

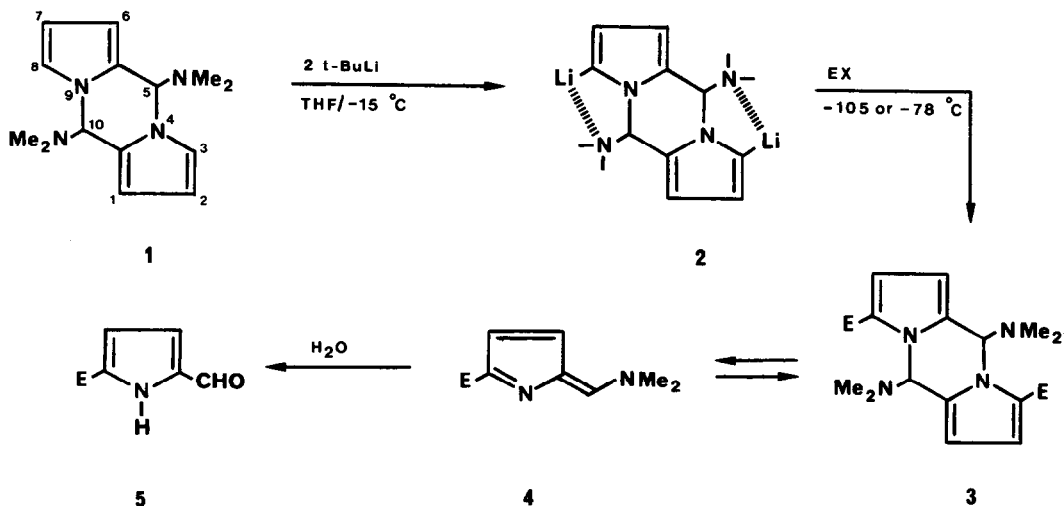
LITHIATION OF THE 6-DIMETHYLAMINO-1-AZAFULVENE DIMER.
A VERSATILE SYNTHESIS OF 5-SUBSTITUTED PYRROLE-2-
CARBOXALDEHYDES.¹

Joseph M. Muchowski* and Petr Hess²

Syntex Research, Institute of Organic Chemistry,
3401 Hillview Ave., Palo Alto, California 94304

Summary: Metalation of the dimer **1** of 6-dimethylamino-1-azafulvene, with *t*-butyllithium at -15 °C, gave the 3,8-dilithio derivative **2**, which after reaction with diverse electrophilic reagents and hydrolysis, provided a wide variety of 5-substituted pyrrole-2-carboxaldehydes **5**.

5-Substituted pyrrole-2-carboxaldehydes are intermediates of considerable importance for the synthesis of various natural products^{3,4} including porphyrins and related compounds⁵, heteroannulenes⁶ and agents of medicinal chemical interest⁷. In addition, some 5-alkylpyrrole-2-carboxaldehydes have been isolated from marine sources⁸. The most versatile method of preparing these compounds, indubitably, is the Vilsmeier-Haack formylation of 2-substituted pyrroles.⁹ This process, nevertheless, does have two important drawbacks. Firstly, the precursor 2-substituted pyrrole must be independently synthesized and secondly, when the 2-substituent is deactivating, mixtures of 4- and 5-formylated compounds are formed.^{3,6,9} This communication describes a method whereby the title compounds can be prepared in a two step, one pot, sequence from a single precursor.



It occurred to us that the readily available¹⁰ 6-dimethylamino-1-azafulvene dimer 1 should undergo heteroatom assisted lithiation¹¹ at the α -positions (C-3 and C-8) of the pyrrole nuclei, barring some unforeseen steric or conformational impediment thereto.¹² Reaction of the dilithiated species 2 with an electrophilic reagent followed by hydrolysis of the product, presumably via the azafulvene¹³ 4, would be expected to produce the 5-substituted pyrrole-2-carboxaldehyde 5. Therefore, a THF solution of the mp 113 °C dimer¹⁴ was reacted with 2.2 moles of t-butyllithium¹⁵ in pentane (-15 °C/10 min, 0 °C/20 min) and the deep violet colored mixture was quenched with excess D₂O. The pmr spectrum¹⁶ of the dimer (\geq 98% recovery) showed 93% deuterium incorporation at C-3 and C-8. No evidence was found for exchange of the methine carbon atoms (C-5,10) at much shorter reaction times (e.g. 30 sec; 20% deuterium at C-3,8), or at the β -positions (C-1,6) of the pyrrole nuclei, even when the amount of t-butyllithium was doubled (95% exchange at C-3,8); -15 °C/10 min, 0 °C/20 min). The dilithiated species 2, generated under standard conditions (see below), was then reacted with a broad spectrum of electrophilic reagents and the products 3, obtained thereby, were hydrolysed, in the same pot, with hot aqueous sodium hydrogen carbonate or sodium acetate. The expected 5-substituted pyrrole-2-carboxaldehydes 5 were obtained in modest to good yields (see Table)¹⁷. Thus 2 is a very useful formal equivalent of 2-lithio-5-formylpyrrole.

In summary, a most efficacious synthesis of 5-substituted pyrrole-2-carboxaldehydes based on the dilithiation of the azafulvene dimer 1 has been devised. The most notable features of this process are: a single, easily preparable starting material is utilized to produce virtually any desired derivative of 5 in a regiospecific manner.

Lithiation of 1 and Synthesis of 5-Methoxycarbonylpyrrole-2-carboxaldehyde (5, E = CO₂Me).

A 1.7 M solution of t-butyllithium in pentane (3.5 mL, 5.95 mmol) was added dropwise in ca 2 min to a stirred solution of the dimer (0.489 g, 2.00 mmol) in anhydrous THF (40 mL, N₂ atmosphere) kept in a -15 °C cooling bath. The reaction mixture was stirred for 15 min at this temperature and then for 30 min at 0 °C by which time it had become deep violet in color. The reaction mixture was cooled to -105 °C and methyl chloroformate (618 μ L, 0.76 g, 8.0 mmol) was added in one portion. The cooling bath was left to spontaneously reach -30 °C (1.5 h), and then the mixture was stirred at r.t. for 1 h. Water (20 mL) and saturated aqueous sodium bicarbonate (20 mL) were added and the mixture was heated at reflux temperature for 15 h. The mixture was poured into dilute sodium bicarbonate solution, the product was extracted into dichloromethane and the extract was dried (sodium sulfate) and evaporated in vacuo. The residue was subjected to purification by centrifugally accelerated tlc on silica gel using hexane-ethyl acetate (7:1) as the developing solvent. The pmr pure solid (0.393 g, 64%) had mp 98-99 °C after crystallization from hexane.

Table. 5-Substituted pyrrole-2-carboxaldehydes 5 from dilithiated dimer 2 of 5-dimethylamino-1-azafulvene.

Electrophile	Reaction conditions ^a	Hydrolysis conditions	E in product <u>5</u>	% Yield ^b	Mp, °C
MeI	I ^c	A ^d	Me	91	61-67 ^e
Me ₂ SO ₄	II	B, 1.5 h	Me	75	-
n-C ₈ H ₁₇ I	I	A	n-C ₈ H ₁₇	47(69) ^f	oil
n-C ₁₆ H ₃₃ I	I	A	n-C ₁₆ H ₃₃	19(95) ^f	70-71 ^{g,h}
CH ₂ =CHCH ₂ Br	I	A	CH ₂ =CHCH ₂	73	39-41 ⁱ
(i-Pr) ₃ SiOTf	I	B, 15 h	(i-Pr) ₃ Si	68	109-111 ^g
PhSSPh	I	A	PhS	78	94-96 ^j
DMF	III	B, 5 h; r.t., 15 h	CHO	63	118-120 ^{g,k}
n-C ₅ H ₁₁ CON(Me)OMe	II	B, 4 h	n-C ₅ H ₁₁ CO	54	48-49 ^g
CH ₃ OCOC1	I	A	CH ₃ OCO	64	98-99 ^{g,l}

^aReactions were carried out using 2 mmol of dimer 1 and 8 mmol of electrophile.

^bYield of pmr pure product after silica gel chromatography.

^cI = conditions as described in example; II = addition of EX at -78 °C and left 1 h then stirred 1-2 h at r.t.; III = same as II except 15 min at -78 °C.

^dA = hydrolysis as described in example; B = hydrolysis with NaOAc (0.700 g) in water (20 mL) at reflux for time indicated.

^eContains pyrrole-2-carboxaldehyde (≤ 5%); reported^{1*} mp 68 °C.

^fYield in brackets based on recovered pyrrole-2-carboxaldehyde.

^gCrystallized from hexane.

^hReported^{a,b}, mp 72-73 °C.

ⁱCrystallized from methanol-water.

^jCrystallized from hexane-ether.

^kReported,⁶ mp 121-122 °C.

^lReported,^{1*} mp 92-93 °C.

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1. Contribution no. 758 from the Syntex Institute of Organic Chemistry.
2. Syntex Research Post-Doctoral Fellow, 1987-1988.
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12. Neither the configuration of the substituents nor the conformation of this molecule is known.
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14. A solution of pyrrole-2-carboxaldehyde (57.0 g, 0.60 mol) in aqueous dimethylamine (120 mL, 40% in water) was stirred at r.t., in a nitrogen atmosphere, for 3 h. The precipitated solid was collected by filtration and dried in vacuo. The crude dimer (59.0 g, 81% yield) was a 94:6 mixture of two isomers as determined from the pmr integrals of the singlet absorptions at δ 2.22 and 2.34 for the dimethylamino groups. Two crystallizations of this mixture from ethyl acetate gave the pure dimer (50.0 g, 68% yield), mp 113 °C, which was used in this study.
15. Lithiation also occurred at -15 °C with n-butyllithium but at a much slower rate. At -45 °C, lithiation did not take place, even with t-butyllithium.
16. The pmr spectrum, measured at 300 MHz in CDCl₃, showed a twelve proton singlet at δ 2.22 (NMe₂) and two proton absorptions centered at δ 5.87 (d, H-5,10), 6.17 (m, H-1,6), 6.26 (dd, H-2,7) and 6.96 (dd, H-3,8) with $J_{5,6} = J_{1,10} = 0.8$ Hz, $J_{1,2} = J_{6,7} = 3.5$ Hz, $J_{1,9} = J_{6,8} = 1.7$ Hz and $J_{2,9} = J_{7,8} = 2.8$ Hz.
17. All new compounds were characterized by the usual spectroscopic techniques and had satisfactory elemental analyses.
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