A Convenient Synthesis of 1,3-Oxazolidin-4-ones and 1,3-Oxazin-4-ones#

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Dedicated to Professor G. Seitz on the occassion of his 60th birthday

1,3-Oxazolidin-4-ones and 1,3-oxazin-4-ones were synthesized by formal cyclocondensation of imines with α- or β-hydroxy acids.

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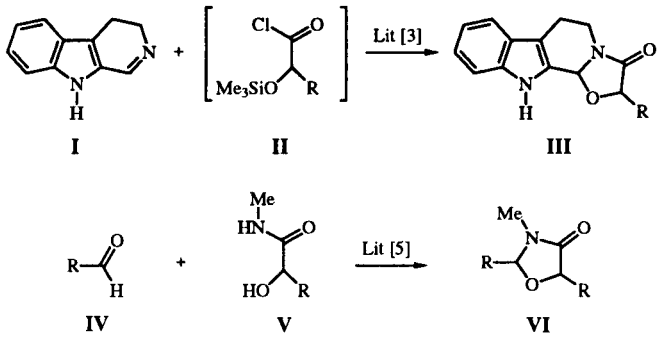
During our investigations concerning the chemistry of *N*-acyliminium ions we established several different methods for the synthesis of anullated 1,3-oxazolidin-4-ones [1,2,3,4] and - moreover - 1,3-oxazin-4-ones [3]. One of these methods is based on α- and β-trimethylsilyloxycarboxylic acid chlorides which undergo smooth cyclocondensation reactions with imines yielding the corresponding heterocyclic compounds, *e.g.* **I** + **II** → **III**. It should be mentioned that this approach is much different from the most common classical methods where the heterocycle is formed, at least in principle, from an α-hydroxycarboxylic acid amide and an appropriate carbonyl compound, *e.g.* **IV** + **V** → **VI** [5].

Scheme 1



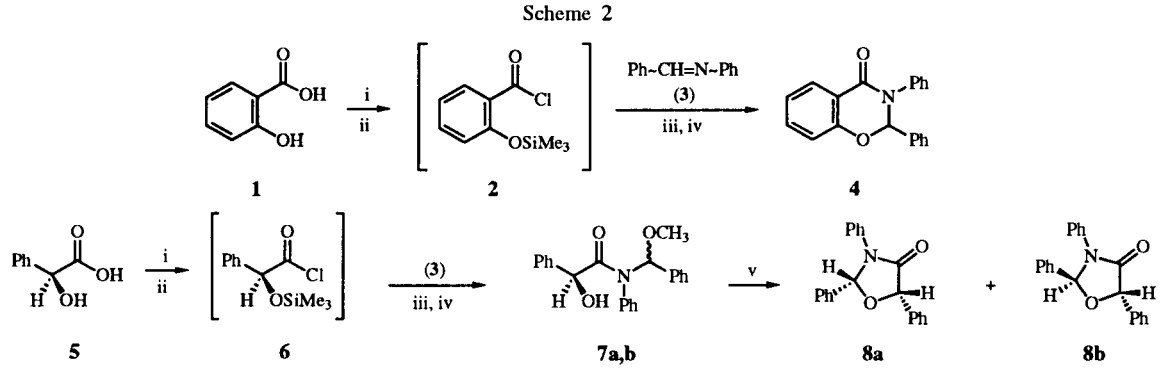
I **II** **III** **IV** **V** **VI**

In our initial study only β-carboline **I** as a representative for cyclic imines was employed. In the present paper we wish to report that our synthetic route can be applied to acyclic imines, *e.g.* **3** as well.

In the first step of our condensation reaction the hydroxy acids have to be converted into α- or β-trimethylsilyloxycarboxylic acid chlorides *in situ* [3,6]. This is accomplished by treating the appropriate α- or β-hydroxy acid with chlorotrimethylsilane in the presence of 4-dimethylaminopyridine and pyridine and by subsequent reaction with oxalyl chloride with DMF as a catalyst. In the next step the aforementioned reaction mixture has to be treated with an imine in pyridine followed by addition of citric acid to perform the cyclocondensation reaction. With regard to our intention to evaluate the suitability of acyclic imines, we chose compound **3** as the imine component. We also found that our synthetic process worked well in this case. When reacting salicylic acid (**1**) with **3** the 1,3-oxazin-4-one **4** was obtained in 54% yield.

With (*S*)-mandelic acid (**5**) our one-pot-procedure yielded a 1:1 mixture (68%) of the two amides **7a** and **7b**, which were easily cyclised to the desired 1,3-oxazolidin-4-ones **8a** (*cis*) and **8b** (*trans*) (yield **8a,b**: 46%, ratio **8a/8b** = 20:3) by acid catalysis (*p*-toluene sulfonic acid in trichloromethane/cyclohexane = 1/1, 55°, 10 minutes).

Scheme 2



1 **2** **4** **5** **6** **7a,b** **8a** **8b**

i: Me_3SiCl, 4-dimethylaminopyridine, pyridine, CH_2Cl_2, room temperature, 4 hours; ii: $(COCl)_2$ DMF, 0° to room temperature; iii: pyridine, room temperature, 4 hours; iv: citric acid, MeOH, room temperature, 30 minutes; v: *p*-TosOH (cat.), CH_2Cl_2/cyclohexane = 1/1, 55°, 10 minutes.

The relative configurations of **8a** and **8b** were assigned by nOe. In accord with earlier results [3], no racemisation of the chiral products **8a** and **8b**, obtained from enantiomerically pure **5**, could be detected by chiral hplc (Pirkle-column [7]).

In summary, our procedure is suitable for the synthesis of 1,3-oxazolidin-4-ones and 1,3-oxazin-4-ones from acyclic imines as well and, in addition, it is compatible with chiral hydroxycarboxylic acids.

EXPERIMENTAL

Melting points were determined on a Büchi-510 melting point apparatus and are uncorrected. Infrared spectra were run on a Perkin Elmer FT-IR-1600 spectrometer; liquids were run as films, solvents as potassium bromide pellets. The ^{1}H-nmr spectra were recorded on a Jeol 400 JNM-GX (400 MHz) in δ (ppm) and with TMS as the internal standard. Mass spectra were obtained on a CH-7-Varian spectrometer. Elemental analysis were determined on a Heraeus microanalyser Model CHN-Rapid. Column (flash) chromatography was performed with Merck silica gel 32-63 μm. Commercially available reagents were used without further purification. Solvents were dried and kept under nitrogen and freshly distilled before use.

2,3-Diphenyl-2*H*-1,3-benzoxazin-4(3*H*)-one (**4**).

A mixture of **1** (2.93 mmoles), 4-dimethylaminopyridine (2 mg), pyridine (0.5 ml) and chlorotrimethylsilane (0.77 ml, 6.07 mmoles) was stirred in 6 ml of dichloromethane over a period of 4 hours at room temperature. Then DMF (3 drops) and oxalyl chloride (0.26 ml, 3 mmoles) were added at 0° and stirring was continued for 1 hour at that temperature and for half an hour at room temperature. After cooling to 0° a solution of **3** (577 mg, 3.19 mmoles) in pyridine (1.77 ml) was added and the resulting mixture was stirred for 2 hours at room temperature. Finally after addition of a solution of citric acid (670 mg) in 6 ml of methanol and stirring for half an hour at room temperature the mixture was diluted with 40 ml of ethyl acetate and washed with 40 ml of 1*N* HCl. The organic layer was separated and the aqueous layer extracted with ethyl acetate (1 x 10 ml). The combined organic layers were consecutively washed with a solution of sodium bicarbonate and with brine, dried over sodium sulfate and evaporated *in vacuo*. The resulting residue was dissolved in diethyl ether. The obtained solution was treated with *n*-hexane until it became cloudy and was allowed to stand for 14 hours at room temperature. The precipitate was filtered off to give, after drying, 0.477 g (54 %) of **4** as white crystals, mp 120°; ^{1}H nmr (400 MHz, deuteriochloroform): δ 6.64 (s, 1H), 6.84 (d, J = 8.8 Hz, 1H), 6.95 (t, J = 8.8 Hz, 1H), 7.12-7.41 (m, 11H), 7.91 (dd, J = 5.1, 8.1 Hz, 1H); ir (potassium bromide): ν 1660 cm^{-1}; ms: (CI) m/z 302 [M+1].

Anal. Calcd. for $C_{20}H_{15}NO_2$: C, 79.72; H, 5.02; N, 4.65. Found: C, 79.51; H, 5.32; N, 4.56.

(*S*)-*N*-[(*R*)-(α-Methoxybenzyl]-*N*-phenyl-2-hydroxy-2-phenylacetamide (**7a**) and (*S*)-*N*-[(*S*)-(α-Methoxybenzyl]-*N*-phenyl-2-hydroxy-2-phenylacetamide (**7b**).

From 0.446 (2.93 mmoles) of **5** as described for **4**, the oily residue obtained after evaporation of the solvent *in vacuo* was purified by column chromatography (petroleum ether/ethyl acetate = 8/2) to give the two isomers **7a** and **7b**.

Isomer **I**, was obtained as colorless crystals, 0.295 g (29%), mp 98-100°; $[\alpha]_D^{20}$ = - 28° (c = 0.01, dichloromethane); ^{1}H nmr (400 MHz, deuteriochloroform): δ 3.55 (s, 3H), 4.64 (d, J = 7.3 Hz, 1H), 4.99 (d, J = 7.3 Hz, 1H), 6.46 (d, J = 7.3 Hz, 1H), 6.88 (d, J = 7.3 Hz, 1H), 7.10-7.34 (m, 14H); ir (potassium bromide): ν 1660 cm^{-1}; ms: (CI) m/z 348 [M+1].

Anal. Calcd. for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 76.01; H, 6.13; N, 4.04.

Isomer **II**, was obtained as colorless crystals, 0.394 g (39%); mp 140°; $[\alpha]_D^{20}$ = -67.1° (c = 0.01, dichloromethane); ^{1}H nmr (400 MHz, deuteriochloroform): δ 3.64 (s, 3H), 4.43 (d, J = 7.3 Hz, 1H), 4.87 (d, J = 7.3 Hz, 1H), 6.82 (d, J = 6.6 Hz, 2H), 7.03-7.26 (m, 14H) ppm; ir (potassium bromide): ν 1647 cm^{-1}; ms: (CI) m/z 348 [M+1].

Anal. Calcd. for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 75.94; H, 6.31; N, 3.93.

(*2R,5S*)-2,3,5-Triphenyl-1,3-oxazolidin-4-one (**8a**) and (*2S,5S*)-2,3,5-Triphenyl-1,3-oxazolidin-4-one (**8b**).

A solution of 1.38 g (3.97 mmoles) of a mixture of the stereoisomers **7a/7b** and of 22 mg of *p*-toluenesulfonic acid in 60 ml of cyclohexane/trichloromethane (1/1) was heated at 55° for 10 minutes. After cooling to room temperature, the reaction mixture was washed with a solution of sodium bicarbonate (5%, 3x), dried over sodium sulfate and evaporated *in vacuo*. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 8/2) yielding the stereoisomers **8a** and **8b**, the former being eluted first.

Compound **8a** was obtained as colorless crystals, 0.500 g (40%), mp 105°; $[\alpha]_D^{20}$ = -6.7° (c = 0.2, dichloromethane); ^{1}H nmr (400 MHz, deuteriochloroform): δ 5.43 (s, 1H), 6.57 (s, 1H), 7.00-7.49 (m, 15H); ir (potassium bromide): ν 1702 cm^{-1}; ms: (EI) m/z 315 [M$^+$].

Anal. Calcd. for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44. Found: C, 79.75; H, 5.37; N, 4.29.

Compound **8b** was obtained as colorless crystals, 0.075 g (6%), mp 116-118°; $[\alpha]_D^{20}$ = + 37.3° (c = 0.4, dichloromethane); ^{1}H nmr (400 MHz, deuteriochloroform): δ 5.59 (s, 1H), 6.70 (s, 1H), 7.11-7.58 (m, 15H); ir (potassium bromide): ν 1698 cm^{-1}; ms: (EI) m/z 315 [M$^+$].

Anal. Calcd. for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44. Found: C, 79.68; H, 5.92; N; 4.64.

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