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The Formation of β-Lactam Derivatives and a C_3-Symmetrical Heterocycle from 5,6-Dihydro-2*H*-1,3-oxazines

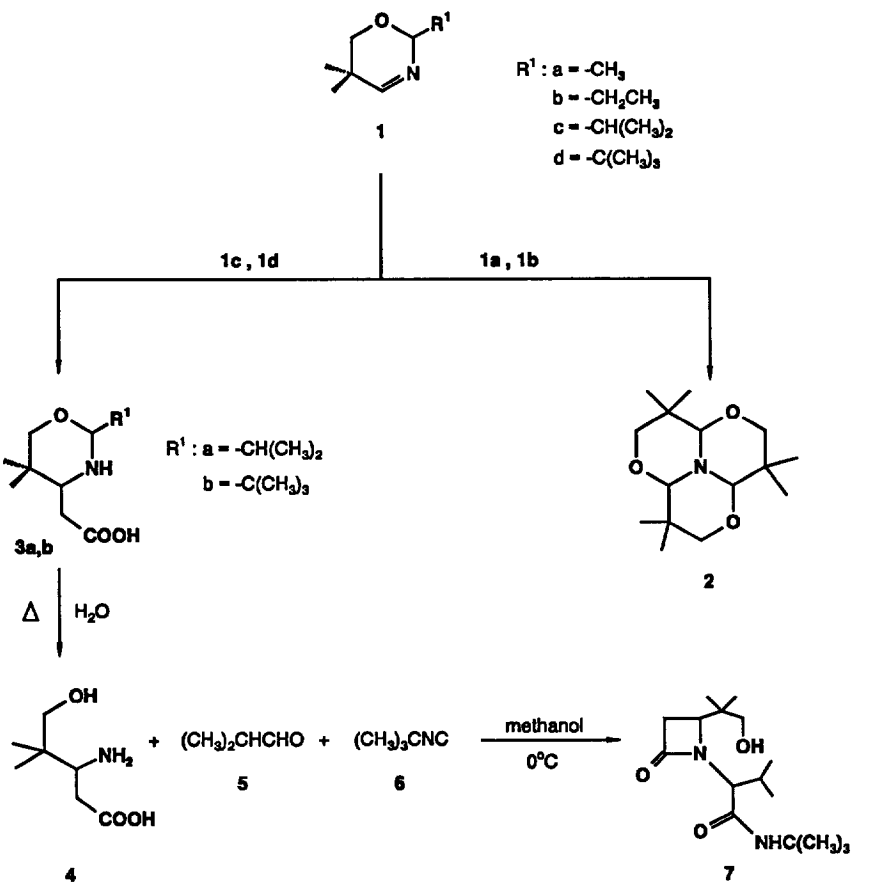
Konstantina Kehagia, Alexander Dömling, Ivar Ugi*

Lehrstuhl I für Organische Chemie und Biochemie
Technische Universität München
Lichtenbergstr. 4, D-85747 Garching, Germany

Abstract: In this article* a short approach towards highly functionalized β-lactam derivatives is described. Diastereoselective addition of malonic acid to 5,6-dihydro-2*H*-1,3-oxazines leads to the corresponding saturated carboxymethyl derivates. After hydrolysis of the O,N-acetal to the β-amino acids, these are transformed to β-lactam derivatives via the Ugi-reaction. Depending on the bulkyness of the rest in 2-position of the 5,6-dihydro-2*H*-1,3-oxazines, a β-amino acid or a tricyclic C_3-symmetrical heterocycle is formed.

Compared to the great biological importance of α-amino acids, the smaller number of known β-amino acids make them seem less important. However, their potential for organic synthesis has found increasing recognition in recent years, due to their function as precursors for β-lactam antibiotics. One important method for the synthesis of the β-lactam ring is the Ugi four component reaction (U-4CR), which utilizes a β-amino acid, an oxo compound and an isocyanide as starting materials. Recently, J. Martens et al.[1] succeeded in synthesizing 4-thiazolidine acetic acids, which might be good precursors for β-lactam syntheses via U-4CR starting from 2,5-dihydro-1,3-thiazoles via decarboxylating addition of malonic acid to thiazolidines.

We have tried an analogous synthesis, starting from 5,6-dihydro-2*H*-1,3-oxazine. Four different oxazines **1a-d**[2] have been tested so far and the results are presented here (Scheme 1). In practice, the described synthesis is quite facile, simply requiring refluxing of a mixture of oxazines **1a-d** with malonic acid in ethanol. The progress of the reaction can be monitored through the evolution of carbon dioxide. Even though malonic acid significantly adds to the imine double bond at room temperature, preferable reaction conditions involve addition in refluxing solvent. However, not all of the four synthesized oxazines yield the desired oxazine acetic acid (Scheme 1).



Scheme 1: Formation of β-lactam derivatives vs. C_3-symmetrical heterocycle from 5,6-dihydro-2*H*-1,3-oxazines depending on the size of the alkyl groups.

The products **3a,b** crystallize during the reaction; product **2**, on the other hand, only crystallizes after cooling of the solvent. All three compounds are obtained analytically pure without recrystallization. The formation of the different products **2**, respectively **3a,b** conceivably results from different spatial requirements of the substituents R^1. Bulky groups such as iso-propyl or tert.-butyl react to yield the desired β-amino carboxylic acid derivates, whereas small groups such as methyl or ethyl lead to products **2**. As the inductive effects of the various alkyl moieties can be considered to be of equal size, the obtained results are rather interpreted in terms of bulky groups impeding protonation of the imine-nitrogen. Thus, the addition of malonic acid to yield **3c,d** proceeds faster compared to the competing retro-Asinger-type opening of the oxazine ring to yield 13-aza-4,4,8,8,12,12-hexamethyl-2,6,10-trioxatricyclo[7,3,1,$0^{5,13}$]tridecane **2**.[3,4]

Hydrolysis of the oxazine acetic acid **3a,b** leads to the corresponding β-amino acids **4**; in accordance with Scheme 1 this is accomplished by simply heating compounds **3a,b** with water for a short period of time.[5] The second cleavage product of the O,N-acetal **3a,b**, aldehyde R^1CHO, is removed from the reaction mixture

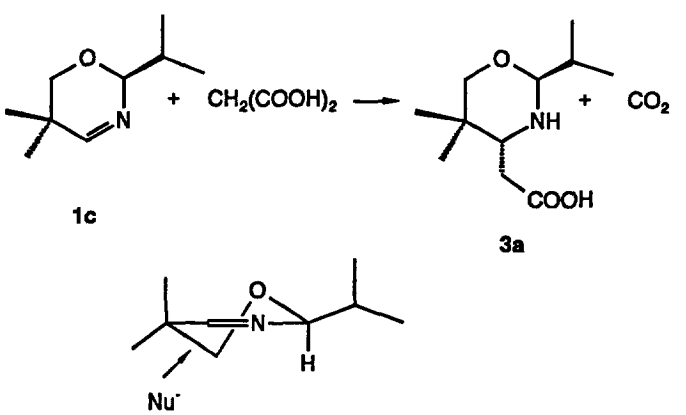
through distillation. Codistillation of the usually oily residues with ethanol leads to the amorphous solids **4** in 62-64% yield. In the last step for the formation of β-lactams **7**, the extraordinary synthetic potential of the Ugi four component reaction (U-4CR) is utilized[6,7,8]; employing isobutyr-aldehyde as oxo component. The desired product **7** is thus obtainable as a colourless solid in 56% yield in a diastereomeric ratio of 1:4.

Asymmetrically substituted 5,6-dihydro-2*H*-1,3-oxazines primarily assume the energetically preferred half-chair conformation[2]. This is indicated by model considerations, ^{1}H NMR spectroscopy, single-crystal X-ray analysis as well as through the chemical reactivity of selected representatives. Simple reflections performed on the basic oxazine structure show that of the two possible half-chair conformations with minimal energy **I** and **II**, conformer **I** is strongly preferred (Scheme 2). As can be seen, conformer **II** suffers from strong steric interactions between the bulky group in 2-position and one of the methylene protons in 6-position. This steric repulsion is greatly reduced in 6-position.

I **II**

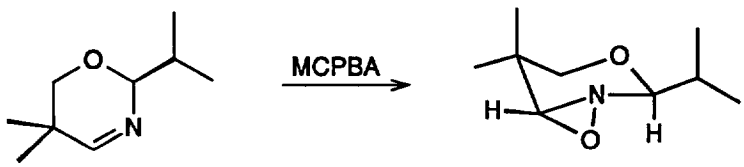
Scheme 2: Conformations **I** and **II** of asymmetrically substituted 5,6-dihydro-2*H*-1,3-oxazines.

In reactions of asymmetrically substituted 5,6-dihydro-2*H*-1,3-oxazines with malonic acid, only one of the two possible diastereomers is formed. This is explained in terms of steric repulsion, the nucleophile being only able to attack *anti* to the pseudo axial methyl group in 5-position; i.e. in the case of the decarboxylating addition of malonic acid to oxazines only the p-isomer of **3a** is formed[9,10,11] (Scheme 3). Derivatives of β–amino acids such as **3a,b** may play an important role as intermediates in the synthesis of the antibiotic β-methyl thienamycine.



Scheme 3: Addition of malonic acid *anti* to the bulky group at 2-position.

In analogy to the decarboxylating addition, the reaction of **1c** to the corresponding oxaziridine **8** also only leads to one of the two possible diastereomers (Scheme 4). Due to the above discussed preferential conformation **I**, the imine double bond is exclusively oxidized *anti* to the i-propyl moiety. The exclusive formation of the n-diastereomer of **8** is confirmed though the absence of an NOE effect in its ^{1}H NMR spectrum between the protons of positions 3 and 7.



1c **8**

Scheme 4: Exclusive formation of n-**8** via oxidation of **1c** with m-chloroperoxybenzoic acid.

EXPERIMENTAL

Typical procedure for 4-oxazine acetic acids 3a-3b:
Malonic acid (20.8 g, 0.2 mol) is dissolved in 120 ml of ethanol. To this solution 0.13 mol of the corresponding oxazine[2] are added and the solution is refluxed for 6 h. Progress of the reaction is monitored via evolution of carbon dioxide. The products begin to crystallize during the reaction as colourless solids. The crystals are filtered off, washed with ether and dried in vacuo.

3,4,5,6-Tetrahydro-5,5-dimethyl-2-i-propyl-2*H*-1,3-oxazine-4-acetic acid (3a).
$C_{11}H_{21}NO_3$= 215.29 g/mol; Yield: 9.8 g (35%) colourless crystals mp: 175°C; ^{1}H-NMR ($CDCl_3$, 360 MHz): 0.88-1.27 (m, 12H, 4x -CH_3); 1.82-1.87 (m, 1H, -CH-(CH_3)$_2$); 2.12 (dd, 1H, ^{2}J= 16.24 Hz, ^{3}J= 12.31 Hz, -CH_2COOH); 2.56 (dd, 1H, ^{2}J= 16.24 Hz, ^{3}J= 2.6 Hz, -CH_2COOH); 2.97 (dd, 1H, ^{3}J= 12.31 Hz, ^{3}J= 2.6 Hz, -CH-NH); 3.4 (d, 1H, ^{3}J= 11.7 Hz, -CH_2O); 3.62 (d, 1H, ^{3}J= 11.7 Hz, -CH_2O); 3.83 (d, 1H, ^{3}J= 5.2 Hz, -O-CH-NH); 9.45 (s, 1H, -COOH). ^{13}C-NMR (DMSO): 18.9 (2x -CH_3); 22.5 (2x -CH_3); 31.8 (-CH-(CH_3)$_2$); 32.5 (-C); 35 (-CH_2COOH); 59.8 (-CH-NH); 78.1 (-CH_2O); 92 (-O-CH-N); 174.6 (-COOH). IR (KBr)(cm^{-1}) : 3500 (s, -COOH, -NH); 1600 (s, C=O); 1400 (s, -O-).
Elemental analysis: calc.:C, 61.37; H, 9.83; N, 6.51; found: C, 61.05; H, 9.85; N, 6.52.

3,4,5,6-Tetrahydro-5,5-dimethyl-2-tert.-butyl-2*H*-1,3-oxazine-4-acetic acid (3b).
$C_{12}H_{23}NO_3$= 229.32 g/mol; Yield: 9.7 g (33%) colourless crystals mp: 169°C. ^{1}H-NMR ($CDCl_3$, 360 MHz): 0.9-1.1 (m, 15H, 5x -CH_3); 2.2 (dd, 1H, ^{2}J= 16.83 Hz, ^{3}J= 12.79 Hz, -CH_2COOH); 2.58 (dd, 1H, ^{2}J= 16.83 Hz, ^{3}J= 2.5 Hz, -CH_2COOH); 2.86 (dd, 1H, ^{3}J= 2.5 Hz, ^{3}J= 12.79 Hz, -CH-NH); 3.38 (d, 1H, ^{2}J= 11.5 Hz, -CH_2O); 3.62 (d, 1H, ^{2}J= 11.5 Hz, -CH_2O); 3.71 (s, 1H, -O-CH-NH); 9.5 (s, 1H, -COOH). ^{13}C-NMR (DMSO): 17.66 (-CH_3); 23.15 (-CH_3); 25.3 (3x -CH_3); 31.36 (-C); 34.11 (-C); 34.64 (-CH_2COOH); 59.76 (-CH-NH); 77.94 (-CH_2O); 94.23 (-O-CH-NH); 174.38 (-COOH).
Elemental analysis: calc.: C, 62.85; H, 10.10; N, 6.10; found: C, 62.78; H, 10.11; N, 6.15.

Typical procedure: 3-Amino-4,4-dimethyl-5-hydroxy-valeric acid (4)
The corresponding oxazine acetic acid 3a and 3b (0.1 mol) are dissolved in 150 ml of boiling water. After addition of 0.5 ml of conc. hydrochloric acid the solvent is distilled off, effecting removal of the aldehyde cleavage product. The resulting oily residue is codistilled several times with ethanol until a colourless solid results. The solid is filtered off, washed with ether and dried in vacuo.

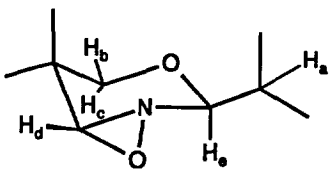
$C_7H_{15}NO_3$= 161.2 g/mol; Yield: 10.3g (64%) colourless crystals mp: 192°C. ^{1}H-NMR (CF_3COOD, 360 MHz): 1.7 (s, 6H, 2x -CH_3); 3.3 (dd, 1H, ^{2}J= 18.78 Hz, ^{3}J= 9.0 Hz, -CH_2COOH); 3.67 (dd, 1H, ^{2}J= 18.78 Hz, ^{3}J= 7.02 Hz, -CH_2COOH); 4.19 (tr, 1H, ^{3}J= 7.1 Hz, -CH-NH_2); 4.52 (s, 2H, -CH_2OH). ^{13}C-NMR (CF_3COOD, 360 MHz): 18.63 (-CH_3); 23.93 (-CH_3); 34.24 (-C); 35.49 (-CH_2COOH); 57.1 (-CH-NH_2); 80.3 (-CH_2OH); 177 (-COOH).
Elemental analysis: calc.: C, 52.16; H, 9.38; N, 8.67; found: C, 52.52; H, 9.36; N, 8.71.

4-(1-Hydroxy-2-methyl-propyl-2)-1-[(N-tert.-butyl carbamoyl)(i-propyl)methyl]-2-azetidinone (7)
3-Amino-4,4-dimethyl-5-hydroxy-valeric acid (1.6 g, 10 mmol) are dissolved in 70 ml of absolute methanol at room temperature. To this solution are added under vigorous stirring isobutyraldehyde (0.6 ml, 10 mmol) and tert.-butyl isocyanide (0.8 ml, 10 mmol). Stirring is continued for 12 h at the same temperature and progress of the reaction is monitored by TLC. The colourless solution is concentrated in vacuo, resulting in a colourless oil. After chromatography on silica gel (60_{F254},Merck) with ethyl acetate/hexane 1:3 a colourless solid results.

$C_{16}H_{30}N_2O_3$= 298.43 g/mol; Yield: 1.66g (56%) colourless crystals mp: 129°C; R_f: 0.89 (E/H 1:3, v/v). ^{1}H-NMR ($CDCl_3$, 360 MHz, major diastereomer): 0.98-1.2 (m, 21H, 7x-CH_3); 2.05-2.28 (m, 1H, -CH(CH_3)$_2$); 2.42-2.7 (m, 1H, -CH_2-CO-N); 2.84-3.0 (dd, 1H, ^{2}J= 13.02 Hz, ^{3}J= 4.95 Hz, -CH_2-CON); 3.35 (s, 2H, -CH_2OH); 3.6 (d, 1H, ^{3}J= 9.42 Hz, -CH-CH(CH_3)$_2$); 4.02 (dd, 1H, -CH-N); 6.3 (s, 1H, -NH). ^{13}C-NMR ($CDCl_3$, 360 MHz): 17.28 (CH_3); 18.31 (CH_3); 19.9 (CH_3); 22.1 (CH_3); 32.19 (-CH(CH_3)$_2$); 35.77 (-CH_2-CO-N); 51.6 (C); 57.9(C); 58.1(-CH-N); 68.6 (-CH-CH(CH_3)$_2$); 77 (-CH_2OH); 161.0 (C=O); 173.2 (C=O). GC-MS: m/e (%): 298 (M^+, 20); 268,3 (39); 198.2 (55); 156.1 (51); 126.1 (27); 72.1 (100); 41 (32).
Elemental analysis: calc.: C, 64.39; H, 10.13; N, 9.38; found: C, 64.91; H, 10.06; N, 9.35.

5,5-Dimethyl-2-i-propyl-tetrahydro-*2H*-oxazirino[3,2-c]oxazine (8)
70% m-Chloroperoxybenzoic acid (5.1 g, 22 mmol) in 50 ml of CH_2Cl_2 are added dropwise at 22°C in the course of 1 h to a mixture of 5,6-dihydro-5,5-dimethyl-2-i-propyl-*2H*-1,3-oxazine (3.1 g, 20 mmol) in 50 ml of CH_2Cl_2 and 75 ml of saturated sodium hydrogen carbonate solution. After stirring for 18 h at the same temperature, the phases are separated, the organic phase dried over magnesium sulfate and the solvent is evaporated in vacuo. The resulting oil is fractionally distilled in vacuo.

$C_9H_{17}NO_2$= 171.24 g/mol Yield: 1.6g (47%) colourless liquid b.p.: 82-94°C / 14 Torr
Elemental analysis: calc.: C, 63.13; H, 10.00; N, 8.18; found: C, 63.16; H, 10.03; N, 8.11.



^{1}H-NMR ($CDCl_3$, 360 MHz) : 1.02 (s, 3H, -CH_3) 1.04 (d, 3H, -CH_3, ^{3}J= 6.8 Hz) 1.05 (d, 3H, -CH_2, ^{3}J= 6.9 Hz) 1.25 (s, 3H, -CH_3) 2.00-2.09 (m, 1H, H_a) 3.23 (dd, 1H, ^{2}J= 1.47 Hz, ^{4}J= 11.02 Hz, H_b) 3.32 (d, 1H, ^{2}J=11.02 Hz, H_c) 4.03 (s, br, 1H, H_d) 4.20 (d, 1H, ^{3}J= 4.34 Hz, H_e). ^{13}C-NMR ($CDCl_3$) : 17.3; 17.5, 21.6; 21.8; 31.3; 33.3; 69.2; 82.3; 93.7.

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*) This article we dedicate to **Madame Madeleine Joullié.**

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