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Studies on Pyrrolidinones. An Improved One Pot Synthesis of 1,2,3,5,10,10a-Hexahydrobenz[f]indolizine-3,10-dione

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STUDIES ON PYRROLIDINONES.
AN IMPROVED ONE POT SYNTHESIS OF 1,2,3,5,10,10a-HEXAHYDROBENZ[f]INDOLIZINE-3,10-DIONE

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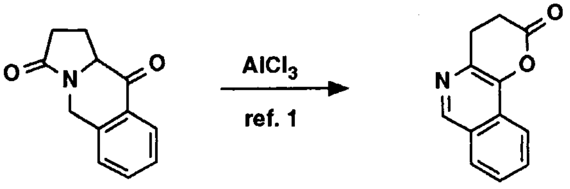
Abstract: *Starting from the readily available N,O-bis trimethylsilyl pyroglutamate, an easy high yield one pot synthesis of ketone 1 was described.*

The title ketone 1 proved to be of great interest due to the large diversity of rearrangements observed in this family of compounds (scheme 1):



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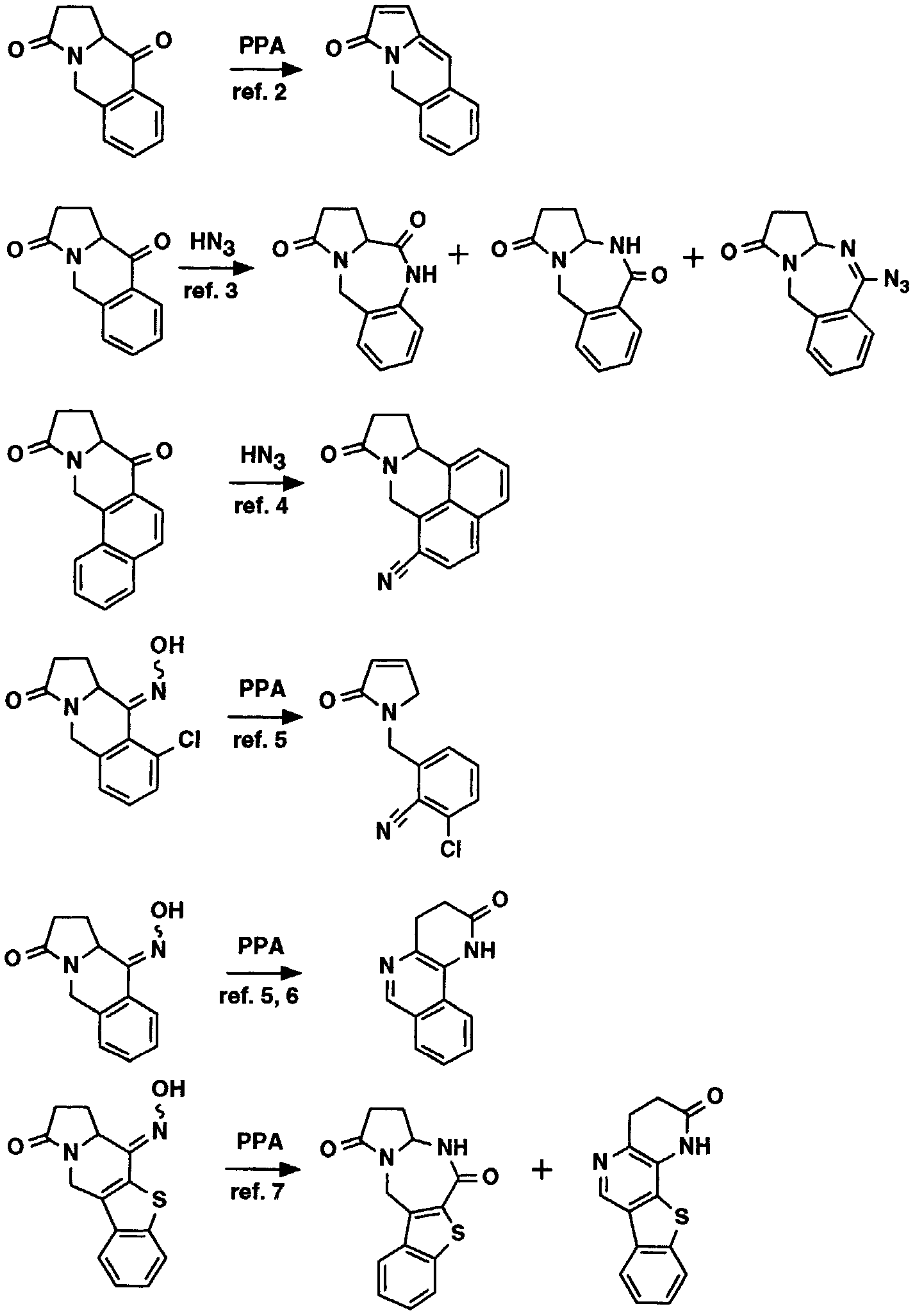
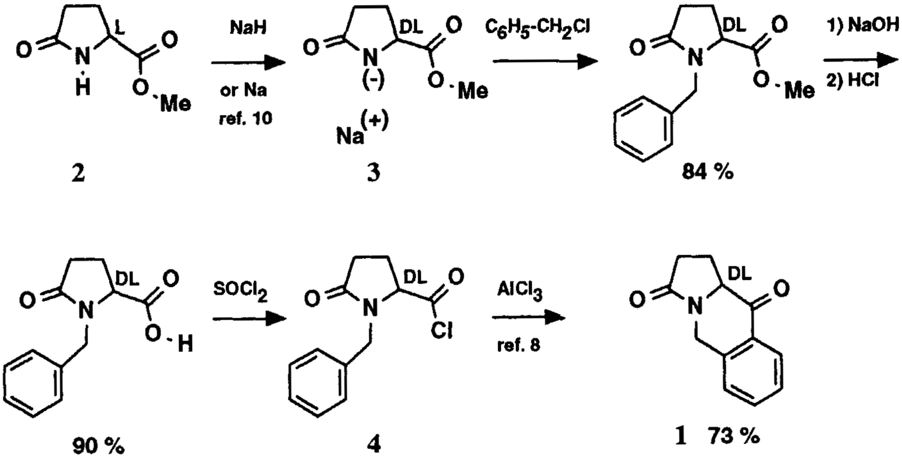


Scheme 1

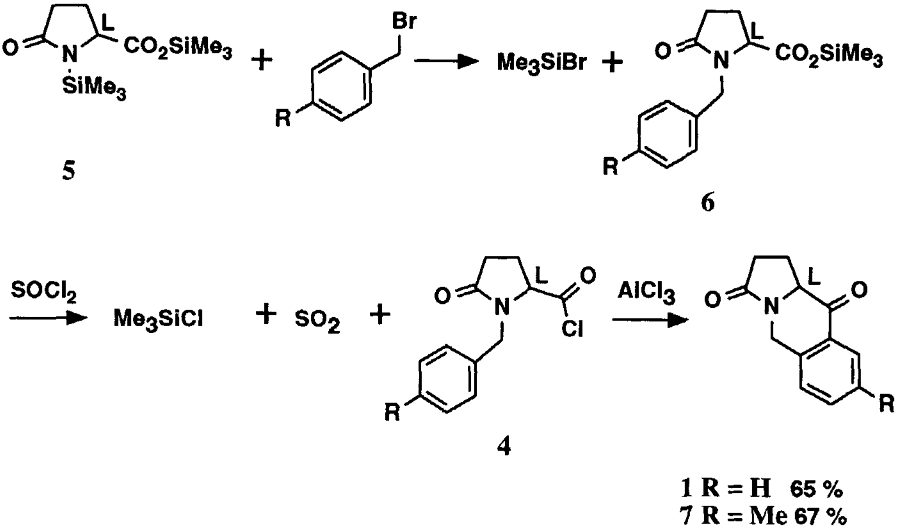
We have already described[8] a five-step synthesis of the racemic form of ketone 1, starting from the readily available L-methyl pyroglutamate 2[9] (scheme 2):



Scheme 2

While this reaction scheme gives a satisfactory 55% overall yield, it suffers from several drawbacks, including the racemization of the sodium salt 3[11], the need of multiple reaction pots and of purification of intermediates.

We now wish to report a one-pot synthesis of ketone 1: the reaction of benzyl bromide with N,O-bis trimethyl silyl pyroglutamate 5[12] while distilling trimethylsilyl bromide[13] gives the trimethylsilyl ester 6 ; in the same pot thionyl chloride was added and after heating, the acid chloride 4 was formed[14] in a quantitative crude yield ; the trimethylsilyl chloride formed was distilled off and aluminum chloride was added ; after



Scheme 3

hydrolysis and distillation, the heterocycle 1 was obtained in 65% overall yield (this mainly reflects the yield of the distillation step and could be improved by working on a larger scale) (scheme 3).

The advantages included in this reaction scheme are the simplicity and the rapidity of the method (2 days *vs.* more than a week), and a best overall yield (65% of an optically active product 1 *vs.* 55% of a racemic compound) ; it should be noted that these reactions can be generalized to this whole heterocyclic family, and by the same way we obtained the ketone 7 in 67% yield.

Experimental

A stirred mixture of N,O-bis trimethylsilyl pyroglutamate 5 (8 g, 29.2 mmol) and benzyl bromide (5 g, 29.2 mmol) was heated under nitrogen atmosphere for 18 hours at 150°, in a vessel equipped with a short distillation head. During the course of the reaction, trimethylbromosilane evolved and silyl ester 6 was formed.

After cooling, CH_2Cl_2 (50 ml) and thionyl chloride (3.9 g, 2.4 ml, 32.8 mmol) were added and the mixture was refluxed for 6 hours. The dichloromethane and the trimethylchlorosilane formed were distilled at once, giving a 100 % nmr crude yield of acid chloride 4.
The residue was dissolved in dichloromethane, the solution was cooled at -2°C then aluminum chloride (12 g, 90 mmol) was slowly added (45 mn).
The next day, the mixture was hydrolyzed with ice cooled water, the organic phase was washed with water and the dichloromethane solution was dried (sodium sulfate), evaporated, and the residue was vacuum distilled, giving 65 % yield of ketone 1, identical to the authentic product[8].

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Our supplier of pyroglutamic acid is UCIB, Ivry-la Bataille, France, which can provide this acid in bulk quantities.

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