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Molecular iodine-catalyzed diastereoselective synthesis of cis-fused pyranobenzopyrans and furanobenzopyrans

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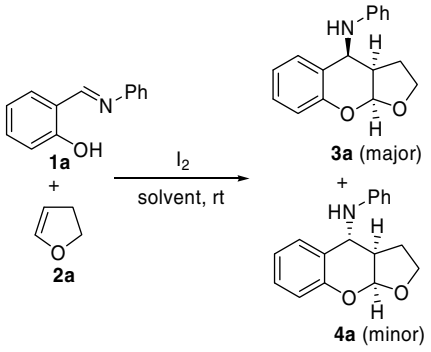
ABSTRACT

A highly efficient method for the diastereoselective synthesis of cis-fused pyranobenzopyrans and furanobenzopyrans via 2 mol % of molecular iodine-catalyzed reaction of *o*-hydroxybenzaldimines with 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran at ambient temperature is described. 2-Butoxy-4-*N*-aryl-aminobenzopyrans were also synthesized from *o*-hydroxybenzaldimine and *n*-butyl vinyl ether using this procedure.

2*H*-1-Benzopyrans (2*H*-chromenes) and 3,4-dihydro-2*H*-1-benzopyrans (chromans) have proved to be very important due to the biological activity of naturally occurring representatives.[1] 4-Aminobenzopyrans and their derivatives show a wide range of biological activities.[2] Particularly, fused tetrahydropyranobenzopyran derivatives are frequently found in naturally occurring bioactive molecules. In 1999, Miyazaki and co-workers reported a *p*-toluene-sulfonic acid-catalyzed intramolecular [4+2] cycloaddition reaction of *o*-quinonemethides for the synthesis of angularly *trans*-fused pyranobenzopyrans.[3] The aza-Diels–Alder reaction of *o*-hydroxybenzaldimines with 3,4-dihydro-2*H*-pyran (DHP) and 2,3-dihydrofuran (DHF) is a convenient protocol for the synthesis of fused pyranobenzopyrans and furanobenzopyrans.[4–8] Several proton acids and Lewis acids have been used to catalyze this reaction, such as H_2NSO_3H,[4] $KHSO_4$,[5] $LiBF_4$,[6] PPh_3-$HClO_4$,[7] and $Bi(OTf)_3$.[8] Although these methods are available, new efficient, selective, and facile protocols are still in strong demand.

Recently, molecular iodine has received considerable attention as an inexpensive and readily available catalyst for various organic transformations due to its moderate Lewis acidity and water tolerance.[9] Previously, we reported the molecular iodine-catalyzed synthesis of 1,2,3,4-tetrahydroquinolines and quinolines.[10] In continuation of our efforts to develop new synthetic methods of heterocycles,[11] we herein describe a diastereoselective synthesis of cis-fused pyranobenzopyrans and furanobenzopyrans via a molecular iodine-catalyzed reaction of *o*-hydroxybenzaldimines with DHP and DHF.

The selected model reaction was carried out with *N*-phenyl-salicylaldimine (**1a**) and DHF (**2a**) at room temperature (Scheme 1). We examined several organic solvents, which are commercially available and used without further purification or drying (Table 1). A mixture of diastereoisomers **3a** and **4a** was obtained. We found that a remarkable solvent effect existed in our iodine-catalyzed reaction. THF (Table 1, entries 1–3) and MeCN (Table 1, entry 4) are the best solvents for good transformation and high diastereoselectivity, while the others afford either poor yields (Table 1, entries 5–7) or even no products (Table 1, entries 8 and 9). Furthermore, the diastereoselectivity decreased when the amount of catalyst was increased to 5 mol % and 10 mol %, although the reaction was accelerated (Table 1, entries 1–3).



Scheme 1.

Using the optimized reaction conditions, we examined a variety of salicylaldimines **1a**–**k** as well as DHF (Table 2, entries 1–11) and DHP (Table 2, entries 12–14). We obtained the corresponding furanobenzopyrans and pyranobenzopyrans as a mixture of diastereoisomers **3** and **4** in 54–96% yields.[12] In most cases, **3** was the major product. In the case of *N*-(2-bromophenyl)imine **1e**, however, the ratio of the isomers **3e** and **4e** was 47:53 (Table 2, entry 5).

The ratio of the diastereoisomers **3** and **4** was determined by ^1H NMR spectroscopy of the crude products. The stereochemistry of the isomers was assigned on the basis of coupling constant and

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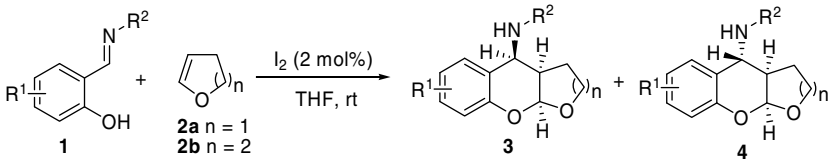
Table 1
Solvent effect on iodine-catalyzed synthesis of cis-fused furanobenzopyrans[a]

Entry	Catalyst (mol %)	Solvent[b]	Time (h)	Yield[c] (%)	Product ratio (**3a**/**4a**)[d]
1	2	THF	2.5	96	97:3
2	5	THF	1.0	93	84:16
3	10	THF	0.5	92	84:16
4	2	MeCN	1.5	92	80:20
5	2	CH_2Cl_2	3.5	32	75:25
6	2	DMF	3.5	77	82:18
7	2	MeOH	3.5	51	91:9
8	2	1,4-Dioxane	3.0	—	—
9	2	Toluene	3.5	Trace	—

[a] Reaction condition: **1a** (1 mmol), **2a** (1.2 mmol, 1.2 equiv), I_2, and solvent (3 mL) at room temperature.
[b] Solvents are commercially available and used without drying.
[c] Isolated yield.
[d] Product ratio was determined by ^{1}H NMR spectroscopy.

Table 2
Iodine-catalyzed diastereoselective synthesis of cis-fused pyranobenzopyrans and furanobenzopyrans[a]



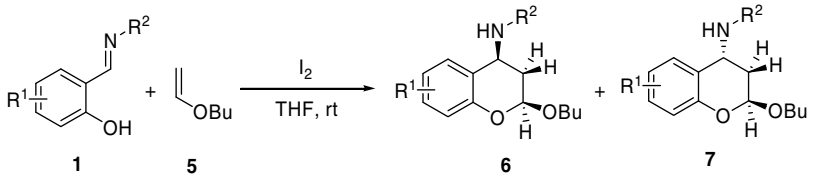
Entry	R^1/R^2	Enol ether	Time (h)	Product	Yield[b] (%)	Product ratio (**3**/**4**)[c]
1	H/C_6H_5 (**1a**)	DHF (**2a**)	2.5	**3a** + **4a**	96	97:3
2	H/4-MeC_6H_4 (**1b**)	**2a**	3.0	**3b** + **4b**	89	86:14
3	H/4-BrC_6H_4 (**1c**)	**2a**	2.0	**3c** + **4c**	93	81:19
4	H/3-ClC_6H_4 (**1d**)	**2a**	2.5	**3d** + **4d**	91	78:22
5	H/2-BrC_6H_4 (**1e**)	**2a**	2.0	**3e** + **4e**	90	47:53
6	H/4-MeOC_6H_4 (**1f**)	**2a**	8.0	**3f** + **4f**	69	88:12
7	4-OMe/ C_6H_5 (**1g**)	**2a**	5.0	**3g** + **4g**	54	94:6
8	4-OMe/4-BrC_6H_4 (**1h**)	**2a**	5.0	**3h** + **4h**	80	90:10
9	5-Br/C_6H_5 (**1i**)	**2a**	3.0	**3i** + **4i**	91	87:13
10	5-Br/4-MeC_6H_4 (**1j**)	**2a**	6.0	**3j** + **4j**	77	87:13
11	5-Br/4-$NO_2C_6H_4$(**1k**)	**2a**	2.0	**3k** + **4k**	94	76:24
12	**1a**	DHP (**2b**)	6.0	**3l** + **4l**	64	81:19
13	**1c**	**2b**	4.0	**3m** + **4m**	88	77:23
14	**1d**	**2b**	5.0	**3n** + **4n**	87	79:21

[a] Reaction conditions: **1** (2 mmol), **2** (2.4 mmol, 1.2 equiv), I_2 (10.6 mg, 2 mol %), and THF (6 mL) at room temperature.
[b] Isolated yield.
[c] Determined by ^{1}H NMR spectroscopy.

chemical shifts of the protons, which was compared with the presentation of the literature.[6,7]

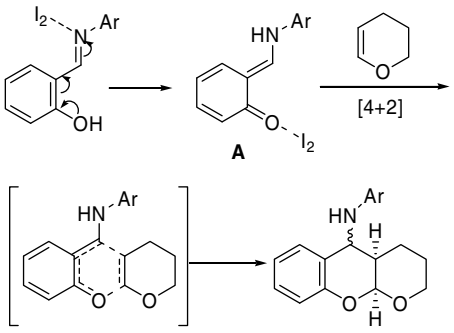
Furthermore, we performed the reaction with *N*-aryl-salicylaldimines **1** and vinyl ether **5** using the established procedure (Table 3). The reactions gave the corresponding 2-butoxy-4-*N*-arylaminobenzopyran as a mixture of diastereoisomers **6** and **7** in 90–93% yields.[13] In this case, however, we obtained low diastereoselectivity with isomer **7** as the major product. It is a possible explanation for this diastereoselectivity that the *trans-endo* isomer **7** is favored under thermodynamic control. The stereochemistry of

Table 3
Iodine-catalyzed synthesis of 2-butoxy-4-aryl chromans[a]



Entry	R^1/R^2	Time (h)	Product	Yield[b] (%)	Product ratio (**6**/**7**)[c]
1	H/4-BrC_6H_4 (**1c**)	3.0	**6a** + **7a**	93	41:59
2	H/2-BrC_6H_4 (**1e**)	3.0	**6b** + **7b**	90	42:58
3	5-Br/4-$NO_2C_6H_4$ (**1k**)	2.5	**6c** + **7c**	92	42:58

[a] Reaction conditions: **1** (2 mmol), **5** (2.4 mmol, 1.2 equiv), I_2 (10.6 mg, 2 mol %), and THF (6 mL) at room temperature.
[b] Isolated yield.
[c] Determined by ^{1}H NMR spectroscopy.



Scheme 2.

the product was assigned by ^{1}H NMR spectroscopy based on the coupling constants and chemical shifts.[7,14]

We believe that iodine catalyzes the reaction as a mild Lewis acid.[7,10] The tentative mechanism is shown in Scheme 2. Lewis acid promotes the transformation of *o*-hydroxybenzaldimine to oxadiene **A**, which is followed by a [4+2] cycloaddition[3,4] to give pyranobenzopyrans or furanobenzopyrans.

In summary, we developed a simple and efficient method for the diastereoselective synthesis of cis-fused pyranobenzopyrans and furanobenzopyrans via a molecular iodine-catalyzed reaction of *o*-hydroxybenzaldimines with 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran at ambient temperature. Using this method, 2-butoxy-4-*N*-arylaminobenzopyrans were also synthesized from *o*-hydroxybenzaldimine and *n*-butyl vinyl ether. The notable features of the procedure include mild and metal-free reaction conditions, operational simplicity, using a catalytic amount of molecular iodine (2 mol %), short reaction time, and good yields.

Acknowledgement

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12. *General procedure*: A mixture of salicylaldimine (2 mmol), dihydrofuran or dihydropyran (2.4 mmol, 1.2 equiv), and I_2 (10.6 mg, 2 mol %) in the THF (6 mL) was stirred at room temperature for the appropriate time. After the reaction was completed, the reaction mixture was quenched by 10% aq $Na_2S_2O_3$ solution (10 ml) and extracted with ethyl acetate (2 × 15 ml). The combined organic layers were dried over Na_2SO_4 and then concentrated in vacuo. The resulting product was purified by column chromatography on silica gel column with hexane–EtOAc (10:1). Spectral data for product **3a**: IR (KBr): 3368, 2980, 1915, 1601, 1521, 1483, 1453, 1313, 1227, 1095, 1037, 749 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (m, 1H), 1.93 (m, 1H), 3.13 (m, 1H), 3.65–4.15 (br s, 1H), 3.86 (ddd, 1H, *J* = 8.0, 8.0, 8.0 Hz), 3.94 (ddd, 1H, *J* = 8.4, 8.4, 4.0 Hz), 4.99 (d, 1H, *J* = 5.2 Hz), 5.90 (d, 1H, *J* = 5.2 Hz), 6.78 (d, 2H, *J* = 7.6 Hz), 6.82 (t, 1H, *J* = 7.2 Hz), 6.94 (d, 1H, *J* = 8.0 Hz), 6.97 (t, 1H, *J* = 7.6 Hz), 7.22–7.26 (m, 3H), 7.39 (d, 1H, *J* = 8.0 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.95, 43.24, 48.91, 68.02, 102.3, 113.6, 117.2, 118.5, 121.8, 124.5, 126.2, 128.8, 129.6, 146.9, 152.9 ppm. MS (ESI): *m*/*z* = 268 ([M+H]$^+$). For **4a**: IR (KBr): 3389, 2952, 2897, 1601, 1503, 1458, 1314, 1224, 1115, 1045, 954, 751 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71 (m, 1H), 2.20 (m, 1H), 2.97 (m, 1H), 3.80–4.30 (br s, 1H), 3.98 (ddd, 1H, *J* = 8.0, 8.0, 8.0 Hz), 4.09 (ddd, 1H, *J* = 8.0, 8.0, 4.0 Hz), 4.57 (d, 1H, *J* = 2.0 Hz), 5.70 (d, 1H, *J* = 4.8 Hz), 6.68 (d, 2H, *J* = 7.6 Hz), 6.81 (t, 1H, *J* = 7.2 Hz), 6.95–7.00 (m, 2H), 7.23–7.29 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.83, 43.15, 50.44, 67.73, 99.80, 113.1, 117.6, 118.2, 121.4, 121.6, 129.5, 129.8, 129, 146.1, 152.5 ppm. MS (ESI): *m*/*z* = 268 ([M+H]$^+$). For **3l**: IR (KBr): 3342, 2937, 1604, 1517, 1484, 1455, 1202, 1135, 1090, 980, 756 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (m, 1H), 1.60–1.76 (m, 3H), 2.52 (m, 1H), 3.65–4.15 (br s, 1H), 3.78 (m, 1H), 4.03 (ddd, 1H, *J* = 12.0, 12.0, 2.4 Hz), 5.03 (d, 1H, *J* = 5.2 Hz), 5.59 (d, 1H, *J* = 2.0 Hz), 6.76 (d, 2H, *J* = 6.8 Hz), 6.80 (t, 1H, *J* = 6.8 Hz), 6.93 (d, 1H, *J* = 7.6 Hz), 6.94 (t, 1H, *J* = 6.8 Hz), 7.20–7.26 (m, 3H), 7.45 (d, 1H, *J* = 7.6 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.92, 24.04, 34.68, 50.97, 60.84, 96.24, 113.2, 116.3, 117.9, 121.6, 126.6, 128.9, 129.5, 146.6, 152.9 ppm. MS (ESI): *m*/*z* = 282 ([M+H]$^+$).
13. *Spectral data of compounds* **6c** *and* **7c**: For **6c**: IR (KBr): 3365, 2933, 1600, 1538, 1502, 1477, 1295, 1112 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, 3H, *J* = 7.6 Hz), 1.31 (m, 2H), 1.56 (m, 2H), 1.92 (m, 1H), 2.41 (m, 1H), 3.60 (dt, 1H, *J* = 9.6, 6.4 Hz), 3.83 (dt, 1H, *J* = 9.6, 7.2 Hz), 4.35–4.75 (br s, 1H), 5.04 (dd, 1H, *J* = 10.0, 5.2 Hz), 5.30 (br s, 1H), 6.67 (d, 2H, *J* = 9.2 Hz), 6.78 (d, 1H, *J* = 8.4 Hz), 7.31 (dd, 1H, *J* = 8.4, 2.0 Hz), 7.42 (d, 1H, *J* = 2.0 Hz), 8.13 (d, 2H, *J* = 8.8 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.73, 19.15, 31.49, 32.80, 44.56, 68.61, 97.24, 111.5, 113.4, 119.2, 125.4, 126.6, 129.4, 132.2, 138.7, 151.1, 152.2 ppm. MS (ESI): *m*/*z* = 421 ([M+H]$^+$). For **7c**: IR (KBr): 3395, 2957, 1596, 1522, 1501, 1475, 1298, 1108, 1019 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, 3H, *J* = 7.6 Hz), 1.30 (m, 2H), 1.54 (m, 2H), 2.25 (m, 1H), 2.35 (m, 1H), 3.54 (dt, 1H, *J* = 9.2, 6.4 Hz), 3.81 (dt, 1H, *J* = 9.2, 6.8 Hz), 4.75 (d, 1H, *J* = 5.2 Hz), 5.39 (br s, 1H), 5.10–5.80 (br s, 1H), 6.62 (d, 2H, *J* = 9.2 Hz), 6.81 (d, 1H, *J* = 8.8 Hz), 7.32 (dd, 1H, *J* = 8.4, 2.0 Hz), 7.41 (d, 1H, *J* = 2.0 Hz), 8.13 (d, 2H, *J* = 8.8 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.57, 19.13, 31.42, 31.45, 44.26, 68.63, 96.66, 111.4, 113.5, 119.6, 124.3, 126.5, 132.2, 132.5, 138.2, 149.9, 151.6 ppm. MS (ESI): *m*/*z* = 421 ([M+H]$^+$).
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