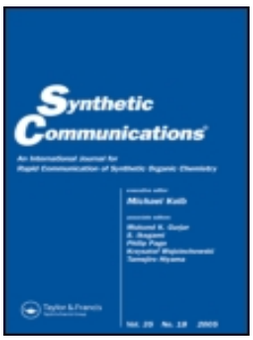

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A NOVEL BASE PROMOTED REACTION OF METHYL 2-ISOXAZOLINE-5-ACETATES TO 5-(2-OXOETHYL)-3-ISOXAZOLIDINONES

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Abstract: The 5-(2-aryl-2-oxoethyl)-3-isoxazolidinones **3a-e** were prepared from the methyl 3-aryl-2-isoxazoline-5-acetates **2a-e** and sodium hexanolate in boiling hexanol in yields from 46 to 86 %. The reaction conditions were optimized and a mechanism for this reaction is proposed and discussed.

During investigations of the reactivity of alkyl 2-isoxoazoline-5-acetates towards nucleophiles it was found, that the esters **2a-e** react with bases to give the 3-isoxazolidinones **3a-e**. Due to the importance of some β-oxoalkyl isoxazolidinones as pharmaceuticals and intermediates, a number of special syntheses for key substances is described[1-6]. Among the known general methods for the syntheses of 3-isoxazolidinones[7-11] none is particularly suited for the introduction of β-oxoalkyl groups at C-5.

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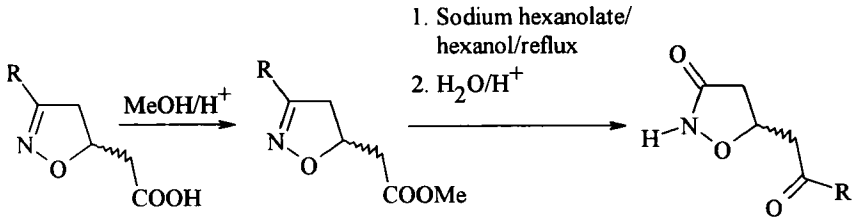
The reaction of **2a-e** with bases to **3a-e** was studied in more detail, with the aim to develop a useful synthesis of 5-(2-oxoethyl)-3-isoxazolidinones.

Scheme



1, 2, 3	a	b	c	d	e
R	C_6H_5	4-CH_3O-C_6H_5	4-C_6H_5-C_6H_4	4-Cl-C_6H_4	3-Br-C_6H_4

In order to optimize the yields of **3a-e**, the reaction conditions with **2b** as standard substrate, were systematically varied. The results are summarized in the table.

The use of strong bases with low nucleophilicity (NaH, 1,8-diazabicyclo[5.4.0]undec-4-ene, LDA) as well as weak bases with high nucleophilicity (C_6H_6SNa) lead to no or very small conversions of **2b** to **3b**. Only strong nucleophiles with high basicity (CH_3ONa, $CH_3(CH_2)_5ONa$) gave acceptable yields. The best yields and very short reaction times were achieved with sodium hexanolate in boiling hexanol.

Table.

Reaction of (±)-methyl 3-(4-methoxyphenyl)-2-isoxazoline-5-acetate **(2b)** to (±)-5-[2-(4-methoxyphenyl)-2-oxoethyl]-3-isoxazolidinone **(3b)**. Variation of base, temperature and solvent.

Reaction conditions for **2b**[a, b]	Yield of **3b** [%]
CH_3ONa/CH_3OH, reflux, 72 hrs.	32
NaH/DMF, reflux, 2 hrs.	0
C_6H_5SNa/DMF, 50 °C, 9 hrs.	9
CH_3ONa/DMF, reflux, 2.5 hrs	0
$CH_3(CH_2)_5ONa/CH_3(CH_2)_5OH$, reflux, 0.5 hrs.	82
1,8-Diazabicyclo[5.4.0]undec-4-ene/CH_3OH, 24 hrs.	0
LDA/THF, -50 °C to -30 °C, 24 hrs.	0

[a]The bases were used in 5 fold excess to **2b**.

[b]All solvents and reagents.were anhydrous.

The structures of **3a-e** were unambigously confirmed by ^{1}H-NMR- and IR spectroscopy. Due to the dominating tautomeric carbonyl structure in **3a-e** their IR spectra show strong absorptions in the range from 1705 to 1720 cm^{-1}. This is in accordance with the IR spectroscopic data of Olive et al.[8, 9] obtained with other substituted 3-isoxazolidinones.

The mechanism of the reaction **2a-e** to **3a-e** deserves further comment, since the usual ring opening reactions of 2-isoxazolines with bases proceed via C-O cleavage, α-enoximes[12], 6-substituted 2-aminopyridine-N-oxides[13], hydroxy-nitriles[14-16], nitriles together with α-diketones[17] or β-hydroxycarboxylic acids[18] are finally obtained.

In the case of the reaction **2a-e** to **3a-e** is necessary to assume the cleavage of the 2-isoxazoline C=N-bond to explain the structures of **3a-e**. Considering the results given in the table it may be concluded, that the mechanism of this reaction proceeds via addition of the base at the C=N-bond. Subsequent nucleophilic attack of the resulting N-anion at the ester group, cleavage of the C-N-bond and hydrolysis could lead to the 3-isoxazolidinones **3a-b**. A further remarkable aspect of this mechanism is the ease of intramolecular nucleophilic substitution. 5-Cyanomethyl-2-isoxazolines, which are structuraly closely related to **2a-e**, are cleaved at the C-O-bond by catalytic amounts of base (DBU) via intramolecular elimination[13].

Experimental

The ^{1}H-NMR spectra were recorded with a Bruker 200 FT-NMR spectrometer. Internal standards: $CHCl_3$ at δ =7.26 ppm or DMSO-d_6 at δ = 2.50 ppm.

The IR spectra were obtained with a Bio-Rad FT-IR spectrometer. Melting points: Kofler instrument, uncorrected.

Syntheses of (±)-2-isoxazoline-5-acetic acids (1a-e):

1a-c are known[19]. **1d** was obtained from 4-chloroacetophenone oxime[20] and **1e**

from 3-bromoacetophenone oxime[21] according to a general procedure[19].

(±)-3-(4-Chlorophenyl)-2-isoxazoline-5-acetic acid (1d):

Yield: 41 %, m. p. 172-173 °C (toluene).

^{1}H-NMR (50 % $CDCl_3$ / 50 % DMSO-d_6): δ = 2.25-2.54 (m, 2H), 2.72-2.88 (m, 1H), 3.10-3.32 (m, 1H), 4.60-4.83 (m, 1H), 7.00 (d, 2H, J = 8 Hz), 7.24 (d, 2H, J = 8 Hz) ppm.

$C_{11}H_{10}ClNO_3$ (239.66). Calcd. %: C 55.13, H 4.21, N 5.84. Found %: C 55.12, H 4.25, N 5.83.

(±)-3-(3-Bromophenyl)-2-isoxazoline-5-acetic acid (1e):

Yield: 52 %, m. p. 151-153 °C (toluene).

^{1}H-NMR ($CDCl_3$): δ = 2.61-2.82 (m, 1H), 2.85-3.05 (m, 1H), 3.08-3.26 (m, 1H), 3.49-3.68 (m, 1H), 7.35-7.77 (m, 4H) ppm.

$C_{11}H_{10}BrNO_3$ (284.11). Calcd. % C 46.50, H 3.55, N 4.93. Found % C 46.72, H 3.54, N 4.88.

General procedure for the syntheses of (±)-methyl 2-isoxazoline-5-acetates (2a-e):

To a solution of a (±)-2-isoxazoline-5-acetic acid **(1a-e)** (6.0 mmol) in anhydrous methanol (40 ml) was added conc. H_2SO_4 (4 ml). The mixture was refluxed for 3 hours, poured on ice water and extracted with ether. The extracts were washed with saturated $NaHCO_3$ solution, dried with Na_2SO_4 and evaporated to dryness.

(±)-Methyl 3-phenyl-2-isoxazoline-5-acetate (2a):

Acid **1a**[1], yield: 91 %, m. p. 51-53 °C (diisopropylether).

^{1}H-NMR ($CDCl_3$): δ = 2.54-2.60 (m, 1H), 2.78-2.92 (m, 1H), 3.00-3.19 (m, 1H), 3.44-3.58 (m, 1H), 3.73 (s, 3H), 5.02-5.19 (m, 1H), 7.34-7.75 (m, 3H), 7.63-7.75 (m, 2H) ppm.

$C_{12}H_{13}NO_3$ (219.24). Calcd. %: C 65.74, H 5.98, N 6.39. Found %: C 65.53, H 5.87, N 6.20.

(±)-Methyl 3-(4-methoxyphenyl)-2-isoxazoline-5-acetate (2b):

Acid **1b**[19], yield: 88 %, m. p. 102-104 °C (diisopropylether).

^{1}H-NMR ($CDCl_3$): δ = 2.53-2.70 (m, 1H), 2.80-2.96 (m, 1H), 3.07-3.19 (m, 1H), 3.45-3.60 (m, 1H), 3.75 (s, 1H), 3.87 (s, 3H), 4.98-5.19 (m, 1H), 6.85-6.95 (m, 2H), 7.56-7.67 (m, 2H) ppm.

$C_{13}H_{15}NO_4$ (249.27). Calcd. %: C 62.64, H 6.07, N 5.62. Found %: C 62.35, H 5.87, N 5.62.

(±)-Methyl 3-(4-biphenylyl)-2-isoxazoline-5-acetate (2c):

Acid **1c**[19], yield: 91 %, m. p. 143-144 °C (diisopropylether).

^{1}H-NMR ($CDCl_3$): δ = 2.58-2.78 (m, 1H), 2.80-2.99 (m, 1H), 3.51-3.70 (m, 1H), 3.75 (s, 3H), 5.05-5.22 (m, 1H), 7.30-7.82 (m, 9H) ppm.

$C_{18}H_{17}NO_3$ (295.34). Calcd. %: C 73.20, H 5.80, N 4.74. Found %: 73.11, H 5.72, N 4.64.

(±)-Methyl 3-(4-chlorophenyl)-2-isoxazoline-5-acetate (2d):

Acid **1d**, yield: 76 %, m. p. 81-82 °C (diisopropylether).

^{1}H-NMR ($CDCl_3$): δ = 2.60-2.73 (m, 1H), 2.71-2.97 (m, 1H), 3.05-3.20 (m, 1H),

3.46-3.61 (m, 1H), 3.75 (s, 3H), 5.05-5.21 (m, 1H), 7.34.7.42 (m, 2H), 7.57-7.66 (m, 2H) ppm.

$C_{12}H_{12}ClNO_3$ (253.69). Calcd. %: C 56.82, H 4.77, N 5.52. Found %: C 56.77, H 4.63, N 5.49.

(±)-Methyl 3-(3-bromophenyl)-2-isoxazoline-5-acetate (2e)

Acid **1e**, yield: 89 %, m. p. 48-50 °C (diisopropylether).

^{1}H-NMR ($CDCl_3$): δ =2.58-2.17 (m, 1H), 2.82-2.96 (m, 1H), 3.07-3.18 (m, 1H), 3.48-3.62 (m, 1H), 3.75 (s, 3H), 5.05-5.18 (m, 1H), 7.35-7.72 (m, 4H) ppm.

$C_{12}H_{12}BrNO_3$ (298.14). Calcd. %: C 48.34, H 4.06, N 4.70. Found %: C 48.21, H 3.99, N 4.55.

General procedure for the syntheses of the 5-(2-oxoethyl)-3-isoxazolidinones (3a-e):

To a solution of Na (0.09 g, 4.0 mmol) in anhydrous hexanol (50 ml) was added **2a-e** (0.8 mmol) and the solution was refluxed for 30 minutes. The reaction mixture was poured on ice and acidified with concentrated HCl. The resulting precipitate was extracted with CH_2Cl_2. The organic extracts were dried with Na_2SO_4 and evaporated to dryness. The residue was recrystallized from toluene.

(±)-5-(2-Phenyl-2-oxoethyl)-3-isoxazolidinone (3a):

Ester **2a**, yield: 76 %, m. p. 152-153 °C (ethyl acetate).

IR (KBr): ν = 3681, 3072, 2972, 1712, 1610 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ =2.40-2.58 (m, 1H), 2.60-2.77 (m,1H), 2.92-3.15 (m, 1H), 3.32-3.55 (m, 1H), 4.88-5.06 (m,1H), 7.16-7.40 (m, 3H), 7.40-7.62(m, 2H) ppm.

$C_{11}H_{11}NO_3$ (205.22). Calcd. %: C 64.38, H 5.40, N 6.83. Found %: C 64.24, H 5.37, N 6.80.

(±)-5-[2-(4-Methoxyphenyl)-2-oxoethyl]-3-isoxazolidinone (3b):

Ester **2b**, yield: 82 %, m. p. 180-182 °C (toluene).

IR (KBr): ν = 3683, 3070, 2975, 1720, 1610 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 2.27-2.43 (m, 1H), 2.46-2.62 (m, 1H), 2.80-2.95 (m, 1H), 3.19-3.32 (m, 1H), 3.58 (s, 3H), 4.81-4.95 (m, 1H), 6.58-6.70 (m, 2H), 7.28-7.39 (m, 2H) ppm.

$C_{12}H_{13}NO_4$ (235.24). Calcd. %: C 61.27, H 5.57, N 5.95. Found %: C 61.01, H 5.44, N 5.76.

(±)-5-[2-(4-Biphenylyl)-2-oxoethyl]-3-isoxazolidinone (3c):

Ester **2c**, yield: 86 %, m. p. 232-234 °C (ethyl acetate).

IR (KBr): ν = 3681, 3075, 2970, 1710, 1615 cm^{-1}.

^{1}H-NMR (DMSO-d_6): δ = 2.60-2.73 (m, 2H), 3.10-3.70 (m, 3H, 1H exchangeable with D_2O), 4.91-5.10 (m, 1H), 7.32-7.83 (m, 9H) ppm .

$C_{17}H_{15}NO_3$ (281.31). Calcd. %: C 72.58, H 5.37, N 4.98. Found %: C 72.29, H 5.17, N 4.66.

(±)-5-[2-(4-Chlorophenyl)-2-oxoethyl]-3-isoxazolidinone (3d):

Ester **2d**, yield 50 %, m. p. 174-175 °C).

IR (KBr): ν = 3681, 3070, 2980, 1705, 1620 cm^{-1}.

^{1}H-NMR (50 % $CDCl_3$ / 50 % DMSO-d_6): δ =2.31-2.46 (m, 1H), 2.46-2.62 (m,

1H), 2.79-2.96 (m, 1H), 3.20-3.38 (m, 1H), 2.78-2.92 (m, 1H), 7.04-7.14 (m, 2H), 7.31-7.42 (m, 2H) ppm.

$C_{11}H_{10}ClNO_3$ (239.66). Calcd. %: C 55.13, H 4.21, N 5.84. Found %: C 54.91, H 4.19, N 5.81.

(±)-5-[2-(3-Bromophenyl)-2-oxoethyl]-3-isoxazolidinone (3e):

Ester **2e**, yield 46 %, m. p. 151-153 °C (toluene).

IR (KBr): ν = 3690, 3077, 2970, 1720, 1600 cm^{-1}.

^{1}H-NMR ($CDCl_3$ / 20 % DMSO-d_6): δ = 2.41-2.55 (m, 1H), 2.55-2.63 (m, 1H), 2.91-3.19 (m, 1H), 3.29-3.48 (m, 1H), 4.88-5.03 (m, 1H), 7.21-7.55 (m, 4H) ppm.

$C_{11}H_{10}BrNO_3$ (284.11). Calcd. %: C 46.50, H 3.55, N 4.93. Found %: C 46. 27, H 3.38, N 4.83.

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