A Practical Synthesis of 1-Oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid Esters

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A practical synthetic method for methyl 1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate was developed by means of triphosgene. Several analogues were prepared by this new method.

Keywords triphosgene, methyl 1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate, $AlCl_3$

Introduction

1-Oxo-1,2,3,4-tetrahydroisoquinoline is a basic structure of some compounds with central nervous system activity[1] or with α_2-adrenoceptor inhibiting activity.[2] Such a compound has been synthesized mostly by Bischler-Napieralski reaction. The procedures involved some drastic reaction conditions and some moisture sensitive catalysts such as $SnCl_4$, Tf_2O were often used.[2,3] In our work, we designed to synthesize some substituted methyl 1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylates. Although methyl 1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate was ever manufactured by means of phosgene,[4] this method has been little applied due to its low yield and the toxicity of phosgene. In our attempt to synthesize methyl 1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate by Bischler-Napieralski reaction following literature's method,[2] no product was detected by TLC.

Bis(trichloromethyl) carbonate (triphosgene, BTC) is a safe alternative of dangerous phosgene, and it has been widely used in organic synthesis in recent years.[5] BTC reacts with primary amine to yield isocyanate.[3c] When we treated the isocyanate derived from phenylalanine with $AlCl_3$ in CH_2Cl_2, *D*(−)-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl ester (**2a**) was afforded with a good yield. Furthermore, all reactions could be carried out in one-pot, thus avoiding the appearance of sticky reaction mixture when CS_2 was used as the solvent.[4] This will make it suitable for large-scale preparation.

Several substituted methyl 1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylates (**2b**— **2d**) and methyl (*R*)-1-oxo-β-carboline-3-carboxylate (**3**) have been synthesized by our improved method (Scheme 1). But for the reason of the inactivation of nitro group, the corresponding isocyanate derived from *p*-nitrophenylalanine (R = NO_2) did not react with $AlCl_3$. 7-Methoxy-substituted derivative (R = OCH_3) was obtained in low yield, which might be due to the demethylation by $AlCl_3$ in CH_2Cl_2. This might also explain why 7-benzyloxy-substituted derivative (R = OCH_2Ph) can not be produced from *p*-benzyloxyphenylalanine.

Secondary amine reacts with BTC to give *N*-chloroformyl derivatives.[5a] However, the reaction of *N*-chloroformyl derivatives attaching to an aromatic compound was rarely reported before. So *N*-benzyl-phenylalanine was also tried in our new method, and *N*-benzyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl ester (**4**) was synthesized successfully in a moderate yield (Scheme 1).

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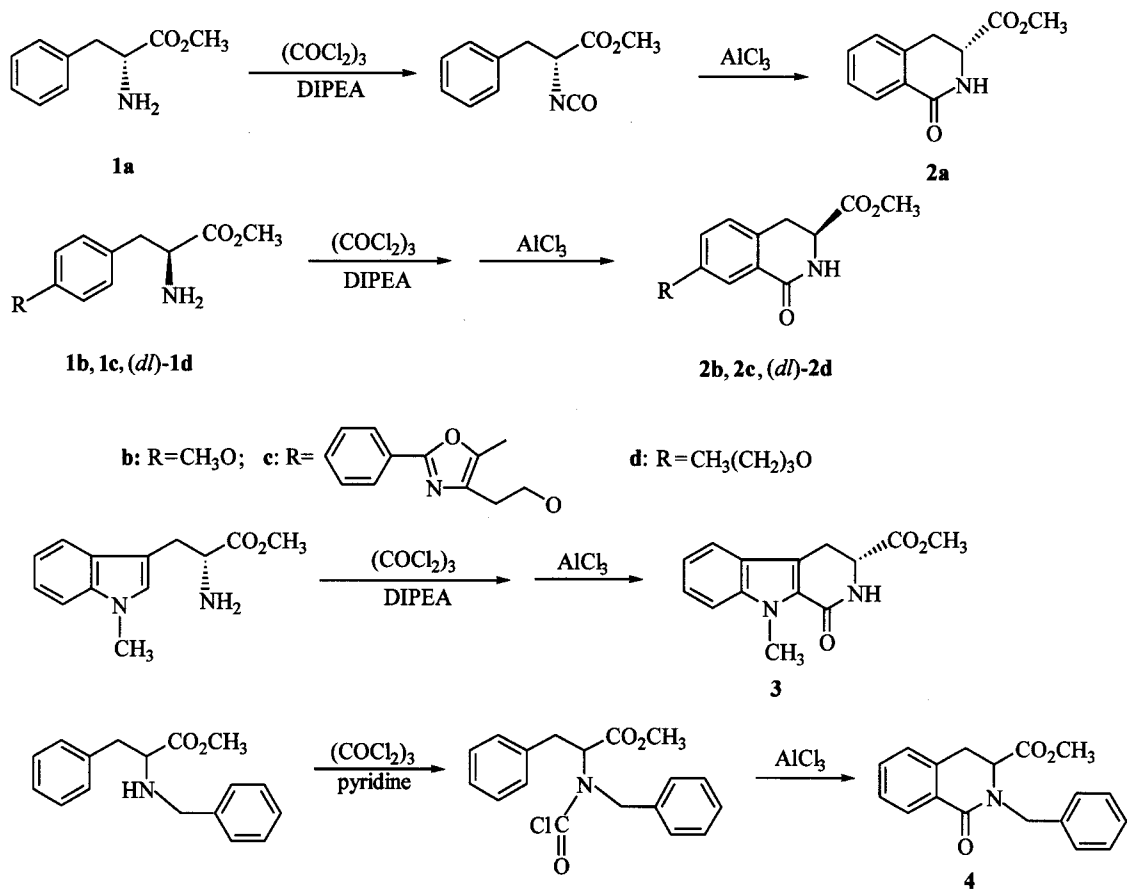
Scheme 1



Experimental

^{1}H NMR spectra were recorded on a Varian Mercury 400 NMR instrument. Mass spectra were determined with a Finnigan MAT-95 spectrometer. Elemental analyses were carried out on a Vario EL element analyzer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. Infrared spectra were recorded on a Nicolet Magna FT-IR-750 spectrometer. All melting points were uncorrected. CH_2Cl_2 was dried over CaH_2 and distilled out before used.

General procedure for the preparation of compounds **2a** — **2d** and **3**

Triphosgene (210 mg, 0.7 mmol) was dissolved in CH_2Cl_2 (4 mL). A mixture of 2 mmol of the starting material and 1.04 mL of diisopropylethylamine in CH_2Cl_2 (6 mL) was added slowly to the stirred solution of triphosgene over a period of 30 min using a syringe pump.[5c] After stirring for another 30 min at room temperature, $AlCl_3$ (0.6 g) was added to the solution at 0 ℃. The mixture was refluxed for 1 h, then cooled to 0 ℃ and treated with 5 mL of water; the addition of water was drop-wise first, more rapid later. After stirring for 30 min, the CH_2Cl_2 layer was separated, and dried over $MgSO_4$. CH_2Cl_2 was distilled off and the residue was purified by column chromatography on silica gel to give **2a** —**2d** and **3**.

Methyl (3*R*)-1-*oxo*-1,2,3,4-*tetrahydroisoquinoline*-3-*carboxylate* (**2a**) Yield, 73.1%, m.p. 88—90 ℃, $[\alpha]_D^{25}$ - 99.4 (*c* 0.90, CH_3OH), Lit.[3] $[\alpha]_D^{27}$ - 83 (*c* 2, CH_3OH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 3.15 (dd, J = 16.1 Hz, 3.3 Hz, 1H), 3.38 (dd, J = 16.1 Hz, 7.0 Hz, 1H), 3.59 (s, 3H), 4.16—4.21 (m, 1H), 7.29 (d, J = 7.7 Hz, 1H), 7.35 (t, J = 7.7 Hz, 1H), 7.47 (t, J = 7.4 Hz, 1H), 7.83 (d, J = 7.7 Hz, 1H), 8.18 (br, 1H, D_2O exchangeable); MS (70 eV) *m/z* (%): 205 (M^+, 22). Anal. calcd

for $C_{11}H_{11}NO_3$: C 64.39, H 5.36, N 6.83; found C 64.39, H 5.19, N 6.82.

Methyl (3S)-7-methoxy-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**2b**) Yield, 36.2%, m.p. 85—87 ℃, $[\alpha]_D^{25}$ +49.5 (*c* 0.49, CH_3OH); ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.16 (dd, J = 15.4 Hz, 9.9 Hz, 1H), 3.25 (dd, J = 5.7, 5.1 Hz, 1H), 3.78 (s, 3H), 3.81 (s, 3H), 4.34—4.40 (m, 1H), 6.61 (br, 1H), 7.00 (dd, J = 8.4, 2.6 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 3.0 Hz, 1H); MS (70 eV) *m/z* (%): 235 (M^+, 18). Anal. calcd for $C_{12}H_{13}NO_4$: C 61.27, H 5.53, N 5.96; found C 61.41, H 5.70, N 6.15.

Methyl 7-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**2c**) Yield, 65.9%, m.p. 88—90 ℃, $[\alpha]_D^{25}$ + 20.6 (*c* 0.48, CH_3OH); ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.39 (s, 3H), 2.98 (t, J = 6.6 Hz, 2H), 3.11 (dd, J = 15.4, 9.9 Hz, 1H), 3.23 (dd, J = 15.7, 5.1 Hz, 1H), 3.78 (s, 3H), 4.30 (t, J = 6.6 Hz, 2H), 4.33—4.40 (m, 1H), 6.40 (br, 1H), 7.00 (dd, J = 8.4, 2.5 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 7.37—7.43 (m, 3H), 7.59 (d, J = 2.9 Hz, 1H), 7.94—8.00 (m, 2H); MS (70 eV) *m/z* (%): 406 (M^+, 56). Anal. calcd for $C_{23}H_{22}N_2O_5$: C 67.98, H 5.42, N 6.89; found C 68.11, H 5.46, N 6.72.

Methyl 7-butoxy-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate [(*dl*)-**2d**] Yield, 85.0%, m.p. 90—91 ℃; ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.98 (t, J = 7.3 Hz, 3H), 1.42 ~ 1.50 (m, 2H), 1.70—1.80 (m, 2H), 3.11 (dd, J = 15.5, 10.1 Hz, 1H), 3.25 (dd, J = 15.4, 5.1 Hz, 1H), 3.78 (s, 3H), 3.99 (t, J = 6.6 Hz, 2H), 4.33—4.40 (m, 1H), 6.42 (br, 1H), 6.99 (dd, J = 8.2, 2.7 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 2.7 Hz, 1H); MS (70 eV) *m/z* (%): 277 (M^+, 22); Anal. calcd for $C_{15}H_{19}NO_4$: C 64.98, H 6.86, N 5.05; found C 65.06, H 7.32, N 5.06 (HRMS calcd for $C_{15}H_{19}NO_4$ 277.1314, found 277.1327).

Methyl (3R)-9-methyl-1-oxo-β-carboline-3-carboxylate (**3**) Yield, 82.1%, m.p. 136—138 ℃, $[\alpha]_D^{25}$ −23.5 (*c* 1.22, CH_3OH); ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.25 (dd, J = 16.1, 9.9 Hz, 1H), 3.45 (dd, J = 15.8, 5.9 Hz, 1H), 3.80 (s, 3H), 4.12 (s, 3H), 4.48—4.54 (m, 1H), 6.04 (br, 1H), 7.13—7.18 (m, 1H), 7.35—7.39 (m, 2H), 7.60 (d, J = 8.0 Hz, 1H); MS (70 eV) *m/z* (%): 258 (M^+, 51). Anal. calcd for $C_{14}H_{14}N_2O_3$: C 65.12, H 5.43, N 10.85; found C 64.80, H 5.75, N 10.59.

Procedure for the preparation of compound **4**

Triphosgene (102 mg, 0.34 mmol) was dissolved in CH_2Cl_2 (2 mL). A mixture of 0.269 g of *N*-benzylphenylalanine methyl ester (2 mmol) and 80 μL of dry pyridine in CH_2Cl_2 (3 mL) was added slowly to the stirring solution of triphosgene. The resultant solution was stirred for 48 h at room temperature and $AlCl_3$ (0.4 g) was added at 0 ℃. Stirring was continued for 4 h at room temperature, and the left procedure was similar to that for compound **2**.

Methyl 2-benzyl-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**4**) Yield, 47.4%, m.p. 112—114 ℃; ^1H NMR ($CDCl_3$, 300 MHz) δ: 3.10 (dd, J = 16.2, 2.2 Hz, 1H), 3.30 (dd, J = 16.0, 6.3 Hz, 1H), 3.59 (s, 3H), 3.99 (AB system, d, J = 15.1 Hz, 1H), 4.20 (dd, J = 6.6, 2.2 Hz, 1H), 5.70 (AB system, d, J = 15.1 Hz, 1H), 7.12 (d, J = 7.4 Hz, 1H), 7.25—7.45 (m, 7H), 8.13 (dd, J = 7.7, 1.6 Hz, 1H); MS (70 eV) *m/z* (%): 295 (M^+, 27). Anal. calcd for $C_{18}H_{17}NO_3$: C 73.22, H 5.76, N 4.74; found C 73.36, H 5.84, N 4.78.

References

1 Maeda, H.; Suzuki, M.; Sugano, H.; Yamamura, M.; Ishida, R. *Chem. Pharm. Bull.* **1988**, *36*, 190.

2 Gary, L. G.; Timothy, M. C.; Qifang, L.; Vilas, H. D.; Brynn, M.; Kevin, R. C. *J. Med. Chem.* **1999**, *42*, 4351.

3 (a) Tsuda, Y.; Isobe, K.; Taga, J. *Heterocycles* **1976**, *5*, 157.
(b) James, M.; Justin, M.; Romelo, G.; Ruowei, M.; Sonja, W.; George, R. P.; Delbert, L. H.; Michael, R. B. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 169.

4 Cohen, S. G.; Schultz, R. M. *J. Biol. Chem.* **1968**, *243*, 2607.

5 (a) Cotarca, L.; Delogu, P.; Nadell, A.; Šunjiç, V. *Synthesis* **1996**, 553.
(b) Cortez, R.; Rivero, I. A.; Somanathem, R.; Aguirre, G.; Ramirez, F. *Synth. Commun.* **1991**, *21*, 285.
(c) Majer, P.; Randad, R. S. *J. Org. Chem.* **1994**, *59*, 1937.

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