One-Pot Synthesis of Polyfunctionalized Isoxazol(in)es[1]

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Introduction

Heterocyclic compounds having some functional groups are widely used for a variety of functional materials such as medicines, agricultural chemicals, and dyes. As one of synthetic strategies for these compounds, a polyfunctionalized unit is built in during the ring construction. Thus, development of novel synthetic units is highly desired in order to obtain functional compounds.

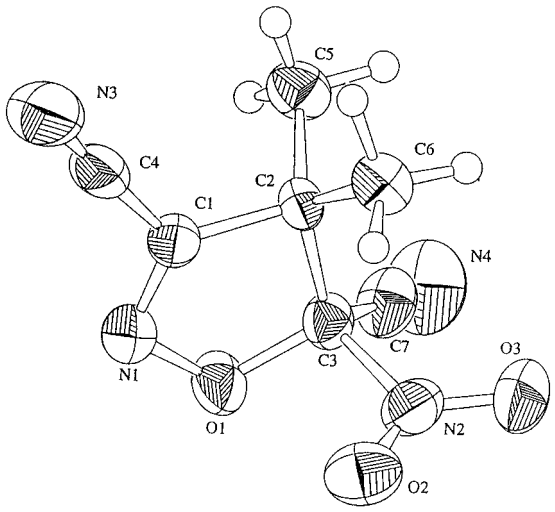
We recently reported a facile preparative method for pentanedinitrile-2,4-dinitronates **3** (Scheme 1).[1] Pyridinium salt of 4-nitroisoxazolin-5(2*H*)-one (**1**) was converted to cyano-*aci*-nitroacetate **2**,[2] which condensed with ketones or aldehydes to furnish dinitronates **3**. Although antitumor activity of **3** was known,[3] chemical transformations of **3** have not been performed yet. Consideration of dinitronate **3** as a novel polyfunctionalized unit encouraged us to investigate the application of **3** to organic syntheses.

Being one of 1,3-dipoles, the nitronate, however, is not active enough to react with dipolarophiles. *O*-Acylation of a nitronate is known to raise its electrophilicity.[4] When dinitronate **3** is acylated, the activated electrophilic nitronate group is located beside the nucleophilic site of the other nitronate group in the molecule. We consider that *O*-acylation of **3** promotes the intramolecular cyclization of **3** leading to polyfunctionalized isoxazol(in)es (Scheme 2).

Results and Discussion

To a suspension of dipyrrolidinium 3,3-dimethylpentanedinitrile-2,4-dinitronate (**3a**) in benzene, 5 equiv of acetyl chloride was added (Scheme 3). The surface of dinitronate **3a** immediately turned to red. After 1 h of stirring the suspension at room temperature, product **4a** was isolated together with *N*-acetylpyrrolidine.

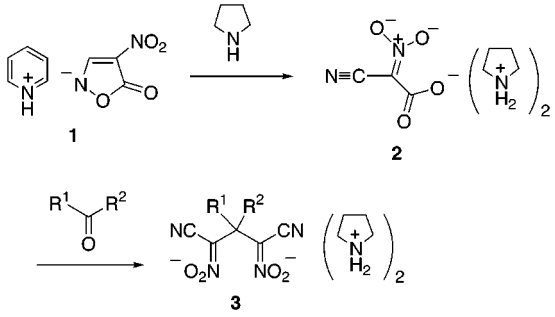
The elemental analysis of the product revealed that one water and two pyrrolidines were lost from dinitronate



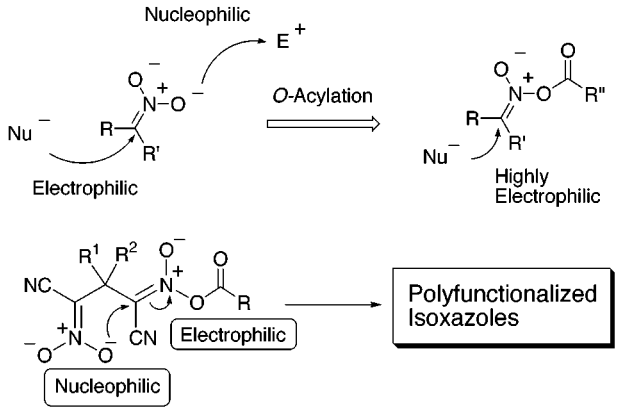
4a

Figure 1.

Scheme 1



Scheme 2



3a. Nonequivalence of two methyl groups in the NMR suggested **4a** being cyclic. Furthermore three singlet signals were found between 100 and 110 ppm in the ^{13}C NMR. Two of them were assigned to cyano groups and the rest to an electron deficient sp^3 carbon. On the basis of the analytical and spectral (IR, MS, NMR) data, the structure was determined as 3,5-dicyano-4,4-dimethyl-5-nitro-2-isoxazoline (**4a**). This structure was confirmed by X-ray analysis, and the ORTEP view is shown in Figure 1.

Although acetic anhydride and trimethylsilyl chloride also effected the formation of isoxazoline **4a**, acetyl

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(1) Application of Cyano-*aci*-nitroacetate to Organic Syntheses Part 2; For Part 1, see: Nishiwaki, N.; Nogami, T.; Tanaka, C.; Nakashima, F.; Inoue, Y.; Asaka, N.; Tohda, Y.; Ariga, M. *J. Org. Chem.* **1999**, *64*, 2160.

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(4) Torssell K. G. B. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH: Weinheim, 1988; pp 107−109.

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Scheme 3

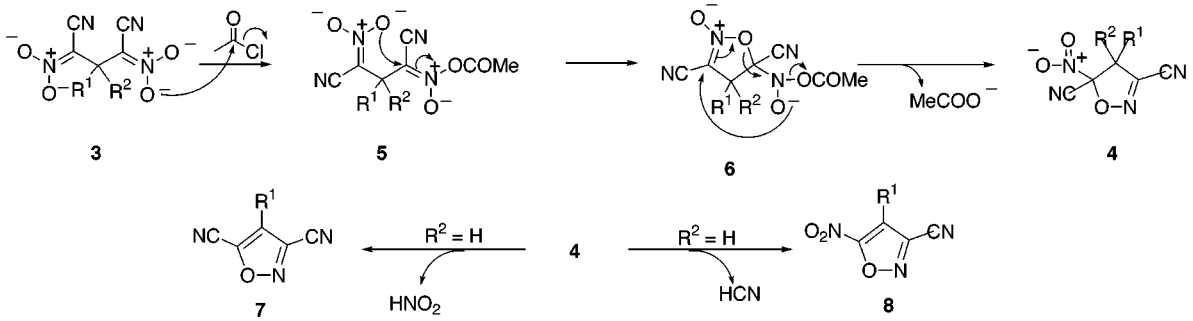
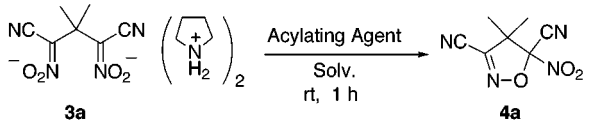
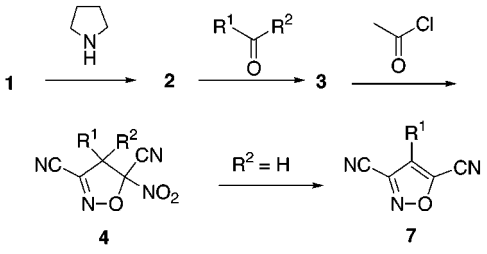


Table 1



Activating Agent	Solv.	Yield / %
MeCOCl	benzene	86
$(MeCO)_2O$	benzene	60
Me_3SiCl	benzene	2
MeCOCl	hexane	96

Table 2



R^1	R^2	Product	Yield / %
Me	Me	**4a**	92
Me	Et	**4b**	89 [a]
Ph	Me	**4c**	0
—$(CH_2)_4$—		**4d**	53
—$(CH_2)_5$—		**4e**	93
p-$MeOC_6H_4$	H	**7f**	93
Ph	H	**7g**	90
p-$NO_2C_6H_4$	H	**7h**	15
Heptyl	H	**7j**	52
t-Bu	H	**7j**	86
	H	**7k**	10

a A mixture of diastereomeric isomers

chloride was found to be the most suitable activating agent (Table 1). When hexane was employed instead of benzene as the solvent, byproducts were excluded as the insoluble oil. From the upper hexane solution, almost pure **4a** was obtained. Further purification was readily performed by passing through a short column giving **4a** in a higher yield.

Experimental simplification was achieved by one-pot synthesis of **4a** from pyridinium salt **1**. To a suspension of **1** in benzene were added pyrrolidine, acetone, and acetyl chloride sequentially (Table 2). In this case, the yield of isoxazoline **4a** was unsatisfactory (65% based on acetone). We considered that generated free pyridine and unreacted pyrrolidine prevented the succeeding reactions. The exchange of the solvent to hexane before the addition of acetyl chloride improved the yield of **4a** to 92%.

The reaction using butanone similarly proceeded to give isoxazoline **4b** in a good yield as a mixture of diastereomers. In the case of acetophenone, dinitronate **3c** was not formed even though the reaction mixture was heated under reflux.[1] Spiro isoxazolines **4d**−**e** could be prepared when cyclic ketones were used.

The plausible reaction mechanism is as follows. The *O*-acetylated nitronate of **5** is attacked by the other nitronate causing cyclization. The cyclic nitronate **6** is also highly electrophilic. Intramolecular ring transformation accompanied by elimination of acetate ion furnishes isoxazoline derivative **4**. The alternative mechanism involving the ring cleavage of **6** by chloride ion before second cyclization should also be considered. Meanwhile, aromatization is anticipated when aldehydes are used as the substrate ($R^2 = H$). Elimination of HNO_2 affords 3,5-dicyanoisoxazoles **7** and that of HCN affords 3-cyano-5-nitroisoxazole **8**.

Similar treatment using *p*-methoxybenzaldehyde in one-pot gave 3,5-dicyano-4-(4-methoxyphenyl)isoxazole (**7f**) in 93% yield. In this case, no **8f** was detected because cyanide ion was the inferior leaving group to nitrite ion. The structure of **7f** was confirmed by X-ray crystallography in addition to spectral and analytical data. The present reaction was applicable to other aromatic and aliphatic aldehydes leading to corresponding isoxazoles in excellent yields except for cases of *p*-nitrobenzaldehyde and furfral, whose reaction mixtures were complicated during the formation of dinitronates **3h** and **3k**.

Cyano-*aci*-nitroacetate **2** and pentanedinitrile-2,4-dinitronate **3** are proved to be useful building blocks for constructing polyfunctionalized compounds. Polyfunctionalized isoxazol(in)es **4** and **7** are also readily obtained from pyridinium salt **1** in one-pot with simple manipulations. Although this procedure involves multisteps of reactions, all of them effectively proceed at room temperature. Chemical transformations of cyano-*aci*-nitroacetate **2** and dinitronate **3** leading to other skeletons are under investigation.

Experimental Section

Synthesis of Isoxazoline 4a from Dinitronate 3a. To a suspension of dinitronate (**3a**, 354 mg, 1.0 mmol) in hexane (6.0

mL) was added acetyl chloride (0.36 mL, 5.0 mmol), and the mixture was stirred at room temperature for 1 h. The upper solution was decanted, and the residual oil was extracted with hexane. The combined hexane solution was concentrated to give white solid, which was a mixture of **4a** and *N*-acetylpyrrolidine (97/3, determined by ^{1}H NMR). Column chromatography of the mixture on silica gel (ϕ 3 cm × 5 cm) afforded isoxazoline derivative (**4a**, 186 mg, 0.96 mmol, eluted with benzene/hexane = 1/1).

3,5-Dicyano-4,4-dimethyl-5-nitro-2-isoxazoline (4a): colorless plates; mp 90−91 °C; IR (Nujol) 2260, 1591, 1348 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48 (s, 3H), 1.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.0 (s), 109.3 (s), 106.3 (s), 105.1 (s), 60.0 (s), 23.3 (q), 17.4 (q); MS (EI) 148 ($M^+ - NO_2$, 100). Anal. Calcd for $C_7H_6N_4O_3$: C, 43.31; H, 3.12; N, 28.86. Found: C, 43.51; H, 3.02; N, 29.74. The structure was confirmed by X-ray crystallography (Figure 1).

One-Pot Syntheses of Isoxazol(in)es 4 and 7 from Pyridinium Salt 1. To a suspension of pyridinium salt (**1**, 418 mg, 2.0 mmol) in benzene (6.0 mL), pyrrolidine (0.35 mL, 4.2 mmol) was added, and the mixture was stirred at room temperature for 0.5 h. To the resultant solution, ketone or aldehyde (1.0 mmol) was added. After 2 h of stirring, hexane (20 mL) was added, and the mixture was allowed to stand overnight. Upper solution was decanted off, and hexane (12.0 mL) and acetyl chloride (0.36 mL, 5.0 mmol) were added. After 1 h of stirring, the upper solution was decanted, and the residual oil was extracted with hexane. The combined hexane solution was concentrated to give almost pure **4** or **5**. Further purification was performed by column chromatography on silica gel (ϕ 3 cm × 5 cm).

3,5-Dicyano-4-ethyl-4-methyl-5-nitro-2-isoxazoline (4b): colorless oil; a mixture of geometric isomers (3/2); IR (neat) 2258, 1587, 1335 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) major isomer δ 1.18 (dd, J = 7.5, 7.5 Hz, 3H), 1.73 (s, 3H), 1.7−1.8 (m, 1H), 1.91 (dq, J = 14.9, 7.5 Hz, 1H); minor isomer δ 1.16 (dd, J = 7.5, 7.5 Hz, 3H), 1.46 (s, 3H), 2.09 (dq, J = 14.9, 7.5 Hz, 1H), 2.18 (dq, J = 14.9, 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) major isomer δ 145.2 (s), 110.7 (s), 107.8 (s), 107.0 (s), 64.8 (s), 25.1 (t), 21.3 (q), 8.0 (q); minor isomer δ 144.1 (s), 110.7 (s), 107.8 (s), 106.8 (s), 65.3 (s), 31.3 (t), 17.4 (q), 8.3 (q). Anal. Calcd for $C_8H_8N_4O_3$: C, 46.16; H, 3.87; N, 26.91. Found: C, 46.52; H, 3.87; N, 26.79.

3,5-Dicyano-5-nitro-2-isoxazoline-4-spirocyclopentane (4d): colorless oil; IR (neat) 2258, 1597, 1336 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.82 (dt, J = 14.2, 7.2 Hz, 1H), 1.95−2.25 (m, 6H), 2.5−2.6 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.8 (s), 111.3 (s), 107.8 (s), 106.9 (s), 70.6 (s), 37.6 (t), 32.4 (t), 25.0 (t), 24.7 (t). Anal. Calcd for $C_9H_8N_4O_3$: C, 49.09; H, 3.66; N, 25.45. Found: C, 49.51; H, 3.71; N, 25.44.

Cyclohexanespiro-4′-(3′,5′-dicyano-5′-nitro-2′-isoxazoline) (4e): colorless oil; IR (neat) 2260, 1593, 1336 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.5−2.4 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.2 (s), 110.3 (s), 107.1 (s), 107.1 (s), 62.7 (s), 33.0 (t), 26.8 (t), 22.5 (t), 20.3 (t), 18.7 (t). Anal. Calcd for $C_{10}H_{10}N_4O_3$: C, 51.28; H, 4.30; N, 23.92. Found: C, 51.07; H, 4.17; N, 24.02.

3,5-Dicyano-4-(4-methoxyphenyl)isoxazole (7f): yellow needles; mp 130−131 °C; IR (Nujol) 2241 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.90 (s, 3H), 7.09 (d, J = 6.9 Hz, 2H), 7.72 (d, J = 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.3 (s), 139.7 (s), 130.6 (s), 129.2 (d), 115.5 (d), 114.2 (s), 109.4 (s), 108.6 (s), 107.8 (s), 55.6 (q); MS (FAB) 226 ($M^+ + 1$, 43), 225 (100). Anal. Calcd for $C_{12}H_7N_3O_2$: C, 64.00; H, 3.13; N, 18.66. Found: C, 64.25; H, 3.02; N, 18.63.

3,5-Dicyano-4-phenylisoxazole (7 g): colorless needles; mp 121−122 °C; IR (Nujol) 2243 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.6−7.7 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.1 (s), 141.4 (s), 133.3 (s), 132.3 (d), 131.6 (d), 129.2 (d), 123.7 (s), 109.8 (s), 108.9 (s). Anal. Calcd for $C_{11}H_5N_3O$: C, 67.69; H, 2.58; N, 21.53. Found: C, 67.84; H, 2.50; N, 21.64.

3,5-Dicyano-4-(4-nitrophenyl)isoxazole (7h): pale yellow needles; mp 143−144 °C; IR (Nujol) 2249 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 (d, J = 8.6 Hz, 2H), 8.49 (d, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.5 (s), 141.7 (s), 139.6 (s), 129.0 (d), 128.2 (s), 127.8 (s), 125.2 (d), 107.7 (s), 106.7 (s). Anal. Calcd for $C_{11}H_4N_4O_3$: C, 55.01; H, 1.68; N, 23.33. Found: C, 54.77; H, 1.52; N, 23.47.

3,5-Dicyano-4-heptylisoxazole (7i): pale yellow oil; IR (neat) 2245 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, J = 7.0 Hz, 3H), 1.2−1.5 (m, 8H), 1.65−1.85 (m, 2H), 2.75 (t, J = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.7 (s), 142.1 (s), 132.5 (s), 108.2 (s), 107.1 (s), 31.9 (t), 29.2 (t), 29.0 (t), 28.9 (t), 22.9 (t), 22.5 (t), 14.4 (q). Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 65.95; H, 7.03; N, 19.01.

4-*t*-Butyl-3,5-dicyanoisoxazole (7j): colorless needles; mp 55−56 °C; IR (Nujol) 2243 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.55 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.5 (s), 140.2 (s), 139.5 (s), 109.0 (s), 107.8 (s), 30.7 (s), 29.5 (q). Anal. Calcd for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.43; H, 5.13; N, 24.07.

3,5-Dicyano-4-(2-furyl)isoxazole (7k): pale yellow needles; mp 95−100 °C; IR (Nujol) 2245 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.67 (dd, J = 3.6, 1.6 Hz, 1H), 7.25 (d, J = 3.6 Hz, 1H), 7.72 (d, J = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.2 (d), 138.0 (s), 137.7 (s), 137.4 (s), 121.7 (s), 114.0 (d), 112.8 (d), 108.0 (s), 107.2 (s). Anal. Calcd for $C_9H_3N_3O_2$: C, 58.39; H, 1.63; N, 22.70. Found: C, 58.00; H, 1.80; N, 22.42.

Supporting Information Available: X-ray data of **4a** and **7f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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