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A SIMPLE SYNTHESIS OF α-NITRO-δ-KETO NITRILE

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Abstract – α-Nitro-δ-keto nitrile was effectively synthesized in one-pot from pyridinium salt of nitroisoxazolone by ring opening reaction followed by condensation with two molecules of acetone via pyrrolidinium salt of 2,4-di-*aci*-nitropentanedinitrile. The obtained α-nitro-δ-keto nitrile has a highly acidic hydrogen in addition to multi-functionality. These structural features are considered to be useful for the syntheses of polyfunctionalized compounds.

INTRODUCTION

4-Nitro-3-isoxazolin-5-one derivatives have been proved to be excellent synthetic intermediates for versatile frameworks.[1] For example, 2-methyl-4-nitroisoxazolone (**1**) (Figure 1) reacts with sodium enolates of 1,3-dicarbonyl compounds to afford polyfunctionalized pyrroles.[2] Isoxazolone (**1**) also behaves as a precursor of nitrile oxide having a carbamoyl group by only stirring in water, which causes the cycloaddition with alkynes or alkenes leading to functionalized isoxazol(in)es in high yields.[3]

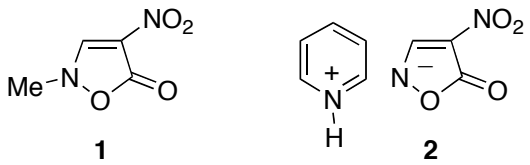
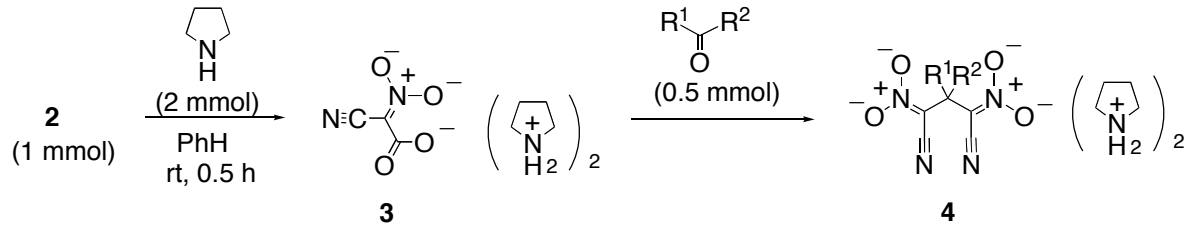


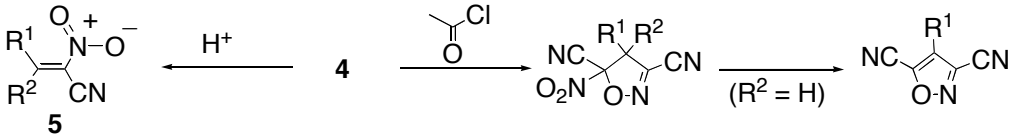
Figure 1. Nitroisoxazolones

On the other hand, pyridinium salt of nitroisoxazolone (**2**) shows different reactivity from **1** (Figure 1). Pyrrolidine undergoes deprotonation at the 3-position despite anionic property of the isoxazolone ring to cause the ring opening reaction accompanied by N-O bond cleavage, which furnishes dipyrrolidinium cyano-*aci*-nitroacetate (**3**) quantitatively.[4] This trifunctionalized methane derivative (**3**) is readily transformed to dipyrrolidinium salt of 2,4-di-*aci*-nitroglutaroitrile (2,4-di-*aci*-nitropentanedinitrile) (**4**) in the reaction with stoichiometric amounts of aldehydes or ketones (Scheme 1).[5]



Scheme 1. Preparation of glutaronitrile (**4**)

Since the resultant dianionic dinitriles (**4**) possess two cyano and two *aci*-nitro groups in the single molecule, they are expected to serve as the synthetic intermediate for polyfunctionalized systems. Indeed, α-nitro-α,β-unsaturated nitriles (**5**) are obtained accompanied by C-C bond cleavage when dinitriles (**4**) are allowed to stand under acidic conditions.[5] Furthermore, the intramolecular ring transformation easily occurs upon treatment with acetyl chloride to furnish polyfunctionalized isoxazol(in)es those can be prepared in one-pot from pyridinium salt (**2**) in good to high yields (Scheme 2).[6] In the present paper, we would like to demonstrate a new diversity of the dinitrile (**4**) leading to α-nitro-δ-keto nitrile (**6**).

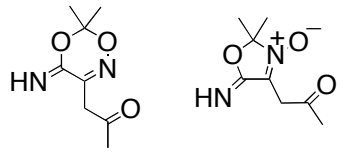


Scheme 2. Chemical conversion of glutaronitrile (**4**)

RESULTS AND DISCUSSION

When cyano-*aci*-nitroacetate (**3**) was subjected to the reaction with acetone, was isolated small amount of unidentified product (**6**) other than glutaronitrile (**4a**) (R^1, R^2 = Me) by column chromatography on silica gel. The same yellow solid product (**6**) was also isolated in the reaction of glutaronitrile (**4a**) with acetone. The empirical formula $C_8H_{12}N_2O_3$ of the product suggested the nitroacetonitrile moiety in **4a** was substituted by acetone. In the ^{1}H NMR, two hydrogen atoms of the methylene group were unequivalently observed together with a large coupling constant (J = 18.9 Hz). Since three methyl groups were also unequivalent, this product was regarded to have a rigid structure. In addition to these signals, a singlet signal was observed at 6.29 ppm which was exchangeable with deuterated water. This signal was assigned to a methine hydrogen by DEPT and C-H COSY spectra, hence the possibility of cyclic products such as **7** and **8** was excluded (Figure 2). While absorptions of a carbonyl and a nitro groups were observed in the IR spectrum, that of a cyano group did not appear enough detectable.

However, observation of a signal at 111.8 ppm in the ^{13}C NMR revealed the presence of a nitrile function. On the basis of these spectral and analytical data, this compound is determined as α-nitro-δ-keto nitrile (**6**).

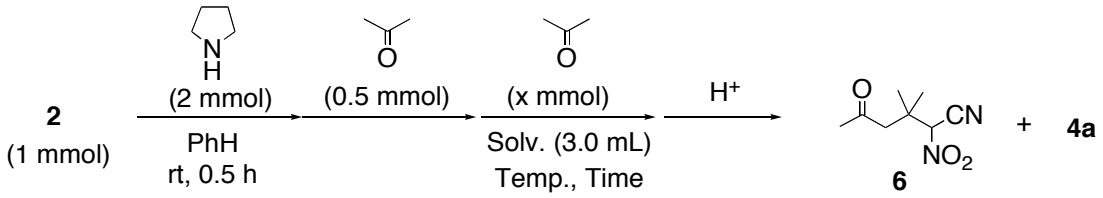


7 **8**

Figure 2. Other possibility of the product structures

α-Nitro-δ-keto nitriles are generally synthesized by Michael addition of nitroacetonitrile to α,β-unsaturated carbonyl compounds.[7] However, this procedure often suffers from difficulty to deal with nitroacetonitrile[7,8] and complication of the reaction mixture. Because of these restrictions, α-nitro-δ-keto nitrile has not been employed for organic syntheses except for a few examples.[9,10] From this viewpoint, the present reaction will provide a new preparative method for α-nitro-δ-keto nitrile.

Table Optimization of reaction conditions

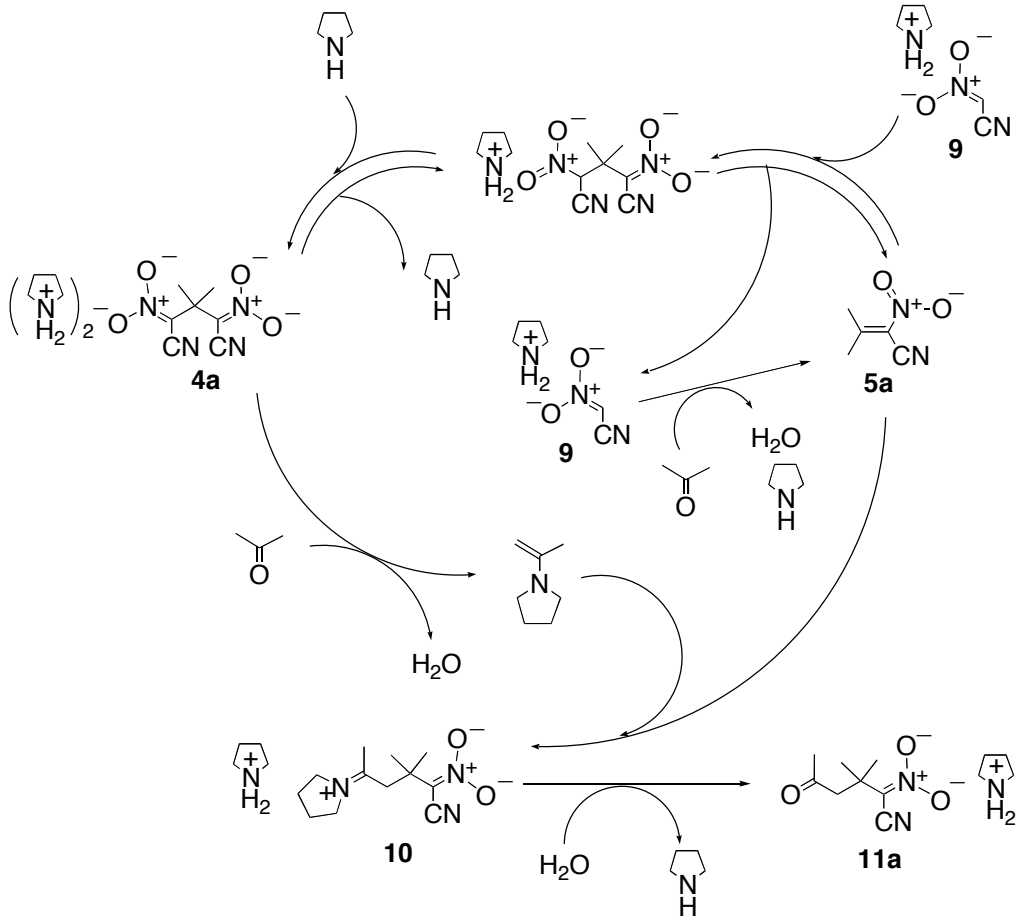


run	Acetone x / mmol	Solv.	Temp. ˚C	Time h	Yield / **5**[a] **6**	**4a**
1	0.5	PhH	rt	24	4	89
2	0.5	MeOH	rt	24	12	88
3	0.5	MeOH	65	3	20	62
4	0.5	MeOH	65	24	40	38
5	0.5	MeOH	65	48	22	41
6	1	MeOH	65	3	19	79
7	5	MeOH	65	3	42	55
8	10	MeOH	65	3	56	44
9	solv.	acetone	rt	24	92	0

[a] Based on pyridinium salt **2**

Reaction conditions were surveyed to improve the yield of **6** (Table). Since intermediate dianionic species (**3**) and (**4a**) gradually decompose during the storage for several days even at room temperature, the reaction was conducted in one-pot from pyridinium salt (**2**), which afforded glutaronitrile (**4**) *in situ*

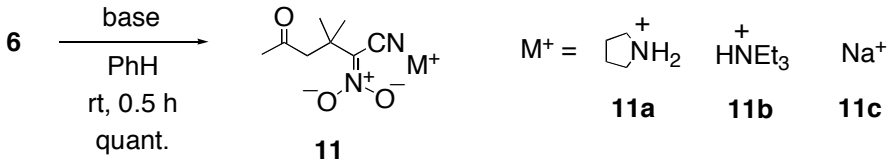
via cyano-*aci*-nitroacetate (**3**). When the successive reaction with acetone was performed in methanol under reflux for 24 h, the yield of **6** was increased to 40%, however heating for a longer time caused the decomposition of the product (runs 1-5). The use of larger amount of acetone was found to be rather effective for the present reaction (runs 6-8), and the yield of keto nitrile (**6**) was improved up to 92% by employing acetone as the solvent (run 9). This preparative method is more advantageous than conventional one since only simple experimental manipulations are required.



Scheme 3. A plausible mechanism

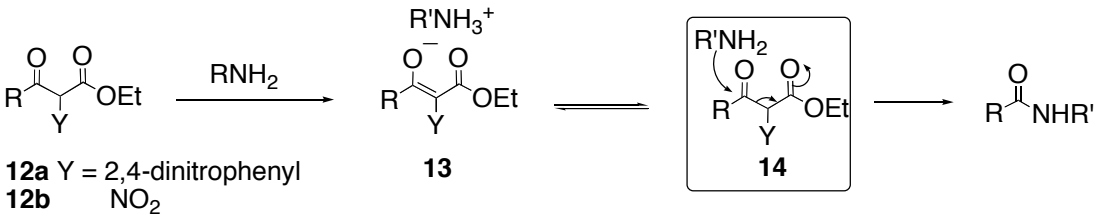
A plausible mechanism for the present reaction is illustrated in Scheme 3. When glutaronitrile (**4b**) (R^1 = Et, R^2 = Me) derived from butanone was stirred in acetone at room temperature for 1 day, only keto nitrile (**6**) was formed, which indicated the center part of the glutaronitrile (**4b**) was replaced with surrounding acetone molecule under equilibrium. Protonation of glutaronitrile (**4a**) causes splitting into acrylonitrile (**5a**) (R^1, R^2 = Me) and anionic nitroacetonitrile (**9**). Acrylonitrile (**5a**) is also formed by the reaction of anion (**9**) and acetone. The electrophilic carbon of **5a** is readily attacked by enamine

generated from acetone and pyrrolidine to afford adduct (**10**), and then its hydrolysis leads to anionic α-nitro-δ-keto nitrile (**11a**).



Scheme 4. Treatment of **6** with bases

The acidic hydrogen of **6** was easily deprotonated by pyrrolidine, triethylamine and sodium hydroxide to give corresponding α-*aci*-nitro-δ-keto nitriles (**11a-c**), respectively (Scheme 4). In the IR spectra of **11**, a strong absorption of a cyano group was observed as well as a carbonyl group. Since this spectral feature is quite similar to spectrum of cyano-*aci*-nitroacetate,[4] the formation of the α-*aci*-nitro nitrile skeleton is confirmed. Recently, anionic 2-nitro-5-oxo-3-pentenenitrile was found to form an ionic crystal that has strong interaction with sodium ion and a water molecule.[11,12] Thus, these anions (**11**) are also expected to reveal similar property.



Scheme 5. Pseudo intramolecular reactions

Meanwhile, we have reported transacylation reactions using α-aryl- or α-nitro-β-keto esters (**12a**) and (**12b**), which effectively proceeds under mild conditions without formation of any by-products (Scheme 5).[13,14] Acidity of the enol hydrogen is considerably increased by a bulky aryl group in the former case, and by an electron-withdrawing nitro group in the latter case, as a result, ammonium enolate (**13**) is readily formed. When amine is liberated under equilibrium, the intimate-pair (**14**) is formed, namely nucleophilic amine and electrophilic keto ester locate close together. This spatial relationship between two reagents realizes the pseudo intramolecular process to cause effective reaction. α-Nitro-δ-keto nitrile (**6**) also has both multi-functionality and an acidic hydrogen in the molecule. These structural features are considered to be suitable for designing effective reactions using the intimate-pair effect.

Synthesis of polyfunctionalized compounds from α-nitro-δ-keto nitrile (**6**) is in progress and results will be demonstrated in due course.

EXPERIMENTAL

General

The melting points were determined on a Yanaco micro-melting apparatus, and were uncorrected. All the reagents and solvents were commercially available and used as received. ^{1}H and ^{13}C NMR spectra were measured on a Bruker DPX-400 at 400 and at 100 MHz with TMS as an internal standard. Assignment of ^{13}C NMR spectra were performed by DEPT experiments. IR spectra were recorded on a HORIBA FT-200 spectrometer. Elemental microanalyses were performed using a Yanaco CHN corder.

One-pot synthesis of α-nitro-δ-keto nitrile 6

To a suspension of pyridinium salt (**2**) (209 mg, 1.0 mmol) in benzene (3 mL), pyrrolidine (167 μL, 2.0 mmol) was added, and the mixture was stirred at rt for 0.5 h. To the resultant solution, acetone (40 μL, 0.5 mmol) was added. After 2 h of stirring, hexane (10 mL) was added, and the mixture was allowed to stand overnight. Upper solution was decanted off, and the residual white solid was dissolved into acetone (3 mL). After stirring at rt for 1 day, the solvent was evaporated. The residue was dissolved in $CHCl_3$ (20 mL), and washed with 1 M hydrochloric acid (5 mL x 1, 5 mmol). The organic layer was dried over magnesium sulfate, and was concentrated to afford 3,3-dimethyl-5-oxo-2-nitrohexanenitrile (**6**) (167 mg, 0.92 mmol) as a single product. Yellow solid. Mp 45-46 °C. IR (neat / cm^{-1}) 1714, 1568, 1365; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, 3H), 1.34 (s, 3H), 2.18 (s, 3H), 2.65 (d, J = 18.9 Hz, 1H), 2.73 (d, J = 18.9 Hz, 1H), 6.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4 (CH_3), 25.0 (CH_3), 31.3 (CH_3), 38.6 (C), 50.5 (CH), 82.8 (CH_2), 111.8 (C), 206.9 (C). Anal. Calcd for $C_8H_{12}N_2O_3$: C, 52.17; H, 6.57; N, 15.21. Found: C, 52.09; H, 6.58; N, 15.43.

Reaction of Keto Nitrile 6 with Base

To a suspension of keto nitrile (**6**) (184 mg, 1mmol) in benzene (10 mL), pyrrolidine (84 μL, 1 mmol) was added, and the mixture was stirred at rt for 0.5 h. The solvent was removed under reduced pressure to afford pyrrolidinium salt (**11a**) (255 mg, 1 mmol, quant.). Triethylammonium salt (**11b**) was similarly prepared in the same way, and methanol solution of sodium hydroxide was employed for preparation of **11c**. Each salt did not afford satisfactory analytical data because of their hygroscopic property.

Pyrrolidinium salt 11a. Pale brown oil. IR (neat / cm^{-1}) 2193, 1714; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 6H), 1.7-1.9 (m, 4H), 2.08 (s, 3H), 2.95 (s, 2H), 3.3-3.4 (m, 4H), 7.8-9.8 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6 (CH_2), 26.2 (CH_3), 30.9 (CH_3), 34.0 (C), 45.3 (CH_2), 50.4 (CH_2), 104.2 (C), 118.8 (C), 207.6 (C).

Triethylammonium salt 11b. Pale yellow solid. Mp 56-59 °C (decomp). IR (neat / cm^{-1}) 2191, 1716; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 6H), 1.30 (t, J = 7.3 Hz, 9H), 2.07 (s, 3H), 2.96 (s, 2H), 3.11 (q, J = 7.3 Hz, 6H), 9.0-10.0 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6 (CH_3), 26.3 (CH_3), 30.7 (CH_3), 34.2 (C), 45.8 (CH_2), 50.7 (CH_2), 103.0 (C), 118.6 (C), 207.7 (C).

Sodium salt 11c. Yellow oil. IR (neat / cm^{-1}) 2099, 1714; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.18 (s, 6H), 2.00 (s, 3H), 2.87 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.5 (CH_3), 30.7 (CH_3), 33.6 (C), 50.1 (CH_2), 98.9 (C), 119.9 (C), 207.6 (C).

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