# Synthesis of *N*-1-Substituted 2-Amino-3-*t*-butoxycarbonyl-4,5-dimethylpyrroles

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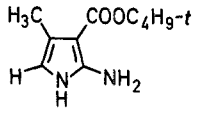
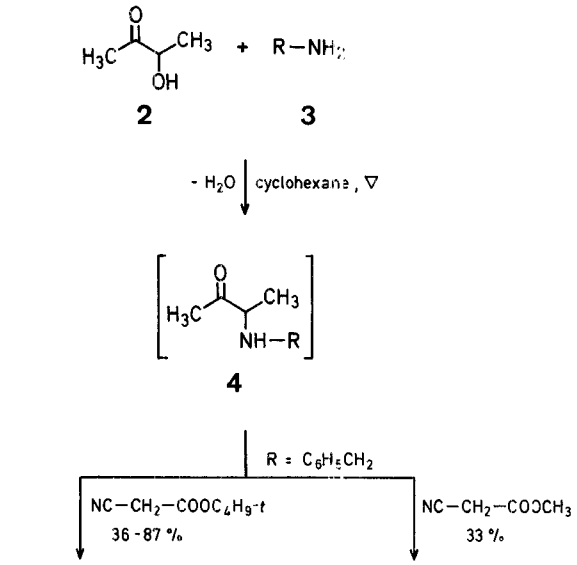
In previous publications we have described the synthesis[1,2] of various 2-aminopyrroles and their selective *N*-1-methylation[3]. These 2-aminopyrroles have served as precursors to several series of pharmacologically active compounds.

The desire for a more synthetically flexible series of 2-aminopyrroles, prompted the current research. The condensation of acetylaminoacetone with *t*-butyl cyanoacetate to yield 2-amino-3-*t*-butoxycarbonyl-4-methylpyrrole (**1**) has been reported[4]. We now report a facile method for the synthesis of a series of 2-amino-3-*t*-butoxycarbonyl-4,5-dimethylpyrroles (**5**).



**1**

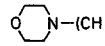
Condensation of 3-hydroxy-2-butanone (**2**) with primary amines **3a–k** in refluxing cyclohexane resulted[5] in the formation of intermediate α-aminoketones **4a–k**. These were condensed, without purification, with *t*-butyl cyanoacetate to yield the various 2-amino-3-*t*-butoxycarbonyl-4,5-dimethylpyrroles **5a–k** in yields ranging from 36 to 87%. Condensation of the α-aminoketone **4a** with methyl cyanoacetate gave 1-benzyl-2-amino-3-methoxycarbonyl-4,5-dimethylpyrrole (**6**) in 33% yield.



**2** **3**

**4**

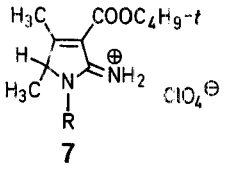
**5** **6**

| 3-5 | R | 3-5 | R |
|---|---|---|---|
| a |  | g | c-$C_5H_9$ |
| b |  | h | c-$C_6H_{11}$ |
| c |  | i | n-$C_3H_7$ |
| d |  | j | n-$C_4H_9$ |
| e |  | k | i-$C_4H_9$ |
| f | $(H_3CO)_2$—CH—$CH_2$— | | |

The I.R. spectra of the 2-aminopyrroles **5a–k** and **6** contained typical N—H absorption from 3240 to 3450 $cm^{-1}$. Strong carbonyl absorption was observed from 1640 to 1660 $cm^{-1}$, with typical carbon to oxygen stretching in the region from 1240 to 1270 $cm^{-1}$. The relatively low carbonyl absorption frequency can be attributed to intramolecular H-bonding between the amine and the ester.

The $^1$H-N.M.R. spectra of the products **5a–k** showed a singlet at $\delta = 1.51–1.57$ ppm due to the tertiary butyl group. The methyl groups at the 4- and 5-positions were observed as singlets at $\delta = 1.92–2.10$ and $\delta = 2.05–2.15$ ppm, respectively. The amine was observed as a broad singlet from 4.50–5.80 ppm. The $^1$H-N.M.R. spectrum of compound **6** was consistent with **5a**, except for the methyl of the methoxycarbonyl group of **6**, which appeared as a singlet at $\delta = 3.77$ ppm.

Compounds **5j–k** were obtained as thick viscous oils; therefore, these products were characterized as their crystalline perchlorate salts. The $^1$H-N.M.R. spectra of these salts in deuterochloroform strongly indicate that protonation occurred at the 5-position to give **7** rather than on the primary amine.



**7**

Structure **7** was assigned based on the appearance in $^1$H-N.M.R. spectra of a doublet at $\delta = 1.5$ ppm (5-C—$CH_3$) and a quartet at $\delta = 4.70$ ppm ($C_5$—H) for the perchlorate salt of **5j** and a doublet at $\delta = 1.5$ ppm and a quartet at $\delta = 4.65$ ppm for the perchlorate salt of **5k**. The protons on the charged amine were observed as two broad singlets (at $\delta = 7.9$ and 8.15 ppm for **5j**; and at $\delta = 8.0$ and 8.2 ppm for **5k**) due to their nonequivalence. The same anomalous behaviour has been reported for 2-amino-3-cyano-4,5-dimethylpyrrole in trifluoroacetic acid[6], for 2-amino-3-cyano-4-methylpyrrole[4] and for the corresponding 3-*t*-butoxycarbonyl analog[4] **1**.

Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. The $^1$H-N.M.R. spectra were determined on a Varian EM 360A or EM 390 NMR spectrometer. Infrared spectra were determined on a Beckman Acculab 4 spectrophotometer. T.L.C. were performed on Eastman Chromatogram Sheets, type 6060 (silica gel).

**1-Substituted 2-Amino-3-*tert*-butoxycarbonyl-4,5-dimethylpyrroles 5a–k, 6; General Procedure:**

An 85% aqueous solution of 3-hydroxy-2-butanone (**2**, 103.7 g, 1 mol) and benzylamine (107.2 g, 1.0 mol) in cyclohexane (400 ml) is refluxed under a Dean-Stark trap until the separation of water (27.0 ml) has ceased (~0.5 h). The solution is cooled, *t*-butyl cyanoacetate (148.2 g, 1.05 mol) is added and the solution is refluxed for 2 h under a Dean-Stark trap to yield an additional amount of water (17.2 ml). The cyclohexane is removed in vacuo and the residue is crystallized from methanol-water (3:1, 800 ml), after standing overnight in the freezer. The crude product (261 g, 87%) is further recrystallized from methanol-water (7:3, 1000 ml) to give off-white crystals; yield: 225 g (75%). (Table)

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**Table.** 1-Substituted 2-Amino-3-*t*-butoxycarbonyl-4,5-dimethylpyrroles **5a–k** and Analog **6**

| Product No. | Yield[a] [%] | m.p. [°C] (solvent) | Molecular formula[b] | I.R. (KBr) $\nu$ [cm$^{-1}$] | $^1$H-N.M.R. ($CDCl_3$/TMS) $\delta$ [ppm] |
|---|---|---|---|---|---|
| **5a** | 87 | 93–94° (70% $CH_3OH$) | $C_{18}H_{24}N_2O_2$ (300.4) | 3420, 3240, 2960, 1660, 1600, 1510, 1360, 1240, 1100 | 1.53 (s, 9H, *t*-$C_4H_9$); 2.0 (s, 3H, 4-$CH_3$); 2.1 (s, 3H, 5-$CH_3$); 4.70 (s, 2H, $NH_2$); 4.83 (s, 2H, $CH_2$); 6.9–7.3 (m, 5H$_{arom}$) |
| **5b** | 76 | 99.5–100.5° (67% $CH_3OH$) | $C_{17}H_{23}N_3O_2$ (301.4) | 3380, 3270, 2970, 1650, 1610, 1520, 1300, 1240, 1100 | 1.53 (s, 9H, *t*-$C_4H_9$); 2.03 (s, 3H, 4-$CH_3$); 2.10 (s, 3H, 5-$CH_3$); 4.87 (s, 2H, $CH_2$); 5.45 (s, 2H, $NH_2$); 6.9–7.7; 8.4–8.55 (m, 4H$_{arom}$) |
| **5c** | 54 | 124–125° ($CH_3OH$) | $C_{17}H_{23}N_3O_2$ (301.4) | 3360, 3240, 2960, 1650, 1615, 1520, 1300, 1240, 1100 | 1.53 (s, 9H, *t*-$C_4H_9$); 1.96 (s, 3H, 4-$CH_3$); 2.10 (s, 3H, 5-$CH_3$); 4.83 (s, 2H, $NCH_2$); 4.95 (s, 2H, $NH_2$); 7.15–7.25 (m, 2H$_{arom}$); 8.3–8.55 (m, 2H$_{arom}$) |
| **5d** | 69 | 77–79° ($CH_3OH$) | $C_{19}H_{26}N_2O_2 \cdot 0.25H_2O$ (314.4) | 3400, 3320, 2960, 1650, 1610, 1490, 1360, 1270, 1095 | 1.51 (s, 9H, *t*-$C_4H_9$); 1.92 (s, 3H, 4-$CH_3$); 2.06 (s, 3H, 5-$CH_3$); 2.80 (t, 2H, $J$ = 7.2 Hz, $CH_2$); 3.75 (t, 2H, $J$ = 7.2 Hz, $CH_2$—N); 4.50 (s, 2H, $NH_2$); 6.9–7.3 (m, 5H$_{arom}$) |
| **5e** | 68 | 109–111° (*n*-Hexane) | $C_{18}H_{31}N_3O_3 \cdot 0.3H_2O$ (337.4) | 3410, 3290, 2960, 1640, 1600, 1525, 1370, 1290, 1240, 1100 | 1.4–1.7 (m, 2H, $CH_2$—$CH_2$—$CH_2$—N); 1.55 (s, 9H, *t*-$C_4H_9$); 2.05 (s, 3H, 4-$CH_3$); 2.10 (s, 3H, 5-$CH_3$); 2.3–2.6 (m, 6H, $CH_2CH_2CH_2$—N + ring $CH_2$—N—$CH_2$); 3.55–3.85 (m, 6H, N—$CH_2$ + $CH_2$—O—$CH_2$); 5.8 (s, 2H, $NH_2$) |
| **5f** | 79 | 111–113° (75% $CH_3OH$) | $C_{15}H_{26}N_2O_4$ (298.4) | 3430, 3340, 2960, 1650, 1600, 1550, 1300, 1250, 1110 | 1.53 (s, 9H, *t*-$C_4H_9$); 2.03 (s, 3H, 4-$CH_3$); 2.10 (s, 3H, 5-$CH_3$); 3.4 (s, 6H, $OCH_3$); 3.75 (d, 2H, $J$ = 5.0 Hz, N—$CH_2$); 4.35 (t, 1H, $J$ = 5.0 Hz, CH); 5.22 (s, 2H, $NH_2$) |
| **5g** | 36 | 137–139° ($CH_3OH$) | $C_{16}H_{26}N_2O_2$ (278.4) | 3450, 3350, 2980, 1650, 1600, 1510, 1270, 1120 | 1.57 (s, 9H, *t*-$C_4H_9$); 2.0 (s, 3H, 4-$CH_3$); 2.10 (s, 3H, 5-$CH_3$); 1.3–2.1 (m, 8H, *c*-$C_5H_9$); 4.4 (m, 1H, N—CH); 5.0 (s, 2H, $NH_2$) |
| **5h** | 57 | 125–128° ($CH_3OH$) | $C_{17}H_{28}N_2O_2$ (292.4) | 3450, 3340, 2970, 2920, 1640, 1600, 1590, 1270, 1230, 1110 | 1.2–2.0 (m, 10H, *c*-$C_6H_{11}$); 1.55 (s, 9H, *t*-$C_4H_9$); 2.10 (s, 6H, 4- and 5-$CH_3$); 3.8 (m, 1H, N—CH); 5.0 (s, 2H, $NH_2$) |
| **5i** | 77 | 72.0–73.5° (90% $CH_3OH$) | $C_{14}H_{24}N_2O_2 \cdot 0.5H_2O$ (252.4) | 3430, 3370, 2960, 2920, 1645, 1600, 1500, 1360, 1270, 1240, 1100 | 0.92 (t, 3H, $J$ = 7.0 Hz, N—$CH_2$—$CH_2$—$CH_3$); 1.4–1.8 (m, 2H, N—$CH_2CH_2CH_3$); 1.53 (s, 9H, *t*-$C_4H_9$); 2.0 (s, 3H, 4-$CH_3$); 2.05 (s, 3H, 5-$CH_3$); 3.52 (t, 2H, $J$ = 7.3 Hz, N—$CH_2$); 4.85 (s, 2H, $NH_2$) |
| **5j** · $HClO_4$[c] | 80 | 142–144° ($C_2H_5OH$/Ether) | $C_{15}H_{26}N_2O_2 \cdot HClO_4$ (366.8) | 3400, 3280, 3220, 2980, 1700, 1670, 1570, 1390, 1200, 1170, 1120, 1050, 830 | 0.93 (t, 3H, $J$ = 5.4Hz, N—$CH_2$—$CH_2$—$CH_2$—$CH_3$); 1.1–1.7 (m, 4H, N—$CH_2$—$CH_2$—$CH_2$—$CH_3$); 1.5 (d, 3H, 5-$CH_3$); 1.6 (s, 9H, *t*-$C_4H_9$); 2.45 (s, 3H, 4-$CH_3$); 3.50 (m, 2H, N—$CH_2$); 4.7 (q, 1H, $J$ = 6.9 Hz, 5-CH); 7.9, 8.15 (2s, 2H, $NH_2^{\oplus}$) |
| **5k** · $HClO_4$[c] | 72 | 159–161° ($C_2H_5OH$) | $C_{15}H_{26}N_2O_2 \cdot HClO_4$ (366.8) | 3380, 3260, 3210, 2980, 1700, 1660, 1570, 1390, 1280, 1150, 1120, 1090, 1050, 825 | 0.85–1.10 [m, 6H, $CH(CH_3)_2$]; 1.2–1.5 [m, 1H, N—$CH_2CH(CH_3)_2$]; 1.5 (d, 3H, 5-$CH_3$); 1.6 (s, 9H, *t*-$C_4H_9$); 2.5 (s, 3H, 4-$CH_3$); 3.25–3.90 (m, 2H, N—$CH_2$); 4.65 (q, 1H, $J$ = 7.0 Hz, 5-CH); 8.0, 8.2 (2s, 2H, $NH_2^{\oplus}$) |
| **6** | 33 | 138–139° ($CH_3OH$) | $C_{15}H_{18}N_2O_2$ (258.3) | 3440, 3330, 1645, 1615, 1520, 1450, 1360, 1305, 1250, 1120, 1100, 780, 720 | 2.0 (s, 3H, 4-$CH_3$); 2.15 (s, 3H, 5-$CH_3$); 3.77 (s, 3H, $COOCH_3$); 4.8 (s, 2H, $NH_2$); 4.85 (s, 2H, N—$CH_2$) 6.85 7.35 (m, 5H$_{arom}$) |

[a] Yield of crude product before recrystallization.

[b] Satisfactory microanalyses obtained: C ±0.27, H ±0.23, Cl ±0.10, N ±0.10.

[c] Characterized as the perchlorate salt.

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