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A NEW 5,6-DIHYDRO-2*H*-1,3-OXAZINE SYNTHESIS VIA ASINGER-TYPE CONDENSATION

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Abstract: In this article - which we dedicate to the lifework[1] of **Professor Teruaki Mukaiyama** - a new general 5,6-dihydro-2*H*-1,3-oxazine synthesis is described. 3-Hydroxy-2,2-dimethylpropionaldehyde is condensed with a second oxo component and ammonia to the title compound in several examples. In the case of citronellal diastereoselectivity is observed.

Many heterocycles are available through Asinger condensations. These are 2,5-dihydro-1,3-thiazolines (**1**),[2] 5,6-dihydro-2*H*-1,3-thiazines (**2**),[2] 1,2,5-trihydro-1,3-imidazolines (**3**),[2] 1,2,5,6-tetrahydro-1,3-pyrimidines (**4**)[2] and 2,5-dihydro-1,3-oxazolines (**5**)[3] (Figure 1). This general synthesis is highly versatile: Hundreds of compounds have been made.

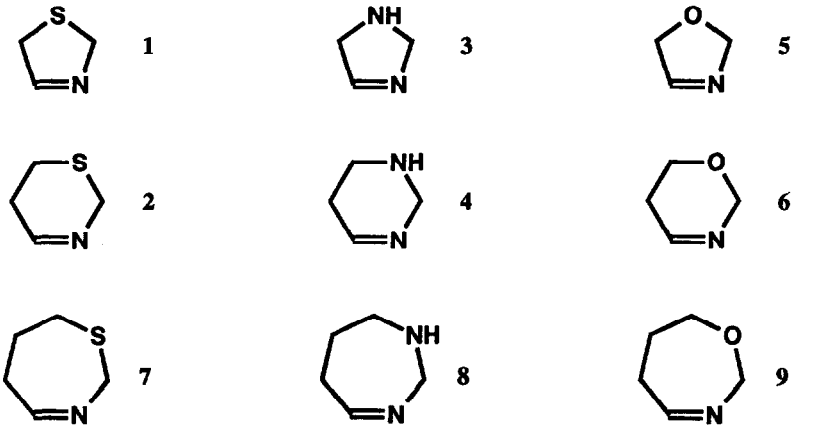


Figure 1 Through Asinger condensation available heterocycles 1-6.

In the context of our investigations to extend the seven component reaction[4] to other heterocyclic systems we found a new simple approach to the hitherto little known class of 5,6-dihydro-2*H*-1,3-oxazines (**6**) via an Asinger-type condensation. Despite their potential value as intermediates in organic synthesis and their technological importance,[5] only one general 5,6-dihydro-2*H*-1,3-oxazine synthesis - which is complimentary to ours - has been reported.[6] Several alkaloids as for example nitraramine from *Nitraria sp.*, demethylxestospongin or haematopodin from *Mycena haematropus*,[7] containing an oxazine subunit are known.

Our new synthesis is quite simple and can easily be performed on a multigram scale. All described products are worked up through simple distillation. A ß-hydroxyaldehyde component reacts with a second oxo component and ammonia under dehydration (Figure 2). Many aliphatic aldehydes and ketones can act as oxo compound.

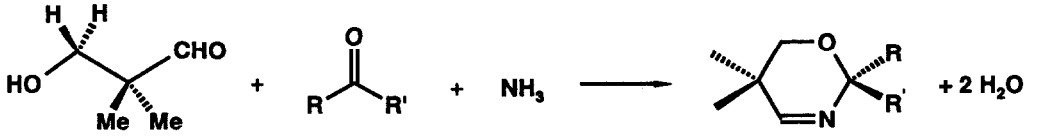


Figure 2 Stoichiometry of the Asinger condensation.

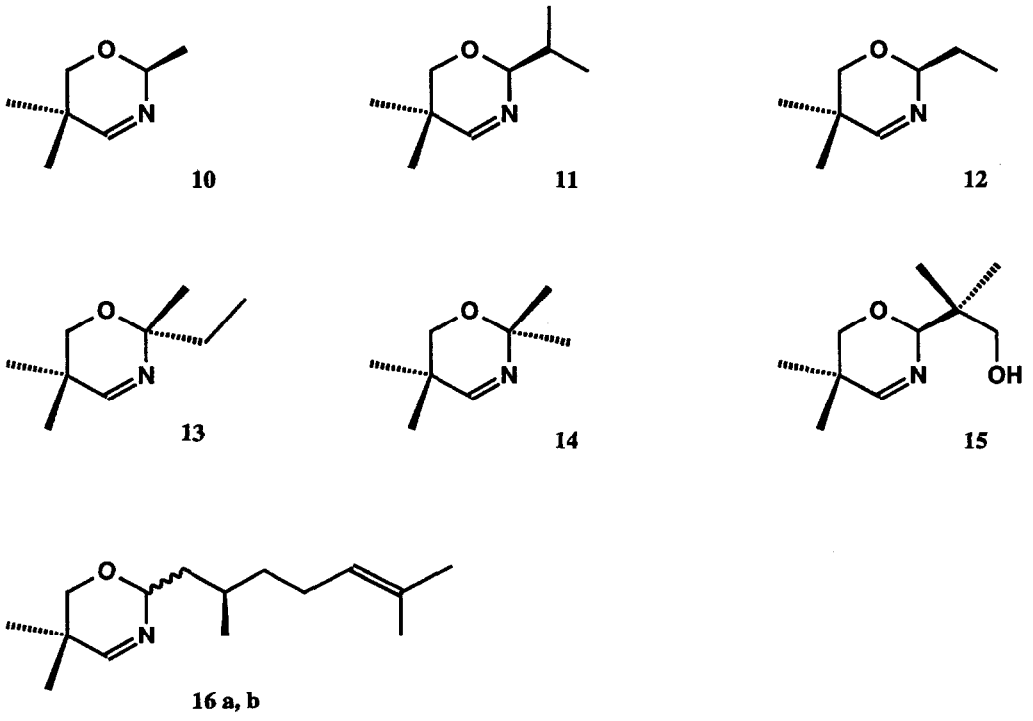


Figure 3 5,6-Dihydro-2*H*-1,3-oxazines prepared via Asinger condensation.

Condensation of *technical* 3-hydroxy-2,2-dimethylpropionaldehyde as ß-hydroxyaldehyde component with several oxocompounds furnishes the corresponding oxazines (**10 - 16a, b**) in up to 50% yield (Figure 3).

Despite several attempts we were not able to condense formaldehyde neither in its aqueous, polymeric or trimeric form in higher yields. Generally, aliphatic aldehydes gave better yields than ketones. Therefore the latter must be used in excess to get good yields. In the case of aromatic aldehydes selfcondensation to **15** is much faster. Thus only traces of condensation products could be obtained with benzaldehyde, p-fluorobenzaldehyde or furfurol. If a ß-hydroxyketone is employed, no reaction at all takes place (Figure 4).

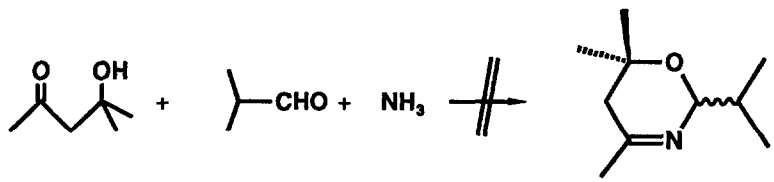
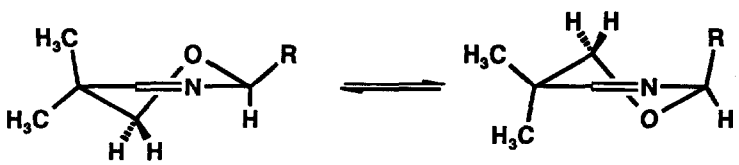


Figure 4 ß-Hydroxyketones do not undergo Asinger condensation.

When citronellal is brought to reaction with 3-hydroxy-2,2-dimethylpropionaldehyde both the p- and n-products[8] **16a, b** result in a ratio[9] of 1:2. This is remarkable, because the inducing stereogenic center is several bonds apart from the new formed stereocenter. We were not able to determine the relative configuration of the two diastereomers.

The oxazines **10 - 14** are - when freshly distilled - volatile colorless liquids and perform an intensive woodlike odour[10] while **p-** and **n-16** perform a slightly lemonlike smell. Their IR spectra have a characteristic imine stretching band at 1650 - 1660 cm^{-1}. Typically, the iminecarbon absorbs at about 165 ppm in ^{13}C-NMR spectrum. Diastereomeric oxazines show an interesting behaviour in ^{1}H-NMR spectroscopy: Imineproton coupling with one of the two protons of the cyclic methylene group through four bonds is observed. Consequently, one proton shows a doublet by geminal coupling, while the doublet of the other methylene proton is split up into a double doublet by longrange coupling with the imineproton. Similar effects are known from sterically fixed systems with a W- or M-like conformation of the coupling protons. We assume diastereomeric oxazines to exist mostly as conformere I (Figure 5).



I II

Figure 5 Two possible conformeres of oxazines.

Future attention will be directed to extend Asinger condensation to the seven-membered rings **7**, **8** and **9** and to introduce oxazine rings in seven component reaction.[4]

EXPERIMENTAL

3-Hydroxy-2,2-dimethylpropionaldehyde (Aldrich, techn., 70%) and (-)-Citronellal (Fluka, techn., 85 - 90%) were used without further purification. Acetaldehyde was freshly distilled before usage. All other oxo components were used without further purification of the commercial products.

Typical procedure:

14.6 g (0.1 mol) of technical 70% 3-hydroxy-2,2-dimethylpropionaldehyde (Aldrich) in 80 ml chloroform are slowly added to a solution of 5.6 ml (0.1 mol) of acetaldehyde (in the case of **13** and **14** the ketone component is used in fivefold excess) in 10 ml of concentrated ammonia at 0 °C. After stirring for 18 h at 22 °C, 50 ml of water is added and the two phases are separated. The waterphase is extracted two times with 50 ml of ethyl acetate and the combined organic phases are dried with $MgSO_4$. The solvents are evaporated in vacuo and the residue is distilled at 14 Torr to give 6.5 g of 5,6-dihydro-2,5,5-trimethyl-2*H*-1,3-oxazine (50%) at 45°C.

All products except **11** were >95% pure according to GC-MS and ^{1}H-NMR and gave the correct $[MH]^+$-peak in the CI-MS. **11** can not be seperated of a compound with MW = 125 g/mol and is assumed to be > 80% pure by GC-MS and NMR. All oxazines are stored at 4°C under nitrogen for several months without any significant ^{1}H-NMR-provable decomposition. However, they get highly colored after several weeks.
All reactions were performed on a 100 mmol scale.

5,6-Dihydro-2,5,5-trimethyl-2*H*-1,3-oxazine (10)

^{1}H-NMR (360 MHz): 0.98 (s, 3H), 1.15 (s, 3H), 1.41 (d, 3H, ^{3}J = 6.5 Hz), 3.46 (d, 1H, ^{2}J = 11.0 Hz), 3.66 (dd, 1H, ^{2}J = 11.0 Hz, ^{4}J = 1.6 Hz), 4.88 (dq, 1H, ^{3}J = 6.2 Hz, ^{4}J = 2.5 Hz), 7.47 (tr, 1H, ^{4}J = ^{4}J = 2.5 Hz); ^{13}C-NMR (90 MHz): 22.1, 22.3, 23.8, 33.1, 72.2, 84.8, 166.3; IR (film): 1650 cm^{-1}; Bp.: 45°C, 14 Torr; Yield: 6.5 g (50%); $C_7H_{13}NO$ = 127.19 g/mol;

2-Ethyl-5,6-dihydro-2,5,5-trimethyl-2*H*-1,3-oxazine (13)

^{1}H-NMR (360 MHz): 0.91 (tr, 3H, ^{3}J = 7.5 Hz), 1.02 (s, 3H), 1.08 (s, 3H), 1.35 (s, 3H), 1.72 (q, 2H, ^{3}J = 7.5 Hz), 3.49 (dd, 1H, ^{2}J 11.3 Hz, ^{4}J = 1.3 Hz), 3.56 (d, 1H, ^{2}J = 11.3 Hz), 7.47 (d, 1H, ^{4}J = 1.0 Hz; ^{13}C-NMR (90 MHz): 7.9, 23.1, 23.4, 24.3, 32.6, 33.3, 67.7, 88.5, 165.4; IR (film): 1657 cm^{-1}; Bp.: 80°C, 14 Torr; Yield: 2.6 g (16%); $C_9H_{17}NO$ = 155.24 g/mol.

5,6-Dihydro-2,2,5,5-tetramethyl-2*H*-1,3-oxazine (14)

^{1}H-NMR (200 MHz): 1.05 (s, 6H), 1.41 (s, 6H), 3.54 (s, 2H), 7.42 (s, 1H); ^{13}C-NMR (50 MHz): 23.0, 27.1, 32.5, 67.8, 86.5, 164.9; IR (film): 1655 cm^{-1}; Bp.: 50°C, 14 Torr; Yield: 2.8 g (20%); $C_8H_{15}NO$ = 141.21 g/mol.

2-Ethyl-5,6-dihydro-5,5-dimethyl-2*H*-1,3-oxazine (12)

^{1}H-NMR (360 MHz): 0.99 (s, 3H), 1.01 (tr, 3H, ^{3}J= 7.3 Hz), 1.5-1.85 (m, 2H), 3.45 (d, 1H, ^{2}J = 11.0 Hz), 3.66 (dd, 1H, ^{4}J = 2.0 Hz, ^{2}J = 11.0 Hz), 4.71 (dtr, 1H, ^{3}J = 5.5 Hz, ^{4}J = 2.5 Hz), 7.50 (tr, 1H, ^{4}J = ^{4}J = 2.2 Hz); ^{13}C-NMR (90 MHz): 8.5, 22.5, 23.9, 33.5. 72.5, 89.1, 170.0; IR (film): 1652 cm^{-1}; Bp.: 64°C, 14 Torr; Yield: 3.7 g (26%); $C_8H_{15}NO$ = 141.21 g/mol.

5,6-Dihydro-5,5-dimethyl-2-*i*-propyl-2*H*-1,3-oxazine (11)

^{1}H-NMR (360 MHz): 0.96 - 1.00 (m, 9H), 1.14 (s, 3H), 1.94-2.12 (m, 1H), 3.44 (d, 1H, ^{2}J = 11.0 Hz), 3.66 (dd, 1H, ^{2}J = 11.0 Hz, ^{4}J = 2.1 Hz), 4.58 (dd, 1H, ^{4}J = 2.7 Hz, ^{3}J = 3.9 Hz), 7.53 (tr, 1H, ^{4}J = ^{4}J = 2.3 Hz); ^{13}C-NMR (90 MHz): 16.8, 17.4, 22.5, 33.2, 33.6, 72.7, 92.1, 167.3; IR (film): 1652 cm^{-1}; Bp.: 72°C, 14 Torr; Yield: 8.8 g (57%); $C_9H_{17}NO$ = 155.24 g/mol.

5,6-Dihydro-2-(2-hydroxy-1,1-dimethylethyl)-5,5-dimethyl-2*H*-1,3-oxazine (15)

^{1}H-NMR (360 MHz): 0.92 (s, 3H), 0.94 (s, 3H), 0.96 (s, 3H), 1.14 (s, 3H), 3.35 (d, 1H, ^{2}J = 11.2 Hz), 3.43 (d, 1H, ^{2}J = 11.1 Hz), 3.61 (d, 1H, ^{2}J = 11.2 Hz), 3.67 (dd, 1H, ^{2}J = 11.0 Hz, ^{4}J = 2.2 Hz), 4.51 (d, 1H, ^{4}J = 2.6 Hz), 7.51 (tr, 1H, ^{4}J = ^{4}J = 2.4 Hz); ^{13}C-NMR (90 MHz): 17.8, 21.1, 22.3, 23.9, 33.6, 39.6, 70.9, 72.6, 94.4, 167.7; IR (film): 1660 cm^{-1}; Bp.: 90-100 °C, 0.2 Torr; Mp.: 63°C; Yield: 3.7 g (20%); $C_{10}H_{19}NO_2$ = 185.27 g/mol.

5,6-Dihydro-2-(2,5-dimethyl-hept-5-enyl)-5,5-dimethyl-2*H*-1,3-oxazine (16a,b)

Mixture of diasteromers:

^{1}H-NMR (360 MHz): 0.82 - 1.92 (m, 22 H), 3.34 -3.38 (m, 1H), 3.56 - 3.59 (m, 1H), 4.69 - 4.77 (m, 1H), 5.01 - 5.05 (m, 1H), 7.39 (m, diastereomer I), 7.43 (m, diastereomer II); ^{13}C-NMR (90 MHz): 17.6, 17.9, 19.3, 19.9, 21.1, 22.5, 22.6, 23.9, 25.6, 25.7, 28.6, 28.8, 33.5, 36.9, 37.6, 39.7, 43.4, 72.3, 72.4, 72.5, 86.7, 86.9, 94.3, 124.9, 130.9, 166.5, 167.5; the diastereomers could be enriched via distillation with a 30 cm vacuum sealed Vigreux column; Bp.: 104-115°C, 0.1 Torr; Yield: 5.9 g (25%); $C_{15}H_{27}NO$ = 237.39 g/mol.

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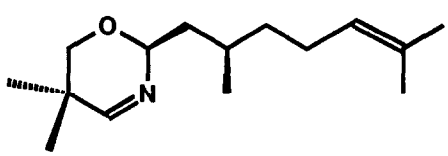
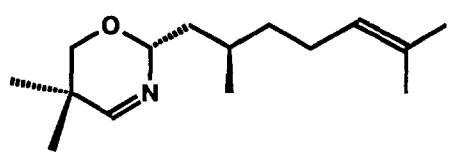
8. According to priority rule we prefer the older pn-nomenclature over the more common ullc-nomenclature, which was introduced many years later: analogously to mathematics ((-) x (-) = (+) x (+) = (+) and (-) x (+) = (+) x (-) = (-)) a diastereomer is called **p** (=positive) if the two stereocenters have the same absolute configuration: **S x S = p** or **R x R = p**, a diastereomer is called **n** (=negative) if the two stereocenters have opposite absolute configuration: **R x S = n** or **S x R = n**.
I.Ugi, *Z. Naturforsch.*, **1965**, *20B*, 405; D.Seebach, V.Prelog, *Angew. Chem., Int. Ed. Engl.*, **1982**, *21*, 654; I.Ugi, *Nachr. Chem. Techn. Lab.*, **1983**, *31*, 276.



S x R = n-16



R x R = p-16

9. The diastereomeric ratio was determined by ^{1}H-NMR: The only peak showing a characteristic shift difference is the iminepeak (7.39 ppm vs. 7.43 ppm).
10. "On the other hand, everyday language would soon prove inadequate for designating all the olfactory notions that he had accumulated within himself. Soon he was no longer smelling mere wood, but kinds of wood: maple-wood, pear-wood, old, young, rotting, mouldering, mossy wood ..."; Patrick Süskind, Perfume - The Story of a murderer, Penguin Books, London, 1987