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A New Synthesis of Monosubstituted Succinaldehydes and 3-Substituted Pyrroles from Acetonitriles. Formal Synthesis of 2,3-Dihydro-7-methyl-2H-pyrrolizidin-1-one (Danaidone), a Semiochemical of Danaid Butterflies.

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Abstract. A convenient and versatile synthesis of monosubstituted succinaldehydes and 3-substituted pyrroles from acetonitriles was devised. The methodology was applied to the preparation of <u>9</u>, the penultimate intermediate in the Meinwald and Meinwald synthesis of Danaidone.¹² Copyright © 1996 Elsevier Science Ltd

3-Substituted pyrroles are intermediates of great importance in the synthesis of certain natural products,¹ medicinal agents,² and conducting polymers.³ Convenient synthetic access to 3-substituted pyrroles has however, been a long standing problem because kinetic electrophilic substitution of pyrrole occurs predominantly or exclusively at the α -position(s).⁴ Consequently, numerous methods have been devised to circumvent this problem.⁵ This publication describes an efficient four steps route to such compounds, the central feature of which involves the generation of α -substituted succinaldehydes from readily availabe acetonitriles.⁶

The process is carried out in the following manner. The acetonitriles $\underline{1}$ (Scheme 1) are converted into the corresponding anions with *n*-BuLi or LDA (1.1 eq.) in THF-HMPA (10:1) at -70 °C, and then alkylated with bromoacetaldehyde diethylacetal (2 eq.; -70 °C to r.t.). The substituted acetonitriles $\underline{2}$ thus obtained in 70-80% yields,⁷ are reduced with DIBAL in anhydrous toluene (-70 °C) to the imines $\underline{3}$, which are hydrolyzed *in situ* with 2N HCl at room temperature to the α -substituted succinaldehydes $\underline{4}$.⁸ The 3-substituted pyrroles are then obtained by a Paal-Knorr type cyclization of the crude succinaldehydes with methanolic ammonium acetate or a primary amine in the presence of a catalytic amount of acetic acid at room temperature.⁹

The noteworthy features of this process are simplicity, versatility, readily and often commercially available starting materials, and good overall yields of the 3-substituted pyrroles (see Table). In design it is similar to the synthesis of 3-substituted pyrroles described by Babler, *et. al.*¹⁰



 Table

 Synthesis of 3-Substituted Pyrroles 5.

Compound:	R ¹	R ²		Overall % yield
<u>5a</u>	Ph	H	Oil (ref ¹⁴ , m.p. 40-42 °C).	37
<u>5b</u>	2-ClPh	H	Oil (ref ²).	36
<u>5c</u>	Ph	Ph	Solid, m.p. 120-121 °C (ref ¹⁵ , m.p. 122-123 °C).	40
<u>5d</u>	Ph	c-C6H11	Liquid.	48
<u>5e</u>	Ph	HO(CH ₂) ₃	Oil.	44
<u>5f</u>	2-ClPh	Ph	Solid, m.p. 41-42 °C.	41
<u>5g</u>	2-CIPh	c-C6H11	Liquid.	47
<u>5h</u>	(CH3)2CH	c-C6H11	Liquid.	33

The utility of this methodology is further illustrated by the synthesis of 1-(2-cyanoethyl)-3-methyl pyrrole (2, Scheme 2). Because of the difficulty encountered in the selective monoalkylation of propionitrile (1, R=Me) with bromoacetaldehyde diethyl acetal, a minor modification of the above process was developed. The ethylene acetal of 3-cyanopropionaldehyde (7, Scheme 2), prepared in 95% yield from the known iodide $\underline{6}$,¹¹ was lithiated with LDA in the usual manner, and then alkylated with methyl iodide. This modified procedure provided the required nitrile $\underline{8}$ in 80% yield. This substance was then transformed into $\underline{9}$ by the reaction sequence described above in 40% yield. Meinwald and Meinwald have reported the two step conversion of $\underline{9}$ into the bicyclic ketone

<u>10</u>, a semiochemical of certain Danaid butterflies.¹² The work described herein thus constitutes a formal and only the third synthesis of this bicyclic ketone.¹³



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