# REGIOSELECTIVE HYDRIDE REDUCTION OF 2-(*N*-CYANOIMINO)THIAZOLIDINE DERIVATIVES

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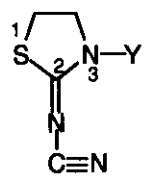
**Abstract** - Treatment of 3-alkyl-2-(*N*-cyanoimino)thiazolidines with lithium aluminum hydride caused reductive cleavage of the imino double bond to afford 3-alkylthiazolidines, while diisobutylaluminum hydride reduction of 3-alkyl- and 3-sulfonyl derivatives resulted in the nitrile reduction or imino-nitrile bond cleavage to give 2-formyliminothiazolidines and/or 2-iminothiazolidines.

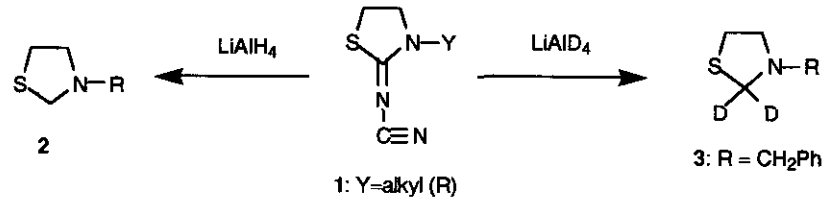
2-(*N*-Cyanoimino)thiazolidine[1] (NCT)(1: Y=H) derivatives exhibit various reactivities according to the substituent at the ring nitrogen ($N_3$) and the reagents used. For example, in 3-acyl-NCTs (1: Y=COR), $N_3$-CO bond cleavage took place by the reaction with amines, alcohols, and thiols.[2] In the compounds bearing active methylene group (1: *e.g.*, Y=$CH_2COR$) at $N_3$, hydrogen abstraction by the base occurred initially and followed by the production of bicyclic heterocycles.[3] On the reaction with hydrazine, 3-alkyl-NCTs (1: Y=alkyl) caused the $C_2$-S bond cleavage followed by intramolecular cyclization to afford 1,2,4-triazoles, while 3-sulfonyl-NCTs (1: Y=$SO_2R$) gave rise to the $C_2$-$N_3$ bond fission to produce different 1,2,4-triazoles.[4] In order to find out new reactivities of NCT derivatives, we investigated the reaction of 3-alkyl- and 3-sulfonyl-NCTs with lithium aluminum hydride (LAH) and diisobutylaluminum hydride (DIBAH). In this paper, we describe the reductive cleavage of the imino double bond (C=N) by LAH and the reduction of the nitrile group and/or the cleavage of the imino-nitrile bond (N-CN) by DIBAH.




**1**

The $C_2$- and the nitrile carbon atoms are expected to be attacked by hydride. At first, we tried LAH reduction of several 3-alkyl-NCTs[5] (Scheme 1) and the results are summarized in the Table 1. In every case, 3-alkyl-NCTs were converted to 3-alkylthiazolidines (**2**) selectively. On the reaction of 3-benzyl-NCT with lithium aluminum deuteride ($LiAlD_4$), 2,2-dideutero-3-benzylthiazolidine (**3**: R=$CH_2Ph$) was obtained in 69 % yield (Scheme 1). In this compound, the methylene proton signals of $C_2$ [δ 4.01 ppm for **2** (Y=$CH_2Ph$)] was disappeared in the $^1H$-nmr spectrum.

**Scheme 1**




**2** **1**: Y=alkyl (R) **3**: R = $CH_2Ph$

**Table 1** 3-Alkylthiazolidines (**2**) from 3-Alkyl-NCTs by the Reduction with LAH

| R | **2**[a] | **2**•HCl | | |
|---|---|---|---|---|
| | Yield (%) | Yield (%) | mp (°C) | Ms *m/z* ($M^+$) |
| Me | b | 57 | 159-160 | 103 |
| Et | 78 | 52 | 213-214 | 117 |
| *n*-Pr | 62 | 46 | 189-190 | 131 |
| *i*-Pr | 54 | 31 | 218-219.5 | 131 |
| *n*-Bu | 57 | 52 | 199-200 | 145 |
| *i*-Bu | 41 | 39 | 214-215 | 145 |
| *sec*-Bu | 44 | 35 | 145-146 | 145 |
| *t*-Bu | 40 | 34 | 197-198 | 145 |
| $CH_2Ph$ | 60 | 55 | 199.5-200.5 | 179 |

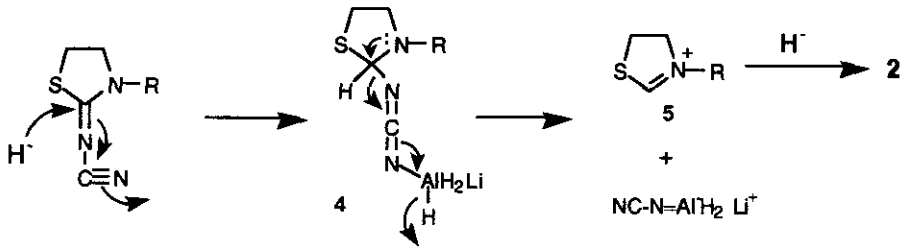
a: All compounds were characterized as their hydrochlorides (**2**•HCl): see Experimental.

b: Yield varied due to its volatility.

This result shows that hydride attacked twice the $C_2$-carbon in this reduction. The reaction mechanism is conceivable as follows. Initially, a hydride attacked the $C_2$-carbon to produce a

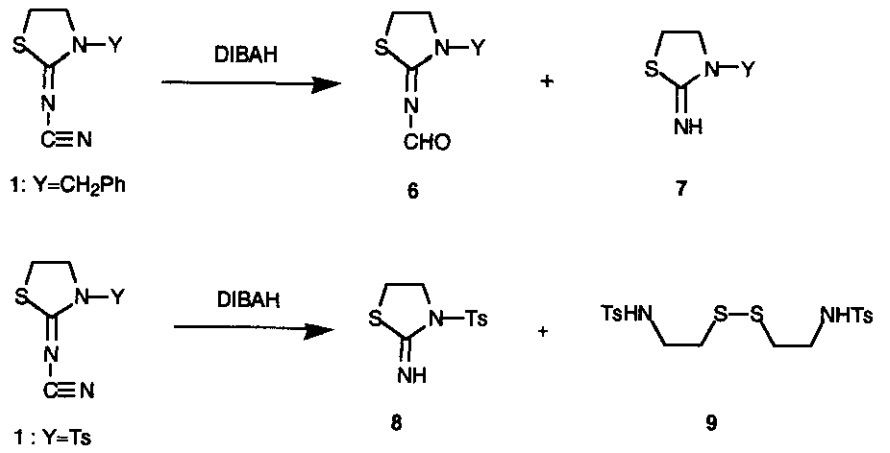
carbodiimide intermediate (**4**), in which aluminum residue attached to the nitrile nitrogen. Subsequently, cyanamide was eliminated by the assistance of the electron-donating $N_3$ to give an iminium intermediate (**5**). Then, second hydride attacked the $C_2$-carbon of **5** to give a 3-alkylthiazolidine (**2**) (Scheme 2).

**Scheme 2**




Next, we investigated the reduction with DIBAH as a bulky reagent. 3-Benzyl-NCT was treated with DIBAH under several conditions to give a mixture of 2-formyliminothiazolidine (**6**)[6] and 2-iminothiazolidine (**7**)[7] (Scheme 3), and the results are given in the Table 2.

**Scheme 3**




Under the conditions of lower reaction temperature and smaller amount of reducing agent, the selectivity of **6** increased. However, *p*-toluenesulfonyl (Ts) derivative (1: Y=Ts) gave an iminothiazolidine (**8**) preferentially at low temperature (Table 3 and Scheme 3). At higher temperature, a disulfide (**9**) was obtained as a by-product.

**Table 2** DIBAH Reduction of 3-Benzyl-NCT

| DIBAH | Temp.(°C) | Solvent | Yield (%) | |
|---|---|---|---|---|
| | | | **6** | **7** |
| 2 eq. | -15 | $C_6H_6$ + toluene | 41 | 21 |
| 3 eq. | -15 | $C_6H_6$ + toluene | 28 | 37 |
| 3 eq. | -50 | $C_6H_6$ + toluene | 50 | 12 |
| 3 eq. | -78 | $CH_2Cl_2$ | 56 | 3 |

**Table 3** DIBAH Reduction of 3-Ts-NCT

| DIBAH | Temp.(°C) | Solvent | Yield (%) | |
|---|---|---|---|---|
| | | | **8** | **9** |
| 2 eq. | -78 | $CH_2Cl_2$ | 65 | - |
| 2 eq. | -50 | $C_6H_6$ + toluene | 64 | - |
| 2 eq. | room temperature | $C_6H_6$ | 39 | 2 |
| 4 eq. | -20 ~ room temperature | $C_6H_6$ + toluene | 29 | 13 |

The reaction mechanism is considered as shown in Scheme 4. The bulky hydride reagent attacked the nitrile carbon, not the $C_2$-carbon, at first to give an intermediate (**10**). Hydrolysis of **10** at this point afforded the formyl derivative (**6**). The more reagent remained in the reaction system promoted further reduction of **10** to give an iminothiazolidine (**7**) *via* a bond cleavage.

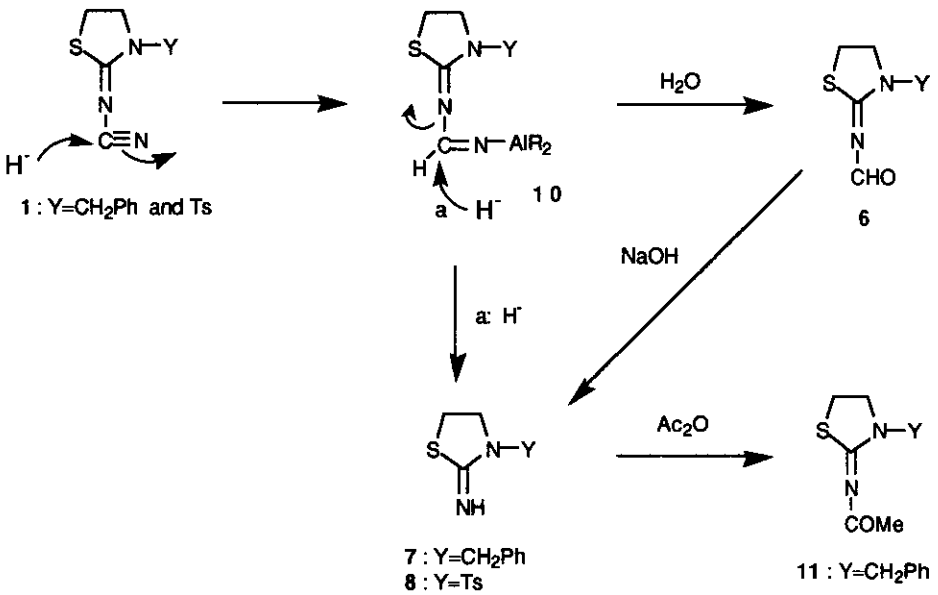
In the meantime, on the reduction of 3-Ts-NCT, the Ts group facilitated the second hydride attack due to its strong electron withdrawing ability, thereby providing **8** directly. The formation of **9** is not understandable. Compound (**8**) did not afford **9** under tha same reaction conditions. Probably, the reductive elimination of the cyanoimino part might have occurred at higher temperature.

The 2-formylimino compound (**6**) was easily converted to a 2-imino derivative (**7**) by the hydrolysis with aqueous sodium hydroxide. And the compound (**7**) was treated with acetic anhydride to give a 2-acetyliminothiazolidine (**11**).

As described above, NCT derivatives exhibited new reactivities toward hydride reagents, LAH and DIBAH. In other words, it was found that the reactive site of NCTs varied according to the reagents

used. LAH reduction of 3-alkyl-NCTs (**1**: Y=R) presented a new general synthetic route to 3-alkylthiazolidines (**2**).[8] On the other hand, DIBAH reduction afforded a 2-formyliminothiazolidine (**6**) and also gave 2-iminothiazolidine derivatives[9] (**7** and **8**).

**Scheme 4**




## EXPERIMENTAL

Melting points are uncorrected. Infrared (Ir) spectra were recorded with a Hitachi 2650-50 or a Hitachi 260-10 spectrophotometer. Mass spectra (Ms) were taken with a Hitachi M80-A, a Shimadzu QP1000, or a JEOL JMS-D300 spectrometer. $^1$H-Nmr spectra were recorded with a Hitachi R24-B, a JEOL JNM-PMX60SI, or a JEOL JNM-FX90Q spectrometer.

**General Procedure for the LAH Reduction of 3-Alkyl-NCTs (1: Y=alkyl)**

To a solution of 3-alkyl-NCT (0.02 mol) in THF (100 ml) was added LAH (760 mg : 0.02 mol) at 0°C, and the mixture was stirred for 1 h. After decomposition of the reagents and complex with ethyl acetate and 2N HCl, the solvent was evaporated. After neutralization of the residue by the addition of 5N NaOH, and the mixture was extracted with ether. The extract was washed with brine, dried on anhydrous $MgSO_4$ and evaporated. The crude product was chromatographed on silica gel to give **2**. Compound (**2**) was dissolved in ether, and dry HCl gas was passed through the solution The precipitate (**2**•HCl) was collected and recrystalized from ethanol-ether. The ir, $^1$H-nmr, and elemental analysis data were summarized in the Table 4. **3-Benzyl-2,2-dideuterothiazolidine**

**(3)** was prepared in a manner similar to that described above using $LiAlD_4$. Ms *m/z*: 181 ($M^+$). $^1$H-Nmr ($CDCl_3$) δ: 2.75-3.20 (4H, m), 3.50 (2H, s), 7.27 (5H, m).

**Table 4** Hydrochlorides of 3-Alkylthiazolidines (**2**•HCl)

| R | Ir (KBr) $cm^{-1}$ | $^1$H-Nmr (DMSO-$d_6$): δ | Formula | Elemental Analysis Found (Calcd) |
|---|---|---|---|---|
| Me[10] | 2610, 2500, 1620, 1460 | 2.89 (3H, s), 3.03-3.06 (2H, m), 3.36-3.75 (2H, m), 4.33 (2H, s) | $C_4H_9NS$ •HCl | C: 34.40 (34.40) H: 7.47 (7.22) N: 10.05 (10.03) |
| Et | 2620, 2510, 1620, 1430 | 1.30 (3H, t, *J*=7 Hz), 2.90-3.78 (6H, m), 4.32 (2H, s) | $C_5H_{11}NS$ •HCl | C: 39.07 (39.08) H: 8.08 (7.87) N: 9.19 (9.11) |
| *n*-Pr | 2610, 2520, 1630, 1435 | 0.91 (3H, t, *J*=7 Hz), 1.38-2.16 (2H, m), 2.88-3.38 (4H, m), 3.38-3.80 (2H, m), 4.34 (2H, s) | $C_6H_{13}NS$ •HCl | C: 42.86 (42.97) H: 8.75 (8.42) N: 8.36 (8.35) |
| *i*-Pr | 2610, 2520, 1630, 1430 | 1.37 (6H, d, *J*=7 Hz), 2.88-4.00 (6H, m), 4.35 (2H, br s) | $C_6H_{13}NS$ •HCl | C: 42.75 (42.97) H: 8.62 (8.42) N: 8.40 (8.35) |
| *n*-Bu | 2600, 2520, 1640, 1430 | 0.79-2.10 (7H, m), 2.93-3.86 (6H, m), 4.35 (2H, br s) | $C_7H_{15}NS$ •HCl | C: 46.13 (46.27) H: 9.11 (8.87) N: 7.66 (7.71) |
| *i*-Bu | 2600, 2520, 1620, 1420 | 1.01 (6H, d, *J*=7 Hz), 1.54-2.83 (1H, m), 2.91-3.85 (5H, m), 3.07 (2H, d, *J*=7 Hz), 4.37 (2H, br s) | $C_7H_{15}NS$ •HCl | C: 46.23 (46.27) H: 9.20 (8.87) N: 7.70 (7.71) |
| *sec*-Bu | 2600, 2500, 1630, 1430 | 0.90 (6H, d, *J*=7 Hz), 1.31 (2H, d, *J*=7 Hz), 1.50-2.23 (2H, m), 2.95-4.00 (6H, m), 4.34 (2H, br s) | $C_7H_{15}NS$ •HCl | C: 46.36 (46.27) H: 9.27 (8.87) N: 7.70 (7.71) |
| *t*-Bu | 2530, 1620, 1430, 1380, 1180 | 1.42 (9H, s), 2.98-3.97 (4H, m), 4.36 (2H, br s) | $C_7H_{15}NS$ •HCl | C: 46.17 (46.27) H: 9.20 (8.87) N: 7.73 (7.71) |
| $CH_2Ph$[11] | 2580, 2520, 1620, 1440, 750, 700 | 3.00-3.35 (2H, m), 3.35-3.68 (2H, m), 4.21 (2H, s), 4.42 (2H, s) 7.25-7.87 (5H, m) | $C_{10}H_{13}NS$ •HCl | C: 55.54 (55.67) H: 6.69 (6.54) N: 6.53 (6.49) |

**The Reduction of 3-Benzyl-NCT with DIBAH**

3-Benzyl-NCT (1 mmol) was dissolved in benzene (5 ml) followed by the addition of toluene (5 ml) or dissolved in $CH_2Cl_2$ (10 ml). After cooling to the temperature shown in the Table 2, 2 equiv. or 3

equiv. of DIBAH solution was added dropwise. And the mixture was stirred at that temperature until the starting material had disappeared on tlc. Methanol, water, and satd. $NaHCO_3$ were added slowly, and the resulting mixture was stirred 1 h at room temperature. The mixture was extracted with $CHCl_3$, and the extract was washed with brine, dried on anhydrous $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=100/1) to give **3-benzyl-2-thiazolidinylidene-formamide (6)** and **3-benzyl-2-iminothiazolidine (7)**. To a solution of **6** (33 mg) in MeOH (1 ml) was added 10% NaOH (1 ml), and the mxiture was stirred at 0°C for 1 h, then extracted with $CHCl_3$. The extract was washed with brine, dried on anhydrous $MgSO_4$, and evaporated. The residue was chromatographed on silica gel ($CHCl_3$/MeOH=100/1) to give **7** (20 mg: 69%). **6**: Light yellow oil. Ir ($CHCl_3$): 2900, 1690, 1630 $cm^{-1}$. Ms *m/z*: 220 ($M^+$). $^1$H-Nmr ($CDCl_3$) δ: 3.04-3.32 (2H, m), 3.44-3.76 (2H, m), 3.84 (2H, s), 7.30 (5H, s), 8.95 (1H, s). **7**: Light brown oil. Ir ($CHCl_3$): 3340, 1660, 1600 $cm^{-1}$. Ms *m/z*: 192 ($M^+$). $^1$H-Nmr ($CDCl_3$) δ: 1.24 (1H, s), 3.00-3.24 (2H, m), 3.28-3.52 (2H, m), 4.52 (2H, s), 7.22 (5H, s).

### 3-Benzyl-2-thiazolidinylideneacetamide (11)

Compound (**7**) was dissolved in acetic anhydride (5 ml), and then the mixture was evaporated at 50°C under reduced pressure. To the residue was added satd. $NaHCO_3$ and $CHCl_3$. The organic layer was washed with brine, dried on anhydrous $MgSO_4$, and evaporated. The residue was chromatographed on silica gel (*n*-hexane:AcOEt=3:1) to give **11** (49 mg: 80%). Mp 39.0-39.5°C. Ir ($CHCl_3$): 1630, 1540 $cm^{-1}$. MS m/z: 234 ($M^+$). $^1$H-Nmr ($CDCl_3$) δ: 2.23 (3H, s), 2.83-3.23 (2H, m), 3.27-3.67 (2H, m), 4.80 (2H, s), 7.20 (5H, s). Anal. Calcd for $C_{12}H_{14}N_2OS$: C, 61.54; H, 5.98; N, 11.97; S, 13.68. Found: C, 61.32; H, 6.06; N, 11.79; S, 13.19.

### Reduction of 3-Ts-NCT (1: Y=Ts) with DIBAH

Reduction was performed in a manner similar to that for 3-Alkyl-NCTs (1: Y=alkyl). The crude product was chromatographed on silica gel (*n*-hexane:AcOEt=2:1) to afford **2-imino-3-*p*-toluenesulfonylthiazolidine (8)** and **bis(*p*-toluenesulfonylaminoethy) disulfide (9)**. **8**: Colorless crystals, mp 118-121°C (from ethyl acetate and hexane). Ir ($CHCl_3$): 3320, 1630 $cm^{-1}$. Ms *m/z*: 256 ($M^+$). $^1$H-Nmr ($CDCl_3$) δ: 2.45 (3H, s), 3.05-3.12 (2H, m), 4.03-4.18 (2H, m), 7.15-8.00 (4H, AA'BB'). Anal. Calcd for $C_{10}H_{12}N_2O_2S_2$: C, 46.98; H, 4.72; N, 10.93; S, 24.98. Found: C, 46.85; H, 4.76; N, 10.82; S, 24.80. **9**: Colorless oil. MS *m/z*: 460 ($M^+$). $^1$H-Nmr ($CDCl_3$) δ: 2.43 (6H, s), 2.71 (4H, m), 3.20 (4H, m), 5.21 (2H, t-like), 7.26-7.81 (10H, AA'BB'). High resolution ms *m/z*: 460.062 (Calcd for $C_{18}H_{24}N_2O_4S_4$: 460.061).

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