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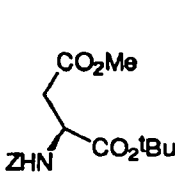
The Synthesis of γ-Substituted Glutamic Acids *via* a Glutamic Acid γ-Enolate Synthon.

Andrew N.C. Johnstone, Stefania Lopatriello, and Michael North*

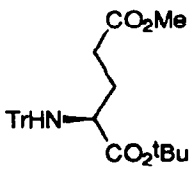
Department of Chemistry, University of Wales, Bangor, Gwynedd, LL57 2UW

Abstract: *Treatment of α-t-butyl γ-methyl N-Z-glutamate (4) with lithium hexamethyldisilazide results in the regiospecific formation of the γ-anion, which reacts with electrophiles to give γ-substituted glutamic acid derivatives.*

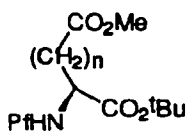
Over recent years we have developed asymmetric syntheses of β-substituted aspartic acids[1], and γ-substituted glutamic acids[2] utilising the regiospecific deprotonation of aspartic acid derivative (1) and glutamic acid derivative (2) respectively. The resulting compounds could then be further manipulated into a variety of natural and unnatural amino acids[3]. Whilst the dianion of compound (1) was a reactive aspartic acid β-enolate synthon, the monoenolate of compound (2) was not very reactive, and would react only with carbonyl compounds, thus limiting the range of γ-substituted glutamic acid derivatives that could be prepared from it[2]. Concurently with this work, Rappoport *et al.* had developed an alternative synthesis of aspartic and glutamic acid derivatives[4] utilising compounds of structure (3) in which the amine is protected by a 9-phenylfluorenyl (Pf) group. Additionally a number of groups have developed γ-anion synthons based on pyroglutamic acid[5] or β-anion synthons based upon β-lactams derived from aspartic acid[6]. Very recently Hanessian *et al.* have reported the reaction of the enolates of aspartic acid derivatives related to compound (1), and of dimethyl *N*-Z-glutamate with MoOOPh and oxaziridines to give β-hydroxyaspartic and γ-hydroxyglutamic acids respectively[7]. This prompts us to report our own recent results on the reaction of the γ-enolate of the orthogonally protected glutamic acid derivative[8] (4) with carbon electrophiles.



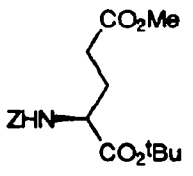
(1)



(2)

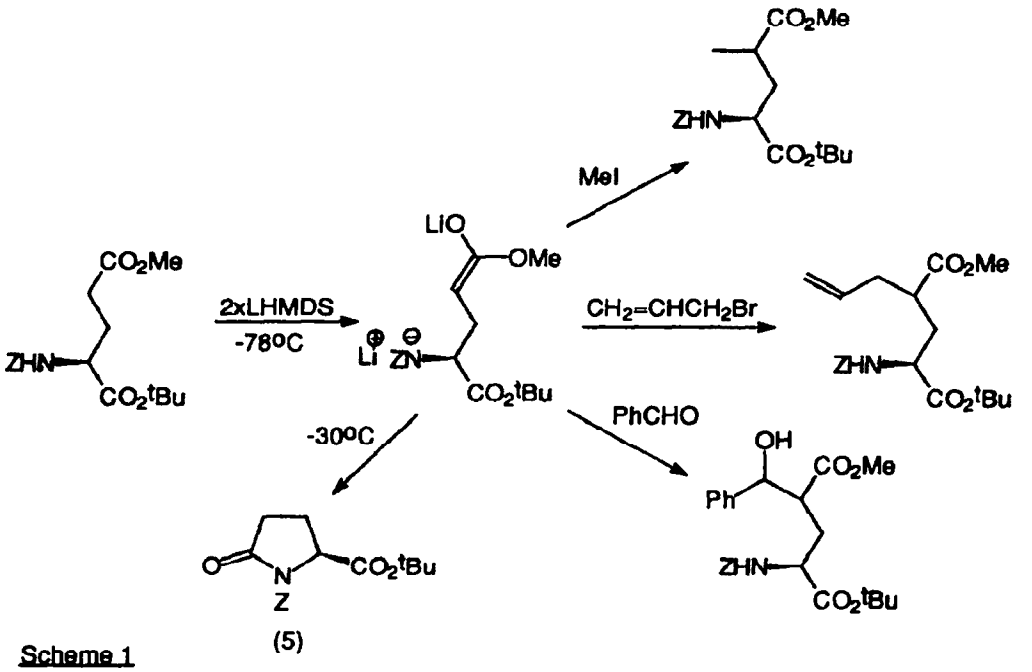


(3)



(4)

Treatment of compound (4) (prepared in three steps from (S)-glutamic acid by the literature procedure[8]) with 2 equivalents of lithium hexamethyldisilazide (LHMDS) in THF at -78°C resulted in the formation of the *N,C*-dianion, which could be trapped with electophiles (alkyl halides or aldehydes) to give the corresponding γ-substituted glutamic acid derivatives[9] in 50-80 yields as shown in Scheme 1. The choice of LHMDS as the base for this reaction was prompted by our previous and ongoing work using the corresponding aspartic acid derivative (1), where less hindered bases (such as LDA) caused significant racemisation due to competing α-deprotonation[1]. Control of the reaction temperature was found to be important for formation of the dianion of glutamate (4), as allowing the reaction temperature to rise to -30°C during formation of the dianion resulted in extensive cyclisation to the corresponding pyroglutamate (5). This is in contrast to the situation with the corresponding aspartate derivative (2), where warming the reaction mixture to -30°C was found to be essential for dianion formation.



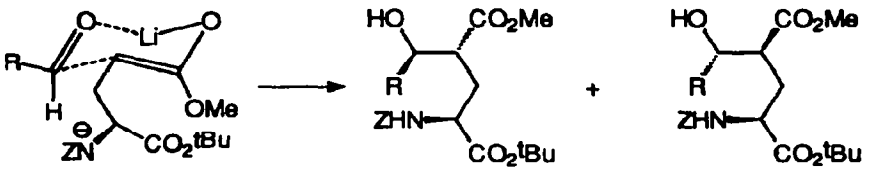
(5)

Scheme 1

As expected based on our previous results[1] with the aspartic acid derivative (1), and Hanessian's recent results with dimethyl *N*-Z-glutamate[7], the benzyloxycarbonyl protecting group electronically prevented α-deprotonation by acidifying the adjacent NH which was subsequently deprotonated. That no racemisation of the α-carbon had occurred was proven by chiral HPLC on the allyl, methyl and benzaldehyde adducts which indicated an enantiomeric purity in excess of 95%[11].

During the reaction of the glutamate enolate with allyl bromide or methyl iodide, a new chiral centre is created, and a 1:1 ratio of stereoisomers is obtained at the γ-carbon for the allyl derivative, a 2:1 ratio being obtained for the methyl adduct[12]. Upon reaction with benzaldehyde, two new chiral centres are created,

however only two stereoisomers[12] are observed in a ratio of 1:1. This is consistent with our previous results on the corresponding aspartate derivative[1], where again alkyl halides gave both possible stereoisomers, and aldehydes gave just 2 of the 4 possible stereoisomers which were later assigned as the *syn*-diastereomer at the newly formed chiral centres by subsequent manipulation[3]. The lack of stereoselectivity in the reaction with alkyl halides suggests that the dianion of compound (4) does not adopt a chelated, cyclic structure as both faces of the enolate are equally accessible. The formation of only the presumably *syn*-isomers of the benzaldehyde adduct however is explained by the formation of a six membered, chelated, cyclic transition state between the enolate and aldehyde in which all the substituents adopt equatorial positions as shown in Scheme 2. Thus the chiral centre at the α-carbon appears to have little effect on the induced stereochemistry at the chiral centres formed during the reaction.



Scheme 2

Further investigations both into the range of electrophiles that will react with the dianion of compound (4), and the manipulation of the adducts into other natural and unnatural products are currently in progress, and will be reported in due course.

Acknowledgements

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9. All new compounds gave satisfactory spectral data.
10. Typical Experimental Procedure: To compound (4) (0.5g, 1.4mMol) dissolved in dry THF (4ml) and cooled to -78°C under an atmosphere of nitrogen was added lithium hexamethyldisilazide (1.0M solution in THF; 3.2ml, 2.2 eq.). The resulting solution was stirred at -78°C for 1 hour, then the electrophile (methyl iodide, allyl bromide, or benzaldehyde) (5.6mmol, 4eq.) was added. The resulting solution was stirred for 1 hour at -78°C, then hydrochloric acid (1.0M, 20ml) was added and the solution allowed to warm to room temperature. The resulting solution was extracted with ether (3x 20ml), the combinated organic phases were dried ($MgSO_4$), and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel using diethyl ether as the eluent.
11. Chiral HPLC was performed on an (R,R)-Whelk column (25cm x 4.6mm) using a solvent system of 90% hexane and 10% propan-2-ol. Peaks were detected by their absorbance at 254nm.
12. Diastereomer ratio were obtained both by integration of suitable peaks in the ^1H nmr spectra and by HPLC[11] with integration of the u.v. detector output; before purification of the reaction products by flash chromatography.

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