216. Lithiated Azafulvenes by Halogen/Metal Interchange of Brominated 6-(Diisopropylamino)-1-azafulvene Derivatives. Novel Synthesis of 5-Mono- and 4,5-Disubstituted 1*H*-Pyrrole-2-carbaldehydes[1])

by **Brian L. Bray**[2]), **Petr Hess**[3]), **Joseph M. Muchowski***, and **Markus E. Scheller**[4])

Syntex Research, Institute of Organic Chemistry, 3401 Hillview Avenue, Palo Alto, California 94304, U.S.A.

(18.VIII.88)

The first known lithiated 1-azafulvene derivatives were generated by low-temperature halogen/metal interchange, with *t*-BuLi, from the corresponding brominated 6-diisopropylamino compounds **3b** and **12**. These Li species reacted with sundry electrophilic reagents to give products which, on basic hydrolysis, were converted into 5-mono- or 4,5-disubstituted pyrrole-2-carbaldehydes **10** and **16**, respectively.

The generation of pyrroles lithiated on a C-atom requires the presence of a *N*-substituent, and if a formal *N*-unsubstituted lithiopyrrole is desired, this *N*-substituent of which several types have been utilized [1–7] must be readily removable. It was of interest to us to examine the possibility of effecting *C*-metalation of the pyrrole nucleus in the absence, at least in the formal sense, of a protecting group for the N-atom[5]). We have now devised two complementary strategies which demonstrate that this is indeed a viable concept. The first of these, which has already been disclosed in preliminary form [10], involves the lithiation of the readily available dimer of 6-(dimethylamino)-1-azafulvene and of the corresponding 3-bromo derivative. The lithiated species thus generated have provided access to a great variety of 4- or 5-mono- and 4,5-disubstituted 1*H*-pyrrole-2-carbaldehydes. A description of the second synthetic strategy constitutes the subject of this communication.

The 3,4-disubstituted 6-(dimethylamino)-2-halo-1-azafulvenes, synthesized twenty years ago by *von Dobeneck* and coworkers [11], are readily hydrolyzed to the corresponding aldehydes under mildly alkaline conditions. It was, therefore, apparent that, if the proclivity for nucleophilic addition to C(6) of azafulvenes could be overcome [12] and barring stability problems, halogen/Li exchange of a 3,4-unsubstituted congener (see **3**) would generate a lithiated 1-azafulvene derivative, functionally equivalent to 5-lithio-1*H*-pyrrole-2-carbaldehyde.

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[1]) Contribution No. 735 from the *Syntex Research*, Institute of Organic Chemistry.

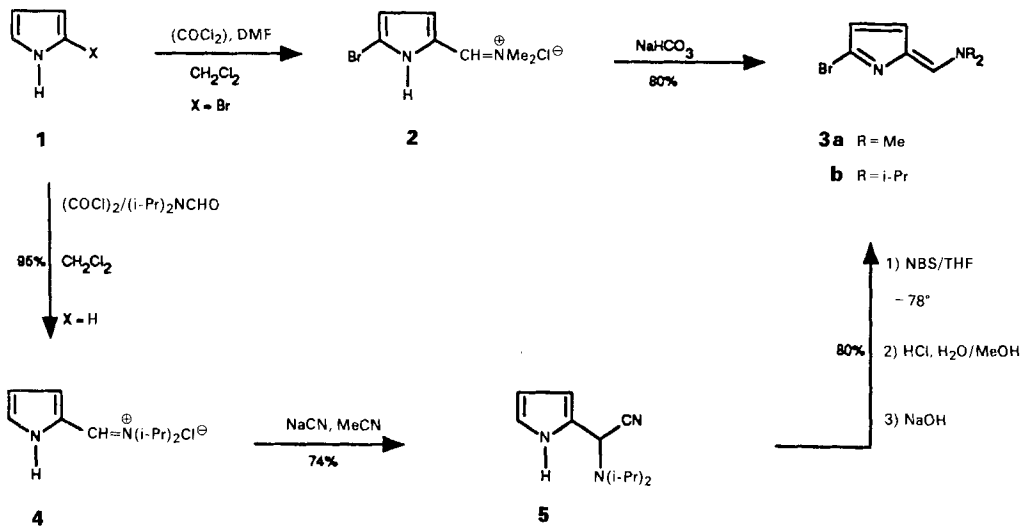
[2]) *Syntex Research* post-doctoral fellow, 1987–present.

[3]) *Syntex Research* post-doctoral fellow, 1987–1988.

[4]) *Syntex Research* post-doctoral fellow, 1985–1986.

[5]) *Farnier* and *Fournari* [8] have reported that 3,4-diiodo-1*H*-pyrrole is converted into the 1,3-dilithio derivative with BuLi (2 equiv.) in THF solution (–78°) containing tetramethylethylenediamine, as judged by the formation of 4-iodo-1*H*-pyrrole-3-carbaldehyde (45% yield), after quenching with dimethylformamide. This does not promise to be a generally useful process since 2-bromo-1*H*-pyrrole is not lithiated on a C-atom even with excess *t*-BuLi [9].

Scheme 1



Deprotonation of the iminium chloride **2**, obtained by a *Vilsmeier-Haack* reaction [13] on 2-bromo-1*H*-pyrrole (**1**, X = Br) [14], with 0.5M aqueous $NaHCO_3$ gave the stable 2-bromo-1-azafulvene derivative **3a** (m.p. 101–103°; *Scheme 1*)[6]). Reaction of **3a** with 2 equiv. of *t*-BuLi in THF at −78° yielded the unstable addition product **6a** (88% yield; *Scheme 2*), after quenching with H_2O, with no evidence for the formation of the expected lithioazafulvene. This propensity for nucleophilic addition at the extraannular C-atom could, however, be dramatically reduced by increasing the steric encumbrance about C(6) of the azafulvene system (see below).

Low-temperature bromination (*N*-bromosuccinimide (NBS), THF, −78°) of the α-(diisopropylamino)acetonitrile derivative **5** (m.p. 113–115°; *Scheme 1*), obtained by reaction of the iminium salt **4** with excess NaCN (5 equiv.) in MeCN, followed by brief (20 min) treatment with MeOH/0.5N HCl 1:1 and basification (NaOH), gave the remarkably stable 2-bromo-6-(diisopropylamino)-1-azafulvene **3b** (m.p. 110–112°)[7,8]). When Br/Li exchange of **3b** was effected at −78°, *ca.* equal amounts of the addition product **6b** (*via* **8**; *Scheme 2*) and 1*H*-pyrrole-2-carbaldehyde (**10**; E = H) were obtained, after quenching the reaction mixture with H_2O. Metalation at lower temperature under carefully controlled conditions (−105°, 15 min; warming to −78° within 1 h), gave 1*H*-pyrrole-2-carbaldehyde (**10**; E = H) as the sole product, in 90% yield. The lithiated azafulvene derivative **7**,

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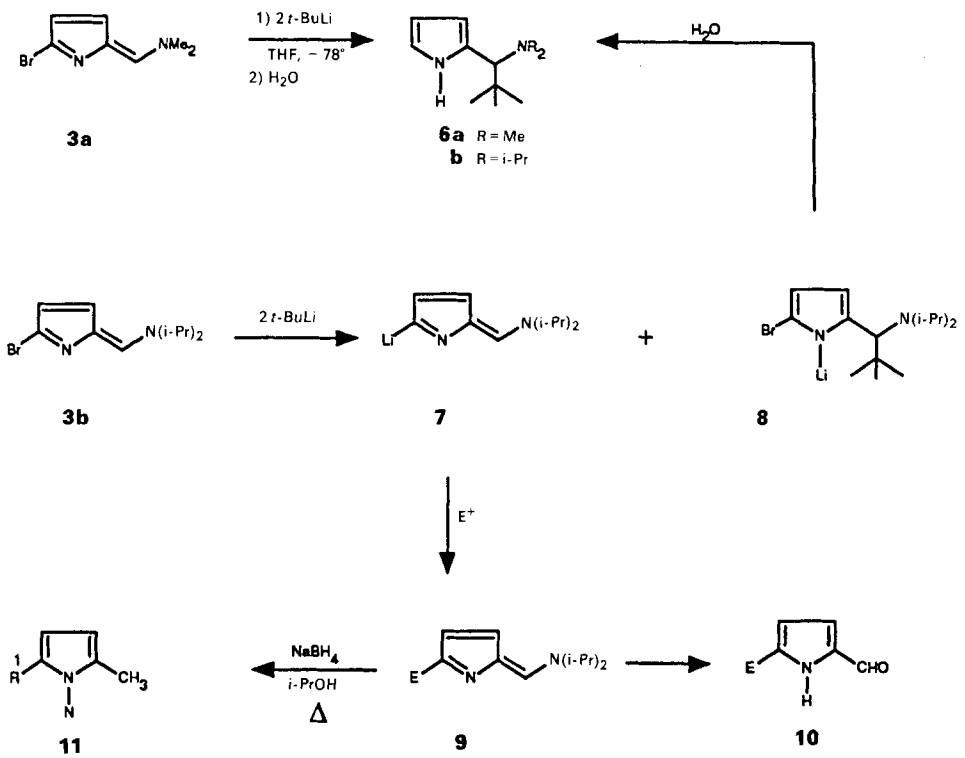
[6]) All new compounds were characterized by IR, ^{1}H-NMR, and mass spectra and had satisfactory elemental analyses.

[7]) Complete hydrolysis to 5-bromo-1*H*-pyrrole-2-carbaldehyde (m.p. 94–96°) with NaOH (6 equiv.) in MeOH/H_2O required 5 h at room temperature.

[8]) The ^{1}H-NMR spectrum (300 MHz, $CDCl_3$) showed, in addition to the absorptions for the i-Pr groups at 1.31 (*d*, 6 H), 1.35 (*d*, 6 H), 3.82 (*sept.*, 1 H), and 6.40 ppm (*sept.*, 1 H) with J = 6.73 Hz, two 1-H *d*'s at 6.31 and 6.39 ppm with $J(3,4)$ = 3.74 Hz and a *s* at 7.01 ppm for H–C(6). The presence of *ca.* 15% of an isomeric 1-azafulvene was indicated by weak absorptions at 4.64 (*sept.*), 6.52 (*d*), 7.01 (*d*), and 7.80 ppm (*s*). The spectrum of the major isomer exhibited temperature dependence with $T_c \approx 370$ K for the i-Pr *d*'s.

Scheme 2



generated in this way, was also reacted with various other electrophilic reagents (2 equiv., −78° to room temperature), and the 2-substituted azafulvenes **9** obtained thereby, though detectable by NMR spectroscopy[9]), were either hydrolyzed directly to the 5-substituted 1*H*-pyrrole-2-carbaldehydes **10** or reduced ($NaBH_4$ in hot 2-propanol [16]) to 5-alkyl-2-methyl-1*H*-pyrroles **11** (see *Table*), usually in a one-pot reaction.

It is noteworthy that the lithioazafulvene derivative **7** reacted with a broad spectrum of electrophilic reagents to give the expected product in every case. Thus, BuI was not dehydrohalogenated, although 2 equiv. of hexamethylphosphoric triamide (HMPA) were required for the reaction to be successful[10]), and enolization of cyclohexanone appears to have been minimal. Therefore, **7** is a useful formal equivalent of 5-lithio-1*H*-pyrrole-2-carbaldehyde (**10**; E = Li).

The methodology described above could also be applied to the synthesis of a 4,5-disubstituted 1*H*-pyrrole-2-carbaldehyde. For this purpose, the 2,3-dibromo-1-azafulvene derivative **12** (m.p. 135–137°; *Scheme 3*) was prepared by heating 4,5-dibromo-1*H*-pyrrole-2-carbaldehyde [20] (**11**) with excess $(i\text{-Pr})_2NH$ in the presence of type 4 Å

[9]) These compounds are hydrolytically too sensitive to permit isolation and purification under conditions which were successfull for **3a** and **3b**.

[10]) In the absence of HMPA, a complex mixture of products was obtained.

Table. *2,5-Disubstituted 1H-Pyrroles from 6-(Diisopropylamino)-2-lithio-1-azafulvene*

Electrophile	Hydrolysis conditions[a])	Product	E or R^1	Yield [%]	M.p. [°]
MeI	*A*	**10**	Me	80	66–67[b])
BuI[c])	*B*	**10**	Bu	62	41–43
$(i\text{-Pr})_3SiCl$[c])	*B*	**10**	$(i\text{-Pr})_3Si$	69	107–108
MeSSMe	*A*	**10**	MeS	67	103–104[d])
PhSSPh	*A*	**10**	PhS	60	95–96
DMF	*A*	**10**	CHO	63	121–122[e])
$ClCO_2Et$	*A*	**10**	CO_2Et	36	73–74[f])
PhCOCl	*C*	**10**	PhCO	70	118–119
PhCHO	*D*	**11**	$PhCH_2$	60	oil
Cyclohexanone	*D*	**11**	cyclo-C_6H_{11}	39	oil

[a]) *A* = 3 equiv. of NaOAc in H_2O, one-pot reaction, heat at reflux, 15 h; *B* = 3 equiv. of NaOAc in $MeOH/H_2O$, after removal of THF, 2 h, r.t.; *C* = 3 equiv. of $NaHCO_3$ in H_2O, one-pot reaction, at reflux, 15 h; *D* = 2 parts of $NaBH_4$ (by wt.) in i-PrOH, one-pot reaction, at reflux, 1 h.

[b]) [17]: m.p. 68°.

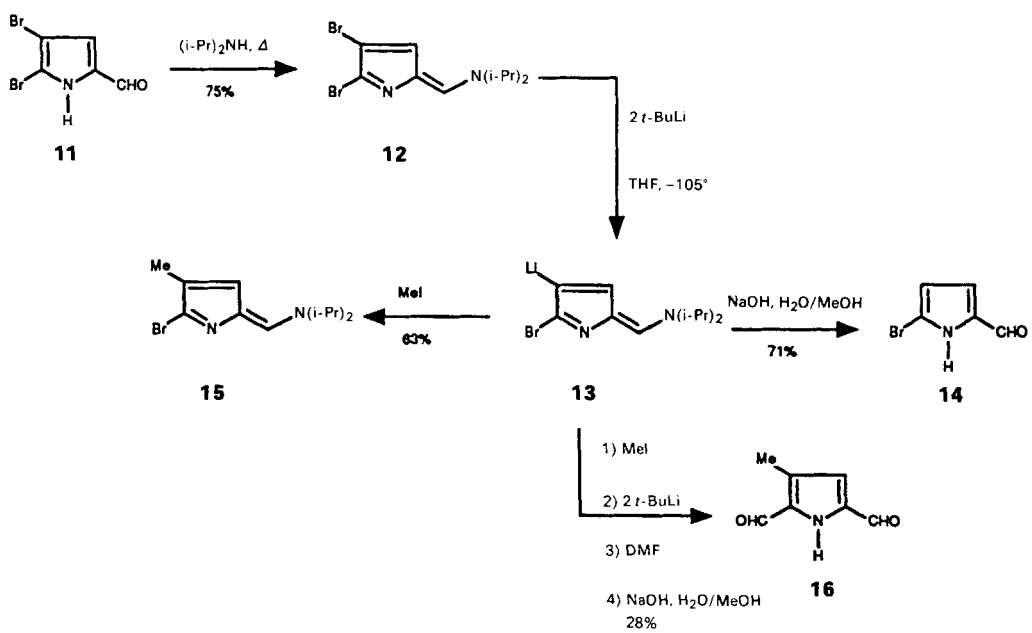
[c]) HMPA (2 equiv.) added.

[d]) [18]: m.p. 105–106°.

[e]) [19]: m.p. 121–122°.

[f]) [20]: m.p. 75°.

Scheme 3



molecular sieves. Br/Li exchange of **12** with 2 equiv. of *t*-BuLi at −105° (15 min) occurred with high selectivity at C(3) (→**13**), as determined by hydrolysis to 5-bromo-1*H*-pyrrole-2-carbaldehyde (**14**)[11]) and by the formation of the 3-methyl-1-azafulvene derivative **15** (m.p. 84–86°) upon quenching with MeI. Generation of this azafulvene *in situ*, followed by a second halogen/metal interchange as described for **3b**, reaction with DMF, and hydrolysis with NaOH in $MeOH/H_2O$, gave 5-formyl-4-methyl-1*H*-pyrrole-2-carbaldehyde (**16**; m.p. 80–81°), albeit in modest yield. Thus, 2,3-dibromo-6-(diisopropylamino)-1-azafulvene **12** is a potentially useful formal source of 4,5-dilithio-1*H*-pyrrole-2-carbaldehyde.

Our current studies are centered on endeavors to extend the concepts disclosed herein to the synthesis of substituted 2-acyl-1*H*-pyrroles in general.

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[11]) The presence of *ca.* 1% of 4-bromo-1*H*-pyrrole-2-carbaldehyde was detected in one of the chromatographic fractions by NMR spectroscopy.