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2-Thiazolidinone: a novel thiol protective surrogate of complete atom efficiency, a practical synthesis of (+)-biotin

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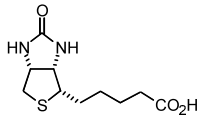
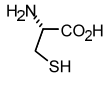
Abstract—2-Thiazolidinone derivatives were shown to be novel protective surrogates of a thiol group in L-cysteine derivatives. After elaboration at the C-4 substituent, the thiol group was completely liberated by simple heating in DMF whose atom efficiency is 100%. A practical synthesis of (+)-biotin was accomplished by the use of the strategy employing 4-functionalized 2-thiazolidinone derivatives as the intermediates, allowing a synthesis of (+)-biotin in 10 steps and in 31% overall yield. Short steps, high yield, and ease of operation of the present approach would permit the hitherto most efficient access to (+)-biotin.

Proper selection of a protective group is one of the most significant criteria for developing an efficient synthetic method. When a functional group is to be protected, it usually requires two steps involving '*protection and deprotection*' otherwise not needed. One should thus intend minimizing the use of the protective group in order to reduce the number of steps leading to the target compound.[1] In the course of our investigation toward a practical synthesis of (+)-biotin (**1**),[2] development of a novel and efficient thiol protective group of cysteine (**2**) was needed.



(+)-Biotin (**1**)

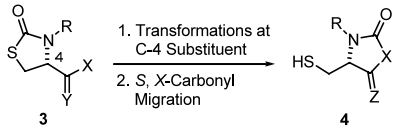


L-Cysteine (**2**)

However, so far employed thiol protective groups are not satisfactory due to instability or need for harsh conditions for their cleavage.[3] We envisioned a possible use of 2-thiazolidinones **3** for protecting the thiol group in the cysteine derivatives. The compounds **3** involving a thiocarbamate moiety in the molecule should be stable enough to be elaborated at the C-4 substituent. After the transformations, if the relative hardness[4] of the carbonyl group in **3** is closer to *X* atom (*N*, *O*, etc.) than to *Sulfur* atom, thermal *S*, *X*-carbonyl migration of **3** to **4** should readily take place to liberate the thiol group (Scheme 1).

As the process is a kind of isomerization reaction, the atom efficiency[5] of the conversion is 100%, and when the migrated carbonyl group is a part of the target molecule, the use of the surrogates can remove the protection and deprotection sequence that is usually required for the conventional protective groups. Reported herein are the novel use of the 2-thiazolidinones for protecting the thiol group in the cysteine derivatives and demonstration of its efficiency in a practical synthesis of (+)-biotin (**1**).

Our retrosynthetic analysis of **1** is depicted in Scheme 2. Thiolactone **9**[6] has been recognized to be a key intermediate for **1** and efficient installation of 4-carboxybutyl chain to **1** has been accomplished by our procedure[2d] based on $Pd(OH)_2$/C-catalyzed Fukuyama coupling reaction[7] (Scheme 2). Thiol carboxylic acid **8**, a direct precursor to **9**, may be obtained from C-4 functionalized 2-thiazolidinone **7** by conducting the *S*, *N*-carbonyl migration (vide supra). The compound **7** should be readily derived from L-cysteine through Strecker reaction of aldehyde **5**.



3 **4**

Scheme 1.

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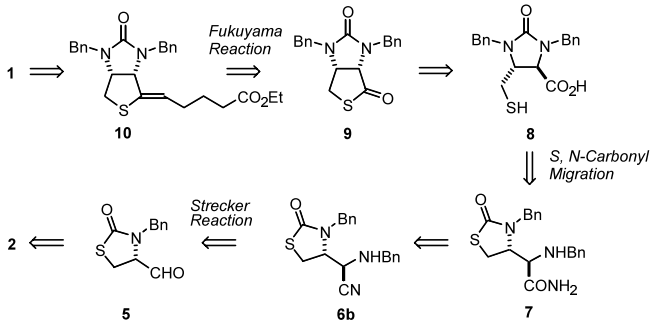
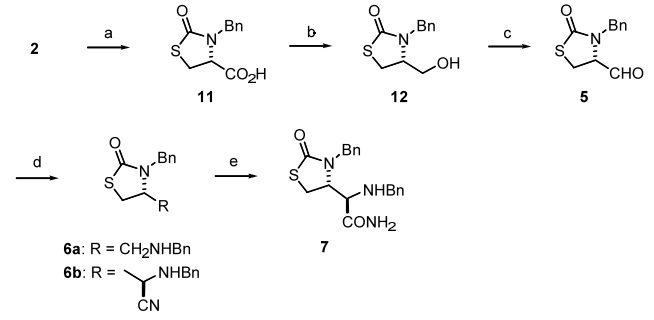


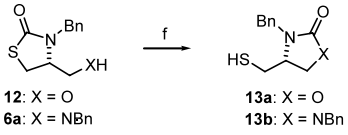
Scheme 2.

To begin with, we synthesized C-4 functionalized 2-thiazolidinone derivative **7** (Scheme 3). L-Cysteine was first converted into (*R*)-*N*-benzyl-2-thiazolidinone-4-carboxylic acid **11** in high yield by the treatment with phenyl chloroformate and NaOH followed by benzyl chloride. It is noteworthy that these transformations, i.e. cyclization and *N*-benzylation, were successfully attained in one-pot procedure and that the selective *N*-benzylation was only achieved when DMSO was employed as a co-solvent. Borane reduction of **11** and subsequent Moffatt oxidation under mild conditions (25–45°C) provided aldehyde **5** in high yield with the original chiral center retained as such.

At this stage, the *S*, *N*-carbonyl migration was examined with alcohol **12** and amine **6a** used as substrates (Scheme 4). Gratifyingly, in accord with our expectation, simple heating of **12** or **6a** in DMF at 115°C for 2 h allowed the facile *S*, *O*- or *S*, *N*-carbonyl migration to provide the corresponding thiol **13a** and **13b** in 93 and 90% yield, respectively.



Scheme 3. *Reagents and conditions*: (a) $ClCO_2Ph$, NaOH, H_2O then BnCl, NaOH, DMSO, 83%; (b) $Me_2S{\cdot}BH_3$, 89%; (c) DCC, pyridine, TFA, DMSO, 89%; (d) for **6a**: $BnNH_2$, $NaBH_3CN$, 80%; for **6b**: $BnNH_2$ then TMSCN, toluene, 96%, *syn*/*anti* = 28:1; (e) H_2O_2, K_2CO_3, DMSO, 93%.



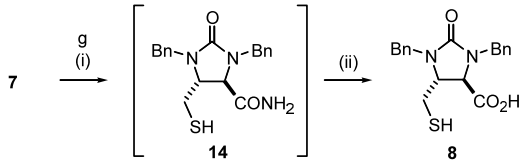
Scheme 4. *Reagents and conditions*: (f) 115°C, 2 h, **13a**: 93%; **13b**: 90%.

Prompted by the results, we undertook the synthesis of (+)-biotin (**1**) based on the concept. Strecker reaction of aldehyde **5** with benzylamine and TMSCN in toluene provided α-amino nitrile **6b** with high stereoselectivity and in high yield (*syn*/*anti* = 28:1, 96%). Conversion of α-amino nitrile **6b** to amide **7** was best conducted by using Katritzky's protocol[8] employing H_2O_2 in the presence of K_2CO_3 in DMSO.

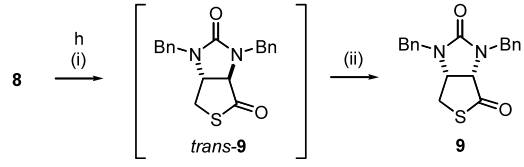
With the C-4 functionalized 2-thiazolidinone derivative **7** carrying the required biotin framework in hand, the ring transformation and simultaneous deblocking the thiol protective group was investigated (Scheme 5). The *S*, *N*-carbonyl migration of **7** had started upon heating at 90°C in DMF and was completed in 1 h. The resulting thiol amide **14**[9] was directly treated with conc. HCl to afford thiol carboxylic acid **8** in 95% yield.[10] The optical purity of **8** was determined to be >99% ee by HPLC, indicating no racemization occurred during the transformation.

The conversion of **8** to thiolactone **9** was conducted by modifying the reported procedure[11] using DCC (Scheme 6). The transformation was found to involve cyclization to *trans*-thiolactone *trans*-**9**[12] followed by epimerization to **9**, which was optimized by the use of DCC in the presence of various acid-base catalysts. While Boden's catalyst (DMAP·HCl)[13] for macrolactonization moderately effected the reaction (63%), the use of more acidic PPTS or TFA·pyridine proved to provide **9** in excellent yields (87 and 93%, respectively).[14] The latter catalyst is advantageous over the former one in terms of the low catalyst loading (0.4 equiv. versus 2 equiv.) required for the transformation.

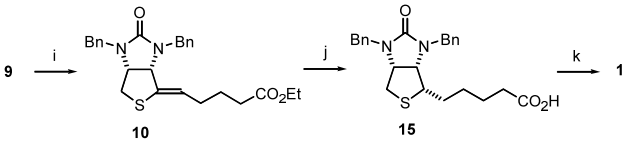
The installation of 4-carboxybutyl chain to **9** was carried out by using $Pd(OH)_2$/C-catalyzed Fukuyama coupling reaction with 5-ethoxy-5-oxopentylzinc iodide (Scheme 7).[2d] The reaction can be conducted under very mild conditions amenable for scale up and the expensive Pd catalyst was recovered (recovery: >95%) by simple filtration.



Scheme 5. *Reagents and conditions*: (g) (i) DMF, 90°C, 1 h; (ii) HCl, 90°C, 3 h, 95%.



Scheme 6. *Reagents and conditions*: (h): (i) DCC (1.5 equiv.), pyridine (1.4 equiv.), TFA (0.4 equiv.), $CHCl_3$, 10°C; 1 h, (ii) 60°C, 6 h, 93%.



Scheme 7. *Reagents and conditions*: (i) (i) $IZn(CH_2)_4CO_2Et$, $Pd(OH)_2/C$ (0.65 mol%), THF, toluene, DMF, 30°C, (ii) HCl, 92%; (j) (i) H_2, $Pd(OH)_2/C$; MeOH, H_2O, (ii) NaOH, 90%; (k) $MeSO_3H$, mesitylene, 74%.

The resulting vinyl sulfide **10** was subjected to low pressure hydrogenation (0.9 MPa) by the use of $Pd(OH)_2/C$ and subsequent removal of the protective groups by $MeSO_3H$[15] to furnish (+)-biotin (**1**) in 67% yield (two steps involving recrystallization of **1**). The product **1** obtained by the present synthesis showed complete identity with an authentic sample with respect to IR, NMR, MS, and optical rotation.[16]

In conclusion, a novel and practical synthesis of (+)-biotin (**1**) was accomplished. The use of the minimally protected intermediates, i.e. 2-thiazolidinone derivatives, considerably reduced the number of steps and (+)-biotin is now accessible in 10 steps and in 31% overall yield from readily available L-cysteine. The synthesis of **1** using thiolactone **9** as a key intermediate was accomplished by Goldberg and Sternbach 50 years ago,[6a,b] which was thoroughly revised by the present work. Short steps, high yield, and ease of operation of the present approach would permit the hitherto most efficient access to **1**. Since the thermal migration of the carbonyl group to oxygen atom other than sulfur atom is possible (as for **12** to **13a**), the use of 2-thiazolidinone derivatives for protecting a thiol group would allow not only the facile synthesis of 4-mercaptomethyl-2-imidazolidinone derivatives (e.g. **13b** and **14**) but also 4-mercaptomethyl-2-oxazolidinone counterparts (e.g. **13a**).

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9. Compound **14** was isolated as stable solids in high yield by simple addition of water to the reaction mixture.
10. Synthesis of **8**: A solution of **7** (100 g, 0.28 mol) in DMF (200 mL) was stirred at 90°C for 3 h under N_2 atmosphere. To the mixture was added dropwise conc. HCl (200 mL, 1.9 mol) at 90°C over 1.75 h. After stirring the mixture at the same temperature for 1.25 h, water (100 mL) was added dropwise at 85°C over 30 min. The mixture was cooled down to 0°C and the solids formed were collected to afford **8** (95.1 g, 95%) as colorless crystals. mp 159–160°C; $[\alpha]_D^{20}=+48.8$ (*c* 0.62, DMF); optical purity: >99% ee [HPLC: Chiralcel AD (Daicel), EtOH/hexane/THF = 10:90:0.1, 0.8 mL/min, 40°C, 225 nm]; IR (KBr) $\nu=1735$, 1625 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.58 (1H, s), 7.37–7.22 (10H, m), 4.83 (1H, d, $J=16.0$ Hz), 4.54 (1H, d, $J=16.0$ Hz), 4.13 (1H, d, $J=16.0$ Hz), 4.06 (1H, d, $J=16.0$ Hz), 3.82 (1H, d, $J=4.0$ Hz), 3.61–3.58 (1H, m), 2.75–2.65 (2H, m), 2.13–2.11 (1H, m); ^{13}C NMR (DMSO-d_6) δ 170.6, 160.7, 136.9, 136.4 (4s), 128.8–127.5, 58.3, 58.0 (8d), 46.5, 46.3, 23.4 (3t); SIMS m/z 357 (M^++1). Anal. calcd for $C_{19}H_{20}N_2O_2S$; C, 64.02; H, 5.66; N, 7.86; Found: C, 63.83; H, 5.38; N, 7.96.
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14. Synthesis of **9**: To a solution of **8** (100 g, 0.28 mol) in $CHCl_3$ (400 mL) were added pyridine (32 mL, 0.39 mol) and TFA (8.7 mL, 0.11 mol) at 0°C followed by a solution of DCC (86.8 g, 0.42 mol) in $CHCl_3$ (136 mL) at 25°C and the mixture was stirred at 0°C for 1 h and refluxed for 6 h. The mixture was cooled down to 25°C and the solids formed were collected. The filtrate was evaporated and the residue was purified by silica gel column chromatography (hexane/AcOEt = 2:1) to afford **9** (88.1 g, 93%) as colorless crystals. Mp 122–123°C (lit.:[6c] 125.5–127°C); $[\alpha]_D^{25}=+90.5$ (*c*, 1.0, $CHCl_3$) {lit.:[6c] $[\alpha]_D^{20}=+91.3\pm0.9$ (*c*, 1.0, 0.1N NaOH)}; IR (KBr) $\nu=1697$, 1686 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39–7.25 (10H, m), 5.04 (1H, d, $J=15.0$ Hz), 4.69 (1H, d, $J=15.0$ Hz), 4.37 (1H, d, $J=15.0$ Hz), 4.36 (1H, d, $J=15.0$ Hz), 4.16–4.09 (1H, m), 3.81 (1H, d, $J=7.8$ Hz), 3.38 (1H, dd, $J=13.0$, 5.6 Hz), 3.29 (1H, dd, $J=13.0$, 2.2 Hz); ^{13}C NMR (DMSO-d_6) δ 205.6, 158.1, 137.1, 136.7 (4s), 128.5–127.3, 62.4, 56.0 (12d), 45.2, 44.6, 32.5 (3t); SIMS m/z 339 (M^++1).
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