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Received 00th January 20xx, Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

**nitroacetonitrile**– Nagatoshi Nishiwaki, \*<sup>a,b</sup> Yuta Kumegawa,<sup>a</sup> Kento Iwai,<sup>a</sup> and Soichi Yokoyama<sup>a,b</sup>

cyanonitrile oxide -1,3-dipolar cycloaddition of

Development of safely handleable synthetic equivalent of

Abstract. Dianionic cyano-*aci*-nitroacetate affords 3cyanoisoxazol(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 to 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<sup>3,4</sup> 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 using spectroscopy.5 Vacuum pyrolysis6 or base-induced dehydrochlorination<sup>7,8</sup> 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<sup>10</sup> 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).<sup>3,13</sup> Hence, the development of a safe and concise for generating 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.<sup>3,15</sup> 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.



Scheme 1 Generation methods of cyanonitrile oxide 1.

Although it is possible to isolate dianion 5, decarboxylation gradually occurs.<sup>14</sup> 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)<sup>16</sup> 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

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Electronic Supplementary Information (ESI) available: [experimental methods, monitoring experiments using <sup>1</sup>H NMR, DSC measurement, copies of <sup>1</sup>H and <sup>13</sup>C NMR spectral. See DOI: 10.1039/x0xx00000x

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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 <sup>1</sup>H 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 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, formation of cycloadduct **8a** was confirmed after heating of this solution in the presence of **7a**.

Subsequently, the 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 is 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,<sup>14</sup> 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.



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

Table 2 Optimization of the reaction conditions.				View Article Online
			DOI: 10.1	039/C9CC03875B
K+		Ph 7a (5 e HCl (3 equiv.)	quiv.)	CN
	-0 <sup>-N</sup> 0- К+ -	in a sealed tube	Ph	O N
	5b			8a
Entry	Solv	Temp./°C	Time/h	Yield/%
1	MeCN	100	24	78
2	MeCN/H <sub>2</sub> O (1/4)	100	24	90
3	MeCN/H <sub>2</sub> O (1/4)	70	24	0
4	MeCN/H <sub>2</sub> O (1/4)	100	3	0
5	MeCN/H <sub>2</sub> O (1/4)	100	6	43
6	MeCN/H <sub>2</sub> O (1/4)	100	12	96

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). 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 in the reaction with cycloadduct **8a** obtained in high yield after heating for 12 h (entries 4–6).<sup>‡</sup>



Under the optimized conditions dipolarophiles 7 and 10 were subjected to the cycloaddition reaction (Scheme 3). Electrondeficient alkyne 7b underwent the cycloaddition reaction to afford  $8b^{16}$  in quantitative yield. On the contrary, alkenes 7c and 7d, which possess an electron-donating group furnished their corresponding cycloadducts 8c and 8d in moderate yields. Since a considerable amounts of acetophenone derivatives were

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formed during these reactions, competitive hydration was considered to suppress the cycloaddition. *trans*-Stilbene **10e** was also usable as a dipolarophile leading to 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 carboxylic acid **10i** as a substrate without protection in this reaction, which afforded **11i** in high yield.



Scheme 4 A plausible mechanism for our 1,3-dipolar cycloaddition reaction.

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 construct 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.<sup>3,13</sup> 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<sub>2</sub>O (v/v = 1/1, 2 mL). After adding 1-ethynyl-4trifluoromethylbenzene 7b (144  $\mu L,$  1mmol) 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 3cvano-5-(4-trifluoromethylphenyl)isoxazole 8b (239 mg, 1 mmol, quant.) as a pale yellow solid. Mp 92-95 °C. 1H NMR (400 MHz,  $\hat{D}MSO-d_6$ )  $\hat{\delta}$  8.04 (s, 1H), 8.05 ( $\hat{d}$ , J = 8.2 Hz, 2H), 8.23 (d, J = 8.2 8.2 Hz, 2H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) 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<sup>-1</sup>) 2261, 1570, 1400, 1319; HRMS (ESI/TOF) calcd. for (M+H<sup>+</sup>) C<sub>11</sub>H<sub>6</sub>F<sub>3</sub>N<sub>2</sub>O: 239.0427, found: 239.0428.

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View Article Online DOI: 10.1039/C9CC03875B

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Cyano-*aci*-nitroacetate serves as a safely handleable precursor of nitroacetonitrile to undergo the 1,3-dipolar cycloaddition leading to 3-cyanoisoxazol(in)es.