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A highly efficient synthesis of 1,2,3,4-tetrahydroquinolines by molecular iodine-catalyzed domino reaction of anilines with cyclic enol ethers

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Abstract—A highly efficient method for the synthesis of 1,2,3,4-tetrahydroquinoline derivatives via a molecular iodine catalyzed domino reaction of anilines with cyclic enol ethers, such as 2,3-dihydrofuran and 3,4-dihydro-2*H*-pyran, is described. The reaction may proceed through an aza-Diels–Alder process between an in situ generated 2-azadiene and another equivalent of cyclic enol.

Substituted tetrahydroquinolines offer a high degree of structure diversity and have proven to be very important in medicinal chemistry. Thus, a variety of approaches have been developed for the synthesis of tetrahydroquinoline skeleton.[1] The aza-Diels–Alder reaction of electron-rich dienophiles with *N*-aryl aldimines has provided a convenient protocol for the synthesis of tetrahydroquinolines.[2] Recently, polycyclic pyrano- and furano[3,2-*c*]quinoline derivatives have been synthesized via a domino coupling of anilines with cyclic enol ethers or cyclic hemiacetals.[3] Various Lewis acids such as $InCl_3$,[3a,b] $FeCl_3$–NaI,[3c] and $Dy(OTf)_3$[3d] have been found to catalyze this reaction. Heterogeneous catalyst montmorillonite KSF[3e] and cation-exchange resin[3f] have also been reported to be effective. Although these methods are available, new efficient, selective and facile protocols are still in strong demand.

Molecular iodine has been used as a mild and efficient catalyst for various organic transformations.[4] In continuation of our efforts to develop new synthetic routes of heterocycles,[5] herein we describe a highly efficient synthesis of 1,2,3,4-tetrahydroquinolines via a molecular iodine-catalyzed domino reaction of anilines with cyclic enol ethers, such as 2,3-dihydrofuran (DHF) and 3,4-dihydro-2*H*-pyran (DHP), under mild reaction conditions.

The selected model reaction was carried out with aniline and 2,3-dihydrofuran (DHF) in several organic solvents at room temperature (Table 1). A mixture of *endo*-isomer **2a** and *exo*-isomer **3a** was isolated. It is found that a remarkable solvent effect exists in our iodine-catalyzed domino process. CH_2Cl_2 and MeCN are the best solvents for good transformation in very short time (5 min), while other solvents afford either poor yields or trace products. It is noteworthy that the highest diastereoselectivity is obtained when CH_2Cl_2 is used as a solvent (Table 1, entries 9–11). Furthermore, the yields increase slightly as the amount of catalyst is increased from 10 to 20 mol % (Table 1, entries 9–11). So 10 mol % amount of iodine appears to be sufficient to drive the reaction forward.

Under the optimized reaction conditions, a variety of anilines **1** were tested to react with 2 equiv of 2,3-dihydrofuran (DHF) using 10 mol % of I_2 as a catalyst in CH_2Cl_2 at room temperature for 5 min (Table 2).[6] As shown in Table 2, electron-rich anilines (Table 2, entries a, and e–i) were more reactive than electron-deficient anilines (Table 2, entries b–d, and j). The strong electron-withdrawing group substituted 4-nitroaniline only gave a trace of product (Table 2, entry j). In all cases, the products were obtained as a mixture of *endo*/*exo*-isomers (**2** and **3**). The ratio of isomers was determined by the ^1H NMR spectra of the crude products. The stereochemistry of the isomers was assigned on the basis of coupling constants and chemical shifts of protons, which was accordant with the presentation of the literatures.[3]

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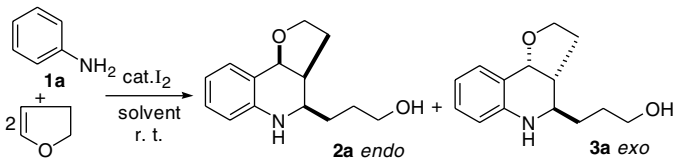
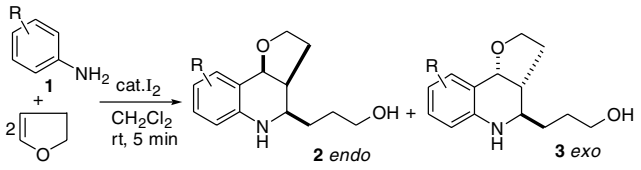
Table 1. Solvent effect on I_2-catalyzed synthesis of pyrano[3,2-*c*]quinolines[a]



Entry	Catalyst (mol %)	Solvent	Time (min)	Yield (%)[b]	*endo*/*exo*[c]
1	10	Acetone	15	45	40:60
2	10	THF	15	50	48:52
3	10	Benzene	15	55	36:64
4	10	Toluene	15	52	38:62
5	10	MeOH	30	Trace	—
6	10	Et_2O	15	34	45:55
7	10	MeCN	5	84	47:53
8	20	MeCN	5	87	47:53
9	5	CH_2Cl_2	15	72	31:69
10	10	CH_2Cl_2	5	88	30:70
11	20	CH_2Cl_2	5	90	33:67

[a] Reaction conditions: aniline (1 mmol), DHF (2 mmol), I_2 and solvent (5 ml) at room temperature.
[b] Isolated yield by silica gel column chromatography.
[c] Determined by ^1H NMR spectroscopy.

Table 2. Iodine-catalyzed reaction of anilines with 2,3-dihydrofuran[a]



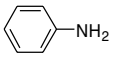
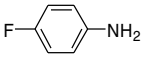
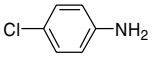
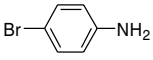
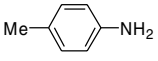
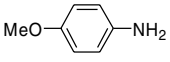
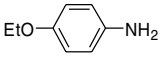
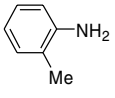
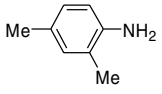
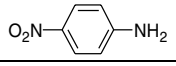
Entry	Aromatic amines	Yields (%)[b]	*endo*/*exo*[c]
A		88	30:70
B		85	57:43
C		77	54:46
D		80	56:44
E		93	37:63
F		87	56:44
G		88	52:48
H		90	28:72

Table 2 (*continued*)

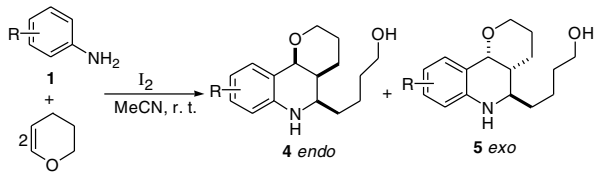
Entry	Aromatic amines	Yields (%)[b]	*endo*/*exo*[c]
I		90	27:73
J		Trace	—

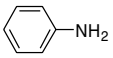
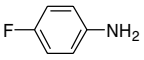
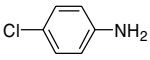
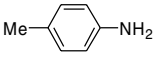
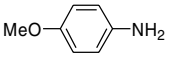
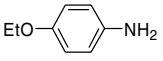
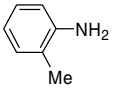
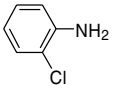
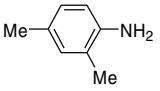
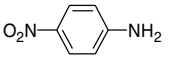
[a] Reaction conditions: aromatic amine (1 mmol), DHF (2 mmol) and CH_2Cl_2 (5 ml) at room temperature using iodine (0.1 mmol) for 5 min.
[b] Isolated yield by silica gel column chromatography.
[c] Determined by ^1H NMR spectroscopy.

We also performed the domino reaction of aniline with less active 3,4-dihydro-2*H*-pyran (DHP) using the above reaction conditions but obtained pyrano[3,2-*c*]quinoline **4a** and **5a** in poor yield (10%). Delightfully, we found that the yield could be improved to 85% when MeCN was used as a solvent; the reaction time was prolonged to 50 min and the catalytic amounts of iodine were increased to 20 mol %. The methodology has been generalized by reacting a series of substituted anilines with DHP to give pyrano[3,2-*c*]quinoline derivatives **4** and **5** in good yields with the exception of 4-nitroaniline (Table 3).[7] In all cases, the products were obtained as a mixture of *endo*/*exo*-isomers.

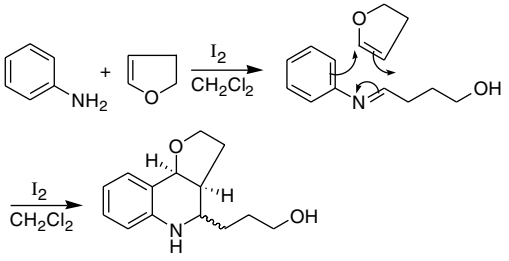
It is noteworthy that our method has several advantages including mild conditions, improved yields, short reaction time, simple operation and work-up. Additionally, the protocol does not require anhydrous solvents. According to the literatures,[4g,h] we think that iodine catalyzes the reaction as a mild Lewis acid. The tentative mechanism to rationalize the product formation is shown in Scheme 1. The reaction may proceed via an aza-Diels–Alder process of 2-azadiene, which is generated in situ from cyclic enol ether and aniline, with

Table 3. Iodine-catalyzed reaction of anilines with 3,4-dihydro-2*H*-pyran[a]



Entry	Aromatic amines	Yields (%)[b]	*endo*/*exo*[c]
a		85	34:66
b		75	64:36
c		70	30:70
d		85	34:66
e		83	33:67
f		90	42:58
g		92	40:60
h		72	35:65
i		93	35:65
j		Trace	—

[a] Reaction conditions: aromatic amine (1 mmol), DHP (2 mmol) and MeCN (5 ml) at room temperature using iodine (0.2 mmol) for 50 min.
[b] Isolated yield by silica gel column chromatography.
[c] Determined by ^{1}H NMR spectroscopy.



Scheme 1.

another equivalent of cyclic enol resulting in the formation of tetrahydroquinolines.

In summary, we have developed a highly efficient domino reaction of anilines with cyclic enol ether using a catalytic amount of molecular iodine to provide 1,2,3,4-tetrahydroquinoline derivatives. The notable features of this procedure are mild reaction conditions, good yields, short reaction time, metal-free, and operational simplicity.

Acknowledgements

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4. (a) Samajdar, S.; Basu, M. K.; Becker, F. F. *Synlett* **2002**, 319–322; (b) Basu, M. K.; Samajdar, S.; Becker, F. F.; Banik, B. K. *Tetrahedron Lett.* **2001**, *42*, 4425–4428; (c) Banik, B. K.; Samajdar, S.; Banik, I. *J. Org. Chem.* **2004**, *69*, 213–219; (d) Banik, B. K.; Manhas, M. S.; Bose, A. K.

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6. Typical procedure for the synthesis of furano[3,2-*c*]quinolines **2** and **3**. To a mixture of anilines **1** (1 mmol) and 2,3-dihydrofuran (2 mmol) in CH_2Cl_2 (5 ml) was added iodine (25 mg, 0.1 mmol), and the solution was stirred at room temperature for 5 min. Then, to the reaction mixture was added 10% aq $Na_2S_2O_3$ solution (10 ml) and the products were separated by thorough extraction with CH_2Cl_2 (10 ml). The solvent was evaporated after drying (Na_2SO_4) and the pure compounds were obtained by silica gel column chromatography with hexane-EtOAc (1:2). For the representative compounds **2e** and **3e**: liquid; IR (neat): $v = 3345$, 2931, 1618, 1501, 1063 cm^{-1}. MS (ESI): $m/z = 247$ [M^+]. HRMS (EI): m/z [M^+] calcd for $C_{15}H_{21}NO_2$: 247.1572; found: 247.1578. *endo*-Isomer (**2e**): ^1H NMR ($CDCl_3$, 400 MHz): δ 1.50–1.92 (m, 5H), 2.02–2.04 (m, 1H), 2.22 (s, 3H), 2.56–2.58 (m, 1H), 2.80 (br, 1H), 3.45–3.47 (m, 1H), 3.72–3.75 (m, 2H), 3.86–3.88 (m, 2H), 5.05 (d, $J = 7.6$ Hz, 1H), 6.49 (d, $J = 7.6$ Hz, 1H), 6.90 (dd, $J = 2.2$, 7.6 Hz, 1H), 7.10 (d, $J = 2.2$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.85, 24.28, 29.35, 30.95, 42.85, 53.06, 62.55, 66.96, 76.15, 115.00, 122.90, 128.17, 129.32, 130.55, 142.96. *exo*-Isomer (**3e**): ^1H NMR ($CDCl_3$, 400 MHz): δ 1.50–1.90 (m, 5H), 2.17–2.19 (m, 1H), 2.22 (s, 3H), 2.76–2.79 (m, 1H), 2.82 (br, 1H), 3.69–3.71 (m, 2H), 3.76–3.78 (m, 2H), 3.93–3.96 (m, 1H), 4.52 (d, $J = 5.6$ Hz, 1H), 6.59 (d, $J = 8.4$ Hz, 1H), 6.90 (dd, $J = 2.2$, 8.4 Hz, 1H), 7.15 (d, $J = 2.2$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.75, 28.90, 29.45, 30.19, 41.66, 52.58, 62.66, 65.83, 76.11, 115.24, 120.77, 127.75, 129.83, 131.39, 142.85.
7. Typical procedure for the synthesis of pyrano[3,2-*c*]quinolines **4** and **5**. To a mixture of anilines **1** (1 mmol) and 3,4-dihydro-2*H*-pyran (2 mmol) in MeCN (5 ml) was added iodine (50 mg, 0.2 mmol), and the solution was stirred at room temperature for 50 min. Then, to the reaction mixture was added 10% aq $Na_2S_2O_3$ solution (20 ml) and the products were separated by thorough extraction with CH_2Cl_2 (20 ml). The solvent was evaporated after drying (Na_2SO_4) and pure compounds were obtained by silica gel column chromatography with hexane/EtOAc (1:2). For the representative compounds **4e** and **5e**: liquid; IR (neat): $v = 3365$, 2931, 1628, 1498, 1071 cm^{-1}. MS (ESI): $m/z = 291$ [M^+]. HRMS (EI): m/z [M^+] calcd for $C_{17}H_{25}NO_3$: 291.1834; found: 291.1839. *endo*-Isomer (**4e**): ^1H NMR ($CDCl_3$, 400 MHz): δ 1.30–1.80 (m, 10H), 2.01–2.04 (m, 1H), 3.30–3.40 (m, 2H), 3.61–3.65 (m, 1H), 3.66 (t, $J = 6.5$ Hz, 2H), 3.75 (s, 3H), 5.01 (d, $J = 5.6$ Hz, 1H), 6.49 (d, $J = 8.2$ Hz, 1H), 6.68 (dd, $J = 2.6$, 8.4 Hz, 1H), 6.95 (d, $J = 2.6$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.02, 22.44, 25.45, 32.33, 32.71, 35.57, 53.95, 55.96, 61.05, 62.45, 72.58, 112.04, 115.03, 115.67, 121.53, 139.35, 152.70. *exo*-Isomer (**5e**): ^1H NMR ($CDCl_3$, 400 MHz): δ 1.30–1.80 (m, 10H), 1.97–1.99 (m, 1H), 3.48–3.51 (m, 1H), 3.74–3.77 (m, 3H), 3.76 (s, 3H), 3.95–3.98 (m, 1H), 4.45 (d, $J = 2.6$ Hz, 1H), 6.51 (d, $J = 8.2$ Hz, 1H), 6.68 (dd, $J = 2.6$, 8.2 Hz, 1H), 6.85 (d, $J = 2.6$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.75, 23.25, 24.69, 33.09, 33.20, 36.82, 50.95, 56.17, 62.56, 67.68, 74.26, 114.73, 116.10, 116.72, 121.74, 139.20, 152.17.