Selective *N*-1-Methylation of 2-Aminopyrroles with Sodium Hydride and Dimethyl Sulfate

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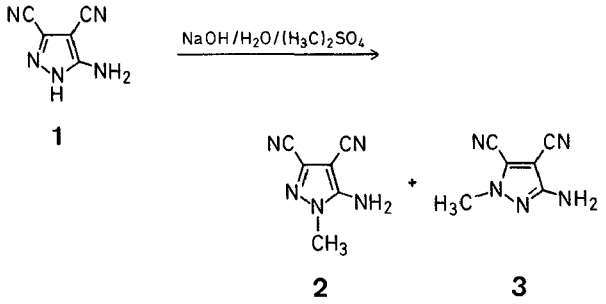
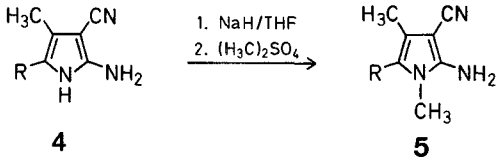
Although several efficient methods for the mono- and dimethylation of aromatic and heterocyclic amines have been reported[1], the *N*-1-methylation of 2-aminopyrroles has been less thoroughly studied. It has been well documented[2] that alkali metal salts of pyrrole react with alkyl halides to give *N*-alkylated products and that polar solvents favor *N*-alkylation. In one recent example[3], the reaction of 5-amino-3,4-dicyanopyrazole (**1**) with aqueous sodium hydroxide and dimethyl sulfate was shown to give two products (**2** and **3**).

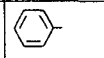
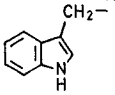
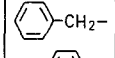
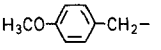
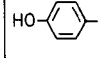
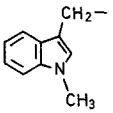


1 **2** **3**

Our research has centered around 5-substituted 2-amino-3-cyano-4-methylpyrroles[4,5,6] **4a–h** as potential precursors of active medicinal agents. We now report a facile method for the selective *N*-1-methylation of these compounds. The pyrroles **4a–h** were treated in anhydrous tetrahydrofuran with sodium hydride (1.1 equiv). The resulting metallated derivatives were then reacted with dimethyl sulfate (1.1 equiv) to give the *N*-1-methylpyrroles **5a–f, i, j** in yields from 69 to 98%. Since the side chains of compounds **4g** and **4h** were also methylated during the reaction, two equivalents of both sodium hydride and dimethyl sulfate were required for the conversion of **4g** and **4h** to **5i** and **5j**.



4 **5**

	R		R		R
a	H_3C	**e**		**h**	
b	C_2H_5	**f**		**i**	
c	$(H_3C)_2CH-CH_2$	**g**		**j**	
d	$H_3C-S-CH_2-CH_2$				

The ^{1}H-N.M.R. spectra of these products **5a–f, i, j** showed singlets at 1.93–2.10 ppm and 3.06–3.30 ppm due to the methyl groups at C-4 and N-1 respectively, and a broad singlet at 3.60–3.91 ppm due to the amino moiety. The I.R. spectra contained a strong nitrile absorption at 2175–2200 cm^{-1} and three characteristic ring stretching absorptions at 1635–1655, 1550–1565, and 1495–1510 cm^{-1}. The

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Table. 5-Substituted 2-Amino-3-cyano-1,4-dimethylpyrroles **5a–f, i,** and **j**

Product	Yield[a] [%]	m.p. (solvent)	color	Rf (ethyl acetate)	Molecular formula[b]	I.R. (KBr) ν_{max} [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
5a	67	128.5–129.5° (CH_3OH)	golden needles	0.64	$C_8H_{11}N_3$ (149.2)	3350, 2175, 1635, 1560, 1508	2.0 (s, 6H, $2CH_3$); 3.25 (s, 3H, N—CH_3); 3.75 (br s, 2H, NH_2)
5b	77	114.5–116° (80% CH_3OH)	beige	0.62	$C_9H_{13}N_3$ (163.2)	3370, 3330, 3230, 2965, 2200, 1635, 1550, 1495, 1205	1.03 (t, 3H, J=7.5 Hz, CH_2CH_3); 1.93 (s, 3H, CH_3); 2.58 (q, 2H, J=7.5 Hz, CH_2CH_3); 3.27 (s, 3H, N—CH_3); 3.83 (br s, 2H, NH_2)
5c	98	130–130.5° (c-C_6H_{12})	light yellow	0.64	$C_{11}H_{17}N_3$ (191.3)	3360, 3320, 3220, 2940, 2180, 1645, 1560, 1505	0.88 [d, 6H, J=5.4 Hz, $CH(CH_3)_2$]; 1.4–2.0 [m, 1H, $CH(CH_3)_2$]; 1.97 (s, 3H, CH_3); 2.26 (d, 2H, J=7.8 Hz, CH_2); 3.24 (s, 3H, N—CH_3); 3.71 (br s, 2H, NH_2)
5d	93	134.5–135° (CH_3OH)	brown	0.61	$C_{10}H_{15}N_3S$ (209.9)	3380, 3330, 3230, 2910, 2190, 1645, 1565, 1505, 1210	2.01 (s, 3H, S—CH_3); 2.09 (s, 3H, CH_3); 2.50–2.75 (m, 4H, CH_2—CH_2); 3.30 (s, 3H, N—CH_3); 3.74 (br s, 2H, NH_2)
5e	95	148.5–149° (CH_3OH)	beige	0.63	$C_{13}H_{13}N_3$ (211.3)	3320, 3220, 2195, 1655, 1600, 1560, 1510, 755, 700	2.02 (s, 3H, CH_3); 3.23 (s, 3H, N—CH_3); 3.91 (br s, 2H, NH_2); 7.20–7.35 (m, $5H_{arom}$)
5f	98	184–185° (CH_3OH)	tan	0.66	$C_{14}H_{15}N_3$ (225.3)	3370, 3320, 3230, 2190, 1640, 1560, 1510, 695	2.07 (s, 3H, CH_3); 3.06 (s, 3H, N—CH_3); 3.60 (br s, 2H, NH_2); 3.78 (s, 2H, CH_2); 7.18 (m, $5H_{arom}$)
5i	69	164.5–165° (CH_3OH)	tan	0.61	$C_{15}H_{17}N_3O$ (255.3)	3370, 3320, 3210, 2185, 1640, 1560, 1505, 1245	2.08 (s, 3H, CH_3); 3.08 (s, 3H, N—CH_3); 3.75 (s, 7H, OCH_3, CH_2, and NH_2); 6.86 (m, $4H_{arom}$)
5j	93	191–192° (dec.) (C_2H_5OH)[c]	tan powder	0.53	$C_{17}H_{18}N_4$ (278.3)	3360, 3320, 2180, 1635, 1560, 1505, 1470, 730	2.10 (s, 3H, CH_3); 3.11 (s, 3H, N—CH_3); 3.66 (s, 5H, CH_2 and indole N—CH_3); 3.87 (s, 2H, NH_2); 6.5 (m, $1H_{arom}$, indole H—C-2); 7.2 (m, $4H_{arom}$, H—C-4, 5, 6, 7 of indole)

[a] Yield of crude product before recrystallization.
[b] All products gave satisfactory microanalyses (C ±0.23, H ±0.06, N ±0.12).
[c] Crude product washed with boiling absolute ethanol.

products were assigned the N-1-methyl structure on the basis of microanalyses, T.L.C., and spectral data.

Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. The N.M.R. spectra were determined in $CDCl_3$ on a Hitachi Perkin-Elmer R24 High Resolution spectrometer using TMS as internal reference. I.R. spectra were determined on a Beckman IR-20A Grating Spectrophotometer using the KBr technique. Microanalyses were carried out by Atlantic Microlab, Inc., Atlanta, Georgia. T.L.C. were performed on Eastman Chromatogram sheets, type 6060 (silica gel).

5-Substituted 2-Amino-3-cyano-1,4-dimethylpyrroles 5a–f, i, j; General Procedure:

A solution of 2-amino-3-cyano-4-methyl-5-substituted pyrrole[4,5] **4a–h** (0.05 mol) dissolved in tetrahydrofuran (100 ml; dried over metallic sodium) is stirred in an ice bath while sodium hydride (a 50% mineral oil dispersion; 2.64 g, 0.055 mol) is slowly added. After all bubbling has ceased, dimethyl sulfate (6.9 g, 0.055 mol) is added, and the ice bath removed. The mixture is stirred at room temperature for 15 min and then heated under reflux for 1 h. This mixture is poured over crushed ice (300 g), diluted with water (100 ml), and stirred until the ice has melted. The insoluble solid is filtered, washed with distilled water, and air dried. To remove the mineral oil, the crude produce is suspended in *n*-pentane, filtered, and air dried (see Table).

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