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PAPER

One-step synthesis of differently bis-functionalized isoxazoles by cycloaddition of carbamoylnitrile oxide with β-keto esters†

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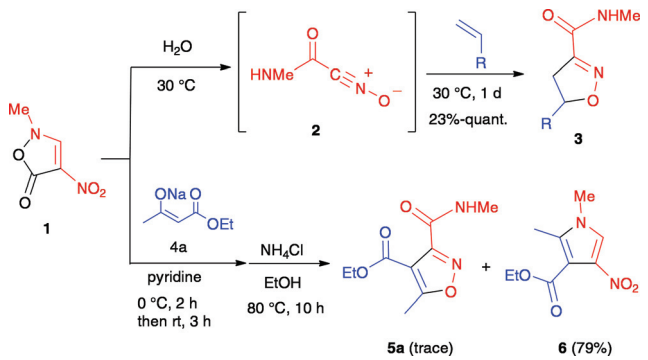
A new protocol for synthesizing different functionalized isoxazoles is provided. Carbamoylnitrile oxide generated from nitroisoxazolone underwent inverse electron-demand 1,3-dipolar cycloaddition with 1,3-dicarbonyl compounds in the presence of magnesium acetate that formed magnesium enolate *in situ*. Although electron-deficient trifluoroacetoacetate did not undergo this cycloaddition under the same conditions, conversion to sodium enolate furnish the corresponding bis-functionalized trifluoromethylisoxazole. The DFT calculations using B3LYP 6-31G+(d,p) also supported the aforementioned reactivity.

Introduction

Functional groups on heterocyclic frameworks serve as scaffolds for further chemical transformation for the development of functional materials such as medicines, dyes, agrochemicals, and optical materials. Heterocyclic systems with multiple functional groups are synthetic intermediates of great importance; however, it is often difficult to introduce more than two different functional groups onto a heterocyclic framework. Because of the increasing demand, the development of a new functionalized building block is highly desired.

1,3-Dipolar cycloaddition has been employed as a powerful synthetic procedure by which five-membered heterocyclic frameworks are constructed together with forming two bonds in a single manipulation.[1] In particular, 1,3-dipoles having a functional group serve as useful building blocks for obtaining functionalized heterocyclic compounds. Recently, we demonstrated a generation method for generating carbamoylnitrile oxide **2** by treating nitroisoxazolone **1** with just water under mild conditions,[2] which underwent cycloadditions with alkynes, alkenes, and nitriles to afford carbamoyl-substituted isoxazoles,[2] isoxazolines **3** (Scheme 1),[2,3] and 1,2,4-oxadiazoles,[4] respectively. We also demonstrated a preparative method for 1,2-dimethyl-3-ethoxycarbonyl-4-nitropyrrole (**6**) from nitroisoxazolone **1** and sodium enolate of ethyl acetoacetate **4a** (Scheme 1).[5] In this reaction, a trace amount of bis-functionalized isoxazole **5a** was isolated as a by-product, which indicated that enolate **4a** or its protonated form, ethyl acetoacetate **7a**, served as a dipolarophile. Indeed, the same product **5a** was prepared with a 41% yield by the cycloaddition of **2** with enamine **8a**,[6] which was easily prepared by heating ethyl acetoacetate **7a** with pyrrolidine without solvent (Scheme 2). These experimental facts prompted us to study direct syntheses of differently bis-functionalized isoxazoles by cycloaddition of **2** with β-keto esters.



Scheme 1 Cycloaddition of nitrile oxide **2** with alkene leading to isoxazoline **3** and ring transformation of nitroisoxazolone **1** with sodium enolate **4a** leading to pyrrole **6**.

Results and discussion

Among the numerous studies on nitrile oxides, only those examples, in which a 1,3-dicarbonyl compound was employed as a dipolarophile are found in the literature (Scheme 3).

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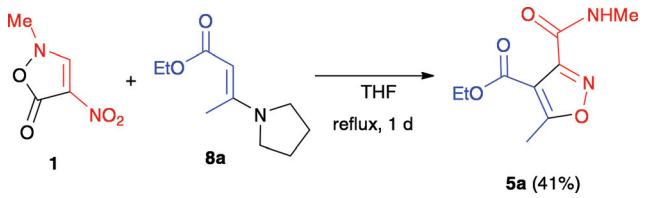
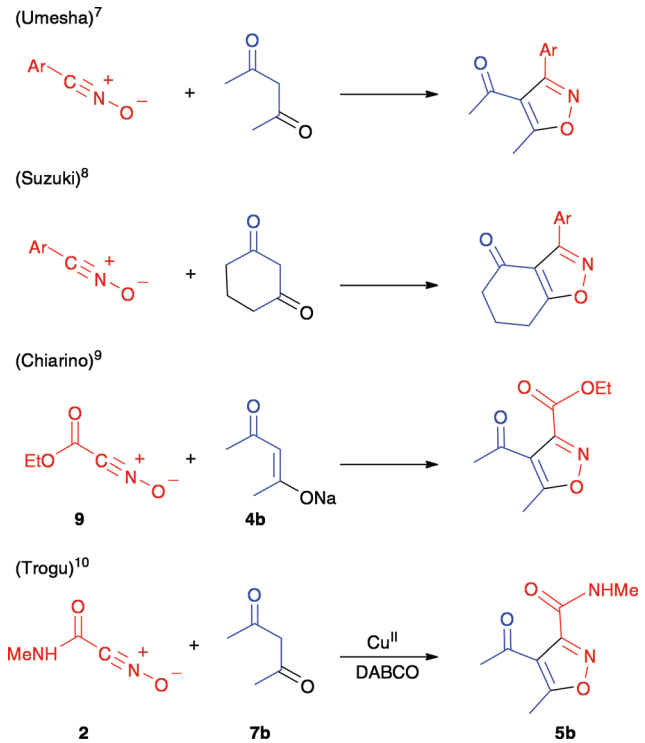
†Electronic supplementary information (ESI) available: Experimental procedures and spectral data of cycloadducts **5a–h** and magnesium enolate **9a**. See DOI: 10.1039/c2ob06925c



Scheme 2 Cycloaddition using enamine **8a**.



Scheme 3 Other cycloadditions of nitrile oxides with 1,3-dicarbonyl compounds.

Umesha *et al.* prepared 4-acetyl-3-arylisoxazoles by the cycloaddition of isolable aromatic nitrile oxides with acetylacetone **7b**.[7] Suzuki and co-workers developed the cyclocondensation of hindered aromatic nitrile oxides with cyclic β-diketones, which was applied to the synthesis of natural products.[8] In these reactions, nitrile oxide was stable enough for isolation; thus a substituent at the 3-position of the cycloadducts was limited to an aromatic group.

On the other hand, a nitrile oxide **9** possessing an electron-withdrawing ester function is also usable for the cycloaddition with β-diketones to afford 3,4-bis(functionalized) isoxazoles, in which the diketone is converted to an electron-rich sodium enolate **4b**.[9] Recently, Trogu *et al.* synthesized a similar framework by the copper catalyzed cycloaddition/condensation of β-diketones with several functionalized nitrile oxides derived from α-nitrated carbonyl compounds.[10] In contrast to these successful studies using β-diketones, less reactive β-keto esters have not been employed as dipolarophiles for nitrile oxide cycloadditions except for a few examples that suffer from limited scope[11] and low yields.[10,12] These facts and our experimental results strongly encouraged us to study the cycloaddition of carbamoyl nitrile oxide **2** with β-keto esters as well as β-diketones.

Table 1 Calculated HOMO–LUMO energy gaps (eV) using DFT method

		Nitrile Oxide					
		2		**9**		**10**	
Dipolarophile		H[a]	L	H	L	H	L
4a	H	—	0.75	—	1.29	—	4.85
	L	10.77	—	11.08	—	9.82	—
4b	H	—	0.73	—	1.28	—	4.98
	L	10.90	—	11.20	—	5.73	—
7a	H	—	5.13	—	4.58	—	5.10
	L	6.49	—	6.79	—	5.54	—
7b	H	—	5.17	—	4.63	—	5.14
	L	6.03	—	6.33	—	5.08	—

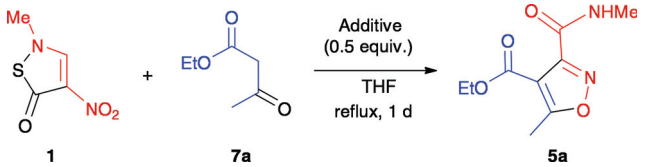
[a] H: HOMO, L: LUMO.

In order to realize the aforementioned reactivities, the HOMO/LUMO energy gaps between nitrile oxides **2**, **9**, **10** and enolates **4a**,**b** or enols **11a**,**b** were estimated by DFT methods using B3LYP 6-31G+(d,p) in advance (Table 1). In the cycloadditions of phenylnitrile oxide **10** (Ar = Ph) with 1,3-dicarbonyl compounds **11a**,**b**, the conversion of dipolarophiles to the corresponding enolates **4a**,**b** seems to be somewhat advantageous. To the contrary, nitrile oxides **2** and **9** having an electron-withdrawing group are considerably effective and the cycloadditions with enolates **4a**,**b** are predicted to proceed with high efficiency. In particular, carbamoylnitrile oxide **2** is expected to reveal higher reactivity than ethoxycarbonylnitrile oxide **9**. These encouraging results indicated that enolates of less reactive β-keto esters surely serves as the dipolarophile if nitrile oxide **2** is employed.

Initially, we employed THF as a solvent, because it was found to be superior from the viewpoint of the reactivity control to the mixture of water and acetonitrile reported in our previous work.[2,4] However, no reaction of nitroisoxazolone **1** was observed even after heating **1** with ethyl acetoacetate **7a** under reflux in THF for 1 d (Table 2, run 1). Therefore, copper acetate was added in anticipation of fixing **7a** to an enol form by chelation or forming metal enolate **9**. In contrast to the result of run 1, the addition of 0.5 equivalent of copper acetate was effective in promoting the cycloaddition with **2** under the same conditions leading to desired isoxazole **5a** with a 33% yield (run 2). The amount of **7a** was found to be an influential factor, and the employment of 5 equivalents of **7a** increased the yield of **5a** to 67% (runs 2–5). Dried copper acetate revealed the same reactivity as the hydrated form (runs 4 and 6), which means the cycloaddition proceeded irrespective of the presence of water. This successful result prompted us to search for a more effective metal salt. Several commonly used several transition metal acetates exhibited similar chelation effects (runs 7–10). Intriguingly, environmentally benign magnesium salts also served as activating agents to promote the cycloaddition (runs 11–15). Among several salts, magnesium acetate was found to be the most efficient promoter affording isoxazole **5a** with an 80% yield (run 11).

The role of magnesium acetate was monitored by ^{1}H NMR. The spectrum of ethyl acetoacetate **7a** in THF-d_8 revealed signals of both keto and enol forms in an 85 : 15 ratio. When the

Table 2 Optimization of reaction conditions for cycloaddition of nitrile oxide **2** with **7a**



Run	**7a**(equiv.)	Additive	Yield of **5a** (%)
1	0	None	0
2	1	$Cu(OAc)_2 \cdot H_2O$	33
3	3	$Cu(OAc)_2 \cdot H_2O$	51
4	5	$Cu(OAc)_2 \cdot H_2O$	67
5	7	$Cu(OAc)_2 \cdot H_2O$	64
6	5	$Cu(OAc)_2$	66
7	5	$Mn(OAc)_2 \cdot 4H_2O$	54
8	5	$Co(OAc)_2 \cdot 4H_2O$	59
9	5	$Ni(OAc)_2 \cdot 4H_2O$	49
10	5	$Zn(OAc)_2 \cdot 2H_2O$	59
11	5	$Mg(OAc)_2 \cdot 4H_2O$	80
12	5	$Mg(ClO_4)_2$	50
13	5	$MgCl_2$	31
14	5	MgO	30
15	5	$MgSO_4$	0

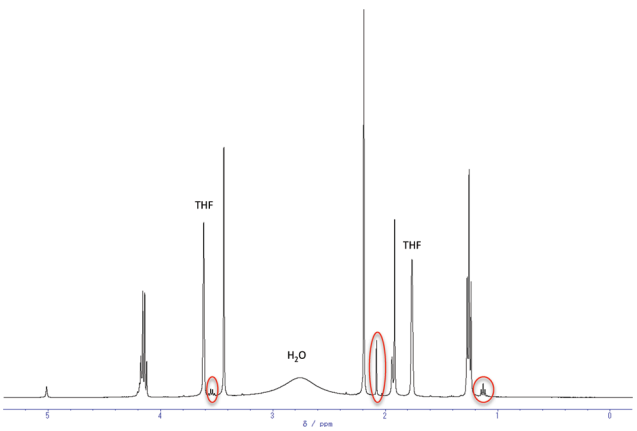
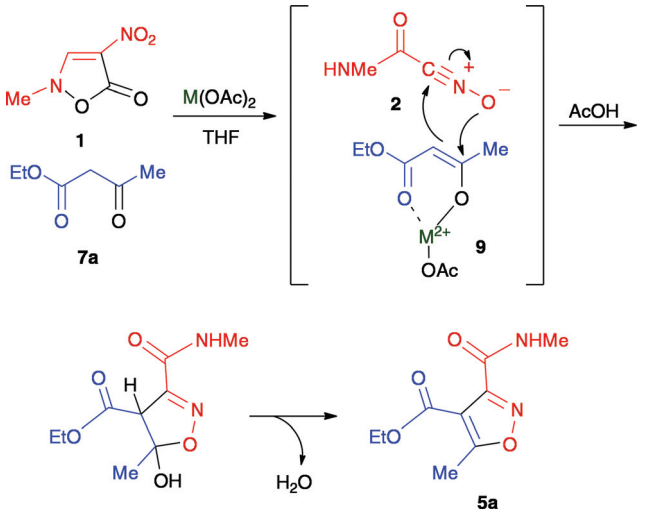


Fig. 1 ^{1}H NMR spectrum after heating **7a** with $Mg(OAc)_2$ for 1 d in THF-d_8.

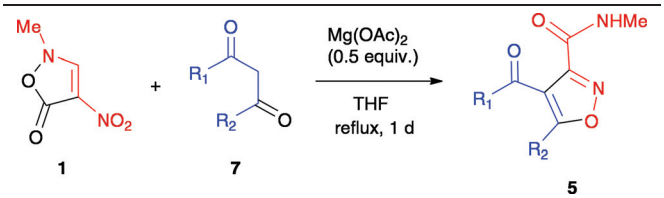
solution of **7a** was heated at 70 °C for 1 d in the presence of magnesium acetate, minor signals were observed in addition to the above-mentioned signals as indicated in Fig. 1 (detailed spectra are shown in the Supporting Information†). Since the electron density of the newly formed species is higher than that of **7a**, magnesium enolate **9a** possibly forms *in situ* and serves as an electron-rich dipolarophile for the present cycloaddition (Scheme 4).

Acetylacetone **7b** exhibited higher reactivity than keto ester **7a** to afford cycloadduct **5b**[10] quantitatively (Table 3, run 2). In the case of benzoylacetone **7c**, the formation of the two regioisomers **5c** and **5c′**[13] was possible, of which 4-benzoyl derivative **5c** was formed in preference to 4-acetyl one **5c′** (run 3). Other β-keto esters **7d–i** were subjected to the present cycloaddition under the same conditions (runs 4–8). As a result, it was possible to introduce an ethyl or phenyl group at the 5-position by the use of the corresponding keto esters **7d** and **7e** (runs 4 and 5).



Scheme 4 Cycloaddition with keto ester **7a**.

Table 3 Cycloaddition using other 1,3-dicarbonyl compounds



Run	R^1	R^2		Yield (%)
1	OEt	Me	**a**	80
2	Me	Me	**b**	quant.
3	Ph/Me	Me/Ph	**c**/**c′**	96 (67/29)
4	OMe	Et	**d**	88
5	OEt	Ph	**e**	96
6	OMe	CH_2OMe	**f**	60
7	OEt	CH_2COOEt	**g**	59
8	OEt	CF_3	**h**	0
9	OEt	OEt	**j**	0

The cycloaddition of nitrile oxide **2** also proceeded to afford polyfunctionalized isoxazoles **7f** and **7g**, even though an electron-withdrawing group was substituted at the keto moiety (runs 6 and 7). However, trifluoroacetoacetate **7h** did not undergo any change under the present conditions (run 8). When an α-substituted β-keto ester, α-methylacetoacetate **7i**, was employed, a complex mixture was formed without detectable tetrasubstituted isoxazoline, in which furoxan **10** was the main product (56% yield) as a result of the self-cycloaddition of nitrile oxide **2** (Fig. 2). While keto esters served well as dipolarophiles, diester **7j** was inactive and was recovered under the same conditions.

As mentioned above, highly electron-deficient keto ester **7h** was an inactive dipolarophile. This disadvantage was overcome by converting keto ester **7h** to electron-rich sodium enolate **4h** beforehand, which underwent an inverse electron-demand 1,3-dipolar cycloaddition[4] with nitrile oxide **2** even at room temperature leading to 5-trifluoromethylisoxazole **5h** with 57% yield (Scheme 5).

Isoxazoles having vicinal functionalities at the 3- and 4-positions are important scaffolds for developing medicines[14] and

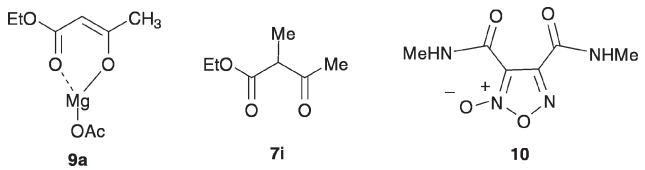
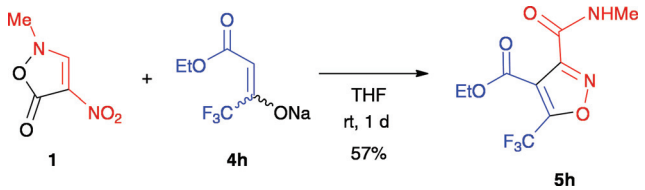


Fig. 2 Magnesium acetate **9a**, α-methylacetoacetate **7i**, and furoxan **10**.



Scheme 5 Synthesis of 5-trifluoromethylisoxazole **5h**.

agrochemicals;[15] however, multi-step processes are often necessary for their synthesis. In contrast, our protocol using a 1,3-dipolar cycloaddition realizes an easier access to these frameworks. The present reaction does not require troublesome manipulations, environmentally hazardous reagents, or severe reaction conditions. Hence, this protocol will be a practical and useful tool in organic syntheses.

Experimental

General

The melting points were determined on a Yanaco micro-melting-point 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 at 400 MHz with TMS as an internal standard. The ^{13}C NMR spectra were measured on a Bruker DPX-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. The mass spectra were recorded on a JEOL JMS-AX505HA a mass spectrometer. The high resolution mass spectra were measured on a JEOL JMS-DX303HF. The elemental microanalyses were performed using a Yanaco MT-3 CHN recorder.

2-Methyl-4-nitro-3-isoxazolin-5(2*H*)-one (2)[2]

Nitroisoxazolone **2** was easily prepared from commercially available ethyl nitroacetate through three steps with simple experimental manipulations; 1) the condensation of nitroacetate with orthoformate, 2) the condensation with hydroxylamine, and 3) the *N*-methylation with dimethyl sulfate (Details are given in Supporting Information†).

Cycloaddition of nitrile oxide with dipolarophiles

General procedure. To a solution of nitroisoxazolone **1** (144 mg, 1 mmol) in THF (10 mL), were added ethyl acetoacetate **7a** (0.63 mL, 5 mmol) and magnesium acetate tetrahydrate (108 mg, 0.5 mmol), and the resultant mixture was heated under reflux for 1 d. After addition of 1 M hydrochloric acid (10 mL, 10 mmol), THF was removed under reduced pressure. The resultant aqueous solution was extracted with chloroform (50 mL × 5), and the organic layer was dried over magnesium sulfate, and concentrated. The residue was subjected to column chromatography on silica gel to afford cycloadduct **5a** (170 mg, 0.80 mmol, 80%) eluted with ethyl acetate. Further purification was performed by recrystallization from a mixed solvent of hexane and benzene (1 : 1).

Cycloadditions of **1** with other 1,3-dicarbonyl compounds **5b–j** were conducted in the same way.

4-Ethoxycarbonyl-5-methyl-3-(*N*-methylcarbamoyl)isoxazole (5a). Colorless needles (from benzene/hexane = 1 : 1). Mp 55–58 °C. IR (KBr) 3271, 1721, 1663 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.38 (t, J = 7.1 Hz, 3H), 2.70 (s, 3H), 3.00 (d, J = 4.8 Hz, 3H), 4.37 (q, J = 7.1 Hz, 2H), 8.2-8.4 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 13.8 (CH_3), 14.1 (CH_3), 26.5 (CH_3), 61.9 (CH_2), 108.0 (C), 157.3 (C), 158.9 (C), 162.5 (C), 176.3 (C); MS (FAB) m/z = 213 (M^+ + 1, 100%). Anal. Calcd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.64; H, 5.88; N, 13.17.

4-Benzoyl-5-methyl-3-(*N*-methylcarbamoyl)isoxazole (5c). Yellow oil. IR (KBr) 3357, 1672, 1649 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H), 2.90 (d, J = 5.0 Hz, 3H), 6.9-7.0 (br, 1H), 7.47 (dd, J = 8.4, 7.5 Hz, 2H), 7.55 (dt, J = 7.5, 1.2 Hz, 1H), 7.78 (dd, J = 8.4, 1.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.4 (CH_3), 26.3 (CH_3), 115.9 (C), 128.7 (CH), 129.2 (CH), 133.8 (CH), 137.5 (C), 157.2 (C), 158.6 (C), 172.2 (C), 189.1 (C); MS (FAB) m/z = 245 (M^+ + 1, 100%), 105 (40). Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.91; H, 4.78; N, 11.35.

4-Acetyl-3-(*N*-methylcarbamoyl)-5-phenylisoxazole (5c′). Colorless needles (from benzene/hexane = 1 : 1). Mp 155–159 °C. IR (KBr) 3321, 1706, 1662 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.57 (s, 3H), 3.04 (d, J = 5.0 Hz, 3H), 6.9-7.0 (br, 1H), 7.45-7.55 (m, 3H), 7.73 (dd, J = 8.3, 1.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 26.3 (CH_3), 32.0 (CH_3), 117.3 (C), 126.1 (C), 127.7 (CH), 129.1 (CH), 131.5 (CH), 156.6 (C), 159.0 (C), 169.0 (C), 196.0 (C); MS (FAB) m/z = 245 (M^+ + 1, 100%). Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 64.12; H, 4.95; N, 11.45.

5-Ethyl-4-methoxycarbonyl-3-(*N*-methylcarbamoyl)isoxazole (5d). Colorless needles (from benzene/hexane = 1 : 1). Mp 86–88 °C. IR (Nujol) 3273, 1713, 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.34 (t, J = 7.6 Hz, 3H), 3.03 (d, J = 4.9 Hz, 3H), 3.10 (q, J = 7.6 Hz, 2H), 3.91 (br, 1H), 7.6-7.8 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 11.5 (CH_3), 21.3 (CH_2), 26.5 (CH_3), 52.6 (CH_3), 107.1 (C), 157.3 (C), 158.1 (C), 162.7 (C), 180.6 (C); MS (FAB) m/z = 213 (M^+ + 1, 100%). Anal. Calcd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.88; H, 5.94; N, 13.14.

4-Ethoxycarbonyl-3-(*N*-methylcarbamoyl)-5-phenylisoxazole (5e). Colorless needles (from benzene/hexane = 1 : 1). Mp 113–116 °C. IR (KBr) 3299, 1726, 1664 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, J = 7.1 Hz, 3H), 3.03 (d, J = 4.8 Hz, 3H), 4.36 (q, J = 7.1 Hz, 2H), 7.1-7.3 (br, 1H), 7.45-7.60 (m, 3H), 7.84 (dd, J = 8.4, 1.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.8 (CH_3),

26.4 (CH_3), 61.2 (CH_2), 108.0 (C), 126.1 (C), 128.2 (CH), 128.8 (CH), 131.6 (CH), 157.8 (C), 158.9 (C), 162.1 (C), 171.4 (C); MS (FAB) m/z = 275 (M^+ + 1, 100%). Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.38; H, 5.30; N, 10.21.

4-Methoxycarbonyl-5-methoxymethyl-3-(*N*-methylcarbamoyl) isoxazole (5f). Colorless needles (from benzene/hexane = 1 : 1). Mp 40–44 °C. IR (KBr) 3267, 1723, 1671 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.02 (d, J = 4.9 Hz, 3H), 3.49 (s, 3H), 3.92 (s, 3H), 4.82 (s, 2H), 7.7-7.8 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 26.5 (CH_3), 52.9 (CH_3), 59.5 (CH_3), 64.9 (CH_2), 109.3 (C), 157.3 (C), 158.7 (C), 161.9 (C), 174.2 (C); MS (FAB) m/z = 229 (M^+ + 1, 100%). Anal. Calcd for $C_9H_{12}N_2O_5$: C, 47.37; H, 5.30; N, 12.28. Found: C, 47.01; H, 5.67; N, 12.42.

4-Ethoxycarbonyl-5-ethoxycarbonylmethyl-3-(*N*-methylcarbamoyl)isoxazole (5g). Brown oil. IR (KBr) 3303, 1739, 1674 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 3H), 1.36 (t, J = 7.1 Hz, 3H), 3.02 (d, J = 5.0 Hz, 3H), 4.13 (s, 2H), 4.20 (q, J = 7.1 Hz, 2H), 4.35 (q, J = 7.1 Hz, 2H), 8.2-8.4 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3), 14.1 (CH_3), 26.5 (CH_3), 33.9 (CH_2), 62.1 (CH_2), 109.7 (C), 157.3 (C), 158.5 (C), 161.8 (C), 166.3 (C), 171.8 (C); MS (FAB) m/z = 285 (M^+ + 1, 100%). Anal. Calcd for $C_{12}H_{16}N_2O_6$: C, 50.70; H, 5.67; N, 9.85. Found: C, 50.54; H, 5.85; N, 9.63.

Cycloaddition using sodium enolate of ethyl trifluoroacetate 4h. To a solution of ethyl trifluoroacetoacetate **7h** (0.59 mL, 5 mmol) in ethanol (10 mL), sodium (115 mg, 5 mmol) was gradually added. After stirring at room temperature for 15 min, the mixture was dried up under reduced pressure, and then the residue was dissolved in THF (10 mL). To the solution, a solution of nitroisoxazolone **1** (144 mg, 1 mmol) in acetonitrile (10 mL) was added, and the resultant mixture was stirred at room temperature for 3 d. After addition of 1 M hydrochloric acid (10 mL, 10 mmol), solvents were removed under reduced pressure. The resultant aqueous solution was extracted with chloroform (50 mL × 5), and the organic layer was dried over magnesium sulfate, and concentrated. The residue was subjected to the column chromatography on silica gel to afford cycloadduct **5h** (125 mg, 0.51 mmol, 51%) eluted with ethyl acetate. Further purification was performed by recrystallization from a mixed solvent of hexane and benzene (1 : 1).

4-Ethoxycarbonyl-5-trifluoromethyl-3-(*N*-methylcarbamoyl) isoxazole (5h). Colorless needles (from benzene/hexane = 5 : 4). Mp 81–83 °C. IR (KBr) 3291, 1745, 1656 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (t, J = 7.1 Hz, 3H), 3.04 (d, J = 5.0 Hz, 3H), 4.44 (q, J = 7.1 Hz, 2H), 7.2-7.4 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 13.6 (CH_3), 26.5 (CH_3), 63.2 (CH_2), 113.5 (C), 117.1 (q, $J_{C\text{-}F}$ = 271 Hz, CF_3), 157.1 (C), 157.35 (C), 158.8 (C), 159.0 (q, $J_{C\text{-}F}$ = 41 Hz, $\underline{C}\text{-}CF_3$); MS (FAB) m/z = 213 (M^+ + 1, 100%). Anal. Calcd for $C_9H_9N_2O_4F_3$: C, 40.61; H, 3.41; N, 10.52. Found: C, 40.80; H, 3.36; N, 10.63.

Notes and references

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