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Working with Hazardous Chemicals

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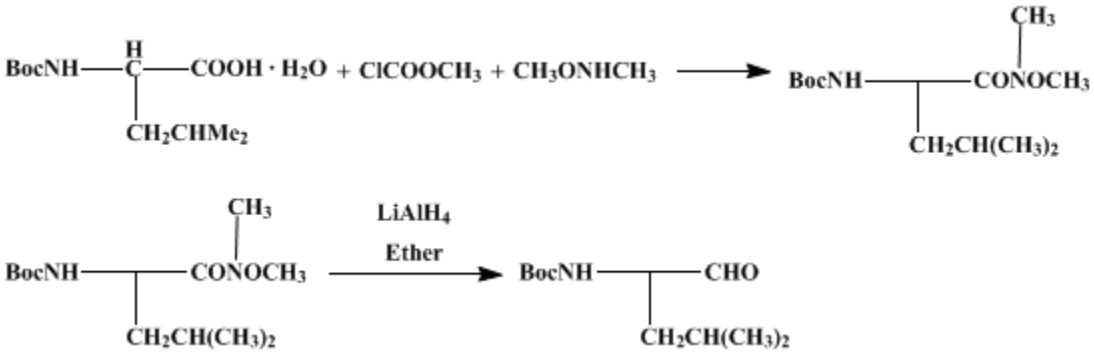
N-tert-BUTOXYCARBONYL-L-LEUCINAL

[Carbamic acid, (1-formyl-3-methylbutyl)-, 1,1-dimethylethyl ester, (*S*)-]



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1. Procedure

A. *Boc-L-leucine N-methyl-O-methylcarboxamide.* A 1-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer, an electronic digital thermometer, and a graduated addition funnel. The flask is charged with 39.1 g (0.4 mol) of *N,O*-dimethylhydroxylamine hydrochloride (Note 1) and 236 mL of methylene chloride (Note 2). The suspension is stirred and cooled to 2°C with an ice–water bath. *N*-Methylpiperidine. (Note 3), 48.8 mL (0.41 mol), is placed in the addition funnel and added dropwise while the temperature is maintained at 2° ± 2°C. A clear colorless solution results which is kept cold and used in the following reaction.

A 5-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer, a thermometer, and an addition funnel with drying tube. The flask is charged with 100 g (0.4 mol) of Boc-L-leucine hydrate (Note 4), 458 mL of tetrahydrofuran (Note 2), and 1.8 L of methylene chloride. A clear solution results on stirring, which is cooled to −20° ± 2°C by immersing the flask in a dry ice–2-propanol bath. *N*-Methylpiperidine, 48.8 mL (0.41 mol), is placed in the addition funnel and added rapidly to the mixture, while the temperature is allowed to rise to −12° ± 2°C. Methyl chloroformate (Note 5), 31 mL (0.4 mol), is then placed in the addition funnel and added rapidly to the mixture with good stirring, while the temperature is kept at −12° ± 2°C. Two minutes later the solution of *N,O*-dimethylhydroxylamine, prepared as described earlier, is added. The cooling bath is removed and the clear solution allowed to warm to room temperature over 4 hr (Note 6). The solution is again cooled to 5°C and extracted with two 500-mL portions of aqueous 0.2 *N* hydrochloric acid and two 500-mL portions of aqueous 0.5 *N* sodium hydroxide (Note 7). The solution is washed with 500 mL of saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated on a rotary evaporator at a bath temperature of 30–35°C. The residue is further evacuated on an oil pump to constant weight. The residual colorless syrup weighs 100–102 g (91–93%), $[\alpha]_D^{23}$ −24 to −25° (1.5% in methanol) (Note 8).

B. *N-tert-Butoxycarbonyl-L-leucinal*: *Boc-L-leucinal*. A 5-L, four-necked, round-bottomed flask is equipped with an efficient mechanical stirrer, a thermometer, a pressure-equalizing addition funnel, and an air-cooled condenser fitted with an argon blanket adapter. The flask is charged under an argon blanket with 17.7 g (95% pure, 0.44 mol) of lithium aluminum hydride (Note 9), and 1.5 L of anhydrous ethyl ether (Note 10). The gray suspension is stirred at room temperature for 1 hr or until most of the solid is finely dispersed. The flask is immersed in a dry ice–2-propanol bath and the suspension cooled to −45°C. A solution of the Boc-L-leucine *N*-methyl-*O*-methycarboxamide, obtained in Part A, in 300 mL of anhydrous ethyl ether is placed in the addition funnel and added to the lithium aluminum hydride suspension in a steady stream (Note 11) while the reaction temperature is maintained −35° ± 3°C. The

cooling bath is removed and the mixture is stirred and allowed to warm to +5°C. The mixture is once again cooled to −35°C and a solution of 96.4 g (0.71 mol) of potassium bisulfate (Note 12) in 265 mL of deionized water is placed in the addition funnel. This is added cautiously at first and then rapidly, while the temperature is allowed to rise to −2° ± 3°C. The cooling bath is removed and the mixture stirred for 1 hr. The reaction mixture is filtered through a 2-in. pad of Celite (Note 13). The filter cake is washed with two 500-mL portions of ethyl ether. The combined ether layers are washed in sequence with three 350-mL portions of cold (5°C) 1 *N* hydrochloric acid, two 350-mL portions of saturated aqueous sodium bicarbonate solution, and 350 mL of saturated sodium chloride solution. The organic solution is dried over magnesium sulfate and evaporated on a rotary evaporator (bath at 30°C). The residual, slightly cloudy syrup weighs 69–70 g (87–88%), $[\alpha]^{23}$ −49 to −51° (1.65% in methanol) (Note 14). The product is stored in a freezer (−17°C) prior to use. It solidifies readily at 5°C (Note 15).

2. Notes

1. *N,O*-Dimethylhydroxylamine hydrochloride was obtained from the Aldrich Chemical Company, Inc., and used as received.
2. Methylene chloride and tetrahydrofuran were obtained from the Fisher Scientific Company.
3. *N*-Methylpiperidine was obtained from the Aldrich Chemical Company, Inc., and used as received.
4. Bachem Inc. was the source of Boc-L-leucine hydrate. It was not necessary to prepare anhydrous Boc-L-leucine. The yield and quality of the product were unaffected by the presence of water during the reaction.
5. Methyl chloroformate was obtained from the Aldrich Chemical Company, Inc.
6. The reaction mixture may be stirred overnight for convenience.
7. The organic solution should be kept at 5–15°C during extractions.
8. The crude product is 96–99% pure by HPLC and is satisfactory for use in the next reaction. HPLC was carried out on a Varian 5500 instrument using a 250-cm × 4.6-mm-i.d. Alltech C-18 column with 60 : 40 methanol : 0.5 *M* $NH_4H_2PO_4$ (pH 3) as the mobile phase, UV detector at 210 nm. Thin-layer chromatography on silica gel plates (EM) and development with hexane : EtOAc (3 : 1) indicates that the major product spot is at $R_f = 0.32$. Starting Boc-L-leucine, if present, appears at $R_f = 0.16$; detector: ninhydrin and gradual warming on a hot plate. The physical properties are as follows: IR (liquid film) cm^{-1}: 2960(s), 1714(s), 1665(s); ^1H NMR (200 MHz, $CDCl_3$) δ: 0.92 [2d appear as t, 6 H, $J = 6.8$, CH $(CH_3)_2$], 1.40, [s, 9 H, $C(CH_3)_3$], 1.38–1.44 (m, 2 H, C_3-H), 1.59–1.76 (m, 1 H, C_4-H), 3.17, and 3.14 (s and a rotamer singlet, 3 H, N-CH_3), 3.76 and 3.67 (s, and a rotamer singlet, 3 H, O-CH_3), 4.7 (m, 1 H, C_2-H), 5.06 (m, 1 H, N-H).
9. Lithium aluminum hydride was obtained from Alfa Products, Morton/Thiokol Inc.
10. Ethyl ether was obtained from the Fisher Scientific Co.
11. The lithium aluminum hydride suspension should be cooled to −45°C prior to addition of the amide. Higher initial temperatures (−30°C and above) lead to an impurity as shown by TLC.
12. Potassium bisulfate was obtained from the Matheson, Coleman and Bell Co. A saturated aqueous solution is obtained after stirring overnight. Aqueous potassium bisulfate will react vigorously if tetrahydrofuran is the reaction medium in place of ethyl ether.
13. A gel-like precipitate is formed from the inorganic by-products. A thick Celite pad helps to prevent clogging of the filter funnel.
14. Consistently higher optical rotations than reported were obtained.[2] NMR and capillary gas-chromatographic analyses indicated chemical purity of 98–99%. Varian 6000, RSL-310, 15-m, fused silica column, 0.25 mm i.d., film thickness 0.25 μm, at 60°C for 4 min and then 60–220°C at 10°C/min, H_2 as carrier gas at 10 psi. TLC under the conditions described in Note 8 shows the major spot at R_f = 0.53. The spectral properties are as follows: IR (liquid film) cm^{-1}: 2961(s), 1736(s), 1698(b); ^1H NMR (200 MHz, $CDCl_3$) δ: 0.96 (d, 6 H, $J = 6.4$, CH $(CH_3)_2$), 1.45 (s, 9 H, $C(CH_3)_3$), 1.48–1.81 (m, 3 H, C_3-H, C_4-H): 4.24 (m, 1 H, C_2-H); 4.92 (broad singlet, 1 H, N-H); 9.59 (s, 1 H, C_1-H).
15. Boc-L-leucinal racemizes if stored at room temperature. Although it solidified in the cold it became liquid at room temperature. It is very soluble in pentane at room temperature, but crystallizes from pentane at −30°C. It is reported[2] to melt at 63–66°C.

3. Discussion

Boc-L-leucinal is a useful chiral synthon in the preparation of the natural amino acid statine[3] [*S*-

(*R**,*R**)]-4-amino-3-hydroxy-6-methylheptanoic acid (3*S*,4*S*). The procedure reported here is based on the method of Fehrentz and Castro[2] for the preparation of optically active Boc amino aldehydes from α-amino acids. It is satisfactory on a kilogram scale. Boc-L-leucinal has also been prepared by the reduction of Boc-L-leucine methyl ester with diisobutylaluminum hydride[4] or oxidation of Boc-L-leucinol.[5] The reaction conditions described here differ from those in the literature.[2] The *N*-methoxy-*N*-methylamide is prepared simply and in high yield by the mixed anhydride method[6] rather than with the very expensive reagent benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate. In addition, the amide can be added to a cold lithium aluminum hydride suspension rather than inversely as recommended.[2] This is an important consideration for scale-up. Reduction of this amide with bis(2-methoxy-ethoxy)aluminum hydride solution (Red-Al) gave a substantially impure aldehyde.

References and Notes

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

Boc-L-leucine N-methyl-O-methycarboxamide

N-methoxy-N-methylamide

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether,
ethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

potassium bisulfate (7646-93-7)

Pentane (109-66-0)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

methyl chloroformate (79-22-1)

lithium aluminum hydride (16853-85-3)

hexane (110-54-3)

diisobutylaluminum hydride (1191-15-7)

N-Methylpiperidine (626-67-5)

ninhydrin (938-24-9)

benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (56602-33-6)

bis(2-methoxy-ethoxy)aluminum hydride

N,O-dimethylhydroxylamine hydrochloride (6638-79-5)

Carbamic acid, (1-formyl-3-methylbutyl)-, 1,1-dimethylethyl ester, (S)-,
N-tert-BUTOXYCARBONYL-L-LEUCINAL,
Boc-L-leucinal (58521-45-2)

N,O-dimethylhydroxylamine (1117-97-1)

Boc-L-leucine N-methyl-O-methylcarboxamide

Boc-L-leucine hydrate

Boc-L-leucine

Boc-L-leucine methyl ester

Boc-L-leucinol