REACTION OF 3-ARALKYLSULFONYL-2-(*N*-CYANOIMINO)-THIAZOLIDINES WITH OXYGEN NUCLEOPHILES

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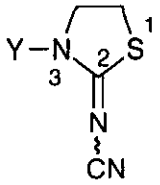
Abstract — 3-Aralkylsulfonyl-2-(*N*-cyanoimino)thiazolidines react with oxygen nucleophiles, such as sodium alkoxides and carboxylates, at the 3-sulfonyl group to give 3-alkyl- and 3-acyl-2-(*N*-cyanoimino)thiazolidines, respectively.

+ *Dedicated to the memory of Professor Yoshio Ban*

Controlling the reactivity of multifunctional compounds is important in effective synthetic transformations. 2-(*N*-Cyanoimino)thiazolidine[1] (NCT; **1a**) is one of these multifunctional compounds, and we have found a variety of chemoselective reactions during our investigation of the reactivity of **1a** and its derivatives (**1b**—**1e**).



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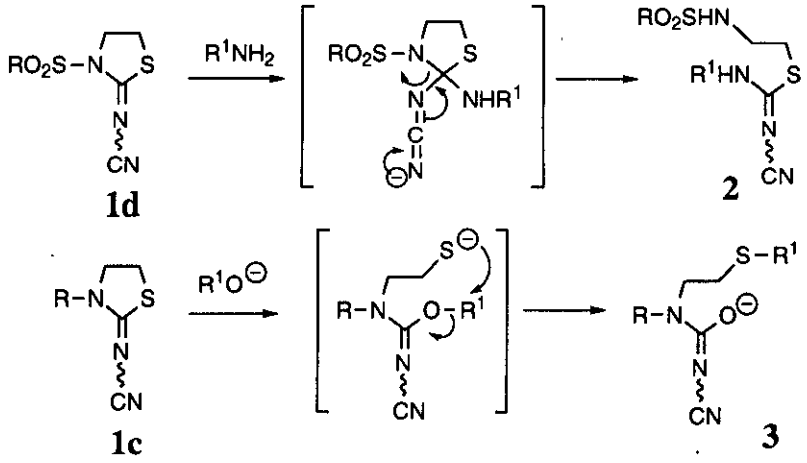
a: Y = H
b: Y = COR
c: Y = alkyl (R)
d: Y = SO_2R
e: Y = $CH(OMe)_2$

For example, 3-acyl-NCT (**1b**) acted as an acylating agent for amines, alcohols, and thiols by selective reaction with the 3-acyl group.[2] Although C(2)=N reductive fission occurred with the reaction of 3-alkyl-NCT (**1c**) with lithium aluminum hydride, the cyano group was selectively reduced by diisobutylaluminum hydride.[3] 3-Alkyl-NCTs (**1c**) reacted with amine at C(2), and this was followed by C(2)-S cleavage to afford cyanoguanidines. Contrary to the result with **1c**, C(2)-N(3) cleavage was observed in the reaction of 3-sulfonyl-NCT (**1d**) with amine to give an isothiourea derivative (**2**) (Scheme 1).[4] Compounds (**1c**) and (**1d**) reacted with hydrazine at C(2), and this was followed by cyclization to provide triazole derivatives.[5] Furthermore, triazine-formation was discovered in the reaction of 3-dimethoxymethyl-NCT

(**1e**) with amines.[6] The formation of other bicyclic heterocycles was also observed.[7] On the other hand, an O→S alkyl migration reaction was found in the reaction of 3-alkyl-NCT (**1c**) with sodium alkoxide, an oxygen nucleophile, to give a cyanourea sodium salt (**3**) (Scheme 1).[4] In this reaction, the alkyl group of the alkoxide was transferred to the sulfur atom after the addition of the alkoxide to C(2), and this was followed by C(2)-S cleavage. In the present paper, we describe the unexpected sulfonyl–alkyl and sulfonyl–acyl exchange reactions in the reaction of 3-sulfonyl-NCT (**1d**) with oxygen nucleophiles such as sodium alkoxides and sodium carboxylates.



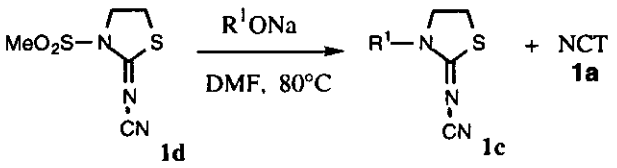
Scheme 1

As described above, it is apparent that both the reaction of **1d** with amine and the reaction of **1c** with sodium alkoxide begin with the addition of the nucleophile to C(2). Therefore, the reaction of **1d** with sodium alkoxide is expected to begin with the addition of the alkoxide to C(2), followed by C(2)-N(3) cleavage. We first examined the reaction of 3-methanesulfonyl(Ms)-NCT (**1d**: R=Me) and 1 equiv. of EtONa at 80 °C in *N,N*-dimethylformamide (DMF). Although the reaction progressed smoothly, the main product, surprisingly, was 3-ethyl-NCT (**1c**: R=Et; 82 % yield), and NCT (**1a**) was also isolated. In this reaction, the 3-sulfonyl group of **1d** was replaced with the alkyl group of the alkoxide. This result shows that the reaction took place at the sulfonyl group instead of C(2). The results of other reactions of 3-Ms-NCT and various sodium alkoxides are summarized in Table 1.

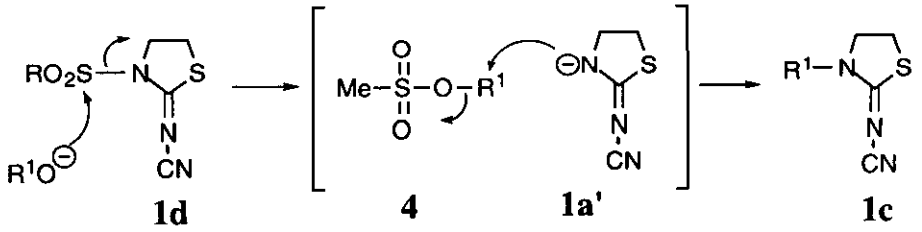
The proposed reaction mechanism is shown in Scheme 2. The alkoxide anion (R^1O^-) attacks the sulfonyl group to give an alkyl sulfonate (**4**) and NCT anion (**1a'**) *via* sulfonamide cleavage. Thereafter, the former acts as an alkylating agent for the latter to produce 3-

alkyl-NCT (**1c**) *via* an S_N2-type reaction. Primary alkoxides generally gave **1c** in good yield, while **1c** was only product at low yield in the reaction of secondary alkoxides. However, sodium *tert*-butoxide or phenoxide gave **1a** in good yield, but no **1c**. These results support the reaction mechanism presented above.[8]

Table 1 Reaction of 3-Mesyl-NCT with R^1ONa



Run	R^1	Yield (%) 1c	1a
1	Me	79	16
2	Et	82	13
3	*n*-Pr	83	16
4	$PhCH_2$	66	29
5	*i*-Pr	24	68
6	*c*-Hex	6	81
7	*t*-Bu	0	80
8	Ph	0	84



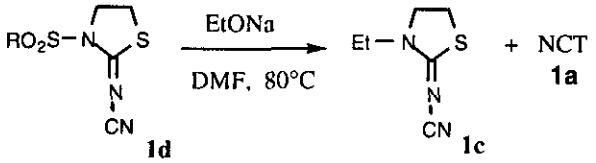
Scheme 2

Next, we investigated the reactions of various 3-sulfonyl-NCTs (**1d**) with sodium ethoxide, and the results are listed in Table 2. In these cases, the yields varied widely according to the substituents, and no tendency was observed. The reactivity of the sulfonyl group seems to be affected considerably by steric and/or electronic factors.

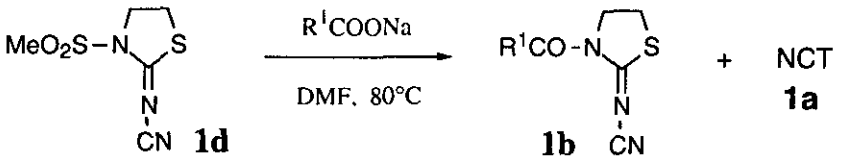
Carboxylate anions are generally much less reactive nucleophiles than alkoxides, which makes the cleavage of the sulfonamide by carboxylate anion difficult to predict.[9]

Anticipating a different reactivity, we investigated the reaction of 3-Ms-NCT (**1d**: R=Me) with sodium acetate in DMF. Contrary to our expectations, sulfonamide cleavage gave 3-acetyl-NCT (**1b**: R=Me) as the main product along with NCT (**1a**). Other examples with several carboxylates are shown in Scheme 3. In this case, an acyl sulfonyl mixed anhydride (**5**) was an expected reaction intermediate.

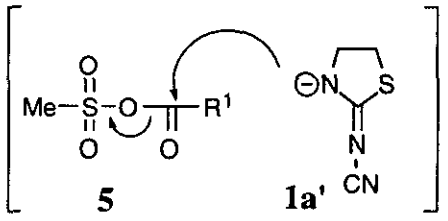
Table 2 Reactions of 3-Aralkylsulfonyl-NCTs with Sodium Ethoxide



Run	R	Yield (%) 1c	1a	1d
1	Me	82	13	0
2	4-MeC_6H_4	22	7	16
3	4-$NO_2C_6H_4$	24	59	8
4	3-$NO_2C_6H_4$	79	10	6
5	2-$NO_2C_6H_4$	20	33	32
6	4-$MeOC_6H_4$	19	38	28
7	4-ClC_6H_4	56	9	20



R^1	Yield (%) 1b	1a
Me	85	6
Et	71	8
n-Pr	79	8
Ph	61	14



Scheme 3

As described above, 3-aralkylsulfonyl-NCT (**1d**) was shown to selectively react with oxygen nucleophiles at the sulfonyl group, which differs from the results of the reaction with amines.[4] Although it is difficult to explain the difference in chemoselectivity between amines and oxygen nucleophiles in **1d**, the sulfonamide bond of **1d** has similar properties to those of 1-sulfonyl-indols or -pyrroles.[10]

EXPERIMENTAL

Melting points are uncorrected. Infrared (ir) spectra were recorded with Hitachi 260-10 spectrophotometer. Mass (ms) and high resolution mass (High-ms) spectra were taken with a Shimadzu QP1000, or a JEOL JMS-D300 spectrometer. ^{1}H-Nmr spectra were recorded with a JEOL JNM-FX90Q or a Varian VXR200. Merck Kieselgel 60 was used for column chromatography.

General Procedure for the Preparation of 3-Sulfonyl-NCT (1d) — Et_3N (556 mg, 5.5 mmol) was added to a suspension of NCT (635 mg, 5 mmol) in $CHCl_3$ (20 ml), and the mixture was stirred until NCT was dissolved. Sulfonyl chloride (5.5 mmol) was added to the above solution at 0 °C, and the whole was stirred overnight at room temperature. $CHCl_3$ (20 ml) was added, and the whole was washed with water, saturated $NaHCO_3$, and brine, then dried over anhydrous magnesium sulfate, and the solvent was evaporated. The residue was purified by recrystallization. **3-Ms-NCT** (Yield 86 %): mp 143—144 °C (from i-PrOH). Ir (KBr) cm^{-1}: 2200, 1570, 1360, 1170. ^{1}H-Nmr (DMSO-d_6) δ: 3.26 (3H, s), 3.54 (2H, t, J = 8 Hz), 4.35 (2H, t, J = 8 Hz). *Anal.* Calcd for $C_5H_7N_3O_2S_2$: C, 29.27; H, 3.44; N, 20.49. Found: C, 29.28; H, 3.45; N, 20.62. **3-Ts-NCT** (Yield 81 %): mp 154.5—155.5 °C (from EtOH). Ir (KBr) cm^{-1}: 2200, 1580, 1370, 1170. ^{1}H-Nmr ($CDCl_3$) δ: 2.46 (3H, s), 3.43 (2H, t, J = 7 Hz), 4.42 (2H, t, J = 7 Hz), 7.75—7.94 (4H, AA'BB' type aromatic H). *Anal.* Calcd for $C_{11}H_{11}N_3O_2S_2$: C, 46.94; H, 3.94; N, 14.94. Found: C, 47.00; H, 3.91; N, 14.85. **3-(4-Nitrophenyl)sulfonyl-NCT** (Yield 67 %): mp 222—223 °C (from EtOAc). Ir (KBr) cm^{-1}: 2200, 1560, 1530, 1380, 1350, 1185. ^{1}H-Nmr (DMSO-d_6) δ: 3.77 (2H, t, J = 7 Hz), 4.68 (2H, t, J = 7 Hz), 8.22—8.55 (4H, AA'BB' type aromatic H). *Anal.* Calcd for $C_{10}H_8N_4O_4S_2$: C, 38.47; H, 2.58; N, 17.95. Found: C, 38.42; H, 2.37; N, 18.04. **3-(3-Nitrophenyl)sulfonyl-NCT** (Yield 72 %): mp 192—193 °C (from EtOAc). Ir (KBr) cm^{-1}: 2200, 1560, 1540, 1380, 1360, 1190. ^{1}H-Nmr (DMSO-d_6) δ: 3.67 (2H, t, J = 7 Hz), 4.59 (2H, t, J = 7 Hz), 7.88—8.70 (4H, m). *Anal.* Calcd for

$C_{10}H_8N_4O_4S_2$: C, 38.47; H, 2.58; N, 17.95. Found: C, 38.32; H, 2.52; N, 18.06. **3-(2-Nitrophenyl)sulfonyl-NCT** (Yield 57 %): mp 230—231 °C (from EtOAc). Ir (KBr) cm^{-1}: 2200, 1575, 1540, 1380, 1195. ^{1}H-Nmr (DMSO-d_6) δ: 3.69 (2H, t, J = 7 Hz), 4.51 (2H, t, J = 7 Hz), 7.91—8.36 (4H, m). *Anal.* Calcd for $C_{10}H_8N_4O_4S_2$: C, 38.47; H, 2.58; N, 17.95. Found: C, 38.33; H, 2.49; N, 18.16. **3-(4-Methoxyphenyl)sulfonyl-NCT** (Yield 84 %): mp 153.5—154.5 °C (from EtOH). Ir (KBr) cm^{-1}: 2200, 1600, 1560, 1370, 1170. ^{1}H-Nmr (DMSO-d_6) δ: 3.27 (3H, s), 3.60 (2H, t, J = 8 Hz), 4.49 (2H, t, J = 8 Hz), 7.11—8.03 (4H, AA'BB' type aromatic H). *Anal.* Calcd for $C_{11}H_{11}N_3O_3S_2$: C, 44.45; H, 3.73; N, 14.14. Found: C, 44.53; H, 3.63; N, 14.19. **3-(4-Chlorophenyl)sulfonyl-NCT** (Yield 79 %): mp 181.5—183 °C (from i-PrOH). Ir (KBr) cm^{-1}: 2200, 1560, 1370. ^{1}H-Nmr (DMSO-d_6) δ: 3.60 (2H, t, J = 7 Hz), 4.51 (2H, t, J = 7 Hz), 7.66—8.11 (4H, AA'BB' type aromatic H). *Anal.* Calcd for $C_{10}H_8N_3O_2ClS_2$: C, 39.80; H, 2.67; N, 13.93. Found: C, 39.83; H, 2.66; N, 13.94.

General Procedure for the Reaction of 1d with Sodium Alkoxides — An alcohol (2.10 mmol) was added to a suspension of NaH (60 %; 84 mg, 2.10 mmol) in DMF (3 ml). After hydrogen evolution had ceased, a solution of 3-sulfonyl-NCT (**1d**: 2.00 mmol) in DMF (2 ml) was added to the resulting solution, then the whole was stirred at 80 °C until the starting material disappeared on tlc. Water (0.5 ml) and $CHCl_3$ (10 ml) were added. The resulting precipitates were filtered off, then the filtrate was evaporated. The residue was chromatographed on silica gel ($CHCl_3$–MeOH) to give 3-alkyl-NCT, which was identical to the compound prepared by the reported procedure.[7] **3-Methyl-NCT**: mp 100—101 °C (from EtOAc–hexane). Ms *m/z*: 141 (M^+). Ir ($CHCl_3$) cm^{-1}: 2180, 1590. ^{1}H-Nmr ($CDCl_3$) δ: 3.04 (3H, s), 3.41 (2H, t, J = 7.5 Hz), 3.89 (2H, t, J = 7.5 Hz). *Anal.* Calcd for $C_5H_7N_3S$: C, 42.54; H, 5.00; N, 29.76. Found: C, 42.59; H, 4.94; N, 29.82. **3-Ethyl-NCT**: mp 82—84 °C (from EtOAc–hexane). Ms *m/z*: 155 (M^+). Ir ($CHCl_3$) cm^{-1}: 2190, 1595. ^{1}H-Nmr ($CDCl_3$) δ: 1.23 (3H, t, J = 8.0 Hz), 3.37 (2H, m), 3.54 (2H, t, J = 8.0 Hz), 4.05 (2H, m). *Anal.* Calcd for $C_5H_7N_3S$: C, 46.43; H, 5.84; N, 27.07. Found: C, 46.37; H, 5.81; N, 27.35. **3-*n*-Propyl-NCT**: mp 36—38 °C (from petr. ether). Ms *m/z*: 169 (M^+). Ir ($CHCl_3$) cm^{-1}: 2160, 1580. ^{1}H-Nmr ($CDCl_3$) δ: 0.90—0.97 (3H, t, J = 6.0 Hz), 1.60—1.70 (2H, m), 3.37—3.45 (4H, m), 3.90 (2H, t, J = 7.5 Hz). *Anal.* Calcd for $C_7H_{11}N_3S$: C, 49.68; H, 6.55; N, 24.83. Found: C, 49.65; H, 6.57; N, 24.86. **3-Benzyl-NCT**: mp 104—105 °C (from EtOAc–hexane). Ms *m/z*: 217 (M^+). Ir ($CHCl_3$) cm^{-1}: 2160, 1565. ^{1}H-Nmr

($CDCl_3$) δ: 3.35 (2H, t, *J* = 7.2 Hz), 3.73 (2H, t, *J* = 7.2 Hz), 4.62 (2H, s), 7.20—7.45 (5H, m). *Anal.* Calcd for $C_5H_7N_3S$: C, 60.80; H, 5.10; N, 19.34; S, 14.75. Found: C, 61.02; H, 5.07; N, 19.02. **3-*iso*-Propyl-NCT**: mp 111—112 °C (from EtOAc–hexane). Ms *m/z*: 169 (M^+). Ir ($CHCl_3$) cm^{-1}: 2175, 1585. ^{1}H-Nmr ($CDCl_3$) δ: 1.21 (6H, d, *J* = 7.0 Hz), 3.24—3.48 (2H, m), 3.91—3.95 (2H, m), 4.45 (1H, hep, *J* = 7.0 Hz). *Anal.* Calcd for $C_7H_{11}N_3S$: C, 49.68; H, 6.55; N, 24.83. Found: C, 49.68; H, 6.56; N, 24.80. **3-Cyclohexyl-NCT**: oil. Ms *m/z*: 209 (M^+). Ir ($CHCl_3$) cm^{-1}: 2227, 1452. ^{1}H-Nmr ($CDCl_3$) δ: 1.20—2.10 (10H, m), 3.50 (2H, t, *J* = 7.5 Hz), 4.17 (2H, t, *J* = 7.5 Hz), 4.70 (1H, m). High-ms: Calcd for $C_{10}H_{15}N_3S$: 209.2001. Found: 209.1999.

The Reaction of 3-Ms-NCT (1d) with Sodium Acetate A solution of 3-Ms-NCT (**1d**: 500 mg; 2.44 mmol) in DMF (3 ml) was added to a suspension of AcONa (300 mg; 3.65 mmol) in DMF (3 ml), and the resulting mixture was stirred overnight at 80 °C. The DMF was evaporated off *in vacuo*, and to the residue was added $CHCl_3$. After filtration of the insoluble materials, the filtrate was concentrated, and the residue was chromatographed on silica gel (*n*-Hexane : AcOEt = 1 : 1) to give 3-acetyl-NCT (**1b**: 350 mg; 85 %) as colorless crystals, mp 143—145 °C (from benzene). Ms *m/z*: 169 (M^+). Ir ($CHCl_3$) cm^{-1}: 2192, 1700. ^{1}H-Nmr ($CDCl_3$) δ: 2.57 (3H, s), 3.39 (2H, t, *J* = 7.5 Hz), 4.41 (2H, t, *J* = 7.5 Hz). *Anal.* Calcd for $C_6H_7N_3OS$: C, 42.61; H, 4.17; N, 24.83. Found: C, 42.59; H, 4.25; N, 24.73.

General Procedure for the Reaction of 3-Ms-NCT (1d) with Sodium Carboxylates A solution of a carboxylic acid (2.56 mmol) in DMF (2 ml) was added dropwise to a suspension of NaH (60 % in oil: 102.3 mg; 2.56 mmol) in DMF (3 ml). After hydrogen evolution had ceased, a solution of 3-Ms-NCT (**1d**: 500 mg; 2.44 mmol) in DMF (3 ml) was added to the resulting solution, then the whole was stirred overnight at 80 °C. After cooling, the solvent was evaporated off *in vacuo*, and the residue was purified by silica gel chromatography ($CHCl_3$) to give 3-acyl-NCT (**1b**), which was identical to the compound prepared by the reported procedure.[2] **3-Propionyl-NCT**: mp 91—93 °C (from benzene–hexane). Ms *m/z*: 183 (M^+). Ir ($CHCl_3$) cm^{-1}: 2186, 1716. ^{1}H-Nmr ($CDCl_3$) δ: 1.65 (3H, t, *J* = 7.0 Hz), 2.95 (2H, q, *J* = 7.0 Hz), 3.39 (2H, t, *J* = 7.5 Hz), 4.42 (2H, t, *J* = 7.5 Hz). *Anal.* Calcd for $C_7H_9N_3OS$: C, 45.89; H, 4.95; N, 22.93. Found: C, 46.08; H, 4.83; N, 23.01. **3-Butyryl-NCT**: mp 44—46 °C (from benzene–hexane). Ms *m/z*: 197 (M^+). Ir

($CHCl_3$) cm^{-1}: 2192, 1710. ^{1}H-Nmr ($CDCl_3$) δ: 0.97 (3H, t, *J* = 6.5 Hz), 1.68 (2H, m), 2.92 (2H, t, *J* = 7.0 Hz), 3.40 (2H, t, *J* = 7.5 Hz), 4.40 (2H, t, *J* = 7.5 Hz). *Anal.* Calcd for $C_8H_{11}N_3OS$: C, 51.06; H, 6.20; N, 19.91. Found: C, 51.35; H, 6.20; N, 19.91. **3-Benzoyl-NCT**: mp 128—130 °C (from MeOH). Ms *m/z*: 231 (M^+). Ir ($CHCl_3$) cm^{-1}: 2200, 1700. ^{1}H-Nmr ($CDCl_3$) δ: 3.55 (2H, t, *J* = 7.5 Hz), 4.45 (2H, t, *J* = 7.5 Hz). *Anal.* Calcd for $C_{11}H_9N_3OS$: C, 57.13; H, 3.92; N, 18.17. Found: C, 57.40; H, 3.71; N, 18.38.

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8. Although the formation of alkyl sulfonates was not confirmed experimentally, we proved independently that NCT anion prepared from NCT (**1a**) and NaH in DMF was alkylated by ethyl methanesulfonate to give 3-ethyl-NCT (**1c**: R=Et) in good yield.
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Received, 6th February, 1995