

THE SIDE-CHAIN ACYLAMINATION OF ALICYCLIC NITRONES. A NEW SYNTHESIS OF AN  $\alpha$ -AMINO ACID

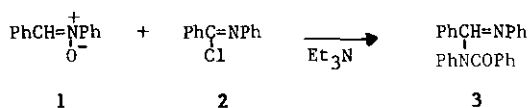
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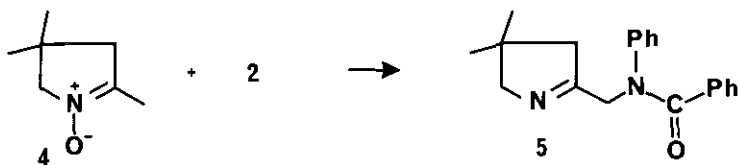
**Abstract** - 2,4,4-Trimethyl- $\Delta^1$ -pyrroline-1- (4) and 2-n-butyl-4,4-dimethyloxazoline-3-oxide (6) are acylaminated in the presence of base at the  $\alpha$ -position of the side-chain at C-2 to give 5 and 10, respectively. Ethanolysis of 10 gives the corresponding  $\alpha$ -amino ester (11) in good yield.

The reaction of 2- and 4-picolines with an imidoyl chloride in the presence of a base has been shown to give the side-chain acylaminated product.<sup>1</sup> We have also shown that five-membered cyclic nitrones also undergo acylation at the nitron carbon in the absence of base, and we now confirm that this is also true of acyclic nitrones. We have also extended the side-chain acylation to five-membered nitrones. The publication of a paper on the cycloaddition reactions of oxazoline N-oxides<sup>3</sup> encourages us to report our preliminary observations.

$\alpha$ ,N-Diphenylnitron (1) reacted with N-phenylbenzimidoyl chloride (2) in the presence of triethylamine to give N-benzoyl-N,N'-diphenylbenzamidine (3) (76%).

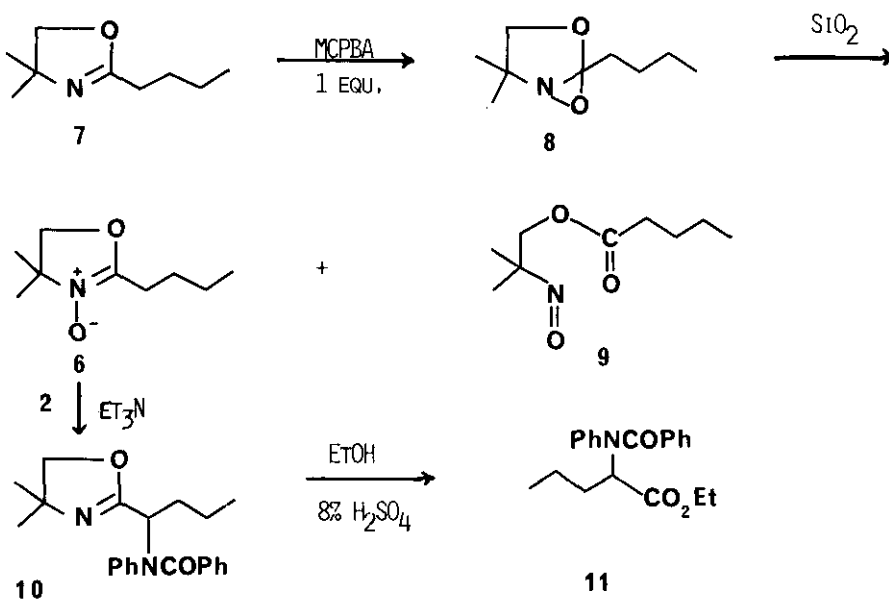


2,4,4-Trimethyl- $\Delta^1$ -pyrroline-1-oxide (4)<sup>4</sup> reacted smoothly with 2 in the presence of Et<sub>3</sub>N in ethylene chloride at room temperature to give triethylamine hydrochloride (72%), and an oil which was resolved by dry column chromatography into benzanilide and 2-(N-benzoyl-N-phenylaminomethyl)-4,4-dimethyl- $\Delta^1$ -pyrroline (5) (23%), mp 77-78°C [IR 1645 (C=O), 1598 cm<sup>-1</sup> (C=N); NMR (CDCl<sub>3</sub>)  $\delta$  7.1 (10H, m, 2C<sub>6</sub>H<sub>5</sub>), 4.80 (bs, 2H, = $\overset{\cdot}{\text{C}}$ -CH<sub>2</sub>- $\overset{\cdot}{\text{N}}$ -), 3.57 (bs, 2H, CH<sub>2</sub>), 2.49 (bs, 2H, CH<sub>2</sub>), 1.08 (s, 6H, Me<sub>2</sub>)]. Preliminary indications are that 4,4-dimethyl-2-ethyl- $\Delta^1$ -pyrroline-1-oxide behaves similarly.



The same sequence of reactions could be achieved starting with 2-n-butyl-4,4-dimethyloxazoline-3-oxide (6). This was prepared from 2-n-butyl-4,4-dimethyloxazoline (7) using a procedure modelled after that of Lee and Keane:<sup>5</sup> oxidation of 7 with 1 equiv. of m-chloroperbenzoic acid followed by ring-opening of the oxaziridine (8) gave 6 (67%) together with the nitroso-ester 9 (blue monomer, colorless dimer) by chromatography on a silica gel column. The chromatography has to be carried out expeditiously. If the epoxide  $\rightleftharpoons$  N-oxide is allowed to remain on the column for too long (45 min in this case) some degradation of the oxazoline ring occurred and valeric acid (37%) was isolated. If the time was too short (10 min) 50% of starting material was recovered. The optimum time for the conversion 8  $\rightarrow$  6 was 20 min in the present instance. It is also important to avoid using more than one equivalent of m-chloroperbenzoic acid. With two equivalents only the blue nitroso-esters are obtained.<sup>5,6</sup>

Treatment of 6 with 2 in the presence of  $\text{Et}_3\text{N}$  at room temperature gave 10 (85%) as an oil [ $\delta$ 7.6-7.2 (m, 10H, 2Ph), 5.5 (t, 1H,  $-\overset{\text{H}}{\text{C}}-\overset{\text{H}}{\text{C}}=\text{N}$ ); 4.0 (br s, 2H,  $-\text{CH}_2-\text{O}$ ), 2.3-1.0 (m, 15H, gem- $\text{Me}_2$  and  $\text{C}_4\text{H}_9$ );  $\text{M}^+$  m/e 350.1995 (Calcd. for  $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_2$ : m/e 350.1994), together with benzanilide (15%). The purity of 10 was confirmed by gas chromatography (10% OV 101 on Gas Chrom Q column at 220°C) which showed the presence of only one compound. Ethanolysis of 10 gave



ethyl 2-(N-benzoyl-N-phenyl)aminovalerate (11) (93%): bp 150°C at 10<sup>-4</sup> mm; IR (film) 1730 (s) (ester C=O), 1650 (s) cm<sup>-1</sup> (amide C=O); NMR (CDCl<sub>3</sub>) δ 7.3 (br, 10H, 2Ph), 4.9 (t, 1H, -CH(NR<sub>2</sub>)CO<sub>2</sub>Et), 4.25 (q, 2H, O-CH<sub>2</sub>CH<sub>3</sub>), 2.2-0.8 (m, 12H, C<sub>4</sub>H<sub>9</sub> and OCH<sub>2</sub>CH<sub>3</sub>). This reaction sequence effectively represents the replacement of an α-hydrogen atom in valeric acid by an aniline residue, and is the first example of what, it is hoped, will be a new general synthesis of substituted α-amino acids -- and thence to the corresponding aldehydes<sup>7</sup> --, particularly in view of the ready availability now of 2,5,5-trimethyloxazoline N-oxide.<sup>3</sup>

## ACKNOWLEDGEMENTS

This work was supported by a grant from the National Institutes of Health (GM 25242). H. B. thanks Pensacola Junior College for the sabbatical leave during which time this work was carried out.

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Received, 12th September, 1984