Palladium-Catalyzed Reduction of an Allylic Amine : A Formal Access to Both Diastereoisomers of Cyclopentenyl Glycine

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<u>Abstract</u>.: The easily accessible bicyclic amines **3** (exo or endo) are regioselectively transformed to the methyl esters of the diastereoisomers (1c or 1d) of N-benzyl cyclopentenyl glycine by reaction with hydride donors (mainly NaBH₃CN) in the presence of a palladium(0) catalyst.

Cyclopentenyl glycine 1, a non-proteinogenic natural amino-acid as well as its saturated homolog cyclopentyl glycine 2^{-1} have been shown to exhibit interesting biological activities. Although natural 1 is a mixture of (2S,2'R) and (2S,2'S) diastereoisomers, only the (2S,2'R) 1a displays biological activity as was demonstrated by Trowitsch *et al* who prepared the four stereoisomers of 1^{-2} .



Until now, all the preparations of either 1a^{1, 2} or of the biologically active 2 (S) ³ involved a resolution step and, in the case of 1, the reactions showed no diastereoselectivity in the formation of the $C_2C_{2'}$ bond regardless of whether an electrophilic ² or a nucleophilic ¹ cyclopentenyl unit was used.

Recently, numerous studies have been devoted to the imino-Diels Alder reactions and more particularly to the cycloadditions of cyclopentadiene with functionnalized immonium salts ⁴; this reaction can lead stereoselectively to exo-3 when run with the benzylimine prepared from methyl glyoxylate ⁵ (scheme). This compound exo-3 contains the carbon skeleton of racemic **1a** which could be obtained **stereospecifically** in a few steps if an efficient method for the hydrogenolysis of the allylic carbon-nitrogen bond was available.

As it is possible to observe enantioselection in such cycloadditions ⁶, this route could constitute a diastereospecific access to enantiomerically enriched 1a. For its own part, the (2S, 2'S) isomer 1b could be formed from the endo-3 isomer, a minor product of the imino-Diels reaction (in our hands, exo-3 / endo-3 = 3.5).

For all these reasons we became interested in the possibility of carrying out the reduction of the carbonnitrogen bond of exo-3 and endo-3 by a palladium-catalyzed process. It is now well known that allylic esters (acetates, carbonates) and oxiranes can be regioselectively reduced by hydride donors (NaBH₄, NaBH₃CN or ammonium formate) in the presence of a palladium(0) catalyst ⁷. This reaction is generally believed to occur via a π -allyl palladium species. However, i) the only report of the reductive cleavage of a carbon-nitrogen bond is concerned with an amine being both an allylic and benzylic amine ⁸ and ii) π -allyl palladium species are not easily formed from allylic amines and, to our knowledge, only two of their reactions are supposed to involve such an intermediate ⁹.

Consequently, we have treated exo 3 (easily separated from its isomer endo-3 by column chromatography) by hydride donors in the presence of palladium catalysts. The main results are listed in the table and show that the expected reduction is observed in some cases but, for it to occur, the solution (solvent : THF, dioxanne, acetonitrile) must be refluxed for a prolonged period; a systematic study proved that the best results were obtained by using THF as the solvent and 10% of palladium tetrakis triphenylphosphine as catalyst. The choice of the hydride source is important, sodium borocyanohydride being the more efficient since it gives a good yield (77%) of the mixture of the two amino-esters 1c and 4 with good regioselectivity (1c/4 = 7). This selectivity can be greatly improved by using 0.05 eq. of the catalyst in the presence of 0.7 eq. of triphenylphosphine but the evolution of the reaction mixture is slower and the inactivation of the catalyst leads to incomplete transformation of the starting material. In many cases, the reaction is accompanied by polymerisation, the mixture 1c + 4 being easily separated by column-chromatography over silica-gel and its composition determined by GC and ¹H NMR spectroscopy (the two compounds can be separated by flash-chromatography). Also, it was possible to isolate under certain conditions small quantities (< 10%) of a mixture of the deaminated products **5a** and **6a**, whose origin is unclear.



This transformation exo-3 \rightarrow 1c + 4 shows that it is possible, in certain cases, to carry out the hydrogenolysis of an allylic amine. The interest of this synthetic procedure is underlined by the observation that dl-1c, a potential precursor of dl-1a is obtained in good yield. Its mechanism is presently uncertain but the existence of a π -allyl intermediate is doubtful since i) there is no difference in the regioselectivity obtained with the diverse hydride sources, 1c being always the major compound ¹⁰ ii) no reaction was observed when exo-3 was treated with the sodium enolate of methylmalonate in the presence of catalytic quantities of Pd(PPh₃)₄.

Having determined the best conditions for the reduction of the allylic carbon-nitrogen bond of exo-3, we ran the reaction on the endo isomer in order to obtain 1d, the potential precursor of the other diastereoisomer 1b of cyclopentenyl glycine. Surprisingly, the reaction is much less regioselective (1d/4 = 1.3) and its yield is lower because of intense polymerisation.



Finally, to develop a preparative method for obtaining homologs of cyclopentenyl glycine, the enolate of 3 (obtained by the reaction of 1 eq. of LDA in THF at 0° C) was alkylated by methyl iodide. The reaction gave





exo-3 (dl)



. NHBn 4 (dl)

Reducing agent (2 eq)	Catalyst	Reaction time	Yield 1c + 4 (1c/4)	Recovered exo-3
NaBH4	$Pd(PPh_2) = 0.05 eq$	48 h	5% (10)	37%
NaBH ₃ CN	Pd(PPh ₃) ₄ 0.05 eq PPh ₃ 0.7 eq	48 h	25% (67)	24%
	Pd(PPh ₃) ₄ 0.1 eq PPh ₃ 0.7 eq	24 h	56% (7)	0%
	Pd(PPh ₃) ₄ 0.1 eq	16 h	77% (7)	0%
	Pd(OAc) ₂ 0.1 eq	12 h	20% (1.2)	nd*
	Pd(dba) ₂ 0.1 eq dppe 0.1 eq	48 h	25% (11)	15%
HCO ₂ NH ₄	Pd(PPh ₃) ₄ 0.1 eq	16 h	37% (7)	0%
HCO ₂ H	$Pd(PPh_3)_4$ 0.1 eq	16 h	47% (26)	0%

(All the reactions were performed in refluxing THF and stopped when no evolution was noticeable in

the GC analysis of the reaction mixture). * nd = not determined ; the analysis was only run by GC , during which exo-3 decomposed. In other cases, the products were isolated by flash-chromatography.

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a mixture of the two diastereoisomers 7a and 7b with 86% yield but which were unseparable on a preparative scale. The palladium-catalyzed reduction of this mixture proved to be quite sluggish, giving besides 10% of the mixture of the deaminated products 5b and 6b, only 27% of the unsaturated esters 8 (both diastereoisomers) and 9 in the proportions $3/2.5/1^{-11}$.



In spite of this lack of general efficiency, it appears that the palladium-catalyzed reduction of these bicyclic allylic amines is particularly useful for obtaining a precursor of the biologically active diastereoisomer of cyclopentenyl glycine 1 from readily available starting materials and without the involvement of sophisticated separations.

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References and notes

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- With allylic esters, an inversion of the direction of the hydride attack is observed when NaBH₄ or NaBH₃CN are replaced by ammonium formate. See Ref. 7
- 11. The yield and the proportions were determined by the separation of the reaction products by flash chromatography which gave pure samples of both diastereoisomers of **8** and mixed fractions, the composition of which being deduced from GC and ¹H NMR analysis

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