A Convenient One-Pot Synthesis of 4-Substituted 3,5-Bis(alkoxycarbonyl)-4,5-dihydroisoxazole 2-Oxides from Aldehydes and Nitroacetic Esters in a Solid-Liquid Reaction System and Subsequent Deoxygenation

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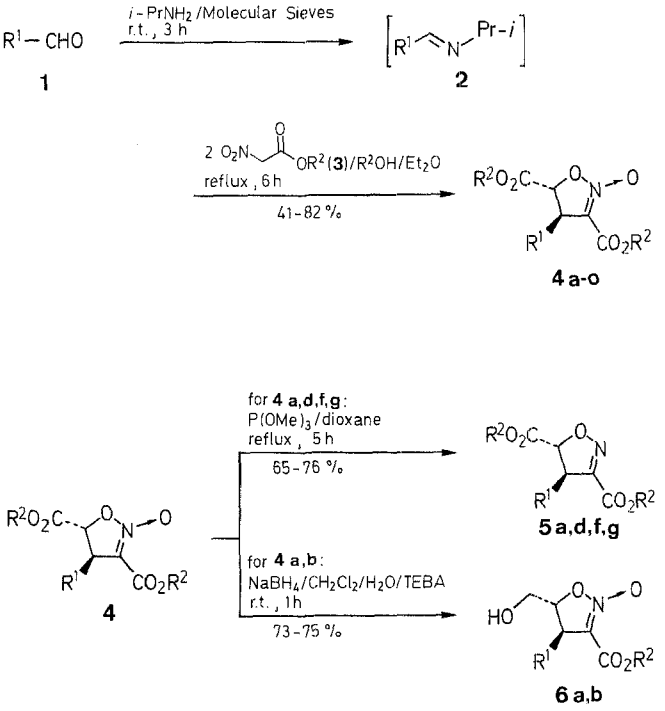
4-Substituted 3,5-bis(alkoxycarbonyl)-4,5-dihydroisoxazole 2-oxides are obtained from nitroacetic esters and imines which are prepared from aldehydes and isopropylamine in the presence of molecular sieves. Reduction of the *N*-oxides with trimethyl phosphite in dioxane gives the corresponding 4,5-dihydroisoxazoles in good yields.

4,5-Dihydroisoxazole 2-oxides may be employed as precursors to 4,5-dihydroisoxazoles,[1] which are important intermediates in organic synthesis.[2-5] 4,5-Dihydroisoxazole 2-oxides[6] have been prepared from nitroacetic esters[7] and Schiff bases,[8,9] aldehydes,[10] or iodoalkanes[11] and from nitroalkenes and selenium ylides[12] or sulfurane *S*-oxides,[13] and from the reaction of bromonitroalkenes with nitro compounds.[14]

We now report a convenient method for the synthesis of 4-substituted 3,5-bis(alkoxycarbonyl)-4,5-dihydroisoxazole 2-oxides in a solid-liquid reaction system.

N-Isopropylaldimines **2** were prepared prior to use from aldehydes **1** and isopropylamine without solvent in the presence of molecular sieves. Then, the nitroacetic ester **3**[7] in alcohol/ether (1:1) was added and the mixture heated to boiling (6 h) to give the 4,5-dihydroisoxazole 2-oxides **4** in good yields (Table 1). The pure diastereoisomers **4**, with R^1 and CO_2R^2 in *trans* position, were obtained. Indeed, the ^{1}H-NMR spectra of **4** show that the values of the H_4-H_5 coupling constants are small (J = 2-3 Hz).[10]

It appears that the molecular sieves (4 Å) are the best catalyst (alumina or montmorillonite K 10 are less efficient). The use of a volatile alkylamine is necessary to avoid side reactions. The yields of **4** decrease when amines with higher boiling points are used. The reduction of *N*-oxides **4** with trimethyl phosphite in dioxane (reflux 5–8 h) yielded the corresponding 4,5-dihydroisoxazoles **5** (Table 2), whereas the reduction of **4** with sodium borohydride under liquid-liquid phase-transfer conditions[15] gave the 3-alkoxycarbonyl-5-hydroxymethyl-4,5-dihydroisoxazole 2-oxides **6**. Thus, the latter reduction is regioselective, only the ester group in position 5 being reduced.



4, 5, 6	R^1	R^2
a	C_6H_5	CH_3
b	4-$CH_3OC_6H_4$	CH_3
c	4-$CH_3C_6H_4$	CH_3
d	1-naphthyl	CH_3
e	4-$NO_2C_6H_4$	CH_3
f	4-ClC_6H_4	CH_3
g		CH_3
h	t-C_4H_9	CH_3
i	C_6H_5	C_2H_5
j	4-ClC_6H_4	C_2H_5
k	4-$NO_2C_6H_4$	C_2H_5
l	2,4,6-$(CH_3O)_3C_6H_2$	C_2H_5
m	2-naphthyl	C_2H_5
n	3-$NO_2C_6H_4$	C_2H_5
o	4-$C_6H_5OC_6H_4$	C_2H_5

Table 1. 4-Substituted 3,5-Bis(alkoxycarbonyl)-4,5-dihydroisoxazol 2-Oxides **4** Prepared

Product	Yield[a] (%)	mp (°C)	Molecular Formula[b] or Lit. Data	^{1}H-NMR ($CDCl_3$/TMS)[c] δ, J(Hz)
4a[d]	76	96	94–95[10]	3.74 (s, 3H, OCH_3); 3.89 (s, 3H, OCH_3); 4.88, 4.94 (AB, 2H, J = 2.5); 7.38 (s, 5H_{arom})
4b	81	94	$C_{14}H_{15}NO_7$ (309.3)	3.75 (s, 3H, OCH_3); 3.82 (s, 3H, OCH_3); 3.89 (s, 3H, OCH_3); 4.84, 4.93 (AB, 2H, J = 3.5); 6.85–7.32 (m, 4H_{arom})
4c	77	98	$C_{14}H_{15}NO_6$ (293.3)	2.34 (s, 3H, CH_3); 3.70 (s, 3H, OCH_3); 3.85 (s, 3H, OCH_3); 4.81, 4.92 (AB, 2H, J = 2.5); 7.19 (s, 4H_{arom})
4d	75	164 (dec)	$C_{17}H_{15}NO_6$ (329.3)	3.71 (s, 3H, OCH_3); 3.95 (s, 3H, OCH_3); 4.91, 5.73 (AB, 2H, J = 2.5); 7.20–8.30 (m, 7H_{arom})
4e	69	177 (dec)	$C_{13}H_{12}N_2O_8$ (324.2)	(acetone-d_6): 3.69 (s, 3H, OCH_3); 3.85 (s, 3H, OCH_3); 5.28 (m, 2H); 7.73–8.31 (m, 4H_{arom})
4f	75	148	$C_{13}H_{12}ClNO_6$ (313.7)	3.75 (s, 3H, OCH_3); 3.86 (s, 3H, OCH_3); 4.85, 4.91 (AB, 2H, J = 2.5); 7.25–7.40 (m, 4H_{arom})
4g	82	128	$C_{14}H_{13}NO_8$ (323.3)	3.76 (s, 3H, OCH_3); 3.87 (s, 3H, OCH_3); 4.75, 4.89 (AB, 2H, J = 2.5); 5.97 (s, 2H, OCH_2O); 6.78 (s, 3H_{arom})
4h	41	127	$C_{11}H_{17}NO_6$ (259.3)	1.06 [s, 9H, $C(CH_3)_3$]; 3.51 (d, 1H, J = 1.5); 3.85 (s, 3H, OCH_3); 3.87 (s, 3H, OCH_3); 4.93 (d, 1H, J = 1.5)

Table 1. (Continued)

Product	Yield[a] (%)	mp (°C)	Molecular Formula[b] or Lit. Data	^{1}H-NMR ($CDCl_3$/TMS)[c] δ, J(Hz)
4i	73	74	$C_{15}H_{17}NO_6$ (307.3)	1.13 (t, 3H, $CH_2C\underline{H}_3$, J = 7); 1.34 (t, 3H, $CH_2C\underline{H}_3$, J = 7); 4.09 (q, 2H, $C\underline{H}_2$–CH_3, J = 7); 4.33 (q, 2H, $C\underline{H}_2CH_3$, J = 7); 4.84, 4.93 (AB, 2H, J = 2.5); 7.34 (s, 5H_{arom})
4j	79	98	$C_{15}H_{16}ClNO_6$ (341.7)	1.17 (t, 3H, $CH_2C\underline{H}_3$, J = 7); 1.35 (t, 3H, $CH_2C\underline{H}_3$, J = 7); 4.19 (q, 2H, $C\underline{H}_2CH_3$, J = 7); 4.32 (q, 2H, $C\underline{H}_2CH_3$, J = 7); 4.85, 4.92 (AB, 2H, J = 2.5); 7.32 (m, 4H_{arom})
4k	52	98 (dec)	$C_{15}H_{16}N_2O_8$ (352.3)	1.18 (t, 3H, $CH_2C\underline{H}_3$, J = 7); 1.38 (t, 3H, $CH_2C\underline{H}_3$, J = 7); 4.21 (q, 2H, $C\underline{H}_2CH_3$, J = 7); 4.38 (q, 2H, $C\underline{H}_2CH_3$, J = 7); 4.93, 5.07 (AB, 2H, J = 2.5); 7.60–8.30 (m, 4H_{arom})
4l	52	150	$C_{18}H_{23}NO_9$ (397.4)	1.09 (t, 3H, $CH_2C\underline{H}_3$, J = 7); 1.30 (t, 3H, $CH_2C\underline{H}_3$, J = 7); 3.82 (s, 9H, 3OCH_3); 4.12 (q, 2H, $C\underline{H}_2CH_3$, J = 7); 4.30 (m, 2H); 4.82 (d, 1H, J = 6); 5.51 (d, 1H, J = 6); 6.16 (s, 2H_{arom})
4m	81	93	$C_{19}H_{19}NO_6$ (357.4)	1.06 (t, 3H, $CH_2C\underline{H}_3$, J = 7); 1.31 (t, 3H, $CH_2C\underline{H}_3$, J = 7); 4.10 (q, 2H, $C\underline{H}_2CH_3$, J = 7); 4.31 (q, 2H, $C\underline{H}_2CH_3$, J = 7); 4.98, 5.06 (AB, 2H, J = 2); 7.32–7.95 (m, 7H_{arom})
4n	54	81 (dec)	$C_{15}H_{16}N_2O_8$ (352.3)	1.19 (t, 3H, $CH_2C\underline{H}_3$, J = 7); 1.38 (t, 3H, $CH_2C\underline{H}_3$); 4.23 (q, 2H, $C\underline{H}_2CH_3$, J = 7); 4.39 (q, 2H, $C\underline{H}_2CH_3$, J = 7); 5.00 (m, 2H); 7.50–8.40 (m, 4H_{arom})
4o	75	104	$C_{21}H_{21}NO_7$ (399.4)	1.08 (t, 3H, $CH_2C\underline{H}_3$, J = 7); 1.33 (t, 3H, $CH_2C\underline{H}_3$, J = 7); 4.20 (q, 2H, $C\underline{H}_2CH_3$, J = 7); 4.30 (q, 2H, $C\underline{H}_2CH_3$, J = 7); 4.82, 4.94 (AB, 2H, J = 2); 6.80–7.50 (m, 9H_{arom})

[a] Isolated pure product, recrystallised from R^2OH.
[b] Satisfactory microanalyses obtained: C ±0.3, H ±0.2, N ±0.23. Exceptions: **4f** (C −0.70), **4k** (C +0.53), **4o** (C −0.62).
[c] Recorded on a Bruker WP 80 spectrometer.
[d] Exact Mass ($C_{13}H_{13}NO_6$): calc. 279.0743, found 279.0736.
^{13}C-NMR (20.115 MHz, $CDCl_3$/TMS): δ [J(Hz)] = 52.7 (q, J = 148.5); 52.8 (dd, J = 139, 3.3, C-4); 53.3 (q, J = 148.5); 78.9 (dd, J = 160.6, 3.3, C-5); 109 (d, J = 6.6, C-3); 127.1, 129.0, 129.6, 139.0 (C_6H_5); 158.8, 168.8 (C=O).

Table 2. 4,5-Dihydroisoxazole Derivatives **5** and **6** Prepared

Product	Reaction Time (h), Temp. (°C)	Yield[a] (%)	mp (°C)	Molecular Formula[b]	IR (nujol) ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[c] δ, J(Hz)
5a[d]	5, 10	65	82 (MeOH)	$C_{13}H_{13}NO_5$ (263.3)	1755, 1730, 1650, 1600	3.79 (s, 3H, OCH_3); 3.85 (s, 3H, OCH_3); 4.88, 5.10 (AB, 2H, J = 5); 7.25 (m, 5H_{arom})
5d	8, 100	70	110 (MeOH)	$C_{17}H_{15}NO_5$ (313.3)	1740, 1730, 1635	3.71 (s, 3H, OCH_3); 3.84 (s, 3H, OCH_3); 5.10 (d, 1H, J = 4.5); 5.71 (d, 1H, J = 4.5); 7.10–8.30 (m, 7H_{arom})
5f	5, 100	75	110 (MeOH)	$C_{13}H_{12}ClNO_5$ (297.7)	1755, 1730, 1590	3.79 (s, 3H, OCH_3); 3.85 (s, 3H, OCH_3); 4.88 (d, 1H, J = 5); 5.08 (d, 1H, J = 5); 7.10–7.40 (m, 4H_{arom})
5g	5, 100	76	141 (MeOH)	$C_{14}H_{13}NO_7$ (307.3)	1740, 1710, 1630	3.81 (s, 6H, OCH_3); 4.78 (d, 1H, J = 4.5); 5.02 (d, 1H, J = 4.5); 5.95 (s, 2H, OCH_2O); 6.70 (m, 3H_{arom})
6a	1, 20	75	108–109 (C_6H_6)	$C_{12}H_{13}NO_5$ (251.2)	3510, 1720	3.10 (s, 1H, OH); 3.68 (s, 3H, OCH_3); 3.88 (m, 2H); 4.66 (m, 2H); 7.32 (s, 5H_{arom})
6b	1, 20	73	118 (C_6H_6)	$C_{13}H_{15}NO_6$ (281.3)	3505, 1705, 1615	2.87 (s, 1H, OH); 3.69 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3); 3.89 (m, 2H); 4.62 (m, 2H); 6.8–7.2 (m, 4H_{arom})

[a] Yield of recrystallized product.
[b] Satisfactory microanalyses obtained: C ±0.41, H ±0.24, N ±0.1.
[c] Recorded on a Bruker WP 80 Spectrometer.
[d] ^{13}C-NMR (20.115 MHz, $CDCl_3$): δ [J(Hz)] = 52.9 (q, J = 148.5); 53.1 (q, J = 148.5); 56.6 (dd, J = 139, 3.3, C-4); 87.8 (dd, J = 158.4, 3.3, C-5); 127.5, 128.6, 129.5, 136.9 (C_6H_5); 153.3 (dd, J = 6.5, C-3); 159.8, 169.0 (C=O).

The structure of compounds **6** was assigned on the basis of IR-spectrometric data: ν = 1705–1720 cm^{-1} (C=O of a conjugated ester); the carbonyl stretching frequencies for compounds **5** are ν = 1740–1755 cm^{-1} (ester group at C-5) and ν = 1710–1730 cm^{-1} (conjugated ester group at C-3) (Table 2); for compound **4a**, these stretching frequences are ν = 1740–1760 cm^{-1}. The structure of compounds **6** is confirmed by spin-decoupling experiments with the H-4 and H-5 signals of **6a** (CH_2OH gave a singlet) and on the CH_2OH signal (H-4 and H-5 gave an AB system). The procedure reported here demonstrates the ease of performance of the reaction. With R^1 = aryl, the yields are higher than those obtained by the previous methods.[9,10] When diethylamine was used as base,[8] products **4** could not be obtained, the 3-alkoxycarbonyl group being converted into an amide group.

4-Substituted 3,5-Bis(alkoxycarbonyl)-4,5-dihydroisoxazole 2-Oxides 4; General Procedure:
To molecular sieves (4 Å, powder; 5 g) is added, at 0–5 °C, the aldehyde **1** (10 mmol) and then, dropwise and with stirring, *i*-$PrNH_2$ (0.9 g, 15 mmol). The mixture is left at room temperature for 3 h. Excess *i*-$PrNH_2$ is then removed under reduced pressure. A solution of methyl or ethyl nitroacetate (22 mmol) in Et_2O/R^2OH (1:1, 8 mL) is added dropwise at 0 °C, with stirring, and the mixture is refluxed for 6 h. Molecular sieves are separated by filtration through a celite layer, and washed with CH_2Cl_2 (2 × 20 mL). The product **4** is obtained by evaporation of the filtrate and recrystallization of the residue from R^2OH.

4-Substituted 3,5-Bis(alkoxycarbonyl)-4,5-dihydroisoxazoles 5; General Procedure:
To a solution of the *N*-oxide **4** (10 mmol) in dioxane (15 mL) is added trimethyl phosphite (1.55 g, 12.5 mmol) under a well ventilated hood. The mixture is refluxed for the appropriate time (Table 2). After removal of the solvent under reduced pressure, the residual oil is crystallized from MeOH.

4-Aryl-5-hydroxymethyl-3-methoxycarbonyl-4,5-dihydroisoxazole 2-Oxides 6a, b:
To a stirred solution of the *N*-oxide **4a, b** (10 mmol) in CH_2Cl_2 (20 mL) is added a solution of $NaBH_4$ (500 mg, 13 mmol) and TEBA (250 mg, 1.1 mmol) in H_2O (4 mL) and stirring is continued for 1 h at room temperature. Excess $NaBH_4$ is destroyed by addition of 1 M aqueous HCl (3 mL). The mixture is transferred to a separatory funnel, the

organic phase is separated, and the aqueous layer is extracted with CH_2Cl_2 (10 mL). The combined organic extracts are dried ($MgSO_4$) and evaporated. The crude product **6** is recrystallized from benzene.

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