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ARTICLE

Concise and efficient syntheses of methyl 4-(1-methylpyrrolidin-2-yl)-3-oxobutanoate and hygrine

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Abstract: Methyl 4-(1-methylpyrrolidin-2-yl)-3-oxobutanoate and hygrine are important biosynthetic intermediates for tropane alkaloids. We have developed a concise method to synthesize these two compounds from the key intermediate *N*-methylpyrrolinium cation. Methyl 4-(1-methylpyrrolidin-2-yl)-3-oxobutanoate and hygrine were obtained in four and six steps from commercially available 4,4-diethoxybutylamine with overall yields of 42% and 25%, respectively.

Key words: methyl 4-(1-methylpyrrolidin-2-yl)-3-oxobutanoate, hygrine, biosynthetic intermediate, tropane alkaloid, *N*-methylpyrrolinium cation.

Résumé : Le 4-(1-méthylpyrrolidin-2-yl)-3-oxobutanoate de méthyle et l'hygrine sont des intermédiaires biosynthétiques importants pour la synthèse des alcaloïdes tropaniques. Nous avons mis au point une méthode pour synthétiser ces deux composés tk;4à partir du cation *N*-méthylpyrrolinium comme intermédiaire clé. Nous avons obtenu le 4-(1-méthylpyrrolidin-2-yl)-3-oxobutanoate de méthyle et l'hygrine en quatre et six étapes, respectivement, à partir de la 4,4-diéthoxybutylamine, qui est commercialement disponible, avec des rendements respectifs de 42 % et de 25 %. [Traduit par la Rédaction]

Mots-clés : 4-(1-méthylpyrrolidin-2-yl)-3-oxobutanoate de méthyle, hygrine, intermédiaire biosynthétique, alcaloïde tropanique, cation *N*-méthylpyrrolinium.

Introduction

Tropane alkaloids, a family of important natural products found in plants throughout the world, have attracted growing attention because of their significant biological and pharmacological activity.[1–5] These alkaloids contain complex core architectures, and their synthesis via traditional organic methods has been very challenging.[5,6] Accordingly, the biosynthesis of tropane alkaloids has been of great interest for several decades[2,7–10], and the representative members of this family include cocaine, cinnamoylcocaine, atropine, and scopolamine, which could be synthesized from methyl 4-(1-methylpyrrolidin-2-yl)-3-oxobutanoate (**1**) or hygrine (**2**) in the biosynthesis (Fig. 1).[7,10–12]

1 is one of the key intermediates in cocaine and cinnamoylcocaine biosynthesis. To the best of our knowledge, there are only two reports on the synthesis of this compound hitherto, including the racemic synthesis reported by Leete et al. in 1991[13] and the asymmetric synthesis by Li and co-workers in 2019;[14] both of these had rather lengthy synthetic routes. Additionally, the lack of commercial availability of compound **1** makes the synthesis of this intermediate necessary. **2**, the prototype of pyrrolidine alkaloids, has served as a precursor for the tropane skeleton.[15] Despite the fact that many strategies for preparing **2** have been described,[16–29] the design and development of a novel method to access this compound has always been in high demand due to its potential utility in biosynthesis of tropane alkaloids. We now present a concise and efficient synthesis that provides **1** in good yield from the key *N*-methylpyrrolinium cation, and **2** could also be prepared from the same intermediate after another two steps. These two compounds were respectively used as reference standards for the intermediate and by-product in our biosynthesis of tropane alkaloids.[11]

Experimental

General

All moisture- or oxygen-sensitive reactions were carried out under an argon or nitrogen atmosphere in oven- or heat-dried flasks. The solvents used were purified by distillation over the drying agents indicated and were transferred under argon: THF (Na), CH_2Cl_2 (CaH_2), and DMF (CaH_2). All reactions were monitored by thin-layer chromatography (TLC) on silica gel F_{254} plates using UV light as visualizing agent (if applicable), and a solution of phosphomolybdic acid (50 g/L) in EtOH followed by heating were used as developing agents. The products were purified by flash column chromatography on silica gel (200∼300 mesh sizes, Anhui Liangchen Silicon Material Company, China). ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$, DMSO-d_6, or acetone-d_6 solution on a Bruker AM 400 MHz instrument. Chemical shifts were denoted in ppm (δ) and calibrated by using residual undeuterated

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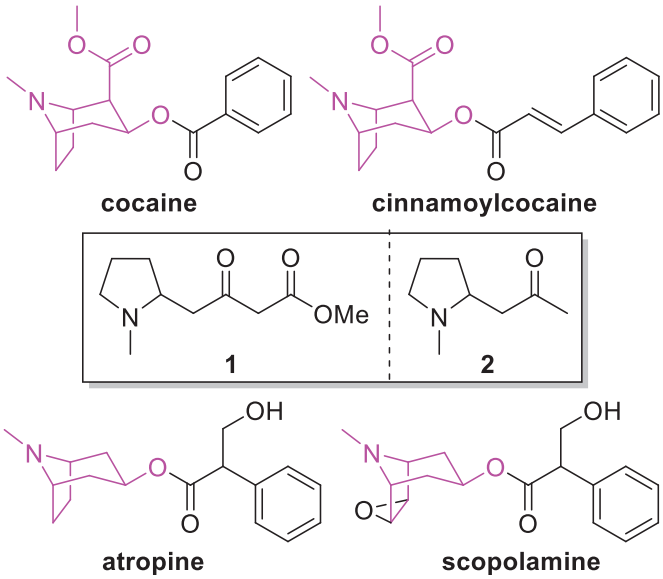
Fig. 1. Representative tropane alkaloids. [Colour online.]



solvent $CDCl_3$ (7.27 ppm), DMSO-d_6 (2.50 ppm), acetone-d_6 (2.05 ppm), or tetramethylsilane (0.00 ppm) as internal reference for ^{1}H NMR and the deuterated solvent $CDCl_3$ (77.00 ppm), DMSO-d_6 (39.5 ppm), acetone-d_6 (29.8 ppm), or tetramethylsilane (0.00 ppm) were used as internal standard for ^{13}C NMR. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, brs = broad singlet, dd = double doublet, td = triplet double, and m = multiplet. IR spectra of the compound were recorded in the range of 400–4000 cm^{-1} with a PerkinElmer Frontier FTIR/NIR spectrometer using KBr pellets. The high-resolution mass spectral analysis (HRMS) data were measured on Thermo Fisher Orbitrap Elite mass spectrometer by means of the ESI technique.

Synthesis

tert-Butyl (4,4-diethoxybutyl)carbamate (4)

4,4-Diethoxybutan-1-amine **3** (8.01 g, 50.00 mmol) was dissolved in THF (200 mL) then NEt_3 (13.9 mL, 0.10 mol), di-*tert*-butyldicarbonate (21.8 g, 0.10 mol), and DMAP (185 mg, 1.50 mmol) were added. The mixture was stirred at room temperature for 18 h, and then all volatiles were removed in vacuo. The pure product was obtained by column chromatography on silica gel eluting with petroleum ether/EtOAc (5:1) to afford compound **4** as an oil (12.2 g, 92%).

tert-Butyl (4,4-diethoxybutyl)(methyl)carbamate (5)

Sodium hydride (60% dispersion in oil, 1.44 g, 36.00 mmol) was added to a solution of **4** (7.84 g, 30.00 mmol) in DMF (50 mL). After 1 h, iodomethane (2.8 mL, 45.00 mmol) was added and the resulting mixture was stirred for 18 h. It was poured into water (200 mL) and extracted with EtOAc (300 mL). The organic portion was washed with water (5 × 100 mL), dried with Na_2SO_4, filtered, and evaporated in vacuo. The pure product was obtained by column chromatography on silica gel eluting with petroleum ether/EtOAc (5:1) to afford compound **5** (6.20 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.45 (s, 1H), 3.65–3.54 (m, 2H), 3.49–3.37 (m, 2H), 3.17 (s, 2H), 2.79 (s, 3H), 1.62–1.56 (m, 4H), 1.41 (s, 9H), 1.19–1.12 (m, 6H) ppm; ^{13}C NMR ($CDCl_3$): δ = 155.7, 102.5, 79.0, 61.04, 60.97, 33.9, 30.7, 28.3, 15.2 ppm (one carbon signal for CH_2 overlapped).

1

3-Oxoglutaric acid (1.00 g, 6.84 mmol) was added by portions to a solution of acetic acid (1 mL) and acetic anhydride (1.5 mL) at 5 °C and stirred below 10 °C. The acid dissolved slowly and a pale yellow solid precipitated over 3 h. The product was filtered, washed with acetic acid (1 mL), followed by toluene (1 mL × 3). The resultant white powder was dried at high vacuum to afford 0.65 g of the desired 3-oxoglutairc anhydride (74%), which was used directly in the following step.

A solution of 3-oxoglutaric anhydride (128 mg, 0.36 mmol) in methanol (0.5 mL) was stirred at room temperature for 2 h, and the resulting solution of monomethyl 3-oxoglutarate **7** was used directly for convergent reaction with **6**.

A solution of compound **5** (50 mg, 0.18 mmol) in MeOH (0.25 mL) was cooled in an ice bath for 10 min. A solution of HCl (4 mol/L, 0.25 mL) was added dropwise. Then, the mixture was stirred at 0 °C for 20 min and then at room temperature for 16 h to afford **6**, which was used in the next step without further purification. HRMS (ESI): *m/z* calcd for $C_5H_{10}N^+$, 84.0804; found, 84.0809 [M$^+$].

N-methylpyrrolinium cation **6** in methanol and 4 mol/L HCl (0.5 mL, 1:1, *v:v*) obtained before was added to the solution of **7**, and saturated aqueous sodium bicarbonate was then added to adjust the pH to 7~8. The reaction mixture was stirred for 3 h, and methanol was removed under reduced pressure. 10 mL water was added, and the aqueous solution was extracted thrice with CH_2Cl_2/MeOH (55 mL, 10:1). The organic extracts were combined, dried over Na_2SO_4 and filtered, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with CH_2Cl_2/MeOH (30:1) to afford **1** (18.9 mg, 53% for two steps) as a light-yellow liquid. ^{1}H NMR (400 MHz, acetone-d_6): δ = 3.54 (s, 3H), 3.44 (s, 2H), 2.86–2.74 (m, 2H), 2.46–2.36 (m, 2H), 2.12 (s, 3H), 2.00 (q, *J* = 8.0 Hz, 1H), 1.93–1.85 (m, 1H), 1.47–1.49 (m, 2H),1.32–1.23 (m, 1H) ppm; ^{13}C NMR (acetone-d_6): δ = 202.8, 168.4, 62.3, 57.3, 52.2, 50.2, 47.9, 40.6, 31.7, 22.8 ppm.

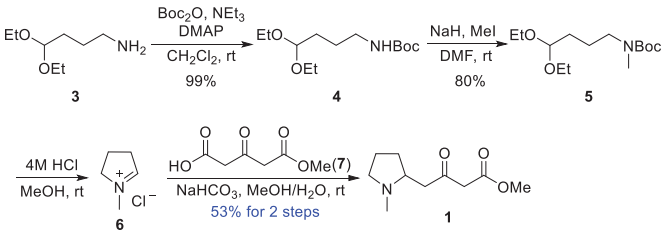
2

A solution of compound **5** (275 mg, 1.00 mmol) in MeOH (1.5 mL) was cooled in an ice bath for 10 min. A solution of HCl (4 M, 1.5 mL) was added dropwise. Then, the mixture was stirred at 0 °C for 20 min and then at room temperature for16 h to afford the mixture of **6**, which was used for the next step.

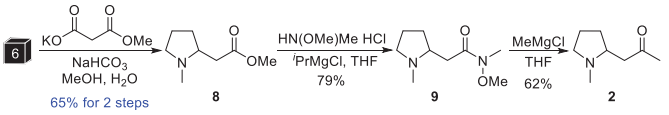
Methyl potassium malonate (234 mg, 1.50 mmol) was added to the mixture of *N*-methylpyrrolinium cation **6** in methanol and 4 mol/L HCl (3.0 mL, 1:1, *v:v*), and saturated aqueous sodium bicarbonate was then added to adjust the pH to 7~8. The reaction mixture was stirred for 3 h, and methanol was removed under reduced pressure. 10 mL water was added, and the aqueous solution was extracted thrice with CH_2Cl_2/MeOH (110 mL, 10:1). The organic extracts were combined, dried over Na_2SO_4 and filtered, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with CH_2Cl_2/MeOH (20:1) to afford compound **8** (113.2 mg, 72% for two steps) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.56 (s, 3H), 2.93 (td, *J* = 8.4, 1.6 Hz, 1H), 2.54 (dd, *J* = 4.4, 14.8 Hz, 1H), 2.45–2.36 (m, 1H), 2.20 (s, 3H), 2.18–2.06 (m, 1H), 1.99–1.88 (m, 1H), 1.71–1.54 (m, 2H), 1.48–1.35 (m, 1H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ = 172.4, 62.2, 56.7, 51.2, 40.1, 38.7, 30.9, 21.7 ppm.

To a solution of compound **8** (113 mg, 0.72 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (109 mg, 1.12 mmol) in dry THF (3 mL) was added a solution of isopropylmagesium chloride in THF (2 mol/L, 1.08 mL, 2.16 mmol) at –20 °C. After stirring for 20 min, water (10 mL) was added at –20 °C. The reaction mixture was warmed to room temperature and the aqueous layer was extracted with CH_2Cl_2/MeOH (55 mL, 10:1). The organic extracts were combined, dried with Na_2SO_4, and the solvents evaporated in vacuo. Purification by silica gel column chromatography CH_2Cl_2/MeOH (20:1) afforded pure **9** (109 mg, 79%) as a colourless oil. ^{1}H NMR (400 MHz, acetone-d_6): δ = 3.61 (s, 3H), 2.99 (s, 3H), 3.01–2.96 (m, 2H), 2.77 (dd, *J* = 4.4, 16.0 Hz, 1H), 2.71–2.62 (m, 1H), 2.39–2.30 (m, 1H), 2.26 (s, 3H), 2.25–2.19 (m, 1H), 2.00–1.92 (m, 1H), 1.69–1.56 (m, 2H), 1.47–1.36 (m, 1H) ppm; ^{13}C NMR (acetone-d_6):

Scheme 1. Synthesis of 4-(1-methylpyrrolidin-2-yl)-3-oxobutanoate **1**. [Colour online.]



Scheme 2. Synthesis of hygrine **2**. [Colour online.]



δ = 173.0, 63.5, 61.6, 57.2, 40.3, 36.6, 32.0, 22.6 ppm (one carbon signal for CH_3 overlapped); IR: $\tilde{U}$ = 3436, 2949, 1643, 1459 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_9H_{18}N_2O_2$, 187.1441; found, 187.1443 $[M + H]^+$.

To a solution of compound **9** (105.9 mg, 0.58 mmol) in THF (2 mL) at 0 °C a solution of methylmagnesium chloride in THF (1 mol/L, 1.74 mL, 1.74 mmol) was added dropwise. The reaction mixture was stirred for 2 h. The solution was cooled to –20 °C and quenched by addition of water (10 mL). The reaction mixture was warmed to room temperature, and the aqueous layer was extracted with CH_2Cl_2/MeOH (55 mL, 10:1). The organic extracts were combined, dried with Na_2SO_4, and the solvents evaporated in vacuo. Purification by silica gel column chromatography CH_2Cl_2/MeOH (30:1) to afford **2** (50.8 mg, 62%) as a colourless oil. ^1H NMR (400 MHz, DMSO-d_6): δ = 3.14–3.21 (m, 1H), 3.03 (brs, 1H), 2.87 (dd, *J* = 3.6, 18.4 Hz, 1H), 2.51 (dd, *J* = 8.4, 18.4 Hz, 1H), 2.33 (s, 3H), 1.84–1.74 (m, 1H), 1.70 2.33 (s, 3H), 1.56–1.39 (m, 2H), 1.20–1.08 (m, 1H) ppm; ^{13}C NMR (DMSO-d_6): δ = 205.4, 63.4, 55.0, 43.6, 38.9, 30.1, 29.6, 21.4 ppm; HRMS (ESI): *m/z* calcd for $C_8H_{15}NO$, 142.1226; found, 142.1230 $[M + H]^+$.

Results and discussion

The synthesis procedure began with commercially available 4,4-diethoxybutan-1-amine **3**. Initially, acylation of **3**[30] followed by methylation[31] gave amide **5** in 79% yield over two steps. Cyclization of **5** with 4 mol/L HCl in MeOH afforded the key *N*-methylpyrrolinium cation **6**, which was used directly in the following step. Then, treatment of **6** with monomethyl 3-oxoglutarate **7**[32] in aqueous methanol in the presence of sodium carbonate gave **1** in 53% yield over two steps from compound **5** with spectroscopic characteristics identical to those reported in the literature[11–13] (Scheme 1).

Divergently, from the common intermediate **6**, access to compound **8** was smoothly achieved in 65% yield under similar reaction conditions. Compound **8** was then efficiently converted in two steps into **2**[17] by reaction of methylmagnesium chloride with Weinreb amide **9** (Scheme 2), and its NMR spectroscopic data are identical to those from previous syntheses.[16–29]

Conclusion

In conclusion, we could synthesize **1** in four steps with 42% overall yield and **2** in six steps with 25% overall yield. This is a concise and efficient synthetic method, in which the two compounds could be prepared from the same intermediate *N*-methylpyrrolinium cation and used as reference standards in our biosynthesis of tropane alkaloids.

Supplementary data

Supplementary data are available with the article through the journal Web site at http://nrcresearchpress.com/doi/suppl/10.1139/cjc-2019-0442.

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