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On the Chemoselectivity of Pyroglutamates in Reactions with Indole Derivatives

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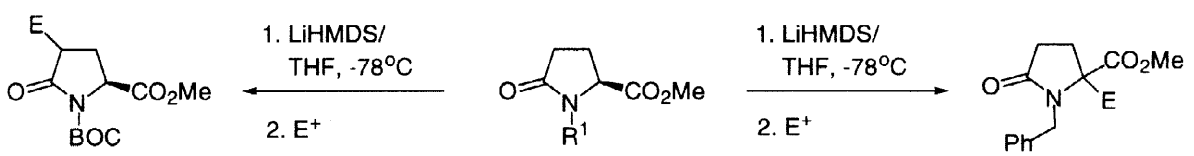
Abstract: Control of the chemoselectivity of reactions of pyroglutamates is determined by the nature of the nitrogen protecting group. Alkylation, aldol and Michael reactions of indole derivatives are explored.

Pyroglutamic acid is a useful starting material for the synthesis of several natural products such as pyrrolidine alkaloids,[1] kainoids,[2] and derivatives of proline[3] and other unnatural aminoacids.[4] We are particularly interested in its use as a scaffold for mimetics of β-turns.[5] Moreover, we wanted to introduce the indole nucleus tethered to different positions of the ring. Previous reports have described the enolization at C4 of hydroxymethylpyrrolidinones or pyroglutamates, the protection of the nitrogen as carbamate being necessary in the latter case.[6] The deprotonation at C2 has been studied in *N*-benzyl thiopyroglutamates,[7] and in alkylations and enantioselective aldol reactions of pyroglutamic acid derived hemiaminals (Seebach's methodology).[8] The possibility of deprotonation at C2 of pyroglutamates and subsequent reactions with electrophiles has been mentioned without description of any examples.[9] No reaction of pyroglutamates involving indole derivatives has been reported. In addition, we have found no studies of Michael-type reactions in these systems. We wish to report here, the easy control of the chemoselectivity of the enolization of pyroglutamates by switching the protecting group on the nitrogen from carbamate to benzyl. Thus alkylations, aldol reactions and Michael reactions of indole derivatives can be carried out either at C2 or at C4 by choosing the appropriate amide protecting group (Scheme 1).



1, R^1 = Bn
2, R^1 = BOC

Scheme 1

Thus *N*-benzyl-L-methyl pyroglutamate **1**, prepared from glutamic acid following literature procedures,[10] was treated with LiHMDS at -78 °C to give the ester enolate which reacted with electrophiles affording compounds **3-5** as mixtures of diastereomeric racemates. (Table 1). On the other hand, the reaction of *N*-BOC-L-methyl pyroglutamate **2** with LiHMDS under the same conditions, gave the enolates at C4 which reacted with the same electrophiles to give compounds **6-8** as mixtures of diastereomers.[11]

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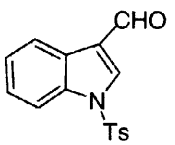
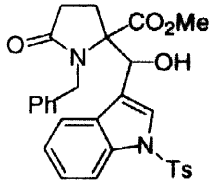
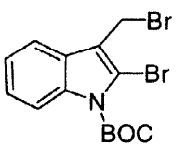
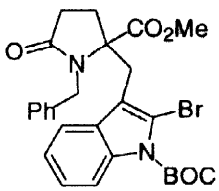
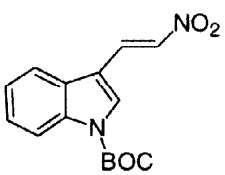
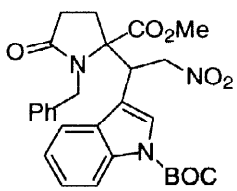
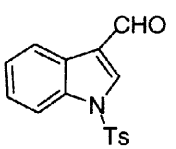
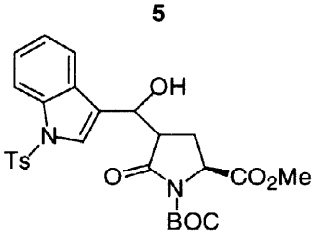
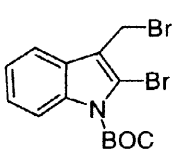
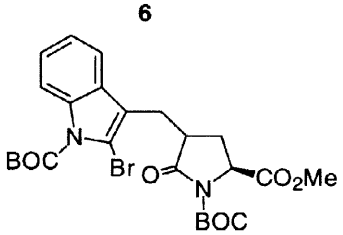
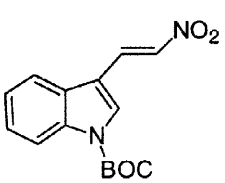
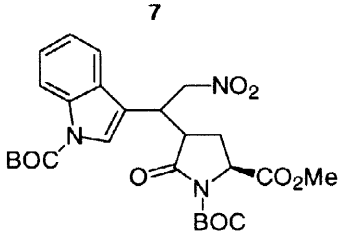
Table1. Reaction products of pyroglutamate enolates with electrophiles

Entry	Starting Material	Electrophile	Product	Yield (%)
1	**1**		 **3**	34 (Major)
2	**1**		 **4**	65
3	**1**		 **5**	30:25
4	**2**		 **6**	11:18:30
5	**2**		 **7**	35:20
6	**2**		 **8**	59 (Mixture)

In all cases no reaction products at any other position or multiple alkylation products were detected by NMR. Cleavage of the pyroglutamic ring was not observed. The nitrogen protecting group seems to direct the deprotonation depending on its electronic effects. In addition the carbamate group probably stabilizes the lactam enolate by coordinating with the lithium as shown in Figure 1.[12]

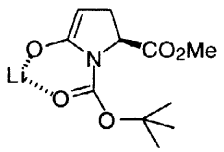


Figure 1

Compound **3** was obtained as a 2 : 1 mixture of diastereomeric racemates. Chromatographic separation allowed us to obtain the major isomer in a 34% yield. Compound **4** was a racemic mixture isolated in a 65% yield. Michael product **5** was a 1 : 1 mixture of racemates which were separated in 30% and 25% yields respectively.

On the other hand, aldol condensation of compound **2** with a protected indole-3-carboxaldehyde gave a mixture of three of the four possible diastereomers **6** (1 : 1.8 : 2.6, HPLC).[13] The isomers were separated and the relative configurations of C2 and C4 were assigned by NOE experiments and confirmed by coupling constants following previously reported data for related compounds.[14] The first two products (11% and 18% yields, respectively) have *trans*-stereochemistry while the major third compound (30% yield) is a *cis*-isomer.

Compound **7** was obtained as a mixture of *cis*- and *trans*- isomers which were separated by chromatography. NMR showed that the major product (2 : 1) was the *trans*- isomer. The yield was 35% and 20% for the pure separated *trans*- and *cis*- isomers respectively.

The Michael reaction of compound **2** afforded a mixture of two compounds (1.5 : 1, HPLC, 59% yield). On separation by preparative HPLC[15] of part of this mixture, NMR showed that in both products the relative stereochemistry of the pyroglutamic ring was *trans*-. Thus, the products have opposite configuration at the stereogenic carbon situated outside the ring. This shows an interesting diastereoselectivity of the Michael reaction in sharp contrast with both aldol and alkylation processes. As Michael reactions have scarcely been explored in pyroglutamic acid derivatives, and in view of this stereochemical result, we are currently studying more examples of this reaction.

In summary, enolization of pyroglutamates with LiHMDS is directed to the 2 or 4 position by the group situated on nitrogen. Electronic and chelation factors may be responsible for this selectivity which can be used to direct aldol condensations, alkylations or Michael reactions to either position of the pyroglutamic ring by choosing the appropriate group on the nitrogen.

Acknowledgments

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