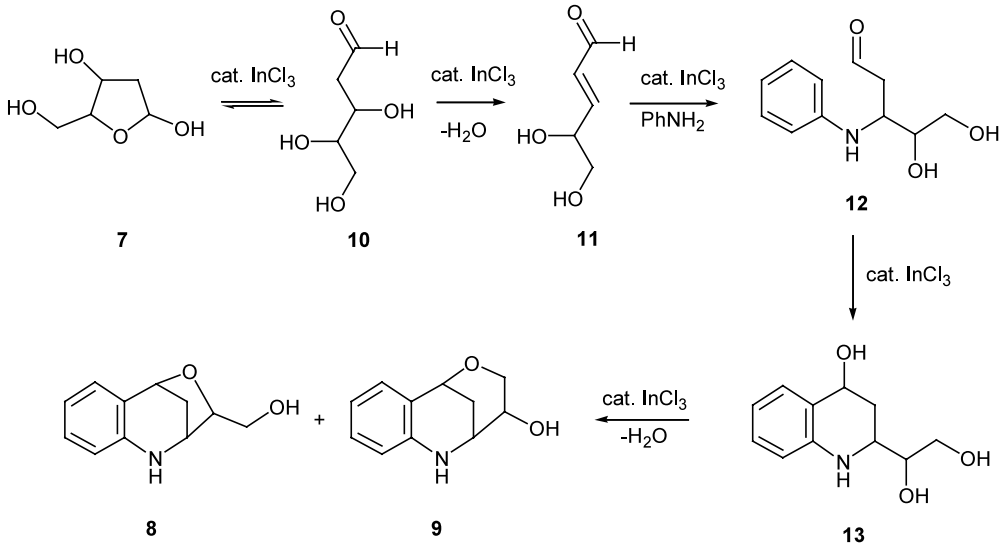
[a] All reactions were carried out at 0.5 mmol scale, with aniline/hemiacetal (1:2.5), and 8–12 mol% of $InCl_3$.
[b] Isolated yields were referred to. *syn*/*anti* Ratios were determined by ^1H NMR measurement of the crude product.



Scheme 2.



Scheme 3.



Scheme 4.

Diels–Alder reaction gave the tetrahydroquinoline intermediate **13**. Finally, intramolecular condensation of **13** by losing water afforded two tricyclic tetrahydroquinoline derivatives **8** and **9**. The structure of **9** was confirmed by X-ray crystallography.

In summary, we have demonstrated an efficient and simple one-pot method to form tetrahydroquinoline derivatives that have various pharmaceutical applications. The air and water stability of the reaction system and its environmentally benign feature are the advantages of present synthetic method. The application of the method in natural product synthesis is currently under investigation.

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