Iodine as a Mild, Efficient, and Cost-Effective Reagent for the Synthesis of *cis*-1-Oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acids

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Abstract: Arylimines generated in situ from aromatic aldehydes and anilines undergo smooth coupling with homophthalic anhydride in the presence of 10 mol% of molecular iodine under mild and neutral conditions to afford the corresponding *cis*-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acids in excellent yields with high *cis* selectivity. The use of iodine makes this procedure simple, convenient, and cost-effective.

Key words: three-component reaction, iodine, isoquinolines, heterocycles, carboxylic acids

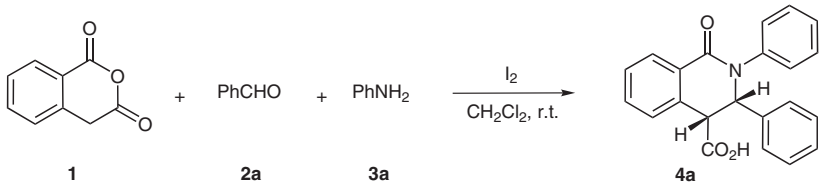
Tetrahydroquinoline derivatives make up an important class of compounds in the field of pharmaceuticals, and exhibit a wide spectrum of biological activities including psychotropic, antiallergenic, anti-inflammatory, and estrogenic behavior.[1] Oxoisoquinolinecarboxylic acids possess a vast range of pharmacological activities.[2] Also, oxoisoquinolinecarboxylic acids are useful precursors for the total synthesis of naturally occurring phenanthridine alkaloids[3] such as corynoline, oxocorynoline, and epicorynoline as well as indenoisoquinolines[4] possessing significant antitumor activity.

The cycloaddition of homophthalic anhydride with aldimines provides a useful access to the preparation of oxoisoquinolinecarboxylic acids.[5] The cycloaddition of homophthalic anhydride with imines has been reported to occur under base catalysis or without a catalyst under thermal conditions;[6,7] this often produces a mixture of *cis*- and *trans*-isomers, with the *cis*-isomer favored. Recently, trimethyl orthoformate has also been employed for the synthesis of *trans*-oxoisoquinolinecarboxylic acids.[8] However, many of these classical methods often involve the use of expensive reagents, extended reaction times, and also generate a mixture of products.[6,7] Therefore, the development of a simple and efficient protocol using inexpensive and readily available reagents would extend the scope of this transformation in natural product synthesis.[3,4]

In recent years, molecular-iodine-catalyzed or -mediated reactions have gained importance in organic synthesis as an inexpensive, nontoxic, and readily available method for various organic transformations, affording the corresponding products in high selectivity and excellent yields.[9] The mild Lewis acidity associated with iodine enhances its usage in organic synthesis, so that several organic transformations can be performed at stoichiometric to catalytic levels. The advantages associated with this eco-friendly catalyst has led to molecular iodine being explored as a powerful reagent in organic synthesis.[10]

In continuation of our interest in the use of molecular iodine for various transformations,[11] we herein report the direct synthesis of highly substituted oxoisoquinolinecarboxylic acids from homophthalic anhydride and arylimines in the presence of molecular iodine under neutral conditions. Accordingly, treatment of homophthalic anhydride (**1**), benzaldehyde (**2a**), and aniline (**3a**) with iodine in dichloromethane at room temperature afforded the corresponding *cis*-oxoisoquinolinecarboxylic acid derivative **4a** in 85% yield (Scheme 1).

Similarly, several arylimines (generated in situ from aldehydes **2** and amines **3**) reacted well with homophthalic anhydride (**1**) to give the corresponding *cis*-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acids **4** in 72–92% yield (Table 1). It is noteworthy that benzylamine (**3b**) and phenethylamine (**3f**) (Table 1, entries 2, 9, and 11) gave higher yields than arylamines. In all cases, the reactions proceeded smoothly at room temperature under mild conditions. However, aliphatic aldehydes such as *n*-decanal and cyclohexanecarbaldehyde failed to produce the desired product under similar conditions. This method



1 **2a** **3a** **4a**

Scheme 1

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was successful only with imines derived from aromatic aldehydes **3** (Table 1). In the absence of iodine, the reactions did not yield the desired products even after a long reaction time (8–16 h). As solvent, dichloromethane appeared to give the best results. The reactions were clean and the products were obtained in excellent yields and with high diastereoselectivity as determined by ^{1}H NMR analysis of the crude products. In all reactions, the product was obtained as a *cis*-diastereomer, the structure of which was established on the basis of the coupling constants of the hydrogens in the ^{1}H NMR spectra of the products. The stereochemistry of the products was further confirmed by direct comparison of the spectroscopic data of the products with authentic samples.[12] All the products were characterized by ^{1}H NMR and IR spectroscopy, and mass spectrometry.

Compared to conventional syntheses, this method avoids the preparation and isolation of unstable imines. Most of the conventional Lewis acids, such as boron trifluoride–diethyl ether, titanium(IV) chloride, and tin(IV) chloride, were decomposed or deactivated by amines and water during imine formation. However, iodine was found to be compatible with the amines and water present during imine formation, and also effectively activate the imines (formed in situ from aldehydes and amines) to undergo cyclization. The results of the scope and generality of this process with respect to various aldehydes, amines, and homophthalic anhydride are presented in Table 1.

Table 1 Iodine-Catalyzed Preparation of *cis*-1-Oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acids **4** from Aldehydes **2**, Amines **3**, and Homophthalic Anhydride (**1**)

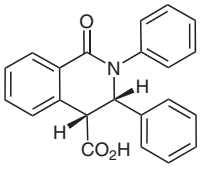
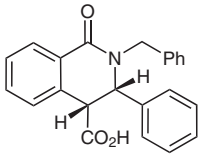
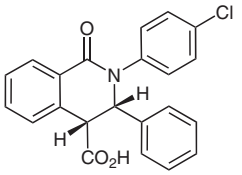
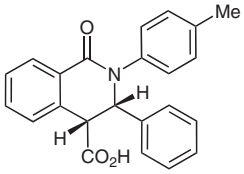
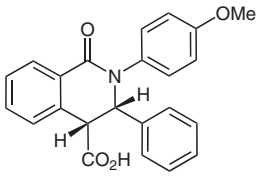
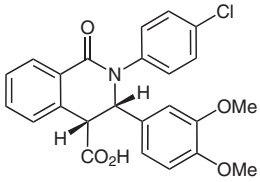
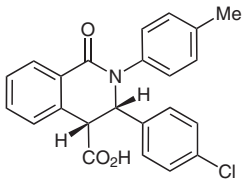
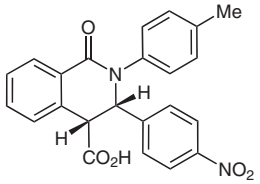
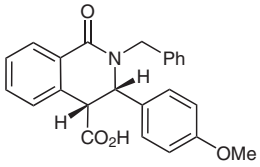
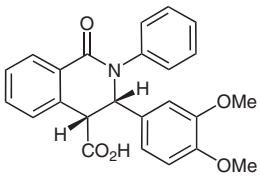
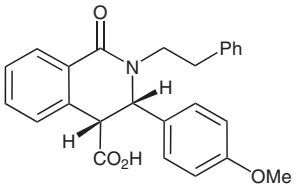
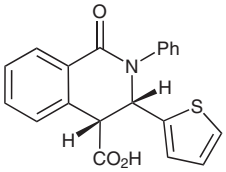
Entry	Ar in ArCHO	**2**	R in RNH_2	**3**	Product[a]	**4**	Time (h)	Yield[b] (%)
1	Ph	**2a**	Ph	**3a**		**4a**	6.0	85
2	Ph	**2a**	Bn	**3b**		**4b**	6.5	90
3	Ph	**2a**	4-ClC_6H_4	**3c**		**4c**	7.0	82
4	Ph	**2a**	Tol	**3d**		**4d**	6.5	80
5	Ph	**2a**	PMP	**3e**		**4e**	7.0	83
6	3,4-$(MeO)_2C_6H_3$	**2b**	4-ClC_6H_4	**3c**		**4f**	6.0	85

Table 1 Iodine-Catalyzed Preparation of *cis*-1-Oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acids **4** from Aldehydes **2**, Amines **3**, and Homophthalic Anhydride (**1**) (continued)

Entry	Ar in ArCHO	**2**	R in RNH_2	**3**	Product[a]	**4**	Time (h)	Yield[b] (%)
7	4-ClC_6H_4	**2c**	Tol	**3d**		**4g**	6.0	81
8	4-$O_2NC_6H_4$	**2d**	Tol	**3d**		**4h**	7.0	72
9	PMP	**2e**	Bn	**3b**		**4i**	6.0	91
10	3,4-$(MeO)_2C_6H_3$	**2b**	Ph	**3a**		**4j**	6.0	86
11	4-ClC_6H_4	**2e**	$(CH_2)_2Ph$	**3f**		**4k**	6.0	92
12	2-thienyl	**2f**	Ph	**3a**		**4l**	5.5	84

[a] All products were characterized by ^1H NMR and IR spectroscopy, and mass spectrometry.
[b] Yields refer to pure products after column chromatography.

In summary, molecular iodine was proved to be a useful and novel catalyst for the synthesis of *cis*-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acids by the three-component coupling of aldehydes, amines, and homophthalic anhydride under mild and neutral conditions. The experimental procedure is simple and convenient and the reaction conditions are amenable to scale-up. This method provides an easy access to highly substituted 1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acids with diverse chemical structures.

Melting points were recorded on a Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr discs. ^1H and ^{13}C NMR spectra of samples in $CDCl_3$ were recorded on Gemini-200 and Varian Bruker-300 spectrometers using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

cis-1-Oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acids 4; General Procedure

A mixture of aldehyde **2** (1 mmol), amine **3** (1 mmol), homophthalic anhydride (**1**; 1 mmol), and I_2 (10 mol%) in CH_2Cl_2 (5 mL) was stirred at 23 °C for the specified amount of time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with aq $Na_2S_2O_3$ (2 × 10 mL) and brine (2 × 10 mL) and dried over anhyd Na_2SO_4. Removal of the solvent followed by purification by column chromatography (silica gel, Merck, 100–200 mesh, EtOAc–hexane,

0.5–9.5) gave the pure *cis*-acid **4**. All the products thus obtained were characterized by IR, NMR, and mass spectroscopy, and as all products **4** have been reported in the literature, the spectroscopic data were compared and found to be consistent with authentic samples.[12] Spectral data for selected products are given below.

1-Oxo-2,3-diphenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (4a)
White solid; mp 198 °C.

IR (KBr): 3035, 1723, 1635, 1496, 1223, 1025, 771, 698 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 4.86 (d, *J* = 6.0 Hz, 1 H), 5.41 (d, *J* = 6.0 Hz, 1 H), 7.10 (m, 8 H), 7.39 (m, 3 H), 7.71 (d, *J* = 8.0 Hz, 1 H), 8.19 (dd, *J* = 2.1, 8.0 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.2, 163.4, 139.5, 137.2, 136.2, 135.8, 132.7, 129.7, 129.1, 128.9, 128.4, 128.1, 126.7, 65.5, 49.6.

MS (EI, 70 eV): *m*/*z* = 343 [M^+], 182, 134, 106, 89, 78.

2-Benzyl-3-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (4i)
White solid; mp 197 °C.

IR (KBr): 3441, 1740, 1619, 1511, 1258, 1169, 1021, 831, 750 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.61 (d, *J* = 14.0 Hz, 1 H), 3.76 (s, 3 H), 4.79 (d, *J* = 6.0 Hz, 1 H), 5.86 (d, *J* = 6.0 Hz, 1 H), 5.69 (d, *J* = 14.0 Hz, 1 H), 6.72 (d, *J* = 8.0 Hz, 2 H), 6.90 (d, *J* = 8.0 Hz, 2 H), 7.20–7.36 (m, 6 H), 7.59–7.61 (m, 2 H), 8.24 (dd, *J* = 2.0, 8.0 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.6, 162.6 158.4, 136.1, 132.1, 130.8, 128.1, 127.6, 127.1, 126.9, 126.4, 126.1, 112.6, 59.1, 54.1, 47.1.

MS (EI, 70 eV): *m*/*z* = 387 [M^+], 381, 282, 237, 226, 165, 134, 121, 91, 77, 65.

3-(4-Methoxyphenyl)-1-oxo-2-phenethyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (4k)
White solid; mp 166 °C.

IR (KBr): 3033, 2930, 1725, 1625, 1511, 1470, 1251, 1170, 1032, 760, 703 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.89–3.05 (m, 4 H), 3.71 (s, 3 H), 4.41 (d, *J* = 5.7 Hz, 1 H), 4.79 (d, *J* = 5.7 Hz, 1 H), 6.64 (d, *J* = 8.0 Hz, 2 H), 6.90 (d, *J* = 8.0 Hz, 2 H), 7.26–7.62 (m, 8 H), 8.21 (dd, *J* = 8.0, 1.8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 162.6 159.1, 139.1, 133.6, 131.8, 128.9, 128.5, 128.1, 127.9, 127.4, 127.1, 126.3, 113.6, 61.1, 55.1, 48.1, 47.5, 33.6.

MS–FAB: *m*/*z* = 401 [M^+], 356, 337, 255, 238, 162, 152, 132, 118, 107, 93, 77, 65, 43.

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