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An anomalous hydration/dehydration sequence for the mild generation of a nitrile oxide

Nagatoshi Nishiwaki,*[a] Kazuya Kobiro,[a] Hideyuki Kiyoto,[a] Shotaro Hirao,[a] Jun Sawayama,[a] Kazuhiko Saigo,[a] Yoshikazu Okajima,[b] Toshiharu Uehara,[b] Asaka Maki[b] and Masahiro Ariga[b]

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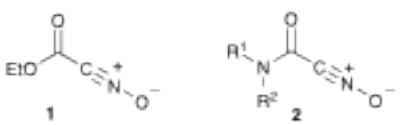
A nitrile oxide having a carbamoyl group is readily generated upon the treatment of 2-methyl-4-nitro-3-isoxazolin-5(2*H*)-one with water under mild reaction conditions, even in the absence of special reagents. The obtained nitrile oxide undergoes cycloaddition with dipolarophiles, alkynes and alkenes, to afford the corresponding isoxazol(in)es, which are useful intermediates in the synthesis of polyfunctionalized compounds. A plausible mechanism underlying the formation of the nitrile oxide is proposed, which involves an anomalous hydration/dehydration sequence. DFT calculations were also performed to support this mechanism.

Introduction

1,3-Dipolar cycloaddition plays an important role in synthetic chemistry because it affords five-membered heterocyclic rings in a single step. Moreover, the cycloadducts formed in this reaction and the ring-opened products obtained from the adducts are precursors of a variety of versatile functional materials.[1] With the growing demand for environment-friendly synthesis protocols, there has been increased focus on 1,3-dipolar cycloaddition reactions in aqueous media.[2] Nitrile oxide, one of the most popular classes of 1,3-dipoles, affords isoxazoles, 2-isoxazolines, and 1,2,4-oxadiazoles upon treatment with alkynes, alkenes, and nitriles, respectively.[1-4] While there are numerous reports on nitrile oxides, most of them are related to aryl- or alkyl-substituted nitrile oxides. Nitrile oxides having a suitable functional group are considered useful for the synthesis of functional materials; however, such substituted nitrile oxides are not very common in organic synthesis, probably because they are highly reactive and their precursors are not readily availabile.



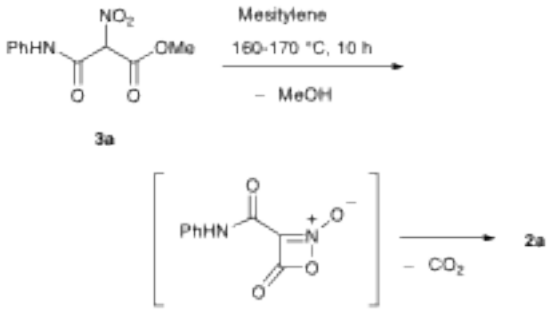
R^1	R^2	
Ph	H	a
MeO	Me	b
Camphorsultam	H	c
Me	H	d

Figure 1. Nitrile oxides having a functional group.

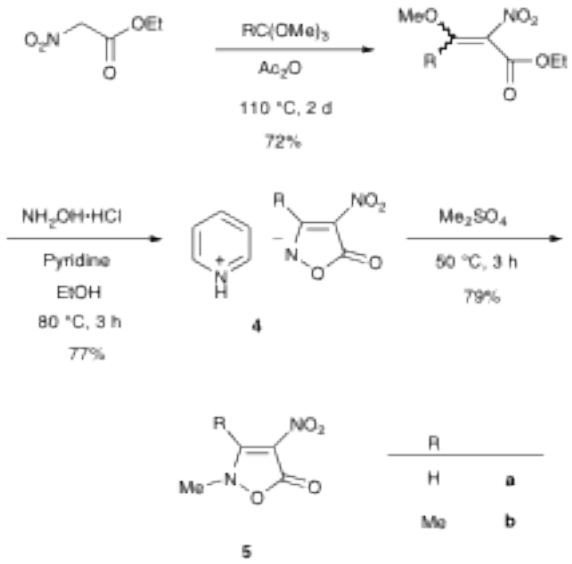
Among the various functionalized nitrile oxides reported, the ethoxycarbonyl derivative **1** is most commonly used in organic synthesis. Nitrile oxide **1** is generated by the dehydrochlorination of hydroximoyl chlorides, which is synthesized from ethyl glyoxylate or glycine ethyl ester.[5] A method for the dehydration of ethyl nitroacetate to **1** has also been established; in this reaction, tolylene diisocyanate (modified Mukaiyama method),[6] manganese(III) acetate,[7] acid chloride,[8] or trifluoroborane etherate[9] is employed as the generating agent. In addition, nitromalonate[10] and nitroacetoacetate[11] are known to be precursors of **1**; however, these compounds have certain disadvantages: severe reaction conditions must be employed when using nitromalonate, and nitroacetoacetate is highly unstable. Although De Sarlo and Machetti demonstrated an excellent protocol for preparation of functionalized isoxazol(in)es from nitroalkanes, active species were not functionalized nitrile oxides but activated nitronates.[12]

Nitrile oxides bearing an amide function have not been widely utilized in organic syntheses, except in a few intriguing cases. Paul and Tchelitcheff were the first to isolate the cycloadduct of *N*-phenylcarbamoylnitrile oxide **2a** as a by-product in a reaction between nitromethane, phenyl isocyanate, and triethylamine.[13] Huisgen and Christl showed that *N*-phenylnitroacetamide is the precursor of **2a** in the above mentioned reaction.[14] Joule *et al.* also generated a carbamoylnitrile oxide by treating nitroacetamide with thionyl chloride.[8a] Shimizu,[15] Webb,[6b] and Schults[16] reported a different method involving the use of α-nitromalonic acid amide ester **3a** as a precursor for generating **2a**; however, in this method, severe reaction conditions were required (Scheme 1). Moreover, although dehydrochlorination of carbamoylformhydroxymoyl chloride by triethylamine is also known to be another route to **2a**, multi-step reactions are necessary for preparation of the starting chloride.[17] Recently, nitrile oxides having an *N*-modified carbamoyl group such as Weinreb amide **2b**[18] and chiral amide **2c**[19] have been synthesized. Although these nitrile oxides possess inherent

high synthetic values, the corresponding precursors are troublesome to prepare. Therefore, development of a facile method to generate **2** under mild conditions is necessary. In the present paper, we demonstrate a new route to carbamoylnitrile oxide **2d** from 2-methyl-4-nitro-3-isoxazolin-5(2*H*)-one (**5a**) which can be easily prepared as shown in Scheme 2.[20]



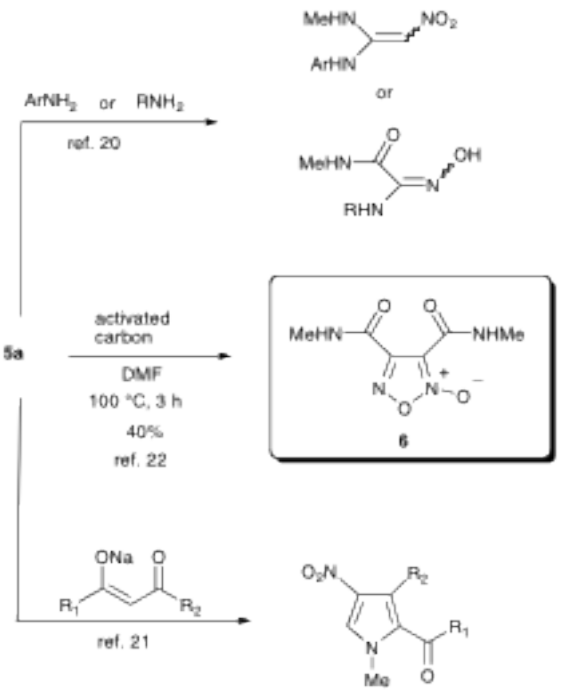
Scheme 1. Conversion of malonic acid amide ester **3a** to nitrile oxide **2a**.



Scheme 2. Preparation of nitroisoxazolone **5**.

Results and Discussion

Nitroisoxazolone **5a** readily reacted with amines to afford α-amino-β-nitroenamines (nitroketene aminals) and amidoximes[21] and underwent ring transformation to afford polyfunctionalized pyrroles upon treatment with sodium enolates of 1,3-dicarbonyl compounds (Scheme 3).[22] Upon heating in DMF at 100 °C in the absence of nucleophile, isoxazolone **5a** was found to remain intact, but bubbles were formed in the reaction mixture after activated carbon was added. From this mixture, bis(*N*-methylcarbamoyl)-1,2,5-oxadiazole-2-oxide (furoxan) (**6**) could be isolated in 40% yield (based on **5a**), indicating the in situ generation of carbamoylnitrile oxide (**2d**, R^1 = Me, R^2 = H) from nitroisoxazolone **5a** and the concurrent elimination of carbon dioxide. However, the role of activated carbon in this reaction has not yet been clarified. Cycloaddition of **2d** proceeded to afford 3-(*N*-methylcarbamoyl)-5-phenylisoxazole (**8a**) in 66% yield when activated carbon was added to a solution of **5a** and ethynylbenzene **7a** under the same conditions mentioned above (heating at 100 °C in DMF).[23] A small amount of furoxan **6** was also isolated from the aqueous solution used for the workup of the other reaction involving nitroisoxazolone **5a**. In this case, nitrile oxide **2d** was formed even when activated carbon was not employed, indicating that this nitrile oxide was generated by another generating agent, presumably water. This hypothesis prompted us to reinvestigate the generation of carbamoylnitrile oxide **2d** in aqueous media.

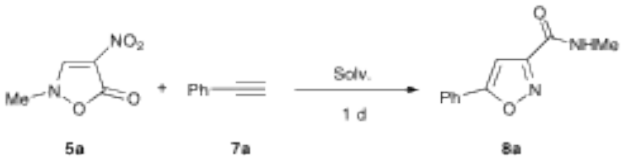


Scheme 3. Chemical transformation of nitroisoxazolone **5a**.

An aqueous solution of nitroisoxazolone **5a** was stirred at 30 °C for 1 day without adding any other reagent, and then, water was removed under reduced pressure. The residue was purified by silica gel column chromatography to afford furoxan **6** in 80% yield (based on **5a**), together with a trace amount of *N*-methylnitroacetamide **9**.[24] The successful isolation of furoxan **6** indicated that water triggered the generation of nitrile oxide **2d** under the abovementioned reaction conditions, as expected. Cycloaddition of **2d** to **7a** proceeded under the same conditions mentioned above to afford isoxazole **8a** in 22% yield (Table 1, run 1). Since the low efficiency of the cycloaddition reaction was attributed to the low solubility of **7a** in water, an acetonitrile/water (3/1,

v/*v*) mixture was used to improve the solubility of both isoxazolone **5a** and the dipolarophile **7a**. Although the amount of water could be diminished to the ratio (6/1, *v*/*v*), almost all nitroisoxazolone **5a** was recovered in the case of (9/1, *v*/*v*) ratio (runs 2-4). Under these conditions, considerable amounts of furoxan **6** were formed as the by-product; a similar result was obtained even at higher temperature (run 5). The above disadvantage was overcome by using excess dipolarophile, and the yield of **8a** in this case was improved up to 72% (run 6). When THF was used as a co-solvent in the present reaction, the yield of **8a** was comparable to that mentioned in the previous sentence (run 7); however, acetonitrile was preferred because of the high solubility of **5a** in this solvent.

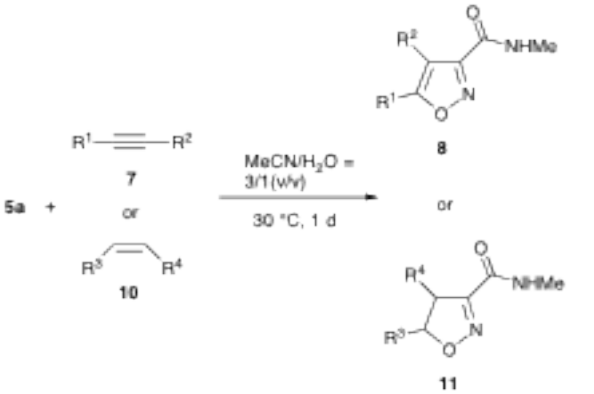
Table 1. Study on reaction conditions.



run	Solv.	**7a**/equiv.	Temp./°C	Yield/%
1	H_2O	1.2	30	22
2	MeCN/H_2O (3/1)	1.2	30	55
3	MeCN/H_2O (6/1)	1.2	30	47
4	MeCN/H_2O (9/1)	1.2	30	trace
5	MeCN/H_2O (3/1)	1.2	60	55
6	MeCN/H_2O (3/1)	5.0	30	72
7	THF/H_2O (3/1)	5.0	30	65

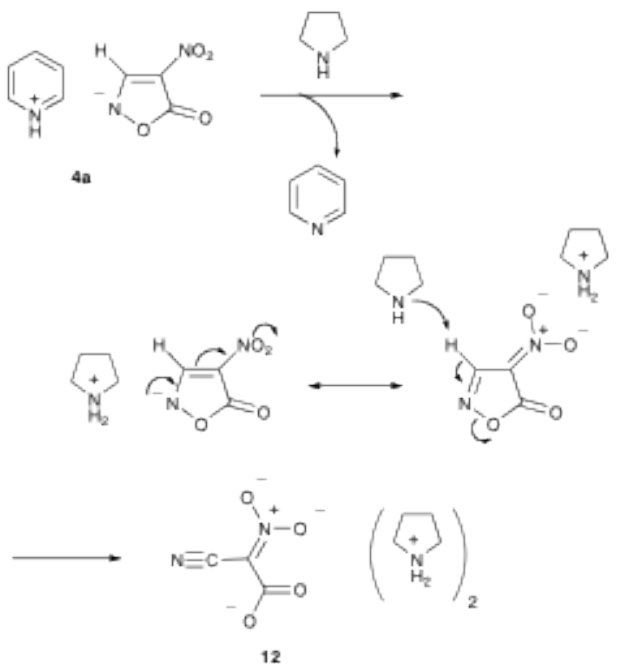
Other dipolarophiles **7b-d** and **10a-l** were subjected to cycloaddition under the optimized conditions used for ethynylbenzene **7a** (Table 2, run 1). Propargyl derivatives **7b** and **7c** underwent this cycloaddition reaction to afford cycloadducts **8b** and **8c**, respectively (runs 2 and 3). A trifunctionalized isoxazole **8d** was prepared in a similar manner from electron-deficient alkyne **7d** (run 4). Nitrile oxide **2d** also underwent the aforementioned cycloaddition with olefinic hydrocarbons **10a-c** to afford the corresponding 2-isoxazolines (4,5-dihydroisoxazoles) **11a-c** (runs 5-7). Allyl alcohol **10d** had higher reactivity than did hydrocarbons and allyl ethyl ether **10e**; the hydroxy group in **10d** was thought to participate in the generation of nitrile oxide **2d** (runs 8 and 9). On the other hand, allylamine **10f** afforded a complex mixture, in which desired cycloadduct **11f** could not be detected presumably because of competitive reactions triggered by the nucleophilic amino group, as shown in Scheme 3 (run 10). This problem was partially solved by protecting the amino group with an acetyl group, in which case **11g** was obtained, albeit in low yield (run 11). The present reaction was applicable to electron-rich alkenes such as vinyl ethers **10h** and **10i** as well as to electron-deficient alkenes such as acrylate **10j**, maleate **10k**, and enone **10l**: alkenes **10h-l** gave the corresponding cycloadducts **11h-l** in good to excellent yields (runs 12-16). It is noteworthy that the cycloaddition of **2d** with monosubstituted alkenes proceeded regioselectively to afford 5-substituted 2-isoxazolines **11** independent of the electronic property of the dipolarophiles.

Table 2. Cycloaddition of nitrile oxide **2d** generated from **5a** and dipolarophiles **7** and **10**.



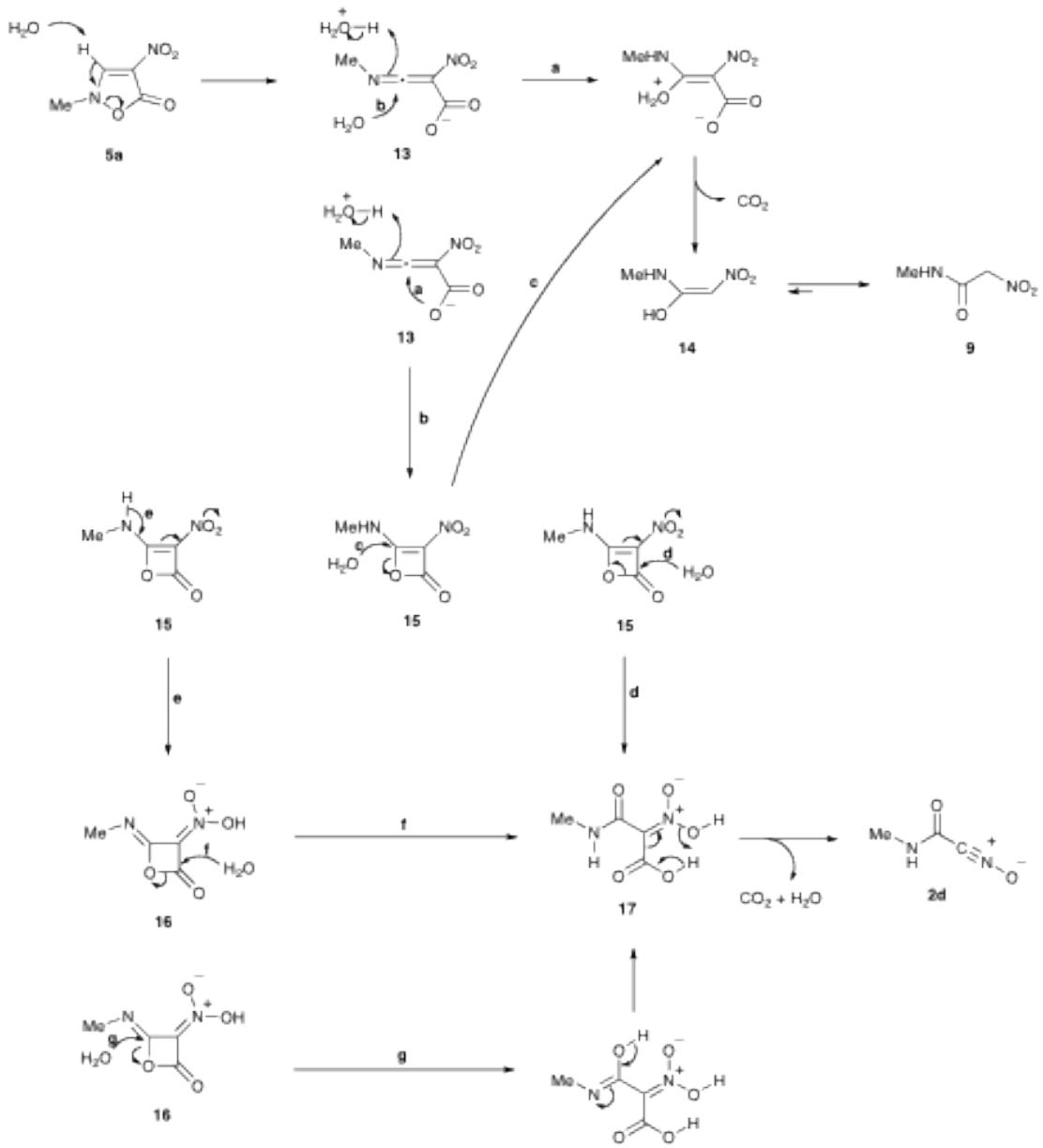
run	Substrate	R^1	R^2	R^3	R^4	Product	Yield/%
1	**7a**	Ph	H			**8a**	72
2	**7b**	CH_2OH	H			**8b**	84
3	**7c**	CH_2Br	H			**8c**	58
4	**7d**	COOEt	COOEt			**8d**	74
5	**10a**			Ph	H	**11a**	85
6	**10b**			Pr	H	**11b**	73
7	**10c**			-$(CH_2)_3$-		**11c**	63
8	**10d**			CH_2OH	H	**11d**	quant.
9	**10e**			CH_2OEt	H	**11e**	76
10	**10f**			CH_2NH_2	H	**11f**	0
11	**10g**			CH_2NHAc	H	**11g**	23
12	**10h**			OEt	H	**11h**	78
13	**10i**			-$(CH_2)_2O$-		**11i**	78
14	**10j**			COOEt	H	**11j**	92
15	**10k**			COOMe	COOMe	**11k**	67[a]
16	**10l**			COMe	H	**11l**	63

[a] A mixture of *cis*- and *trans*-isomers was formed in a 93/7 ratio.



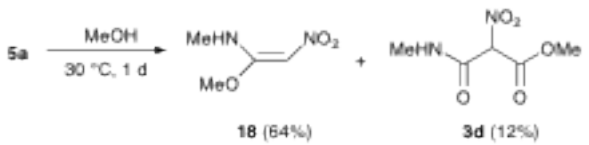
Scheme 4. Ring opening reaction of anionic isoxazolone **4a**

We have previously demonstrated that the anionic nitroisoxazolone **4a** undergoes ring opening to form dianionic cyano-*aci*-nitroacetate **12** by cation exchange and subsequent deprotonation at the 3-position of the isoxazolone ring (Scheme 4).[20c] Since even anionic isoxazolone **4a** is deprotonated by pyrrolidine, the ring proton of *N*-methylisoxazolone **5a** should be sufficiently acidic for easy deprotonation by water. 2,3-Dimethylnitroisoxazolone **5b**,[25] which has no ring protons, remains intact under the same conditions to be recovered, although the steric effect of the additional methyl group in this compound must be taken into consideration. On the basis of these observations, we propose a plausible mechanism for the generation of nitrile oxide **2d**, as shown in Scheme 5. According to this mechanism, the first step in the formation of **2d** is deprotonation at the 3-position by water. The successive ring-opening reaction furnishes the ketenimine intermediate **13**. As reviewed by Prager and Williams,[26] a number of base-induced ring-opening reactions of 3-isoxazolin-5-ones have been studied; in these reactions, the N-O bond fission initiated by deprotonation at the 3-position affords malonic acid derivatives via the formation of ketenimine and β-lactone intermediates.[27] In our reaction, the cummulene carbon of ketenimine **13** is attacked by water to afford α-hydroxy-β-nitroenamine **14** (route **a**), which in turn undergoes a tautomeric rearrangement to form nitroacetamide **9** by tautomerism. Another reaction path (route **b**), which involves the intramolecular attack of carboxylate on the cummulene carbon to give β-lactone **15**, can also be considered.

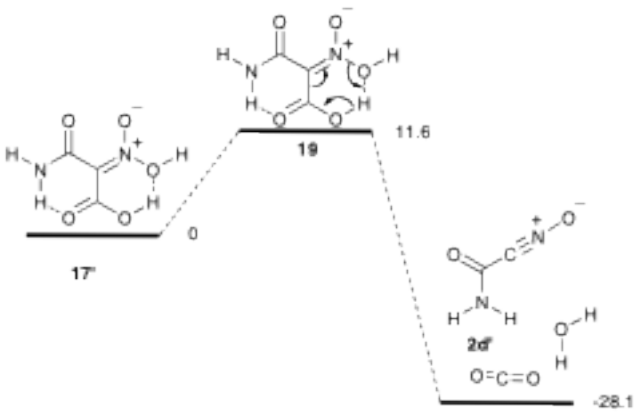


Scheme 5. A plausible mechanism for generation of nitrile oxide **2d**.

Compound **15** is expected to be highly reactive and hence reacts readily with water. When the enamine moiety is attacked by water (route **c**), the resulting intermediate is **14**, which tautomerizes to nitroacetamide **9**. On the other hand, when water attacks the carbonyl group of **15** (route **d**), nitromalonic acid monoamide **17** is formed which readily undergoes dehydration and decarboxylation in a concerted manner to afford nitrile oxide **2d**. Another possibility is that **15** may undergo prototropic rearrangement to form the less-strained intermediate **16** (route **e**), the two electrophilic carbons in which are attacked by water to give the nitromalonic acid derivative **17** (route **f** or **g**). In the present mechanism, nitroenamine **14** and nitromalonic acid derivative **17** are considered the key intermediates. This consideration is supported by the experimental fact that methanolysis of isoxazolone **5a** affords a mixture of methoxynitroenamine **18** and a small amount of nitromalonic acid amide ester **3d**, which are corresponding to hydroxy derivatives **14** and **17**, respectively (Scheme 6).



Scheme 6. Methanolysis of nitroisoxazolone **5a**.



Scheme 7. Relative energies (kcal/mol) for the formation of **2d'** from **17'** via transition state **19** with simultaneous decarboxylation and dehydration.

Nitroacetates can be used as the precursors of nitrile oxide **1**, which has an ester function; however, dehydrating agents and severe conditions need to be employed for this conversion.[6-9] Indeed, nitroacetamide **9**, the tautomer of hydroxynitroenamine **14**, is not converted to nitrile oxide **2d** upon treatment with an acetonitrile/water (3/1, *v*/*v*) mixture alone. Hence, the precursor of **2d** is thought to be nitromalonic acid derivative **17** and not nitroenamine **14**. As shown in Scheme 1, the nitromalonic acid amide ester **3a** serves as the precursor of nitrile oxide **2a** under severe reaction conditions.[10] In contrast, our method efficiently generates nitrile oxide **2d** at room temperature even when no special reagent is employed; the carbamoyl group of **16** is thought to play an important role in dehydration as well as decarboxylation.

Theoretical calculations were performed to investigate the plausible reaction pathway by using a simplified model compound nitromalonic acid monoamide **17'**, which is converted to carbamoylnitrile oxide **2d'**. For this purpose, the DFT method based on Becke's nonlocal three-parameter hybrid functional is employed in combination with the Lee, Yang, and Parr correlation functional (B3LYP). A split valence double-ζ basis set with extra polarization and diffuse functions (6-31+G**) is used. Model compound **17'** has ten conformers, each with two or three intramolecular hydrogen bonds. Among them, one conformer **17'** nicely leads to **2d'** via transition state **19**; the activation energy in this case is 11.6 kcal/mol, as shown in Scheme 7 and Figure 2. The interatomic distance (2.68 Å) between N1 of the carbamoyl group and O5 of the carboxyl group in **19** clearly indicates the existence of strong intramolecular hydrogen bonding in this compound even in the transition state; this hydrogen bonding is responsible for the planar geometry of the transition state. The generation of **2d** from **17** under the quite mild conditions can be ascribed to the planarity of the transition state, which favors concerted decarboxylation and dehydration.

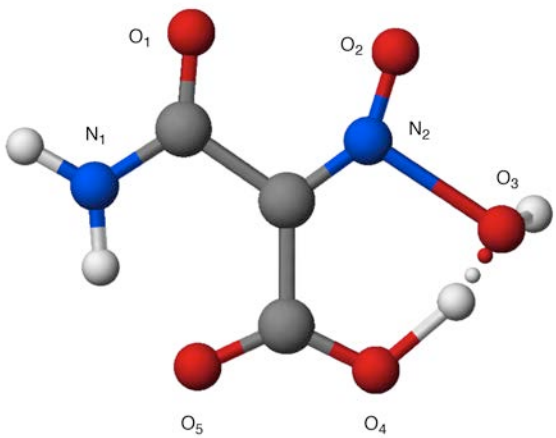


Figure 2. Calculated geometry of transition state **19**.

Conclusions

Nitroisoxazolone **5a** serves as the precursor of nitrile oxide **2d**, which has a carbamoyl group and undergoes cycloaddition with various dipolarophiles at 30 °C to afford functionalized isoxazol(in)es **8** and **11** in good yield. In the present method, only water is required for the generation of **2d**, while other methods for synthesizing nitrile oxides require the use of special generators such as bases, oxidants, and dehydrating agents. Moreover, the present reaction can be conducted in air with simple experimental manipulations. These advantages make the proposed method a very useful tool in organic syntheses.

A plausible mechanism for this reaction is also proposed. According to this mechanism, nitromalonic acid monoamide **17** is the precursor of nitrile oxide **2d**; this assumption is well supported by the results of DFT calculations performed using B3LYP/6-31+G**. The calculation result also indicates that the carbamoyl group takes part in the concerted decarboxylation and dehydration assisted by intramolecular hydrogen bonding. This concerted reaction enables the easy formation of nitrile oxide **2d** even under mild conditions.

Experimental

General

The melting points were determined on a Yanaco micro-melting- points apparatus, and were uncorrected. All the reagents and solvents were commercially available and used as received. The ^{1}H NMR spectra were measured on a Bruker DPX-400 or Varian UNITY INOVA 400 at 400 MHz with TMS as an internal standard. The ^{13}C NMR spectra were measured on a Bruker DPX-400 or Varian UNITY INOVA 400 at 100 MHz, and assignments of ^{13}C NMR spectra were performed by DEPT experiments. The IR spectra were recorded on a Horiba FT-200 IR spectrometer and a JASCO FT/IR- 4200 Spectrophotometer. The mass spectra were recorded on a JEOL JMS-AX505HA. The high resolution mass spectra were measured on a JEOL JMS-700 MStation. The elemental microanalyses were performed using a Yanaco MT-3 CHN corder.

2-Methyl-4-nitro-3-isoxazolin-5(2*H*)-one (**5a**). Nitroisoxazolone **5a** was easily prepared from commercially available ethyl nitroacetate by three steps with simple experimental manipulations; 1) condensation of nitroacetate with orthoformate, 2) condensation with hydroxylamine, and 3) *N*-methylation with dimethyl sulfate (Details are given in Electronic Supplementary Information).[20]

3,4-Bis(*N*-methylcarbamoyl)-1,2,5-oxadiazole 2-Oxide (Furoxan) (6).[8a,23] A solution of nitroisoxazolone **5a** (72 mg, 0.50 mmol) in water (5.0 mL) was stirred at 30 °C for 1 day. When the solvent was removed under reduced pressure, a colorless crystalline product was obtained which contained furoxan. Further purification was performed by recrystallization from benzene to give **6** (40 mg, 0.20 mmol, yield 80% based on **5a**). Mp 168-169 °C (lit.[8a] 163-165 °C). IR (KBr) 3323, 1695, 1653, 1460 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.05 (d, *J* = 4.8 Hz, 3H), 3.06 (d, *J* = 4.8 Hz, 3H), 8.5-8.7 (br, 1H), 9.6-9.8 (br, 1H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.63 (d, *J* = 4.8 Hz, 3H), 2.65 (d, *J* = 4.8 Hz, 3H), 8.7-8.9 (br, 1H), 9.1-9.2 (br, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.3 (CH_3), 26.4 (CH_3), 110.3 (C), 151.7 (C), 154.3 (C), 156.7 (C); MS (EI) 170 (8), 143 (73), 113 (32), 58 (100), 53 (62). Anal. Calcd for $C_6H_8N_4O_4$: C, 36.00; H, 4.03; N, 27.99%. Found: C, 36.19; H, 4.01; N, 28.26%.

Cycloaddition of Nitrile Oxide with Dipolarophiles General Procedure

To a solution of nitroisoxazolone **5a** (86 mg, 0.60 mmol) and dipolarophile **7** or **10** (3.0 mmol) in acetonitrile (4.5 mL), water (1.5 mL) was added, and the resultant mixture was stirred at 30 °C for 1 day. After removal of the solvent under reduced pressure, the residue was subjected to column chromatography on silica gel or recrystallization to isolate cycloadduct **8** or **11**.

3-(*N*-Methylcarbamoyl)-5-phenylisoxazole (8a).[12,23] Eluted with hexane/AcOEt (80/20). Pale yellow plates. Mp 199-200 °C (lit.[12c] 198-199°C). IR (KBr) 3327, 1668 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.04 (d, *J* = 5.0 Hz, 3H), 6.8-6.9 (br, 1H), 6.97 (s, 1H), 7.46-7.51 (m, 3H), 7.78-7.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4 (CH_3), 99.3 (CH), 125.9 (CH), 126.7 (C), 129.1 (CH), 130.7 (CH), 159.1 (C), 159.5 (C), 171.5 (C); MS (EI) 202 (M^+, 9), 105 (31), 58 (100). Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86%. Found: C, 65.36; H, 5.01; N, 13.88%.

5-Hydroxymethyl-3-(*N*-methylcarbamoyl)isoxazole (8b). Eluted with hexane/AcOEt (80/20). Colorless plates. Mp 96-97 °C. IR (KBr) 3600-3100 (br), 1671 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.3-2.6 (br, 1H), 3.00 (d, *J* = 5.2 Hz, 3H), 4.81 (br s, 2H), 6.69 (s, 1H), 6.7-6.9 (br, 1H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.75 (d, *J* = 5.2 Hz, 3H), 4.60 (dd, *J* = 6.0, 0.8 Hz, 2H), 5.73 (t, *J* = 6.0 Hz, 1H), 6.63 (d, *J* = 0.8 Hz, 1H), 8.6-8.7 (br, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.0 (CH_3), 54.8 (CH_2), 101.2 (CH), 158.8 (C), 159.1 (C), 174.6 (C); MS (EI) 156 (3), 125 (11), 68 (25), 58 (100). HRMS Calcd for $C_6H_8N_2O_3$: 156.0535. Found: 156.0535.

5-Bromomethyl-3-(*N*-methylcarbamoyl)isoxazole (8c). Eluted with hexane/AcOEt (80/20). Colorless plates. Mp 133-134 °C. IR (KBr) 3343, 1671 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.00 (d, *J* = 4.8 Hz, 3H), 4.48 (s, 2H), 6.76 (s, 1H), 6.7-6.9 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0 (CH_2), 26.1 (CH_3), 103.5 (CH), 158.8 (C), 158.9 (C), 169.0 (C); MS (EI) 220 (M^+, 1), 125 (17), 68 (14), 58 (100). Anal. Calcd for $C_6H_7N_2O_2Br$: C, 32.90; H, 3.22; N, 12.79%. Found: C, 32.83; H, 3.22; N, 12.82% .

4,5-Bis(ethoxycarbonyl)-3-(*N*-methylcarbamoyl)isoxazole (8d). Eluted with hexane/AcOEt (80/20). Cololess plates. Mp 116-118 °C. IR (neat) 3300, 1732, 1670 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.400 (t, *J* = 7.2 Hz, 3H), 1.404 (t, *J* = 7.2 Hz, 3H), 3.02 (d, *J* = 5.2 Hz, 3H), 4.45 (q, *J* = 7.2 Hz, 2H), 4.46 (q, *J* = 7.2 Hz, 2H), 6.8-6.9 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.82 (CH_3), 13.84 (CH_3), 26.2 (CH_3), 62.7 (CH_2), 63.0 (CH_2), 117.3 (C), 155.2 (C), 156.2 (C), 157.3 (C), 158.7 (C), 160.3 (C); MS (EI) 225 (2), 197 (6), 140 (9), 112 (11), 68 (18), 58 (100). Anal. Calcd for $C_{11}H_{14}N_2O_6$: C, 48.89; H, 5.22; N, 10.37%. Found: C, 48.87; H, 5.24; N, 10.41%.

4,5-Dihydro-3-(*N*-methylcarbamoyl)-5-phenylisoxazole (11a).[12] Recrystallized from a mixed solvent of benzene and hexane (1/1). Colorless solid. Mp 113-115 °C (lit.[12c] 111 °C). IR (KBr) 3287, 1655, 1544 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.94 (d, *J* = 5.1 Hz, 3H), 3.27 (dd, *J* = 17.9, 8.8 Hz, 1H), 3.66 (dd, *J* = 17.9, 11.5 Hz, 1H), 5.74 (dd, *J* = 11.5, 8.8 Hz, 1H), 6.6-6.8 (br, 1H), 7.3-7.45 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1 (CH_3), 41.2 (CH_2), 84.6 (CH), 125.9 (CH), 128.6 (CH), 128.8 (CH), 139.6 (C), 153.6 (C), 160.2 (C); MS (FAB) 205 (M^++1, 92), 107 (100), 105 (92). HRMS Calcd for $C_{11}H_{12}N_2O_2$: 204.0899. Found: 204.0899.

4,5-Dihydro-3-(*N*-methylcarbamoyl)-5-propylisoxazole (11b). Eluted with hexane/AcOEt (50/50). Colorless solid. Mp

60-62 °C. IR (KBr) 3297, 1656, 1551 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.2 Hz, 3H), 1.3-1.45 (m, 2H), 1.5-1.6 (m, 1H), 1.65-1.75 (m, 1H), 2.85 (dd, *J* = 17.6, 8.4 Hz, 1H), 2.89 (d, *J* = 4.8 Hz, 3H), 3.25 (dd, *J* = 17.6, 10.8 Hz, 1H), 4.75 (dddd, *J* = 10.8, 8.4, 6.8, 5.6 Hz, 1H), 6.6-6.8 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8 (CH_3), 18.5 (CH_2), 26.1 (CH_3), 37.2 (CH_2), 38.3 (CH_2), 83.6 (CH), 153.8 (C), 160.6 (C); MS (FAB) 171 (M^++1, 100). HRMS Calcd for $C_8H_{14}N_2O_2$: 170.1055. Found: 170.1056.

3-(*N*-Methylcarbamoyl)-3a,5,6,6a-tetrahydro-4*H*-cyclopent[*d*]isoxazole (11c). Eluted with hexane/AcOEt (50/50). Colorless solid. Mp 72-75 °C. IR (KBr) 3330, 1655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.3-1.45 (m, 1H), 1.65-1.85 (m, 3H), 2.05-2.15 (m, 2H), 2.89 (d, *J* = 5.2 Hz, 3H), 3.92 (dd, *J* = 8.8, 8.8 Hz, 1H), 5.20 (dd, *J* = 8.8, 4.8 Hz, 1H), 6.5-6.7 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2 (CH_2), 26.0 (CH_3), 31.5 (CH_2), 35.7 (CH_2), 51.0 (CH), 89.8 (CH), 155.4 (C), 160.5 (C); MS (FAB) 169 (M^++1, 100). Anal. Calcd for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66%. Found: C, 56.95; H, 7.08; N, 16.37%.

4,5-Dihydro-5-hydroxymethyl-3-(*N*-methylcarbamoyl)isoxazole (11d). Recrystallized from benzene. Colorless plates. Mp 85-86 °C. IR (KBr) 3500-3200 (br), 1654, 1558 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.6-2.0 (br, 1H), 2.92 (d, *J* = 5.2 Hz, 3H), 3.15 (dd, *J* = 18.0, 8.0 Hz, 1H), 3.28 (dd, *J* = 18.0, 11.2 Hz, 1H), 3.65 (dd, *J* = 12.4, 4.4 Hz, 1H), 3.84 (dd, *J* = 12.4, 3.2 Hz, 1H), 4.88 (dddd, *J* = 11.2, 8.0, 4.4, 3.2 Hz, 1H), 6.4-6.8 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1 (CH_3), 34.8 (CH_2), 63.3 (CH_2), 83.5 (CH), 154.5 (C), 159.1 (C), 160.3 (C); MS (EI) 158 (M^+, 1), 85 (10), 58 (100). HRMS Calcd for $C_6H_{10}N_2O_3$: 158.1522. Found: 158.1528.

4,5-Dihydro-5-ethoxymethyl-3-(*N*-methylcarbamoyl)isoxazole (11e). Eluted with AcOEt. Colorless granules. Mp 43-44 °C. IR (KBr) 3336, 1663, 1543 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.0 Hz, 3H), 2.91 (d, *J* = 5.0 Hz, 3H), 3.13 (dd, *J* = 17.8, 8.0 Hz, 1H), 3.26 (dd, *J* = 17.8, 11.1 Hz, 1H), 3.55 (d, *J* = 4.7 Hz, 2H), 3.55 (q, *J* = 7.0 Hz, 2H), 4.8-4.95 (m, 1H), 6.65-6.8 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4 (CH_3), 26.4 (CH_3), 35.9 (CH_2), 67.5 (CH_2), 71.4 (CH_2), 82.5 (CH), 154.3 (C), 160.7 (C); MS (FAB) 187 (M^++1, 100). HRMS Calcd for $C_8H_{14}N_2O_3$: 186.1004. Found: 186.1004.

5-Acetylaminomethyl-4,5-dihydro-3-(*N*-methylcarbamoyl)isoxazole (11g). Recrystallized from chloroform. White solid. Mp 169-171 °C. IR (KBr) 3308, 1655 (with shoulder), 1597 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.82 (s, 3H), 2.67 (d, *J* = 4.7 Hz, 3H), 2.91 (dd, *J* = 17.9, 7.6 Hz, 1H), 3.20 (dd, *J* = 17.9, 10.9 Hz, 1H), 3.22 (dd, *J* = 5.7, 5.6 Hz, 2H), 4.72 (ddt, *J* = 10.9, 7.6, 5.6 Hz, 1H), 8.12 (br t, *J* = 5.7 Hz, 1H), 8.38 (br q, *J* = 4.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3 (CH_3), 26.6 (CH_3), 37.5 (CH_2), 42.4 (CH_2), 81.5 (CH), 155.0 (C), 160.6 (C), 170.6 (C); MS (FAB) 200 (M^++1, 100). HRMS Calcd for $C_8H_{13}N_3O_3$: 199.0957. Found: 199.0959 .

4,5-Dihydro-5-ethoxy-3-(*N*-methylcarbamoyl)isoxazole (11h). Eluted with hexane/AcOEt (50/50). Orange plates. Mp 99-101 °C. IR (KBr) 3305, 1655, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (dd, *J* = 7.2, 7.2 Hz, 3H), 2.93 (d, *J* = 4.8 Hz, 3H), 3.13 (dd, *J* = 18.8, 2.4 Hz, 1H), 3.26 (dd, *J* = 18.8, 6.8 Hz, 1H), 3.60 (dq, *J* = 9.2, 7.2 Hz, 1H), 3.87 (dq, *J* = 9.2, 7.2 Hz, 1H), 5.67 (dd, J = 6.8, 2.4 Hz, 1H), 6.6-6.7 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0 (CH_3), 26.1 (CH_3), 40.1 (CH_2), 64.3 (CH_2), 104.9 (CH), 154.3 (C), 159.9 (C); MS (FAB) 173 (M^++1, 96), 127 (100). Anal. Calcd for $C_7H_{12}N_2O_3$: C, 48.83; H, 7.02; N, 16.27%. Found: C, 48.70; H, 6.84; N, 16.45%.

3-(*N*-Methylcarbamoyl)-3a,4,5,6a-tetrahydrofuro[3,2-*d*]isoxazole (11i). Recrystallized from a mixed solvent of benzene and hexane (1/1). Colorless solid. Mp 138-139 °C. IR (KBr) 3329, 1662, 1557, 1091 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.22 (dddd, *J* = 8.9, 8.3, 5.1, 5.0 Hz, 1H), 2.40 (dd, *J* = 13.1, 5.0 Hz, 1H), 2.92 (d, *J* = 5.0 Hz, 3H), 3.54 (ddd, *J* = 13.1, 8.9, 5.1 Hz, 1H), 4.04 (dd, *J* = 8.9, 6.2 Hz, 1H), 4.10 (dd, *J* = 8.9, 8.3 Hz, 1H), 6.27 (d, *J* = 6.2 Hz, 1H), 6.7-6.9 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1 (CH_3), 29.7 (CH_2), 50.8 (CH), 67.0 (CH_2), 110.6 (CH), 154.2 (C), 160.0 (C); MS (FAB) 171 (M^++1, 100). Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.40; H, 5.92; N, 16.47%. Found: C, 49.26; H, 5.96; N, 16.53%.

4,5-Dihydro-5-ethoxycarbonyl-3-(*N*-methylcarbamoyl)isoxazole (11j). Eluted with hexane/AcOEt (50/50). Pale yellow oil. IR (neat) 3337, 1747, 1666, 1556 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.1 Hz, 3H), 2.68 (d, *J* = 4.7 Hz, 3H), 3.34 (dd, *J* = 17.9, 6.9 Hz, 1H), 3.52 (dd, *J* = 17.9, 12.1 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 5.23 (dd, *J* = 12.1, 6.9 Hz, 1H), 8.45-8.5 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 26.2 (CH_3), 38.0 (CH_2), 62.2 (CH_2), 79.3 (CH), 153.5 (C), 159.5 (C), 169.3 (C); MS (FAB) 187 (M^++ 1, 100). HRMS Calcd for $C_8H_{12}N_2O_4$: 200.0797. Found: 200.0799.

4,5-Bis(methoxycarbonyl)-4,5-dihydro-3-(*N*-methylcarbamoyl)isoxazole (11k). Eluted with hexane/AcOEt (20/80). Colorless oil. IR (neat) 3375, 1746, 1674, 1558 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *cis*/*trans* = 93/7, *cis*-isomer δ 2.93 (d, *J* = 5.2 Hz, 3H), 3.82 (s, 3H), 3.84 (s, 3H), 4.69 (d, *J* = 6.4 Hz, 1H), 5.33 (d, *J* = 6.4 Hz, 1H), 6.5-6.7 (br, 1H), *trans*-isomer δ 2.92 (partially overlapped with a signal of *cis*-isomer), 3.76 (s, 3H), 3.79 (s, 3H), 4.72 (d, *J* = 12.0 Hz, 1H), 5.38 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1 (CH_3), 53.2 (CH_3), 53.4 (CH_3), 55.4 (CH), 83.0 (CH), 151.3 (C), 158.3 (C), 167.9 (C), 168.0 (C); MS (FAB) 245 (M^++1, 100). HRMS Calcd for $C_9H_{12}N_2O_6$: 244.0695. Found: 244.0694.

5-Acetyl-4,5-dihydro-3-(*N*-methylcarbamoyl)isoxazole (11l). Recrystallized from a mixed solvent of benzene and hexane (1/1). Pale yellow solid. Mp 106-108 °C. IR (KBr) 3296, 1718, 1656, 1559 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H), 2.93 (d, *J* = 5.0 Hz, 3H), 3.41 (dd, *J* = 18.2, 12.1 Hz, 1H), 3.52 (dd, *J* = 18.2, 7.2 Hz, 1H), 5.05 (dd, *J* = 12.1, 7.2 Hz, 1H), 6.45-6.5 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2 (CH_3), 26.3 (CH_3), 36.1 (CH_2), 85.7 (CH), 153.8 (C), 159.3 (C), 205.1 (C); MS (FAB) 171 (M^++1, 100). Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.41; H, 5.92; N, 16.46%. Found: C, 49.13; H, 5.53; N, 16.42%.

Methanolysis of nitroisoxazolone 5a. A solution of

nitroisoxazolone **5a** (72 mg, 0.50 mmol) in methanol (5.0 mL) was stirred at 30 °C for 1 day. After removal of the solvent under reduced pressure, the reaction mixture was extracted with benzene (10 mL x 3). The organic layer was concentrated, and the residue was subjected to column chromatography to afford a mixture of **18** and **3d** (eluted with hexane/$CHCl_3$ = 2/1, 23 mg, yield of **18**; 18%, yield of **3d**; 12%) and nitroenamine **18** (eluted with hexane/$CHCl_3$ = 1/1, 30 mg, 0.23 mmol, yield 46%). Although further purification of **3d** was attempted by column chromatography again, impurity could not be removed. The structural determination was performed by comparing spectral data with those of **3e**, which was prepared from commercially available ethyl nitroacetate and ethyl isocyanate.

1-Methoxy-1-methylamino-2-nitroethene (18). Colorless plates. Mp 110-112 °C. IR (Nujol) 3327, 1662, 1564 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.00 (d, *J* = 5.2 Hz, 3H), 3.88 (s, 3H), 6.67 (s, 1H), 9.6-10.0 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.3 (CH_3), 56.9 (CH_3), 97.9 (CH), 165.1 (C); MS (EI) 132 (M^+, 100). HRMS Calcd for $C_4H_8N_2O_3$: 132.0535. Found: 132.0531. Anal. Calcd for $C_4H_8N_2O_3$: C, 36.36; H, 6.16; N, 21.20%. Found: C, 36.21; H, 6.19; N, 21.53% .

Methyl 4-Aza-2-nitro-3-oxopentanoate (3d). Yellow oil. IR (neat) 3325, 1759, 1686, 1568, 1304 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.94 (d, *J* = 5.0 Hz, 3H), 3.92 (s, 3H), 5.90 (s, 1H), 7.2-7.5 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.4 (CH_3), 54.9 (CH_3), 89.1 (CH), 158.9 (C), 165.1 (C).

Ethyl 4-Aza-2-nitro-3-oxohexanoate (3e). Yellow solid. Mp 45-46 °C. IR (melt) 3308, 1755, 1682, 1570, 1304 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (t, *J* = 7.2 Hz, 3H), 1.35 (dd, *J* = 7.2, 7.2 Hz, 3H), 3.40 (dq, *J* = 7.2, 5.6 Hz, 2H), 4.30-4.35 (m, 2H), 5.77 (s, 1H), 7.0-7.2 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (CH_3), 14.1 (CH_3), 35.4 (CH_2), 64.2 (CH_2), 88.9 (CH), 157.8 (C), 161.5 (C); MS (EI) 204(5), 72 (21). HRMS Calcd for $C_7H_{12}N_2O_5$: 204.1806. Found: 204.1809.

Computational Methods

All calculations were performed with the Firefly Quantum Chemistry Package.[28] The DFT with the B3LYP functional[29] and the 6-31+G** basis sets were used for the geometry optimization. No imaginary frequency and one imaginary frequency were ascertained for each equilibrium geometry and transition state, respectively. IRC calculation was carried out to check that the transition state connected reactant and product. The energy was evaluated at 298 K with the evaluated potential energy and the evaluated zero-point energy.

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Notes and references

[a] *School of Environmental Science and Engineering, Kochi University of Technology, Tosayamada Kami, Kochi 782-8502, Japan. Fax: +81 887 57 2520; Tel:+81 887 57 2517; E-mail: nishiwaki.nagatoshi@kochi-tech.ac.jp*

[b] *Department of Chemistry, Osaka Kyoiku University, Asahigaoka, Kashiwara, Osaka 582-8582, Japan.*

† Electronic Supplementary Information (ESI) available: [^1H and ^{13}C NMR spectra of products **3**, **8**, **11**, and **18**, preparative method for nitroisoxazolone **5a**, Cartesian coordinates of all reported structures and the energies are also available]. See DOI: 10.1039/b000000x/

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