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CONVENIENT SYNTHESIS OF 1,2,3,4-TETRAHYDROISOQUINOLINE-1-CARBOXYLIC ACID DERIVATIVES VIA ISOCYANIDE-BASED, THREE-COMPONENT REACTIONS

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The three-component reactions of 3,4-dihydroisoquinolines, isocyanides, and benzyl chloroformate furnished 2-benzyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamides in moderate to good yields. Hydrogenolysis or selective hydrolysis of the benzyloxycarbonyl group provided 1,2,3,4-tetrahydroisoquinoline-1-carboxamides, further hydrolysis of which resulted in the corresponding 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids.

Keywords: α-Amino acids; isocyanides; isoquinolines; multicomponent reactions

INTRODUCTION

Thanks to their convenience, rapid scaffold construction, considerable molecular diversity, and high degree of atom economy, isocyanide-based multicomponent reactions have received significant interest for both organic synthesis and drug research.[1] In particular, the three- or four-component couplings of isocyanides and various iminium species (Ugi reactions) resulting in α-acylaminocarboxamide derivatives have been widely employed.[1,2]

Isocyanide-based multicomponent reactions are procedures that are often applied for the synthesis of heterocyclic compounds, among them isoquinoline derivatives.[3] Recent examples include the preparation of various 1,2-disubstituted 1,2-dihydro- or 1,2,3,4-tetrahydroisoquinolines via the coupling of the corresponding isoquinolines, isocyanides, and carboxylic acids[4] or strong CH acids[5] or chloroformate esters.[6] The hydrolysis of 2-acyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamides formed in Ugi three-component reactions provides a convenient approach to 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids,[4a] which, as conformationally constrained α-amino acids, are of interest as potential building blocks of modified peptides or other pharmacologically active compounds.[7]

As a continuation of our studies on the utilization of isocyanide-based multicomponent reactions in the synthesis of difunctional tetrahydroisoquinolines,[4a]

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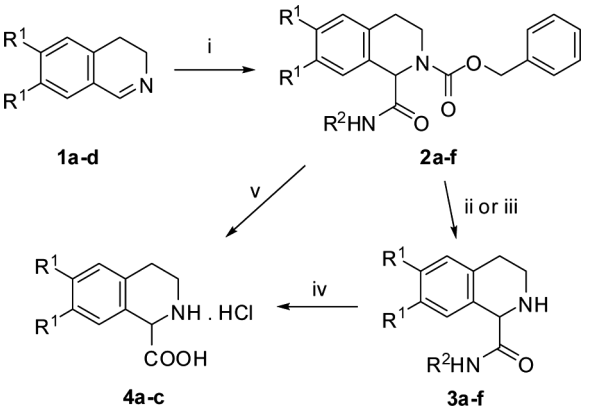
our present aim was to apply benzyl chloroformate as an activating agent to generate reactive dihydroisoquinolinium salts for coupling with isocyanides. It was expected that presence of the readily and selectively removable *N*-benzyloxycarbonyl (*N*-Cbz) group in the products would promote access to 2-unsubstituted 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid derivatives.

RESULTS AND DISCUSSION

On the basis of the method described by Díaz et al.,[6a] who generated acylazinium salts from nitrogen-containing aromatic heterocycles for isocyanide coupling using chloroformates, a mixture of 6,7-dimethoxy-3,4-dihydroisoquinoline (**1a**),[8] benzyl chloroformate, and cyclohexyl isocyanide was allowed to react in $CHCl_3$ at room temperature. The aqueous quenching during the workup extraction gave diamide **2a** in 89% yield. Similar reactions of **1a** with benzyl or *tert*-butyl isocyanide furnished the corresponding **2b** and **2c** in somewhat lesser yields. To test the scope and limitations of the C=N component, couplings with 6,7-unsubstituted (**1b**),[9] 6,7-diethoxy- (**1c**),[10] and 6,7-methylenedioxy-3,4-dihydroisoquinoline (**1d**)[11] were also performed and resulted in **2d–f** in moderate yields (Scheme 1). As Ugi reactions are known to proceed in aqueous media,[12] coupling of **1a** with benzyl chloroformate and cyclohexyl isocyanide was also attempted in water, but **2a** was isolated in only poor yield (24%).



1 / 4	R^1
a	MeO
b	H
c	EtO
d	OCH_2O

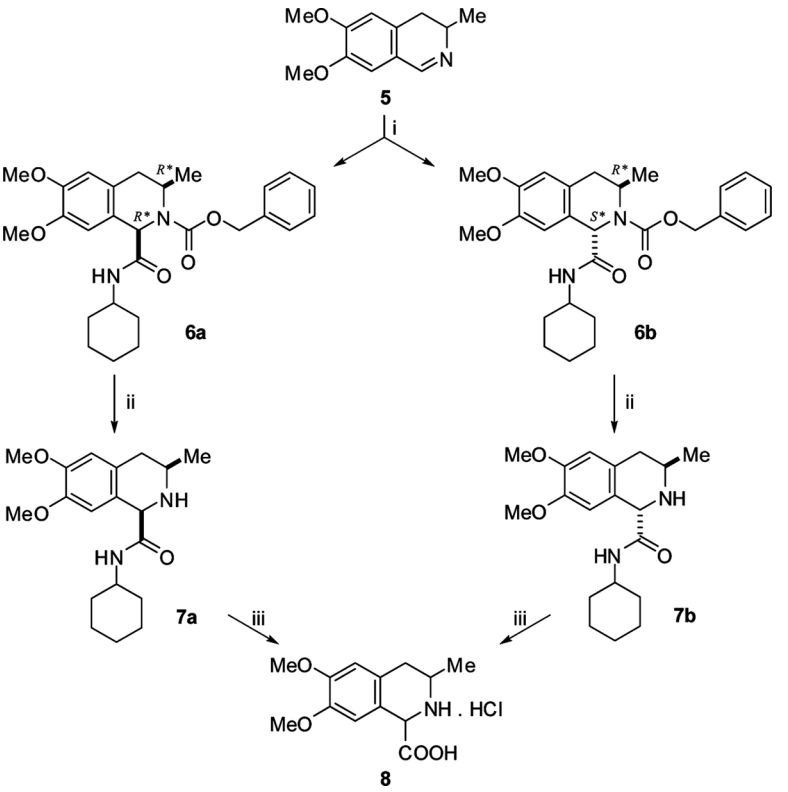
2 / 3	R^1	R^2
a	MeO	cyclohexyl
b	MeO	benzyl
c	MeO	*tert*-butyl
d	H	cyclohexyl
e	EtO	cyclohexyl
f	OCH_2O	cyclohexyl

Scheme 1. Reagents and conditions: (i) $PhCH_2OCOCl$, isocyanide, $CHCl_3$, rt, 5–24 h, then H_2O, rt, 30 min (46–89%); (ii) (1) 33% HBr in AcOH, 30 min, rt, (2) NaOH (83–95%); (iii) H_2 (1 atm), Pd/C, EtOH, rt, 4–6 h (61–89%); (iv) 10% HCl, reflux, 20–25 h (62–76%); (v) 10% HCl, reflux, 20–65 h (36–76%).

As common methods for removal of the benzyl carbamate group,[13] hydrogenolysis and acidic hydrolysis were investigated for **2a**–**f** (Scheme 1). Hydrogenation of **2a**–**f** under atmospheric pressure in the presence of palladium on charcoal catalyst resulted in the corresponding 2-unsubstituted 1,2,3,4-tetrahydroisoquinoline-1-carboxamides **3a**–**f** in good to moderate yields (61–89%). Somewhat better yields (83–95%) were achieved from the reactions of **2a**–**f** with 33% HBr in acetic acid, with subsequent alkaline treatment to liberate the free bases **3a**–**f** from the hydrobromide salts formed.

When **2a**,**d** and **3a**,**d**,**e** were subjected to acidic hydrolysis in refluxing 10% aqueous HCl, the hydrochloride salts of the corresponding 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids **4a**–**c** were obtained (Scheme 1). Compounds **3a**,**d**,**e** underwent hydrolysis in a shorter time and with better yields than the corresponding reactions of **2a**,**d**. Hydrolysis of the 6,7-methylenedioxy derivatives **2f** and **3f** led to complex mixtures from which the corresponding amino acid could not be isolated; this was probably due to the sensitivity of the 1,3-dioxolane moiety to the harsh reaction conditions.

To test the effect of a 3-methyl substituent on the starting dihydroisoquinoline and to devise a procedure for the synthesis of 3-methyl-substituted tetrahydroisoquinoline-1-carboxylic acid derivatives, coupling of 3-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**5**)[14] was also attempted (Scheme 2). The integrals of the 3-H



Scheme 2. Reagents and conditions: (i) $PhCH_2OCOCl$, cyclohexyl isocyanide, $CHCl_3$, rt, 24 h, then H_2O, rt, 30 min, followed by fractional crystallization (**6a**: 31%, **6b**: 44%); (ii) H_2 (1 atm), Pd/C, EtOH, rt, 6 h (56–68%); (iii) 10% HCl, reflux, 40 h (30–32%).

multiplets in the ^{1}H NMR spectrum of the crude product did not reveal any diastereoselectivity in the formation of the *cis* and *trans* isomers of the corresponding 1,3-disubstituted tetrahydroisoquinolines (**6a**,**b**). The steric hindrance caused by the 3-Me substituent resulted in the total yields for **6a** and **6b** being less than that observed for **2a**. Diastereomers **6a** and **6b** were separated by fractional crystallization, and their relative configurations were determined by nuclear Overhauser effect spectroscopy (NOESY) measurements, where NOE interactions were detected between 3-Me and NH in **6a** and between 3-Me and 1-H in **6b**. Removal of the *N*-Cbz group in **6a**,**b** was achieved by hydrogenolysis afforded the corresponding diastereomeric carboxamides **7a**,**b**. When either **7a** or **7b** was submitted to acidic hydrolysis in refluxing 10% HCl, the reaction was accompanied by a total loss of diastereomeric purity, and a 1:1 mixture of *cis*- and *trans*-6,7-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid hydrochloride (**8**) was obtained. This phenomenon can be rationalized by the ease with which tetrahydroisoquinoline-1-carboxylic acids undergo racemization in acidic medium.[4a,7d] All of our efforts to separate the diastereomers of **8** have so far failed.

In conclusion, our results indicate that the readily available 3,4-dihydroisoquinolines are convenient starting materials for the synthesis of 1,2,3,4-tetrahydroisoquinoline-1-carboxamides, via coupling with benzyl chloroformate and isocyanides, and subsequent selective removal of the *N*-Cbz substituent of the Ugi-type intermediates. Further hydrolysis of the carboxamides provides the corresponding tetrahydroisoquinoline-1-carboxylic acids.

EXPERIMENTAL

Melting points were recorded on a Kofler hot-plate microscope apparatus and are uncorrected. For column chromatography, silica gel 60 (0.063–0.200 mm) was used, and for thin-layer chromatography (TLC), Merck Kieselgel 60 F_{254} plates were used. ^{1}H NMR spectra were recorded at 400 MHz in dimethylsulfoxide (DMSO-d_6), $CDCl_3$, or D_2O at ambient temperature on a Bruker Avance DRX 400 spectrometer. Chemical shifts are given in δ (ppm) relative to tetramethylsilane (DMSO or $CDCl_3$) or to sodium 3-(trimethylsilyl)propanoate-d_4 (D_2O) as internal standards.

General Procedure for the Preparation of Compounds 2a–f and 6a,b

A solution of the corresponding 3,4-dihydroisoquinoline (**1**, 3 mmol), 2 equivalents of benzyl chloroformate (6 mmol), and 1.2 equivalents of the appropriate isocyanide (3.6 mmol) in $CHCl_3$ (45 ml) was stirred at room temperature until TLC indicated complete consumption of the starting materials (5–24 h). Water (10 ml) was then added, and the mixture was stirred for 30 min. The layers were separated, and the aqueous phase was washed twice with $CHCl_3$. The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica gel, with $CHCl_3$ as eluent.

For **6a**,**b**, chromatographic purification resulted in an oily diastereomeric mixture, which crystallized on treatment with Et_2O. The crystalline product was filtered off, and its ^{1}H NMR spectrum showed it to be diastereomerically pure **6b**. Evaporation of the filtrate afforded diastereomerically pure **6a**.

Selected Data

2-Benzyloxycarbonyl-1-cyclohexylcarbamoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (2a). Yield: 1.21 g (89%), a white crystalline solid, mp 153–154.5 °C; ^{1}H ($CDCl_3$): δ 7.37 (5H, m, Ph), 6.93 and 6.80 (rotamers in a ratio of 52:48, 1H, br s, C_6H_2), 6.61 (1H, s, C_6H_2), 6.16 and 5.75 (rotamers in a ratio of 57:43, 1H, br s, N*H*), 5.41 (1H, br s, C*H*N), 5.21 (2H, br s, CH_2Ph), 3.97 (1H, m, C*H*), 3.86 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.70 (1H, m, C*H*), 2.80 (2H, m, CH_2CH_2N), 1.78–1.12 (10H, m, 5 × CH_2) ppm. Anal. calcd. for $C_{26}H_{32}N_2O_5$: C, 69.01; H, 7.13; N, 6.19. Found: C, 68.87; H, 7.01; N, 6.33.

1-Benzylcarbamoyl-2-benzyloxycarbonyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (2b). Yield: 0.69 g (50%), a white crystalline solid, mp 169–172 °C; ^{1}H ($CDCl_3$): δ 8.81–8.77 (1H, m, N*H*), 7.39–7.11 (11H, m, 11 × C*H* aromatic protons), 6.77 (1H, s, C_6H_2), 5.36 (1H, s, C*H*N), 5.13 (2H, s, CH_2Ph), 4.32 (1H, dt, $J = 6.0$, 15.5 Hz, CH_2N), 4.18 (1H, dq, $J = 5.0$, 15.0 Hz, CH_2N), 3.93–3.86 (1H, m, CH_2NH), 3.72 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 3.62 (1H, m, CH_2NH), 2.93–2.87 (1H, m, CH_2CH_2N), 2.73–2.66 (1H, m, CH_2CH_2N) ppm. Anal. calcd. for $C_{27}H_{28}N_2O_5$: C, 70.42; H, 6.13; N, 6.08. Found: C, 70.38; H, 6.02; N, 6.20.

2-Benzyloxycarbonyl-6,7-dimethoxy-1-*tert*-butylcarbamoyl-1,2,3,4-tetrahydroisoquinoline (2c). Yield: 1.07 g (84%), a white crystalline solid, mp 136–139 °C; ^{1}H (DMSO-d_6): 7.87 (1H, s, N*H*), 7.42–7.32 (5H, m, Ph), 7.15 (1H, s, C_6H_2), 6.74 (1H, s, C_6H_2), 5.28 (1H, s, C*H*N), 5.11 (2H, m, CH_2Ph), 3.89–3.79 (1H, m, CH_2N), 3.74 (1H, m, CH_2N), 3.72 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 2.87–2.81 (1H, m, CH_2CH_2N), 2.70–2.63 (1H, m, CH_2CH_2N), 1.15 (9H, s, 3 × CH_3) ppm. Anal. calcd. for $C_{24}H_{30}N_2O_5$: C, 67.59; H, 7.09; N, 6.57. Found: C, 67.73; H, 7.21; N, 6.47.

2-Benzyloxycarbonyl-1-cyclohexylcarbamoyl-1,2,3,4-tetrahydroisoquinoline (2d). Yield: 0.55 g (47%), a white crystalline solid, mp 126–127 °C; ^{1}H (DMSO-d_6): δ 8.15 (1H, d, $J = 7.6$ Hz, N*H*), 7.49–7.18 (9H, m, 9 × C*H* aromatic protons), 5.39 (1H, s, C*H*N), 5.22–5.03 (2H, m, CH_2Ph), 3.97–3.89 (1H, m, C*H*), 3.69–3.62 (1H, m, CH_2N), 3.42–3.37 (1H, m, CH_2N), 3.01–2.98 (1H, m, CH_2CH_2N), 2.79–2.72 (1H, m, CH_2CH_2N), 1.72–1.07 (10H, m, 5 × CH_2) ppm. Anal. calcd. for $C_{24}H_{28}N_2O_3$: C, 73.44; H, 7.19; N, 7.14. Found: C, 73.69; H, 7.31; N, 6.98.

2-Benzyloxycarbonyl-1-cyclohexylcarbamoyl-6,7-diethoxy-1,2,3,4-tetrahydroisoquinoline (2e). Yield: 0.90 g (62%), a white crystalline solid, mp 171–174 °C; ^{1}H (DMSO-d_6): δ 8.09 (1H, d, $J = 7.8$ Hz, N*H*), 7.37–7.07 (5H, m, Ph), 7.13 (1H, s, C_6H_2), 6.73 (1H, s, C_6H_2), 5.28–5.01 (3H, m, C*H*N and CH_2Ph), 3.98 (4H, q, $J = 7.0$ Hz, 2 × CH_2CH_3), 3.99–3.83 (1H, m, C*H*), 3.70–3.61 (1H, m, CH_2N), 3.43 (1H, m, CH_2N), 2.89–2.84 (1H, m, CH_2CH_2N), 2.68–2.61 (1H, m, CH_2CH_2N), 1.60–1.09 (10H, m, 5 × CH_2), 1.30 (6H, t, $J = 7.0$ Hz, 2 × CH_2CH_3) ppm. Anal. calcd. for $C_{28}H_{36}N_2O_5$: C, 69.98; H, 7.55; N, 5.83. Found: C, 70.13; H, 7.68; N, 5.71.

2-Benzyloxycarbonyl-1-cyclohexylcarbamoyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (2f). Yield: 0.61 g (46%), a white crystalline solid, mp 150–152 °C; ^{1}H (DMSO-d_6): δ 8.02 (1H, d, $J = 7.4$ Hz, N*H*), 7.38–7.30 (5H, m,

Ph), 7.05 (1H, s, C_6H_2), 6.74 (1H, s, C_6H_2), 5.96 (2H, s, OCH_2O), 5.29–5.01 (3H, m, CHN and CH_2Ph), 3.88 (1H, m, CH cyclohexyl), 3.57 (1H, m, CH_2N), 3.41 (1H, m, CH_2N), 2.90 (1H, m, CH_2CH_2N), 2.66 (1H, m, CH_2CH_2N), 1.59–1.07 (10H, m, $5 \times CH_2$) ppm. Anal. calcd. for $C_{25}H_{28}N_2O_5$: C, 68.79; H, 6.47; N, 6.42. Found: C, 68.65; H, 6.39; N, 6.58.

(1*R,3*R**)-2-Benzyloxycarbonyl-1-cyclohexylcarbamoyl-6,7-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (6a).** Yield: 0.43 g (31%), a yellow oil; ^{1}H (DMSO–d_6): δ 7.95 (1H, br s, NH), 7.37–7.31 (5H, m, Ph), 7.08 (1H, s, C_6H_2), 6.75 (1H, s, C_6H_2), 5.37 (1H, br s, CHN), 5.10 (2H, s, CH_2Ph), 3.72 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 3.49–3.47 (1H, m, $CHCH_3$), 3.33 (1H, m, CH), 2.84 (1H, dd, $J = 5.4$, 15.3 Hz, CH_2CH_2N), 2.68 (1H, dd, $J = 5.6$, 15.3 Hz, CH_2CH_2N), 1.65–1.09 (10H, m, $5 \times CH_2$), 1.23 (3H, d, $J = 4.5$ Hz, $CHCH_3$) ppm. Anal. calcd. for $C_{27}H_{34}N_2O_5$: C, 69.50; H, 7.35; N, 6.00. Found: C, 69.61; H, 7.46; N, 5.87.

(1*S,3*R**)-2-Benzyloxycarbonyl-1-cyclohexylcarbamoyl-6,7-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline (6b).** Yield: 0.52 g (44%), a white crystalline solid, mp 190–192 °C; ^{1}H ($CDCl_3$): δ 7.83 (1H, m, NH), 7.36–7.29 (6H, m, $6 \times$ CH aromatic protons), 6.75 (1H, s, C_6H_2), 5.19–5.01 (3H, m, CHN and CH_2Ph), 4.52–4.50 (1H, m, $CHCH_3$), 3.73 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.35 (1H, m, CH), 2.44 (1H, m, CH), 1.51–0.97 (10H, m, $5 \times CH_2$), 0.87 (3H, d, $J = 6.3$ Hz, $CHCH_3$) ppm. Anal. calcd. for $C_{27}H_{34}N_2O_5$: C, 69.50; H, 7.35; N, 6.00. Found: C, 69.65; H, 7.51; N, 5.92.

General Procedure for the Preparation of 3a–f by Hydrolysis of 2a–f

A mixture of **2** (1 mmol) and 33% HBr in AcOH (5 mL) was heated gently in a flask equipped with a $CaCl_2$ tube, with occasional shaking, until all of the substance had dissolved. The bubbling solution was left to stand at ambient temperature for 30 min, and Et_2O (10 mL) was then added. The crystals of the hydrobromides (**3**) that formed were filtered off and washed with a mixture of MeOH and Et_2O. The dried crude crystalline product was dissolved in 95% aqueous MeOH, and Et_2O was then added until crystallization started.

Selected Data

***N*-Cyclohexyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxamide hydrobromide (3a.HBr).** Yield: 0.34 g (88%), a white crystalline solid, mp 262–265 °C; ^{1}H (D_2O): 7.02 (1H, s, C_6H_2), 6.94 (1H, s, C_6H_2), 5.12 (1H, s, CHN), 3.93 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.83–3.77 (2H, m, CH_2N and CH), 3.52 (1H, ddd, $J_1 = 5.5$ Hz, $J_2 = 8.8$ Hz, $J_3 = 12.6$ Hz, CH_2N), 3.20 (1H, ddd, $J_1 = 5.9$ Hz, $J_2 = 8.8$ Hz, $J_3 = 17.1$ Hz, CH_2CH_2N), 3.08 (1H, dt, $J_1 = 5.4$ Hz, $J_2 = 17.4$ Hz, CH_2CH_2N), 1.95–1.38 (10H, m, $5 \times CH_2$) ppm. Anal. calcd. for $C_{18}H_{27}BrN_2O_3$: C, 54.14; H, 6.82; N, 7.02. Found: C, 54.20; H, 6.89; N, 6.97.

***N*-Benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxamide hydrobromide (3b.HBr).** Yield: 0.39 g (95%), a white crystalline solid, mp

251–254 °C; ^{1}H (D_2O): δ 7.46–7.36 (5H, m, 5 × C*H* aromatic protons), 7.00 (1H, s, C_6H_2), 6.80 (1H, s, C_6H_2), 5.21 (1H, s, C*H*N), 4.69 (1H, d, $J = 14.8$ Hz, CH_2Ph), 4.39 (1H, d, $J = 14.8$ Hz, CH_2Ph), 3.90 (3H, s, OCH_3), 3.78–3.72 (1H, m, CH_2N), 3.64 (3H, s, OCH_3), 3.55–3.49 (1H, m, CH_2N), 3.17–3.05 (2H, m, CH_2CH_2N) ppm. Anal. calcd. for $C_{19}H_{23}BrN_2O_3$: C, 56.03; H, 5.69; N, 6.88. Found: C, 56.12; H, 5.76; N, 6.80.

***N*-(*tert*-Butyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxamide hydrobromide (3c.HBr).** Yield: 0.33 g (88%), a white crystalline solid, mp 251–253 °C; ^{1}H (D_2O): δ 7.03 (1H, s, C_6H_2), 6.96 (1H, s, C_6H_2), 5.07 (1H, s, C*H*N), 3.93 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.80 (1H, dt, $J_1 = 5.7$ Hz, $J_2 = 12.5$ Hz, CH_2N), 3.52–3.48 (1H, m, CH_2N), 3.20 (1H, dt, $J_1 = 7.9$ Hz, $J_2 = 17.5$ Hz, CH_2CH_2N), 3.08 (1H, dt, $J_1 = 4.9$ Hz, $J_2 = 17.6$ Hz, CH_2CH_2N), 1.46 (9H, s, 3 × CH_3) ppm. Anal. calcd. for $C_{16}H_{25}BrN_2O_3$: C, 54.14; H, 6.82; N, 7.02. Found: C, 53.95; H, 6.76; N, 7.13.

***N*-Cyclohexyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide hydrobromide (3d.HBr).** Yield: 0.29 g (86%), a white crystalline solid, mp 148–152 °C; ^{1}H (D_2O): δ 7.51–7.42 (4H, m, C_6H_4), 5.21 (1H, s, C*H*N), 3.84–3.73 (2H, m, CH_2N), 3.59–3.52 (1H, m, C*H*), 3.27 (1H, dt, $J_1 = 7.0$ Hz, $J_2 = 17.7$ Hz, CH_2CH_2N), 3.16 (1H, dt, $J_1 = 5.5$ Hz, $J_2 = 17.7$ Hz, CH_2CH_2N), 1.95–1.23 (10H, m, 5 × CH_2) ppm. Anal. calcd. for $C_{16}H_{23}BrN_2O_3$: C, 56.64; H, 6.83; N, 8.26. Found: C, 56.52; H, 6.76; N, 8.35.

***N*-Cyclohexyl-6,7-diethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxamide hydrobromide (3e.HBr).** Yield: 0.35 g (83%), a white crystalline solid, mp 272–274 °C; ^{1}H (D_2O): δ 7.02 (1H, s, C_6H_2), 6.95 (1H, s, C_6H_2), 5.10 (1H, s, C*H*N), 4.23–4.11 (4H, m, 2 × CH_2CH_3), 3.82–3.75 (2H, m, CH_2N), 3.54–3.48 (1H, m, C*H*), 3.22–3.03 (2H, m, CH_2CH_2N), 1.95–1.22 (10H, m, 5 × CH_2), 1.45 (6H, t, $J = 7.0$ Hz, 2 × CH_2CH_3) ppm. Anal. calcd. for $C_{20}H_{31}BrN_2O_3$: C, 56.21; H, 7.31; N, 6.55. Found: C, 56.12; H, 7.26; N, 6.49.

***N*-Cyclohexyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline-1-carboxamide hydrobromide (3f.HBr).** Yield: 0.32 g (84%), a white crystalline solid, mp 226–230 °C; ^{1}H (D_2O): δ 6.89 (1H, s, C_6H_2), 6.88 (1H, s, C_6H_2), 6.07 (1H, s, OCH_2O), 6.05 (1H, s, OCH_2O), 5.10 (1H, s, C*H*N), 3.76 (2H, m, CH_2N), 3.53–3.46 (1H, m, C*H*), 3.15 (1H, dt, $J_1 = 7.2$ Hz, $J_2 = 17.4$ Hz, CH_2CH_2N), 3.06 (1H, dt, $J_1 = 5.5$ Hz, $J_2 = 17.4$ Hz, CH_2CH_2N), 1.96–1.24 (10H, m, 5 × CH_2) ppm. Anal. calcd. for $C_{17}H_{23}BrN_2O_3$: C, 53.27; H, 6.05; N, 7.31. Found: C, 53.42; H, 6.16; N, 7.19.

General Procedure for the Preparation of 3a–f and 7a,b by Hydrogenolysis of 2a–f and 6a,b

A mixture of **2** (1 mmol), 10% Pd/C (0.3 g), and EtOH (50 ml) was stirred under a H_2 atmosphere at ambient temperature until TLC indicated complete conversion of the starting material (4–6 h). The catalyst was then filtered off, and the solution was evaporated. The residue was purified by column chromatography on silica gel, with EtOAc as eluent.

Selected Data

***N*-Cyclohexyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3a).** Yield: 0.46 g (89%), a white crystalline solid, mp 138–140 °C; ^{1}H ($CDCl_3$): δ 7.11 (1H, s, C_6H_2), 7.07 (1H, d, $J = 7.0$ Hz, N*H*), 6.55 (1H, s, C_6H_2), 4.43 (1H, s, C*H*N), 3.86 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.77–3.68 (1H, m, C*H*), 3.05 (2H, t, $J = 5.8$ Hz, CH_2N), 2.77 (1H, td, $J = 6.0$, 15.8 Hz, CH_2CH_2N), 2.66 (1H, td, $J = 5.5$, 15.8 Hz, CH_2CH_2N), 1.91–1.06 (10H, m, $5 \times CH_2$) ppm. Anal. calcd. for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80. Found: C, 67.76; H, 8.11; N, 8.92.

***N*-Benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3b).** Yield: 0.69 g (75%), a white crystalline solid, mp 159–160 °C (lit.[15] mp 160–162 °C); ^{1}H ($CDCl_3$): δ 7.56 (1H, br s, N*H*), 7.26–7.22 (5H, m, Ph), 7.07 (1H, s, C_6H_2), 6.56 (1H, s, C_6H_2), 4.61 (1H, s, C*H*N), 3.83 (6H, s, $2 \times OCH_3$), 3.08 (2H, m, CH_2), 2.77–2.68 (2H, m, CH_2CH_2N), 20.4 (2H, s, CH_2Ph) ppm. Anal. calcd. for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 70.05; H, 6.87; N, 8.43.

***N*-(*tert*-Butyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3c).** Yield: 0.47 g (62%), a white crystalline solid, mp 139–142 °C; ^{1}H ($CDCl_3$): δ 7.07 (1H, s, C_6H_2), 7.06 (1H, s, N*H*), 6.56 (1H, s, C_6H_2), 4.34 (1H, s, C*H*N), 3.85 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.06 (2H, br s, CH_2N), 2.80–2.62 (2H, m, CH_2CH_2N), 1.32 (9H, s, $3 \times CH_3$) ppm. Anal. calcd. for $C_{16}H_{24}N_2O_3$: C, 65.73; H, 8.27; N, 9.58. Found: C, 65.89; H, 8.42; N, 9.39.

***N*-Cyclohexyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3d).** Yield: 0.38 g (61%), a white crystalline solid, mp 138–139 °C; ^{1}H ($CDCl_3$): δ 7.45–7.08 (4H, m, $4 \times CH$ aromatic protons), 6.99 (1H, d, $J = 6.8$ Hz, N*H*), 4.64 (1H, s, C*H*N), 3.79–3.69 (1H, m, C*H*), 3.16 (1H, m, CH_2N), 3.07 (1H, m, CH_2N), 2.89 (1H, m, CH_2CH_2N), 2.78 (1H, m, CH_2CH_2N), 1.90–1.05 (10H, m, $5 \times CH_2$) ppm. Anal. calcd. for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.51; H, 8.63; N, 10.79.

***N*-Cyclohexyl-6,7-diethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3e).** Yield: 0.32 g (66%), a white crystalline solid, mp 147–148 °C; ^{1}H ($CDCl_3$): δ 7.00 (1H, s C_6H_2), 6.97 (1H, br s, N*H*), 6.57 (1H, s, C_6H_2), 4.52 (1H, s, C*H*N), 4.09–4.03 (4H, m, $2 \times CH_2CH_3$), 3.77–3.70 (1H, m, C*H*), 3.13–3.02 (2H, m, CH_2N), 2.81–2.74 (1H, m, CH_2CH_2N), 2.70–2.64 (1H, m, CH_2CH_2N), 1.89–1.03 (10H, m, $5 \times CH_2$), 1.44–1.40 (6H, m, $2 \times CH_2CH_3$) ppm. Anal. calcd. for $C_{20}H_{30}N_2O_3$: C, 69.33; H, 8.73; N, 8.09. Found: C, 69.57; H, 8.86; N, 7.89.

***N*-Cyclohexyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3f).** Yield: 0.38 g (74%), a white crystalline solid, mp 138–140 °C; ^{1}H ($CDCl_3$): δ 6.99 (1H, s, C_6H_2), 6.53 (1H, s, C_6H_2), 5.90 (1H, s, OCH_2O), 5.89 (1H, s, OCH_2O), 4.59 (1H, s, C*H*N), 3.71–3.69 (1H, m, C*H*), 3.20–3.05 (2H, m, CH_2N), 2.83–2.67 (2H, CH_2CH_2N), 1.88–1.09 ($5 \times CH_2$) ppm. Anal. calcd. for $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.33; N, 9.26. Found: C, 67.41; H, 7.18; N, 9.39.

(1*R,3*R**)-*N*-Cyclohexyl-6,7-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (7a).** Yield: 0.46 g (56%), a white crystalline solid, mp 160–163 °C; ^{1}H ($CDCl_3$): δ 7.09 (1H, s, C_6H_2), 6.94 (1H, d, $J = 7.7$ Hz, N*H*), 6.45

(1H, s, C_6H_2), 4.53 (1H, s, C*H*N), 3.76 (6H, s, $2 \times OCH_3$), 3.68–3.58 (1H, m, C*H*), 3.03–2.95 (1H, m, C*H*CH_3), 2.53–2.40 (2H, m, CH_2N), 1.82–0.97 (10H, m, $5 \times CH_2$),), 1.17 (3H, d, $J = 6.0$ Hz, CHCH_3) ppm. Anal. calcd. for $C_{19}H_{28}N_2O_3$: C, 68.65; H, 8.49; N, 8.43. Found: C, 68.55; H, 8.63; N, 8.39.

(1*S,3*R**)-*N*-Cyclohexyl-6,7-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (7b).** Yield: 0.66 g (68%), a white crystalline solid, mp 161–162.5 °C; ^{1}H ($CDCl_3$): δ 7.04 (1H, d, $J =$ Hz, N*H*), 6.94 (1H, s, C_6H_2), 6.56 (1H, s, C_6H_2), 6.43 (1H, br s, N*H*), 4.53 (1H, s, C*H*N), 3.86 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.78–3.71 (1H, m, C*H*), 3.12–3.06 (1H, m, C*H*CH_3), 2.74 (1H, dd, $J = 4.0$, 16.2 Hz, CH_2N), 2.46 (1H, dd, $J = 10.0$, 16.2 Hz, CH_2N), 1.86–1.09 (10H, m, $5 \times CH_2$), 1.24 (3H, d, $J = 6.4$ Hz, CHCH_3) ppm. Anal. calcd. for $C_{19}H_{28}N_2O_3$: C, 68.65; H, 8.49; N, 8.43. Found: C, 68.81; H, 8.61; N, 8.29.

General Procedure for the Preparation of 4a–c and 8

To the corresponding *N*-Cbz-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (**2a**,**d**, 1 mmol) or 1,2,3,4-tetrahydroisoquinoline-1-carboxamide (**3a**,**d**,**e**, 1 mmol), 10% aqueous HCl (10 mL) was added, and the mixture was refluxed until no more carboxamide could be detected by TLC (20–65 h). The solvent was then evaporated off, and the residue was purified by column chromatography, with MeOH as eluent.

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid hydrochloride (4a). Yield: 169 mg (62%, starting from **2a**), 197 mg (70%, starting from **2c**), 205 mg (75%, starting from **3a**). The physical and analytical data on **4a** correspond to the data in Ref. 4a.

1,2,3,4-Tetrahydroisoquinoline-1-carboxylic acid hydrochloride (4b). Yield: 160 mg (75%, starting from **2d**); yield: 162 mg (76%, starting from **3d**). The physical and analytical data on **4b** correspond to the data in Ref. 4a.

6,7-Diethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (4c). Yield: 108 mg (36%, starting from **3e**); a white crystalline solid, mp 224–225 °C; ^{1}H (D_2O): δ 7.71 (1H, s, C_6H_2), 6.86 (1H, s, C_6H_2), 5.11 (1H, s, C*H*N), 4.09 (4H, q, $J = 6.5$ Hz, $2 \times OCH_2CH_3$), 3.57–3.46 (2H, m, CH_2N), 2.97 (2H, br s, CH_2CH_2N), 1.34 (6H, t, $J = 6.5$ Hz $2 \times OCH_2CH_3$) ppm. Anal. calcd. for $C_{14}H_{20}ClNO_4$: C, 54.26; H, 6.31; Cl, 12.32, N, 4.87. Found: C, 54.09; H, 6.45; N, 4.71.

6,7-Dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid, a 1:1 mixture of *cis* and *trans* isomers (8). Yield: 92 mg (32% starting from **7a**), 86 mg (30% starting from **7b**); a yellowish-white crystalline solid; ^{1}H (D_2O): δ 6.95 (1H, s, C_6H_2), 6.87 (1H, s, C_6H_2), 6.61 (1H, s, C_6H_2), 6.59 (1H, s, C_6H_2), 4.62 (1H, s, C*H*N), 4.61 (1H, s, C*H*N), 3.61 (6H, s, $2 \times OCH_3$), 3.64–3.52 (1H, m, C*H*), 3.34–3.30 (1H, m, C*H*), 2.78–2.50 (2H, m, CH_2), 1.25 (3H, d, $J = 6.4$ Hz, CHCH_3), 1.21 (3H, d, $J = 6.5$ Hz, CHCH_3) ppm. Anal. calcd. for $C_{13}H_{18}ClNO_4$: C, 54.26; H, 6.31; Cl, 12.32, N, 4.87. Found: C, 54.09; H, 6.45; N, 4.71.

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