Reduction of Ethanethiol Esters to Aldehydes

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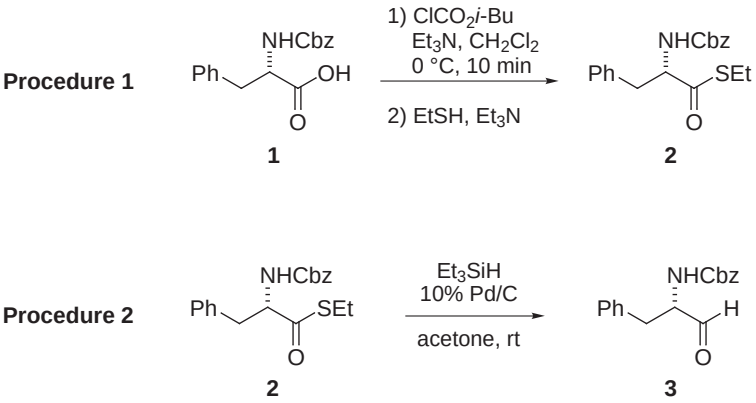
Abstract: Reduction of ethanethiol esters of α-amino acids to α-amino aldehydes by triethylsilane and catalytic palladium-on-carbon is described. α-Amino aldehydes with Boc, Cbz, or Fmoc protection could be obtained without racemization in high yield.

Key words: reductions, aldehydes, thiol esters, amino aldehydes



Scheme 1

Conversion of carboxylic acids to aldehydes has been the subject of intense investigation among synthetic organic chemists. With a few exceptions, derivatives of acids, such as acid chlorides, amides, and esters, are usually converted to aldehydes by selective reduction. Alternatively, the most frequently employed procedure is the reduction of acids or their derivatives followed by mild oxidation of the resulting alcohols. In the case of the reduction using aluminum reagents, care must be taken to remove the aluminum residue from the crude product in the work-up procedure. Herein we describe a practical method for preparation of aldehydes from carboxylic acids via their ethanethiol esters.

Ethanethiol esters are easily derived from the corresponding carboxylic acids via their mixed anhydrides, or utilizing various dehydrating agents, such as DCC. The resulting ethanethiol esters can be reduced with triethylsilane in the presence of palladium-on-carbon to afford aldehydes.[1] Due to the mild conditions of the procedures, various functional groups are compatible as shown in Table 1. Esters, silyl ethers, sulfides, acetals, and amides were tolerated in this transformation. Although some of the less substituted olefins were reduced during the reduction, tri-substituted olefins were not affected.

In addition, one of the advantages of the reduction of the thiol esters is the simplicity of the reaction and work-up protocol. Thus, after completion of the reaction, simple filtration through a pad of Celite is enough to remove the catalyst, and the resulting aldehydes can be used without further purification. If needed, recrystallization or silica gel column chromatography affords the pure aldehyde in high yield.

α-Amino aldehydes have been used as useful chiral synthons and hence several synthetic methods have been developed.[2] However, since α-amino aldehydes tend to easily racemize under acidic or basic conditions and even during purification by silica gel column chromatography, treatment of the compounds should be performed carefully. The mild conditions of the present procedure and simple work-up after the reduction proved particularly useful for the preparation of α-amino aldehydes. Thus, by means of these procedures various α-amino acids can be trans-

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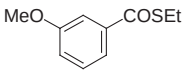
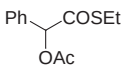
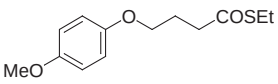
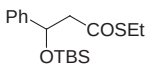
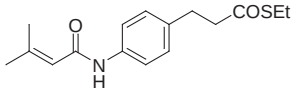
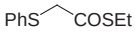
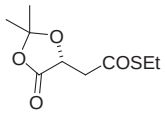
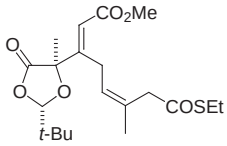
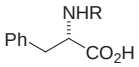
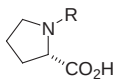
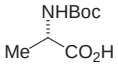
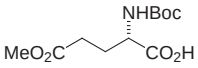
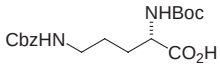
Table 1 Reduction of Ethanethiol Esters with Triethylsilane and Pd/C

Thiol ester	Aldehyde (% yield)[a]	Thiol ester	Aldehyde (% yield)
	91[b,c]		84
	94		88
	97		75[c,e]
	93[d]		92

[a] Isolated yields after chromatographic purification. Pd/C (2 mol%) and Et_3SiH (3 equiv) in acetone were used unless noted otherwise.
[b] Et_3SiH (2 equiv) was used.
[c] Isolated as tosylhydrazone.
[d] 5.8-g-scale reaction. Pd/C (0.5 mol%) and Et_3SiH (1.5 equiv) were used. CH_2Cl_2 was used as a solvent.
[e] 4 mol% of Pd/C was used.

formed into the corresponding α-amino aldehydes without racemization[3] (Table 2).

Table 2 Formation of Ethanethiol Esters from α-Amino Acids, and Reduction with Triethylsilane and Pd/C Leading to α-Amino Aldehydes

a-Amino Acid	Thiol ester (% yield)[a]	Aldehyde (% yield)[a,b]
	89 (R = Boc) 89 (R = Cbz) 86 (R = Fmoc)	93 (R = Boc)[c] 91 (R = Cbz) 83 (R = Fmoc)
	90 (R = Boc) 81 (R = Cbz)	87 (R = Boc) 96 (R = Cbz)
	85	93[c]
	82	92[c]
	79	84

[a] Isolated yields after chromatographic purification.
[b] Pd/C (5 mol%) and Et_3SiH (2 equiv) in acetone were used unless noted otherwise.
[c] 2,6-Lutidine (1.5 equiv) was added.

The Cbz group turned out to be the best protective group for the amino group, and Fmoc group could also be employed. In the case of the Boc group, however, a by-product was formed in some cases to lower the yield. Formation of the by-product was completely suppressed, when the reduction was performed in the presence of 1.5 equiv of 2,6-lutidine.

In summary, the procedures described here provide an efficient and convenient route for preparation of a variety of aldehydes from carboxylic acids. Especially, these mild procedures have been extended to the preparation of racemization-prone α-amino aldehydes. The general applicability of this reactions has been fully demonstrated in a total synthesis of (+)-neothramycin A methyl ester[1] and Leinamycin[4] as well as in the recent total syntheses of complex natural products.[5]

Herein, we describe typical procedures of the simple and convenient transformation from carboxylic acid to aldehyde by way of the thiol ester. In Procedure 1, we report the preparation of thiolester Cbz-L-phenylalanine ethanethiol ester (**2**) starting from Cbz-L-phenylalanine (**1**) via its mixed anhydride without racemization. In the second procedure (Procedure 2), the reduction of the thiolester was performed to give Cbz-L-phenylalaninal (**3**) in 69–70% yield (Scheme 1).

Cbz-L-Phenylalanine Ethanethiol Ester (2)

An oven-dried, 500 mL, round-bottomed flask was equipped with a magnetic stirring bar, and a three-way stopcock attached to an Ar balloon. The flask was charged with Cbz-L-phenylalanine (**1**) (22.0 g, 73.5 mmol) and anhyd CH_2Cl_2 (150 mL) with cooling in an ice-water bath. To the flask were added dropwise isobutyl chloroformate (10.5 mL, 80.9 mmol) and Et_3N (10.2 mL, 73.5 mmol) via syringe at 0 °C, successively. After stirring vigorously for 10 min, ethanethiol (12.0 mL, 162 mmol) and Et_3N (10.2 mL, 73.5 mmol) were added and immediately the color of the solution turned pink. The mixture was diluted with Et_2O (50 mL) to cause precipitation of triethylamine hydrochloride. The salt was filtered off and the filter cake was washed with Et_2O (100 mL). The combined Et_2O solution was evaporated on a rotary evaporator. The residue was

dissolved in EtOAc (50 mL) and transferred to a 300 mL separating funnel. The solution was diluted with Et_2O (100 mL), and washed with aq 1 M HCl (50 mL), water (50 mL), 1 M aq NaOH (50 mL), H_2O (20 mL), and brine (50 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated on a rotary evaporator. After azeotropic distillation of the crude oil with hexane, a white solid was obtained and recrystallized (EtOAc–hexane, 10 mL:200 mL) to afford white crystals.

Yield: 19.1 g, 76%; mp 69–70 °C (EtOAc–hexane).

IR (CCl_4): 3433, 3032, 2932, 1731, 1686, 1548, 1498, 1216 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.5 Hz, 3 H), 2.88 (q, *J* = 7.5 Hz, 2 H), 3.07 (dd, *J* = 7.0, 13.8 Hz, 1 H), 3.16 (dd, *J* = 5.4, 13.8 Hz, 1 H), 4.67–4.74 (m, 1 H), 5.10 (s, 2 H), 5.13 (br d, 1 H), 7.12–7.35 (m, 10 H).

^{13}C NMR (67.5 Hz, $CDCl_3$): δ = 14.4, 23.4, 38.4, 61.3, 67.1, 127.2, 128.1, 128.5, 128.6, 128.8, 129.3, 135.4, 136.0, 155.6, 200.4.

Anal. Calcd for $C_{19}H_{21}NO_3S$: C, 66.44; H, 6.16; N, 4.08. Found. C, 66.26; H, 6.06; N, 3.85.

Cbz-L-Phenylalaninal (3)

A 200 mL, two-necked, round-bottomed flask equipped with a pressure-equalizing funnel fitted with an Ar balloon and a magnetic stirring bar was charged with Cbz-L-phenylalanine ethanethiolester (20 g, 58.2 mmol), 10% Pd/C (3.1 g, 5 mol%), and acetone (58 mL). To the suspension was added triethylsilane (13.9 mL, 87.3 mmol) over 1 h via addition funnel at r.t.. The completion of the reaction could be checked by TLC. The solvent was carefully removed on a rotary evaporator. The residue was suspended in Et_2O (60 mL) and the catalyst was filtered off through a Celite pad and rinsed with Et_2O (6 × 20 mL). The filtrate was concentrated under reduced pressure to obtain a crude product as a colorless oil, which solidified upon addition of hexane (30 mL). The solid was collected by filtration and washed with cooled hexane (7 × 10 mL) to obtain analytically pure product (11.3–11.6 g, 68.5–70.3%).

IR (CCl_4): 3337, 3032, 2952, 1740, 1691, 1535, 1454, 1264, 1065, 738 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.15 (d, *J* = 6.6 Hz, 2 H), 4.53 (q, *J* = 6.6 Hz, 1 H), 5.12 (s, 2 H), 5.30 (br d, 1 H), 7.13–7.39 (m, 10 H), 9.65 (s, 1 H).

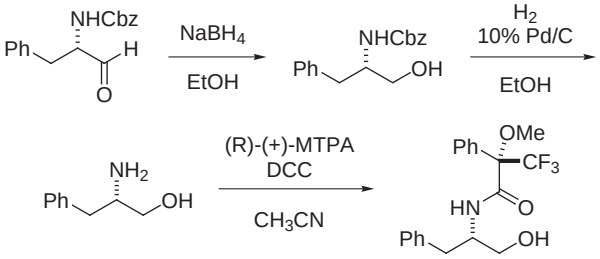
^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.3, 61.0, 67.1, 127.2, 128.1, 128.2, 128.5, 128.8, 129.3, 135.4, 136.1, 155.9, 198.8.

References

(1) Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050.

(2) For a review on α-amino aldehydes, see: Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149.

(3) In Procedure 2, the optical purity of the resulting α-amino aldehyde was determined by the following procedure. An amide was obtained via a three-step sequence: (a) $NaBH_4$, EtOH; (b) 10% Pd/C, H_2, EtOH; (c) (*R*)-(+)-MTPA, DCC, MeCN]. No peak due to *N*-Cbz-D-phenylalaninal (δ = 3.29) was detected (Scheme 2).



Scheme 2

(4) Kanda, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **1993**, *115*, 8451.

(5) (a) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497. (b) Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446. (c) Morimoto, Y.; Iwahashi, M.; Nishida, K.; Hayashi, Y.; Shirahama, H. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 904. (d) Evans, D. A.; Trotter, B. W.; Côté, B.; Coleman, P. J. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2741. (e) Smith, A. B. III; Chen, S. S.-Y.; Nelson, F. C.; Reichert, J. M.; Salvatore, B. A. *J. Am. Chem. Soc.* **1997**, *119*, 10935. (f) Fujiwara, A.; Kan, T.; Fukuyama, T. *Synlett* **2000**, 1667.