Supporting Information

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

aSchool of Environmental Science and Engineering, Kochi University of Technology, Tosayamada, Kami, Kochi 782-8502, Japan
bDepartment of Chemistry, Osaka Kyoiku University, Asahigaoka, Kashiwara, Osaka 582-8582, Japan
e-mail: nishiwaki.nagatoshi@kochi-tech.ac.jp
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**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 spectra were measured on a Bruker DPX-400 spectrometer at 400 MHz, with TMS as an internal standard, and the $^{13}$C NMR spectra were measured on a Bruker DPX-400 spectrometer at 100 MHz. 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 spectrometer. The elemental microanalyses were performed using a Yanaco MT-3 CHN corder.

**Preparation of nitroisoxazolone 2**

Nitroisoxazolone 2 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.

1) Condensation of nitroacetate with orthoformate$^1$

To a solution of ethyl nitroacetate (40 mL, 0.36 mol) in acetic anhydride (80 mL), trimethyl orthoformate (58 mL, 0.53 mol) was added, and the resultant mixture was heated at 100 °C for 2 d. The mixture was concentrated under reduced pressure, and the residue was used for next step without further purification.

2) Condensation with hydroxylamine$^2$

To a solution of ethyl 3-methoxy-2-nitropropenoate (17.5 g, 100 mmol) in ethanol (175 mL), were added hydroxylamine hydrochloride (7.73 g, 120 mmol) and pyridine (20.2 mL, 250 mmol). The mixture was heated at 60 °C for 3 h. After cooling, pale yellow precipitates were formed and were collected to give pyridinium salt of nitroisoxazolone (14.8 g, 71 mmol, 71% yield).
3) \(N\)-Methylation with dimethyl sulfate

Pyridinium salt of nitroisoxazolone (4.18 g, 20 mmol) was heated with freshly distilled dimethyl sulfate (2.3 mL, 24 mmol) without solvent at 65 °C for 3 h. The reaction mixture was cooled to room temperature, and water (100 mL) was added. Generated white precipitates were collected, and recrystallized from acetonitrile to afford isoxazolone 2 (2.26 g, 15.7 mmol, 79%).

**General procedure of the cycloaddition**

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\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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\(_9\)H\(_{12}\)N\(_2\)O\(_4\): C, 50.94; H, 5.70; N, 13.20. Found: C, 50.64; H, 5.88; N, 13.17.
$^1$H NMR (CDCl$_3$)

$^{13}$C NMR (CDCl$_3$)
4-Acetyl-5-methyl-3-(N-methylcarbamoyl)isoxazole (5b)

Brown plates (from benzene/hexane = 1/1). Mp 111-114 °C. IR (KBr) 3378, 1684 (br) cm⁻¹; ¹H NMR (CDCl₃) δ 2.59 (s, 3H), 2.65 (s, 3H), 3.02 (d, J = 5.0 Hz, 3H), 7.2-7.4 (br, 1H); ¹³C NMR (CDCl₃) δ 13.3 (CH₃), 26.5 (CH₃), 31.1 (CH₃), 116.8 (C), 156.2 (C), 159.6 (C), 175.3 (C), 193.4 (C); MS (FAB) m/z = 183 (M⁺+1, 100%). Anal. Calcd for C₈H₁₀N₂O₃: C, 52.74; H, 5.53; N, 15.38. Found: C, 53.06; H, 5.61; N, 15.16.

¹H NMR (CDCl₃)
$^{13}$C NMR (CDCl$_3$)

4-Benzoyl-5-methyl-3-(N-methylcarbamoyl)isoxazole (5c)

Yellow oil. IR (KBr) 3357, 1672, 1649 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_2$O$_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.91; H, 4.78; N, 11.35.
$^1H$ NMR (CDCl$_3$)
Colorless needles (from benzene/hexane = 1/1). Mp 155-159 °C. IR (KBr) 3321, 1706, 1662 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_2$O$_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 64.12; H, 4.95; N, 11.45.

4-Acetyl-3-(N-methylcarbamoyl)-5-phenylisoxazole (5c$'$)
$^1$H NMR (CDCl$_3$)
$^{13}$C NMR (CDCl$_3$)

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$_3$) $\delta$ 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$_3$) $\delta$ 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$_9$H$_{12}$N$_2$O$_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.88; H, 5.94; N, 13.14.

$^1$H NMR (CDCl$_3$)
$^{13}$C NMR (CDCl$_3$)

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.

¹H NMR (CDCl₃)
$^{13}$C NMR (CDCl$_3$)