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An efficient and practical procedure for Strecker reaction: a highly diastereoselective synthesis of a key intermediate for (+)-biotin

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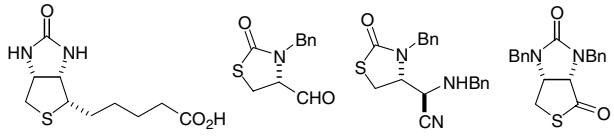
Abstract—Treatment of α-amino aldehyde **2**, which was prepared through Moffatt oxidation of the corresponding β-amino alcohol **5**, with aqueous sodium bisulfite allowed clean conversion to a water-soluble bisulfite adduct **6** [>99% conversion, 89% yield (two steps)]. The aqueous solution of **6** was treated with benzylamine followed by easy-handling NaCN to effect the Strecker reaction to afford α-amino nitrile **3** with high diastereoselectivity and in high yield (*syn*/*anti* = 11:1, 95% assay yield). Both the compounds *syn*-**3** and *anti*-**3** were converted to a key intermediate **4** for (+)-biotin through *S*,*N*-carbonyl migration in high yields.

The Strecker reaction has gained considerable attention due to its significance in the synthesis of α-amino acid derivatives from aldehydes.[1] In our synthetic studies on (+)-biotin (**1**),[2] a *syn*-selective Strecker reaction of α-amino aldehyde **2** to β-amino-α-amino nitrile *syn*-**3** was required to allow an access to thiolactone **4**, a key intermediate for **1**.[2j] However, our previously reported procedure[2j] has suffered from such drawbacks as need for employing expensive trimethylsilyl cyanide (TMSCN). Although, as a solution to the problem, we initially attempted to use HCN, which was generated by the treatment of NaCN with acetic acid (**2** → **3**, 77% yield, *syn*/*anti* = 11:1), it was hard to apply to a large scale preparation due to difficulty in handling toxic and low-boiling HCN. Taylor and co-workers have reported that the Strecker reaction takes place by the treatment of bisulfite adducts of achiral aldehydes with inexpensive and easy-handling NaCN.[3] However, to the best of our knowledge, there have not been any reports on the diastereoselective Strecker reaction of the bisulfite adducts of chiral aldehydes with an asymmetric centre α to the carbonyl group. We envisioned a possible use of the protocol for our diastereoselective synthesis employing the chiral α-amino aldehyde **2**. The use of the bisulfite adduct may have an additional and significant advantage of easy purification due to the water solubility. Reported herein are the successful results of highly diastereoselective Strecker reaction of the bisulfite adduct **6** employing NaCN.



In our initial study, conversion of α-amino aldehyde **2** to the corresponding bisulfite adduct **6** was undertaken. β-Amino alcohol **5** was allowed to the Moffatt oxidation employing DCC[4] in the presence of TFA and pyridine to effect a clean conversion to α-amino aldehyde **2** (90% yield).[2j] The resulting solution of **2** in AcOEt was treated with sodium bisulfite (1.1 equiv) in water to provide the bisulfite adduct **6** in 99% conversion. As expected, a simple work-up involving extraction and separation provided **6** pure enough for the subsequent step (Scheme 1).

The Strecker reaction of **6** was the next subject for our investigation. The aqueous solution of **6** (vide supra) was treated with benzylamine in a biphasic system involving CH_2Cl_2[5] and water at 20 °C for 2 h. The resulting

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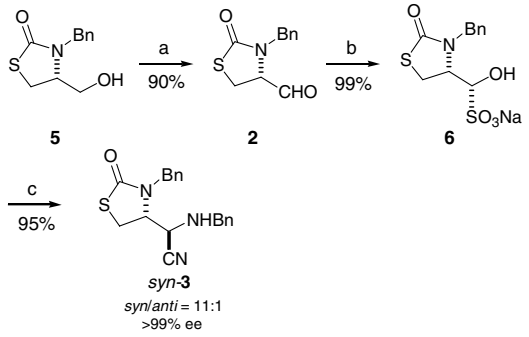
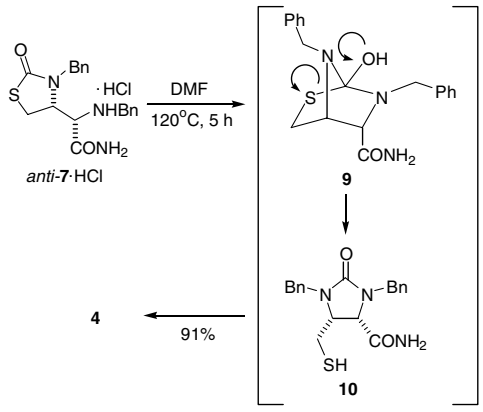


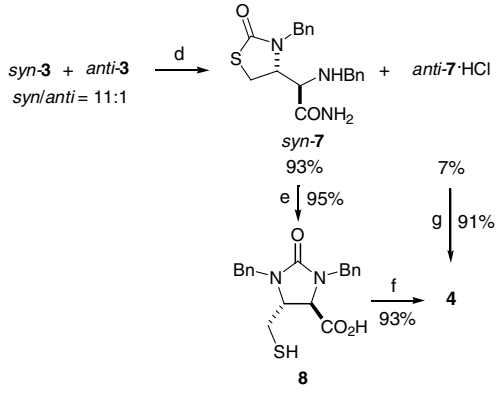
Scheme 1. Reagents and conditions: (a) DCC, TFA, pyridine, DMSO, AcOEt, 50 °C, 3 h; (b) $NaHSO_3$, AcOEt, H_2O, 20 °C, 18 h; (c) (i) $BnNH_2$ (1.7 equiv), CH_2Cl_2, 20 °C, 2 h, (ii) NaCN (1.2 equiv), 8–20 °C 20 h, (iii) $NaHSO_3$ (0.3 equiv), NaCN (0.3 equiv), 20 °C, 1.5 h.



Scheme 3.

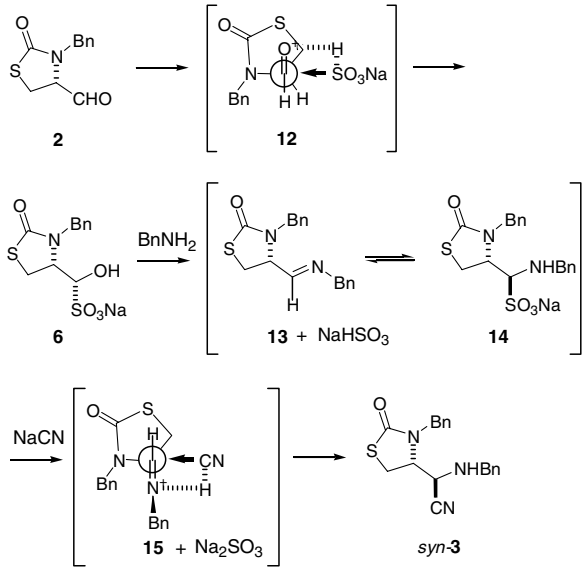
mixture involving an imine (Scheme 4, compound **13**) and a bisulfite adduct of the imine (Scheme 4, compound **14**) was treated with NaCN (1.2 equiv) at 8 °C and the whole was stirred at ambient temperature for 20 h. To complete the reaction were added NaCN (0.3 equiv) and sodium bisulfite (0.3 equiv) and the mixture was further stirred for 1.5 h. Then, 10% aq NaOH was added and the organic phase was washed with water to completely remove the toxic cyanide to provide α-amino nitrile **3** as a solution of CH_2Cl_2 with high diastereoselectivity and in high yield (*syn*/*anti* = 11:1, 95% assay yield).[6] The ee value of **3** was confirmed to be >99% ee by HPLC analysis.[7] It should be noted that, during the reaction, the reaction mixture was always basic and evolution of HCN gas in the reaction flask was much less than that observed in the reaction employing NaCN/AcOH.[8]

The resulting CH_2Cl_2 solution of **3** was directly allowed to amidation employing H_2O_2, K_2CO_3 and DMSO (Scheme 2).[2j] The reaction smoothly proceeded even in a mixed solvent of DMSO and CH_2Cl_2 to afford the corresponding amide **7** in quantitative yield. The *syn*-isomer *syn*-**7** was obtained as solids by just adding water to the reaction mixture and filtration. The oily *anti*-isomer *anti*-**7** solidified by converting to HCl salt and was obtained in 7% yield without tedious purification such as silica-gel column chromatography. According to our reported procedure,[2j] *syn*-**7** was allowed to undergo the ring transformation from 2-thiazolidinone to 2-imidazolidinone through *S*,*N*-carbonyl migration and subsequent hydrolysis to give thiol carboxylic acid **8** in 95% yield. The compound **8** obtained was cyclized and isomerized to thiolactone **4** in 93% yield. In contrast, the *anti*-isomer *anti*-**7**·HCl was directly converted to **4** in 91% yield with heating at a higher temperature (120 °C) through the *S*,*N*-carbonyl migration followed by spontaneous cyclization (Scheme 3). The structure of **4** obtained either from *syn*-**7** or *anti*-**7**·HCl was fully characterized by comparison with an authentic sample with respect to IR, ^1H NMR and MS spectra and the ee value of **4** was confirmed to be >99% ee by HPLC.[9]



Scheme 2. Reagents and conditions: (d) (i) H_2O_2, K_2CO_3, DMSO/CH_2Cl_2, 20 °C, 2.5 h, (ii) H_2O, filtration, (iii) for the filtrate: HCl; (e) (i) DMF, 90 °C, 1 h, (ii) HCl; (f) DCC, TFA, pyridine, $CHCl_3$, 5 °C—reflux, 5 h; (g) 120 °C, 5 h DMF.

The plausible mechanism of the present reaction is depicted in Scheme 4. The compound **6** solidified by concentrating the aqueous solution and the relative



Scheme 4.

configuration of **6** was confirmed to be *syn* by X-ray crystallographic analysis.[10] The *syn*-isomer **6** may be formed through a Felkin–Ahn model[11] in which sodium bisulfite attacks the *re*-face of the carbonyl group. The adduct **6** was treated with benzylamine in a 0.75:1.0 mixture of D_2O and CD_2Cl_2. A mixture of free imine **13** and bisulfite adduct of the imine **14** (**13**/**14** = 61:39) was formed in nearly quantitative yield, as determined by ^1H NMR analysis. The relative configuration of **14** should be *anti* in consideration of the structure of *syn*-**3**[2j] that may be formed through the similar transition state controlled by a Houk model.[12] It is noteworthy that any racemization did not occur during the reaction partly because of the partial trap of the imine **13** as the bisulfite adduct **14**.

In conclusion, an efficient and practical synthesis of a key intermediate for (+)-biotin was worked out through novel and highly diastereoselective Strecker reaction employing bisulfite adduct of α-amino aldehyde and easy-handling NaCN. The ease of operation, the use of inexpensive reagents and mild reaction conditions of the present method would permit facile access to β-amino-α-amino nitriles involving an intermediate for (+)-biotin.

References and notes

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4. Although large scale disposal of dicyclohexylurea (DCU) after the reaction can be an important issue to be solved, DCU is recovered by simple filtration and converted back to DCC according to the known procedure (see: Stevens, C. L. *J. Org. Chem.* **1967**, *32*, 2895).
5. Dichloromethane (CH_2Cl_2) is classified as a class 2 solvent according to ICH guidelines. However, the use of CH_2Cl_2 is required to dissolve α-amino nitrile *syn*-**3**: whose solution can be washed with aq NaOH for complete removal of the toxic cyanide.
6. Preparation of **3** through the formation of the bisulfite adduct and the Strecker reaction therewith: To a solution of β-amino alcohol **5** (40 g, 0.18 mol) in a mixed solvent of AcOEt (90 mL) and DMSO (90 mL) were successively added pyridine (2.92 mL, 0.036 mol), TFA (2.78 mL, 0.036 mol) and DCC (44.4 g, 0.22 mol) at <43 °C. After stirring the mixture at 50 °C for 3 h, AcOEt (200 mL) was added and the mixture was cooled in an ice bath. The precipitated DCU was filtered and the filtrate was washed with 12% aq NaCl (200 mL). The aqueous layer was extracted with AcOEt (100 mL) and the combined organic phases were washed with 12% aq NaCl (200 mL). The AcOEt solution contained α-amino aldehyde **2** (35.9 g, 90%) [HPLC; Capcell Pak C18 SG 120A (Shiseido), 15 cm × 4.6 mm, 15 mM Na_2HPO_4/CH_3CN = 5:1, 1 mL/min, 40 °C, 220 nm]. To the compound **2** (35.9 g, 0.162 mol) in AcOEt were added water (80 mL) and sodium bisulfite (18.6 g, 0.178 mol) and the mixture was stirred at 20 °C for 30 min. After the solution was concentrated under reduced pressure, AcOEt (80 mL) was added to the residue. The mixture was stirred at 20 °C for 17 h and the aqueous layer involving bisulfite adduct **6** (35.4 g, 0.16 mol) was suspended in CH_2Cl_2 (106 mL). To the suspension was added benzylamine (23.2 g, 0.27 mol) and the mixture was stirred at 20 °C for 2 h. The mixture was cooled down to 8 °C and NaCN (9.4 g, 0.19 mol) was added. After stirring the mixture at 20 °C for 20 h, $NaHSO_3$ (5.0 g, 0.048 mol) and NaCN (2.35g, 0.048 mol) were added and the mixture was stirred for 1.5 h. To the mixture was added 10% aq NaOH (40 mL). The organic phase was separated and washed with water (40 mL). The aqueous layer was extracted with CH_2Cl_2 (40 mL) and combined extracts were dried over anhydrous $MgSO_4$ and filtration to afford α-amino nitrile **3** (51.1 g, 95%) in CH_2Cl_2 as a mixture of *syn*- and *anti*-isomers [*syn*/*anti* = 11:1, HPLC; L-Column ODS (Shimadzu), 0.01 M KH_2PO_4 buffer (pH = 3)/CH_3CN = 55:45, 1 mL/min, 40 °C, 225 nm].
7. HPLC conditions: Chiralcel AD-H (Daicel), hexane/EtOH = 90:10, 0.8 mL/min, 225 nm, 40 °C.
8. After the reaction, the concentration of HCN gas in the reaction flask was 50 ppm. Nonetheless, the reaction should be conducted in a well-ventilated draft.
9. HPLC conditions: Chiralcel AD (Daicel), hexane/EtOH = 85:15, 0.8 mL/min, 225 nm, 40 °C.
10. The X-ray data of **6** have been deposited to Cambridge Crystallographic Data Centre.
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12. (a) In the possible stable conformation of **15**, the imino group might orient to the opposite direction as does the carbonyl group in **12** due to the presence of an *N*-benzyl group on the imine. Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D.C.; Metz, J. T.; Li, Y.; Loncharich, R. *J. Sci.* **1986**, *231*, 1108; (b) Merino, P.; Lanaspa, A.; Merchan, F. L.; Tejero, T. *J. Org. Chem.* **1996**, *61*, 9028.