Investigation of Diketopiperazines Containing a Guanidino-Functionalized Sidechain as Potential Catalysts of Enantioselective Strecker Reactions

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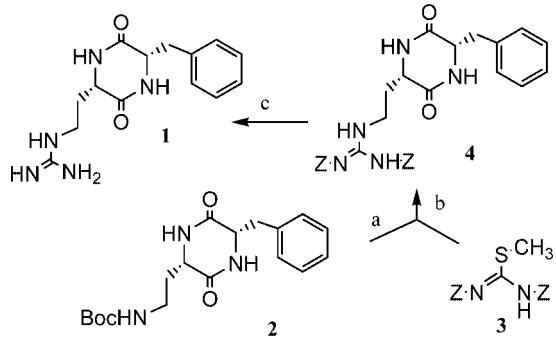
Diketopiperazine **1** consisting of L-(γ-guanidino-α-amino)butyric acid and L-phenylalanine was synthesized as the hydroacetate and as the hydronitrate. Its structure was confirmed by X-ray analysis. In contrast to reports in the literature (Lipton et al.), compound **1** does not induce enantioselevtive catalysis of Strecker reactions.

Enantiomerically pure amino acids are of much interest as building blocks for biologically active compounds, additives for animal feed or as starting materials for syntheses of chiral molecules. The Strecker reaction[1] still plays an important role in the synthesis of amino acids. Most industrial syntheses of amino acids include enzymatic resolutions of racemic mixtures,[2] although efficient stereoselective Strecker reactions based on chiral auxiliaries[3] or enantioselective catalysts,[4] have been developed during the past years.

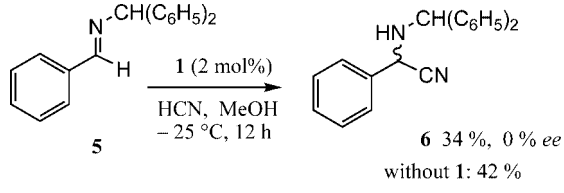
For certain application we had been interested in a metal salt-free preparation of amino acids. The asymmetric Strecker reaction catalyzed by cyclic dipeptide **1** formed from L-(γ-guanidino-α-amino)butyric acid and L-phenylalanine according to Lipton et al.[5] seemed a particularly promising procedure. This catalyst was synthesized as described[5] via diketopiperazine **2** obtained from L-(N^4-*tert*-butyloxycarbonyl)-2,4-diaminobutyric acid and L-phenylalanine (Scheme 1).

However, the physical properties of compound **2** we isolated differed dramatically in optical rotation[6] and solubility from those reported in the literature.[5] Compound **2** was soluble in methanol only after the addition of dichloromethane. In contrast to the data given in the literature,[5] the reaction of *N*-deprotected **2** with 3,5-dimethylpyrazol-1-carboxamidinium nitrate gave the desired 4-guanidino compound as a mixture with impurities, which could not be separated by HPLC. Therefore, after removal of the Boc group from **2** the guanidino group was introduced by the reaction with *N*,*N*′-dibenzyloxycarbonyl-(*S*)-methyl-isothiourea[7] **3** to furnish the double Z-protected diketopiperazine **4**. Hydrogenolyses of the Z-protecting groups in the presence of 0.2% acetic acid afforded the catalyst **1** as the hydroacetate in analytically pure form. Compound **1** was hardly soluble in water, optical rotation had therefore to be measured in dimethylformamide [($[a]_D^{20}$ = –41.1 (*c* = 1, DMF); ref.[5] ($[a]_D^{25}$ = –43.3 (*c* = 3.1, H_2O)].



Scheme 1. a) CF_3COOH/CH_2Cl_2 (2:15); b) $THF/H_2O/NEt_3$ (50:50:1) 83%; c) H_2/Pd-C (10%), THF/MeOH (3:1), 0.2% AcOH, >98%. Boc: *tert*-butyloxycarbonyl; Z: benzyloxycarbonyl.

All efforts to use diketopiperazine **1** as a catalyst in the enantioselective Strecker synthesis turned out quite disappointing. Exposure of *N*-benzhydrylbenzaldimine **5** (1 mmol) to HCN (2 mmol) in 3.6 mL of methanol at –25 °C in the presence of diketopiperazine **1** afforded racemic aminonitrile **6** in moderate yield (Scheme 2).[8]



Scheme 2.

Without addition of **1** the reaction proceeded slightly faster. Also changing solvents, origin of HCN or *N*-substi-

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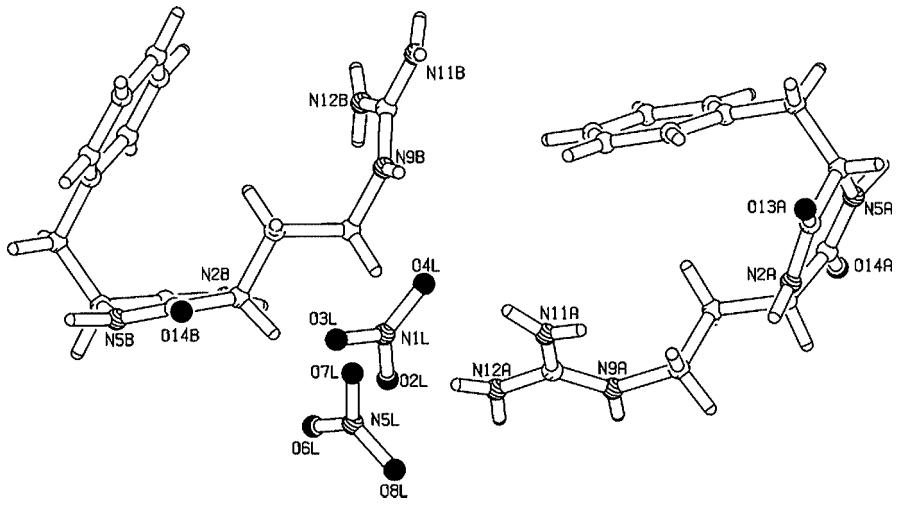

Figure 1. X-ray structure analysis of hydronitrate of **1**.

tution pattern (*p*-MeO-C_6H_4-CH_2-, allyl) of the substrate did not provide any enantioselectivity in those reactions. Performing the reaction at higher temperature (22 °C) or application of the *N*-allylimine improved only the yield of racemic product up to >80%. These aberrations of chemical and mentioned physical properties of compound **1** synthesized by us at first raised the suspicion of an epimerization during the cyclization step which forms the diketopiperazine ring **2**.[8]

Only an X-ray structure analysis could clarify the stereochemistry of diketopiperazine **1**. After numerous unsuccessful efforts the hydronitrate of **1** finally crystallized. It was obtained from the hydroacetate by treatment with nitric acid and evaporation to dryness.[9] This X-ray analysis (Figure 1) shows that the nitrate anions net the diketopiperazine molecules in two almost orthogonal plains through hydrogen bonding to the guanidinium and cycloamide groups. The X-ray analysis in particular gives evidence, that the diketopiperazine we had synthesized in fact is structure **1**.

However, this compound **1** definitely is not an enantioselective catalyst of the Strecker reaction at 0 °C, –25 °C or –70 °C, neither as the hydroacetate nor as the hydronitrate.

Since the reaction proceeds in a clear solution under the conditions applied,[5,8] polymorphism of the solid diketopiperazine[5] does not play any role in the process.

It should be mentioned, that the corresponding arginine-derived diketopiperazine c-[Arg-Phe][10] also does not catalyze the Strecker reaction of aldimines.

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[6] **2**: $[\alpha]_D^{20}$ = –23.1 (*c* = 0.5, MeOH/CH_2Cl_2, 1:1); ref.[5] {$[\alpha]_D^{25}$ = –3.1 (*c* = 9.0, MeOH)}.
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[8] Experimental procedure: A solution of imine **5** (1 mmol) and catalyst **1** (20 μmol) in 3 mL of dry methanol under argon was cooled to –25 °C. A 3 M solution of HCN either generated from H_2SO_4 and KCN or in situ from TMSCN was added by syringe. The solution was stirred at –25 °C for 12 h and then warmed to room temperature. Methanol and excess HCN were removed by evaporation and the crude aminonitrile was purified by flash chromatography (SiO_2, cyclohexane/ethyl acetate, 10:1) to afford aminonitrile **6** as a colourless solid, 93.2 mg (34%), m. p. 101 °C. ^{1}H NMR ($CDCl_3$, 200 MHz, ppm): δ = 7.67–7.24 (m, 15 H, Ar), 5.32 (s, 1 H, C*H*Ar_2), 4.65 (d, ^3J = 11.2 Hz, 1 H, –C*H*–CN), 2.21 (d, ^3J = 11.2 Hz, 1 H, N*H*). ^{13}C NMR ($CDCl_3$, 50 MHz, ppm): δ = 142.9, 141.3, 135.1 (C_{ipso}), 129.1, 128.9, 128.1, 127.4, 127.3 (Ar), 118.9 (CN), 65.7, 52.5 (*C*Ar_2/*C*–CN). $C_{21}H_{18}N_2$: calcd. C 84.52, H 6.08, N 9.39; found C 84.32, H 6.18, N 9.39.
Comparison of NMR-data of herein synthesized compound **1** with those described in ref.[5] gives no information, particularly for there is no signal assignment given in the supporting information pages of ref.[5] Spectra measured in DMSO show significant differences, however, it is not obvious which salt of **1** is described in ref.[5] The HR-MS data given in ref.[5] do not match the formula given.
Crystal structure for **1**·HNO_3: [$C_{14}H_{20}N_5O_2^+ \times NO_3^-$], M_r = 352.36 g•mol^{-1}, size of crystal 0.128 × 0.128 × 0.256 mm^3, triclin, *P*1, *a* = 9.242(3) Å, *b* = 9.502(4) Å, *c* = 11.449(4) Å, α = 112.66(2)°, β = 104.91(3)°, γ = 98.91(3)°, *V* = 859.4(6) Å^3, *z* = 2, $d_{calcd.}$ = 1.362 g•cm^{-3}, μ (Cu-K_α) = 0.89 mm^{-1}, *F*(000) = 372, *T* = –130 °C; *R* = 0.0857, wR_2 = 0.2220 for 5530 reflec-

tions. CCDC-250616 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[9] Hydronitrate of **1***: m.p. 235 °C (dec.).* $[\alpha]_D^{22}$ = –27.3 (*c* = 1, DMSO).
[10] c-[L-Arg-L-Phe]: $[\alpha]_D^{20}$ = 11.3 (*c* = 1, CF_3COOH).

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