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AN EFFICIENT SYNTHESIS OF (±)-6,7-DIMETHOXY-1-OXO-2-(3-PIPERIDYL)-1,2,3,4-TETRAHYDROISOQUINOLINE

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AN EFFICIENT SYNTHESIS OF (\pm) -6,7-DIMETHOXY-1-OXO-2-(3-PIPERIDYL)-1,2,3,4-TETRAHYDROISOQUINOLINE

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ABSTRACT

The synthesis of (\pm) -6,7-dimethoxy-1-oxo-2-(3-piperidyl)-1,2,3,4-tetrahydroisoquinoline (1) via the cyclization of dimethylacetal (3) under acidic condition is described.

As part of our research program, the practical preparation of 6,7-dimethoxy-1-oxo-2-(3-piperidyl)-1,2,3,4-tetrahydroisoquinoline **1** (Fig. 1) was required. In previous reports, 6,7-dimethoxy-1-oxo-1,2,3,4-tetrahydroisoquinolines have been prepared by the Bischler–Napieralski reaction involving the ring-closure of isocyanate with phosphorus oxychloride (POCl₃) (1), as well as cyclization of carbamate with polyphosphoric acid (PPA) (2). However, there are few reports

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Figure 1.

on the synthesis of 2-substituted derivatives (3) and to our knowledge, for the derivatives bearing directly cyclic amine at 2-position such as **1** have never been reported. Hence, we investigated ring-closing processes of the compounds having piperidine moiety. In this communication, we describe an efficient synthesis of compound **1** via the cyclization of dimethylacetal **3**.

Initially, we tried the synthesis of compound **1** from phenethylcarbamate **2** by the Bischler–Napieralski reaction (Fig. 1, Route A). Phenethylcarbamate **2** was prepared in two steps from 1-benzyl-3-piperidone hydrate **4** available from Aldrich (Scheme 1). Compound **4** was condensed with phenethylamine **5** by reductive



Conditions; (a) 3,4-dimethoxyphenethylamine (5), NaBH(OAc)_3, AcOH, THF; (b) ClCO_2Me, Et_3N, THF

Scheme 1.





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alkylation in the presence of sodium triacetoxyborohydride (NaBH(OAc)₃ (4) to obtain amine **6**. Subsequently, amine **6** was converted to the carbamate **2** by using methyl chloroformate. The Bischler–Napieralski reaction with the carbamate **2** was attempted under the same conditions (Scheme 1). However, the cyclized compound **7** was only obtained by using trifluoromethanesulfonic anhydride (Tf₂O) and 4-dimethylaminopyridine (DMAP) in CH₂Cl₂ (5) in low to moderate yields. Moreover, this reaction needed both a long reaction time (3 days) and column purification to obtain pure **7** due to the formation of by-product **8**.

In the search for a more efficient method to prepare 1, we then examined the cyclization of dimethylacetal 3 under acidic conditions (Fig. 1, Route B) (6). Compound 4 was condensed with aminoacetaldehyde dimethylacetal 9 by reductive alkylation followed by benzoylation to afford acetal 3 in 92% yield (Scheme 2). The acetal 3 was successfully cyclized to 1,2-dihydro-1-oxo-isoquinoline 11 when concentrated hydrogen chloride (conc. HCl) and acetic acid (AcOH) were employed, although 11 was obtained in moderate yield (47%) as a hydrochloride salt (Table 1, entry 1). We then attempted to improve the yield of **11** by using other acids. When trifluoroacetic acid (TFA) or methanesulfonic acid (MsOH) was used, the yield of 11 was improved (73% entry 2, 74% entry 3, respectively). Furthermore, the reaction with concentrated sulfuric acid (conc. H₂SO₄) gave 11 in better yield (78% entry 4). Studies of the amount of conc. H_2SO_4 and the reaction temperature were performed (entries 5–10). As a result, the condition using 0.2 times (mL/mmol) of conc. H₂SO₄ at 80°C was optimum (entries 8 and 10), because it allowed the reaction to be completed within an hour and the sulfate of 11 to be crystallized from the resulting reaction mixture. This condition abridged the work-up procedures of the reaction and furnished 11 in excellent reproducibility. Some kilograms of 11 were also synthesized using this condition with minimal modifications.



Conditions; (a) aminoacetaldehyde dimethylacetal (9), NaBH(OAc)₃, AcOH, THF; (b) 3,4-dimethoxybenzoylchloride, CH₃CN; (c) H₂(3-4kg/cm²), 20%Pd(OH)₂/C, AcOH, 90°C

Scheme 2.

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Entry	Scale (mmol)	Condition	Time (h)	Isolated Yield of 11 (%)
1	5.0	conc. HCl 5 mL, AcOH 5 mL, 60°C	4	47^a
2	5.0	TFA 10 mL, 50°C	24	73^{b}
3	5.0	MsOH 2 Eq, AcOH 5 mL, 60°C	20	74^{b}
4	5.0	conc. H_2SO_4 5 mL, AcOH 5 mL, 60°C	8	78^b
5	5.0	conc. H ₂ SO ₄ 5 mL, AcOH 5 mL, 80°C	3	82^{b}
6	5.0	conc. H ₂ SO ₄ 5 mL, AcOH 5 mL, 100°C	1	65^{b}
7	5.0	conc. H ₂ SO ₄ 2.5 mL, AcOH 5 mL, 80°C	2	83 ^b
8	5.0	conc. H ₂ SO ₄ 1 mL, AcOH 5 mL, 80°C	1	85^{c}
9	5.0	conc. H ₂ SO ₄ 0.5 mL, AcOH 5 mL, 80°C	2	d
10	189	conc. H ₂ SO ₄ 37.8 mL, AcOH 189 mL, $80^{\circ}C$	1	82^c

Table 1. Cyclization of 3 Under Acidic Conditions

^aAfter column purification, the hydrochloride was obtained.

^bThe hydrochloride was obtained without column purification.

^cThe sulfate was obtained from the resulting reaction mixture, then was converted to the hydrochloride.

^d The reaction was complicated.

Finally, the resulting **11** was hydrogenated over palladium hydroxide in AcOH to give 1-oxo-1,2,3,4-tetrahydroisoquinoline **1** in 82% yield. In conclusion, we demonstrated an efficient synthesis of (\pm) -6,7-dimethoxy-1-oxo-2-(3-piperidyl)-1,2,3,4-tetrahydroisoquinoline. This method can offer a useful pathway for the synthesis of various 2-substituted-6,7-dimethoxy-1-oxo-1,2,3, 4-tetrahydroisoquinolines.

EXPERIMENTAL

Melting points were measured with a Yanaco MP-500D melting point apparatus without correction. ¹H NMR spectra were obtained on a JEOL JNM-LA300 or a JEOL JNM-EX400 spectometer and the chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard. Mass spectra were obtained on a JEOL JMS-LX2000 mass spectrometer. The elemental analyses were performed with a Yanaco MT-5 microanalyzer (C, H, N) and a Yokogawa IC-7000S ion chromatographic analyzer.

Methyl (\pm)-*N*-(1-Benzyl-3-piperidyl)-*N*'-(3,4-dimethoxyphenethyl) Carbamate (2). To a suspension of 1-benzyl-3-piperidone monohydrochloride monohydrate 4 (10.0 g, 44.3 mmol) and 3,4-dimethoxyphenethylamine 5 (8.03 g, 44.3 mmol) in tetrahydrofuran (THF, 100 mL) were added AcOH (2.54 mL, 44.3 mmol) and NaBH(OAc)₃ (10.3 g, 48.7 mmol), and the mixture was stirred at room temperature for 1 h. The reaction mixture was made alkaline with 5 *N*

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NaOHaq. at 0° C, then extracted with CHCl₃ (50 mL \times 2). The combined extract was dried over anhydrous Na₂SO₄ and concentrated in vacuo to give 1-benzyl-3-[(3,4-dimethoxyphenethyl)amino]piperidine **6** (14.2 g, 90%) as a yellow oil. To a solution of 6 (14.2 g, 40.1 mmol) and Et₃N (6.70 mol, 48.1 mmol) in THF (100 mL) was added dropwise a solution of methyl chloroformate (3.40 mL, 44.1 mmol) in THF (10 mL) at 0°C, and the mixture was stirred at 0°C for 1 h. The resulting mixture was concentrated in vacuo and the residue was dissolved in H_2O (150 mL), then extracted with AcOEt (50 mL \times 2). The combined extract was washed with 1 N NaOHaq. (100 mL), dried over anhydrous Na_2SO_4 , and concentrated in vacuo to give 2 (16.2 g, 98%) as a yellow oil. This material may be used in the next cyclization step or converted to its oxalate salt. The oxalate salt was obtained from MeOH-AcOEt as a colorless powder: m.p. 145-146°C; ¹H NMR (400 MHz, DMSO-d₆) δ 1.68–1.78 (4H, m, 4-H₂ and 5-H₂ of piperidine), 2.41 (2H, br s, 1-H₂ or 6-H₂ of piperidine), 2.66 (2H, br s, 3,4-(OMe)₂PhCH₂), 2.95-2.97 (2H, m, 1-H₂ or 6-H₂ of piperidine), 3.27–3.29 (2H, m, MeO₂ CNCH₂), 3.60 (3H, s, OMe), 3.72 (3H, s, OMe), 3.74 (3H, s, OMe), 3.95 (3H, br s, CH₂Ph and 3-H of piperidine), 6.70 (1H, d, J = 7.2 Hz, 5- or 6-H of 3,4-(OMe)₂Ph), 6.78 (1H, s, 2-H of 3,4-(MeO)₂Ph), 6.86 (1H, d, J = 7.2 Hz, 5- or 6-H of 3,4-(MeO)₂Ph), 7.40 (5H, brs, CH₂Ph); MS (FAB) m/z 413 (MH⁺); Anal. calcd. for C₂₄H₃₂N₂O₄ · C₂H₂O₄: C 62.14, H 6.82, N 5.57. Found: C 62.01, H 6.81, N 5.47.

(\pm)-2-(1-Benzyl-3-piperidyl)-6,7-dimethoxy-1-oxo-1,2,3,4-tetrahydroisoquinoline (7) and (\pm)-6,7-dimethoxy-1-oxo-2-[1-(trifluoromethanesulfonyl)-3-piperidyl]-1,2,3,4-tetrahydroisoquinoline (8). To a solution of 2 (6.31 g, 15.3 mmol) and DMAP (4.67 g, 38.2 mmol) in CH₂Cl₂ (120 mL) was added dropwise a solution of Tf₂O (10.3 mL, 61.2 mmol) in CH₂Cl₂ (10 mL) at 0°C, and the mixture was stirred at room temperature for 3 days. The reaction mixture was partitioned between CHCl₃ (50 mL × 2) and H₂O (150 mL) and the combined CHCl₃ layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo to give a mixture of 7 and 8. The mixture can be separated by column chromatography on silica gel (CHCl₃/MeOH = 49/1 for 7, 99/1 for 8) to give 7 (3.11 g, 53%) as a yellow oil and 8 as a yellow form.

Compound 7 may be converted to its hydrochloride salt. The hydrochloride salt of 7 was obtained from EtOH–AcOEt as a colorless powder: m.p. $232-238^{\circ}$ C; ¹H NMR (400 MHz, DMSO-d₆) δ 1.74–1.93 (4H, m, 4-H₂ and 5-H₂ of piperidine), 2.87 (2H, br s, 4-H₂ of isoquinoline), 2.88 (1H, br s, 1-H or 6-H of piperidine), 3.19–3.24 (2H, m, 1-H and 6-H of piperidine), 3.31 (1H, br s, 1-H or 6-H of piperidine), 3.44 (2H, br s, 3-H₂ of isoquinoline), 3.75 (3H, s, OMe), 3.81 (3H, s, OMe), 4.32 (2H, t, J = 4.8 Hz, CH₂Ph), 4.85–4.87 (1H, m, 3-H of piperidine), 6.89 (1H, s, 5-H of isoquinoline), 7.34 (1H, s, 8-H of isoquinoline), 7.46–7.48 (3H, m, CH₂Ph), 7.59–7.61 (2H, m, CH₂Ph), 10.64 (1H, brs, HCl); MS (FAB) *m/z* 381 (MH⁺); Anal. calcd. for C₂₃H₂₈N₂O₃ · HCl · 0.3H₂O: C 65.41, H 7.06, N 6.63, Cl 8.39. Found: C 65.38, H 7.12, N 6.65, Cl 8.17.

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Compound **8**: ¹H NMR (300 MHz, CDCl₃) δ 1.79–1.96 (4H, m, 4-H₂ and 5-H₂ of piperidine), 2.89–2.93 (2H, m, 4-H₂ of isoquinoline), 2.98–3.02 (1H, m, 1-H or 6-H of piperidine), 3.25–3.33 (1H, m, 1-H or 6-H of piperidine), 3.38–3.57 (2H, m, 3-H₂ of isoquinoline), 3.92 (6H, s, (OMe)₂), 3.94–4.01 (2H, m, 1-H and 6-H of piperidine), 4.47 (1H, br s, 3-H of piperidine), 6.63 (1H, s, 5-H of isoquinoline), 7.58 (1H, s, 8-H of isoquinoline); MS (FAB) *m/z* 423 (MH⁺).

 (\pm) -N-(1-Benzyl-3-piperidyl)-N-(2,2-dimethoxyethyl)-3,4-dimethoxy**benzamide** (3). To a suspension of 1-benzyl-3-piperidonemonohydrochloride monohydrate 4 (46.4 g, 205 mmol) in THF (380 mL) were added aminoacetaldehyde dimethylacetal (21.6 g, 205 mmol), AcOH (11.8 mL, 205 mmol), and NaBH(OAc)₃ (47.9 g, 226 mmol), and the mixture was stirred at room temperature for 2 h. The reaction mixture was made alkaline with 5 N NaOHaq. at 0°C, then extracted with AcOEt (200 mL \times 2). The combined extract was washed with saturated NaClaq. (200 mL), dried over anhydrous Na₂SO₄, and concentrated in vacuo to give 1-benzyl-3-[(2,2-dimethoxyethyl)amino]piperidine 10 (52.7 g, 92%) as a yellow oil. To a solution of 10 (52.7 g, 189 mmol) in CH₃CN (400 mL) was added dropwise a solution of 3,4-dimethoxybenzoylchloride (39.9 g, 199 mmol) in CH₃CN (100 mL) at 0° C, and the mixture was stirred at room temperature for 0.5 h. The reaction mixture was made alkaline with 5 N NaOHaq. at 0° C, then extracted with AcOEt (250 mL \times 2). The combined extract was washed with 0.5 N NaOHaq. (200 mL \times 2), saturated NaClaq. (200 mL), and dried over anhydrous Na₂SO₄, then concentrated in vacuo to give **3** (97.4 g, 99%) as a brown oil. This material may be used in the next cyclization step: ¹H NMR (300 MHz, CDCl₃) δ 1.51–1.89 (4H, m, 4-H₂ and 5-H₂ of piperidine), 2.10 (2H, br s, 1-H and 6-H of piperidine), 2.74-2.84 (2H, m, 1-H and 6-H of piperidine), 3.34-3.68 (10H, m, (OMe)₂ and CONCH₂ and CH₂Ph), 3.80 (3H, s, OMe), 3.91 (1H, brs, CH(OMe)₂), 3.92 (3H, s, OMe), 4.65 (1H, br s, 3-H of piperidine), 6.81-6.88 (3H, m, 3,4-(MeO)₂Ph), 7.24–7.33 (5H, m, CH₂Ph); MS (FAB) *m/z* 443 (MH⁺); HRMS calcd. for C₂₅H₃₄N₂O₅:443.2521. Found: 443.2545.

(\pm)-2-(1-Benzyl-3-piperidyl)-6,7-dimethoxy-1-oxo-1,2-dihydroisoquinoline (11). To a solution of 3 (97.4 g, 196 mmol) in AcOH (196 mL) was added conc. H₂SO₄ (39.2 mL), and the mixture was stirred at 80°C for 1 h. The mixture was cooled to room temperature to allow crystallization from the resulting solution. To the mixture was added acetone (300 mL) and the mixture was further stirred at 4°C for 4 h, then the resulting crystals were collected and washed with acetone to give the sulfate salt of 11 as a slightly brown powder. The sulfate salt of 11 was dissolved in H₂O (200 mL) and made alkaline with 5 N NaOHaq. at 0°C, then extracted with CHCl₃ (200 mL × 2). The combined extract was dried over anhydrous Na₂SO₄ and concentrated in vacuo to give 11 as a brown foam.

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Compound **11** was converted to its hydrochloride salt. The hydrochloride salt of **11** was obtained from EtOH–AcOEt as a slightly brown powder (64.5 g, 82%): m.p. 256–259°C; ¹H NMR (400 MHz, DMSO-d₆) δ 1.86–1.88 (4H, m, 4-H₂ and 5-H₂ of piperidine), 2.03–2.08 (3H, m, 1-H and 6-H of piperidine), 2.97 (1H, br s, 1-H or 6-H of piperidine), 3.85 (3H, s, OMe), 3.88 (3H, s, OMe), 4.30–4.39 (2H, m, CH₂Ph), 5.30 (1H, brs, 3-H of piperidine), 6.63 (1H, d, *J* = 7.2 Hz, 3-H of isoquinoline), 7.16 (1H, s, 5-H of isoquinoline), 7.37 (1H, d, *J* = 7.2 Hz, 4-H of isoquinoline), 7.45–7.46 (3H, m, CH₂Ph), 7.61 (1H, s, 8-H of isoquinoline), 7.76–7.78 (2H, m, CH₂Ph), 11.07 (1H, brs, HCl); MS (FAB) *m/z* 379 (MH⁺); Anal. calcd. for C₂₃H₂₆N₂O₃ · HCl: C 66.58, H 6.56, N 6.75, Cl 8.54. Found: C 66.70, H 6.58, N 6.70, Cl 8.48.

 (\pm) -6,7-Dimethoxy-1-oxo-2-(3-piperidyl)-1,2,3,4-tetrahydroisoquino**line (1).** To a solution of the hydrochloride salt of **11** (21.2 g, 51.0 mmol) in AcOH (106 mL) was added palladium hydroxide on carbon (20 wt% 10.6 g), and the mixture was stirred under hydrogen pressure $(3-4 \text{ kg/cm}^2)$ at 90°C for 2 days. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The residue was dissolved in H₂O (100 mL) and made alkaline with 5 N NaOHaq. at 0°C, then extracted with CHCl₃ (100 mL \times 2). The combined extract was dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residual solid was recrystallized from AcOEt to give 1(12.4 g, 84%) as a colorless powder: m.p. $139-140^{\circ}$ C; ¹H NMR (400 MHz, CDCl₃) δ 1.58–1.73 (2H, m, 4-H₂ of piperidine), 1.80–1.90 (2H, m, 5-H₂ of piperidine), 2.46–2.53 (1H, m, 1-H or 6-H of piperidine), 2.66–2.72 (1H, m, 1-H or 6-H of piperidine), 2.84–2.87 (2H, m, 4-H₂ of isoquinoline), 3.02-3.09 (2H, m, 1-H and 6-H of piperidine), 3.41-3.53 (2H, m, 3-H₂ of isoquinoline), 3.73 (3H, s, OMe), 3.74 (3H, s, OMe), 4.59-4.66 (1H, m, 3-H of piperidine), 6.63 (1H, s, 5-H of isoquinoline), 7.60 (1H, s, 8-H of isoquinoline); MS (FAB) m/z 291 (MH⁺); Anal. calcd. for C₁₆H₂₂N₂O₃: C 66.18, H 7.64, N 9.65. Found: C 65.98, H 7.62, N 9.61.

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