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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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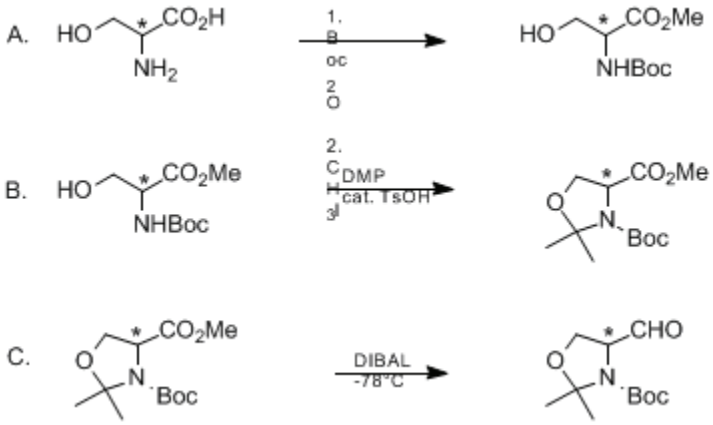
1,1,-DIMETHYLETHYL (S)- OR (R)-4-FORMYL-2,2-DIMETHYL-3-OXAZOLIDINECARBOXYLATE: A USEFUL SERINAL DERIVATIVE

[3-Oxazolidinecarboxylic acid, 4-formyl-2,2-dimethyl-, 1,1-dimethylethyl ester, (S)- or (R)-]



Submitted by Philip Garner and Jung Min Park[1].
Checked by Mayumi Takasu and Hisashi Yamamoto.

1. Procedure

A. *N-[(1,1-Dimethylethoxy)carbonyl]-L-serine methyl ester*. A solution of di-tert-butyl dicarbonate [$(Boc)_2O$] (78.4 g, 0.36 mol, (Note 1)) in dioxane (280 mL, (Note 2)) is added to an ice-cold, magnetically stirred solution of L-serine (31.7 g, 0.30 mol, (Note 3)) in 1 N sodium hydroxide (620 mL) by means of an addition funnel. The two-phase mixture is stirred at 5°C for 30 min, then allowed to warm to room temperature over 3.5 hr at which time TLC analysis shows the reaction to be complete (Note 4). The mixture is concentrated to half its original volume by rotary evaporation at 35°C, cooled in an ice-water bath, acidified to pH 2–3 by the slow addition of 1 N potassium bisulfate (620 mL), and then extracted with ethyl acetate (3 × 1000 mL). The combined extracts are dried over magnesium sulfate, filtered and concentrated to give N-Boc-L-serine (63.0 g) as a colorless, sticky foam which is used without further purification.

To a cold solution of N-Boc-L-serine (32.4 g, 0.16 mol, (Note 5)) in dimethylformamide (150 mL) is added solid potassium carbonate (24.3 g, 0.176 mol). After stirring for 10 min in an ice-water bath, methyl iodide (20.0 mL, 46.3 g, 0.32 mol – *CAUTION! Methyl iodide is toxic and a suspected carcinogen that should be handled in a well-ventilated fume hood.*) is added to the white suspension and stirring continued at 0°C for 30 min whereupon the mixture solidifies. The reaction is warmed to room temperature and stirred for an additional hour or so at which point TLC analysis indicates complete formation of the methyl ester (Note 6). The reaction mixture is filtered by suction and the filtrate partitioned between ethyl acetate (300 mL) and water (300 mL). The organic phase is washed with brine (2 × 300 mL), dried with magnesium sulfate, filtered and concentrated to give 29.8 g (86% yield) of N-Boc-L-serine methyl ester as a pale amber oil which is used without further purification (Note 7) and (Note 8).[2]

B. *3-(1,1-Dimethylethyl) 4-methyl (S)-2,2-dimethyl-3,4-oxazolidinedicarboxylate*. To a 2-L, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, Claisen distilling head, thermometer, and reflux condenser protected from moisture by a calcium sulfate-filled drying tube are added a solution of N-Boc-L-serine methyl ester (48.5 g, 0.22 mol) in benzene (770 mL), 2,2-dimethoxypropane (55 mL, 47 g, 0.45 mol), and p-toluenesulfonic acid monohydrate (0.593 g, 3.1

mmol, (Note 9). The colorless solution is heated under reflux (oil bath temperature, 110°C) for 30 min, then slowly distilled until a volume of 660 mL is collected over 4 hr when the reaction is judged to be complete by TLC (Note 10) and (Note 11). The cooled, amber solution is partitioned between saturated sodium bicarbonate solution (200 mL) and ethyl ether (2 × 500 mL). The organic layer is washed with brine (200 mL), then dried over magnesium sulfate, filtered and concentrated to give the crude product as an amber oil. This material is vacuum distilled through a 10-cm Vigreux column to give 40.3–50.9 g (70–89% yield) of oxazolidine methyl ester as a very pale yellow liquid, bp 101–102° C (2 mm) (Note 12).

C. *1,1-Dimethylethyl (S)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate*. A dry (Note 13), 1-L, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, rubber septa, three-way balloon adapter, and a low temperature thermometer. After the flask is purged with nitrogen (Note 14), a solution of the oxazolidine ester (40.2 g, 0.15 mol) in dry toluene (300 mL, (Note 15)) is added via cannula (using positive nitrogen pressure) and cooled to −78°C with an acetone-dry ice bath. To this cooled solution is added a −78°C solution of 1.5 M diisobutylaluminum hydride in toluene (175 mL, (Note 16)) via cannula (using positive nitrogen pressure). The rate of addition is adjusted so as to keep the internal temperature below −65°C and takes approximately 1 hr to complete. The reaction mixture is stirred for an additional 2 hr at −78°C under an atmosphere of nitrogen when TLC anlaysis shows the reaction to be complete (Note 17). The reaction is quenched by slowly adding 60 mL of cold (−78°C) methanol (*Evolution of hydrogen occurs!*)—again keeping the internal temperature below −65°C. The resulting white emulsion is slowly poured into 1000 mL of ice-cold 1 N hydrochloric acid with swirling over 15 min, and the aqueous mixture is then extracted with ethyl acetate (3 × 1000 mL). The combined organic layers are washed with brine (1000 mL), dried over magnesium sulfate, filtered and concentrated to give 33.6 g of crude product as a colorless oil. This material is vacuum distilled through a 10-cm Vigreux column to give 26.9 g (76% yield) of oxazolidine aldehyde as a colorless liquid, bp 83–88°C (1.0–1.4 mm) (Note 18).

2. Notes

1. The submitters used di-tert-butyl dicarbonate from Aldrich Chemical Company, Inc., and also available from Wako Pure Chemical Industries, LTD.
2. Unless stated otherwise in the procedure, all solvents and reagents were used as purchased without further purification.
3. The submitters used L-serine (and D-serine) from United States Biochemical Corporation, and also available from Tokyo Kasei Kogyo Co., LTD.
4. TLC analysis on Merck silica gel 60F-254 plates eluting with (8:1:1) n-BuOH-H_2O-AcOH showed the clean formation of a product with R_f 0.65 (visualized with 0.3% ninhydrin in (97:3) n-BuOH-AcOH) at the expense of starting amino acid at the origin. If starting material remained, more $(Boc)_2O$ (13.1 g, 0.060 mol) was added.
5. The submitters have also found commercially available N-Boc-L-serine (United States Biochemical Corporation) to be an entirely satisfactory starting material. However, for the unnatural D-series, they find that it is more economical to prepare N-Boc-D-serine as described.
6. TLC analysis on Merck silica gel 60F-254 plates eluting with (1:1) ethyl acetate-hexanes showed the clean formation of ester, R_f 0.38 (visualized with 0.5% phosphomolybdic acid in 95% ethanol), at the expense of starting material at the origin.
7. Optical measurements on this material were not very useful since they were in general low and quite variable. Furthermore, no literature values could be found for comparison. IR (neat) cm^{-1}: 3400, 1720 (br); ^1H NMR (200 MHz, C_6D_6, 17°C) δ: 1.41 (s, 9 H), 2.50 (br, s, H, exchanged with D_2O), 3.26 (s, 3 H), 3.66 (dd, H, J = 11 and 4), 3.76 (dd, H, J = 11 and 4), 4.40 (m, H), 5.60 (m, H, exchanged with D_2O).
8. *Alternatively, the methyl ester could be prepared as follows:* N-Boc-serine (63 g, 0.31 mol) was dissolved in ethyl ether (600 mL) in a 2-L Erlenmeyer flask equipped with a magnetic stirring bar, cooled in an ice-water bath and treated with ten 50-mL aliquots of cold ethereal (approximately 0.6 M) diazomethane prepared from N-nitroso-N-methylurea according to Arndt's procedure.[3] After 30 min at 0°C, TLC analysis showed the reaction to be complete (Note 6). Excess diazomethane was destroyed with acetic acid (the yellow color disappears) and the resulting solution was extracted with half-saturated sodium bicarbonate solution (300 mL), then washed with brine (200 mL), dried with

magnesium sulfate, filtered and concentrated to give 60.1 g (91% over 2 steps) of N-Boc-serine methyl ester as a colorless, sticky foam which was used without further purification. *CAUTION! N-Nitroso-N-methylurea is suspected of being a carcinogen and diazomethane is highly toxic. The utmost care must be used when handling these substances; diazomethane solutions should be restricted to a well-ventilated fume hood at all times.*

9. Moriwake et al. have reported that boron trifluoride etherate can also be used as the acid catalyst for this reaction.[4]

10. TLC analysis on Merck silica gel 60F-254 plates eluting with (1:1) ethyl acetate-hexanes showed the clean formation of product, R_f 0.78 (visualized with 0.5% phosphomolybdic acid in 95% ethanol), at the expense of starting material at R_f 0.23.

11. If starting material remained at this time, more 2,2-dimethoxypropane (14 mL, 12 g, 0.11 mol) and benzene (310 mL) were added and the procedure was repeated, collecting 250 mL of distillate, at which time the TLC analysis generally showed the reaction to be complete.

12. The optical rotation of the L-oxazolidine methyl ester was −46.7° ($CHCl_3$, *c* 1.30). An essentially identical procedure emanating from N-Boc-D-serine methyl ester gave the corresponding D-oxazolidine methyl ester in 80% yield with a rotation of +53°. In either case further purification could be achieved with flash chromatography to give product with a maximum rotation of 57° although we have found distilled material to be entirely satisfactory for our purposes: IR (neat) cm^{-1}: 1760, 1704; ^1H NMR (200 MHz, C_6D_6, 75°C) δ: 1.41 (s, 9 H), 1.53 (br s, 3 H), 1.81 (br s, 3 H), 3.35 (s, 3 H), 3.75 (dd, H, J = 8.5 and 8.1), 3.81 (dd, H, J = 8.5 and 3.5), 4.26 (m, H). (The oxazolidine derivatives exist as slowly interconverting rotamers on the NMR time scale and samples require heating to obtain averaged spectra.)

13. All the glassware (except the low-temperature thermometer) was oven-dried (>100°C) and quickly assembled before use.

14. The checkers used argon.

15. Toluene was distilled from sodium-benzophenone ketyl.

16. The diisobutylaluminum hydride solution (1.5 M in toluene, Aldrich Chemical Company, Inc.) was transferred to a dry, 250-mL, graduated cylinder equipped with a rubber septum and drying tube via cannula (using positive nitrogen pressure). The graduated cylinder was then placed in a Dewar flask and cooled to −78°C with an acetone-dry ice bath.

17. TLC analysis on Merck silica gel 60F-254 plates eluting with (4:1) hexanes-ethyl acetate showed the formation of product, R_f 0.33 (visualized with 0.5% phosphomolybdic acid in 95% ethanol), with only a trace of starting material remaining at R_f 0.41. Some over-reduced product arising within the TLC capillary may be evident at this stage.

18. The optical rotation of the L-oxazolidine aldehyde was −91.7° ($CHCl_3$, *c* 1.34). An identical procedure emanating from the D-oxazolidine methyl ester gave D-oxazolidine aldehyde in 85% yield having a rotation of +95°. These distilled products contained up to 5% of the starting material as judged by their NMR spectra, but were suitable for use without further purification. Homogeneous samples could be obtained in either case by flash chromatography on silica gel eluting with (4:1) hexanes-ethyl acetate and showed a maximum optical rotation of 105°. This material can be stored indefinitely provided it is kept cold (≤ 5°C) and moisture-free. IR (neat) cm^{-1}: 1735, 1705; ^1H NMR (200 MHz, C_6D_6, 60°C) δ: 1.34 (s, 9 H), 1.40 (br s, 3 H), 1.59 (br s, 3 H), 3.52 (dd, H, J = 8.7 and 8.3), 3.65 (dd, H, J = 8.7 and 2.9), 3.90 (m, H), 9.34 (br s, H).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Since its preparation and use was first reported by us,[5] the title compound has been gaining favor as a chiral, nonracemic synthon for the asymmetric synthesis of a variety of amino alcohol- and amino acid-containing targets. Among the virtues of this oxazolidine aldehyde over previously reported N-acylated serinal derivatives are its ease of preparation on a large scale and its configurational stability. The procedure described here provides material that has been determined to be 95% enantiomerically pure by Mosher ester analysis.[6] Homologation (C-C bond formation) of this serinal derivative can be

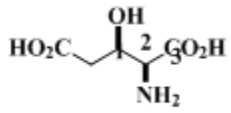
achieved without competing racemization using both olefination[4,7,8,9,10,11,12] and nucleophilic addition[5,13,14,15,16,17,18,19,20,21,22,23,24,25,26] protocols. The latter process can be made to occur with good to excellent diastereoselectivity (i.e., 1,2-asymmetric induction) by simply choosing reagents/conditions so as either to preclude or favor chelation-control. Protocols for diasteroselective additions to the oxazolidine-appended olefins are also known. Once the rest of the target molecule's structure is in place, the oxazolidine can be unravelled to give either an aminoethanol group or, after oxidation of the primary alcohol, an α-amino acid moiety. The products so produced are typically >98% enantiomerically pure. Thus the title compound can serve not only as a serinal derivative but as a penaldic acid equivalent as well. Representative examples of the use of 1,1-dimethylethyl (S)- and (R)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate as a chiral synthon for natural product synthesis are collected in the Table.

This preparation is referenced from:

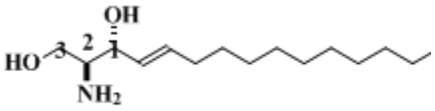
- Org. Syn. Coll. Vol. 10, 320

TABLE

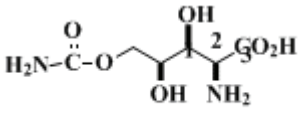
SELECTED EXAMPLES OF THE USE OF 1,1-DIMETHYL (S)- AND (R)-4-FORMYL-2,2-DIMETH OXAZOLIDINECARBOXYLATE FOR NATURAL PRODUCT SYNTHESIS: THE C-3 SUBUNITS EMA FROM SERINE ARE NUMBERED ACCORDINGLY



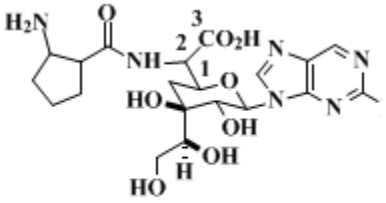
threo-β-hydroxy-L-glutamic acid (ref. 4)



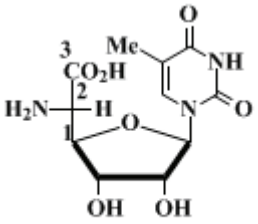
D-*erythro*-sphingosine (refs. 8-10, 12,



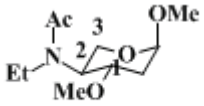
5-carbamoylpolyxamic acid (ref. 11)



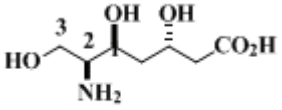
Amipurimycin studies (ref. 5)



Thymine polyoxin C (ref. 16)



Calicheamycin fragment (ref. 19)



(-)-Galantic acid (ref. 26)

References and Notes

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2. We thank Dr. N. S. Chandrakumar of G. D. Searle and Company for alerting us to the fact that N-Boc-serine methyl ester could be prepared without significant racemization via esterification with methyl iodide, thereby avoiding the generation and use of diazomethane on a large scale.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

silica gel

hexanes

brine

sodium-benzophenone ketyl

1,1,-DIMETHYLETHYL (S)- OR (R)-4-FORMYL-2,2-DIMETHYL-3-OXAZOLIDINECARBOXYLATE

$(Boc)_2O$

D-oxazolidine methyl ester

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

ethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

potassium bisulfate (7646-93-7)

toluene (108-88-3)

Methyl iodide (74-88-4)

magnesium sulfate (7487-88-9)

dioxane (123-91-1)

Diazomethane (334-88-3)

dimethylformamide (68-12-2)

serine,
L-serine (56-45-1)

argon (7440-37-1)

boron trifluoride etherate (109-63-7)

diisobutylaluminum hydride (1191-15-7)

2,2-dimethoxypropane (77-76-9)

phosphomolybdic acid (51429-74-4)

ninhydrin (938-24-9)

p-toluenesulfonic acid monohydrate (6192-52-5)

N-Boc-L-serine,
N-Boc-serine Di-tert-butyl dicarbonate (24424-99-5)

N-[(1,1-Dimethylethoxy)carbonyl]-L-serine methyl ester,
N-Boc-L-serine methyl ester,
N-Boc-serine methyl ester (2766-43-0)

3-(1,1-Dimethylethyl) 4-methyl (S)-2,2-dimethyl-3,4-oxazolidinedicarboxylate (108149-60-6)

1,1-Dimethylethyl (S)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate,
3-Oxazolidinecarboxylic acid, 4-formyl-2,2-dimethyl-, 1,1-dimethylethyl ester, (S)-,
1,1,-DIMETHYLETHYL (S)-4-FORMYL-2,2-DIMETHYL-3-OXAZOLIDINECARBOXYLATE
(102308-32-7)

D-serine (312-84-5)

N-Boc-D-serine (6368-20-3)

N-nitroso-N-methylurea (684-93-5)

N-Boc-D-serine methyl ester (95715-85-8)

(R)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate

1,1,-DIMETHYLETHYL (R)-4-FORMYL-2,2-DIMETHYL-3-OXAZOLIDINECARBOXYLATE,
3-Oxazolidinecarboxylic acid, 4-formyl-2,2-dimethyl-, 1,1-dimethylethyl ester, (R)-,
1,1-dimethylethyl (R)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate (95715-87-0)

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