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A CONVENIENT SYNTHESIS OF 3- AND 3,4-SUBSTITUTED 4,5-DIHYDROISOXAZOLE-5-ACETIC ACIDS

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Abstract: *The 4,5-dihydroisoxazole-5-acetic acids* ***4a-j*** *were prepared from the ketoximes* ***1a-j,*** *2,2-dimethyl-5-methoxymethylene-1,3-dioxan-4,6-dione* ***(2)*** *and butyllithium in yields from 35 to 79 %.*

Since 3- and 3,4-substituted 4,5-dihydroisoxazole-5-acetic acids are useful intermediates for the syntheses of antiinflammatory, analgesic and antipyretic isoxazole-5-acetic acids[1,2] we attempted to develop a general method for the synthesis of 4,5-dihydroisoxazole-5-acetic acids with variable substituents at C(3) and C(4). As a result of our work we want to present a convenient regio- and stereoselective synthesis of 3- and 3,4-substituted 4,5-dihydroisoxazole-5-acetic acids, which is applicable even to derivatives with oxygen or sulphur at C(4).

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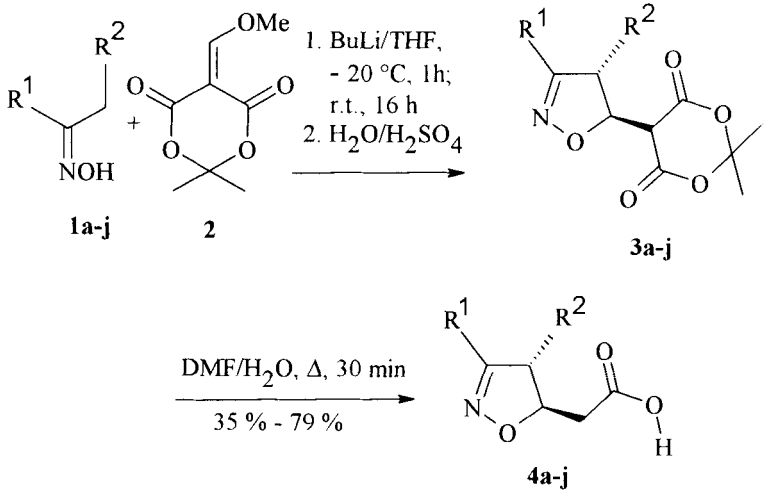
2,2-Dimethyl-5-methoxymethylene-1,3-dioxan-4,6-dione **(2)**[3] was found to react smoothly with the dianions of the ketoximes **1a-j** to give the 4,5-dihydroisoxazoles **3a-j**. Syn- and anti-forms of the ketoximes **1a-j** were both of approximately equal reactivity. The unchanged carbonyl structures in the intermediates **3a-j** indicate, that this reaction proceeds either via 1,4-addition or substitution of the methoxy group in **2**. This is in contrast to the results of Jarrar et al.[4], who describe nucleophilic 1,2-additions of C,O-dilithiated oximes to α,β-unsaturated carbonyl compounds. Only the 4,5-dihydroisoxazole **3c** could be obtained as an analytically pure sample. The 4,5-dihydroisoxazoles **3a,b,d,e,f,g,h,i,j** decomposed during crystallisation or column chromatography on kieselgel. Therefore the 4,5-dihydroisoxazoles **3a-j** were saponified and decarboxylated as crude reaction products to the 4,5-dihydroisoxazole-5-acetic acids **4a-j**. Refluxing dimethylformamide/water as solvent gave the best results for this reaction. Mainly decomposition products were obtained in boiling acidic water/dimethylformamide or water/ethanol or alkaline water/ethanol solutions. The configurations of the substituents at C(4) and C(5) in the 4,5-dihydroisoxazole-5-acetic acids **4b,d,e,f,g,h** could be determined by ^{1}H-NMR-spectroscopy. The coupling constants between the protons at C(4) and C(5) were in the range of 4 - 8 Hz. According to[5] these values are conclusive for trans-coupling at C(4) and C(5) in 4,5-dihydroisoxazoles.

Thin layer chromatography of the reaction mixtures and the ^{1}H-NMR spectra of the crude 4,5-dihydroisoxazole-5-acetic acids **4a-j** gave no indication of cis-

Scheme



1a-j **2** **3a-j** **4a-j**

1,3,4	R^1	R^2
a	Ph	H
b	1,2,3,4-Tetrahydronaphth-1,2-diyl-	
c	CH_3	H
d	$-(CH_2)_4-$	
e	$-(CH_2)_{10}-$	
f	Ph	S–Ph
g	Ph	O–Ph
h	4-Cl–C_6H_4	4-Cl–C_6H_4
i	4-OCH_3-C_6H_4	H
j	4-Ph–C_6H_4	H

products. The described reaction is limited to ketoximes and 2,2-dimethyl-5-methoxy-methylene-1,3-dioxan-4,6-dione **(2)**. Aldoximes (phenylacetaldoxime, acetaldoxime, propionaldoxime) and **2** or ethyl or methyl methoxymethylenemalonate and acetophenonoxime gave only complex reaction mixtures.

Experimental

The ^{1}H-NMR-spectra were recorded with a Bruker 200 FT-NMR spectrometer. Solvent and internal standard: deuterochloroform at 7.26 ppm. All acidic protons (-COOH) gave very broad signals between δ = 10 and 12 ppm.

Butyllithium (1.6 M solution in hexane) was purchased from Aldrich Chemical Co. Anhydrous tetrahydrofuran was obtained by boiling over metallic sodium and distilled prior to use. The oximes **1a-j** were used as mixtures of the Z- and E-forms.

General procedure for the syntheses of 4,5-dihydro-5-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-3-methylisoxazole (3c) and the 4,5-dihydroisoxazole-5-acetic acids (4a-j):

A solution of butyllithium in hexane (97.5 ml, 0.243 mol) was added during 15 min at -20 °C with stirring to a solution of oxime **1a-j** (0.111 mol) in dry tetrahydrofuran (120 ml). After 1 h at -20 °C 2,2-dimethyl-5-methoxymethylene-1,3-dioxan-4,6-dione **(2)** (20.66 g, 0.111 mol) dissolved in dry tetrahydrofuran (200 ml) was added below 0 °C. After additional stirring for 1 h at 0 °C and then for another hour at r.t. the reaction mixture was poured into water (300 ml) and extracted with ether (3 x 100 ml). The aqueous layer was acidified with 5 N

sulphuric acid (150 ml) and extracted with ether (4 x 100 ml). The combined ether extracts were dried with anhydrous sodium sulphate and concentrated under reduced pressure to give **3a-j**.

Pure **3c** was obtained by crystallisation. For the preparation of **4a-j** the crude residue was refluxed in a mixture of dimethylformamide (30 ml) and water (4 ml) for 30 min. This reaction mixture was diluted with water (200 ml) and extracted with ether (3 x 100 ml). The combined organic layers were extracted with saturated sodium hydrogencarbonate solution (4 x 100 ml). The sodium hydrogencarbonate extracts were acidified with 5 N sulphuric acid and extracted with ether (3 x 50 ml). This ether extracts were combined, dried with anhydrous sodium sulphate and evaporated to dryness. The residue was recrystallised from the appropriate solvent.

(±)-trans-3-Methyl-5-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-4,5-dihydroisoxazole (3c):

Oxime **1c**[6], yield: 47 %, m. p. 137 °C (dec.) (ethylacetate).

^{1}H-NMR: δ = 1.75 (s, 3H), 1.83 (s, 3H), 2.00 (s, 3H), 3.15-3.52 (m, 2H), 3.63 (d, 1H, J = 4 Hz, H(5)) ppm.

$C_{10}H_{13}NO_5$ (227.22). Calcd. %: C 52.86, H 5.77, N 6.16. Found %: C 52.70, H 5.83, N 6.01.

(±)-3-Phenyl-4,5-dihydroisoxazole-5-acetic acid (4a):

Oxime **1a**[7], yield: 35%, m. p. 156 °C (ethylacetate).

^{1}H-NMR: δ = 2.60-2.80 (m, 1H), 2.85-3.00 (m, 1H), 3.10-3.15 (m, 1H), 3.48-

3.72 (m, 1H), 5.05- 5.22 (m, 1H), 7.37-7.49 (m, 3H), 7.61-7.73 (m, 2H) ppm.

$C_{11}H_{11}NO_3$ (205.21). Calcd. %: C 64.38, H 5.40, N 6.83. Found %: C 64.52, H 5.33, N 6.75.

(±)-trans-3,3a,4,5-Tetrahydronaphtho[1,2-c]isoxazole-3-acetic acid (4b):

Oxime **1b**[8], yield: 79 %, m. p. 162-163 °C (toluene).

^{1}H-NMR: δ = 1.80-2.05 (m, 1H), 2.27-2.42 (m, 1H), 2.71-3.10 (m, 3H), 3.21 (dd, J = 16 and 7, CHCOOH, 1H), 3,30 (dd, J = 16 and 6, CHCOOH, 1H), 4.58 (ddd. J = 6 and 7 and 8, H(5), 1H), 7.14-7.39 (m, 3H), 7.81-7.99 (m, 1H) ppm.

$C_{13}H_{13}NO_3$ (231.25). Calcd. %: C 67.52, H 5.67, N 6.06. Found %: C 67.61, H 5.55, N 6.11.

(±)-3-Methyl-4,5-dihydroisoxazole-5-acetic acid (4c):

Oxime **1c**[6], yield: 60 %, m. p. 97 °C (diisopropylether).

^{1}H-NMR: δ = 2.00 (s, 3H), 2.51-2.89 (m, 3H), 3.12-3.26 (m, 1H), 4.82-5.01 (m, 1H) ppm.

$C_6H_9NO_3$ (143.14). Calcd. %: C 50.35, H 6.34, N 9.79. Found %: C 50.46, H 6.35, N 9.80.

(±)-trans-3,3a,4,5,6,7-Hexahydrobenzo[c]isoxazole-3-acetic acid (4d):

Oxime **1d**[9], yield: 44 %, m. p. 97 °C (toluene).

^{1}H-NMR: δ = 1.21-2.28 (m, 8H), 2.65 (dd, J = 16 and 7, CHCOOH, 1H), 2.88 (dd, J = 16 and 6, CHCOOH, 1H) 2.75-2.84 (m, 1H), 4.58-4.71 (ddd, J = 6 and 7 and 8, 1H, H(5)) ppm.

$C_9H_{13}NO_3$ (183.21). Calcd. %: C 59.00, H 7.15, N 7.65. Found %: C 58.84, H 7.04, N 7.73.

(±)-trans-3,3a,4,5,6,7,8,9,10,11,12,13-Dodecahydro-3-acetic acid (4e):

Oxime **1e**[10], yield: 72 %, m. p. 159-162 °C (toluene).

^{1}H-NMR: δ = 1.0-2.1 (m, 18H), 2.20-2.45 (m, 2H), 2.48 (dd, J = 16 and 7, 1H), 2.74 (dd, J = 16 and 6, 1H), 3.00 (m, 1H, H(4)), 4,64 (ddd, J = 6 and 7 and 8, 1H, H(5)) ppm.

$C_{15}H_{25}NO_3$ (267.37). Calcd. %: C 67.38, H 9.42, N 5.24. Found %: C 67.49, H 9.50, N 5.27.

(±)-trans-3-Phenyl-4-phenylthio-4,5-dihydroisoxazole-5-acetic acid (4f):

Oxime **1f**[11], yield: 44 %, m. p. 127-130 °C (diisopropylether).

^{1}H-NMR: δ = 2.61 (dd, J = 16 and 7, C<u>H</u>COOH, 1H), 2.88 (dd, J = 16 and 6, C<u>H</u>COOH, 1 H) 4.65 (d, 1H, J = 4 Hz, H(4)), 5.19 (ddd, J = 4 and 6 and 7, 1H, H(5)), 7.21-7.51 (m, 8H), 7.71-7.92 (m, 2H) ppm.

$C_{17}H_{15}NO_3S$ (313.37). Calcd. %: C 65.16, H 4.82, N 4.47. Found %: C 65.22, H 4.67, N 4.53.

(±)-trans-3-Phenyl-4-phenoxy-4,5-dihydroisoxazole-5-acetic acid (4g):

Oxime **1g**[12], yield: 56 %, m. p. 113-129 °C (toluene).

^{1}H-NMR: δ = 2.77 (dd, J = 16 and 3, C<u>H</u>COOH, 1H), 2.97 (dd, J = 16 and 3, C<u>H</u>COOH, 1H), 5.11 (ddd, 1H, J = 3 and 3 and 4, H(5)), 5.83 (d, 1H, J = 4, H(4)), 6.85-7.82 (m, 10H) ppm.

$C_{17}H_{15}NO_4$ (297.31). Calcd. %: C 68.68, H 5.09, N 4.71. Found %: C 68.99, H 4.86, N 4.77 .

(±)-trans-3,4-Bis-(4-chlorphenyl)-4,5-dihydroisoxazol-5-acetic acid (4h):

Oxime **1h**[13], yield: 61 %, m. p. 108-110 °C (toluene).

^{1}H-NMR: δ = 2.75 (dd, J = 16 and 7, C<u>H</u>COOH, 1H), 2.91 (dd, J = 16 and 6, C<u>H</u>COOH, 1H), 4.52 (d, 1H, J = 4 Hz, H(4)), 4.89 (ddd, J = 4 and 6 and 7, 1H, H(5)), 7.08-7.57 (m, 8H) ppm.

$C_{17}H_{13}Cl_2NO_3$ (350.20). Calcd. %: C 58.31, H 3.74, N 4.00. Found %: C 58.52, H 3.74, N 4.26.

(±)-3-(4-Methoxyphenyl)-4,5-dihydroisoxazol-5-acetic acid (4i):

Oxime **1i**[14], yield: 43 %, m. p. 182-183 °C (toluene).

^{1}H-NMR: δ = 2.49-2.68 (m, 2H), 3.05-3.60 (m, 2H), 3.81 (s, 3H), 4.84-5.02 (m, 1H), 7.00 (d, 2H, J = 10 Hz), 7.61 (d, 2H, J = 10 Hz) ppm.

$C_{12}H_{13}NO_4$ (235.24). Calcd. %: C 61.27, H 5.57, N 5.95. Found %: C 61.29, H 5.51, N 5.88.

(±)-3-(4-Biphenylyl)-4,5-dihydroisoxazol-5-acetic acid (4j):

Oxime **1j**[15], yield: 70 %, m. p. 230-232 °C (methanol).

^{1}H-NMR: δ = 2.10-3.65 (m, 4H), 4.57-4.87 (m, 1H), 6.84-7.42 (m, 9H) ppm.

$C_{17}H_{15}NO_3$ (281.31).Calcd. %: C 72.58, H 5.37, N 4.98. Found %: C 72.67, H 5.18, N 4.76.

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