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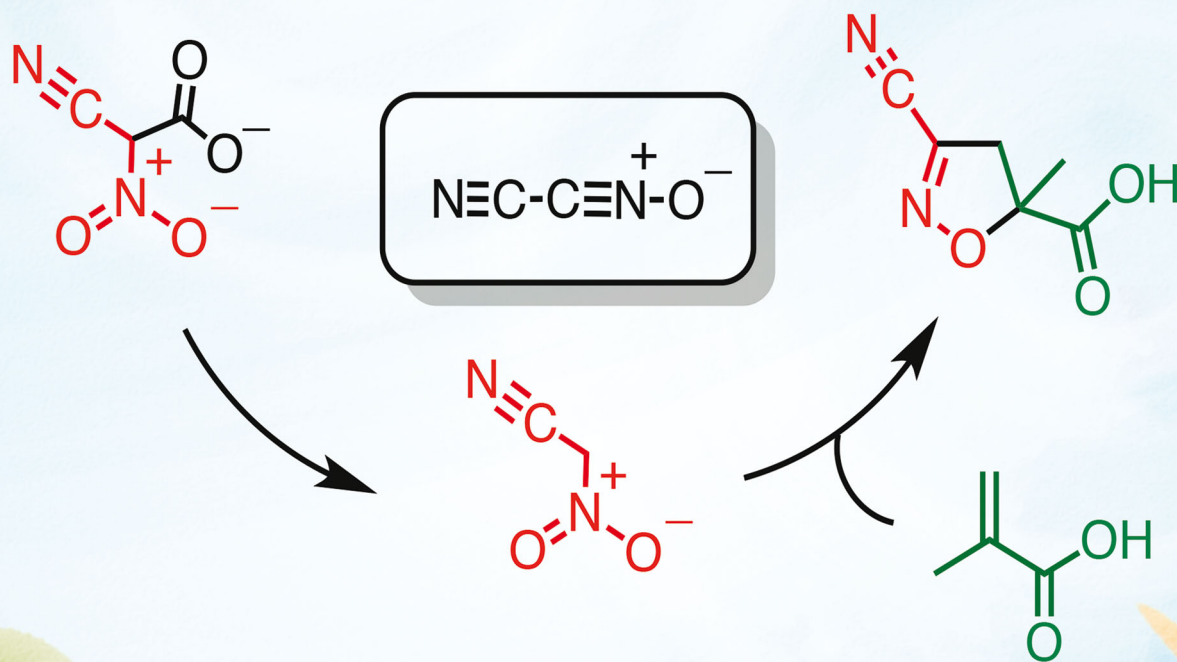
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Nagatoshi Nishiwaki *et al.*
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of cyanonitrile oxide by 1,3-dipolar cycloaddition of
nitroacetonitrile

Development of a safely handleable synthetic equivalent of cyanonitrile oxide by 1,3-dipolar cycloaddition of nitroacetonitrile†

Nagatoshi Nishiwaki, [ID] ★[ab] Yuta Kumegawa,[a] Kento Iwai [ID] [a] and Soichi Yokoyama [ID] [ab]
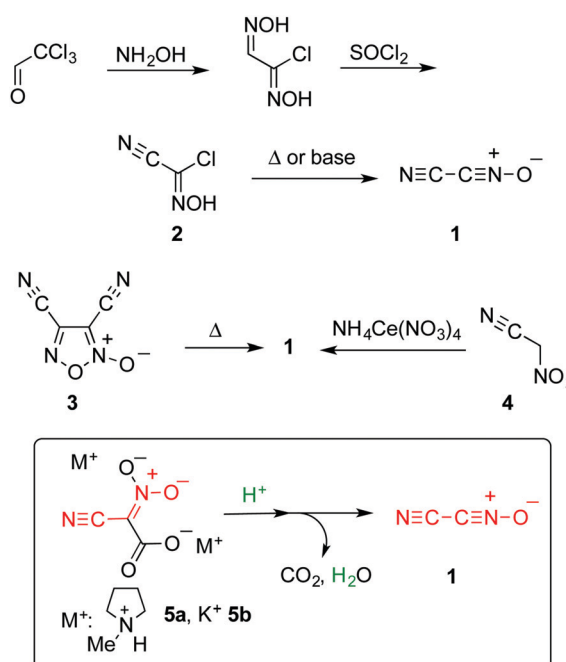
Dianionic cyano-*aci*-nitroacetate affords 3-cyanoisoxazol(in)es upon heating with a range of dipolarophiles in the presence of hydrochloric acid. In this reaction, nitroacetonitrile is formed as an intermediate active species, which serves as a synthetic equivalent of cyanonitrile oxide that can participate in a 1,3-dipolar cycloaddition reaction.

The 1,3-dipolar cycloaddition of cyanonitrile oxide **1** (cyanofulminate or cyanogen *N*-oxide) is a useful preparative method for the synthesis of 3-cyanoisoxazol(in)es, which is superior to other methods such as direct substitution by a cyanide,[1] chemical conversion of other functional groups,[2] and ring construction[3,4] because the five-membered ring can be formed in a single step. In addition, the products are readily transformed into polyfunctionalized compounds upon cleavage of the N–O bond. On the other hand, nitrile oxide **1** is too unstable to be isolated, although its generation can be confirmed by spectroscopy.[5] Vacuum pyrolysis[6] or base-induced dehydrochlorination[7,8] of chloro(cyano)formoxime **2** are common methods used to generate nitrile oxide **1**. In addition, the pyrolysis of dicyanofuroxan **3**[9] and treating nitroacetonitrile **4** with ammonium cerium(III) nitrate[10] are also effective approaches used to prepare **1** (Scheme 1). However, preparation of precursors **2** and **3** suffers from some drawbacks such as low yield, troublesome manipulations, and toxicity.[11,12] In addition, nitroacetonitrile **4** should be handled as an explosive material (see ESI†).[3,13] Hence, the development of a safe and concise method for generation of cyanonitrile oxide **1** is highly desired.

Meanwhile, we have studied the application of dianionic cyano-*aci*-nitroacetate **5**[14] as a cyano(nitro)methylating agent in

organic synthesis leading to the synthesis of functionalized heterocyclic systems.[3,15] The structure of **5** can be regarded as a masked form of cyanonitrile oxide **1**, based on which we envisaged that nitrile oxide **1** should be generated upon protonation of dianion **5** accompanied by decarboxylation and dehydration.

Although it is possible to isolate dianion **5**, decarboxylation gradually occurs.[14] Thus, **5** was generated *in situ* via a ring opening reaction of pyridinium salt **6** upon treatment with *N*-methylpyrrolidine. A solution of **6** and ethynylbenzene **7a** in acetonitrile showed no change even when heated at 100 °C for 1 d in a sealed tube (Table 1, entry 1). On the other hand, a trace amount of 3-cyano-5-phenylisoxazole (**8a**)[16] was obtained when the reaction was conducted under the same conditions in the presence of acetic acid (entry 2). The addition of a stronger acid
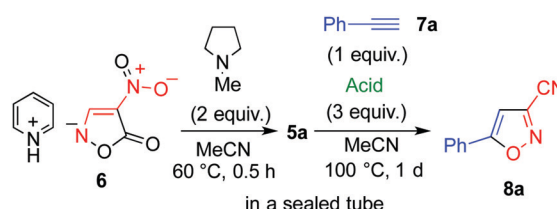
[a] School of Environmental Science and Engineering,
 Kochi University of Technology, Tosayamada, Kami, Kochi 782-8502, Japan.
 E-mail: nishiwaki.nagatoshi@kochi-tech.ac.jp

[b] Research Center for Material Science and Engineering,
 Kochi University of Technology, Tosayamada, Kami, Kochi 782-8502, Japan

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Scheme 1 Methods for the synthesis of cyanonitrile oxide **1**.

Table 1 Assessment of the acid used in the cycloaddition reaction

Entry	Acid	Yield/%
1	—	0
2	AcOH	5
3	p-TsOH·H₂O	15
4	HCl	27

such as *p*-toluenesulfonic acid and hydrochloric acid, was found to be effective (entries 3 and 4).

To obtain further insight into this reaction, each step was monitored using ¹H NMR spectroscopy with deuterated acetonitrile used as the solvent (see ESI†). Cation exchange of **6** occurred after addition of 1 equivalent of *N*-methylpyrrolidine, and the ring opening reaction occurred leading to formation of the dianion, **5a**, when another 1 equivalent of *N*-methylpyrrolidine was added. A new singlet signal appeared at 5.8 ppm when hydrochloric acid was added to the solution of **5a**, in which nitroacetonitrile **4** or its anionic form **9a** was formed as a result of the decarboxylation reaction, and either of these were considered to be the actual species in the cycloaddition reaction. Indeed, the formation of cycloadduct **8a** was confirmed after heating this solution in the presence of **7a**.

Subsequently, a more stable dipotassium salt, **5b**, was employed from the viewpoint of its storage for a long period of time. Although **5a** was more soluble in organic solvents, the reaction mixture was somewhat complicated because of the presence of pyridinium, pyrrolidinium, and ammonium chlorides, among which the last salt was formed during the acid-catalysed hydrolysis of acetonitrile. Thus, **5b** was concluded to be more suitable for use as a reagent in organic synthesis.

Monopotassium salt **9b**,[14] derived from **5b**, did not afford any cycloadduct **8a** upon heating with ethynylbenzene **7a**. However, the formation of **8a** was confirmed when the same reaction was conducted in the presence of hydrochloric acid (Scheme 2). These results indicate that nitroacetonitrile **4** serves as a 1,3-dipole during the cycloaddition reaction.

The reaction conditions were optimized using dipotassium salt **5b** (Table 2). A mixed solvent consisting of acetonitrile and water was suitable because it can dissolve both **5b** and **7a** (entries 1 and 2).
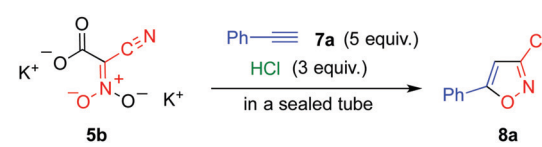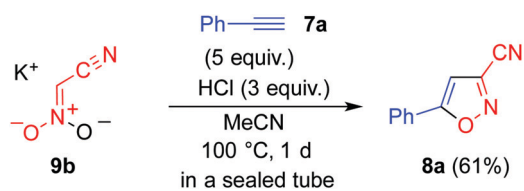

Scheme 2 The cycloaddition reaction using monopotassium salt **9b** under acidic conditions.

**Table 2** Optimization of the reaction conditions

Entry	Solv.	Temp./°C	Time/h	Yield/%
1	MeCN	100	24	78
2	MeCN/H₂O (1/4)	100	24	90
3	MeCN/H₂O (1/4)	70	24	0
4	MeCN/H₂O (1/4)	100	3	0
5	MeCN/H₂O (1/4)	100	6	43
6	MeCN/H₂O (1/4)	100	12	96

However, no reaction occurred at lower temperature, which was presumably due to the low reactivity of nitroacetonitrile **4** when compared with conventional 1,3-dipoles such as nitrile oxide and nitrone (entries 2 and 3). Prolonging the reaction time was found to be effective for the reaction with cycloadduct **8a** obtained in high yield after heating for 12 h (entries 4–6).‡

Under the optimized conditions dipolarophiles **7** and **10** were subjected to the cycloaddition reaction (Scheme 3). Electron-deficient alkyne **7b** underwent the cycloaddition reaction to afford **8b**[16] in quantitative yield. In contrast, alkenes **7c** and **7d**, which possess an electron-donating group furnished their corresponding cycloadducts **8c** and **8d** in moderate yields. Since considerable amounts of acetophenone derivatives were formed during these reactions, competitive hydration was considered to suppress the cycloaddition. *trans*-Stilbene **10e** was also usable as a dipolarophile leading to the formation of diphenylisoxazoline **11e**. Electron-deficient acrylates **10f** and **10h** also undergo the cycloaddition reaction efficiently, however, the ester functionality did not tolerate the reaction conditions, affording carboxylic acids **11g** and **11i**, respectively. Conversely, it was possible to use
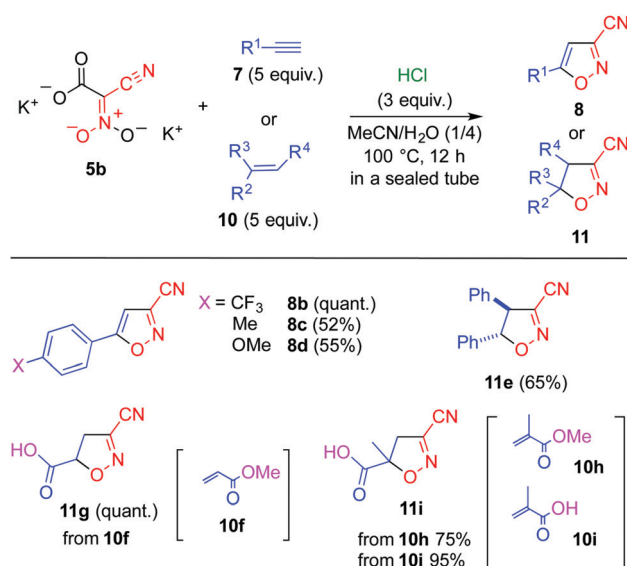
Scheme 3 Synthesis of 3-cyanoisoxazol(in)es **8** and **11**.
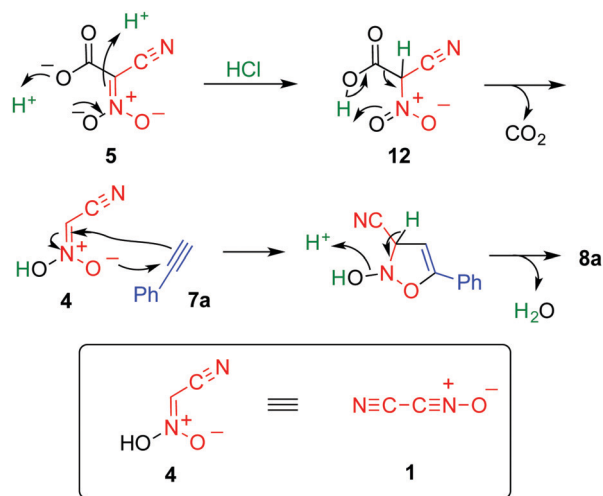
Scheme 4 A plausible mechanism for our 1,3-dipolar cycloaddition reaction.

carboxylic acid **10i** as a substrate without protection in this reaction, which afforded **11i** in high yield.

This reaction was considered to proceed as shown in Scheme 4. Protonation of dianion **5** affords **12**, which immediately undergoes decarboxylation to give nitroacetonitrile **4**. The *aci*-nitro form of **4** serves as a 1,3-dipole and reacts with the dipolarophile to form a five-membered ring. Subsequent dehydration yields the final product. On the basis of this mechanism, the amount of acid necessary for this reaction is 2 equivalents. However, 3 equivalents of hydrochloric acid is necessary for an efficient reaction, which is presumably because the acid is also consumed by forming a salt with ammonia formed during the hydrolysis of acetonitrile.

To conclude, 3-cyanoisoxazol(in)es **8** and **11** were synthesized *via* the cycloaddition of nitroacetonitrile **4**. While nitroacetonitrile **4** is an explosive material, dianion **5** is thermally stable and can be stored for a long period of time without any special care.[3,13] Hence, dianion **5** serves as a safe handleable synthetic equivalent of cyanonitrile oxide **1**, which can be used as a novel tool in organic synthesis.

Conflicts of interest

There are no conflicts to declare.

Notes and references

‡ Typical procedure: in a screw capped test tube, dipotassium salt **5b** (41.2 mg, 0.2 mmol) was dissolved into a mixed solvent of MeCN/H$_2$O (v/v = 1/1, 2 mL). After adding 1-ethynyl-4-trifluoromethylbenzene **7b** (144 μL, 1 mmol) and 1 M HCl (3 mL, 3 mmol), the resultant mixture

was heated at 100 °C for 12 h in a sealed tube. The solvent was removed under reduced pressure, and MeCN (10 mL) was added to the residue. After filtration to remove the insoluble material, the filtrate was concentrated to afford 3-cyano-5-(4-trifluoromethylphenyl)isoxazole **8b** (239 mg, 1 mmol, quant.) as a pale yellow solid. M.p. 92–95 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (s, 1H), 8.05 (d, J = 8.2 Hz, 2H), 8.23 (d, J = 8.2 8.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 105.0 (CH), 110.2 (C), 123.7 (C, q, J = 271 Hz), 126.4 (CH, d, J = 3.5 Hz), 126.9 (CH), 128.7 (C), 131.3 (C, q, J = 32.1 Hz), 140.3 (C), 170.3 (C); IR (ATR/cm^{-1}) 2261, 1570, 1400, 1319; HRMS (ESI/TOF) calcd for (M + H$^+$) C$_{11}$H$_6$F$_3$N$_2$O: 239.0427, found: 239.0428.

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