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]

[a]School of Environmental Science and Engineering, Kochi University of Technology, Tosayamada, Kami, Kochi 782-8502, Japan

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

e-mail: nishiwaki.nagatoshi@kochi-tech.ac.jp

Contents

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 sufate[3]

Pyridinium salt of nitroisoxazolone (4.18 g, 20 mmol) was heated with freshly distilled dimethyl sufate (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

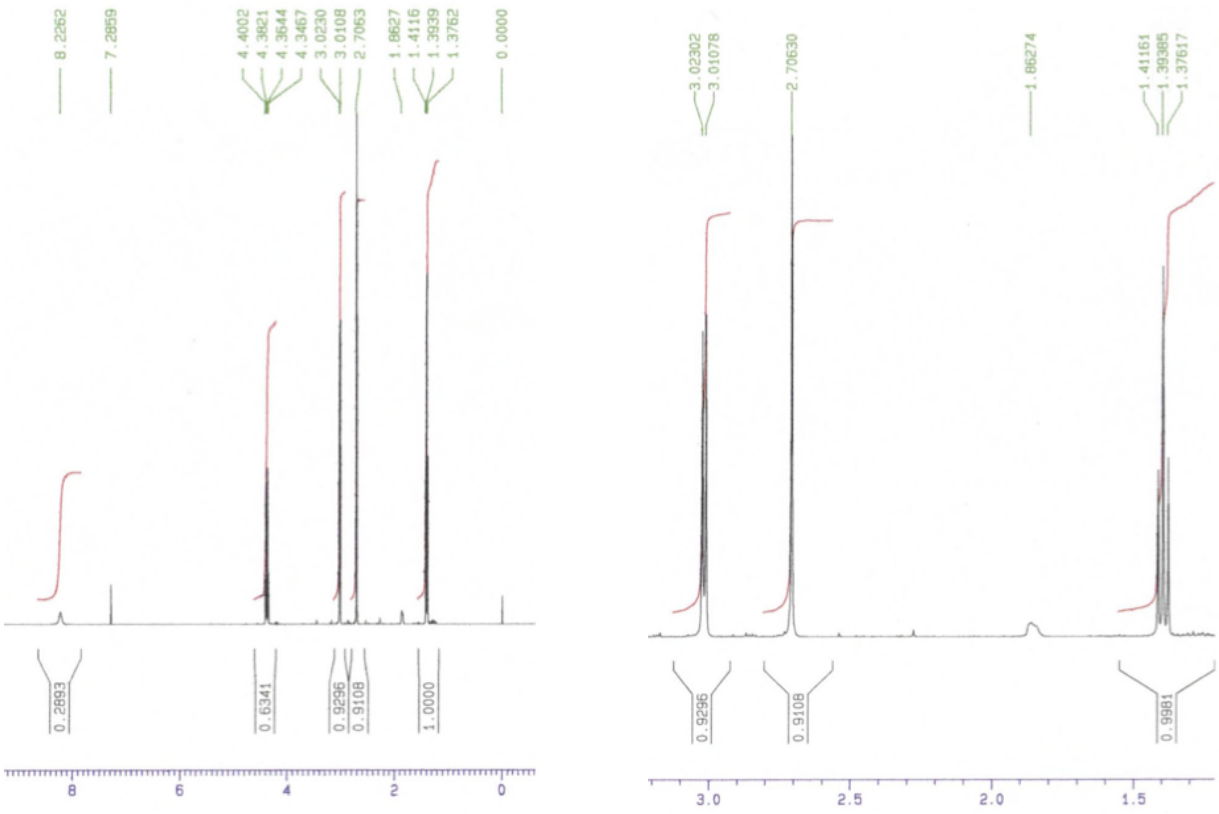
To a solution of nitroisoxazolone **1** (144 mg, 1 mmol) in THF (10 mL), were added ethyl acetoacetate **7a** (0.63 mL, 5 mmol) and magnesium acetate tetrahydrate (108 mg, 0.5 mmol), and the resultant mixture was heated under reflux for 1 d. After addition of 1 M hydrochloric acid (10 mL, 10 mmol), THF 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.

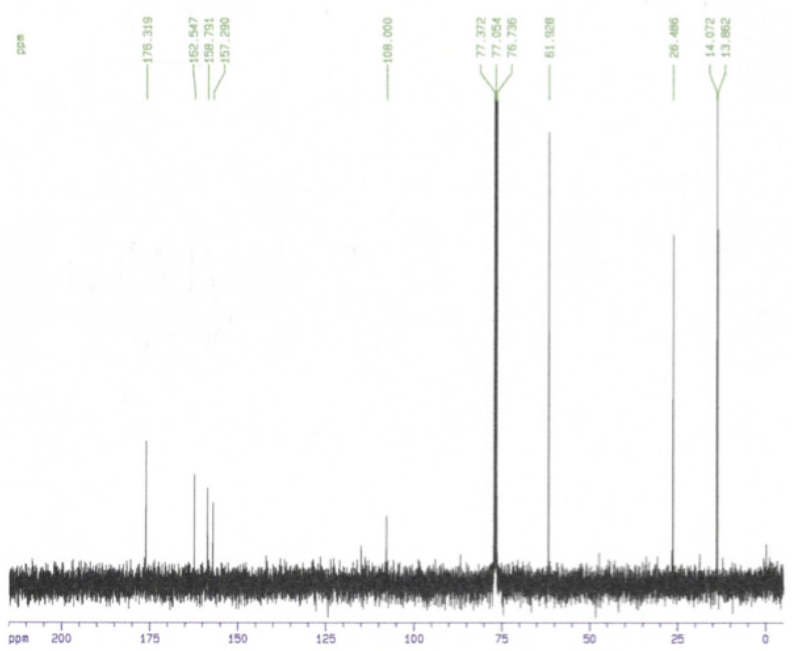
4-Ethoxycarbonyl-5-methyl-3-(*N*-methylcarbamoyl)isoxazole (5a)

Colorless needles (from benzene/hexane = 1/1). Mp 55-58 °C. IR (KBr) 3271, 1721, 1663 cm^{-1}; ^1H 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.

^{1}H NMR ($CDCl_3$)



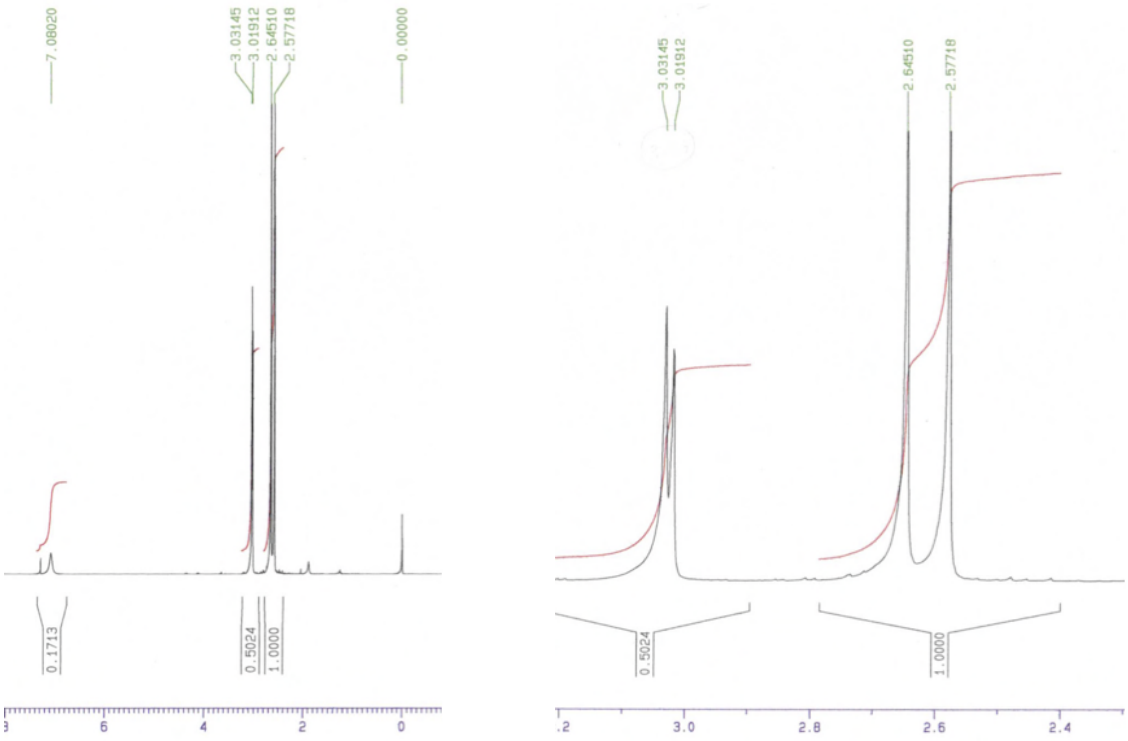
^{13}C NMR ($CDCl_3$)



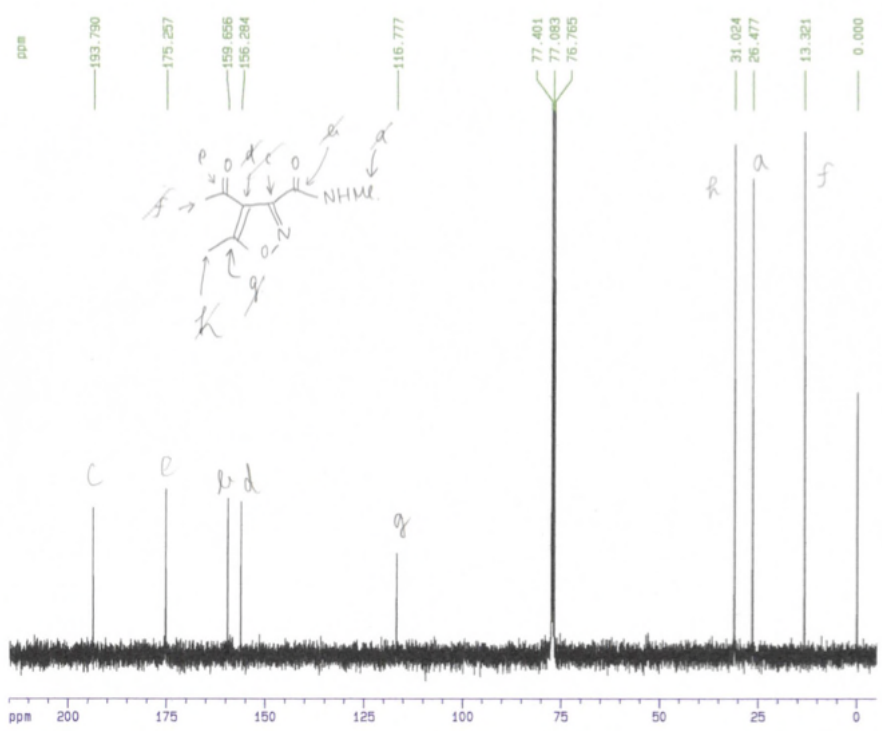
4-Acetyl-5-methyl-3-(*N*-methylcarbamoyl)isoxazole (5b)[4]

Brown plates (from benzene/hexane = 1/1). Mp 111-114 °C. IR (KBr) 3378, 1684 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.59 (s, 3H), 2.65 (s, 3H), 3.02 (d, J = 5.0 Hz, 3H), 7.2-7.4 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 13.3 (CH_3), 26.5 (CH_3), 31.1 (CH_3), 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 $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 53.06; H, 5.61; N, 15.16.

^1H NMR ($CDCl_3$)



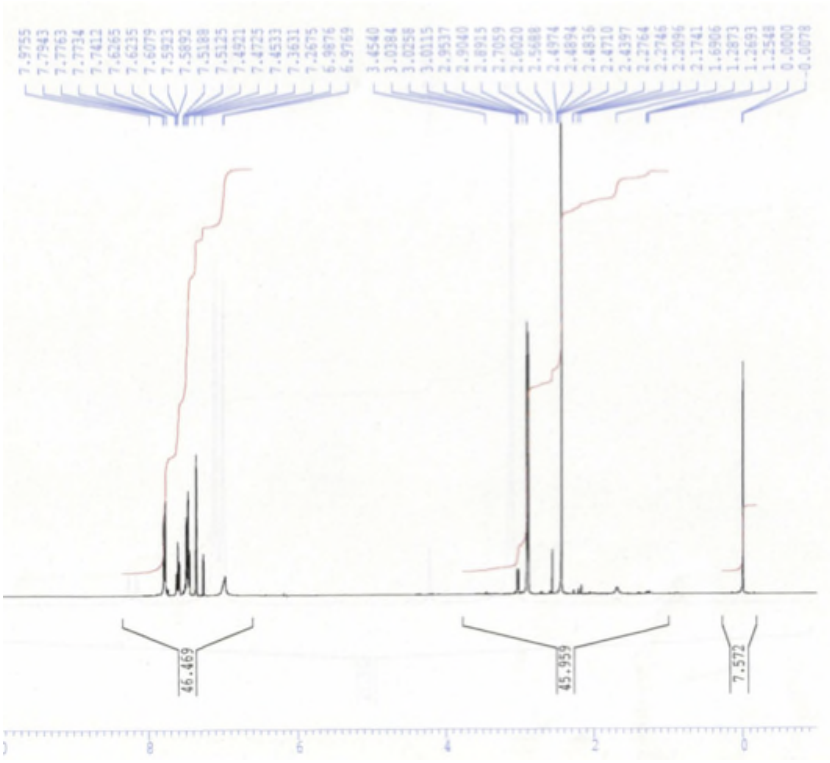
^{13}C NMR ($CDCl_3$)

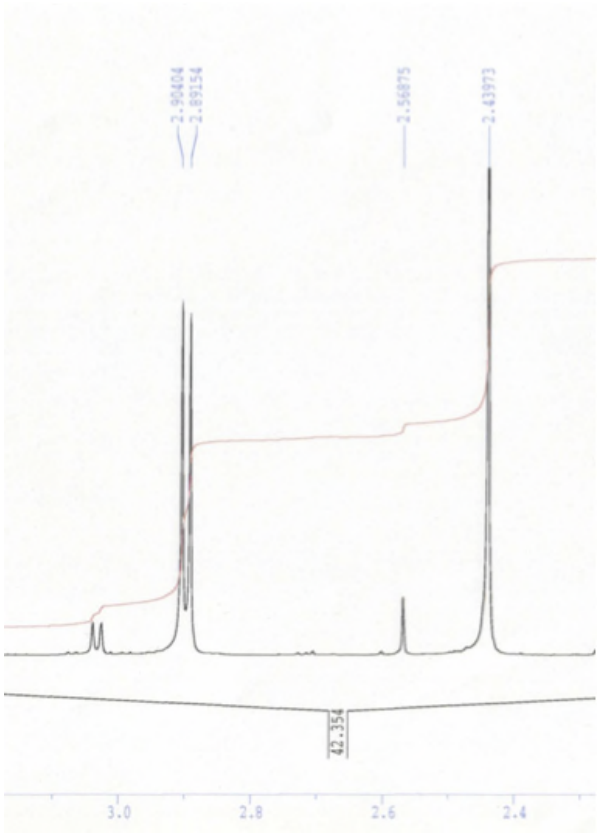


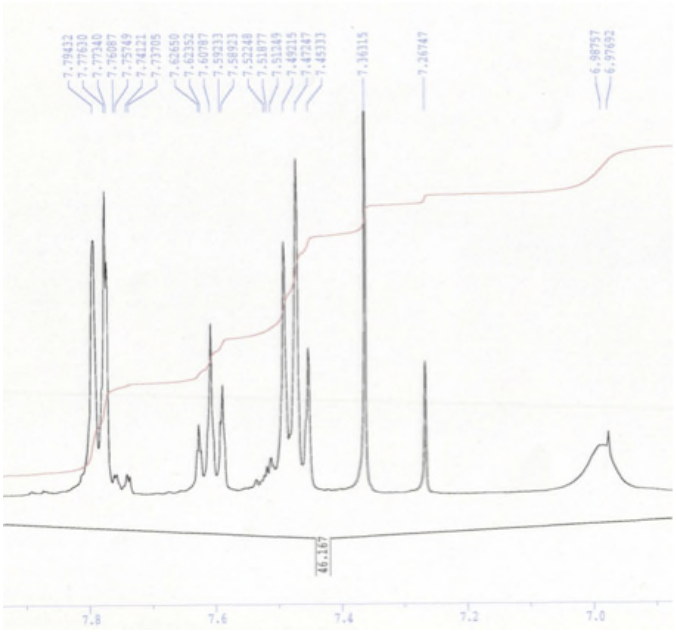
4-Benzoyl-5-methyl-3-(*N*-methylcarbamoyl)isoxazole (5c)

Yellow oil. IR (KBr) 3357, 1672, 1649 cm^{-1}; ^1H 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.

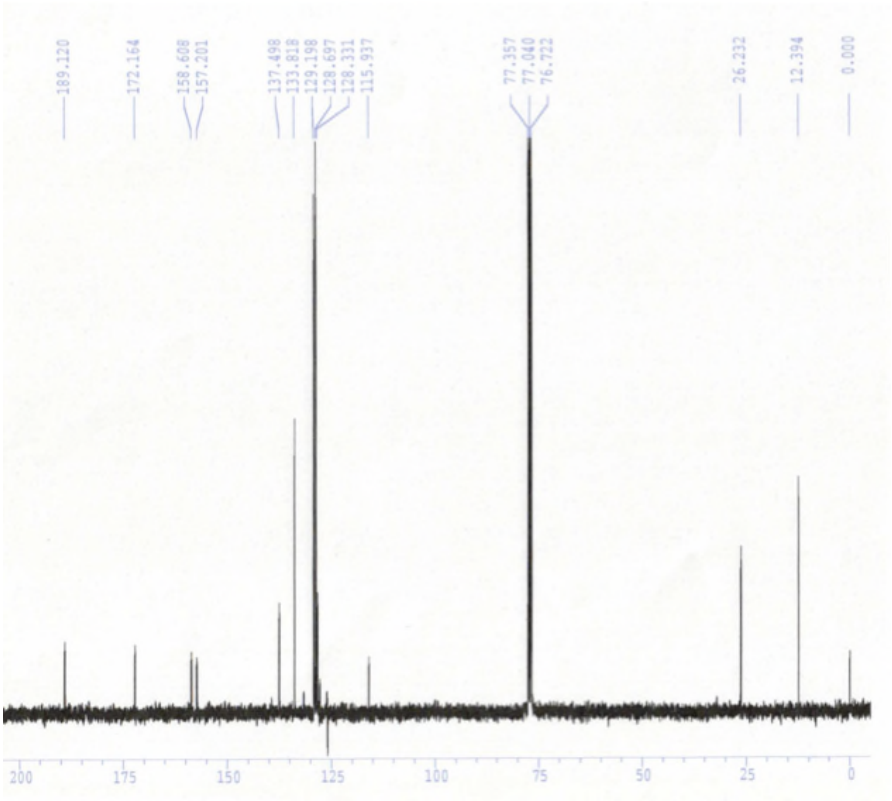
^{1}H NMR ($CDCl_3$)







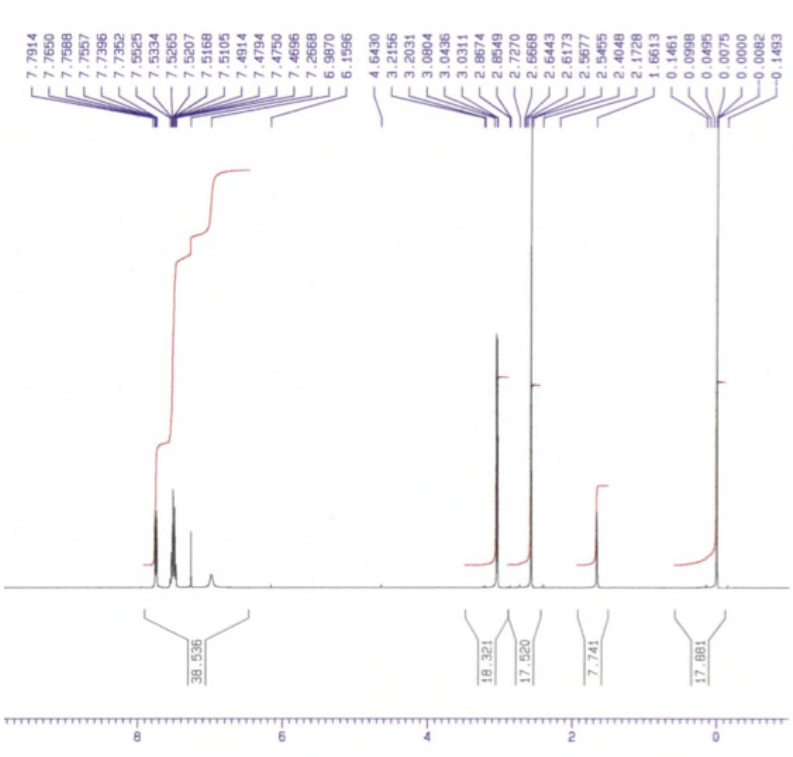
^{13}C NMR ($CDCl_3$)

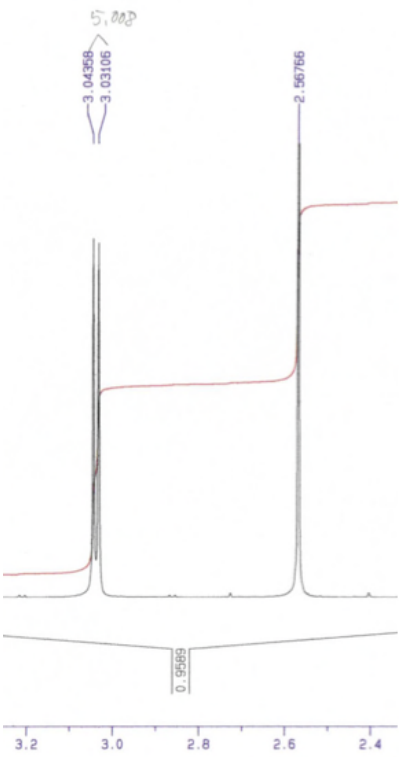


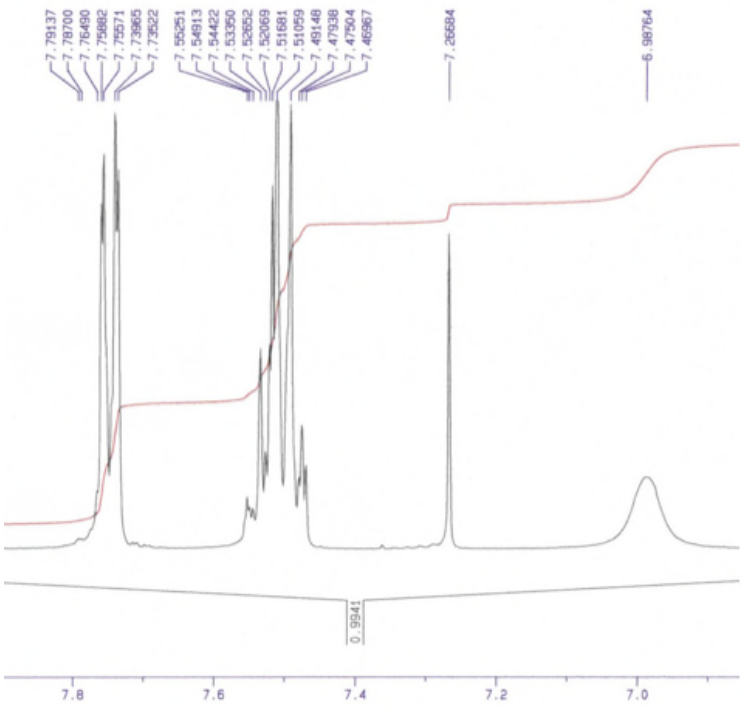
4-Acetyl-3-(*N*-methylcarbamoyl)-5-phenylisoxazole (5c')

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.

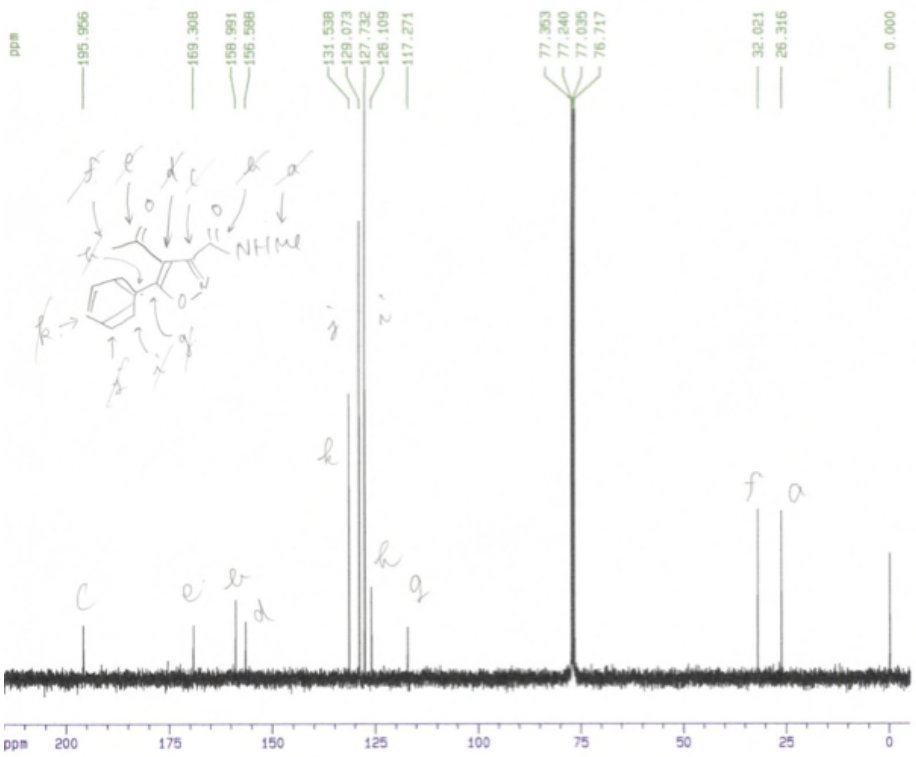
^{1}H NMR ($CDCl_3$)







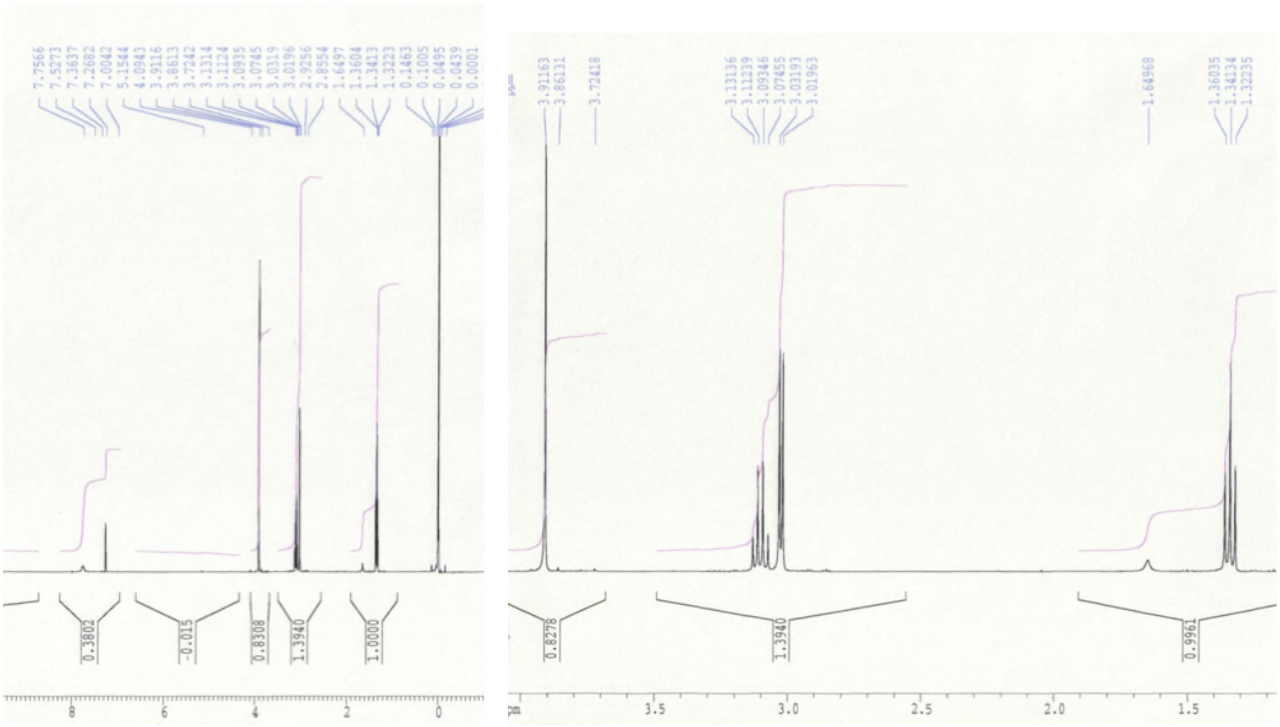
^{13}C NMR ($CDCl_3$)



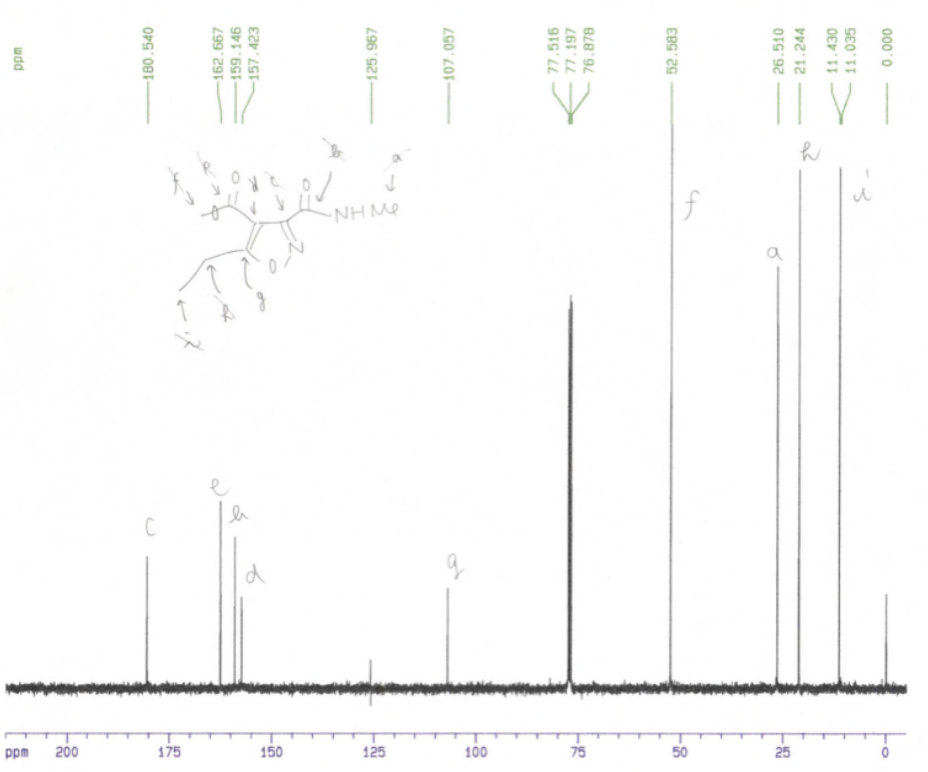
5-Ethyl-4-methoxycarbonyl-3-(*N*-methylcarbamoyl)isoxazole (5d)

Colorless needles (from benzene/hexane = 1/1). Mp 86-88 °C. IR (Nujol) 3273, 1713, 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$) 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.

^{1}H NMR ($CDCl_3$)



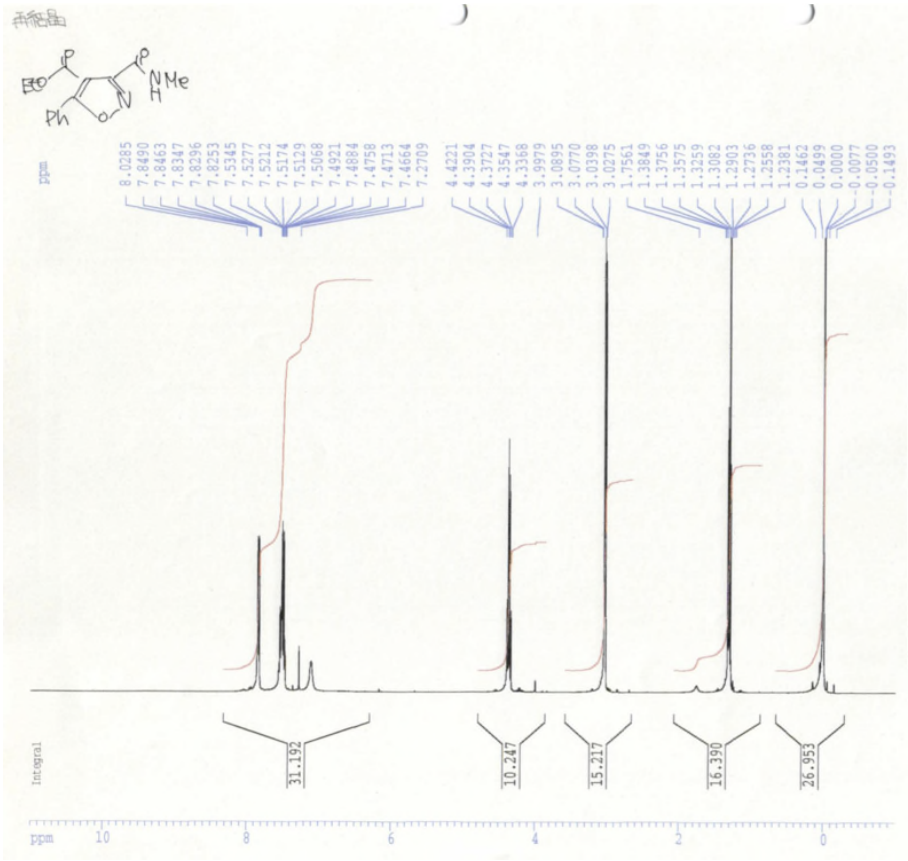
^{13}C NMR ($CDCl_3$)

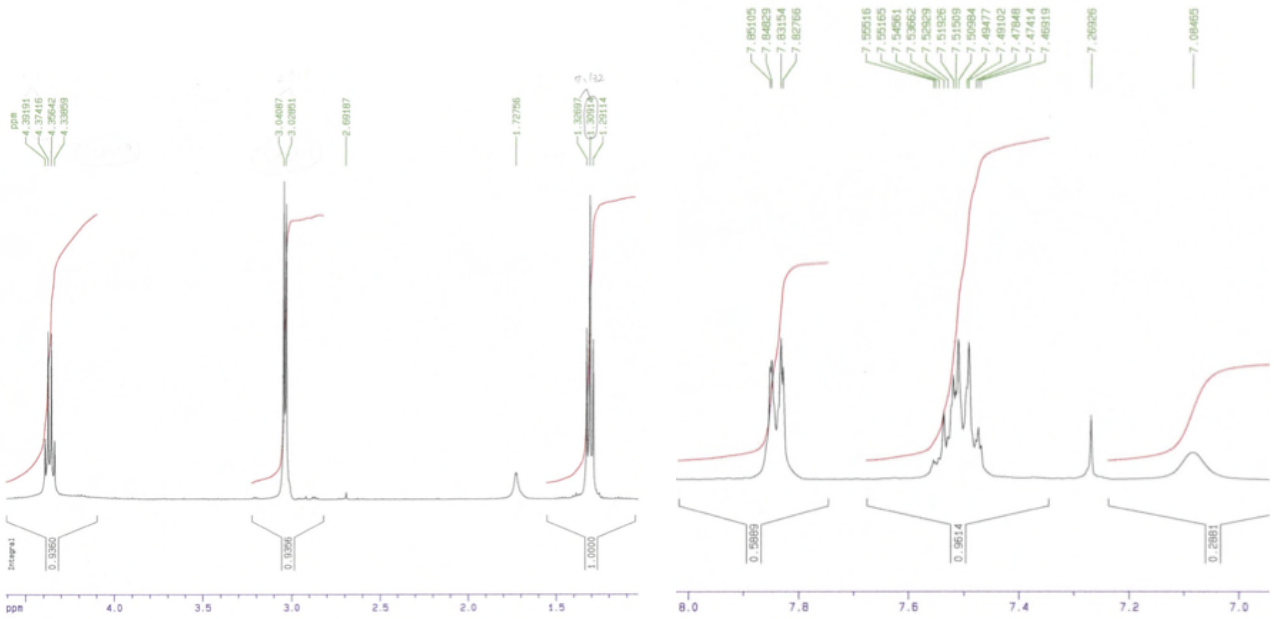


4-Ethoxycarbonyl-3-(*N*-methylcarbamoyl)-5-phenylisoxazole (5e)

Colorless needles (from benzene/hexane = 1/1). Mp 113-116 °C. IR (KBr) 3299, 1726, 1664 cm^{-1}; ^1H NMR ($CDCl_3$) 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.

^1H NMR ($CDCl_3$)





^{13}C NMR ($CDCl_3$)