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The Reaction of Lithium Trimethylsilyldiazomethane with Pyroglutamates - a Facile Synthesis of 6-Diazo-5-oxo-norleucine and Derivatives

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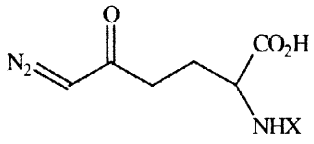
Abstract: The reaction of carbamate derivatives of pyroglutamic acid esters with the lithium salt of trimethylsilyldiazomethane below -100°C gives good yields of the corresponding substituted 6-diazo-5-oxo-norleucine esters; cleavage of Fmoc-substituted products provides a safe, convenient route to the parent acid.

In the course of research into the synthesis of potential enzyme inhibitors, it became necessary to prepare gram quantities of diazoketones of the general structure (**1**), derived from *N*-protected glutamic acid. It was also desirable that the blocking group X should be removable under conditions which did not destroy the diazoketone function.



1 a X = CF_3CO, R = Et
b X = CF_3CO, R = Me
c X = R = H
d X = $PhCH_2CO_2$, R = $PhCH_2$

Few examples of this type of compound have been reported. Esters **1a**, **1b** are intermediates in closely related syntheses [1,2] of 6-diazo-5-oxo-norleucine (DON), **1c**, and **1d** is

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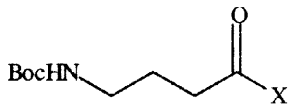
a precursor of 5-hydroxy-L-pipecolic acid [3]. In all of the preparations the diazoketones are obtained by the reaction of the sidechain carboxylic acid group of a glutamate, activated by conversion to an acid chloride or mixed anhydride, with diazomethane, a notoriously hazardous reagent.

Recently trimethylsilyldiazomethane (TMSD), commercially available, (or readily synthesised [4]) has found increasing use as a safe substitute for diazomethane, and we here describe its application to the preparation of the desired diazoketones.

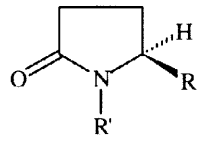
In preliminary experiments no reaction was observed between TMSD and mixed anhydride **2a** or acid fluoride **2b** (used to minimize spontaneous cyclisation [5]).



2 a X = O_2CEt
b X = F

Similar results were obtained when TMSD was replaced by its more reactive lithium salt, LTMSD, but this might be attributed to competing abstraction by the reagent of a proton from the nitrogen of the carbamate blocking group.

To circumvent this problem it was decided to exploit the enhanced reactivity towards nucleophiles of the carbonyl group of lactams having a carbonate function on nitrogen. Following the original discovery [6] that the amide bond of *N-tert*-butoxycarbonyl-2-pyrrolidone is cleaved by hydrolysis/methanolysis, it has been shown that *N-tert*-Boc pyroglutamate esters undergo ring opening with Grignard reagents [7,8], ester lithium enolates [9,10], carbon nucleophiles [11] and heteronucleophiles with KCN catalysis [12].



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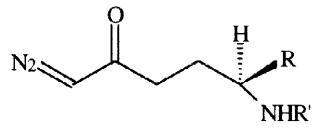

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Treatment of pyrrolidone **3a** with LTMSD at -78°C gave diazoketone **4a** as a minor product, together with polymeric material. If, however, the reaction was kept below -100°C **4a** could be isolated in 60% yield. A similar result was obtained with the Fmoc-pyrrolidone **3b**.

The *N*-protected pyroglutamate esters **3c** to **3h** also reacted cleanly at the lactam carbonyl with LTMSD to give diazonorleucinates **4c** to **4h** in moderate to good yield (see Table).

Table Conversion of pyroglutamates **3** to norleucinates **4**

3	R	R´	4	Yield[a,b] (%)
a	H	t-Boc	**a**	60
b	H	Fmoc	**b**	69
c	CO_2Et	t-Boc	**c**	66
d	CO_2CH_2Ph	t-Boc	**d**	71
e	CO_2t-Bu	t-Boc	**e**	75
f	CO_2Et	Alloc	**f**	63
g	CO_2Et	Fmoc	**g**	72
h	CO_2CH_2Ph	Fmoc	**h**	61

[a]Yields after purification by flash chromatography

[b]All novel compounds gave satisfactory spectroscopic and analytical data

A typical procedure, for the preparation of 4**g,** is as follows.

To a cold (-100°C) solution of trimethylsilyldiazomethane (3.7 ml of a 2M solution in hexane, 7.4 mmol) in THF (35ml) under an inert atmosphere was added n-butyllithium in hexane (4.75 ml; 1.6M, 7.6 mmol). The reaction was stirred for 30 min and transferred via cannula to a solution of **3g** (6.18 mmol) in THF (62 ml) at -105°C at such a rate as to maintain an internal temperature of -100°C or lower. The mixture was stirred for a further 10 min and quenched by addition of the cold solution to saturated ammonium chloride (200 ml). Following a normal workup, purification by flash chromatography (silica gel 60 eluting with 7:3 petroleum ether (b.p. 40-60°C) : ethyl acetate 7:3) afforded the product as pale yellow plates (1.88 g, 72%, m.p. 121-122°C).

It proved difficult to effect removal of the blocking group on nitrogen without destruction of the diazoketone. The t-Boc compounds **4c** to **4e** were decomposed by $SnCl_4$ [13] and by trimethylsilyl iodide [14] or triflate [15], as was allylic compound **4f** by $Pd(Ph_3P)_4$ [16]. Reaction with KF-18-crown 6 [17] or with DNU [18] of Fmoc-containing products **4g**, **4h** gave low yields of the corresponding aminodiazoketones which rapidly decomposed on storage. However, brief treatment of **4g** or **4h** with piperidine gave high yields of DON[1], **1c**, providing the safest and most convenient route to research quantities of this acid so far described.

[1] **3g** (0.73 g, 1.73 mmol) was added to piperidine (15 ml) and the mixture stirred vigorously for 2 min. The resulting solution was poured into ice-cold water (60 ml). The reaction was filtered and the filtrate evaporated under high vacuum at room temperature to afford a pale brown solid. The residue was crystallised from a minimum amount of water by addition of dry methanol to give **1c** as a pale yellow solid (0.241 g, 81%) decomposing at 146°C (Lit. [1] mp 144 - 155°C). The IR and NMR spectra agreed with those previously reported for DON[2].

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