Generation and Lithiation of the Dimers of 6-(Dimethylamino)-1,4-diazafulvene. A Novel Synthesis of 2-Alkanoylimidazoles†

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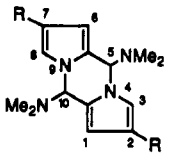
We recently showed that the readily available dimers of 6-(dimethylamino)-1-azafulvenes (e.g., 1, R = H) underwent lithiation at C-3 and C-8 and that these dilithiated species on sequential reaction with electrophilic reagents and hydrolysis provided access to a wide variety of 5-substituted pyrrole-2-carboxaldehydes.[1,2] It was of



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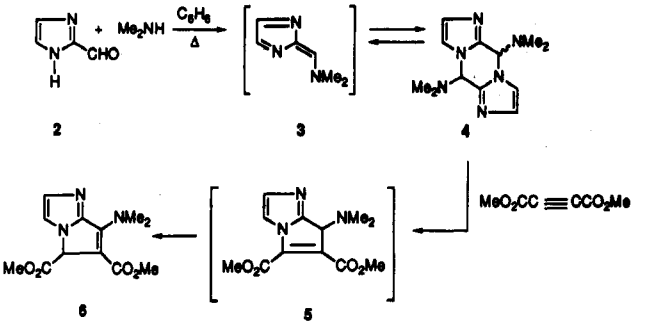
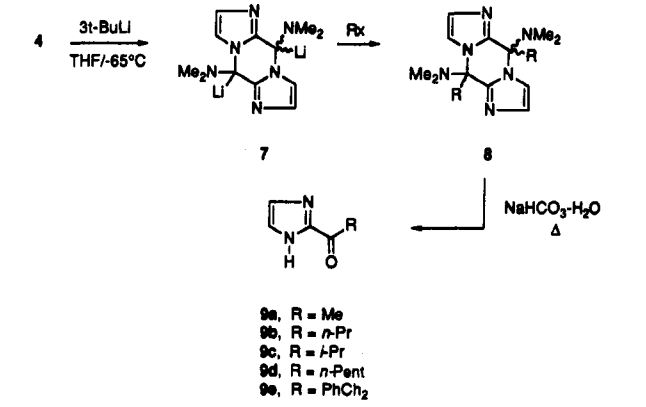
interest to determine if the analogous imidazole compounds could be prepared and if the chemical reactivity thereof corresponded to that of the 1-azafulvene dimers. This paper gives a brief account of the synthesis and some reactions of the imidazole congener 4 of 1 (R = H).[3]

Heating a suspension of imidazole-2-carboxaldehyde (2, Scheme I) in benzene containing excess dimethylamine for 1.5 h at 70 °C resulted in the formation of a new crystalline solid 4 in ca. 70% yield. Although this material was sharp melting, the proton and carbon NMR spectra clearly indicated that it was a 10:1 mixture[4] of isomers (see Experimental Section). The mass spectrum of this mixture showed the expected molecular ion at *m/z* 246 as well as a base peak at *m/z* 123, the latter being ascribed to the monomeric diazafulvene 3. The *m/z* 123 peak augured well for the possible existence of a thermal equilibrium the dimeric and monomeric species 3 and 4 as has been reported[5,6] for 1. Indeed, a 1:1 adduct of structure 6, an isomer of the expected product 5, was

Scheme I



Scheme II



9a, R = Me
9b, R = *n*-Pr
9c, R = *i*-Pr
9d, R = *n*-Pent
9e, R = $PhCH_2$

produced upon heating a solution of 4 in toluene containing dimethyl acetylenedicarboxylate.[7]

The lithiation of 4 with *tert*-butyllithium (1.5 equiv) in THF occurred rapidly at −65 °C, reaching ca. 85% dilithiation by 0.5 h with no further change thereafer, as determined by quenching with D_2O. In contrast to the pyrrole derived dimers, however, lithiation of 4 occurred exclusively α to the dimethylamino groups (i.e., at C-5 and C-10) to give 7 (Scheme II), perhaps as a consequence of the inductive effect of the additional nitrogen atom present in 4. Reaction of the dilithio species 7 with excess methyl iodide gave a new mixture of dimers 8 (R = Me) which could be isolated, but was generally hydrolyzed in situ by heating with excess aqueous sodium bicarbonate. 2-Acetylimidazole (9a) was thus obtained in 55% yield. Similarly, the reaction of 7 with other alkyl halides gave the expected 2-acylimidazoles 9 in acceptable yields (iodides were somewhat better than bromides) in all cases except benzyl iodide (bromide) (see Table I). Given that there are few syntheses of 2-alkanoylimidazoles[8-13] and that only one[10] of these has proven preparative utility, this process constitutes an alternative, though perhaps expensive (see ref 15), route to such compounds.

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(3) The major isomer presumably has trans stereochemistry by analogy to that established for 1 (R = H). Muchowski, J. M.; Hess, P. Unpublished data.

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Table I. Synthesis of 2-Alkanoylimidazoles 9 from 4

compd	RX	TLC solvent	cryst solvent	mp, °C	% yield[a]
9a	MeI	EtOAc–CH_2Cl_2 (9:1)	$CHCl_3$–Hex	130–132[b]	54
9b	*n*-PrBr	EtOAc	EtOAc–Hex	119–121	53
9b	*n*-PrI	EtOAc	EtOAc–Hex	119–121	72
9c	*i*-PrI	CH_2Cl_2–MeOH (95:5)	Hex	95–97	49
9d	*n*-PentBr	EtOAc	$CHCl_3$–Hex	113–115	71
9d	*n*-PentI	EtOAc	$CHCl_3$–Hex	113–115	74
9e	$PhCH_2Br$	CH_2Cl_2–MeOH (95:5)	MeOH	135–137	23[c]
9e	$PhCH_2I$	CH_2Cl_2–MeOH (95:5)	MeOH	135–137	25[c]

[a] Yield of once-crystallized material. [b] Lit.[9] mp 135–137.5 °C. The reported[9] UV and ^1H NMR spectra were identical to those measured for **9a**. [c] Major product isolated from a complex mixture.

An attempt was made to effect lithiation of 8 (R = Me, *n*-Bu) at C-3 and C-8 with *tert*-butyllithium under the conditions used to generate 7. Addition of excess methyl iodide or *n*-butyl iodide to this reaction mixture and subsequent hydrolysis gave only 2-acetylimidazole (**9a**, 55%) or 2-pentanoylimidazole (**9d**, 78%). None of the expected 5-substituted 2-acylimidazoles indicative of the lithiation of the imidazole nuclei of 8 was detected.

Experimental Section

The physical constants of the new compounds described herein were obtained as described previously.[14]

5,10-Bis(dimethylamino)-5*H*,10*H*-diimidazo[1,2-*a*:1′,2′-*d*]pyrazine (4). A suspension of imidazole-2-carboxaldehyde[15] (7.0 g, 73 mmol) in dry benzene (300 mL) containing gaseous dimethylamine (6.0 g, 133 mmol) was heated at reflux temperature (70 °C in Mexico City) for 1.5 h. The reaction mixture was cooled to room temperature and filtered, and the filtrate was evaporated in vacuo. The residue was crystallized from ethyl acetate to give a solid (5.9 g, 66% yield), mp 169–171 °C: UV (MeOH) λ_{max} 264 sh (ϵ 360), 281 sh (400), 340 nm (7440); ^1H NMR ($CDCl_3$, major isomer) δ 2.30 (s, 12 H, NMe_2), 5.99 (s, 2 H, CH), 7.22 (d, 2 H, J = 1.36 Hz, H-2, 7), 7.26 (d, 2 H, J = 1.36 Hz, H-3, 8); (minor isomer) δ 2.46 (s, NMe_2), 5.88 (s, CH), 7.24 (d, J = 1.49 Hz, H-2, 7), 7.30 (d, J = 1.49 Hz, H-3, 8); ^{13}C NMR ($CDCl_3$) δ 39.69 (NMe_2), 72.52 (CH), 118.61 (C-2, 7), 130.05 (C-3, 8), 141.02 (C-5a, 10a); (minor isomer) δ 40.12 (NMe_2), 130.30 (C-3, 8), 140.69 (C-5a, 10a), only peaks visible. Anal. Calcd for $C_{12}H_{18}N_6$: C, 58.52; H, 7.37; N, 34.11. Found: C, 58.48, H, 7.39; N, 33.99.

Dimethyl 7-(Dimethylamino)-5*H*-pyrrolo[1,2-*a*]imidazole-5,6-dicarboxylate (6). A solution of the dimer 4 (0.480 g, 1.95 mmol) in anhydrous toluene (60 mL) containing hydroquinone (0.025 g), dimethyl acetylenedicarboxylate (0.5 mL, 0.58 g, 4.0 mmol), and suspended type 2A molecular sieves (1 g) was stirred at reflux temperature (101 °C) in a nitrogen atmosphere for 2 h. The mixture was filtered, the filtrate was evaporated in vacuo, and the residue was subjected to purification by preparative TLC on silica gel using 1:1 benzene–ether as the developing solvent. Compound 6 was obtained (0.456 g, 44% yield) as an oil: UV (MeOH) λ_{max} 216.5 (ϵ 5420), 260 sh (6540), 275 (9020), 338.5 (11,100) nm; IR (film) 1749, 1691, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.53 (s, 6 H, NMe_2), 3.71 (s, 3 H, OMe), 3.77 (s, 3 H, OMe), 5.38 (s, 1 H, H-7), 7.15 (d, 1 H, J = 1.22 Hz, H-2), 7.28 (d, 14, J = 1.22 Hz, H-3); ^{13}C NMR ($CDCl_3$) δ 44.14 (NMe_2), 51.32 (OMe), 53.57 (OMe), 61.81 (C-7), 95.70, 116.66, 134.66, 149.43, 151.49, 163.91 (CO), 169.71 (CO); HRMS calcd for $C_{12}H_{15}N_3O_4$ 265.1068, found 265.0180.

Lithiation of Dimer 4. General Procedure. A solution of 1.7 M *tert*-butyllithium in pentane (3.5 mL, 6 mmol) was added dropwise to a stirred solution of the dimer 4 (0.490 g, 2 mmol) in anhydrous THF (40 mL) at −65 °C maintained in an argon atmosphere. Stirring was continued at −65 °C for 0.5 h. The solution of the dilithio species 7 was then ready for use.

Generation of the Deuterated Dimer 8 (R = D). A 90:10 mixture of D_2O–MeOD (0.5 mL) was added to the lithiated species at −65 °C. The solution was stirred for 0.5 h at −65 °C and then 3 h at room temperature. The reaction mixture was filtered, the filtrate was evaporated in vacuo, dichloromethane was added, and the mixture produced was filtered once more. The filtrate was washed with water and dried over sodium sulfate, and the solvent was removed in vacuo. Crystallization of the solid residue from ethyl acetate gave the deuterated dimer 8 (R = D) as a solid (0.420 g) with mp 158–160 °C. The ^1H NMR spectrum showed that the total integral for the absorptions at δ 5.88 and 5.99 had been reduced by ca. 85%. The mass spectrum of the parent ions showed 5% d_0, 25% d_1, and 70% d_2.

Alkylation of the Dilithio Species 7 with Alkyl Halides. Synthesis of 2-Alkanoylimidazoles 9. To a stirred solution of 2 mmol of the dilithio species 7, generated as described above and maintained at −65 °C, was added 8 mmol of the appropriate alkyl halide. The solution was stirred at −65 °C for 0.5 h and 2 h at room temperature and then left in the refrigerator (5 °C) for 15 h. Workup of the reaction mixture as described for 8 (R = D) above gave the corresponding alkylated dimer which in some cases was characterized by ^1H NMR spectroscopy. For example, from methyl iodide was obtained a solid 8 (R = Me): NMR (DMSO-d_6) δ 1.91 (s, 3 H, Me), 2.00 (s, 3 H, Me), 2.28 (s, 6 H, NMe_2), 7.09 (d, 2 H, J = 1.2 Hz, H-2, 7), 7.38 (d, 2 H, J = 1.2 Hz, H-3, 8).

To generate the 2-alkanoylimidazoles, water (20 mL) and a saturated aqueous solution of sodium bicarbonate (20 mL) were added to the THF solution of the alkylated dimer, and the mixture thus obtained was heated at reflux temperature for 2 h. The cooled reaction mixture was extracted with ethyl acetate, and the extract was washed with water and dried over sodium sulfate. The solvent was removed in vacuo, the residue was purified by preparative TLC on silica gel plates, and the TLC-pure product was then crystallized from the appropriate solvent system. The yields, mps, TLC purification solvents, etc. for the 2-alkanoylimidazoles are found in Table I.

2-*n*-Butyrylimidazole (9b): UV (MeOH) λ_{max} 276 (ϵ 12 900) nm; IR (KBr) 3345, 1683, 1639 w cm^{-1}; ^1H NMR (CD_3OD) δ 1.00 (t, 3 H, J = 7.36 Hz, Me), 1.75 (quin, 2 H, J = 7.36 Hz, CH_2Me), 2.99 (t, 2 H, J = 7.36 Hz, $ArCH_2$), 7.21 (bs, 1 H, H-4), 7.34 (bs, 1 H, H-5); ^{13}C NMR ($CDCl_3$) δ 14.26 (Me), 18.24 (CH_2), 40.26 ($ArCH_2$), 121.11 (C-4), 131.64 (C-5), 146.76 (C-2), 193.25 (CO). Anal. Calcd for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.27. Found: C, 60.63; H, 7.34; N, 20.14.

2-Isobutyrylimidazole (9c): UV (MeOH) λ_{max} 276 (ϵ 12 700) nm; IR (KBr) 3460, 1678 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (d, 3 H, J = 6.92 Hz, Me), 1.28 (d, 3 H, J = 6.92 Hz, Me), 3.83 (sept, 1 H, J = 6.92 Hz, CH), 7.25 (bs, 1 H, H-4), 7.30 (bs, 1 H, H-5), 10.68 (bs, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 19.25 (Me_2CH), 35.94 (CH), 120.86 (C-4), 131.76 (C-5), 141.94 (C-2), 196.94 (CO). Anal. Calcd for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.27. Found: C, 60.90; H, 7.27; N, 20.20.

2-*n*-Hexanoylimidazole (9d): UV (MeOH) λ_{max} 276 (ϵ 13 200); IR (KBr) 3241, 1678 cm^{-1}; ^1H NMR (CD_3OD) δ 0.93 (t, 3 H, $J \approx 6$ Hz, Me), 1.37 (m, 4 H, $(CH_2)_2$) 1.72 (t, 2 H, $J \approx 6$ Hz, CH_2Me), 3.00 (t, 2 H, J = 7.4 Hz, $COCH_2$), 7.28 (bs, 2 H, H-4, 5); ^{13}C NMR ($CDCl_3$) δ 14.60 (Me), 23.84 (CH_2), 25.32 (CH_2), 32.87 (CH_2), 39.09 ($COCH_2$), 127.00 (b, C-4, 5), 146.68 (C-2), 192.73 (CO); mass spectrum m/z 166 (50, 110 (100), 78 (86). Anal. Calcd for $C_9H_{14}N_2O \cdot 0.25H_2O$: C, 63.32; H, 8.56; N, 16.40. Found: C, 63.52; H, 8.41; N, 16.52.

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2-(Phenylacetyl)imidazole (9e): UV (MeOH) λ_{max} 279 (ϵ 13 500) nm; IR (KBr) 3347, 1682 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.41 (s, 2 H, CH_2), 7.23–7.39 (m, 7 H, aryl H's), 10.59 (s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 14.60 (CH_2), 121.31 (C-4), 127.49, 129.05, 130.36, 132.11 134.44 (C-1 of Ph), 145.37 (C-2), 189.80 (CO); mass spectrum *m/z* 186 (96), 185 (100), 71 (97). Anal. Calcd for $C_{11}H_{10}N_2O \cdot 0.2H_2O$: C, 69.60; H, 5.52; N, 14.76. Found: C, 69.82; H, 5.38; N, 14.81.