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2,5-Dihydro-4-hydroxymethyl-1,3-oxazoles by Asinger Condensation

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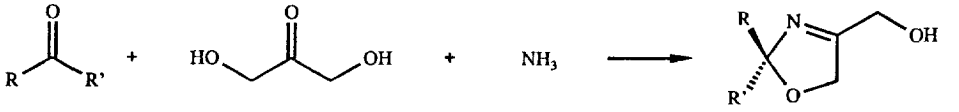
Abstract: In this article* a simple Asinger type one-pot synthesis of 2,5-dihydro-4-hydroxymethyl-1,3-oxazoles is described in six examples. The resulting oxazoles are interesting intermediates in organic synthesis.

Oxazoles and partially reduced oxazoles play an important role as intermediates in preparative organic chemistry[1] as well as in natural products.[2] In contrast to 4,5-dihydro oxazoles, the 2,5-dihydro oxazoles have not sufficiently been investigated.[3] The best method for synthesis of 2,5-dihydro-1,3-oxazoles is an Asinger-type condensation,[4] which is also an important method in the synthesis of 2,5-dihydro thiazoles,[5] 2,5-dihydro-1,3-imidazolidines,[6] 5,6-dihydro-*2H*-1,3-thiazines,[7] 1,2,5,6-tetrahydro-1,3-pyrimidines[8] as well as of 5,6-dihydro-*2H*-1,3-oxazines.[9] The title compounds are thus easily obtained by a one-pot procedure. Due to Asinger's condensations taking place with a high number of otherwise interfering functionalities,[10] Asinger heterocycles have proved to be valuable intermediates in organic synthesis, for example in the synthesis of ß-lactam antibiotics.[11]

We found that dihydroxy acetone dimer forms 2,5-dihydro-4-hydroxymethyl-1,3-oxazoles with ammonia and a great variety of aldehydes and ketones. Depending on the used oxo compound, the yields are between 18% and 100% (Scheme 1, Table 1). These reactions work particularly well as one-pot procedures.



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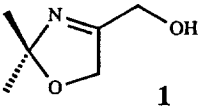
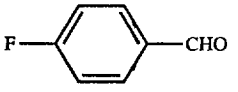
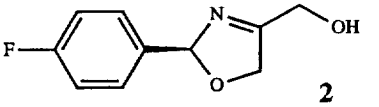
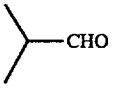
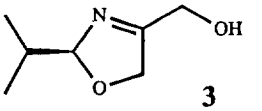
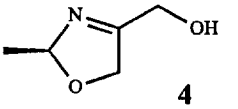
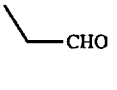
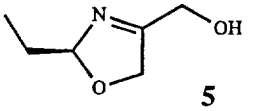
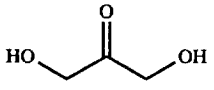
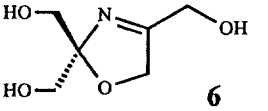
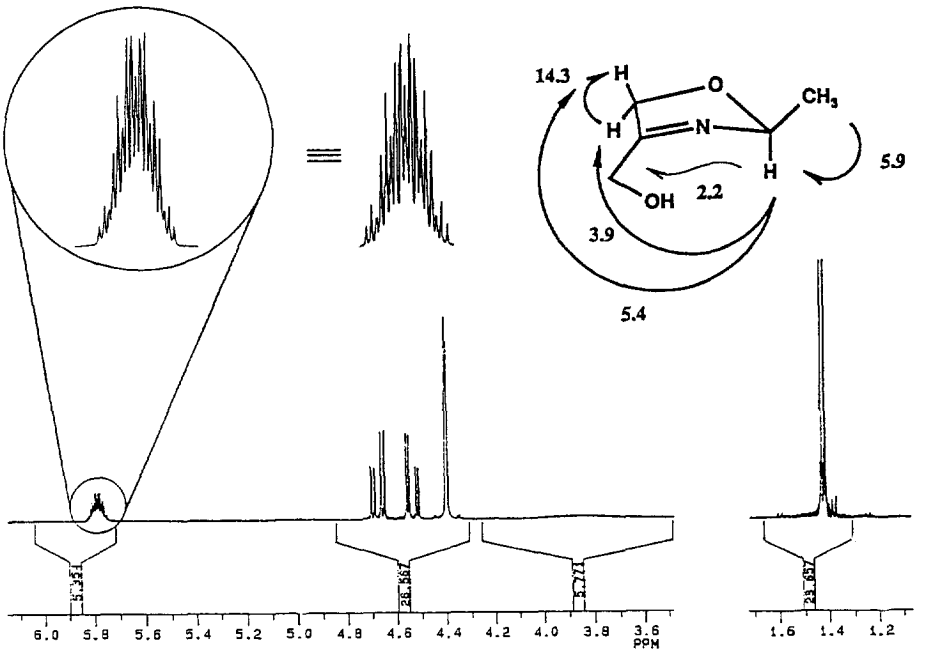
Scheme 1.: 2,5-Dihydro-4-hydroxymethyl-1,3-oxazoles can easily be produced by a one-pot Asinger multi component reaction.

Table 1.: Yields and oxo components of prepared 2,5-dihydro-4-hydroxymethyl-1,3-oxazoles.

Oxo compound	Yield (%)	Asinger Product	No
	19		1
	18		2
	77		3
	28		4
	43		5
	100		6

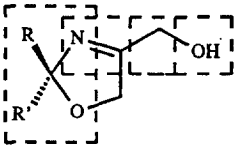
In the case of low molecular-weight oxo components the products are volatile liquids which cannot be distilled due to dehydration. After standing for some time at room temperature, they generally darken markedly and decompose.

A characteristic feature of the title compounds is seen in their ^{1}H NMR spectra. Therein the proton in 2-position of 2,5-dihydro-4-hydroxymethyl-1,3-oxazoles derived from an aldehydic oxo compound generally shows couplings to the diastereotopic protons of the methylene group in the ring as well as to the exocyclic methylene group, resulting in a complex multiplet (Scheme 2). The shown assignments were confirmed by computer simulation.



Scheme 2.: ^1H NMR of a typical 2,5-dihydro-4-hydroxymethyl-1,3-oxazole. Bottom: ^1H NMR (360 MHz) of 2,5-dihydro-4-hydroxymethyl-2-methyl-1,3-oxazole. Top from left to right: expansion of the proton in 2-position, simulation of the corresponding multiplet, found coupling constants.

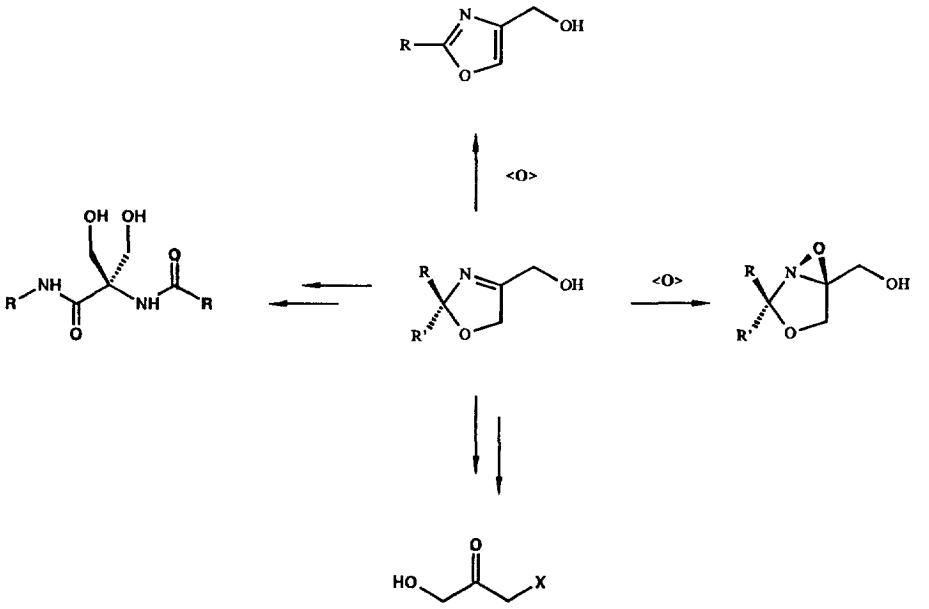
Important from a synthetic viewpoint is the central moiety of the 2,5-dihydro-4-hydroxymethyl-1,3-oxazoles, which contains a set of seven atoms others then hydrogen consisting of as much as four different functional groups (Scheme 3): an O,N-acetal, a hydroxy group, an imine group and a hetero allylic alcohol.



Scheme 3.: The functions of the 2,5-dihydro-4-hydroxymethyl-1,3-oxazoles.

The O,N-acetal may serve as a protecting group for one side of dihydroxy acetone during synthetic operations. Investigations are running towards an asymmetric Sharpless like epoxidation of the hetero allylic alcohol part of the molecule. Nucleophilic substitution reactions of the hydroxy group as its sulfonate derivative are expected to run easily because of the allyl-like moiety. The imine functionality should work

particularly well in multi component reactions such as the Ugi four component reaction (U-4CR), leading to unnatural 1,1-dihydroxymethyl amino acid containing peptides which are otherwise accessible only with difficulty. Last but not least, 2-mono substituted 2,5-dihydro-4-hydroxymethyl-1,3-oxazoles should be easily oxidisable to the aromatic 1,3-oxazoles (Scheme 4).



Scheme 4.: Chemistry of 2,5-dihydro-4-hydroxymethyl-1,3-oxazoles under investigation.

The herein described highly functionalized 2,5-dihydro-4-hydroxymethyl-1,3-oxazoles may in future play an important role as intermediates in organic synthesis.

Experimental

Dihydroxy acetone (Merck) was used without further purification. The volatile oxo components were freshly distilled before usage.

General procedure (100 mmol scale):
To a solution of 100 mmol oxo component in 20 ml of concentrated ammonia and 100 ml of chloroform a solution of (9 g, 100 mmol) dihydroxy acetone in 100 ml methanol is added in 5 portions at 0°C (in the case of **4** twice the amount, in the case of **1** five times of the amount of oxo component were used; in case of **2** twice the amount of dihydroxy acetone were used). After stirring for 18 h at 22 °C, two thirds of the solvent were evaporated at 22 °C and 14 torr. 50 ml of water were added and the two phases were separated. The water phase was extracted twice with 50 ml chloroform and the combined organic phases were dried with $MgSO_4$. The solvent was evaporated at 22°C and 14 torr. The liquid residue was the pure 2,5-dihydro-4-hydroxymethyl-1,3-oxazole **1** or **3** - **6**.
The product **2** is treated by 50 ml cyclohexane and 5 ml of ethyl acetate. After refrigerating for 1 d, the colourless crystals were collected.
All products were at least 95% pure according to ^{1}H NMR, GC and TLC. Due to rapid decomposition, no elemental analyses were taken, except for stable crystalline **2**.

2,5-Dihydro-4-hydroxymethyl-2,2-dimethyl-1,3-oxazole (1)
$C_6H_{11}NO_2$ = 129.16 gmol^{-1}. 2.4 g colorless oil (18.6 %). ^{1}H-NMR ($CDCl_3$, 360 MHz): 1.44 (s, 6H), 4.06 (s, br, 1H, -OH), 4.39 (s, 2H), 4.64 (s, 2H). ^{13}C-NMR ($CDCl_3$, 90 MHz): 26.9, 59.5, 73.1, 109.5, 170.9. EI-MS: 114 (80%), 99 (8%), 84 (46%), 72 (40%), 69 (16%), 42 (100%). CI-MS: 130 (MH^+).

2,5-Dihydro-4-hydroxymethyl-2-(4´-fluorphenyl)-1,3-oxazole (2)
$C_{10}H_{10}NO_2F$= 195.19 gmol^{-1}. 3.5g colorless crystalls (18%). R_f (EE, H, 1:1, V:V) = 0.46. Mp.: 80°C. ^{1}H-NMR ($CDCl_3$, 360 MHz): 2.84 (s, br, 1H), 4.46 (d, 2H, ^3J = 2.15 Hz), 4.69 (dd, 1H, ^2J = 14.2 Hz, ^4J = 4.0 Hz), 4.80 (dd, 1H, ^2J = 14.2 Hz, ^4J = 5.3 Hz), 6.61 (m, 1H), 7.06 (m, 2H), 7.38 (m, 2H). ^{13}C-NMR ($CDCl_3$, 90 MHz): 59.9, 74.3, 105.7, 115.2, 115.5, 127.9, 130.0, 135.2, 173.5. ^{19}F-NMR ($CDCl_3$, 250 MHz): -35.6 (trtr, $^3J_{F-H}$ = 8.4 Hz, $^4J_{F-H}$ = 4.6 Hz). EI-MS: 195 (M^+ 18%), 208 (56%), 166 (100%). Elementar analysis: found: C, 60.35; H, 5.74; N, 7.03. calc.: C, 60.53; H, 5.46; N, 7.18.

2,5-Dihydro-4-hydroxymethyl-2-*iso*propyl-1,3-oxazole (3)
$C_7H_{13}NO_2$ = 143.18 gmol^{-1}. 11.1 g colorless liquid (77 %). R_f ($CHCl_3$, EtOH, 9:1, V:V) = 0.46. ^{1}H-NMR ($CDCl_3$, 360 MHz): 0.94 (d, 3H, ^3J = 4.6 Hz), 0.96 (d, 3H, ^3J = 4.6 Hz), 1.94 (m, 1H), 3.92 (s, br), 4.40 (s, 2H), 4.55 (dd, 1H, ^2J = 14.2 Hz, ^4J = 4.1 Hz), 4.61 (dd, 1H, ^2J = 14.2 Hz, ^4J = 5.56 Hz), 5.48 (m, 1H). ^{13}C-NMR ($CDCl_3$, 90 MHz): 16.4, 17.2, 33.3, 59.6, 73.9, 110.4, 173.1. EI-MS: 143 (M^+).

2,5-Dihydro-4-hydroxymethyl-2-methyl-1,3-oxazole (4)
$C_5H_9NO_2$ = 155,13 gmol^{-1}. 3.2 g colorless liquid (28 %). R_f ($CHCl_3$, EtOH, 9:1, V:V) = 0.37. ^{1}H-NMR ($CDCl_3$, 360 MHz): 1.42 (tr, 3H, ^3J = 5.9 Hz), 4.40 (dd, 2H, ^4J = 2.2 Hz, ^4J = 0.4 Hz), 4.52 (dd, 1H, ^4J = 3.9 Hz, ^2J = 14.1 Hz), 4.67 (dd, 1H, ^4J = 5.3 Hz, ^4J = 14.1 Hz), 5.79 (m, 1H). ^{13}C-NMR ($CDCl_3$, 90 MHz): 21.5, 59.6, 73.5, 102.9, 172.6. EI-MS: 155 (M^+).

2,5-Dihydro-4-hydroxymethyl-2-ethyl-1,3-oxazole (5)
$C_6H_{11}NO_2$ = 129.16 gmol^{-1}. 5.5 g colorless liquid (43 %). R_f ($CHCl_3$, EtOH, 9:1, V:V) = 0.44. ^{1}H-NMR ($CDCl_3$, 360 MHz): 0.96 (tr, 3H, ^3J = 11.3 Hz), 1.74 (m, 2H), 4.40 (s, 2H), 4.53 (dd, 1H, ^2J = 14.0 Hz, ^4J = 3.9 Hz), 4.62 (dd, 1H, ^2J = 14.0 Hz, ^4J = 5.44 Hz), 5.65 (m, 1H). ^{13}C-NMR ($CDCl_3$, 90 MHz): 8.0, 28.4, 59.4, 73.8, 107.1, 173.0. EI-MS: 129 (M^+).

2,5-Dihydro-2,2,4-tri-(hydroxymethyl)-1,3-oxazole (6)
$C_6H_{11}NO_4$ = 161.15 gmol^{-1}. 15.8 g colorless oil (98%). ^{1}H-NMR (d_6-DMSO, 360 MHz): 3.45 (s, 4H), 4.25 (s, 2H), 4.57 (s, 2H). ^{13}C-NMR (d_6-DMSO, 90 MHz): 59.2, 63.6, 75.1, 113.3, 174.3. EI-MS: 161 (M^+).

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*) This article we dedicate to the 65th birthday of **Alan R. Katrizky**.

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