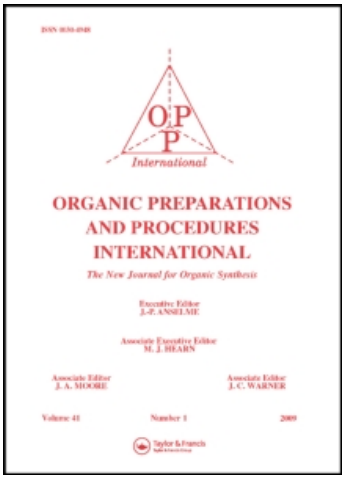

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A NEW ROUTE TO THE SYNTHESIS OF NITROXIDE CARBOXYLIC ACIDS

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A NEW ROUTE TO THE SYNTHESIS OF NITROXIDE CARBOXYLIC ACIDS

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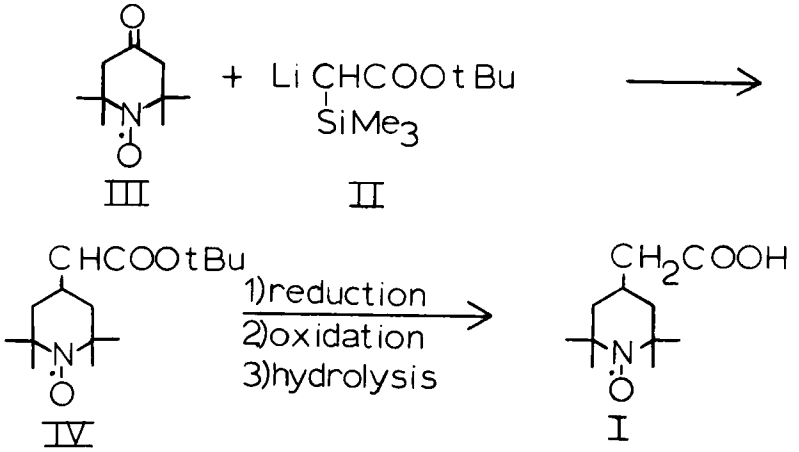
The nitroxyl carboxylic acid I was needed as an intermediate in the preparation of spin labeled esterase inhibitors.[1-3] Kosman and Piette[4] previously reported that the ethyl ester of I could be prepared using a modified Wittig reaction employing the ylide derived from triethylphosphonoacetate to react with the corresponding ketone, followed by reduction of the resulting olefin. Upon reoxidation of the hydroxylamine to the nitroxide using lead dioxide, the desired nitroxide was obtained. We found that the yield of the olefin (IV) from this modified Wittig was unacceptably low. However, reaction of lithio t-butyl trimethylsilylacetate (II) with 4-oxo-2,2,6,6-tetramethylpiperidinoxyl (III)[5] proved to be a highly satisfactory route to the desired product (IV).



The primary advantage of the lithio t-butyl trimethylsilylacetate procedure over the modified Wittig reaction is that the yield of the desired product is high (> 90%) which has been reported to represent a decrease in undesirable side-reactions as well as a greater efficiency of reaction[6]. This appears to be a direct result of the greater reactivity of the lithium ester enolate which is demonstrated by its rapid reaction with ketones at -78°C. On the other hand, phosphonates require higher temperatures (20-80°C) to complete the reaction. Finally, the lack of phosphorus containing products results in a simplified work-up procedure.

EXPERIMENTAL

t-Butyl trimethylsilylacetate.- A hexane solution of n-butyl lithium (12.5 ml, 25 mmoles) was added to a nitrogen flushed, ice cold flask containing 40 ml dry, freshly distilled tetrahydrofuran. Diisopropylamine (4.2 ml, 30 mmoles) was added to this solution with stirring over a 5 min. period, keeping the temperature below 5°C. The flask was then transferred to a dry ice-acetone bath (-78°C) and t-butylacetate (2.9g, 25 mmoles dissolved in 20 ml of dry tetrahydrofuran) was added slowly. After 20 min. of additional stirring at this temperature, chlorotrimethylsilane (3.17 ml, 25 mmoles) was added. The mixture was then allowed to warm to 20°C at which point, it was made acidic with 10% hydrochloric acid and extracted three times with pentane-ether mixture (1:1). The combined extracts were dried over magnesium sulfate and fractionally distilled under vacuum giving 4 g (85%) of t-butyl trimethylsilylacetate, bp. 64-67°/13mm, lit.[6] bp. 65-67°/13mm.

t-Butyl-2,2,6,6-tetramethylpiperidinoxylideneacetate (IV).- A solution of diisopropylamine (4.2ml, 30 mmoles) in 40 ml dry, freshly distilled tetrahydrofuran was slowly added to a solution of n-butyllithium (12.5 ml, 25

mmoles) in hexane contained in a nitrogen flushed magnetically stirred flask which was cooled with ice such that the temperature of the reaction mixture remained below 5°C. The flask was then transferred to a dry ice-acetone bath (-78°C) and t-butyltrimethylsilyl acetate (4.7g, 25 mmoles) dissolved in 20 ml of tetrahydrofuran was added over a 30 min. period. After the addition, the mixture was stirred for 20 min. and 4-oxo-2,2,6,6-tetramethylpiperidinoxyl (III, 4.25g, 25 mmoles) in 20 ml of tetrahydrofuran was added. The mixture was allowed to stir for an additional 10 min. at -78°C and then warmed to 20°C. At this point, water was added and the pH adjusted to 3-4 with 5% HCl. The acidified mixture was extracted three times with pentane-ether (1:1), the combined extracts were dried over magnesium sulfate and evaporated to dryness. The resulting red solid was purified by column chromatography (alumina grade I eluted with ether) to give 6.06g (90.5%) product, mp. 74-75°C (hexane). Anal. Calcd for $C_{15}H_{26}NO_3$ C, 67.13; H, 9.76; N, 5.22. Found: C, 66.91; H, 9.61; N, 4.93.

4-Carboxymethyl-2,2,6,6-tetramethylpiperidinoxyl (I).- Reduction of 4 g of IV with hydrogen (50 psi, Parr shaker) using Pd/C as a catalyst in absolute methanol for 24 hrs. was undertaken. The catalyst was filtered and the solvent evaporated to dryness giving a colorless oil. The absence of the olefin stretching in the ir spectrum showed that the exo double bond was reduced. The amine was re-oxidized to the nitroxide by dissolving the oil in 40 ml methanol and adding 3.5 ml acetonitrile, 1.8 g sodium hydrogen carbonate, 0.25 g sodium tungstate and 10 ml 30% hydrogen peroxide. This mixture was allowed to stand at room temperature for 4 days. At this point, the mixture was diluted with 200 ml of saturated sodium chloride and the pH was adjusted to 3-4 with 5% HCl. After the

solution was exhaustively extracted with ether, the ethereal extract was dried over magnesium sulfate and evaporated to dryness. The remaining oil was hydrolyzed giving 3 g.(93%) of 4-carboxymethyl-2,2,6,6-tetramethyl-piperidinoxyl (I) as a viscous red oil.

Anal. Calcd for $C_{11}H_{20}NO_3$: C, 61.65; H, 9.41; N, 6.54. Found: C, 61.53; H, 9.58; N, 6.62.

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