LITHIATION OF THE DIMER OF 3-BROMO-6-DIMETHYLAMINO-1-AZAFULVENE. EFFICACIOUS SYNTHESIS OF 4-MONO- AND 4,5-DISUBSTITUTED PYRROLE-2-CARBOXALDEHYDES.¹

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<u>Summary</u>: The dimer <u>la</u> of 3-bromo-6-dimethylamino-1-azafulvene, is shown to function as a formal equivalent of 4-lithio- or 4,5-dilithiopyrrole-2-carboxaldehyde and consequently it is a progenitor, par excellence, of 4-mono- and 4,5-disubstituted pyrrole-2-carboxaldehydes.

The 6-dimethylamino-1-azafulvene dimer <u>1b</u> was recently shown to undergo facile heteroatom assisted metalation³ at C-3 and C-8 with t-butyllithium.⁴ The dilithiated species, upon reaction with diverse electrophilic reagents and subsequent hydrolysis, gave access to a wide variety of 5-substituted pyrrole-2-carboxaldehydes. This communication demonstrates that the application of standard metalation-electrophile trapping techniques to the dibromo dimer <u>la</u>, constitutes a most efficient synthetic route to both 4-mono- and 4,5-disubstituted pyrrole-2-carboxaldehydes.

The dimer <u>la</u>, easily prepared ^{5,6} from 4-bromopyrrole-2-carboxaldehyde, was converted into the dilithio species <u>2</u> by halogen-metal interchange with 2 moles of n-butyllithium, or 4 moles of t-butyllithium, in THF at -78 °C (0.5 h) and then reacted with sundry electrophilic reagents. The products <u>3</u>, were hydrolysed, without isolation, by dilution of the reaction mixture with aqueous sodium hydrogen carbonate solution, followed by heating at reflux temperature. In every case, the expected 4-substituted pyrrole-2-carboxaldehyde <u>4</u> was obtained in satisfactory to good yield, uncontaminated by any regioisomer (see Table). This process is particularly advantageous over literature procedures for the synthesis of derivatives of <u>4</u> where the β -substituent is activating. For example, the Vilsmeier-Haack formylation of 3-methylpyrrole is reported⁶ to give a mixture of the 2,3- and 2,4-disubstituted compounds in which the 2,3-isomer predominates by a factor of 4.

An attempt to directly generate the 2,3,7,8-tetralithio species from 2a, with excess t-butyllithium (-78 °C then -15 °C), gave only 2, as determined by the isolation of 4-methylpyrrole-2-carboxaldehyde^{*}, in 97% yield, after methyl iodide trapping and hydrolysis. Tetralithiation could, however, be effected in a formal sense, by means of two consecutive metalation-trapping sequences. Thus, 2 was converted into the dimethyl compound 3 (E = Me) with methyl iodide and this compound was metalated, in situ, with 3 moles of t-butyllithium (-15 °C/15 min, 0 °C/30 min). Quenching the intermediate bis-lithio compound with methyl iodide and subsequent hydrolysis, in the usual way, gave

4,5-dimethylpyrrole-2-carboxaldehyde $(\underline{7}, E = Me)^{10}$ in 87% yield. Similarly, $\underline{5}$ was effectively trapped with DMF, but in this case, the intermediate dimer $\underline{6} (E = CHO)^{11}$ was very difficult to hydrolyse under standard conditions. It was, however, transformed quantitatively into the dialdehyde $\underline{7} (E = CHO)$ with excess methyl iodide (12 moles) in 2.5% aqueous acetonitrile (r.t., 15 h).



In conclusion, it has been shown that the readily available dimer <u>la</u> of 3-bromo-6-dimethylamino-1-azafulvene, serves as a formal equivalent of either 4-lithio- or 4,5-dilithiopyrrole-2-carboxaldehyde, and as such, it can provide access to an immense variety of pyrrole-2-carboxaldehyde derivatives, with an efficiency and economy of steps unmatched by any published procedure¹³.

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Electrophile	Product ^a	E in product	≭ Yield ^b	Mp, °C ^C
Mel	<u>4</u>	Me	87(82) ^d	50-52 ^e
n-C8H17I	<u>4</u>	n-C8H17	58(57)d	40-42f
CH2=CHCH2Br	<u>4</u>	CH2=CHCH2	609	oil
(i-Pr) ₃ SiOTf	<u>4</u>	(i-Pr)3Si	74	122-124
PhSSPh	<u>4</u>	PhS	83	130-132
DMF	<u>4</u>	СНО	78	152-153h
n-C ₅ H _{ll} CON(Me)OMe	<u>4</u>	n-C5H11CO	62	76-77
Me0C0C1	<u>4</u>	MeOCO	71	128-128.5 ¹
MeI	<u>1</u>	Me	87	123–124 ^j
DMF	<u>1</u>	СНО	69	79-80

^aStarting material for <u>4</u> is <u>la</u>: for <u>7</u>, it is <u>3</u> (E = Me). ^bYield of pmr pure product after silica gel chromatography. ^CUnless stated otherwise, mps are those observed after crystallization from hexane. ^dYields in brackets using 2 moles n-BuLi. ^eReported^{*}, mp 47-48 °C. ^fCrystallized from pentane at -20 °C. ^gIsolated admixed with 23% of 4-bromopyrrole-2-carboxaldehyde. ^hCrystallized from hexane-EtOAc. Reported, ¹² mp 149-151 °C. ⁱReported, ¹² mp 126-128 °C. ^jReported, ¹⁰ mp 127.5-128 °C.

Table. Synthesis of 4-mono- and 4,5-disubstituted pyrrole-2-carboxaldehydes from dimer <u>la</u> of 3-bromo-6-dimethylamino-1-azafulvene.

<u>Lithiation of la and Synthesis of 4-Methylpyrrole-2-carboxaldehyde (4, E = Me).</u>

A 1.7 M solution of t-butyllithium in pentane (2.0 mL, 3.4 mmol) was added dropwise to a stirred solution of the dimer (0.342 g, 0.85 mmol) in anhydrous THF (40 mL, argon atmosphere) at -78 °C. The yellow colored solution was stirred for 0.5 h at -78 °C and then methyl iodide (0.483 g, 212 μ L, 3.4 mmol) was added. The reaction temperature was left to rise to -50 °C during 1 h and then it was stirred at room temperature for 0.5 h. Water (15 mL) and saturated aqueous sodium bicarbonate (15 mL) were added and the mixture was heated at reflux temperature for 15 h. The mixture was poured into water, extracted with dichloromethane and the extract was dried over sodium sulfate. The solvent was removed <u>in vacuo</u> and the residue was purified by centrifugally accelerated tlc on silica gel using hexane-ethyl acetate (4:1) as the eluting solvent. The pmr pure solid (0.161 g, 87%) had mp 50-52 °C after crystallization from hexane.

References and Notes:

- 1. Contribution no. 766 from the Syntex Institute of Organic Chemistry.
- 2. Syntex Research Post-Doctoral Fellow, 1987-1988.
- 3. H.W. Gschwend and H.R. Rodriguez, Organic Reactions, <u>26</u>, 1(1979).
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- 5. A solution of 4-bromopyrrole-2-carboxaldehyde⁷ (10.4 g, 60 mmol) in aqueous dimethylamine (50 mL, 40% in water) was stirred at room temperature for 3.5 h and then diluted with an equal volume of water. The solid was collected by filtration, washed successively with 1N sodium hydroxide and ethyl acetate and dried in vacuo. Crystallization of this material from ether-ethyl acetate (9:1) gave a solid (8.3 g, 69%) which decomposed above 121 °C.
- All new compounds were characterized by the usual spectroscopic techniques and had satisfactory elemental analyses.
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- 10. Previously synthesised in poor overall yield [A.H. Corwin and R.H. Krieble, J. Am. Chem. Soc., <u>63</u>, 1829(1941)], via a six step sequence from methyl ethyl ketone. It has recently been shown to be a useful intermediate in the synthesis of protoporphyrin-XIII, one of the metabolic products of coproporphyrinogen-IV by coproporphyrinogen oxidase [H.M.G. Al-Hazimi, A.H. Jackson, D.W. Knight and T.D. Lash, J. Chem. Soc. Perkin Trans. I, 265(1987)].
- 11. Mp 145-147 °C, isolated in ca 70% yield by dilution with water and extraction with dichloromethane. The pmr spectrum, measured at 500 MHz in $CDCl_3$, showed five singlet absorptions at δ 1.94 (NMe₂), 2.42 (Me), 6.01 (H-5, 10), 6.51 (H-1,6) and 9.80 (CHO).
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