# Application of Cyano-*aci*-Nitroacetate to Organic Syntheses. 1. Facile Synthesis of Pentanedinitrile-2,4-dinitronates

Nagatoshi Nishiwaki, Tomoko Nogami, Chitose Tanaka, Fuminori Nakashima, Yoji Inoue, Noriko Asaka,† Yasuo Tohda,‡ and Masahiro Ariga*

*Department of Chemistry, Center for Instrumental Analysis, and Division of Natural Science, Osaka Kyoiku University, Asahigaoka 4-698-1, Kashiwara, Osaka 582-8582, Japan*

*Received September 16, 1998*

## Introduction

Pentanedinitrile (glutaronitrile) and its derivatives are widely used as functional materials including biologically active compounds[1] and employed as excellent precursors for azaheterocycles,[2] polymers, and so on.[3] Hence, novel functionalization of pentanedinitrile and development of facile preparative methods for their preparation are highly demanding subjects.

Pentanedinitrile-2,4-dinitronate **1**[4] has been investigated for its antitumor activity. 2-Aryl (or alkyl) pentanedinitrile-2,4-dinitronates are prepared through two-step reactions from nitroacetonitrile. The condensation of nitroacetonitrile with aldehydes in the presence of thionyl chloride gives α-nitroacrylonitriles **2**. The succeeding treatment of **2** with amine leads to dinitronates **1**. It is known that the condensation of nitroacetonitrile with triethyl orthoformate in the presence of thionyl chloride also gives 4-nitropentanedinitrile-2-nitronate.[5] These procedures are, however, somewhat troublesome and are not able to afford 3,3-disubstituted dinitronates.

Meanwhile, we have been paid attention to 4-nitroisoxazolin-5(2*H*)-ones that show multifunctionalities. Readily available pyridinium salt **3**[6,7] reacts with electrophiles giving *N*-methyl derivative **4a** and *N*-acetyl **4b** (Scheme 1). The former is effectively converted to functionalized nitrile oxide[8] and polysubstituted pyrroles.[9] The latter behaves as the mild acylating agent.[10] Furthermore, deprotonation at the 3-position of **3** followed by N−O fission quantitatively occurs to afford cyano-*aci*-nitroacetate **5** under basic conditions at room temperature.[6]

The estimated electrophilic susceptibility[11] of cyano-*aci*-nitroacetates **5** indicating multidentate nucleophilicity is shown in Scheme 1. However, **5** has not been used for organic syntheses because of the difficulty of synthesizing and treating **5**. By our method, **5** could be easily prepared with various types of countercations. Among them, dipyrrolidinium, dimorpholininium, and bis(DBU−

**Scheme 1**

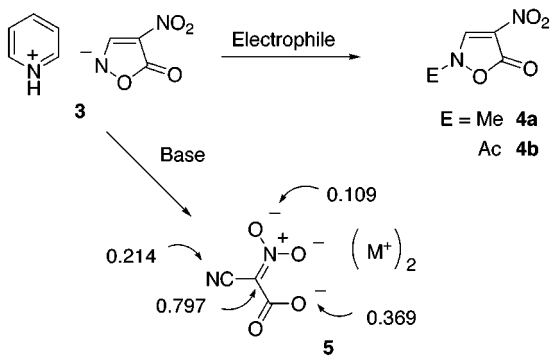
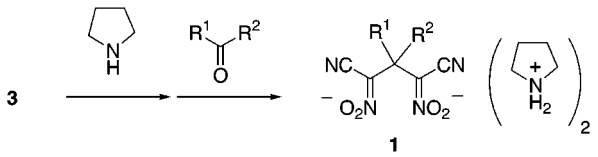



**Table 1**




| $R^1$ | $R^2$ | | Yield / % |
|---|---|---|---|
| Me | Me | **a** | 83 |
| Me | Et | **b** | 83 |
| Et | Et | **c** | 73 |
| ——$(CH_2)_4$—— | | **d** | 64 |
| ——$(CH_2)_5$—— | | **e** | 82 |
| Ph | Me | **f** | 0 |
| Ph | H | **g** | 90 |
| *p*-$MeOC_6H_4$ | H | **h** | quant |
| *p*-$NO_2C_6H_4$ | H | **i** | —— |
| Et | H | **j** | 95 |
| *t*-Bu | H | **k** | 92 |

* To whom correspondence should be addressed. Tel: 81-729-78-3398. Fax: 81-729-78-3399. E-mail: ariga@cc.osaka-kyoiku.ac.jp.
† Center for Instrumental Analysis.
‡ Division of Natural Science.

(1) For example: (a) Wustermann, S.; Siebert, J. *SOFW J.* **1997**, *123*, 398. (b) Anderson, F. A. *J. Am. Coll. Toxicol.* **1996**, *15*, 140.

(2) For example: (a) DiCosimo, R.; Fallon, R. D.; Gavagan, J. E.; Herkes, F. E. *PCT Int. Appl.* WO 9744318 A1 971127; *Chem. Abstr.* **1998**, *128*, 89231. (b) Diker, K.; El Biach, K.; Doe de Maindreville, M.; Levy, J. *J. Nat. Prod.* **1997**, *60*, 791. (c) Heveling, J. *Chem. Ind.* **1996**, *68*, 265.

(3) For example: (a) Lee, J.-Y.; Song, Y.-W.; Shim, M.-J.; Kim, S.-W. *Mater. Chem. Phys.* **1997**, *50*, 256. (b) Maddern, P.; Khalifa, S. *PCT Int. Appl.* WO 9709033 A1 970313; *Chem. Abstr.* **1997**, *126*, 268320. (c) Minagawa, M.; Yoshida, W.; Kurita, S.; Takada, S.; Yoshii, F. *Macromolecules* **1997**, *30*, 1782.

(4) (a) Mechkov, Ts.; Demireva, Z. *Z. Chem.* **1989**, *29*, 291. (b) Mechkov, Ts.; Demireva, Z. *Z. Chem.* **1985**, *25*, 169. (c) Mechkov, Ts.; Demireva, Z. *Z. Chem.* **1985**, *25*, 62. (d) Mechkov, Ts.; Demireva, Z. *Zh. Org. Khim.* **1985**, *21*, 1884; *Chem. Abstr.* **1986**, *105*, 97124.

(5) Reidlinger, G. H.; Junek, H. *Synthesis* **1991**, 835.

(6) Nishiwaki, N.; Takada, Y.; Inoue, Y.; Tohda, Y.; Ariga, M. *J. Heterocycl. Chem.* **1995**, *32*, 473.

(7) Ariga, M.; Tohda, Y.; Nakashima, H.; Tani, K.; Mori, Y.; Matsumura, E. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3544.

(8) Nishiwaki, N.; Uehara, T. Asaka, N.; Tohda, Y.; Ariga, M.; Kanemasa, S. *Tetrahedron Lett.* **1998**, *39*, 4851.

(9) (a) Ariga, M.; Nishiwaki, N.; Miwa, Y.; Tani, K.; Tohda, Y. *Heterocycles* **1997**, *44*, 81. (b) Higashida, S.; Nakashima, H.; Tohda, Y.; Tani, K.; Nishiwaki, N.; Ariga, M. *Heterocycles* **1992**, *34*, 1511.

(10) Nishiwaki, N.; Takada, Y.; Tani, K.; Tohda, Y.; Ariga, M. *Chem. Express* **1992**, *7*, 845.

(11) The electrophilic susceptibilities were estimated by the MOPAC (PM3) molecular orbital calculation using the CAChe system.

10.1021/jo9818879 CCC: $18.00 
Published on Web 02/13/1999

**Scheme 2**

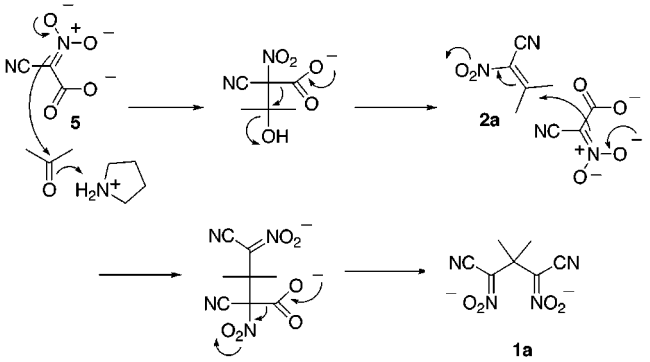
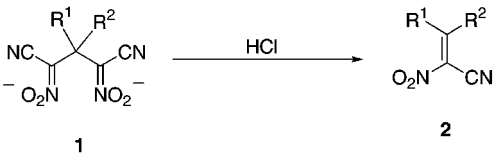


**Table 2**



| $R^1$ | $R^2$ | | Yield / % |
|---|---|---|---|
| Me | Me | **a** | 70 |
| Ph | H | **g** | quant. |
| *p*-$MeOC_6H_4$ | H | **h** | quant. |

$H^+$) salts were soluble into organic solvents such as benzene, $CHCl_3$, methanol, ethanol, acetonitrile, and so on,[6] in contrast with metallic salts (M = Na, K, Ba/2). This improved solubility enabled us to investigate the application of cyano-*aci*-nitroacetate **5** to organic syntheses. We initially focused the synthesis of pentanedinitrile-2,4-dinitronates **1** by using this trifunctionalized methane as a building block.

## Results and Discussion

Dipyrrolidinium cyano-*aci*-nitroacetate **5a** ($M^+$ = pyrrolidinium) was generated in situ, and the following reaction was carried out in the same pot. When **5a** was reacted with acetone in benzene, white solid was precipitated. The empirical formula of the solid was $C_{15}H_{26}N_6O_4$. This result suggested that acetone reacted with two molecules of **5a** accompanied by elimination of two carbon dioxides and a water, and the dianionic property was retained. The signal of methyl groups shifted to higher field in the $^1$H NMR, and the signal of an $sp^3$ carbon appeared at 35.0 ppm in place of carbonyl one in the $^{13}$C NMR. Strong absorptions were observed at 2191 and 1614 $cm^{-1}$ in the IR spectrum. On the basis of these analytical and spectral data, the product was determined as dipyrrolidinium 3,3-dimethylpentanedinitrile-2,4-dinitronate (**1a**). This structure was confirmed by X-ray crystallography.

A plausible mechanism is as follows. Knoevenagel-type condensation of cyano-*aci*-nitroacetate **5** with acetone proceeds to give α-nitroacrylonitrile **2**. Nucleophilic attack of another dianion **5** to **2** followed by decarboxylation gives pentanedinitrile-2,4-dinitronate **1**. Reactions of cyano-*aci*-nitroacetate **5a** with other aliphatic ketones similarly furnished corresponding 3,3-disubstituted dinitronates **1a**−**e** in good yields (Table 1). Acetophenone, however, caused no change even though the reaction mixture was heated. Employment of benzaldehyde and *p*-methoxybenzaldehyde instead of ketones afforded 3-aryl derivatives **1g**,**h**. The reaction mixture using *p*-nitrobenzaldehyde showed a singlet signal at 5.60 ppm in the $^1$H NMR and gave a chart having pattern similar to that of **1h** in the IR. Considerable formation of **1i** occurred, but an analytical sample could not be prepared because of concomitance of unidentified byproduct. 3-Alkyl dinitronates **1j**−**k** were also obtained in excellent yields.

The retrocondensation of the obtained nitronates **1** easily occurred under acidic conditions to yield α-nitroacrylonitriles **2** (Table 2). Acrylonitriles **2g**,**h** bearing an aromatic ring were relatively stable. On the other hand, **2a** was unstable. Although pure **2a** was isolated, gradual decomposition was observed. In consideration of the known reaction,[4] the interconversion between **1** and **2** becomes possible.

In summary, a facile preparative method for pentanedinitrile-2,4-dinitronates **1** was provided. The present reaction does not require any particular reagent such as thionyl chloride and troublesome experimental manipulations. Furthermore, this reaction is conducted at room temperature in one pot. Multifunctionality of dinitronates **1** suggested that **1** can become a building block for various types of compounds. Results of chemical transformations using dinitronates **1** will be reported in due course.

## Experimental Section

**Syntheses of Dipyrrolidinium Pentanedinitrile-2,4-dinitronates.** To a suspension of pyridinium salt (**3**, 418 mg, 2.0 mmol) in benzene (6.0 mL) was added pyrrolidine (0.35 mL, 4.2 mmol), and the mixture was stirred at room temperature for 0.5 h. To the resultant solution was added ketone or aldehyde (1.0 mmol). After the solution was stirred at room temperature for 2 h, hexane (15 mL) was added, and the resulting solution was allowed to stand overnight. The upper solution was decanted off. Washing the residual oil with hot benzene (20 mL × 3) followed by evaporation afforded almost pure dipyrrolidinium pentanedinitrile-2,4-dinitronate **1** as an oil. When the oil was solidified, purification by recrystallization with ethanol was performed. In the cases of **1g** and **1h**, the obtained products were oils whose NMR charts show no other signals; however, further purification giving satisfactory analytical data could not be achieved.

**Dipyrrolidinium 3,3-dimethylpentanedinitrile-2,4-dinitronate (1a):** colorless plates; mp 170−171 °C dec; IR (Nujol) 2191, 1614, 1333, 1225 $cm^{-1}$; $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 1.34 (s, 6H), 1.7−1.9 (m, 8H), 3.0−3.2 (m, 8H), 8.8−9.2 (br, 4H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 119.6 (s), 99.5 (s), 44.1 (t), 35.0 (s), 24.0 (q), 23.2 (t). Anal. Calcd for $C_{15}H_{26}N_6O_4$: C, 50.84; H, 7.39; N, 23.71. Found: C, 50.85; H, 7.44; N, 23.52.

**Dipyrrolidinium 3-ethyl-3-methylpentanedinitrile-2,4-dinitronates (1b):** colorless plates; mp 163−166 °C dec; IR (Nujol) 2191, 1612, 1342, 1223 $cm^{-1}$; $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 0.74 (t, $J$ = 7.4 Hz, 3H), 1.29 (s, 3H), 1.8−1.9 (m, 10H), 3.0−3.1 (m, 8H), 8.8−9.2 (br, 4H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 121.4 (s), 100.1 (s), 45.6 (t), 40.2 (s), 29.0 (t), 24.7 (t), 21.3 (q), 9.6 (q). Anal. Calcd for $C_{16}H_{28}N_6O_4$: C, 52.16; H, 7.66; N, 22.81. Found: C, 51.79; H, 7.63; N, 22.76.

**Dipyrrolidinium 3,3-diethylpentanedinitrile-2,4-dinitronates (1c):** colorless plates; mp 160−164 °C dec; IR (Nujol) 2195, 1637, 1325, 1236 $cm^{-1}$; $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 0.68 (t, $J$ = 7.4 Hz, 6H), 1.8−1.9 (m, 12H), 3.05−3.15 (m, 8H), 8.8−9.2 (br, 4H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 119.8 (s), 96.9 (s), 43.5 (t), 41.7 (s), 22.6 (t), 21.0 (t), 7.1 (q). Anal. Calcd for $C_{17}H_{30}N_6O_4$: C, 53.39; H, 7.91; N, 21.97. Found: C, 53.14; H, 8.04; N, 22.23.

**Dipyrrolidinium 3,3-tetramethylenepentanedinitrile-2,4-dinitronates (1d):** pale yellow plates; mp 138−142 °C dec;

IR (Nujol) 2191, 1612, 1236 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta$ 1.5−1.65 (m, 4H), 1.7−1.9 (m, 8H), 2.0−2.1 (m, 4H), 3.0−3.2 (m, 8H), 5.7−6.2 (br, 4H); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta$ 120.6 (s), 99.5 (s), 47.7 (s), 45.1 (t), 35.7 (t), 24.7 (t), 23.8 (t). Anal. Calcd for $C_{17}H_{28}N_6O_4 \cdot {}^1/_2H_2O$: C, 52.43; H, 7.51; N, 21.58. Found: C, 52.69; H, 7.62; N, 21.94.

**Dipyrrolidinium 3,3-pentamethylenepentanedinitrile-2,4-dinitronates (1e):** pale yellow plates; mp 134−140 °C dec; IR (Nujol) 2193, 1614, 1329, 1219 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.4−1.5 (m, 2H), 1.55−1.65 (m, 4H), 1.95−2.05 (m, 8H), 2.05−2.1 (m, 4H), 3.25−3.35 (m, 8H), 8.0−8.3 (br, 4H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 119.2 (s), 103.8 (s), 45.1 (t), 40.8 (s), 31.1 (t), 25.7 (t), 24.5 (t), 22.6 (t). Anal. Calcd for $C_{18}H_{30}N_6O_4 \cdot {}^1/_2H_2O$: C, 53.58; H, 7.74; N, 20.83. Found: C, 53.64; H, 7.86; N, 20.86.

**Dipyrrolidinium 3-phenylpentanedinitrile-2,4-dinitronates (1g):** reddish brown oil; IR (neat) 2193, 1623, 1319, 1227 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta$ 1.7−1.9 (m, 8H), 3.0−3.2 (m, 8H), 5.38 (s, 1H), 7.1−7.2 (m, 3H), 7.2−7.4 (m, 2H), 7.9−8.7 (br, 4H); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta$ 139.9 (s), 126.8 (d), 126.2 (d), 124.9 (d), 118.6 (s), 93.6 (s), 43.6 (t), 42.3 (d), 22.5 (t).

**Dipyrrolidinium 3-(4-methoxyphenyl)pentanedinitrile-2,4-dinitronates (1h):** yellowish brown oil; IR (neat) 2193, 1610, 1321, 1248 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta$ 1.7−1.9 (m, 8H), 3.0−3.2 (m, 8H), 3.72 (s, 3H), 5.29 (s, 1H), 4.9−6.9 (br, 4H), 6.83 (d, $J$ = 8.6 Hz, 2H), 7.06 (d, $J$ = 8.6 Hz, 2H); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta$ 159.4 (s), 134.7 (s), 130.4 (d), 121.6 (s), 115.1 (d), 96.8 (s), 56.7 (q), 46.6 (t), 44.5 (d), 25.5 (t).

**Dipyrrolidinium 3-ethylpentanedinitrile-2,4-dinitronates (1j):** colorless plates; mp 150−152 °C dec; IR (Nujol) 2189, 1605, 1292, 1230 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta$ 0.85 (t, $J$ = 7.3 Hz, 3H), 1.45−1.6 (m, 2H), 1.75−1.95 (m, 8H), 3.0−3.2 (m, 8H), 3.84 (t, $J$ = 7.8 Hz, 1H), 4.6−6.4 (br, 4H); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta$ 120.6 (s), 96.7 (s), 46.1 (t), 40.3 (d), 25.2 (t), 24.7 (t), 13.5 (q). Anal. Calcd for $C_{15}H_{26}N_6O_4 \cdot {}^1/_2H_2O$: C, 49.58; H, 7.49; N, 23.13. Found: C, 49.95; H, 7.44; N, 23.12.

**Dipyrrolidinium 3-*tert*-butylpentanedinitrile-2,4-dinitronates (1k):** colorless plates; mp 157−159 °C dec; IR (Nujol) 2187, 1624, 1300, 1225 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta$ 0.95 (s, 9H), 1.8−1.9 (m, 8H), 3.05−3.15 (m, 8H), 4.47 (s, 1H), 3.25−3.35 (m, 8H), 8.5−9.4 (br, 4H); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta$ 120.2 (s), 94.1 (s), 45.2 (d), 44.6 (t), 36.7 (s), 27.8 (q), 23.6 (t). Anal. Calcd for $C_{17}H_{30}N_6O_4$ : C, 53.39; H, 7.91; N, 21.97. Found: C, 53.22; H, 7.98; N, 21.80.

**Retrocondensation of Dinitronate 1.** A solution of dinitronate (**1**, 1.0 mmol) in 1 M HCl (20 mL) was extracted with $CHCl_3$ (20 mL × 3). The organic layer was dried over $MgSO_4$ and concentrated to afford acrylonitrile derivative **2** that was pure enough for following analyses.

**3-Methyl-2-nitro-2-butenenitrile (2a):** white solid; mp 88−93 °C dec; IR (Nujol) 2239, 1618, 1576, 1342 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 2.40 (s, 3H), 2.50 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 166.1 (s), 110.7 (s), 26.3 (q), 22.9 (q). When **2a** was standed, hydrolysis gradually proceeded. Thus, satisfactory analytical data were not obtained.

**2-Nitro-3-phenyl-2-propenenitrile (2g):** yellowish brown solid; mp 103−104 °C; IR (Nujol) 2235, 1622, 1591, 1342 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.6−7.9 (m, 3H), 8.0−8.2 (m, 2H), 8.75 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 148.6 (d), 135.6 (d), 132.2 (d), 129.9 (d), 127.3 (s), 123.2 (s), 111.0 (s). Anal. Calcd for $C_9H_6N_2O_2$: C, 62.07; H, 3.47; N, 16.09. Found: C, 62.40; H, 3.40; N, 15.84.

**3-(4-Methoxyphenyl)-2-nitro-2-propenenitrile (2h):** red plates; mp 104−105 °C (lit.[12] 97−98 °C); IR (Nujol) 2231, 1591, 1560, 1319 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 3.97 (s, 3H), 7.11 (d, $J$ = 9.0 Hz, 2H), 8.08 (d, $J$ = 9.0 Hz, 2H), 8.65 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 165.9 (s), 148.1 (d), 135.3 (d), 120.5 (s), 119.9 (s), 115.7 (d), 111.8 (s), 56.0 (q). Anal. Calcd for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72. Found: C, 58.87; H, 3.89; N, 13.87. The structure of **2h** was confirmed by X-ray analysis.

**Supporting Information Available:** X-ray data of **1a** and **2h**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9818879

(12) Brillon, D.; Sauvé, G. *J. Org. Chem.* **1992**, *57*, 1838.