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InCl$_3$-Catalyzed Domino Reaction of Aromatic Amines with Cyclic Enol Ethers in Water: A Highly Efficient Synthesis of New 1,2,3,4-Tetrahydroquinoline Derivatives

Jianheng Zhang and Chao-Jun Li*

Department of Chemistry, Tulane University, New Orleans, Louisiana 70118

cjli@tulane.edu

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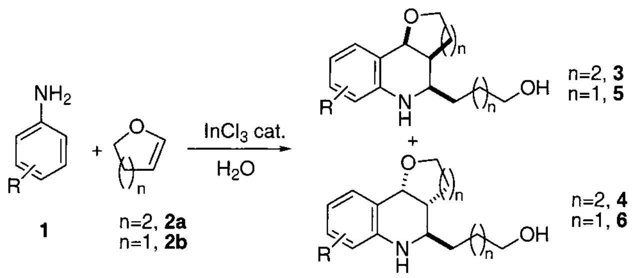
Abstract: The tetrahydroquinoline moiety is a structural feature of many natural products. By using a domino reaction of aromatic amines and cyclic enol ethers or 2-hydroxy cyclic ether catalyzed by indium chloride in water, various tetrahydroquinoline derivatives were synthesized efficiently. Most cyclization products showed cis selectivity. The use of 2,3-dihydrofuran as the cyclic enol ether provided both higher reactivity and cis selectivity than the use of 3,4-dihydro-2*H*-pyran. The cis selectivity was tentatively rationalized due to chelation control in water.

The tetrahydroquinoline moiety is present in various natural products, and many tetrahydroquinoline derivatives exhibit a broad range of biological activities.[1] Therefore, it has attracted continuous interest to develop methods for the synthesis of tetrahydroquinoline derivatives.[2] Among the various methods, Lewis acid catalyzed aza-Diels−Alder reaction of *N*-arylimines with various dienophiles is one of the most powerful tools for constructing 2,3,4-trisubstituted tetrahydroquinoline derivatives.[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 pyranoquinoline derivatives) are obtained.[4] A one-pot procedure for synthesizing such compounds, based on the three-component reaction of a substituted aniline, an aryl aldehyde, and an electon-rich olefin in the presence of Lewis acid catalysts, was reported recently.[5] Since the work of Loh,[6] indium halide has been shown to be an effective Lewis acid for various reactions in aqueous medium.[7] Herein, we wish to report an efficient synthesis of tetrahydroquinoline derivatives via a novel domino coupling of aniline derivatives and cyclic enol ethers catalyzed by indium(III) chloride in water (Scheme 1).

Scheme 1



To begin our study, aniline **1a** (2 mmol) was reacted with 3,4-dihydro-2*H*-pyran **2a** (6 mmol) at room temperature in water, and no reaction was observed for 3 days. On the other hand, when the reaction mixture was stirred in water at room temperature (for 3 days) in the presence of indium(III) chloride (10 mol %), a smooth reaction occurred to generate the corresponding tetrahydroquinoline derivatives **3** and **4** (as a 68:32 mixture of isomers) in 90% yields.[8] The reaction time can be shortened by increasing the reaction temperature to 50−60 °C. Under the same reaction conditions, InBr$_3$, In(OTf)$_3$, Sc(OTf)$_3$, and protonic acids, such as hydrochloride acid and trifluoroacetic acid, were also effective but provided the desired product in lower yields. Subsequently, a series of substituted anilines were reacted with 3,4-dihydro-2*H*-pyran **2a** to give novel 2-(hydroxyalkyl)tetrahydroquinoline derivatives (Table 1). The substituent on anilines has a marked effect on the reactions. Anilines bearing electron-donating groups were found to be more reactive than the ones bearing electron-withdrawing groups. No

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* To whom correspondence should be addressed. Fax: 504-8655596.

(1) (a) Ramesh, M.; Moham, P. S.; Shanmugam, P. *Tetrahedron* **1984**, *40*, 4041. (b) Witherup, K. M.; Ransom, R. W.; Varga, S. L.; Pitzenberger, S. M.; Lotti, V. J.; Lumma, W. J. U.S. Pat. US 5288725, 1994. (c) Perry, N. B.; Blunt, J. W.; McCombs, J. D.; Munro, M. H. G. *J. Org. Chem.* **1986**, *51*, 5476. (d) Williamson, N. M.; March, P. R.; Ward, A. D. *Tetrahedron Lett.* **1995**, *36*, 7721. (e) Johnson, J. V.; Rauckman, S.; Baccanari, P. D.; Roth, B. *J. Med. Chem.* **1989**, *32*, 1942. (f) Biller, S. A.; Misra, R. N. U.S. Pat. US 4843082, 1989. (g) Mohamed, E. A. *Chem. Pap.* **1994**, *48*, 261; *Chem. Abstr.* **1995**, *123*, 9315. (h) Caling, R. W.; Leeson, P. D.; Moseley, A. M.; Baker, R.; Foster, A. C.; Grimwood, S.; Kemp, J. A.; Marshall, G. R. *J. Med. Chem.* **1992**, *35*, 1942. (i) Carling, R. W.; Leeson, P. D.; Moseley, A. M.; Smith, J. D.; Saywell, K.; Trickelbank, M. D.; Kemp, J. A.; Marshall, G. R.; Foster, A. C.; Grimwood, S. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 65. (j) Cuny, G. D.; Hauske, J. D.; Hoemann, M. Z.; Rossi, R. F.; Xie, R. L. *PCT Int. Appl.* **1999**, WO 9967238; *Chem. Abstr.* **1999**, *132*, 64182. (k) Hanada, K.; Furuya, K.; Inoguchi, K.; Miyakawa, M.; Nagata, N. *PCT Int. Appl.* **2001**, WO 0127086; *Chem. Abstr.* **2001**, *134*, 295752.

(2) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031.

(3) (a) Povarov, L. S. *Russ. Chem. Rev., Engl. Transl.* **1967**, *36*, 656. (b) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic: San Diego, 1987; Chapters 2 and 9.

(4) (a) Crousse, B.; Begue, J.; Bonnet-Delpon, D. *J. Org. Chem.* **2000**, *65*, 5009. (b) Mendoza, J. S. *PCT Int. Appl.* **1998**, WO 9827093; *Chem. Abstr.* **1998**, *129*, 95393. (c) Makioka, Y.; Shindo, T.; Taniguchi, Y.; Takaki, K.; Fujiwara, Y. *Synthesis* **1995**, 801. (d) Lucchini, V.; Prato, M.; Scorrano, G.; Stivanello, M.; Valle, G. *J. Chem. Soc., Perkin Trans. 2* **1992**, 259. (e) Kametani, T.; Furuyama, H.; Fukuoka, Y.; Takeda, H.; Suzuki, Y.; Honda, T. *J. Heterocycl. Chem.* **1986**, *23*, 185. (f) Babu, G.; Perumal, P. T. *Tetrahedron Lett.* **1998**, *39*, 3225. (g) Sundararajan, G.; Prabagaran, N.; Varghese, B. *Org. Lett.* **2001**, *3*, 1973.

(5) (a) Ma, Y.; Qian, C.; Xie, M.; Sun, J. *J. Org. Chem.* **1999**, *64*, 6462. (b) Kobayashi, S.; Komiyama, S.; Ishitani, H. *Biotechnol. Bioeng.* **1998**, *61*, 23. (c) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1996**, *118*, 8977.

(6) Loh, T. P.; Pei, J.; Lin, M. *Chem. Commun.* **1996**, 2315.

(7) For reviews on synthetic applications of indium and indium reagents, see: (a) Chan, T. H. *Pure Appl. Chem.* **1996**, *68*, 919. (b) Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149. (c) Cintas, P. *Synlett* **1995**, 1087. (d) Hashmi, A. S. K. *J. Prakt. Chem., Chem. Zeit.* **1998**, *340*, 84. (e) Paquette, L. A. In *Green Chemistry: Frontiers in Benign Chemical Syntheses and Processes*; Anastas, P. A., Williamson, T. C., Eds.; Oxford University Press: New York, 1998. (f) Ranu, B. C. *Eur. J. Org. Chem.* **2000**, 2347. (g) Chauhan, K. K.; Frost, C. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3015.

(8) The structures of two isomers were established on the basis of spectroscopic evidence and characterization data. From the ^{1}H NMR spectra, the signal of proton 10b was observed in lower field and differed from those of other protons. In addition, the coupling constant *J* (10b, 4b) in the cis isomer (**3a**, J = 5.6 Hz) is larger than that in trans isomer (**4a**, J = 3.2 Hz). Therefore, the ratio of two isomers was determined conveniently by comparing the integrations of proton 10b of the two isomers. It was found that the cis isomer is the slightly more favored product in most cases of the reactions of substituted anilines with 3,4-dihydro-2*H*-pyran.

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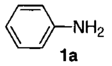
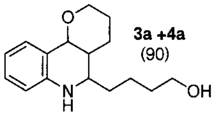
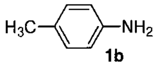
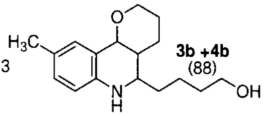
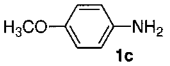
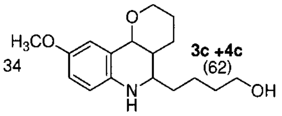
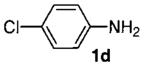
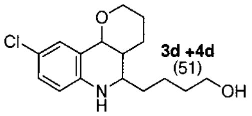
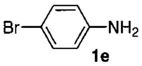
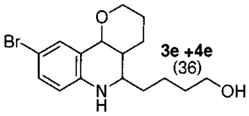
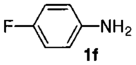
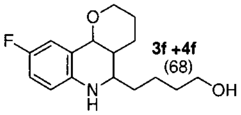
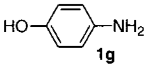
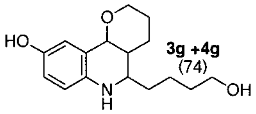
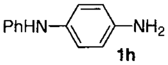
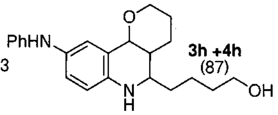
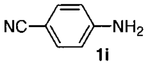
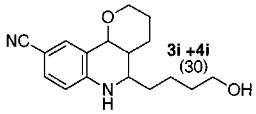
Table 1. Reaction of Anilines with 3,4-Dihydro-2*H*-pyran (2a) in Water

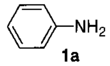
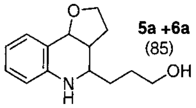
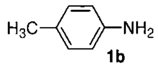
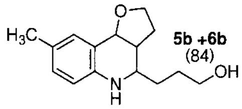
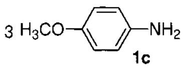
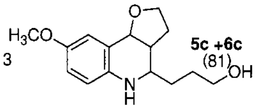
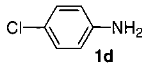
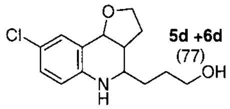
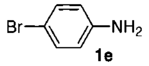
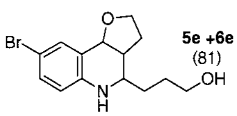
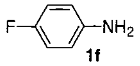
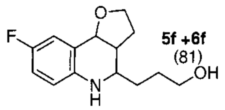
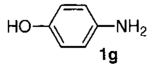
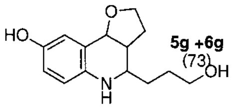
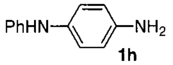
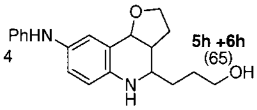
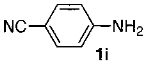
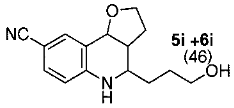
entry	aniline (**1**)	conditions	cis/trans	product (%)
1	 **1a**	r.t./3day	68 : 32	 **3a** +**4a** (90)
2		50°C/10h	62 : 38	(85)
3	 **1b**	50°C/10h	57 : 43	 **3b** +**4b** (88)
4	 **1c**	50°C/10h	66 : 34	 **3c** +**4c** (62)
5	 **1d**	50°C/48h	57:43	 **3d** +**4d** (51)
6	 **1e**	50°C/48h	49:51	 **3e** +**4e** (36)
7	 **1f**	50°C/4h	68 : 32	 **3f** +**4f** (68)
8	 **1g**	50°C/10h	74:26	 **3g** +**4g** (74)
9	 **1h**	r.t./10h	47:53	 **3h** +**4h** (87)
10	 **1i**	50°C/48h	34:66	 **3i** +**4i** (30)

[a] Isolated yields were reported.

reactions occurred between 4-nitroaniline and **2a**. Aniline bearing a hydroxyl group reacted as expected without the need of protection (Table 1, entry 8). When 2,3-dihydrofuran **2b** was employed as the cyclic enol ether to react with anilines, a faster reaction rate and an enhanced cis selectivity (to form **5** and **6**) were observed in each case (Table 2).

The diastereoselectivity of the cyclization can be rationalized by a balance of steric effect (A) and chelation effect (B). Whereas a steric effect favors the trans diastereomer, the chelation of indium(III) ion with the imine and the enol ether favors the cis isomer (Figure 1). This hypothesis is consistent with the observed switch of selectivity for entries 6 and 10 (Table 1). The presence of Br^- and CN^- reduce the electron density of aniline (more effectively than the other substituents), which decreases the chelation ability of the corresponding imines. As the *p*-phenylamino group is mostly likely also coordinated with indium(III) (and thus became an electron-withdrawing group), the observed trans selectivity with entry 9 (Table 1) can be explained similarly. The use of five-membered cyclic enol ethers decreased the steric effect and thus increased the cis selectivity (Table 2).

Table 2. Reaction of Anilines with 2,3-Dihydrofuran (2b) in Water

entry	aniline (**1**)	conditions	cis/trans	product (%)
1	 **1a**	r.t./48h	78:22	 **5a** +**6a** (85)
2	 **1b**	r.t./4h	81:19	 **5b** +**6b** (84)
3	 **1c**	r.t./4h	87:13	 **5c** +**6c** (81)
4	 **1d**	45°C/10h	74:26	 **5d** +**6d** (77)
5	 **1e**	45°C/10h	87:13	 **5e** +**6e** (81)
6	 **1f**	r.t./10h	86:14	 **5f** +**6f** (81)
7	 **1g**	r.t./2h	96:4	 **5g** +**6g** (73)
8	 **1h**	r.t./10h	86:14	 **5h** +**6h** (65)
9	 **1i**	r.t./24h	69:31	 **5i** +**6i** (46)

[a] Isolated yields were reported.

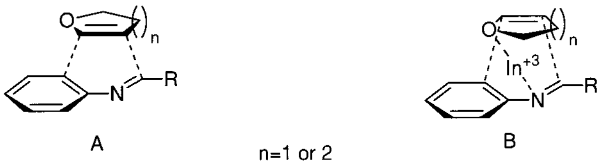


Figure 1.

A tentative mechanism to rationalize the product formation is shown in Scheme 2. The cyclic enol ethers **2** can be hydrated easily in the presence of protonic or Lewis acid in water to give **7a** or **7b**.[9] In contrast, **7a** and **7b** can lose water to give **2a** and **2b**. Substrates **7a** and **7b** then undergoes facile ring opening in the presence of the indium(III) ion to give **8a** and **8b** in water. The condensation reaction between aniline and **8** will gener-

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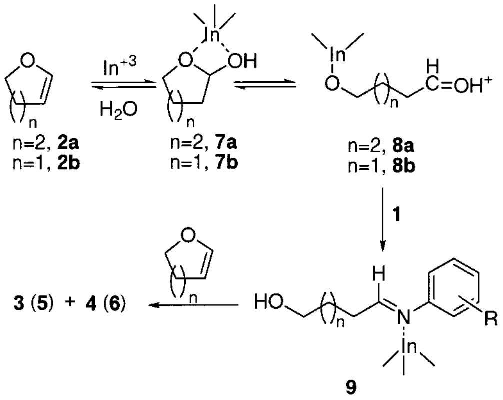
[9] (a) Woods, G. F. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 470. (b) Schniepp, L. E; Geller, H. H. *J. Am. Chem. Soc.* **1946**, *68*, 1646.

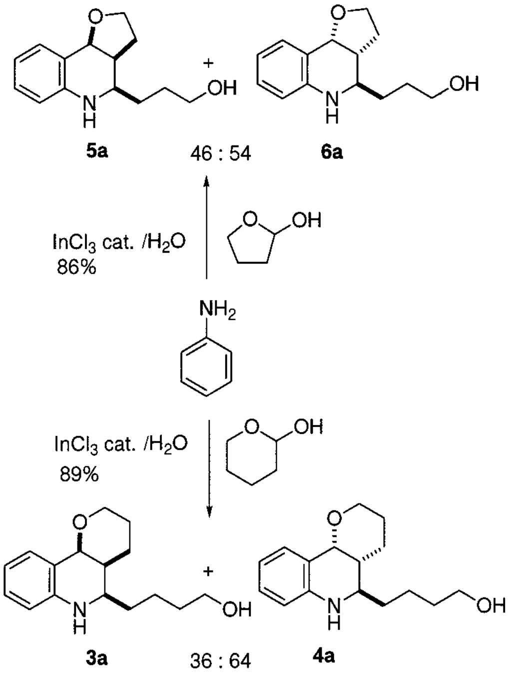
Scheme 2. Proposed Mechanism for the $InCl_3$-Catalyzed Tetrahydroquinoline Synthesis in Water



ate imine **9**, which is coordinated with indium ion. Finally, an aza-Diels–Alder reaction of the imine **9** with **2** will generate the tetrahydroquinoline derivatives **3**, **4**, **5**, and **6**. In this domino reaction, the cyclic enol ether is not only the dienophile but also the precursor of aldehyde. As evidence to the proposed mechanism, when 2-hydroxytetrahrdopyran (**7a**) or 2-hydroxytetrahydrofuran (**7b**), instead of 3,4-dihydro-2*H*-pyran (**2a**) or 2,3-dihydrofuran (**2b**), were reacted with aniline in water in the presence of the indium(III) chloride catalyst, the tetrahydroquinoline derivatives (**3a**, **4a**, **5a**, and **6a**) were also obtained efficiently (Scheme 3).

In conclusion, a highly efficient domino reaction of aromatic amines with cyclic enol ether or 2-hydroxy cyclic ether was developed in water catalyzed by indium(III) chloride to provide new 1,2,3,4-tetrahydroquinoline derivatives. The scope (such as asymmetric synthesis), mechanism, and synthetic applications of this reaction are currently under investigation.

Scheme 3



Experimental Section

Commercially available chemicals were used directly as received. Flash chromatography employed E. Merck silica gel (Kiesegel 60, 230–400 mesh) purchased from Scientific Adsorbents. Elemental analyses were carried out at the Center of Instrumental Facility of Tulane University. High-resolution mass spectrometry was performed at the Chemistry Institute of the Chinese Academy of Science.

General Procedure for $InCl_3$-Catalyzed Domino Tetrahydroquinoline Synthesis in Water. A mixture of aromatic amine (2 mmol), cyclic enol ether or 2-hydroxycyclic ether (4–6 mmol), and indium trichloride (0.2–0.4 mmol) in 10 mL of water was stirred at room temperature or at 50–60 °C, and the reaction progress was monitored by TLC. When the reaction was completed, the reaction mixture was extracted with ethyl ether or methylene chloride. The combined organic phases were dried and concentrated. The crude materials were separated by column chromatography to give tetrahydroquinoline derivatives.

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Supporting Information Available: Full characterization of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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