Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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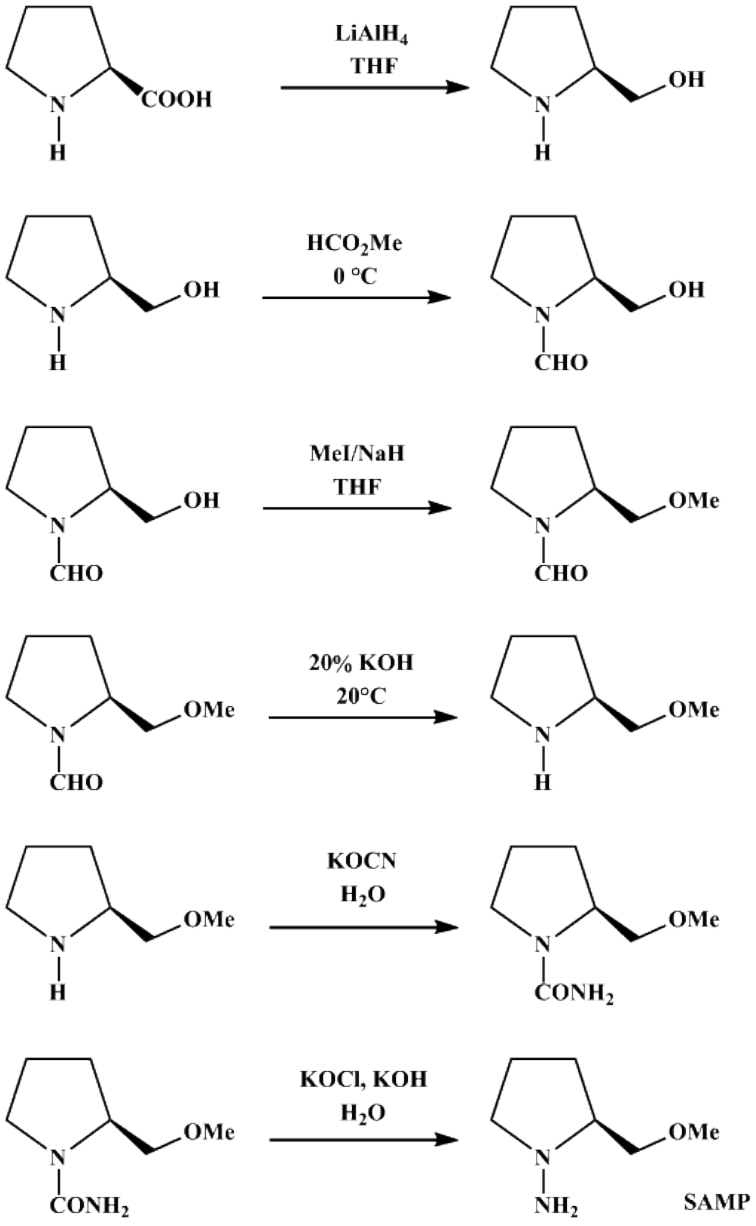
(*S*)-(−)-1-AMINO-2-METHOXYMETHYLPYRROLIDINE (SAMP) AND (*R*)-(+)-1-AMINO-2-METHOXYMETHYLPYRROLIDINE (RAMP), VERSATILE CHIRAL AUXILIARIES

[1-Pyrrolidinamine, 2-(methoxymethyl)-, (*S*) 1-Pyrrolidinamine, 2-(methoxymethyl)-, (*R*)]



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1. Procedure

A. *(S)-(+)-2-Hydroxymethylpyrrolidine.* In a 4-L, three-necked, round-bottomed flask equipped with a heating mantle (Note 1), an overhead stirrer bearing a two-bladed propeller (ca. 2.5-cm

diameter), an effective reflux condenser with a drying tube packed with silica gel, and a plastic stopper are placed 2.5 L of anhydrous tetrahydrofuran (THF, (Note 2)) and 60 g (1.56 mol) of lithium aluminum hydride ($LiAlH_4$, (Note 3)). The suspension is heated under reflux for 15 min, the heating mantle is switched off, and 115.1 g (1 mol) of powdered (*S*)-proline (Note 4) is added in small portions (ca. 2 g, (Note 5)) to the boiling mixture at such a rate as to maintain reflux. The addition requires ca. 45 min and the contents of the flask are kept boiling for an additional 1 hr. Excess lithium aluminum hydride is then decomposed by cautiously adding a solution of 28 g of potassium hydroxide in 112 mL of water (without external heating) through a pressure-equalizing dropping funnel to the boiling mixture. On hydrolysis, white salts precipitate and stirring becomes difficult. After the addition is complete (ca. 25 min), the mixture is refluxed for 15 min and the hot solution is filtered by suction through a large Büchner funnel (18-cm diameter). The precipitate is pressed dry with a beaker. Any remaining prolinol is extracted from the precipitate by refluxing with 1.5 L of tetrahydrofuran for 1 hr under mechanical stirring, followed again by suction filtration. The combined filtrates are concentrated in a 2-L flask at 390°C (Note 6) under reduced pressure to yield 115–125 g of the crude hydroxymethylpyrrolidine as a pale-yellow oil.

B. *(S)-(−)-1-Formyl-2-hydroxymethylpyrrolidine.* The 2-L flask containing the crude hydroxymethyl derivative (ca. 1 mol) is equipped with a dropping funnel and a magnetic stirring bar and cooled to 0°C. Eighty milliliters (1.3 mol) of methyl formate (Note 7) is added over a period of 20 min and stirring is continued for 30 min at 0°C to give a green-colored solution. Excess methyl formate is evaporated at 30°C, affording a dark oil, which is taken up in 600 mL of dichloromethane and dried twice by stirring over a sufficient amount of anhydrous sodium sulfate. The drying agent is removed by suction filtration through Celite (Note 8), using a large column, and the filtrate is concentrated under reduced pressure at 30°C. Any remaining traces of solvents are removed by stirring under reduced pressure using and oil pump (20°C at 1 mm). This procedure takes about 2 hr and yields ca. 130 g (ca. 1 mol) of the dry, crude *N*-formyl compound, which is used in the next step without further purification.

C. *(S)-(−)-1-Formyl-2-methoxymethylpyrrolidine.* A 4-L, three-necked flask, fitted with a magnetic stirrer, a reflux condenser, a low-temperature thermometer, and a mineral oil bubbler is charged with a solution of the crude formyl derivative in 1.5 L of dry tetrahydrofuran (Note 9) and flushed with argon. The solution is cooled to −50 to −60°C (internal temperature, acetone–dry ice), the cooling bath is removed, and 81 mL (1.3 mol) of methyl iodide is added. Then 28.8 g (1.2 mol) of sodium hydride (Note 10) is introduced carefully in one portion.

Caution! To prevent contact of sodium hydride with the cooling medium, it is absolutely necessary to remove the cooling bath before adding the sodium hydride. In addition, argon bubbling is stopped to avoid sodium hydride dust from being blown out of the flask.

The apparatus is flushed again with argon and allowed to warm to room temperature. During this period hydrogen gas evolves and a gray solid precipitates, which causes stirring to become difficult. At about 0°C the precipitate dissolves exothermally under strong evolution of hydrogen. The thermometer is replaced by a pressure-equalizing dropping funnel, and the solution is refluxed for 15 min and quenched by slow addition of 90 mL of 6 *N* hydrochloric acid, without external heating. Tetrahydrofuran is removed under reduced pressure to yield the crude *O*-methylated compound in water.

D. *(S)-(+)-2-Methoxymethylpyrrolidine.* A solution of 180 g of potassium hydroxide in 720 mL of water is added to the crude product and the mixture is vigorously stirred under argon overnight. Saturation with potassium carbonate (500 g) causes precipitation of potassium salts, which are filtered off by suction (large Büchner funnel) and washed with ether. The filtrate is extracted with ether (3 × 300 mL) (Note 11), and the ether layer is acidified with 100 mL of 12 *N* hydrochloric acid under ice cooling in a hood (evolution of fumes) and extracted twice with 100 mL of water to yield an aqueous solution of the hydrochloride of 2-methoxymethylpyrrolidine (Note 12).

E. *(S)-(−)-1-Carbamoyl-2-methoxymethylpyrrolidine.* The aqueous amine hydrochloride solution is adjusted to a pH of 2.8–3.2 (Note 13) with aqueous 50% potassium hydroxide. A solution of 80 g (1 mol) of potassium cyanate (Note 14) in 140 mL of water is then added all at once at 15°C and the mixture is allowed to stir for at least 12 hr at 20°C.

F. *(S)-(−)-1-Amino-2-methoxymethylpyrrolidine (SAMP)*. A 4-L, three-necked flask containing the crude urea is cooled to −5°C (internal temperature) by means of an ice–salt bath and treated with a chilled (−5°C) solution of 168 g of potassium hydroxide in 150 mL of water. After addition of 685 mL (1.3 mol) of 1.9 *N* potassium hypochlorite solution (Note 15), precooled to −5°C, the temperature rises within 10 min to 30–40°C and the cooling bath is removed after the mixture reaches room temperature (Note 16). Stirring is continued for a total of 12–15 hr. Excess potassium hypochlorite is destroyed with a freshly prepared solution of sodium bisulfite (20 g $NaHSO_3$ in 50 mL of H_2O) and the mixture is acidified (pH 2) with a minimum amount of 12 *N* hydrochloric acid (ca. 350 mL) under ice cooling. A strong evolution of carbon dioxide occurs. The mixture is allowed to stir for an additional 15 min at ambient temperature, made alkaline (pH 9) with ca. 100 mL of aqueous 50% potassium hydroxide, and saturated with potassium carbonate (500 g). Precipitated potassium salts are filtered off by suction through a large Büchner funnel and washed twice with ethanol; the filtrate is extracted with a 1 : 1 chloroform/ethanol mixture (1 × 800 mL and 2 × 400 mL). During extraction salt precipitation again occurs and the salts should be filtered off as mentioned above. The organic layers are collected, concentrated under reduced pressure at 30°C (Note 17), taken up in 500 mL of chloroform, and dried twice over sodium sulfate. The drying agent is removed by suction filtration through Celite and the solvent is stripped off as mentioned above to give 80–90 g of a dark oil. Immediate distillation through a 40-cm vacuum-jacketed Vigreux column (the receiver should be cooled with ice to prevent loss of substance) yields a small forerun containing 2-methoxymethylpyrrolidine, followed by SAMP as a colorless liquid, bp 42°C at 1.8 mm (80°C bath temperature), $[\alpha]_D^{20}$ −79.6° (neat). Overall yields of SAMP range from 65 to 75 g (50–58%). A purity of ca. 95% was established by GLC analysis (Note 18). The optical antipode RAMP, $[\alpha]_D^{20}$ + 79.8° (neat), can be prepared likewise, starting from (*R*)-proline (Note 19).

2. Notes

1. The heating mantle should be covered with aluminum foil to prevent contact with lithium aluminum hydride and proline.
2. Peroxide-free tetrahydrofuran (for precautions, see *Org. Synth., Coll. Vol. V*, **1973**, 976) was refluxed over potassium hydroxide pellets for 2 hr, distilled, and dried by addition of ca. 1 g of lithium aluminum hydride prior to use. *Failure to heed the precautions can result in a serious explosion!* Drying the THF over sodium–benzophenone is generally recommended for safety reasons.
3. Lithium aluminum hydride (100%) was used as purchased from Metallgesellschaft AG, Frankfurt, Germany, or Wako Pure Chemical Industries, Ltd., Japan.
4. Both (*S*)- and (*R*)-proline (≥99.5% ee) were obtained from Degussa AG, Hanau, Germany. The checkers used (*S*)-proline (guaranteed reagent) purchased from Wako Pure Chemical Industries, Ltd.
5. A convenient technique is to add the proline portionwise with a spoon that is inserted as far as possible into the flask to prevent the proline from being blown-off the spoon by hydrogen generated during the reaction. The flask is immediately stoppered after every addition.
6. The temperature of the heating bath should not exceed 30°C to avoid significant loss of product. To prevent oxidation the rotary evaporator is flushed with argon.
7. Methyl formate (reagent grade) was used as purchased from Riedel de Haen, Seelze, Germany. The checkers used the product (guaranteed reagent) of Wako Chemical Industries, Ltd.
8. Celite was supplied by Fluka AG, Buchs, Switzerland, or Manville Products Corporation, USA.
9. This time, tetrahydrofuran (Note 2) is made anhydrous by adding ca. 2 g of sodium hydride.
10. Methyl iodide was purchased from Merck-Schuchardt, Hohenbrunn, Germany, or Wako Pure Chemical Industries, Ltd., Japan. Because of its volatility and possible carcinogenicity it should be handled in a well-ventilated hood. Sodium hydride was supplied by Riedel de Haen, Seelze, Germany, or Wako Pure Chemical Industries, Ltd., Japan. In a 1-L, round-bottomed flask 50 g of 80% sodium hydride (mineral oil dispersion) is washed free of oil by stirring with pentane (4 × 300 mL). After the supernatant liquid is decanted for the fourth time, the remaining solvent is removed by evaporation (20° C at 1 mm).
11. After the usual workup, the amine can be obtained pure merely by distilling through a 40-cm Vigreux column, bp 75–77°C/40 mm.
12. The ether layer contains a small amount of the starting material and is discarded.
13. The pH of the solution should be exactly calibrated by means of a pH meter in order to prevent side reactions. The use of pH paper is not recommended.

14. Potassium cyanate (technical grade) was supplied by Degussa AG, Hanau, Germany. Alternatively, sodium cyanate may be used. The checkers used the practical-grade reagent purchased from Wako Pure Chemical Industries, Ltd., Japan.
15. The optimized preparation of an aqueous potassium hypochlorite solution is a modification of an *Organic Syntheses* procedure.[2] Two hundred grams of HTH [commercially available as swimming-pool sanitizer from Olin Chemicals, 120 Long Ridge Road, Stamford, CT 06904, USA, ca. 68% $Ca(OCl)_2$, or Nippon Soda Co., Japan, 70% $Ca(OCl)_2$] is vigorously shaken with 600 mL of water (ca. 10 min), a solution (20°C) of 40 g of potassium hydroxide and 140 g of potassium carbonate in 250 mL of water is added, and shaking is continued for at least 10 min to yield a semifluid gel. The gel is filtered off by suction and thoroughly pressed dry to give 650–770 mL of a yellow potassium hypochlorite solution. These solutions are 1.8–2.2 *M* according to simple iodometric titration (see *Org. Synth., Coll. Vol. VI*, **1988**, 968, (Note 3).)
16. Temperatures lower than those mentioned above inhibit the exothermic reaction, and the reaction time is extended to approximately 24 hr. Less efficient cooling results in warming to 70–80°C, which causes decarboxylation of the intermediate carboxylate and/or simple oxidation by potassium hypochlorite.
17. If the temperature of the water bath exceeds 30°C, significant amounts of product are lost. To prevent oxidation, the rotary evaporator is flushed with argon.
18. The checkers observed contamination of the final product by ca. 4% 2-methoxymethylpyrrolidine according to 270 MHz NMR.
19. The chiral hydrazines are stable over months if stored in a refrigerator under argon. The spectra are as follows. IR (film) cm^{-1}: 3360 (NH_2), 3150, 2980, 2880, 2820, 1610, 1465, 1200, 1120, 960, 920; ^1H NMR ($CDCl_3$, 90 MHz) δ: 1.4–2.1 (m, 4 H, CH_2), 2.1–2.6 (m, 2 H, CH_2N), 3.1 (m, 3 H, NH_2, NCH), 3.3 (s, 3 H, OCH_3), 3.4 (m, 2 H, CH_2O); mass spectrum (70 eV) *m/e* (relative intensity): M^+ 130.1100 (6.7%) (calcd. 130.1106); 97.07 (3.9); 86.07 (8.9); 85.07 (100.0); 83.06 (4.1); 71.06 (16.3); 68.05 (31.3); 57.04 (5.6); 56.05 (4.6); 45.03 (10.7); 43.03 (12.1); 42.04 (3.4); 41.04 (28.9); 39.02 (5.5).

3. Discussion

The previously reported preparation of SAMP and its enantiomer RAMP involved hazardous nitrosamine intermediates.[3,4,5] The new procedure described here circumvents this problem by *N*-amination via Hofmann degradation[6] (step F). The procedure, which required an optimization of the synthesis of the known intermediates,[7,8] is characterized by good yields, mild conditions and readily available starting materials. The entire sequence of six steps can be performed in a week.

The enantiomerically pure hydrazines SAMP and RAMP are versatile chiral auxiliaries with a wide range of applications in asymmetric synthesis.[9] For a detailed description of the SAMP/RAMP–hydrazone method see page 403.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 403

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(S)-(−)-1-AMINO-2-METHOXYMETHYLPYRROLIDINE (SAMP)

(R)-(+)-1-AMINO-2-METHOXYMETHYLPYRROLIDINE (RAMP)

(S)-(−)-1-Formyl-2-hydroxymethylpyrrolidine

(S)-(−)-1-Formyl-2-methoxymethylpyrrolidine

(S)-(−)-1-Carbamoyl-2-methoxymethylpyrrolidine

(S)- and (R)-proline

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid, hydrochloride (7647-01-0)

ether (60-29-7)

hydrogen (1333-74-0)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

aluminum (7429-90-5)

sodium bisulfite (7631-90-5)

carbon dioxide (124-38-9)

potassium hydroxide (1310-58-3)

Benzophenone (119-61-9)

sodium (13966-32-0)

Methyl iodide (74-88-4)

Pentane (109-66-0)

methyl formate (107-31-3)

dichloromethane (75-09-2)

potassium cyanate (590-28-3)

potassium hypochlorite

proline,
(S)-proline (147-85-3)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

sodium hydride (7646-69-7)

sodium cyanate (917-61-3)

argon (7440-37-1)

prolinol,
(S)-(+)-2-Hydroxymethylpyrrolidine (23356-96-9)

1-Pyrrolidinamine, 2-(methoxymethyl)-, (S) (72748-99-3)

1-Pyrrolidinamine, 2-(methoxymethyl)-, (R) (59983-39-0)

hydroxymethylpyrrolidine

2-methoxymethylpyrrolidine

(R)-proline (344-25-2)

(S)-(+)-2-Methoxymethylpyrrolidine (63126-47-6)