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2-Azetidinones from 3-Aminopropanoic Acids and the $Ph_3P/CCl_4(CBr_4)$ or $Ph_3P/Br_2(I_2)$ Condensation Systems

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The title complexes are used as intramolecular cyclization agents to yield under mild conditions and average to good yields 2-azetidinones from variously substituted 3-aminopropanoic acids. The reaction is found to proceed in all examined cases stereospecifically, with one exception. No marked difference with respect to yields and stereospecificity is noted among the four condensation systems.

[Keywords: 3-Aminopropanoic acids; 2-Azetidinones; Cyclization with Ph_3P/CCl_4 *(or* CBr_4*) and* Ph_3P/Br_2 *(or* I_2*)]*

2-Azetidinone aus 3-Aminopropansäuren und $Ph_3P/CCl_4(CBr_4)$ *oder* $Ph_3P/Br_2(I_2)$ *als Kondensationsmittel*

Die im Titel angegebenen Systeme wurden als Cyclisationsreagentien eingesetzt, um aus substituierten 3-Aminopropansäuren 2-Azetidinone unter milden Bedingungen und mit durchschnittlichen bis guten Ausbeuten darzustellen. Mit einer Ausnahme läuft die Reaktion stereospezifisch. Bei den vier untersuchten Systemen wurde kein beträchtlicher Unterschied in bezug auf Ausbeute und Stereospezifität festgestellt.

The condensation properties of the Ph_3P/haloalkane complex have been successful employed in the preparation of amides[1] and peptides[2–5]. On the other hand Ph_3PX_2 ($X = Cl$[6] and $X = Br$[7]) as well as Ph_3P/CCl_4[8] on treatment with organic acids are reported to afford acyl halides in high yields. Variously substituted 3-aminopropanoic acids have been converted into β-lactams via acyl halides formed on treatment with $PhSO_2Cl$[9], $POCl_3$[10], $SOCl_2$[11], PCl_5[13] and CH_3COCl[14]. This approach, however, when applied on diastereomers is found to give only the *trans* β-lactam[15]. There is only one case where a *cis* β-lactam is

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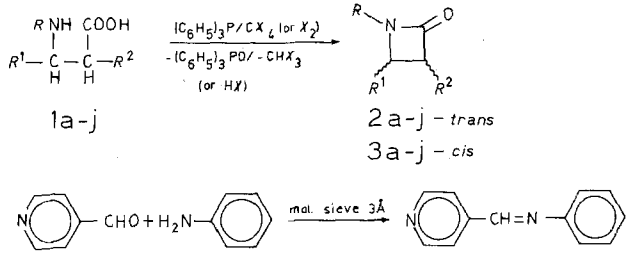
reported to be formed via acyl halide[11]. Therefore, it is of interest to examine the utility of the title systems in an attempt to synthesize 2-azetidinones (Scheme 1).

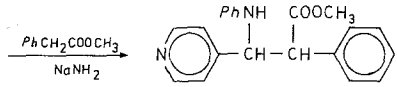
Scheme 1



In the studied cases it was found that the cyclization takes place stereospecifically under mild conditions with the sole exception of the diastereomeric 3-anilino-3-(4′-pyridyl)-2-phenylpropanoic acids (**1 i, j**) which on condensation afforded a diastereomeric mixture of the corresponding β-lactams. The observed isomerization probably takes place at the β-lactam's C-4 chiral center, since (±)-*cis*-1,3-diphenyl-4-(4′-pyridyl)-2-azetidinone (**3 j**) under the conditions of the reaction gave a mixture of *cis* and *trans* β-lactams (**3 j** and **2 i**) in the same ratio as in the *erythro* acid condensation conditions. *Cis*-1,3,4-triphenyl-2-azetidinone (**3 h**) remained unchanged under the same treatment (Table 1).

The methyl esters of **1 i** and **1 j** were prepared according to Scheme 2 in a ratio of 9/1 as determined on the basis of their ^{1}H-NMR spectra the major product being the *erythro* isomer[16].

Scheme 2



erythro and *threo*

The steric assignement of the isolated products was confirmed also by ^{1}H-NMR spectra of the corresponding β-lactams. The configuration of the latter were based on the vicinal coupling constants between the C-3 and C-4 protons[17,18].

The stereochemically pure esters on hydrolysis underwent isomerization and the desired acids were isolated via recrystallyzation. Their sterical assignement was based on correlating the esters that arise on treating them with diazomethane with the initially obtained ones.

Table 1. *Yields of 2-azetidinones depending on the different condensation systems used*

	1					Dehydration system							
	Substituents		Config.	Ref.	Ph_3P/CCl_4		Ph_3P/CBr_4		Ph_3P/Br_2		Ph_3P/I_2	
	R	R^1 R^2			2	3	2	3	2	3	2	3
					Yields [%]							
a	H	*Ph* *Ph*	*threo*	22	52	—	47	—	52	—	23[a]	—
b	H	*Ph* *Ph*	*erythro*	22	—	13	—	15	—	b	—	b
c	H	—(CH_2)—	*cis*	23	—	19[a]						
d	CH_3	*Ph* H	—	19		39						
e	CH_3	*Ph* C_6H_{11}	*erythro*	—	—	66						
f	*Ph*	*Ph* CH_3	*erythro*	24	—	37						
g	*Ph*	*Ph* *Ph*	*threo*	25	35	—	83	—	74	—	63	—
h	*Ph*	*Ph* *Ph*	*erythro*	26	—	34	—	35	—	15	—	34
i	*Ph*	4-pyridyl *Ph*	*threo*	—	33[c]	5[c]						
j	*Ph*	4-pyridyl *Ph*	*erythro*	—	8[c]	49[c]						

[a] Column chromatography followed by preparative TLC.
[b] Traces detected by TLC but not isolated.
[c] Preparative TLC using ether/petroleum wther = 9/1 (**3c**) or ether/petroleum ether = 5/1 (**2i** and **3j**).

The acid **1e** was synthesized according to *Rodionov* and *Yavorskaya*[19] and is of *erythro* configuration assuming stereospecificity of the condensation leading to the β-lactam **3e**. Traces of a compound which could be the other isomer were detected, but not further examined.

The results obtained seem to indicate that the reaction leading to the 2-azetidinones proceeds without the intervention of an acyl halide intermediate since it is known that *erythro* acyl halides fail to afford the desired cis β-lactams[15].

Table 2. *Characteristic data of (±)-cis-3-cyclohexyl-1-methyl-2-azetidinone* (**3e**), *(±)-trans-1,3-diphenyl-4-(4'-pyridyl)-2-azetidinone* (**2i**) *and (±)-cis-1,3-diphenyl-4-(4'-pyridyl)-2-azetidinone* (**3j**)[a]

	m.p. °C	IR cm^{-1}	^{1}H-NMR ($CDCl_3$) ppm
3e	133.5-136.0	1745	7.31 (s, 5H, *Ar*); 4.61 (d, 1H, $J_{3,4} = 5.5$ Hz); 3.15 (d, 1H, $J_{3,4} = 5.5$ Hz, $J_{3,(1\text{-cyclohexyl})} = 9.5$ Hz); 2.72 (s, 3H, NCH_3) 2.2-0.5 ppm (bm, 11H, $C_6\mathbf{H}_{11}$)
2i	176.0-184.0[b]	1760	8.57 d, 2H, α-pyridyl, $J = 4.8$ Hz); 7.3-7.0 (m, 12H, aromatic); 4.86 (d, 1H, $J_{3,4} = 2.7$ Hz); 4.17 (d, 1H, $J_{3,4} = 2.7$ Hz)
3j	190.0-192.0[b]	1760	8.35 (bm, 2H, α-pyridyl) 7.33-6.95 (m, 12H, aromatic); 5.43 (d, 1H, $J_{3,4} = 6.4$ Hz); 5.04 (d, 1H, $J_{3,4} = 6.4$ Hz)

[a] C, H, N analysis for **3e**, N value for **3i** and **3j** in full agreement with the calculated values.

[b] Sealed capillary (decomp.).

Experimental

All melting points are uncorrected and were determined on a Kofler apparatus. The ^{1}H-NMR spectra were taken on a JEOL (100 MHz) instrument with *TMS* as internal standard and deuterochloroform as solvent. The IR spectra were recorded on a UR 20 Carl Zeiss-Jena instrument using chloroform as solvent. All TLC analysis were carried out on silica gel.

D,L-erythro-2-cyclohexyl-3-methylamino-3-phenylpropanoic acid (**1e**)

The solution of cyclohexylmalonic acid[20] (2.27 g, 12.2 mmol) and benzylidenemethylamine (1.53 g, 12.9 mmol) in benzene (20 ml) was heated at 65° for 2 h. Benzene was removed under reduced pressure, the residue was thoroughly washed with ether (30 ml) and after filtration recrystallized twice from ethanol to give 0.86 g (28.0%) of material, m.p. 224-225° (sealed capillary).

$C_{16}H_{23}NO_2$ (261.4). Calc. C 73.53, H 8.87, N 5.36.
Found C 72.01, H 9.00, N 5.19.

Methyl D,L-erythro-2-cyclohexyl-3-methylamino-3-phenylpropanoate

1e (0.20 g) was methylated with diazomethane; the etheral solution was extracted with aqueous $NaHCO_3$, then washed with water, dried (Na_2SO_4) and the solvent evaporated. The residue was recrystallized from petroleum ether to yield 0.10 g of ester, m.p. 94.5–95.5°.

$C_{17}H_{25}NO_2$ (275.4). Calc. C 74.15, H 9.15, N 5.09.
Found C 74.55, H 9.16, N 5.06.

IR ($CHCl_3$): ν_{max} = 3350, 1730 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 7.15 (m, 5 H, *Ar*); 3.81 (d, 1 H, *Ph*C**H**, $J_{2,3}$ = 9.2 Hz); 3.35 (s, 3 H, COOC**H**$_3$); 2.68 (q, 1 H, C**H**COOCH$_3$, $J_{2,3}$ = 9.2 Hz), $J_{2,(1\text{-cyclohexyl})}$ = 4.4 Hz); 2.20 (s, 3 H, NCH_3); 1.75–1.0 ppm (m, 12 H).

4-pyridylmethineaniline

4-pyridinecarbaldehyde (4.97 g, 44.8 mmol) and aniline (4.22 g, 44.8 mmol) are dissolved in dry benzene (5 ml) containing molecular sieve type 3 A (8 g) and the mixture allowed to stand for 24 h. Some chloroform is then added, the solution decanted and the molecular sieve washed with chloroform. The combined filtrates were taken to dryness and the residue recrystallized from benzene-petroleum ether to give the *Schiff* base, m.p. 69–72° (lit.[21] m.p. 72°) (9.2 g, 84.4%).

Methyl D,L-erythro- and D,L-threo-3-anilino-3-(4'-pyridyl)-2-phenylpropanoates

4-pyridylmethineaniline (5.86 g, 32 mmol) and methyl phenylacetate (4.80 g, 32 mmol) dissolved in dry dimethoxyethane (5 ml) were stirred in the presence of sodium amide (0.16 g, 4 mmol) at 60 °C for 1.5 h. Ether (30 ml) was added and the mixture as well stirred and filtered. In this manner a mixture is obtained (8.0 g, 75%) containing the two diastereomers, as evaluated by ^{1}H-NMR in a ratio of 9/1[16].

Recrystallization from chloroform-heptane afforded the one pure diastereomer of the methyl ester of **1j** (5.8 g, 54.5%), m.p. 177.5–180.0°, R_f (ether/acetone = 15/1) = 0.42.

$C_{16}H_{18}N_2O_2$. (332.4) Calc. C 75.88, H 6.06, N 8.43.
Found C 76.11, H 5.97, N 8.64.

IR ($CHCl_3$): ν_{max} = 3410, 1735 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 8.50 (m, 2 H, α-pyridine); 7.22–6.13 (m, 12 H, aromatic); 4.90 (q, 1 H, N—C**H**, $J_{3,NH}$ = 3.8 Hz, $J_{2,3}$ = 9.9 Hz); 3.89 (d, 1 H, NH, $H_{3,NH}$ = 3.8 Hz); 3.78 (d, 1 H, C**H**COOCH$_3$, $J_{2,3}$ = 9.9 Hz) and 3.44 ppm (s, 3 H, COOC**H**$_3$).

The second diastereomeric methyl ester of **1i** (0.29 g, 2.7%) was isolated by subjecting the products of the mother liquor to preparative TLC using ether/acetone = 15/1 as eluant, m.p. 136–139°, R_f (ether/acetone = 15/1) = 0.50.

$C_{16}H_{18}N_2O_2$ (332.4). Calc. C 75.88, H 6.06, N 8.43.
Found C 76.04, H 6.46, N 8.62.

IR ($CHCl_3$): ν_{max} = 3420, 1738 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 8.33 (d, 2 H, α-pyridyl, J = 5.2 Hz); 7.2–6.4 (m, 12 H aromatic); 4,86 (m, 2 H, —C**H**—N**H**—, D_2O-exchange: d, 1 H, —CH—N, J = 8.5 Hz); 3.86 (d, 1 H, C**H**COOMe, J = 8.5 Hz) and 3.62 ppm (s, 3 H, COOC**H**$_3$).

D,L-threo- and D,L-erythro-3-anilino-3-(4'-pyridyl)-2-phenyl-propanoic acids (**1i** and **1j**)

The crude mixture of esters of **1i** and **1j** (6.8 g) dissolved in aqueous methanol (1:1, 60 ml) containing sodium hydroxyde (10 g) was refluxed for 1.5 h. Removal of a part (25 ml) of the solvent and acidification (while still hot) with acetic acid gave a precipitate (5.1 g) from which after repeated recrystallization from ethanol an acid (1.77 g, 27.2%), m.p. 253-254° (dec.) could be isolated which on treatment with diazomethane gave a product identical with the **1j**-methyl ester.

$C_{20}H_{18}N_2O_2$. (318.4). Calc. C 75.45, H 5.70, N 8.80.
Found C 75.53, H 5.97, N 8.96.

The isomer was obtained from the filtrate after concentration (0.61 g, 9.4%, m.p. 220-222°); with diazomethane it gave a product identical with **1i**-methyl ester.

$C_{20}H_{18}N_2O_2$ (318.4). Calc. C 75.45, H 5.70, N 8.80.
Found C 75.15, H 6.61, N 9.00.

Synthesis of 2-azetidinones

Procedure A

To a suspension of the amino acid (2 mmol) and triphenylphosphine (3 mmol) in dry acetonitrile (10 ml) is added carbon tetrachloride/or carbon tetrabromide (3 mmol) and triethylamine (3 mmol/5 mmol for **1a/b**). The reaction mixture is stirred at room temperature for 24 h for the *threo* series and 48 h for the *erythro* series, the precipitate is filtered, washed with acetonitrile and the combined filtrates taken to dryness on a rotary evaporator. Water is added to the residue, which is then acidified* to *pH* 5 with dilute hydrochloric acid and extracted with ether (3 × 40 ml). The ethereal extracts are washed with water, dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue is then chromatographed on silica gel (12 g/mmol) using as eluant a mixture of ether petroleum ether (2/1). In some cases (see Table 1) the pure 2-azetidinones were isolated after preparative TLC.

Procedure B

To triphenylphosphine (3 mmol) dissolved in dry acetonitrile (25 ml) is added finely ground iodine (3 mmol) or a solution of bromine (3 mmol) in the same solvent (2 ml). The amino acid (2 mmol) is added 5 min after the addition of the bromine or 1.5 h after the addition of the iodine and this is immediately followed by adding triethylamine (6 mmol/8 mmol for **1a/b**). After stirring at room temperature for 24 h for the *threo* series and 48 h for the *erythro* series the reaction mixture is worked up as described in procedure A.

The yields of the 2-azetidinones listed in Table 1 are for isolated and characterized products, the data (m.p., ^{1}H-NMR, IR) of the already described lactams agreed compleetely with the ones given in the literature, while these of the newly prepared ones are given in Table 2.

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* In the case of **1i, j** the residue was taken up in chloroform without acidification.

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