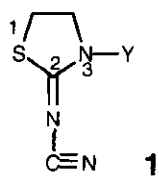
NUCLEOPHILICITY OF 3-ALKYL-2-(*N*-CYANOIMINO)-THIAZOLIDINES: METHYLATED PRODUCTS AND THEIR REACTIVITY

Chuzo Iwata,* Tetsuya Kawakami, Michitaro Fujimoto,
Yumi Nakamoto, and Tetsuaki Tanaka
Faculty of Pharmaceutical Sciences, Osaka University,
1-6 Yamadaoka, Suita, Osaka 565, Japan.

Abstract — 3-Alkyl-2-(*N*-cyanoimino)thiazolidines were methylated mainly at the nitrile nitrogen atom with trimethyloxonium tetrafluoroborate ($Me_3O{\bullet}BF_4$). The reaction of the methylated products, the nitrilium salts, with sodio diethyl malonate was described.

2-(*N*-Cyanoimino)thiazolidine (NCT)(**1**: Y=H)[1] has four nucleophilic and two electrophilic sites in its small molecule. The former are three nitrogen and a sulfur atoms, and the latter are the C(2) and the nitrile carbon atoms. These are sufficient to predict diverse reactivities of **1** and its derivatives. During the investigation of the reactivity of NCT derivatives, we obtained several interesting results.[2] In these studies, the reactions with nucleophiles were investigated. At this time, we were interested in the reactions of the 3-alkyl-NCTs (**1**: Y=R) toward electrophiles such as "Me^+". Namely, we want to know which part of the molecule is methylated, and how the reactivity of the methylated product is altered from the parent compound. Because the methylated product would be much more reactive toward nucleophiles than the parent compound, thereby expecting the reaction not occurring in the parent compound. In this paper, we describe the methylation reaction with trimethyloxonium tetrafluoroborate ($Me_3O{\bullet}BF_4$),[3] the reaction of the methylated products with sodium salt of diethyl malonate, and the estimation of the reactivity of 3-alkyl-NCT using *ab initio* molecular orbital (MO) calculation.



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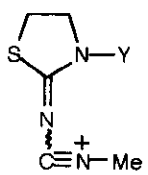

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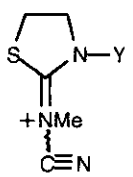
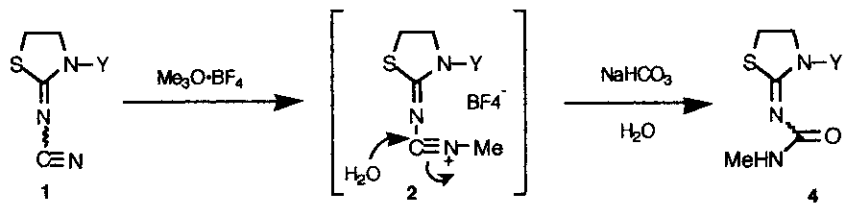


3

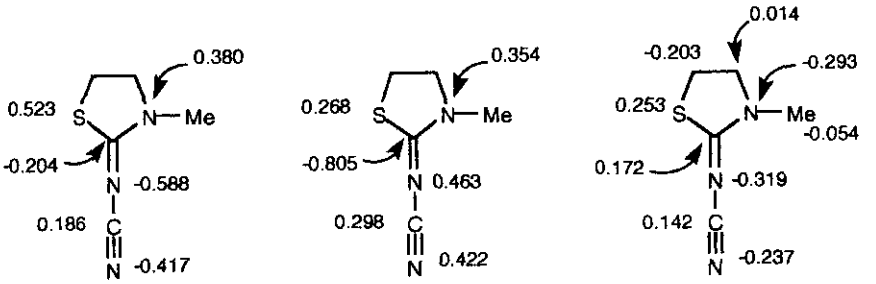
At first, methylation reactions of 3-alkyl-NCT (**1**: Y=R) were tried using several methylating reagents. The reaction with methyl idodide (MeI) did not occur even at an elevated temperature (~150°C) in a sealed tube. Dimethyl sulfate did not work either. Then we tried one of the strongest methylating reagents such as $Me_3O{\bullet}BF_4$, which afforded the quaternary salts (**2**) as crystals.[4] But the products were so labile to confirm the structure directly. Aqueous alkaline hydrolysis of the crude quaternary salts gave a methylurea derivative (**4**) in *ca.* 40 % yield (Scheme 1).[5] This result means that the methylation reaction occurred at the nitrile nitrogen atom in at least 40 % yield. However, as no other product could be characterized, the presence of the products methylated at other than the nitrile nitrogen such as **3** could not be confirmed.

Scheme 1



Here, we estimated the reactivity of 3-methyl-NCT using *ab initio* MO calculation.[6] The LCAO (linear combination of atomic orbital) coefficients of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO),[7] and the formal charge were shown in Figure 1. In general, the reaction with soft reagents would be the orbital-controlled reaction, and the one with hard reagents would be the electrostatically-controlled reaction.[8] Although the methylation reaction with soft reagents such as MeI, the imino nitrogen and the sulfur atom seem to be reactive because of their large coefficient values in the HOMO, the reaction with the hard methylating reagents such as $Me_3O{\bullet}BF_4$ would proceed mainly under the electrostatic-control rather than the orbital-control. So the possibility of methylation at the sulfur atom with hard reagents can be estimated to be very low due to its positive charge. Accordingly, the imino nitrogen seems to be more reactive than other nitrogens. Nevertheless, the steric circumstances and the positive charge around each nucleophilic center must be considered. In this viewpoint, the nitrile nitrogen is the least sterically congested nitrogen atom and there is less positive charge around this nitrogen. In other words, the electrophile (Me^+) can easily approach this electrophilic site. Accordingly, steric and electrostatic factor would have played an important role in this reaction.

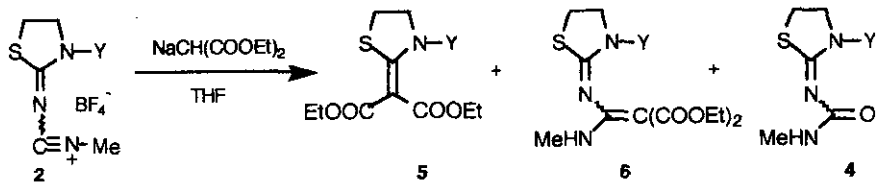
Figure 1



HOMO LUMO Formal Charge

Next, we investigated the reaction of the quaternary salts (**2**) with a carbanion. It is of interest that the reaction of a nitrilium salt[9] conjugated with imino group. We examined the reaction with the sodio diethyl malonate. Although 3-alkyl-NCT does not react with sodio diethyl malonate, the nitrilium salt reacted to afford 2-methylenethiazolidine derivatives (**5**)[10] and/or 2-iminothiazolidine compounds (**6**)[11] along with the methylurea derivatives (**4**) (Table).

Table The reaction of the Nitrilium Salts (**2**) with Sodio Diethyl Malonate



2 5 6 4

2	Reaction	Yield (%)[b]		
Y	Temperature [a]	**5**	**6**	**4**
Me	A	23	11	16
Me	B	27	0	20
Et	A	15	9	13
Et	B	22	7	9
CH_2Ph	A	30	8	7
CH_2Ph	B	38	0	9

a) A = -78°C ~ room temperature; B = -78°C ~ -40°C b) Isolated yields based on **1**.

The formation of **5** and **6** is considered as shown in Scheme 2. In this reaction, two competitive reactions occurred. The one is that the carbanion attacked the C(2) to afford a carbodiimide followed by the elimination of a methylcyanamide (not isolated) to give **5**, and the other is that the carbanion attacked the nitrilium carbon followed by hydrogen shift to produce **6**. The product ratio varied according to the reaction temperature (see Table), and the compound (**4**) was always formed unavoidably.[12] Unexpectedly, the reaction with sodio ethyl acetoacetate gave neither **5** nor **6** type compounds, but only **4** as a sole characterizable product. Judging from the LUMO and the formal charge for the quaternary salt (**2**: Y=Me) (Figure 2), the following estimation might be drawn. The C(2)-carbon would be the most reactive toward soft nucleophiles, and the nitrilium carbon would be the most reactive with hard nucleophiles. In either case, the higher reactivity of the nitrilium carbon compared with the parent nitrile carbon is expected. As sodio diethyl malonate is a soft nucleophile, the difference of the coefficient values of LUMO between the C(2) and the nitrilium carbon seems to be reflected at the lower reaction temperature.

Scheme 2

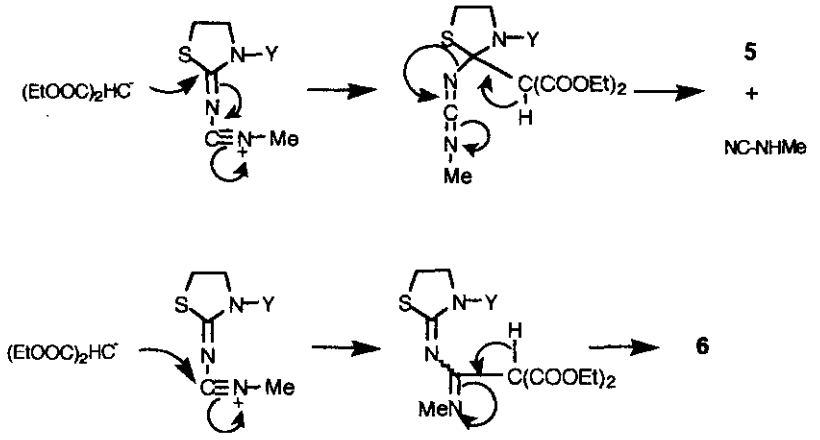
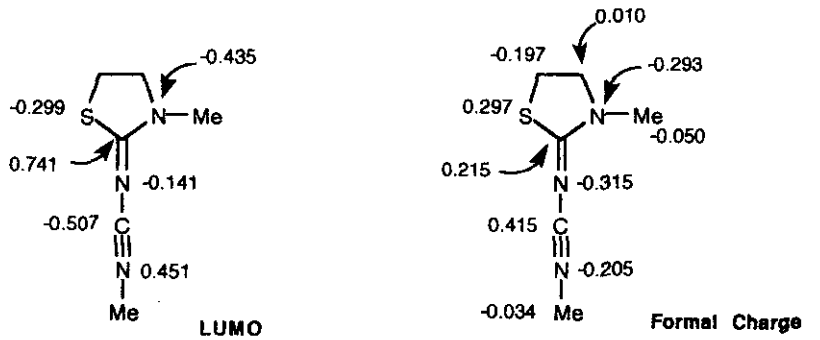


Figure 2



In conclusion, it was found that 3-alkyl-NCTs reacted with the strong methylating reagents mainly at the nitrile nitrogen to afford nitrilium salts which were converted to 2-methylene- (**5**) and/or 2-iminothiazolidine derivatives (**6**) by the reaction with sodio diethyl malonate.

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 the Quaternary Salt (2) — A solution of 3-alkyl-NCT (**1**: 0.52 mmol) in CH_2Cl_2 (2 ml) was added dropwise at 0°C to a suspension of $Me_3O^{\bullet}BF_4$ (0.54 mmol) and CH_2Cl_2 (3 ml), and the mixture was stirred at room temperature until the starting material was no longer detectable on tlc. The solvent was evaporated to afford the crude salt (**2**).

Hydrolysis of the Quaternary Salts (2) — Water (2 ml) and satd. $NaHCO_3$ (10 ml) were added to the crude quaternary salt (**2**) obtained above, and the mixture was stirred for 24 h and extracted with $CHCl_3$ (100 ml). The extract was washed with brine and dried over anhydrous $MgSO_4$, and then the solvent was evaporated. The residue was purified by silica gel column chromatography (hexane:AcOEt=*1:1* → *1:2*) to give an urea derivative (**4**) in *ca.* 40 % yield.

3-Methyl-1-(3-methyl-2-thiazolidinylidene)urea (4: Y=Me) — Colorless crystals, mp 139.0-140.0 °C. ^{1}H-Nmr ($CDCl_3$) δ: 2.85 (3H, d, J = 5 Hz), 2.99-3.17 (2H, m), 3.04 (3H, s), 3.56 (2H, t, J = 7 Hz). Ir ($CHCl_3$) cm^{-1}: 3475, 1640, 1580. Ms *m/z*: 173 (M^+). High-ms: Calcd for $C_6H_{11}N_3OS$: 173.062. Found: 173.062.

1-(3-Ethyl-2-thiazolidinylidene)-3-methylurea (4: Y=Et) — Colorless crystals, mp 123.0-124.0 °C. ^{1}H-Nmr ($CDCl_3$) δ: 1.15 (3H, t. J = 7 Hz), 2.84 (3H, d, J = 5 Hz), 3.06 (2H, t, J = 7 Hz), 3.33-3.65 (4H, m). Ir ($CHCl_3$) cm^{-1}: 3470, 1630, 1570. Ms *m/z*: 187 (M^+). High-ms: Calcd for $C_7H_{13}N_3OS$: 187.078. Found: 187.078.

1-(3-Benzyl-2-thiazolidinylidene)-3-methylurea (4: Y=CH_2Ph) — Colorless crystals, mp 135.0-136.0 °C. ^{1}H-Nmr ($CDCl_3$) δ: 2.86 (3H, d, J = 5 Hz), 3.04 (2H, t, J = 8 Hz), 3.45 (2H, t, J = 8 Hz), 4.74 (2H, s), 7.21-7.32 (5H, m). Ir ($CHCl_3$) cm^{-1}: 3465, 1640,

1580. Ms *m/z*: 249 (M^+). *Anal.* Calcd for $C_{12}H_{15}N_3OS$: C, 57.80; H, 6.06; N, 16.86; S, 12.86. Found: C, 57.68; H, 6.11; N, 16.56; S, 12.65.

General Procedure for the Reaction of the Quaternary Salts (2) with Sodio Diethyl Malonate — A solution of sodio diethyl malonate prepared from diethyl malonate (1.04 mmol) and NaH (1.09 mmol) in THF (5 ml) was added at -78°C to a suspension of the quaternary salt (**2**: prepared from 0.52 mmol of **1**) in THF (2 ml), and the mixture was gradually warmed up to room temperature with stirring. After the addition of water (10 ml), the mixture was extracted with $CHCl_3$ (100 ml). The extract was washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (hexane:AcOEt=1:1 → 1:3) to give **4**, **5**, and **6**.

Diethyl (3-Methyl-2-thiazolidinylidene)malonate (5: Y=Me) — Colorless oil. ^{1}H-Nmr ($CDCl_3$) δ: 1.28 (6H, t, J = 7 Hz), 2.89-3.13 (2H, m), 2.96 (3H, s), 3.70 (2H, t, J = 8 Hz), 4.20 (4H, q, J = 7 Hz). IR ($CHCl_3$) cm^{-1}: 1700, 1665. MS *m/z*: 259 (M^+). *Anal.* Calcd for $C_{11}H_{17}NO_4S$: C, 50.95; H, 6.61; N, 5.40; S, 12.36. Found: C, 50.80; H, 6.65; N, 5.29; S, 12.35.

Diethyl (3-Ethyl-2-thiazolidinylidene)malonate (5: Y=Et) — Colorless crystals, mp 51.0-52.0 °C. ^{1}H-Nmr ($CDCl_3$) δ: 1.20 (3H, t, J = 7 Hz), 1.28 (6H, t, J = 7 Hz), 3.02 (2H, t, J = 7 Hz), 3.34 (2H, t, J = 7 Hz), 3.75 (2H, q, J = 7 Hz), 4.20 (4H, q, J = 7 Hz). Ir ($CHCl_3$) cm^{-1}: 1710, 1670. Ms *m/z*: 273 (M^+). *Anal.* Calcd for $C_{12}H_{19}NO_4S$: C, 52.72; H, 7.01; N, 5.13; S, 11.73. Found: C, 52.44; H, 7.22; N, 4.97; S, 11.50.

Diethyl (3-Benzyl-2-thiazolidinylidene)malonate (5: Y=CH_2Ph) — Colorless oil. ^{1}H-Nmr ($CDCl_3$) δ: 1.21 (6H, t, J = 7 Hz), 2.93 (2H, t, J = 7 Hz), 3.60 (2H, t, J = 7 Hz), 4.12 (4H, q, J = 7 Hz), 4.45 (2H, s), 7.27-7.33 (5H, m). Ir ($CHCl_3$) cm^{-1}: 1700, 1665. Ms *m/z*: 335 (M^+). *Anal.* Calcd for $C_{17}H_{21}NO_4S$: C, 60.87; H, 6.31; N, 4.18; S, 9.55. Found: C, 60.35; H, 6.26; N, 4.12; S, 9.53.

Diethyl [N'-Methyl-N-(3-methyl-2-thiazolidinylidene)]diaminomethylenemalonate (6: Y=Me) — Colorless oil. ^{1}H-Nmr ($CDCl_3$) δ: 1.26 (6H, t, J = 7 Hz), 2.82 (3H, d, J = 5 Hz), 3.05 (3H, s), 3.21 (2H, t, J = 7 Hz), 3.67 (2H, t, J = 7 Hz), 4.14 (4H, q, J = 7 Hz). Ir ($CHCl_3$) cm^{-1}: 3250, 1685, 1620, 1585. Ms *m/z*: 315 (M^+). High-ms Calcd for $C_{13}H_{21}N_3O_4S$: 315.127. Found: 315.125.

Diethyl [N-(3-Ethyl-2-thiazolidinylidene)-N'-methyl]diaminomethylenemalonate (6: Y=Et) — Colorless oil. ^{1}H-Nmr ($CDCl_3$) δ: 1.22 (3H, t, J = 7 Hz), 1.25 (6H, t, J = 7 Hz), 2.82 (3H, d, J = 5 Hz), 3.20 (2H, t, J = 7 Hz), 3.54 (2H, q, J = 7 Hz), 3.69

(2H, t, J = 7 Hz), 4.13 (4H, q, J = 7 Hz). Ir ($CHCl_3$) cm^{-1}: 3250, 1685, 1620, 1580. Ms *m/z* 329 (M^+). High-ms Calcd for $C_{14}H_{23}N_3O_4S$: 329.139. Found: 329.141.

Diethyl [N-(3-Benzyl-2-thiazolidinylidene)-N'-methyl]diaminomethylenemalonate (6: Y=CH_2Ph) — Colorless oil. ^{1}H-Nmr ($CDCl_3$) δ: 1.26 (6H, t, J = 7 Hz), 2.82 (3H, d, J = 5 Hz), 3.18 (2H, t, J = 7 Hz), 3.60 (2H, t, J = 7 Hz), 4.15 (4H, q, J = 7 Hz), 4.69 (2H, s), 7.27-7.34 (5H, m). Ir ($CHCl_3$) cm^{-1}: 3250, 1690, 1620, 1585. Ms *m/z*: 391 (M^+). High-ms Calcd for $C_{19}H_{25}N_3O_4S$: 391.156. Found: 391.156.

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6. This calculation was carried out with use of the GSCF3 program developed by Dr. N. Kosugi, University of Tokyo (present address: Kyoto University), on HITAC S820 computer, and we thank Dr. T. Takagi (Osaka University) for his generous assistance on the calculation. For the program, see: N. Kosugi, *Theoret. Chim. Acta*, 1987, **72**, 149; *J. Comput. Phys.*, 1984, **55**, 426; *Chem. Phys. Lett.*, 1980, **74**, 490.
7. Although LUMO is not important in the present study, a high reactivity of the C(2)-position toward nucleophiles can easily be predictable from its large coefficient value.
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10. We developed here a new synthetic route to 2-thiazolidinylidenemalonates. Some other these type compounds are known as biologically active substances, and as intermediates for the synthesis of various heterocycles. *cf.* M. Patzel and Liebscher, *J. Heterocycl. Chem.*, 1991, **28**, 1257; Y. Tominaga, Y. Matsuoka, Y. Onikawa, Y. Uchiyama, H. Komiya, M. Hirayama, S. Khora, and A. Hosomi, *ibid.*, 1990, **27**, 647; for a patent, *Chem. Abstr.*,1987, **108**, 11244y. Some 2-thiazolidinylidenemalonates bearing no substituent at the ring carbons are known, see: Y. Shvo and I. Belsky, *Tetrahedron*, 1969, **25**, 4649; R. C. Cambie, G. R. Clark, T. C. Jones, P. S. Rutledge, G. A. Strange, and P. D. Woodgate, *Aust. J. Chem.*, 1985, **38**, 745; Z. Huang and X. Shi, *Synthesis*, **1990**, 162; and others are found in the patents: *Chem. Abstr.*, 1983, **98**, 53877w; 1985, **103**, 22618e; 1990, **112**, 188639y.
11. To our knowledge, the compounds such as **6** are hitherto unknown compounds.
12. Compound (**6**) produced neither **5** nor **4** under the same reaction conditions.

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