Preparation of Cyclic and Bicyclic β-Amino Acids Derivatives from Methyl 6-Ethoxy-5,6-dihydro-4*H*-1,2-oxazine-4-carboxylate

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Dedicated to Professor Lutz F. Tietze on the occasion of his 60th birthday

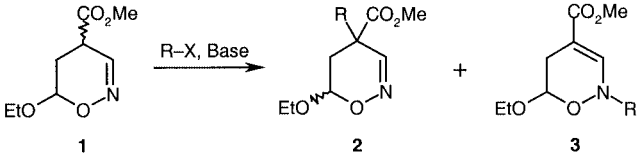
Abstract: The readily available methyl 6-ethoxy-5,6-dihydro-4*H*-1,2-oxazine-4-carboxylate (**1**) was alkylated at C-4 and acylated at the nitrogen atom. 1,2-Oxazine **1** and the resulting new substituted 1,2-oxazines **2** and **3** were suitable precursors for the preparation of derivatives of β-proline, nipecotic acid, as well as indolizine-6- and quinolizine-3-carboxylic acids.

Key words: β-amino acids, 1,2-oxazines, Diels–Alder reaction, alkylation, acylation

Silylation of methyl 3-nitropropionate[1] provided highly reactive methyl β-nitroso acrylate which can efficiently be trapped by ethyl vinyl ether affording 4-methoxycarbonyl-1,2-oxazine **1** in good yield (Scheme 1).[2] This demonstrates that commercially available nitro alkanes can easily be converted into interesting building blocks.[3] The preparation of **1** is particularly valuable since the alternative route for generation of nitrosoalkenes usually provides compounds with substituents at C-3 of the 1,2-oxazine ring.[4]

The presence of the methoxycarbonyl group at C-4 of heterocycle **1** allows its use as very convenient intermediate for the synthesis of cyclic β-amino acid derivatives. It has been previously shown, that differently substituted 1,2-oxazines are suitable precursors for preparation of pyrrolidines.[5] Moreover, 5,6-dihydro-4*H*-1,2-oxazines can be transformed into 2-substituted 2*H*-1,2-oxazines under the influence of hard electrophiles[6] and these easily undergo a [4+2]-cycloreversion to give 1-aza-1,3-butadienes which serve as very reactive 4π-components in Diels–Alder reactions.[7]

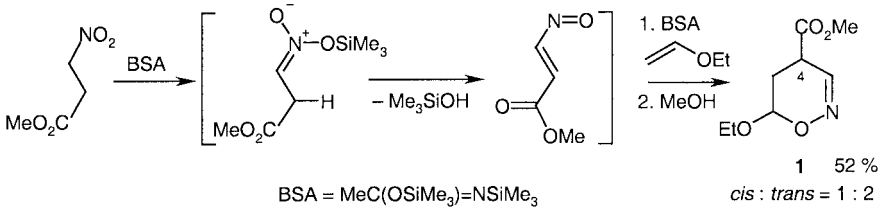
We first studied the reactivity of 1,2-oxazine **1** towards electrophiles. The alkylations of **1** with methyl and allyl iodide required preceding deprotonation with strong bases and occurred with high preference at 4-position (soft center) furnishing C-4-disubstituted 1,2-oxazines **2a** and **2b** in good to excellent yield, but with low diastereoselectivity (Scheme 2, Table 1, entries 1 and 2).[8]



Scheme 2 (for conditions and yields see Table 1)

Acylation of deprotonated 1,2-oxazine **1** with acetyl chloride proceeded exclusively at nitrogen to afford product **3a** in high yield (Table 1, entry 3).[8] This transformation can also be performed without employing a strong base for deprotonation. Thus, treatment of **1** with different acyl chlorides in the presence of triethylamine or Na_2CO_3 provided N-acylated 1,2-oxazines **3b**–**e** in very good yields (Table 1, entries 4–7).[9]

Reductions of 1,2-oxazines **1** and **2a**,**b** with hydrogen and Raney-nickel in the presence of Boc_2O gave the desired β-proline derivatives **4a**–**c** in good yields (Scheme 3, Table 2).[10] Interestingly, the use of Pd/C as catalyst under similar conditions converted 1,2-oxazine **1** into methyl pyrrol-3-carboxylate as the single product in 47% yield.



Scheme 1

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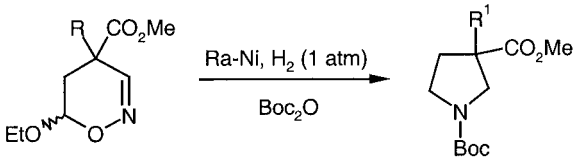
Table 1 Alkylation and Acylation of 1,2-Oxazine **1** to Compounds **2** and **3**

Entry	Base	R–X	Conditions		Product	Yield (%)	Isomeric ratio
			Temp (°C)	Time (h)			
1	LiHMDS	MeI	1. –78 → 0 2. 0	1 2	**2a**	61[a]	1:1.2
2	KHMDS	Allyl iodide	1. –78 → 0 2. 0	1 0.5	**2b**	92	1:1.3
3	LiHMDS	AcCl	1. –78 2. –78 → 0	1 1	**3a**	85	–
4	Et_3N	2-Iodobenzoyl chloride	20	3	**3b**	97	–
5	Na_2CO_3	4-Pentenoyl chloride	20	0.5	**3c**	86	–
6	Na_2CO_3	5-Hexenoyl chloride	20	0.5	**3d**	86	–
7	Na_2CO_3	6-Heptenoyl chloride	20	0.5	**3e**	81	–

[a] The crude product contained 14% of N-alkylation product **3** (R = Me).



1, 2 **4**

Scheme 3

Table 2 Raney-nickel Reduction of 1,2-Oxazines **1** and **2a**,**b** to β-Proline Derivatives **4a**–**c**

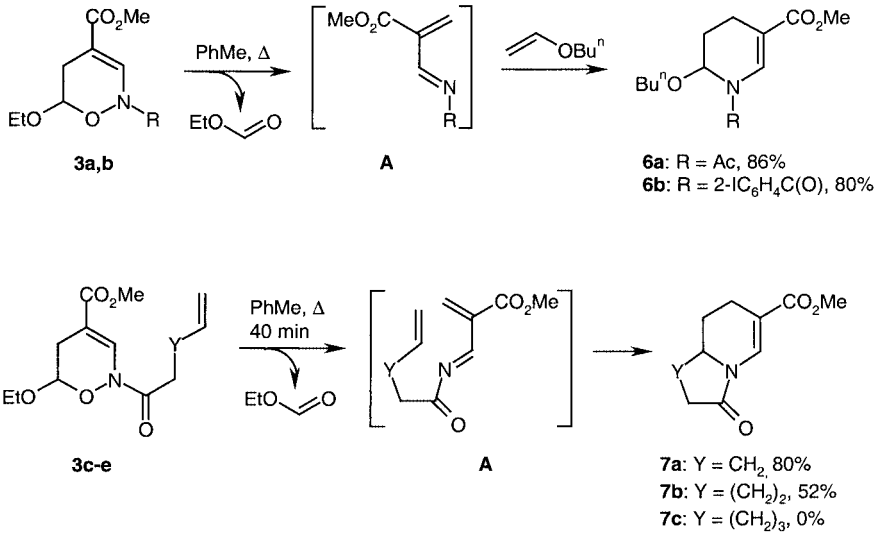
1,2-Oxazine	R	Product	R^1	Yield (%)
1	H	**4a**	H	57[a]
2a	Me	**4b**	Me	68
2b	CH_2=$CHCH_2$	**4c**	$Me(CH_2)_2$	65

[a] The crude product contained 4% of methyl pyrrol-3-carboxylate.

The weakness of the N–O bond of 1,2-oxazines **3** decrease the activation barrier for the thermal [4+2]-cycloreversion which furnishes ethyl formate along with highly reactive conjugated 1-aza-1,3-butadienes **A** as illustrated in Scheme 4.[11] The intermolecular trapping of these intermediates was accomplished by use of an excess of *n*-butyl vinyl ether to furnish nipecotic acid derivatives **6a** and **6b** in good yields.[12]

The intramolecular trapping mode was successfully applied to 1,2-oxazines **3c** and **3d** leading to bicyclic compounds **7a** and **7b**.[13] However, preparation of the corresponding 6/7-membered bicyclic product **7c** starting from **3e** turned out to be impossible, this reaction provided only decomposition products.[14] Indolizine **7a** and quinolizine **7b** are of interest as they contain a common substructure of certain alkaloids.[15,16]

In conclusion, we have demonstrated the synthetic potential of the readily available 1,2-oxazine derivative **1** by its transformation into several cyclic β-amino acids such as β-proline, nipecotic acid, indolizine- and quinolizinecarboxylate derivatives. Further investigations of the presented reactions and application of the synthesized building blocks for the preparation of unnatural β-amino acids and natural products are in progress.



Scheme 4

Acknowledgement

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(7) Recent advances in the chemistry of 1-azabutadienes are surveyed in the following publications: (a) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1. (b) Ishar, M. P. S.; Jayakumar, S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379.

(8) **General Procedure for Alkylation and Acylation via Deprotonation**: 1,2-Oxazine **1** (375 mg, 2.00 mmol) in THF (4 mL) was added to a stirred solution of LiHMDS (2.4 mL of 1 M solution in THF, 2.4 mmol) or KHMDS (4.8 mL of 0.5 M solution in toluene, 2.4 mmol) in THF (4 mL) at –78 °C. After being stirred for 10 min the alkyl iodide (3.0 mmol) was added neat via syringe and the reaction mixture was maintained under conditions as indicated in Table 1. Then Et_2O and sat. aq NH_4Cl solution were added and the organic layer was separated. The water phase was extracted with Et_2O and the combined organic layers were washed with H_2O and brine, dried over $MgSO_4$ and evaporated in vacuum. The residue was subjected to column chromatography (silica gel, hexane/EtOAc 3:1) to give analytically pure products. Analytical data of **2a**, major isomer (higher R_f), colorless oil: ^{1}H NMR ($CDCl_3$, 270 MHz): δ = 7.32 (br s, 1 H, 3-H), 4.97 (ddd, *J* = 5.1, 3.2, 0.9 Hz, 1 H, 6-H), 3.87 (m_c, 1 H, OCH_2), 3.72 (s, 3 H, OMe), 3.54 (m_c, 1 H, OCH_2), 2.49 (dd, *J* = 13.7, 2.9 Hz, 1 H, 5-H), 1.82 (ddd, *J* = 13.7, 5.1, 1.0 Hz, 1 H, 5-H), 1.46 (s, 3 H, 4-Me), 1.18 (t, *J* = 7.1 Hz, 3 H, Me); ^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 173.5 (s, C=O), 151.0 (d, C-3), 96.6 (d, C-6), 64.8 (t, OCH_2), 53.1 (q, MeO), 40.0 (s, C-4), 33.6 (t, C-5), 24.1 (q, 4-Me), 15.5 (q, Me); MS (pos. FAB): *m/z* (%) = 202(100) [M^+ + 1], 69(41), 55(54), 41(53). Anal. Calcd for $C_9H_{15}NO_4$ (201.2): C, 53.72; H, 7.51; N, 6.96. Found: C, 53.21; H, 7.30; N, 6.68. Minor isomer (lower R_f), colorless crystals, mp 29–30 °C (Et_2O/hexane): ^{1}H NMR ($CDCl_3$, 270 MHz): δ = 7.36 (dd, *J* = 2.3, 2.0 Hz, 1 H, 3-H), 5.08 (ddd, *J* = 2.4, 2.3, 2.0 Hz, 1 H, 6-H), 3.73 (m_c, 1 H, OCH_2), 3.69 (s, 3 H, OMe), 3.47 (m_c, 1 H, OCH_2), 2.70 (dt, *J* = 13.7, 2.3 Hz, 1 H, 5-H), 1.70 (dd, *J* = 13.7, 2.4 Hz, 1 H, 5-H), 1.33 (s, 3 H, 4-Me), 1.09 (t, *J* = 7.0 Hz, 3 H, Me); ^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 174.0 (s, C=O), 151.8 (d, C-3), 94.6 (d, C-6), 63.3 (t, OCH_2), 52.6 (q, MeO), 36.1 (s, C-4), 33.7 (t, C-5), 24.5 (q, 4-Me), 15.0 (q, Me); MS (pos. FAB): *m/z* (%) = 202(100) [M^+ + 1], 157(21), 69(43), 55(55), 41(48). Anal. Calcd for $C_9H_{15}NO_4$ (201.2): C, 53.72; H, 7.51; N, 6.96. Found: C, 53.64; H, 7.45; N, 6.90.

(9) **General Procedures for Acylation with Na_2CO_3 as a Base**: The acyl chloride (1.3 equiv) was added at 0 °C to a stirred suspension of dry Na_2CO_3 (3 equiv) in a solution of 1,2-oxazine (1 equiv) in CH_2Cl_2 (5 mL to 1 mmol of oxazine). After being stirred for 10 min at 0 °C, the temperature was increased to ambient, the reaction mixture was stirred for additional 30 min and filtered. The filtrate was evaporated in vacuum to remove the excess of acyl chloride and subjected to column chromatography (silica gel, hexane/EtOAc 3:1) to give analytically pure products. Analytical data of **3c**, colorless oil: ^{1}H NMR ($CDCl_3$, 270 MHz): δ = 8.18 (br s, 1 H, 3-H), 5.73 (ddt, *J* = 17.0, 10.1, 6.5 Hz, 1 H, =CH), 5.08 (t, *J* = 3.6 Hz, 1 H, 6-H), 4.95 (dq, *J* = 17.0, 1.4 Hz, 1 H, $=CH_2$), 4.89 (dq, *J* = 10.1, 1.5 Hz, 1 H, $=CH_2$), 3.76 (m_c, 1 H, OCH_2), 3.61 (s, 3 H, OMe), 3.57 (m_c, 1 H, OCH_2), 2.55 (m_c, 3 H, 5-H, CH_2), 2.39 (ddd, *J* = 17.2, 3.1, 1.3 Hz, 1 H, 5-H), 2.30 (q, *J* = 6.5 Hz, 2 H, CH_2), 1.12 (t, *J* = 7.1 Hz, 3 H, Me); ^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 169.3, 166.7 (2 s, 2 C=O), 136.8 (d, =CH), 129.4 (d, C-3), 115.8 (t, $=CH_2$), 104.2 (s, C-4), 100.2 (d, C-6), 65.6 (t, OCH_2), 51.7 (q, MeO), 31.7 (t, CH_2), 28.6 (t, C-5), 28.1 (t, CH_2), 15.1 (q, Me); MS (EI, 80 eV): *m/z* (%) = 269(42) [M^+], 187(100) [$M^+ – CH_2=CHCH_2CH=C=O$], 155(71), 141(24), 83(19). Anal. Calcd for $C_{13}H_{19}NO_5$ (269.3): C, 57.98; H, 7.11; N, 5.20. Found: C, 58.29; H, 6.96; N, 5.07.

(10) **General Procedure for Reduction with Raney-nickel**: A commercially available 50% water suspension of Raney-nickel (ca. 7 mL to 1 mmol of 1,2-oxazine) was washed 3 times with methanol, fresh methanol (10 mL to 1 mmol of 1,2-oxazine) was placed in the flask and Boc_2O (1.2 equiv) was added. After H_2 was bubbled for 20 min through the resulting suspension, a solution of 1,2-oxazine (1 equiv) in methanol (3 mL to 1 mmol of 1,2-oxazine) was added and the mixture was stirred under H_2 atmosphere for 24 h at ambient temperature. Then the catalyst was filtered off through Celite, the filtrate was evaporated and the residue was subjected to column chromatography (silica gel, hexane/EtOAc 3 1) to give analytically pure products. Analytical data of **4b**, colorless oil: ^{1}H NMR ($C_6D_5CD_3$, 500 MHz, 363 K): δ = 4.03 (d, *J* = 11.0 Hz, 1 H, 2-H), 3.58 (m_c, 1 H, 5-H), 3.57 (s, 3 H, OMe), 3.51 (m_c, 1 H, 5-H), 3.34 (d, *J* = 11.0 Hz, 1 H, 2-H), 2.33 (m_c, 1 H, 4-H), 1.67 (s, 9 H, CMe_3), 1.62 (ddd, *J* = 12.5, 6.0, 1.3 Hz, 1 H, 4-H), 1.31 (s, 3 H, 3-Me); ^{13}C NMR ($C_6D_5CD_3$, 125.8 MHz, 363 K): δ = 175.5 (s, 3-C=O), 154.4 (s, 1-C=O), 79.0, 28.9 (s, q, $OCMe_3$), 55.9 (t, C-2), 51.6 (q, OMe), 48.8 (s, C-3), 45.4 (t, C-5), 36.2 (t, C-4), 22.5 (q, 3-Me); IR (Film): ν = 2975 (C-H), 2955 (C-H), 2930 (C-H), 1735 (C=O), 1700 (C=O), 1455, 1400, 1165, 1140, 1100 cm^{-1}; MS (EI, 80 eV): *m/z* (%) = 243(3) [M^+], 186(19) [$M^+ – CMe_3$], 170(11) [$M^+ – Me_3CO$], 142(21), 128(12), 115(11), 84(14), 57(100), 43(45). Anal. calcd for $C_{12}H_{21}NO_4$ (243.3): C, 59.24; H, 8.70; N, 5.76. Found: C, 59.34; H, 8.62; N, 5.60.

(11) The [4+2]-cycloreversion of 1,2-oxazines of compounds which are structurally similar to **3** is known: (a) Goldberg, I.; Saad, D.; Shalom, E.; Shatzmiller, S. *J. Org. Chem.* **1982**, *47*, 2192. (b) see also ref.[2,6a]

(12) **General Procedure for Intermolecular Trapping of 1-Azabutadiene A**: A solution of 1,2-oxazines (1.00 mmol) and *n*-butyl vinyl ether (1.94 mL, 15.0 mmol) in toluene (50 mL) was refluxed for 1.5 h (for **3a**) or 4 h (for **3b**), cooled down to ambient temperature and evaporated. The residue was subjected to column chromatography (silica gel, hexane/EtOAc 3:1) to give analytically pure products. Analytical data of **6a**, colorless oil: ^{1}H NMR ($CDCl_3$, 270 MHz): δ = 7.69 (br s, 1 H, 2-H), 5.83 (br s, 1 H, 6-H), 3.73 (s, 3 H, OMe), 3.50 (m_c, 2 H, OCH_2), 2.38, 2.05 (2 m_c, 4 H, 4-H, 5-H), 2.30 (s, 3 H, 1-Ac), 1.59–1.20 (m, 4 H, 2 CH_2), 0.85 (t, *J* = 7.3 Hz, 3 H, Me); ^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 170.1, 167.9 (2 s, C=O), 133.7 (d, C-2), 110.8 (s, C-3), 76.4 (d, C-6), 68.7 (t, OCH_2), 51.9 (q, MeO), 32.0, 25.8 (2 t, C-4, C-5), 22.1 (q, 1-Me), 19.6, 16.9 (2 t, 2 CH_2), 14.1 (q, 6-Me); MS (EI, 80 eV): *m/z* (%) = 255(42) [M^+], 212(79) [M^+ – Ac], 156(37), 140(100), 139(89), 138(48), 124(63). Anal. Calcd for $C_{13}H_{21}NO_4$ (255.3): C, 61.16; H, 8.29; N, 5.49; Found: C, 60.98; H, 8.04; N, 5.57.

(13) **General Procedure for Intramolecular Trapping of 1-Azabutadiene A**: A solution of 1,2-oxazines **3c**,**d** (0.50 mmol) in toluene (18 mL) was refluxed for 40 min, cooled down to r.t. and evaporated in vacuum. The residue was subjected to chromatography (silica gel, hexane/EtOAc 1:2) and additionally recrystallized from hexane/toluene to give pure products. Analytical data of **7a**, colorless crystals [mp 142–143 °C (hexane/toluene)]: ^{1}H NMR ($CDCl_3$, 270 MHz): δ = 7.91 (br s, 1 H, 5-H), 3.72 (s, 3 H, OMe), 3.68 (m_c, 1 H, 8a-H), 2.67–2.14 (m, 6 H, 7-H, 8-H, 9-H, 10-H), 1.81–1.61, 1.51–1.32 (2 m, 2 H, 9-H, 8-H); ^{13}C NMR ($CDCl_3$, 67.9 MHz): δ = 172.9, 168.1 (2 s, C=O), 130.7 (d, C-5), 110.9 (s, C-6), 55.7 (d, C-8a), 51.7 (q, MeO), 31.7 (t, C-2), 28.0, 26.8, 22.3 (3 t, C-1, C-7, C-8); MS (EI, 80 eV): *m/z* (%) = 195(100) [M^+], 164(64) [M^+ – MeO], 140(42), 136(52), 108(17). Anal. Calcd for $C_{10}H_{13}NO_3$ (195.2): C, 61.53; H, 6.71; N, 7.17. Found: C, 61.39; H, 6.71; N, 7.03.

(14) Even very slow addition of the diluted solution of **3e** into a large volume of boiling toluene did not lead to formation of a detectable amount of the expected bicyclic compound **7c**; instead, unidentifiable products of high molecular mass were isolated.

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