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

著者	Nishiwaki Nagatoshi, Kobiro Kazuya, Hirao Shotaro, Sawayama Jun, Saigo Kazuhiko, Ise Yumiko, Nishizawa Maho, Ariga Masahiro
journal or publication title	Organic & Biomolecular Chemistry
volume	10
number	10
page range	1987-1991
year	2012
URL	http://hdl.handle.net/10173/1358

doi: 10.1039/C2OB06925C

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxxx

ARTICLE TYPE

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

Nagatoshi Nishiwaki,^a Kazuya Kobiro,^a Shotaro Hirao,^a Jun Sawayama,^a Kazuhiko Saigo,^a Yumiko Ise,^b Maho Nishizawa,^b and Masahiro Ariga^b

⁵ Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

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 abovementioned 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 having 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.

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.

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 2. Cycloaddition using enamine 8a.

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). Umesh 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.

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

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 scope¹¹ 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.

In order to realize the abovementioned 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.

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

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

H: HOMO, L: LUMO

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 • H ₂ O	33
3	3	Cu(OAc) ₂ • H ₂ O	51
4	5	Cu(OAc) ₂ • H ₂ O	67
5	7	Cu(OAc) ₂ • H ₂ O	64
6	5	Cu(OAc) ₂	66
7	5	Mn(OAc) ₂ • 4H ₂ O	54
8	5	Co(OAc) ₂ • 4H ₂ O	59
9	5	Ni(OAc) ₂ • 4H ₂ O	49
10	5	Zn(OAc) ₂ • 2H ₂ O	59
11	5	Mg(OAc) ₂ • 4H ₂ O	80
12	5	Mg(ClO ₄) ₂	50
13	5	MgCl ₂	31
14	5	MgO	30
15	5	MgSO ₄	0

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).

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

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

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

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 ₂ OMe	f	60
7	OEt	CH ₂ COOEt	g	59
8	OEt	CF ₃	h	0
9	OEt	OEt	j	0

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 to be formed, 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). 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** (Figure 2). While keto esters well served well as dipolarophiles, diester **7j** was inactive and was recovered under the same conditions.

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

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 cycloaddition⁴ with nitrile oxide **2** even at room temperature leading to 5-trifluoromethylisoxazole **5h** with 57% yield (Scheme 5).

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

Isoxazoles having vicinal functionalities at the 3- and 4-positions are important scaffolds for developing medicines¹⁴ and 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-points apparatus, and were uncorrected. All the reagents and solvents were commercially available and used as received. The ¹H NMR spectra were measured on a Bruker DPX-400 at 400 MHz with TMS as an internal standard. The ¹³C NMR spectra were measured on a Bruker DPX-400 at 100 MHz, and assignments of ¹³C 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 coder.

2-Methyl-4-nitro-3-isoxazolin-5(2H)-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 the 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; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) δ 13.8 (CH₃), 14.1 (CH₃), 26.5 (CH₃), 61.9 (CH₂), 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 C₉H₁₂N₂O₄: 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; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) δ 12.4 (CH₃), 26.3 (CH₃), 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 C₁₃H₁₂N₂O₃: 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; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) δ 26.3 (CH₃), 32.0 (CH₃), 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 C₁₃H₁₂N₂O₃: 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; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) δ 11.5 (CH₃), 21.3 (CH₂), 26.5 (CH₃), 52.6 (CH₃), 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 C₉H₁₂N₂O₄: 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; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) δ 13.8 (CH₃), 26.4 (CH₃), 61.2 (CH₂), 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 C₁₄H₁₄N₂O₄: 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 (CDCl₃) 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); ¹³C NMR (CDCl₃) δ 26.5 (CH₃), 52.9 (CH₃), 59.5 (CH₃), 64.9 (CH₂), 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 trifluoroacetate **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 $\times$ 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 $^{\circ}C$. 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-F} = 271 Hz, CF_3), 157.1 (C), 157.35 (C), 158.8 (C), 159.0 (q, J_{C-F} = 41 Hz, $C=CF_3$); 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

^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: Experimental procedures and spectral data of cycloadducts **5a–h** and magnesium enolate **9a**.

1 A. Padwa, W. H. Pearson, E. C. Taylor and P. Wipf, *Synthetic Application of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*, Wiley-Interscience, New York (2002).

2 N. Nishiwaki, K. Kobiro, H. Kiyoto, S. Hirao, J. Sawayama, K. Saigo, Y. Okajima, T. Uehara, A. Maki and M. Ariga, *Org. Biomol. Chem.*, 2011, **9**, 2832; N. Nishiwaki, T. Uehara, N. Asaka, Y. Tohda, M. Ariga and S. Kanemasa, *Tetrahedron Lett.*, 1998, **39**, 4851.

3 N. Nishiwaki, A. Maki and M. Ariga, *J. Oleo Sci.*, 2009, **58**, 481.

4 N. Nishiwaki, K. Kobiro, S. Hirao, J. Sawayama, K. Saigo, Y. Ise, Y. Okajima and M. Ariga, *Org. Biomol. Chem.*, 2011, **9**, 6750.

5 N. Nishiwaki, M. Nakanishi, T. Hida, Y. Miwa, M. Tamura, K. Hori, Y. Tohda and M. Ariga, *J. Org. Chem.*, 2001, **66**, 7535.

6 Cycloadditions of nitrile oxide with enamino esters: S. Zhu, S. Shi and S. W. Gerritz, *Tetrahedron Lett.*, 2011, **52**, 4001; G. Stork and J. E. McMurry, *J. Am. Chem. Soc.*, 1967, **89**, 5461.

7 K. B. Umesh, K. A. Kumar and K. M. L. Rai, *Synth. Commun.*, 2002, **32**, 1841.

8 Y. Koyama, R. Yamaguchi and K. Suzuki, *Angew. Chem. Int. Ed.*, 2008, **47**, 1084; T. Matsuura, J. W. Bode, Y. Hachisu and K. Suzuki, *Synlett*, 2003, 1746; J. W. Bode, Y. Hachisu, T. Matsuura and K. Suzuki, *Tetrahedron Lett.*, 2003, **44**, 3555.

9 I. Marchueta Hereu and X. Serra Masia, *PCT Int.*, WO 2008 107064 (2008); D. Chiarino, G. Grancini, V. Frigeni, I. Biasini and A. Carenzi, *J. Med. Chem.*, 1991, **34**, 600.

10 E. Trogu, L. Cecchi, F. De Sarlo, L. Guideri, F. Ponticelli and F. Machetti, *Eur. J. Org. Chem.*, 2009, 5971.

11 4-Methyl-3-oxopentanoic acid esters were employed as the dipolarophile: V. Maywald, T. Kuekenhoefer, P. Muenster and S. Stahl, *Eur. Pat. Appl.*, 562382 (1993).

12 T. Shimizu, Y. Hayashi and K. Teramura, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 2519.

13 The presence of an acetyl group in **5i'** was confirmed by the iodoform reaction.

14 For example: R. Palin, P. D. Ratcliffe, S. G. Kultgen, S. G.; K.-K. Ho, A. L. Roughton and M. Ohlmeyer, *PCT Int. Appl.*, WO 2010 091009 (2010); A. A. Ivashchenko, A. V. Ivashchenko, S. Y. Tkachenko, I. M. Okun, N. F. Savchuk, D. V. Kravchenko, E. A. Rizhova, S. B. Alyabiev and A. V. Khvat, *PCT Int. Appl.*, WO 2009 010925 (2009); M. Takagi, T. Nakamura, I. Matsuda, T. Kiguchi, N. Ogawa and H. Ozeki, *PCT Int. Appl.*, WO 2008 062739 (2008); S.-I. Nishimura and H. Kondo, *PCT Int. Appl.*, WO 2007 081031 (2007); S. Saito, H. Ohta, T. Ishizaka, M. Yoshinaga, M. Tatsuzuki, Y. Yokobori, Y. Tomishima, A. Morita, Y. Toda, K. Tokugawa, A. Kaku, T. Murakami, H. Yoshimura, S. Sekine and T. Yoshimizu, *PCT Int. Appl.*, WO 2006 051704 (2006).

15 For example: R. L. Vozouet, S. Soergel, C. Defieber, S. Gross, K. Koerber, D. L. Culbertson and D. D. Anspaugh, *PCT Int. Appl.*, WO 2011 003793 (2011); C. B. Vicentini, C. Romagnoli, E. Andreotti and D. Mares, *J. Agric. Food Chem.* 2007, **55**, 10331; P. Muenster, W. Freund, V. Maywald, T. Kuekenhoefer, M. Gerber, K. Grossmann and H. Walter, *Pesticide Sci.* 1995, **44**, 21.