Pergamon

Tetrahedron Letters, Vol. 37, No. 24, pp. 4099-4102, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00765-4

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.

Jose Manuel Méndez[a]*, Blas Flores[a], Fernando León[a],
María Eugenia Martínez[a], Alfredo Vázquez[a],
Gustavo Alberto García[a] and Manuel Salmón[b].

[a] Departamento de Química Orgánica, División de Estudios de Posgrado, Facultad de Química,
Universidad Nacional Autónoma de México, Ciudad Universitaria, 04510 México, D.F.
[b] Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior,
Ciudad Universitaria, 04510 México, D.F.

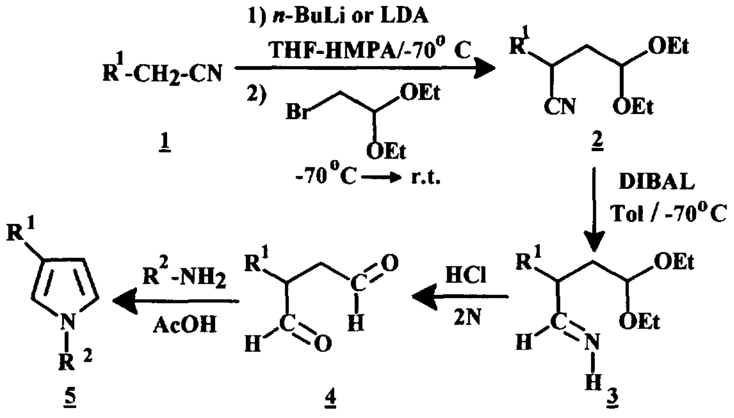
Abstract. A convenient and versatile synthesis of monosubstituted succinaldehydes and 3-substituted pyrroles from acetonitriles was devised. The methodology was applied to the preparation of 9, the penultimate intermediate in the Meinwald and Meinwald synthesis of Danaidone.[12]

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 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 2 thus obtained in 70-80% yields,[7] are reduced with DIBAL in anhydrous toluene (-70 ° C) to the imines 3, which are hydrolyzed *in situ* with 2N HCl at room temperature to the α-substituted succinaldehydes 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]

Scheme 1.



Table

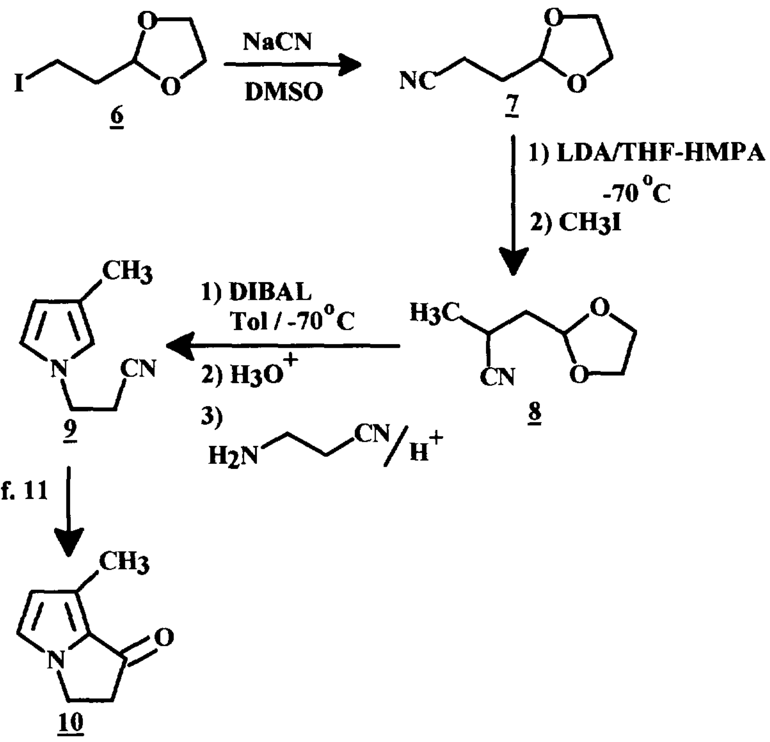
Synthesis of 3-Substituted Pyrroles 5.

Compound:	R^1	R^2		Overall % yield
5a	Ph	H	Oil (ref[14], m.p. 40-42 °C).	37
5b	2-ClPh	H	Oil (ref[2]).	36
5c	Ph	Ph	Solid, m.p. 120-121 °C (ref[15], m.p. 122-123 °C).	40
5d	Ph	c-C_6H_{11}	Liquid.	48
5e	Ph	$HO(CH_2)_3$	Oil.	44
5f	2-ClPh	Ph	Solid, m.p. 41-42 °C.	41
5g	2-ClPh	c-C_6H_{11}	Liquid.	47
5h	$(CH_3)_2CH$	c-C_6H_{11}	Liquid.	33

The utility of this methodology is further illustrated by the synthesis of 1-(2-cyanoethyl)-3-methyl pyrrole (9, 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 6,[11] was lithiated with LDA in the usual manner, and then alkylated with methyl iodide. This modified procedure provided the required nitrile 8 in 80% yield. This substance was then transformed into 9 by the reaction sequence described above in 40% yield. Meinwald and Meinwald have reported the two step conversion of 9 into the bicyclic ketone

10, 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]

Scheme 2.



Acknowledgements.

We gratefully acknowledge financial support from DGAPA-UNAM-IN207791.

We also wish to thank Dr. James H. Babler, Dept. of Chemistry, Loyola University, Chicago, for providing us with copies of the IR and ^{1}H NMR spectra of 5a, Dr. Joseph M. Muchowski for the writing and revision of this manuscript, and Miss Alejandrina Acosta, Graciela Chávez and Maricela Gutiérrez for their assistance in acquiring spectral data.

References and Notes

1. Sundberg, R.J.; In "*Comprehensive Heterocyclic Chemistry*", Bird, C.W.; Cheesman, G.W.H.; Eds.; Pergamon Press; Oxford , Vol. 4, Part III, 1984, 313, and references therein.
2. Sakai, K.; Suzuki, M.; Nunami, K.; Yoneda, N.; Onoda, Y.; Iwasawa, Y.; *Chem. Pharm Bull.* **1980**, 28, 2384.
3. Collard, D.M.; Fox, M.A.; *J. Am. Chem. Soc.* **1991**, 113, 9415.

   Salmón, M.; Saloma, M.; Bidan, G.; Ganies, E.M.; *Electrochimica Acta* **1989**, 34, 117.

   Andrieux, C.P.; Audebert, P.; Hapiot, P.; Saveant, J.M.; *J. Am. Chem. Soc.* **1990**, 112, 2439. For a review see Curran, D.; Grimshaw, J.; Perera, S. D.; *Chem. Soc. Rev.* **1991**, 20, 391.
4. Jackson, A.H.; In "Pyrroles. Part I. The Synthesis and the Physical and Chemical Aspects of the Pyrrole Ring". Jones, R.A., Ed.; John Wiley & Sons, New York, 1990, pp. 295-303.
5. For recent synthesis of β-substituted pyrroles see, Campi, E.M.; Jackson, W.R.; Nilsson, Y.; *Tetrahedron Lett.* **1991**, 32, 1093. Bray, B.L.; Mathies, P.H.; Naef, R.; Solas, D.R.; Tidwell, T.T.; Artis, D.R.; Muchowski, J.M.; *J. Org. Chem.* **1990**, 55, 6317. For a review see, Andersen, H.J.; Loander, C.E.; *Synthesis* **1985**, 353.
6. Vázquez, A.; Flores, B.; León, F.; González, A.; García de la Mora, G.; Méndez,, J.M.; Fourth Chemical Congress of North America, New York, N.Y., Aug., 25-30, **1991**. Abstract ORGN 196.
7. All new compounds were fully characterized by the usual spectroscopic and analytical techniques.
8. If this hydrolysis is conducted at 0°C, the mono acetal of the succinaldehydes can be isolated in good yields.
9. Gilchrist, T.L.; *Heterocyclic Chemistry*, 2nd. Ed.; Longman Scientific & Technical; Hong Kong, 1992, p.190.
10. Babler, J.H.; Spina, K.P.; *Tetrahedron Lett.* **1984**, 25, 1659.
11. Larson, G.L.; Klesse, R.; *J. Org. Chem.* **1985**, 50, 3627.
12. Meinwald, J.; Meinwald, Y.C.; *J. Am. Chem. Soc.* **1966**, 88, 1305. Meinwald, J.; Boriack, C.J.; Schneider, D.; Bopre, M.; Wood, W.F.; Eisner, T.; *Experientia* **1974**, 30, 721, and refs. therein.
13. Röder, E.; Wiedenfeld, H.; Bouranel, T.; *Liebigs Ann. Chem.* **1985**, 1708.
14. Severin, T.; Adhikary, P.; Dehmal, E.; and Eberhard, I.; *Chem. Ber.* **1971**, 104, 2856.
15. Almstrom, K.; *Ann.* **1916**, 411, 376.

(*Received in USA* 12 *March* 1996; *revised* 16 *April* 1996; *accepted* 17 *April* 1996)