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Diastereoselective Protonation after the Birch Reduction of Pyrroles

A. Schäfer, B. Schäfer *

BASF AG, Hauptlaboratorium
Carl-Bosch-Straße 38, D-67056 Ludwigshafen

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Abstract: Non-alkylated 3,4-dehydroprolines are obtained by diastereoselective protonation after Birch reduction of N-Boc-pyrrole carboxylic amides. Based on quantum chemical calculations the mechanism of asymmetric protonation is discussed.

Key words: Birch reduction, dehydroproline, diastereoselective protonation, pyrrole

The Birch reduction is one of the most convenient methods for the synthesis of partially hydrogenated aromatic and heteroaromatic compounds. The scope and limitation of this method is well documented in several reviews [1 2 3 4] and the difficulties of reducing pyrroles by this method are well known.[5] About two years ago, Donohoe published some first examples of reductions and alkylations of pyrrole carboxylic esters and amides.[6]

Relatively little is known about asymmetric Birch reductions. In the eighties Schultz did some fundamental investigations in the case of chiral benzoic acid esters[7] and amides[8 9]. Magnus used this method for the synthesis of a taxane C-ring component.[10] Kinoshita[11] and later Donohoe[12] used furan-2-carboxylic acid amides in diastereoselective Birch reductions with lithium in liquid ammonia. In all cases asymmetric protonation is not as selective as alkylation. Most recently Donohoe published the synthesis of alkylated 3,4-dehydroprolines.[13]

In this paper we deal with the mechanism of the asymmetric protonation of an enolate resulting from Birch reduction of the electron-deficient pyrrole-2-carboxylic amide **1**. Chiral as well achiral methods of syntheses of non-alkylated 3,4-dehydroproline[14] are known in literature, but all of them suffer from several disadvantages.[15]

(S)-3,4-Dehydroproline is an unusual, natural amino acid and useful as an inhibitor of collagen synthesis[16]. It is also a component of phomopsin A (produced by the fungus *Phomopsis leptostromiformis*), which acts like Dolastatin 10 [17] as a potent microtubule inhibitor.[18 19]

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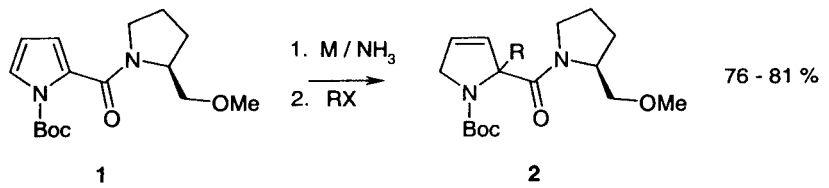
The amide **1** was synthesised by methods known from the literature starting from 2-(trichloroacetyl)-pyrrole, purified by crystallisation or chromatography and characterised by ^{1}H NMR spectroscopy. [20] [21] [22] [23]

Scheme 1



1 **2**

THF was used as cosolvent in all Birch reductions. The reaction was quenched by addition of solid ammonium chloride after 1 h reaction time. After evaporation of ammonia and filtration of lithium chloride, the solvent was removed by a rotary evaporator. The diastereoselectivity of the reaction was detected from the residue by HPLC. Authentic material as well as an epimeric mixture (*S,S*)-**2** / (*R,S*)-**2** were synthesised by a propane phosphonic acid anhydride-coupling reaction [24] starting from commercially available (*S*)-3,4-dehydroproline respectively from racemic 3,4-dehydroproline. Starting from (*S*)-**1**, the major product is (*S,S*)-**2**, detected by HPLC.

Table 1: Influence of Temperature, Metal and Electrophile

T (°C)	M	RX	de (%)
- 30	Li	NH_4Cl	82
- 78	Li	NH_4Cl	90
- 78	Na	NH_4Cl	88
- 78	K	NH_4Cl	/
- 78	Li	MeI	50

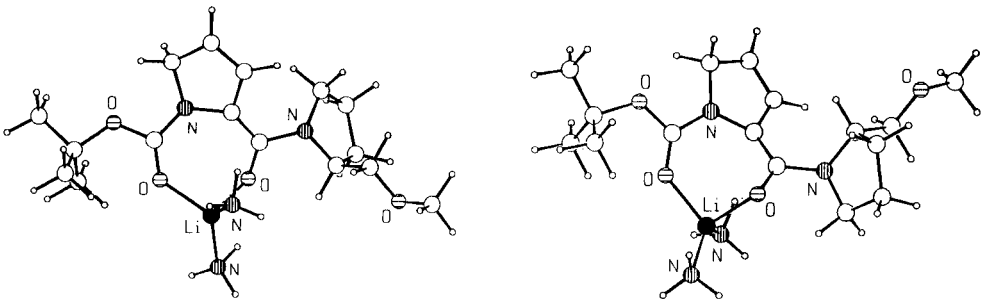
Finally we examined the influence of the temperature, metal and electrophile (Table 1). As expected, the selectivity decreases with increasing temperature. The results using lithium and sodium are similar but the reaction with potassium failed. Remarkably, asymmetric protonation is more selective than methylation.

In order to get an understanding of the selectivity of the reaction, we investigated intermediate lithium enolates by means of quantum chemical methods (see below). We consider the asymmetric protonation of the Li-**2** complex solvated by ammonia to be the key step for the selective formation of (*S,S*)-**2**. Density functional (DFT) calculations give an approximately tetrahedral coordination of Li, with two bonds formed to the carbonyl-O atoms of the amide and ester groups in **2**, and one bond to an ammonia ligand. The fourth position can be occupied by either the ether-O atom or a second ammonia ligand, the latter being energetically more favourable by 24 - 27 kJ/mol (depending on the functional used in DFT). In both cases there are two diastereomeric isomers, as shown in figure 1 for

the complex with two ammonia ligands. The coordination of the ether group or the second ammonia ligand leads to a sterical hindrance of the respective side of the prochiral C atom, so that protonation or alkylation should preferably occur on the opposite side. In the case of two ammonia ligands, the isomer leading to (*S,S*)-**2** is 4.5 – 5.9 kJ/mol lower in energy, which results in a diastereoselectivity of 88 - 95 %, which is in good accordance with the experimental result.

The structures in figure 1 also help to rationalise the higher selectivity of protonation compared to alkylation, since due to the coordination of the two ammonia ligands, the pyrrolidine ring adopts a conformation which partially hinders the reacting side of the prochiral C atom. Since the alkylation is sterically more demanding than the protonation, a lower selectivity for the alkylation is expected.

Figure 1: Diastereomeric complexes leading to (*S,S*)-2 (left) and (*R,S*)-2 (right).



Computational details

All quantum chemical calculations were performed on the density functional theory (DFT) level with the Turbomole program package.[25 26] For the optimisation of the molecular structures we used the functionals of Becke and Perdew (B-P) [27 28] and split valence basis sets [29] with polarisation functions on non-hydrogen atoms. At the equilibrium structures, we calculated molecular energies with valence triple zeta basis sets [30] and one set of polarisation functions on all atoms, using the B-P, B-LYP [27 31] and B3-LYP [31 32] functionals. The RI approximation [26] was used with the B-P and B-LYP functionals.

Experimental

2-((S,S)-N-2-(methyloxymethyl)-pyrrolidinocarbonyl)-1-(t-butyloxy-carbonyl)-Δ3-pyrroline (**2**): A 1 l round-bottomed flask, equipped with a stirrer, a dropping funnel and a reflux condenser, was filled with 160 ml ammonia, 50 ml THF and 0.42 g (60 mmol) lithium. 6.2 g (20 mmol) 2-((*S*)-N-2-(methyloxymethyl)-pyrrolidinocarbonyl)-1-(t-butyloxy-carbonyl)-pyrrole ((*S*)-**1**) dissolved in 20 ml THF was added at – 78 °C. The reaction mixture was stirred for 1 h. After the addition of 10 g of solid ammonium chloride, ammonia was removed at room temperature. After filtration, the solvent was removed by a rotary evaporator. 6.1 g **2** was obtained as a brown oil. HPLC of the crude product (Varian, Merck Lichrospher RP 60 Select B, 250 x 4 mm, 5µm, CH_3CN / H_2O): 79.3 (*S,S*)-**2** and 4.2 % (*R,S*)-**2** (16 mmol, yield: 81 %). ^{13}C NMR (D_6-DMSO, TMS, δ (ppm)): 23.4 (t, C-Pro), 24.4 (t, C-Pro), 26.3 (q, t-Bu), 26.7 (q, t-Bu), 27.6 (q, t-Bu), 45.4 (t, C-Pro), 52.9 (t, C-DHP), 55.9 (d, C-Pro),

57.9 (q, O-Me), 65.4 (d, C-DHP), 71.6 (t, C-OMe), 78.2 (s, t-Bu), 124.7 (d, C-DHP), 127.6 (d, C-DHP), 152.4 (s, COOtBu), 167.2 (s, C=O). The crude product was purified by preparative HPLC (Waters Deltaprep 4000, Merck Lichrospher RP Select B, 250 x 4 mm, 5µm, CH_3CN / H_2O): colourless oil, HPLC 96,2 Fl.%, 93,3 % de. $[\alpha]_{589}^{20}$: –223°, $[\alpha]_{578}^{20}$: –233°, $[\alpha]_{546}^{20}$: –267° (c = 0,061, CH_2Cl_2).

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