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Indium trichloride catalyzed one-pot synthesis of indolo[2,1-*a*]pyrrolo[4′,3′:2,3]-7a,8,13,13b-tetrahydroquinolines through intramolecular imino Diels–Alder reactions

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Abstract—An efficient synthesis of tetrahydroquinolines has been achieved by the reaction of aldimines derived from various substituted aromatic amines and indole-2-carbaldehyde containing an internal dienophile using 20 mol % $InCl_3$ in acetonitrile at room temperature. The reactions are very fast and the products are isolated in good yields and in pure form.

1. Introduction

The Diels–Alder reaction of 2-azadienes is a valuable methodology for synthesis of nitrogen heterocycles[1] bearing endocyclic enamine moieties that are key intermediates in the preparation of complicated heterocycles and natural products.[2] The 4π activity of simple 2-azadienes is rarely observed in normal [4+2] cycloaddition reactions; however, this problem can be circumvented by introducing either electron-withdrawing[1,3] or electron-donating[4] substituents onto the nitrogen. Fowler[2] and Boger[5] have shown that substitution of the azadiene nitrogen by a strongly electron-withdrawing *N*-acyl or *N*-sulfonyl group favors considerably the inverse electron demand Diels–Alder reactivity of the azadienes. Nevertheless, significant efforts have been made toward production of electron-deficient 2-aza-1,3-butadienes which enable 4π participation of α,β-unsaturated imines in [4+2] cycloaddition reactions.[6]

The tetrahydroquinoline unit is a feature of many alkaloids and derivatives thereof are found to exhibit a wide range of biological activities.[7] Examples such as flindersine, oricine, and veprisine and their derivatives exhibit biological activities such as psychotropic, anti-allergic, anti-inflammatory, and estrogenic. In addition, the indole nucleus annealated to carbocyclic or heterocyclic ring(s) is present in an astonishing variety of natural products with potent and varied biological activity.[8] Hence, new and efficient syntheses of such compounds is still important.

Indium trichloride ($InCl_3$) has emerged as a mild and water-tolerant Lewis acid imparting high regio and chemoselectivity in various organic transformations.[9] It can be conveniently used in both aqueous and non-aqueous medium and, in addition, it can be recovered from the aqueous layer on work-up and recycled for use in subsequent reactions. Furthermore, $InCl_3$ is highly efficient in activating nitrogen-containing compounds such as imines and hydrazones[10] (Scheme 1).

With this in mind, we herein report a facile Lewis acid catalyzed imino Diels–Alder reaction for the synthesis of novel tetrahydroquinolines from N-alkylated indole-2-carbaldehydes containing substituted terminal alkenes and various *p*-substituted anilines.

The precursors for the imino Diels–Alder reaction were readily obtained by the treatment of ethyl-1*H*-indole-2-carboxylate and 1-bromo-3-methylbut-2-ene/cinnamyl bromide in benzene with 50% aqueous sodium

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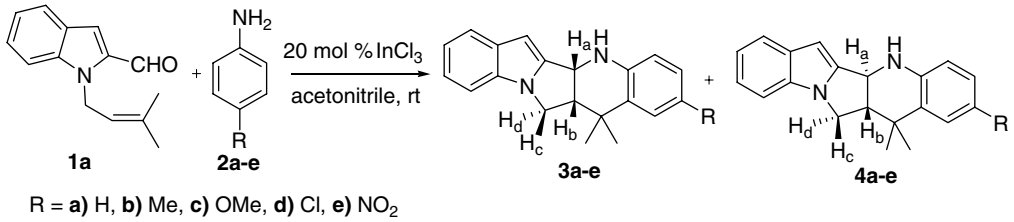


Scheme 1.

hydroxide in the presence of a catalytic amount of TEBA at room temperature for 1–2 h to furnish the ethyl-1-*N*-alkenyl-1*H*-indole-2-carboxylate in moderate yield, which was then reduced to the corresponding alcohol by $LiAlH_4$ in dry THF at 0 °C. The alcohol was then subjected to Swern oxidation to yield **1a** in 85% and **1b** in 83% yield.[11]

Reaction of **1a** with **2a**–**e** in the presence of $MgSO_4$ in acetonitrile afforded the corresponding imine, which was characterized by spectroscopic analysis. The imine (without further purification) underwent [4+2] cycloaddition in the presence of a Lewis acid catalyst to yield *cis*-tetrahydroquinolines **3a**–**e** and *trans*-tetrahydroquinolines **4a**–**e**.[12–15]

In order to study the scope and limitations of the cycloaddition reaction, various Lewis acid catalysts, namely, $AlCl_3$, $BF_3{\cdot}OEt_2$, $ZnCl_2$ and $InCl_3$ were investigated. The *cis*-tetrahydroquinoline derivative was the major product when **1a** and **2c** were reacted in the presence of a Lewis acid. The best overall yield of **3c** and **4c** (84%) was obtained when $InCl_3$ was used as the catalyst (Table 1).

Similarly, the mole ratio of $InCl_3$ was studied and the results are listed in Table 2. It was found that the amount of $InCl_3$ affects the yield of the product, with 20 mol % of $InCl_3$ being optimum.

Next, we examined the effect of solvent on the cycloaddition reaction. Reaction of **1a** and **2c** in acetonitrile gave **3c** and **4c** in 84% yield, while other solvents furnished compounds **3c** and **4c** in 65–72% yields as summarized in Table 3. This outcome probably results from the high polarity of the solvent and miscibility with water during imine formation. The structures assigned to cycloadducts **3c** and **4c** were confirmed by examination of their respective ^1H NMR spectra.

Table 1. Influence of Lewis acid on the reaction of **1a** with **2c**

Entry	Lewis acid	Reaction time	Overall yield (%)
1	$AlCl_3$	24 h	20
2	$BF_3{\cdot}OEt_2$	16 h	18
3	$ZnCl_2$	18 h	40
4	$InCl_3$	30 min	84

Table 2. Study of the mole ratio of $InCl_3$ on the reaction of **1a** with **2c**

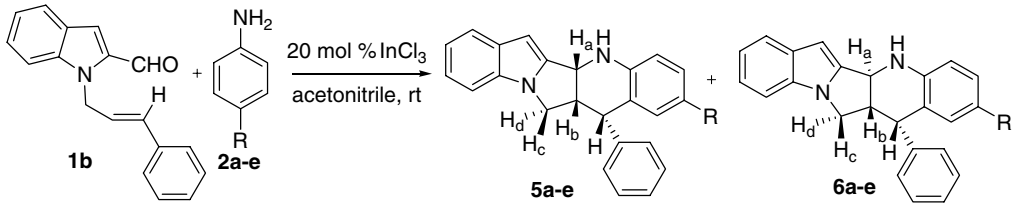
Entry	$InCl_3$ (mol %)	Yield (%)
1	5	20
2	10	53
3	15	65
4	20	84

Table 3. Effect of solvent on the yield of the reaction of **1a** and **2c** with 20 mol % of $InCl_3$

Entry	Solvent	Time (min)	Yield (%)
1	Toluene	70	65
2	CH_2Cl_2	55	72
3	$CHCl_3$	48	70
4	CH_3CN	30	84

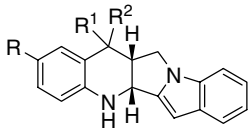
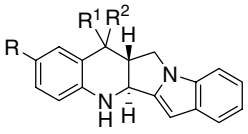
The H_a proton of **3c** appears as a doublet at δ 4.99 ($J = 6.3$ Hz), which is coupled to the H_b proton. This small coupling constant is consistent with a cis-diaxial relationship for these two protons. Furthermore, the stereochemistry of H_a was confirmed by the observation of a strong (8.1%) NOE enhancement of H_a upon the irradiation of H_b. In a similar fashion, the H_a proton of **4c** exhibited a doublet at δ 5.08 ($J = 10.6$ Hz) indicating the trans stereochemistry of H_a with respect to H_b (Scheme 2).

The preparation of tetrahydroquinolines with other *p*-substituted aromatic anilines **2a**,**b** and **2d**,**e** under the



Scheme 2.

Table 4. The reaction of **1a/1b** and **2a–e** in the presence of 20 mol % indium trichloride in acetonitrile

Entry	R	R^1	R^2	Products		Time (min)	Ratio of products cis:trans	Yield (%)
								
1	H	CH_3	CH_3	**3a**	**4a**	45	84:16	78
2	CH_3	CH_3	CH_3	**3b**	**4b**	30	80:20	84
3	OCH_3	CH_3	CH_3	**3c**	**4c**	35	88:12	80
4	Cl	CH_3	CH_3	**3d**	**4d**	30	92:8	76
5	NO_2	CH_3	CH_3	**3e**	**4e**	42	95:5	81
6	H	Ph	H	**5a**	**6a**	35	87:13	86
7	CH_3	Ph	H	**5b**	**6b**	25	82:18	90
8	OCH_3	Ph	H	**5c**	**6c**	30	90:10	92
9	Cl	Ph	H	**5d**	**6d**	40	95:5	90
10	NO_2	Ph	H	**5e**	**6e**	35	96:4	87

optimized conditions was carried out and the results are shown in Table 4.

Further, to examine the effect of introducing substitution at the terminus of the dienophile on the cycloaddition process, we prepared 1-cinnamyl-1*H*-indole-2-carbaldehyde **1b** as previously described. Thus, **1b** and **2d** underwent [4+2] cycloaddition to afford the corresponding cis-and trans-cycloadducts **5d** and **6d** in 90% overall yield.[16,17]

The structures of cycloadducts **5d** and **6d** were established by examination of their ^1H NMR spectra and NOE experiments. The enhanced yields and short reaction time for the formation of products **5d** and **6d** relative to the cycloaddition of **1a** with **2c** in acetonitrile is clearly a testament to the greater reactivity of the phenyl-substituted dienophile in **1b**.

Likewise, other *p*-substituted aromatic anilines **2a–c**,**e** reacted smoothly with **1b** at room temperature in the presence of 20 mol % of $InCl_3$ to give the corresponding *cis*- and *trans*-tetrahydroquinoline derivatives in fairly good yields. The yields and ratios of the isomers are presented in Table 4.

In summary, the work represents our first attempt to use **1a** and **1b** as useful precursors in the synthesis of tetrahydroquinolines.

From our study it is evident that $InCl_3$ catalyzes the intramolecular Diels–Alder reactions of **1** and **2** efficiently, also the phenyl substituent at the terminal of dienophile proves to be reactive.

2. Experimental

General procedure for the synthesis of tetrahydroquinoline derivatives:

$InCl_3$ (20 mol %) was added to a mixture of aniline **2a–e** (1 mmol) and 1-(3-methylbut-2-enyl)-indole-2-carbaldehyde or 1-cinnamyl-indole-2-carbaldehyde (1 mmol) in acetonitrile (5 mL). The reaction mixture was stirred at room temperature until completion of the reaction as indicated by TLC. The mixture was then quenched with water and extracted with ethyl acetate. The organic layer was washed with water and dried over $MgSO_4$. The solvent was evaporated in vacuo and the crude product was purified by chromatography on silica gel (ethyl acetate–hexane) to afford cis- and trans-isomers in good yields.

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References and notes

1. (a) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869; (b) Weinreb, S. M.; Scola, P. M. *Chem. Rev.* **1989**, *89*, 1525.
2. (a) Hwang, Y. O.; Fowler, F. W. *J. Org. Chem.* **1985**, *50*, 2719; (b) Cheng, Y. S.; Lupo, A. T., Jr.; Fowler, F. W. *J. Am. Chem. Soc.* **1983**, *105*, 7696.
3. (a) Boger, D. L.; Weinreb, S. M. In *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987; p 239; (b) Uyehara, T.; Suzuki, I.; Yamamoto, Y. *Tetrahedron Lett.* **1990**, *31*, 3753; (c) Uyehara, T.; Chiba, W.; Suzuki, I.; Yamamoto, Y. *Tetrahedron Lett.* **1991**, *32*, 4371.
4. (a) Serckx-Poncin, B.; Hesbain-Frisque, A.-M.; Ghosez, L. *Tetrahedron Lett.* **1982**, *23*, 3261; (b) Ghosez, L.; Serckx-Poncin, B.; Rivera, M.; Bayard, P.; Sainte, F.; Demoulin, A.; Hesbain-Frisque, A.-M.; Mokel, A.; Munoz, L.; Bernard-Henriat, C. *J. Heterocycl. Chem.* **1985**, 22.
5. (a) Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 1713; (b) Boger, D. L.; Kasper, A. M. *J. Am. Chem. Soc.* **1989**, *111*, 1517; (c) Boger, D. L.; Corbett, W. L.; Wiggins, J. M. *J. Org. Chem.* **1990**, *55*, 2999.
6. (a) Yadav, J. S.; Reddy, B. V. S.; Sadasiv, K.; Reddy, P. S. R. *Tetrahedron Lett.* **2002**, *43*, 3853–3856; (b) Yadav, J. S.; Subba Reddy, B. V.; Sunitha, V.; Srinivasa Reddy, K.; Ramakrishna, K. V. S. *Tetrahedron Lett.* **2004**, *45*,

7947–7950; (c) Buonora, P.; Olsen, J. C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099–6138.
7. (a) Katritzky, A. R.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031–15070, and references cited therein; (b) Yamada, N.; Kadowaki, S.; Takahashi, K.; Umezu, K. *Biochem. Pharmacol.* **1992**, *44*, 1211; (c) Faber, K.; Stueckler, H.; Kappe, T. *J. Heterocycl. Chem.* **1984**, *21*, 1177; (d) Johnson, J. V.; Rauckman, B. S.; Baccanari, D. P.; Roth, B. *J. Med. Chem.* **1989**, *32*, 1942.
8. (a) Szantay, C. In *The Alkaloids*; Cordell, G. A., Ed.; Academic: London, 1998; Vol. 50, (b) Lounasmaa, M.; Hankinen, P.; Westersund, M. In *The Alkaloids*; Cordell, G. A., Ed.; Academic: London, 1999; Vol. 52, Chapter 2.
9. (a) Mukaiyama, T.; Ohno, T.; Han, J. S.; Kobayashi, S. *Chem. Lett.* **1991**, 949; (b) Mukaiyama, T. *Org. React.* **1982**, *28*, 203; (c) Loh, T. P.; Pei, J.; Lin, M. *Chem. Commun.* **1996**, 2315; (d) Kobayashi, S.; Busujima, T.; Nagayama, S. *Tetrahedron Lett.* **1998**, *39*, 1579; (e) Babu, G.; Nagarajan, R.; Perumal, P. T. *Synthesis* **2000**, 661; (f) Babu, G.; Perumal, P. T. *Aldrichim. Acta* **2000**, *33*, 16.
10. (a) Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149; (b) Ghosh, R. *Ind. J. Chem.* **2001**, *40B*, 550.
11. Rathna Durga, R. S. M.; Jayashankaran, J.; Raghunathan, R. *Tetrahedron Lett.* **2007**, *48*, 1385.
12. *7a,13b-cis-8,8-Dimethyl-10-methylindolo[2,1-a]pyrrolo[4′,3′:2,3]-7a,8,13,13b-tetrahydroquinoline* **3b**: Yellow solid; mp 180–181 °C; IR (KBr): 3387 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.65 (s, 3H), 2.01 (s, 3H), 2.22 (s, 3H), 5.01 (d, $J = 5.7$ Hz, $1H_a$), 5.09 (dd, $J = 14.5$, 7.8 Hz, $1H_c$), 5.21 (t, $J = 6.6$ Hz, $1H_d$), 5.36 (dt, $J = 14.5$, 6.6 Hz, $1H_b$), 6.55–8.19 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.25, 18.44, 20.43, 25.47, 25.57, 41.38, 42.88, 97.07, 108.05, 108.92, 113.81, 118.36, 119.95, 120.27, 122.61, 123.01, 125.29, 125.87, 130.04; MS: $m/z = 302$ (M^+). Anal. Calcd for $C_{21}H_{22}N_2$: C, 83.44; H, 7.28; N, 9.27. Found: C, 83.61; H, 7.14; N, 9.40.
13. *7a,13b-trans-8,8-Dimethyl-10-methylindolo[2,1-a]pyrrolo[4′,3′:2,3]-7a,8,13,13b-tetrahydroquinoline* **4b**: Red liquid; IR (KBr): 3394 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.70 (s, 3H), 1.85 (s, 3H), 2.17 (s, 3H), 4.97 (d, $J = 10.5$ Hz, $1H_a$), 5.12 (dd, $J = 14.6$, 7.8 Hz, $1H_c$), 5.19 (t, $J = 6.8$ Hz, $1H_d$), 5.25 (td, $J = 14.6$, 6.8 Hz, $1H_b$), 6.32–7.84 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.81, 18.13, 18.57, 24.52, 25.32, 39.55, 43.71, 100.85, 110.25, 115.52, 115.91, 120.33, 122.73, 124.08, 126.10, 126.38, 128.26, 130.37, 137.34, 138.05; MS: $m/z = 302$ (M^+). Anal. Calcd for $C_{21}H_{22}N_2$: C, 83.44; H, 7.28; N, 9.27. Found: C, 83.58; H, 7.38; N, 9.10.
14. *7a,13b-cis-8,8-Dimethyl-10-methoxyindolo[2,1-a]pyrrolo[4′,3′:2,3]-7a,8,13,13b-tetrahydroquinoline* **3c**: Pale yellow solid; mp 176–178 °C; IR (KBr): 3398 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.66 (s, 3H), 2.01 (s, 3H), 3.71 (s, 3H), 4.99 (d, $J = 6.3$ Hz, $1H_a$), 5.08 (dd, $J = 15.0$, 8.0 Hz, $1H_c$), 5.23 (dt, $J = 15.0$, 6.8 Hz, $1H_b$), 5.36 (t, $J = 6.8$ Hz, $1H_d$), 6.59–7.47 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.42, 18.62, 25.67, 25.75, 41.43, 42.96, 55.75, 97.00, 108.15, 108.97, 114.89, 115.15, 118.41, 118.50, 120.07, 120.27, 122.69, 123.04, 125.38, 125.99, 152.76; MS: $m/z = 318$ (M^+). Anal. Calcd for $C_{21}H_{22}N_2O$: C, 79.24; H, 6.92; N, 8.80. Found: C, 79.40; H, 6.77; N, 8.92.
15. *7a,13b-trans-8,8-Dimethyl-10-methoxyindolo[2,1-a]pyrrolo-[4′,3′:2,3]-7a,8,13,13b-tetrahydroquinoline* **4c**: Red liquid; IR (KBr): 3397 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.75 (s, 3H), 1.93 (s, 3H), 3.52 (s, 3H), 5.08 (d, $J = 10.6$ Hz, $1H_a$), 5.17 (dd, $J = 14.6$, 7.8 Hz, $1H_c$), 5.30 (t, $J = 7.0$ Hz, $1H_d$), 5.35 (td, $J = 14.6$, 7.0 Hz, 1H), 6.54–7.51 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.49, 20.07, 27.81, 29.44, 44.65, 47.84, 50.51, 107.14, 112.48, 117.84, 121.14, 121.36, 123.26, 125.89, 126.72, 127.61, 129.54, 131.33, 133.28, 138.11, 140.49; MS: $m/z = 318$ (M^+). Anal. Calcd for $C_{21}H_{22}N_2O$: C, 79.24; H, 6.92; N, 8.80. Found: C, 79.45; H, 7.10; N, 8.72.
16. *7a,13b-cis-8-Phenyl-10-chloroindolo[2,1-a]pyrrolo[4′,3′:2,3]-7a,8,13,13b-tetrahydroquinoline* **5d**: Yellow solid; mp 168–170 °C; IR (KBr): 3396 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.85 (d, $J = 5.8$ Hz, $1H_a$), 5.10 (dd, $J = 15.0$, 7.8 Hz, $1H_c$), 5.16 (d, $J = 9.2$ Hz, 1H), 5.22 (t, $J = 6.5$ Hz, $1H_d$), 5.27–5.29 (m, $1H_b$), 6.48–7.52 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.32, 25.64, 46.23, 48.19, 110.76, 114.95, 119.12, 120.33, 122.36, 123.00, 123.86, 125.51, 125.80, 126.13, 128.42, 130.30, 130.67, 133.11, 135.04, 137.24, 139.34, 142.39, 143.16; MS: $m/z = 370.8$ (M^+). Anal. Calcd for $C_{24}H_{19}N_2Cl$: C, 77.74; H, 5.13; N, 7.56. Found: C, 77.91; H, 4.99; N, 7.40.
17. *7a,13b-trans-8-Phenyl-10-chloroindolo[2,1-a]pyrrolo[3′,4′:2,3]-7a,8,13,13b-tetrahydroquinoline* **6d**: Red liquid; IR (KBr): 3398 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.03 (d, $J = 11.0$ Hz, $1H_a$), 5.15 (dd, $J = 14.8$, 8.0 Hz, $1H_c$), 5.23 (d, $J = 9.0$ Hz, 1H), 5.27 (t, $J = 7.0$ Hz, $1H_d$), 5.33–5.36 (m, $1H_b$), 6.38-7.44 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.72, 25.52, 40.85, 46.72, 113.29, 115.76, 120.16, 122.37, 123.53, 124.03, 126.37, 127.11, 127.94, 128.42, 130.25, 131.88, 133.36, 133.53, 136.66, 139.30, 140.21, 143.81, 146.24; MS: $m/z = 370.8$ (M^+). Anal. Calcd for $C_{24}H_{19}N_2Cl$: C, 77.74; H, 5.13; N, 7.56. Found: C, 77.56; H, 5.01; N, 7.66.