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REMOTE O, C- DIANION CHEMISTRY OF PYROGLUTAMATES: REACTION AT C-4 WITH ELECTROPHILES[1]

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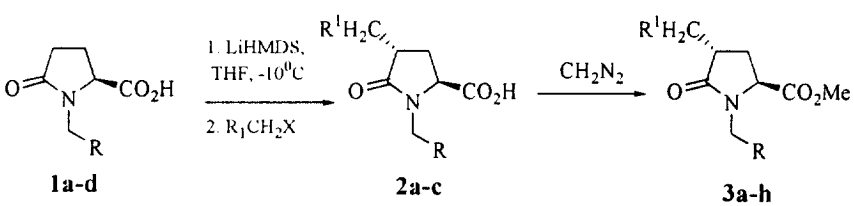
Abstract: *O, C- Di-lithio di-anions derived from N-substituted pyroglutamic acids react with electrophiles to give C-4 α- substituted products.*

The chemistry of l-pyroglutamic acid, the cyclic form of the inexpensive natural l-glutamic acid, has seen exponential growth and pyroglutamates have emerged as the starting material of choice for the synthesis of various natural products.[2] Functionalisation at C-4 of pyroglutamic acid was carried out initially *via* lithium enolates derived from 2-protected hydroxymethyl derivative as a carboxylic acid equivalent.[3] Later it was observed that N-urethane protected pyroglutamates do not undergo racemisation and Li and Ti enolate chemistry was successfully used to prepare C-4 substituted pyroglutamates.[4, 5] However in the case of N-alkyl pyroglutamates the usual Li enolate chemistry gives C-2 substituted racemic products [6] and the only report of C-4 functionalization of such compounds is *via* a thio-Claisen rearrangement.[7] Remote O,C-dianion chemistry has been utilized for the synthesis of various molecules[8] and we thought it fit to investigate O,C-dianion chemistry to prepare exclusively C-4 substituted products. In the present communication we describe the generation of O,C-di-lithio enolates of N-substituted pyroglutamic acids and their reactions with electrophiles to give exclusively the 4-α-substituted products.

In a typical procedure, a solution of N-phenylmethylpyroglutamic acid **1a**[9](1.09g,5 mmol, dissolved in 50ml dry THF) was added dropwise to a magnetically stirred solution of LiHMDS (11ml, 1 M solution in THF) in THF (50 ml, distilled freshly from sodium benzophenone ketyl radical) at -10 °C. The resulting turbid solution was stirred for 1hr at -10 °C. A solution of benzylbromide (0.6ml, 5 mmol in 10 ml THF) was added dropwise and the stirring was continued for an additional hour. The reaction mixture was allowed to warm to room temperature and then



1a-d **2a-c** **3a-h**

No.	R	R^1
2a	C_6H_5	C_6H_5
2b	3-$OCH_3C_6H_4$	C_6H_5
2c	3-$OCH_3C_6H_4$	4-ClC_6H_5
3a	C_6H_5	C_6H_5
3b	C_6H_5-	4-BrC_6H_5
3c	C_6H_5	4-ClC_6H_5
3d	C_6H_5	vinyl
3e	4-$CH_3C_6H_4$	C_6H_5
3f	4-CH_3-C_6H_4	4-BrC_6H_5
3g	H	C_6H_5
3h	C_6H_5	H

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quenched by the addition of 2N HCl. Ethyl acetate (200 ml) was added and the organic layer was washed with sat. brine, dried (Na_2SO_4), and concentrated to give the crude product which was purified using flash chromatography to give **2a** . In similar reactions of **1a-d** with halides, compounds **2b-c** were prepared. However, it was later found convenient to esterify the crude product with diazomethane before column chromatography and to isolate the corresponding esters **3a-h**.[10]

The present procedure has the advantage of using moderate temperatures in contrast to -78°C used for usual enolate chemistry and its applicablity to substitute C-4 of pyroglutamic acid without a N-urethane protection. The limitations of the present methodology appear to be the failure of the O, C-di Li enolate to react with carbonyl electrophiles as evidenced by the attempted reaction of **1a** with various aromatic aldehydes.

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10. (a) 4-α assignments were made on the basis of the ^{1}HMR. **2a** was converted to methyl 4-α- benzylpyroglutamate (1. Li-NH_3, 2. CH_2N_2) for its comparison with a previously made sample. **3h** was assigned 4-α stereochemistry on the basis of N.O.E. (b) Yields: **2a**, 56; **2b**, 52; **2c**, 54; **3a**, 58; **3b**, 50; **3c**, 50; **3e** 54; **3f**, 60; **3g**, 48; **3h**, 8% . Low yields of 4-methylated products have also been reported previously (Ezquerra,J; Pedregal,C; Rubio,A; Yruretagoyena,B; Escribano,A; Ferrando, F.S. *Tetrahedron* **1993**, 49, 8665). (c) The presence of the 4-cis products was not observed by the tlc of the crude reaction mixtures.