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3-CYANO-2-(*N*-CYANOIMINO)THIAZOLIDINE (3-CYANO-NCT): AN EFFICIENT ELECTROPHILIC CYANATING AGENT FOR ACTIVATED METHYLENE COMPOUNDS

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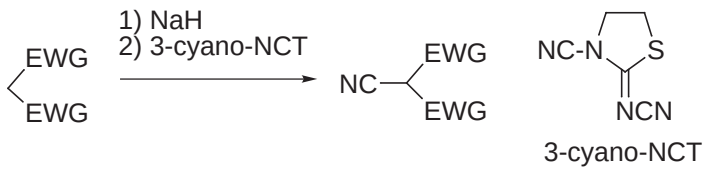
Abstract - We found that 3-cyano-2-(*N*-cyanoimino)thiazolidine (3-cyano-NCT) is a novel electrophilic cyanating agent. Various activated methylene compounds were cyanated in moderate to good yields.

INTRODUCTION

Nitrile is an important synthetic intermediate for a variety of functional groups and is found in various pharmaceuticals and biologically active natural products. The convenient C_1-unit is regularly introduced by nucleophilic attack of cyanide (CN^-). On the other hand, electrophilic cyanation of nucleophiles using a cyano cation (CN^+) equivalent provides another access to synthesize cyano compounds. Cyanogen halides are representative electrophilic cyanating agents. However, this reagent is highly toxic and moisture-sensitive. Therefore, alternative cyano cation equivalents have extensively been developed, *e.g.*, 1-cyanoimidazole,[1] 1-cyanobenzotriazole,[2] 2-chlorobenzyl thiocyanate,[3] and arylsulfonyl cyanides.[4] However, these reagents have been used for cyanation of relatively reactive carbanions such as aryl anions, acetylides, arylacetonitrile anions, enamines, and enolates. In contrast, there are few reports for cyanation of stabilized carbanions.[5]



Scheme 1

We have reported that 2-(*N*-cyanoimino)thiazolidine (NCT) is a novel class of a recoverable leaving group and can transfer the functional groups at the C_3-position, such as sulfenyl,[6] acyl,[7] and dialkylphos-

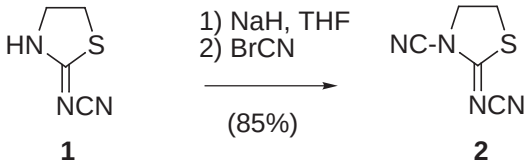
This paper dedicated to the 75th birthday of Professor Yuichi Kanaoka.

phono groups.[8] In connection with this study, we were interested in the reaction of 3-cyano-NCT, since this compound was expected to become a novel electrophilic cyanating agent and also it possesses a unique structure in which four nitrogen atoms and three carbon atoms are alternatively aligned.

In this paper, we describe the development of a new cyanating agent involving 2-(*N*-cyanoimino)thiazolidine structure and its application to the cyanation of stabilized carbanions (Scheme 1).

RESULTS AND DISCUSSION

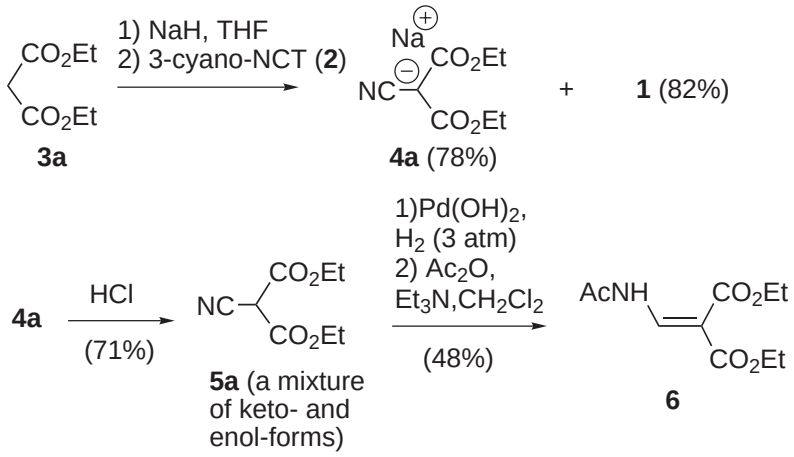
3-Cyano-NCT (**2**) was readily prepared in 85% yield by the reaction of BrCN and the anion of NCT (**1**), generated on treatment of **1** with NaH in THF at 0 °C (Scheme 2). 3-Cyano-NCT (**2**) is a pale yellow powder (mp161–162 °C) and is moisture-stable.



1 **2**

Scheme 2

As shown in Scheme 3, electrophilic cyanation reaction of diethyl malonate (**3a**) proceeded smoothly, giving sodium salt of 2-cyanomalonate (**4a**) in 78% on treatment with two equivalents of **2** with sodium diethyl malonate at room temperature. Use of 1 equivalent of **2** caused considerable decrease of the yield (40%). In the reaction, NCT was recovered for reuse in 82% yield. After protonation with HCl, diethyl 2-cyanomalonate (**5a**) was obtained in 71% yield. Since the resulting **5a** was a mixture of two tautomeric isomers, the structure was confirmed by conversion into *N*-acetylenamine derivative (**6**) *via* hydrogenation of the cyanide to an imine followed by acetylation. On the other hand, cyanation of **3a** with BrCN provided **4a** in 60% yield.

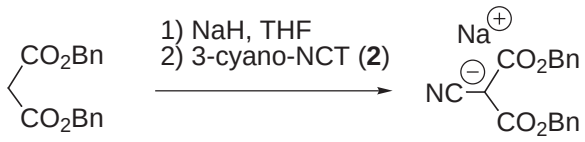


3a **4a** (78%) **5a** (a mixture of keto- and enol-forms) **6**

Scheme 3

Table 1 shows the effect of a base on the cyanation reactions. LiH is less effective than NaH (Entries 1 and 2). Less nucleophilic *t*-BuOK showed a comparable yield to NaH, but nucleophilic EtONa caused decomposition of the reagent (Entries 3 and 4). Bases such as Na_2CO_3 and Et_3N resulted in recovery of the reagent (Entries 5 and 6).

Table 1. Effects of base on electrophilic cyanation of dibenzyl malonate (**3b**) with 3-cyano-NCT (**2**)[a]



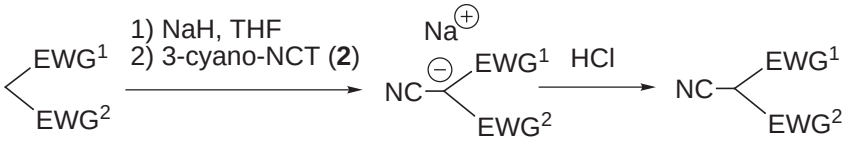
3b **4b**

Entry	Base	Temp (°C)	Time (h)	Yield (%)[b]
1	NaH	rt	5	81[d]
2	LiH	rt	6	13
3	*t*-BuOK	rt	25	72
4	EtONa[c]	rt	12	0
5	Na_2CO_3	rt	114	0
6	Et_3N	rt to reflux	25	0

[a] All reactions were carried out using two equiv. of **2** in THF unless otherwise stated. [b] Isolated yields. [c] Reaction was performed using diethy malonate in EtOH. [d] NCT was recovered in 91% yield.

Next, we examined electrophilic cyanation of several activated methylene compounds (**3a**–**h**). The results are shown in Table 2. On treatment with **2**, sodium salts of the malonates (**3a**–**c**) were converted into the

Table 2. Electrophilic cyanation of various activated methylene compounds (**3a**–**h**) with 3-cyano-NCT (**2**) [a]



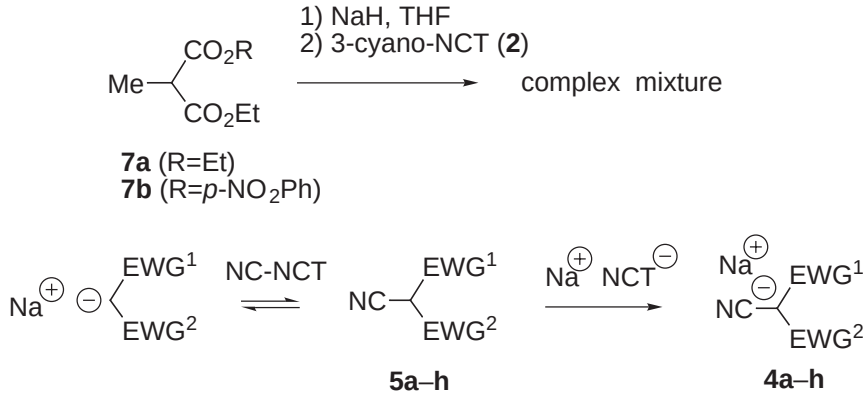
3a–h **4a–h** **5a–h**

Entry	Sub-strate	EWG^1	EWG^2	Time (h)	Pro-duct	Yield of **4** (%)[b]	Yield of **5** (%)[b]
1	**3a**	CO_2Et	CO_2Et	23	**a**	78	71
2	**3b**	CO_2Bn	CO_2Bn	5	**b**	81	70
3	**3c**	CO_2Me	CO_2Me	30	**c**	78	75
4	**3d**	COMe	CO_2Et	4.5	**d**	78	73
5	**3e**	COPh	CO_2Et	37	**e**	74	73
6	**3f**	COMe	CONH(*p*-MeOPh)	37	**f**	60	73
7	**3g**	CO_2Et	$P(O)(OEt)_2$	59	**g**	80	28
8	**3h**	CO_2Et	SO_2Ph	60	**h**	99	63

[a] All reactions were carried using two equiv. of **2** in THF. b Isolated yields.

sodium salt of 2-cyao compounds (**4a**–**c**), which were acidified with HCl to cyanomalonates (**5a**–**c**) (Entries 1–3). Cyanation of other methylenes situated between different electron-withdrawing groups also proceeded smoothly, giving sodium salts (**4d**–**h**) in good to moderate yields.[9,10] The low yield observed in protonation of diethylphosphoranyl compound (**4g**) is presumably due to the instability of **4g** to the acidic conditions.

In contrast to reactions of the malonate derivatives (**3a**–**c**) bearing two α-hydrogens, those of 2-methylated malonates (**7a** and **7b**) were sluggish to give a complex mixture (Scheme 4). We assume that deprotonation of the highly acidic methine proton from the cyanated product (**5a**–**h**) would play an important role to proceed the reaction by generating a stable anion species (**4a**–**h**) in reactions of the compounds (**3a**–**h**). The ionization would also prevent nucleophilic attack to **4a**–**h** of the sodium salt of **3a**–**h** or the resulting sodium salt of NCT in contrast to the 2-methylated malonates (**7a** and **7b**).



Scheme 4

CONCLUSION

In conclusion, we have found that 3-cyano-NCT underwent electrophilic cyanation of the activated methylene compounds. The reaction proceeded in moderate to good yields for the substrates having various functionalities.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ solution at 500 MHz with a JEOL JNM-GX500 spectrometer. ^{13}C NMR spectra were recorded in $CDCl_3$ at 67.8 MHz or 75 MHz with a JEOL JNM-EX270 spectrometer or a JEOL JMN-AL-300, respectively. All signals are expressed as ppm downfield from tetramethylsilane used as an internal standard (δ value). IR spectra were measured with a Horiba FT-210 IR spectrophotometer. MS spectra were taken with a Shimadzu QP-1000 mass spectrometer or a JMS-600 mass spectrometer. High-resolution MS spectra were measured by a JEOL JMS-600H. Merck Kieselgel 60 was used as an adsorbent for column chromatography. All air- or moisture-sensitive reactions were carried out in flame-dried glassware under N_2 atmosphere. All organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated with a rotary evaporator under reduced pressure.

3-Cyano-2-(*N*-cyanoimino)thiazolidine (2). NaH (60% in oil) (167 mg, 4.18 mmol) was added to a suspension of **1** (509 mg, 4.00 mmol) in THF (10 mL) with stirring at rt under N_2. After 30 min, a solution of BrCN (423 mg, 4.00 mmol) in THF (2 mL) was added to the mixture. The stirring was continued at rt for 3 h. The reaction was quenched with water. The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine prior to drying and solvent evaporation. The residue was recrystallized with EtOH to give **2** (518 mg, 85%) as a pale yellow powder. mp 161.0–162.0 °C (EtOH). ^{1}H NMR (DMSO-d_6) δ: 3.80 (t, J = 7.3 Hz, 2H, CH_2S), 4.22 (t, J = 7.3 Hz, 2H, CH_2N). ^{13}C NMR (DMSO-d_6) δ: 31.1, 52.2, 105.5, 113.7, 180.5. IR (KBr) 2242 (CN), 2202 (CN) cm^{-1}. MS *m/z* (%): 152 (M^+, 16.9), 73 (100). *Anal.* Calcd for $C_5H_4N_4S$: C, 39.46; H, 2.65; N, 36.82; S, 21.07. Found: C, 39.30; H, 2.76; N, 36.76; S, 20.96.

General Procedure for Cyanation with 3-Cyano-NCT [Synthesis of Diethyl 2-Cyanomalonate (5a)]. NaH (60% in oil) (192 mg, 4.80 mmol) was added to a solution of diethyl malonate (**3a**) (0.61 mg, 4.00 mmol) in THF (10 mL) with stirring at rt under N_2. After 30 min, 3-cyano-NCT (**2**) (730 mg, 4.80 mmol) was added to the mixture. The stirring was continued at rt for 40 h. The reaction was quenched with saturated NH_4Cl and the resulting mixture was extracted with AcOEt. The extract was washed with brine prior to drying and solvent evaporation. The residue was chromatographed on silica gel with hexane–acetone (1:1) to give a sodium salt of **4a** (646 mg, 78%) as a yellow oil along with NCT (417 mg, 82%). Aqueous solution of the sodium salt of **4a** (550 mg) was acidified with concentrated HCl and extracted with Et_2O. The extract was washed with brine prior to drying and solvent evaporation to give **5a** (348 mg, 71%, keto-form:enol-form=6:1) as an orange oil. ^{1}H NMR (keto-form) δ: 1.34 (t, J=7.3 Hz, 3H, CH_2CH_3), 4.33 (q, J=7.3 Hz, 2H, CH_2CH_3), 4.47 (s, 1H, CHCN). (enol-form) δ: 1.39 (t, J=7.3 Hz, 3H, CH_2CH_3), 4.39 (q, J=7.3 Hz, 2H, CH_2CH_3). ^{13}C NMR (keto-form) δ: 13.6 (2C), 44.5, 63.8 (2C), 111.4, 160.5 (2C). (enol-form) δ: 14.0 (2C), 60.3, 64.2 (2C), 113.7, 176.0 (2C). IR (KBr) 2262 (CN), 2242 (CN), 1763 (C=O) cm^{-1}. MS (FAB): 186 (MH^+). HRMS (FAB) Calcd for $C_8H_{12}NO_4$ (MH^+): 186.0736. Found: 186.0751.

Dibenzyl 2-Cyanomalonate (5b). Yellow oil (keto-form:enol-form=8:5). ^{1}H NMR (keto-form) δ: 4.54 (s, 1H, CHCN), 5.25 (s, 4H, CH_2Ph), 7.30–7.39 (m, 10H, ArH). (enol-form) δ: 5.25 (s, 4H, CH_2Ph), 5.36 (s, 1H, OH), 7.30–7.39 (m, 10H, ArH). ^{13}C NMR (keto-form) δ: 44.7 (2C), 69.4, 111.1, 128.4 (4C), 128.7 (4C), 128.9 (2C), 133.7 (2C), 160.2 (2C). (enol-form) δ: 61.1, 65.8, 69.3, 111.1, 128.2 (4C), 128.5 (4C), 128.9 (2C), 133.9 (2C), 160.2, 175.9. IR (KBr) 2262 (CN), 2225 (CN), 1751 (C=O), 1597 (C=C) cm^{-1}. MS (FAB): 310 (MH^+). HRMS (FAB) Calcd for $C_{18}H_{16}NO_4$ (MH^+): 310.1061. Found: 310.1070.

Dimethyl 2-Cyanomalonate (5c). Yellow oil (keto-form:enol-form=5:4). ^{1}H NMR (keto-form) δ: 3.90 (s, 6H, CH_3), 4.51 (s, 1H, CHCN). (enol-form) δ: 3.90 (s, 6H, CH_3), 3.98 (s, 1H, OH). ^{13}C NMR (keto-form) δ: 54.5 (2C), 60.6, 111.2, 160.9 (2C). (enol-form) δ: 44.2, 54.6, 60.6, 111.2, 160.9, 176.4. IR (KBr) 2262 (CN), 2223 (CN), 1755 (C=O), 1605 (C=C) cm^{-1}. MS (FAB): 158 (MH^+). HRMS (FAB) Calcd for $C_6H_8NO_4$ (MH^+): 158.0469. Found: 158.0461.

Ethyl 2-Cyano-3-oxobutanoate (5d) Pale yellow oil (enol-form only). ^{1}H NMR *δ*: 1.36 (t, *J*=7.3 Hz, 3H, CH_2CH_3), 2.35 (s, 3H, $COCH_3$), 4.32 (q, *J*=7.3 Hz, 2H, CH_2CH_3), 13.6 (s, 1H, OH). ^{13}C NMR *δ*: 13.9, 21.1, 62.3, 81.2, 114.7, 169.9, 187.2. IR (KBr) 2985 (OH), 2226 (CN), 1660 (C=O), 1604 (C=C) cm^{-1}. MS (FAB): 156 (MH^+). HRMS (FAB) Calcd for $C_7H_{10}NO_3$ (MH^+): 156.0673. Found: 156.0667.

Ethyl 2-Cyano-3-oxo-3-phenylpropanoate (5e). Pale yellow powder (enol-form only). mp: 31.0–32.0 °C (*n*-hexane). ^{1}H NMR *δ*: 1.41 (t, *J*=7.3 Hz, 3H, CH_2CH_3), 4.32 (q, *J*=7.3 Hz, 2H, CH_2CH_3), 7.26–8.01 (m, 5H, ArH), 14.3 (s, 1H, OH). ^{13}C NMR *δ*: 14.1, 62.8, 78.8, 115.6, 128.4 (4C), 131.2, 133.1, 171.0, 182.6. IR (KBr) 2985 (OH), 2224 (CN), 1660 (C=O), 1604 (C=C) cm^{-1}. MS (FAB): 218 (MH^+). HRMS (FAB) Calcd for $C_{12}H_{12}NO_3$ (MH^+): 218.0817. Found: 218.0817.

***N*-[4-(Methoxy)phenyl-2-cyano-3-oxobutanamide (5f).** Pale yellow powder (keto-form only). mp: 142.0–143.0 °C (AcOEt). ^{1}H NMR *δ*: 1.65 (br s, 1H, CHCN), 2.35 (s, 3H, $COCH_3$), 3.81 (s, 3H, OCH_3), 6.91–7.38 (m, 4H, ArH), 7.52 (br s, NH). ^{13}C NMR *δ*: 21.9, 55.4, 80.0, 114.2 (2C), 116.5, 123.3 (2C), 128.4, 154.7, 167.3, 188.4. IR (KBr) 3294 (NH), 2218 (CN), 1612 (C=O), 1610 (C=C) cm^{-1}. MS (FAB): 255 (MNa^+). *Anal.* Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.62; H, 5.25; N, 11.99.

Ethyl 2-Diethylphosphono-2-cyanoacetate (5g). Pale yellow oil (keto-form only). ^{1}H NMR *δ*: 1.36 (t, *J*=7.0 Hz, 3H, $CO_2CH_2CH_3$), 1.40 (td, *J*=7.0, 2.0 Hz, 6H, $P(O)(OCH_2CH_3)_2$), 4.09 (d, *J*=25.0 Hz, 1H, CHCN), 4.28–4.38 (m, 6H, $CO_2CH_2CH_3$ and $P(O)(OCH_2CH_3)_2$). ^{13}C NMR *δ*: 13.8, 16.1 (d, *J*(C,P)=1.9 Hz, 2C), 38.4 (d, *J*(C,P)=28.3 Hz), 63.7, 65.1 (d, *J*(C,P)=6.9 Hz), 65.2 (d, *J*(C,P)=6.9 Hz), 111.4 (d, *J*(C,P)=11.2 Hz), 160.7 (d, *J*(C,P)=6.2 Hz). IR (KBr) 3294 (NH), 2218 (CN), 1612 (C=O), 1604 (C=C) cm^{-1}. MS (FAB): 250 (MH^+). HRMS (FAB) Calcd for $C_9H_{17}NO_5P$ (MH^+): 250.0843. Found: 250.0844.

Ethyl 2-Cyano-2-phenylsulfonylacetate (5h). Colorless oil (keto-form only). ^{1}H NMR *δ*: 1.29 (t, *J*=7.3 Hz, 3H, CH_2CH_3), 4.29 (q, *J*=7.3 Hz, 1H, CH_2CH_3), 4.30 (q, *J*=7.3 Hz, 1H, CH_2CH_3), 4.90 (s, 1H, CHCN), 7.67 (t, *J*=8.0 Hz, 2H, ArH), 7.82 (t, *J*=8.0 Hz, 1H, ArH), 8.03 (d, *J*=8.0 Hz, 2H, ArH). ^{13}C NMR *δ*: 13.7, 62.3, 64.6, 109.8, 129.4 (2C), 129.6 (2C), 134.9, 135.7, 157.9. IR (KBr) 2258 (CN), 1751 (C=O), 1350 (SO), 1350 (SO) cm^{-1}. MS (FAB): 254 (MH^+). HRMS (FAB) Calcd for $C_{11}H_{12}NO_4S$ (MH^+): 254.0483. Found: 254.0489.

Diethyl 2-(Acetylaminomethylidene)malonate (6). A solution of **5a** (151 mg, 1.02 mmol) in EtOH (7 mL) was hydrogenated on $Pd(OH)_2$ (20% Pd on carbon, wet) (151 mg, 1.02 mmol) with stirring at rt for 3 h. After filtration, the filtrate was concentrated under reduced pressure to give a crude imine (122 mg, 0.651 mmol). Acetic anhydride (0.60 mL, 6.36 mmol) was added to a mixture of the imine (122 mg) and Et_3N (0.60 mL, 4.56 mmol) in CH_2Cl_2 (6 mL) with stirring at 0 °C. The stirring was continued at rt for 4 h. The reaction was quenched with saturated $NaHCO_3$ and the resulting mixture was extracted with CH_2Cl_2. The extract was washed with brine prior to drying and solvent evaporation. The residue was chromatographed on silica gel with hexane–acetone (3:1) to give **6** (71 mg, 48% in 2 steps) as a colorless

powder. mp 48.5–49.0 °C. ^{1}H NMR δ: 1.30 (t, J=7.3 Hz, 3H, CH_2CH_3), 1.35 (t, J=7.3 Hz, 3H, CH_2CH_3), 2.24 (s, 1H, $COCH_3$), 4.22 (q, J=7.3 Hz, 2H, CH_2CH_3), 4.29 (q, J=7.3 Hz, 2H, CH_2CH_3), 8.50 (d, J=12.2 Hz, 1H, CH=C), 10.9 (br s, 1H, NH). ^{13}C NMR δ: 14.0, 14.1, 23.8, 60.8, 61.2, 102.0, 145.9, 164.2, 167.4, 168.4. IR (KBr) 3291 (NH), 1728 (C=O), 1674 (C=O), 1605 (C=C) cm^{-1}. MS *m/z* (%): 229 (M^+, 74.3), 142 (100). *Anal.* Calcd for $C_{10}H_{15}NO_5$: C, 52.40; H, 6.60; N, 6.11. Found: C, 52.68; H, 6.53; N, 5.90.

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9. All attempts at cyanation with phenymagnesium bromide, 3-pyridyllithium, lithium phenylacetylide, and amines ($BzNH_2$, Bz_2NH, and $PhNH_2$) were unsuccessful.
10. The malonate derivatives (**5a**–**c**) were a mixture of tautomeric isomers in a $CDCl_3$ solution. However, the keto esters (**5d** and **5e**) exist in the enol-form exclusively. On the other hand, the equilibrium lies completely to the keto-form in the compounds (**5f**–**h**).