

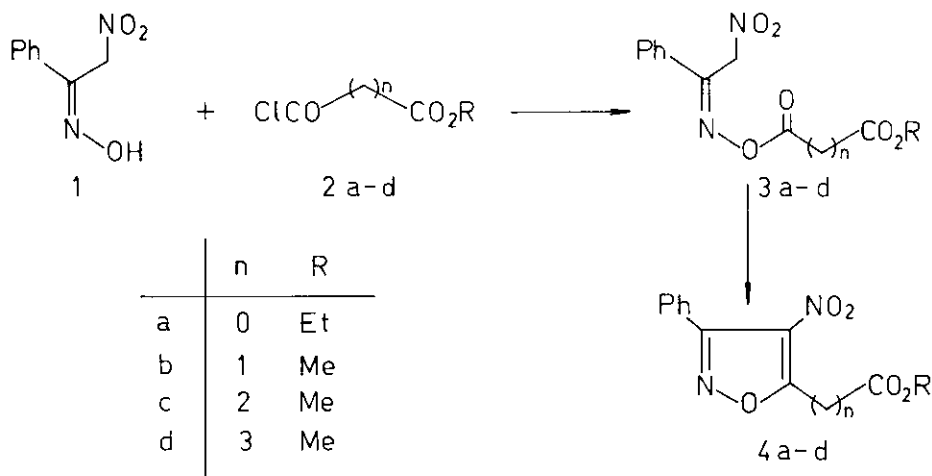
NEW DIFUNCTIONALIZED 4-NITROISOXAZOLES FROM α -NITROACETOPHENONE OXIME

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Abstract — The title compound (1) reacted smoothly with the acyl chlorides (2a-d) to give the derivatives (3a-d) which were converted in high yields into the nitroisoxazoles (4a-d), respectively, through a base-induced cyclization.

The cyclocondensation of compound (1) with aldehydes and ketones has been previously employed advantageously for the synthesis of various 4-nitroisoxazolines.¹ On the other hand, it has been shown more recently that ethyl 3-cyclohexyl-4-nitroisoxazole-5-carboxylate could be obtained in good yield from 1-cyclohexyl-2-nitroethanone oxime and ethyl oxalyl chloride.² In connection with our studies on new spiro annelation reactions in the isoxazole series,³ we became interested in the preparation of difunctionalized 4-nitroisoxazoles of the type (4a-d); so we investigated the behaviour of (1) towards the acyl chlorides (2a-d).



Reaction of the nitro oxime (1) with (2a) in anhydrous ether at room temperature afforded in excellent yield compound (3a) which cyclized into ethyl 3-phenyl-4-nitroisoxazole-5-carboxylate (4a) by treatment with aluminium oxide in dichloromethane; however, the yield of the second step was sensibly lowered by partial hydrolysis of the water-sensitive derivative (3a).

This drawback was fully avoided when the cyclization was carried out in the same solvent with a catalytic amount of triethylamine in the presence of molecular sieves; under these conditions, the reaction gave the desired product nearly quantitatively. Analogously, compound (1) reacted with the chlorides (2b-d) to yield the corresponding acyl oximes (3b-d) which showed a greater stability with respect to (3a); so their conversion into the nitro esters (4b-d) was profitably accomplished with aluminium oxide as catalyst. This procedure may represent a useful route for other 3-phenyl-4-nitroisoxazoles suitably substituted at position 5 which, likewise compounds (4a-d), can be regarded as promising synthetic intermediates; a systematic investigation in this field is now in progress.

EXPERIMENTAL

All melting points were observed with a Büchi 510 apparatus and are uncorrected. Unless otherwise stated, ir spectra were measured for potassium bromide discs with a Perkin-Elmer 283 spectrometer. ^1H - and ^{13}C nmr spectra were recorded in CDCl_3 on a Perkin-Elmer R32 instrument and a Varian FT-80A spectrometer, respectively; 4 chemical shifts are reported in ppm downfield from internal tetramethylsilane, and coupling constants in Hz. Ether refers to diethyl ether and it was dried by distillation over sodium wire and LiAlH_4 .

Ethyl oxo [[(1-phenyl-2-nitroethylidene)amino]oxy]acetate (3a)

Ethyl oxalyl chloride (2a) (24 g) was added dropwise to the nitro oxime (1)¹ (28.8 g) in anhydrous ether (190 ml) and the mixture was stirred at room temperature for 17 h. Compound (3a), which separated as white crystals, was filtered, washed with the minimum amount of the same solvent, and dried (KOH and P_2O_5) (41.6 g, yield 92.8%), mp 92-93°C (from anhydrous ether); ir ν_{max} : 1797, 1755, 1563, 1385, 1345, 1290, 1140, and 1100 cm^{-1} ; ^1H nmr δ : 1.38(3H, t, $J=7$ Hz, OCH_2CH_3), 4.39(2H, q, $J=7$ Hz, OCH_2CH_3), 5.79(2H, s, CH_2NO_2), 7.40-7.60(3H, m, ArH_3), 7.70-7.85(2H, m, ArH_2); ^{13}C nmr δ : 13.6 (OCH_2CH_3), 63.6 (OCH_2CH_3), 69.5 (CH_2NO_2), 153.9 (C=N), 156.1 (CO), 156.2 (CO). Anal. Calcd. for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_6$: C, 51.43; H, 4.32; N, 10.00. Found: C, 51.20; H, 4.30; N, 10.00.

Methyl 3-oxo-3-[[(1-phenyl-2-nitroethylidene)amino]oxy]propionate (3b)

Reaction of (1) (15.8 g) with methyl malonyl chloride (2b) (12 g) was carried out in ether (75 ml) as above. Removal of the solvent left a residue which was quickly neutralized (aqueous KHCO_3) and extracted with ether; evaporation to dryness

gave a yellow oily product (23.0 g, yield 93.6%) mainly containing compound (3b) together with a minor amount (15-20%, ^1H nmr) of the corresponding diastereoisomer;⁵ $\text{ir } \nu_{\text{max}}$ (neat): 1790, 1745, 1565, 1340, and 1120 cm^{-1} ; ^1H nmr δ : [3.44], 3.58 (2H, s, $\text{CH}_2\text{CO}_2\text{CH}_3$), [3.62], 3.72 (3H, s, OCH_3), [5.56], 5.72 (2H, s, CH_2NO_2), 7.40-7.58 (3H, m, ArH_3), 7.68-7.82 (2H, m, ArH_2); ^{13}C nmr δ : 39.65 ($\text{CH}_2\text{CO}_2\text{CH}_3$), [52.3], 52.4 (OCH_3), 69.3, [77.1] (CH_2NO_2), 154.3, [156.2] (C=N), 162.8, [163.2] (CO), [165.6], 165.7 (CO). Anal. Calcd. for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_6$: C, 51.43; H, 4.32; N, 10.0. Found: C, 51.25; H, 4.36; N, 10.19.

Methyl 4-oxo-4-[[(1-phenyl-2-nitroethylidene)amino]oxy]butyrate (3c)

A solution of (1) (15.2 g) and methyl succinyl chloride (2c) (12.7 g) in anhydrous ether (65 ml) was refluxed for 15 h and then allowed to stand overnight in the refrigerator. The solid which separated was filtered, washed with the minimum amount of ether, and dried to give the acyl oxime (3c) (20.92 g, yield 84.2%), mp 67-68°C (after two crystallizations from the same solvent); $\text{ir } \nu_{\text{max}}$: 1790, 1725, 1560, 1365, 1215, 1100, and 1065 cm^{-1} ; ^1H nmr δ : 2.60-3.0 (4H, m, $\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3$), 3.71 (3H, s, OCH_3), 5.73 (2H, s, CH_2NO_2), 7.45-7.60 (3H, m, ArH_3), 7.70-7.83 (2H, m, ArH_2); ^{13}C nmr δ : 27.5, 28.4 ($\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3$), 51.8 (OCH_3), 69.5 (CH_2NO_2), 153.6 (C=N), 168.6 (CO), 172.0 (CO). Anal. Calcd. for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_6$: C, 53.06; H, 4.80; N, 9.52. Found: C, 52.99; H, 4.81; N, 9.83.

Methyl 5-oxo-5-[[(1-phenyl-2-nitroethylidene)amino]oxy]valerate (3d)

Operating as above, compound (1) (20.4 g) and methyl glutaryl chloride (2d) (18.7 g) in ether (90 ml) afforded (3d) as white needles (31.2 g, yield 89.4%), mp 49.5-50.5°C (from ether); $\text{ir } \nu_{\text{max}}$: 1792, 1740, 1567, 1445, 1382, 1350, 1285, 1265, 1110, and 1050 cm^{-1} ; ^1H nmr δ : 1.82-2.20 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3$), 2.32-2.70 (4H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3$), 3.67 (3H, s, OCH_3), 5.69 (2H, s, CH_2NO_2), 7.40-7.60 (3H, m, ArH_3), 7.70-7.85 (2H, m, ArH_2); ^{13}C nmr δ : 19.6 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3$), 31.4, 32.5 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3$), 51.4 (OCH_3), 69.55 (CH_2NO_2), 153.4 (C=N), 168.9 (CO), 172.9 (CO). Anal. Calcd. for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_6$: C, 54.54; H, 5.23; N, 9.09. Found: C, 54.81; H, 5.22; N, 9.41.

Ethyl 3-phenyl-4-nitroisoxazole-5-carboxylate (4a)

A mixture of compound (3a) (8.39 g), triethylamine (5 drops), and molecular sieves (8.5 g; 4 A, Union Carbide), previously activated at 150°C, in dichloromethane (85 ml) was maintained under vigorous stirring at room temperature for 50 h. The inorganic material was filtered off and washed with the same solvent; evaporation to dryness of the combined filtrates gave the nitro ester (4a) as a yellow oil (7.82 g, yield 99.6%), bp 117-118°C at 0.04 mmHg; $\text{ir } \nu_{\text{max}}$ (neat): 1755, 1545, 1450, 1370, 1305, 1215, 1080, and 1005 cm^{-1} ; ^1H nmr δ : 1.41 (3H, t, $J=7$ Hz, OCH_2CH_3), 4.51 (2H, q, $J=7$ Hz, OCH_2CH_3), 7.40-7.50 (5H, m, Ph); ^{13}C nmr δ : 14.4 (OCH_2CH_3), 64.5 (OCH_2CH_3), 133.5 (C-4), 154.7 (C-3/C-5/CO), 156.1 (C-3/C-5/CO), 157.05 (C-3/C-5/CO). Anal. Calcd. for $\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}_5$: C, 54.97; H, 3.84; N, 10.68. Found: C, 55.08; H, 3.93; N, 10.74.

Cyclization of the acyl oximes (3b-d) with aluminium oxide

Aluminium oxide (60 g, Merck 60 Art. 1103) was added to a solution of the acyl oxime (0.1 mol) in dichloromethane (200-250 ml) and the mixture was stirred at room temperature until the starting material disappeared (tlc, 24-70 h). The inorganic material was removed by filtration and washed exhaustively with the same solvent; evaporation to dryness of the combined filtrates afforded the corresponding nitro ester as a semi-solid oil which crystallized on cooling.

Methyl (3-phenyl-4-nitroisoxazol-5-yl)acetate (4b)

Compound (4b) (yield 87.7%) had mp 67.5-68.5°C (from ether); ir ν_{\max} : 1745, 1610, 1600, 1525, 1370, 1350, 1292, 1225, and 1157 cm^{-1} ; ^1H nmr δ : 3.8(3H, s, OCH_3), 4.30 (2H, s, $\text{CH}_2\text{CO}_2\text{CH}_3$), 7.45-7.75(5H, m, Ph); ^{13}C nmr δ : 33.45($\text{CH}_2\text{CO}_2\text{CH}_3$), 52.9(OCH_3), 130.1(C-4), 157.3(C-3), 167.9(C-5/CO), 168.1(CO/C-5). Anal. Calcd. for $\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}_5$: C, 54.97; H, 3.84; N, 10.68. Found: C, 54.83; H, 3.79; N, 10.93.

Methyl 3-(3-phenyl-4-nitroisoxazol-5-yl)propionate (4c)

The nitro ester (4c) (yield 89%) had mp 57-58°C (from ether); ir ν_{\max} : 1730, 1610, 1600, 1523, 1440, 1368, and 1210 cm^{-1} ; ^1H nmr δ : 2.88(2H, t, $J=7.5$ Hz, $\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3$), 3.54(2H, t, $J=7.5$ Hz, $\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3$), 3.70(3H, s, OCH_3), 7.40-7.70(5H, m, Ph); ^{13}C nmr δ : 23.2($\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3$), 29.4($\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3$), 51.9(OCH_3), 129.2(C-4), 157.6(C-3), 171.2(C-5/CO), 173.7(CO/C-5). Anal. Calcd. for $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_5$: C, 56.52; H, 4.38; N, 10.14. Found: C, 56.67; H, 4.37; N, 10.14.

Methyl 4-(3-phenyl-4-nitroisoxazol-5-yl)butyrate (4d)

Compound (4d) (yield 87.8%) had mp 46-47°C (after two crystallizations from ether-light petroleum 30-50°C); ir ν_{\max} : 1730, 1608, 1590, 1512, 1415, 1370, 1208, and 1195 cm^{-1} ; ^1H nmr δ : 2.05-2.60(4H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3$), 3.31(2H, t, $J=7.5$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3$), 3.70(3H, s, OCH_3), 7.45-7.75(5H, m, Ph); ^{13}C nmr δ : 21.4 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3$), 26.9($\text{CH}_2\text{CO}_2\text{CH}_3$), 32.8($\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{CH}_3$), 51.6(OCH_3), 129.4(C-4), 157.7(C-3), 172.4(C-5/CO), 174.7(CO/C-5). Anal. Calcd. for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_5$: C, 57.93; H, 4.86; N, 9.65. Found: C, 58.15; H, 4.81; N, 9.98.

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4. In order to recognize unambiguously the weak C-4 signals of the nitro esters (4a-d), $[\text{Cr}(\text{AcAc})_3]$ was added to the CDCl_3 solutions and the ^{13}C nmr spectra were recorded by the APT technique.
5. Attempts to separate the acyl oxime (3b) from the corresponding isomer by different methods failed; however, the 'crude' product could be advantageously employed for the preparation of (4b).
6. Values in square brackets refer to the resonances of the isomer.

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