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A series of alkyl 1-(aryl)-2-pyrrolicarboxylates were prepared by the condensation of the appropriate aniline with methyl tetrahydro-2,5-dimethoxy-2-furancarboxylate in refluxing acetic acid. It was found that condensation proceeds even in substituents possessing steric bulk are present in the *ortho* positions of the aniline. Strong electron withdrawing substituents if conjugated to the nitrogen diverts the reaction from product to unidentified tars.

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As part of a larger synthesis we have had need of a series of alkyl 1-(aryl)-2-pyrrolicarboxylates **1** as synthetic intermediates. A search of the literature revealed only a few references where examples of this exact type of pyrrole had been reported [1-3]. However, methyl 2-(1*H*-pyrrol-1-yl)benzoate (**4**) is a known compound and can be prepared straightforwardly by the condensation of methyl 2-amino-benzoate (**3**) with tetrahydro-2,5-dimethoxyfuran (**2**) in refluxing acetic acid [4,5]. In fact, this condensation has been mentioned as the method of choice for the preparation of 1-substituted pyrroles [6] by one author.

No indication of the reaction limitations could be found in the existing literature. We were therefore curious as to the scope of this reaction and what factors would become limiting in applying the condensation to a series of substituted anilines. For the purposes of studying structure-activity relationships, we were interested in determining the sensitivity of the reaction to both electronic and steric factors.

The report by Clauson-Kaas and Elming described the condensation of methyl tetrahydro-2,5-dimethoxy-2-furancarboxylate (**5**) with aniline **6a** to give the desired pyrrole **7a** in good yield [2]. We have expanded upon this report and prepared a number of methyl 1-aryl-2-pyrrolicarboxyl-

ates *via* the condensation of **5** with various substituted anilines **6** that gives an indication of the scope of this reaction (Table 1).

The consequence of steric bulk in the *ortho* positions does not appear to be problematic. The bulk of two *ortho* ethyl **7b** substituents is tolerated quite well. Two *ortho* isopropyl groups **7c** diminishes the yield to approximately 50%. With the two isopropyl groups the remainder of the mass balance unfortunately is not unconverted starting materials but is lost to tars and unidentified side products.

In general, it seems that electron-donating substituents on the aryl ring such as alkyl **7b,c** or alkoxy **7f** do not impede the reaction.

The strongly electron-withdrawing nitro group shows an interesting effect. Use of a single nitro substituent **7g** conjugated to the amino moiety results in a noticeable loss in yield. The effect of two nitro groups **7i,j** in conjunction with the amine is to divert the reaction from the expected products to unidentifiable tars. In contrast, if not conjugated to the amino nitrogen **7h**, two nitro groups can be tolerated without any apparent loss in reaction efficiency. Less potent electron-withdrawing groups such as (phenyl-methoxy)carbonyl **7e** and phenyl **7d** are wholly compatible with the reaction even when in conjugation with the ani-

Table 1

Compound No.	Yield %	mp (°C)	Molecular Formula	C Calcd./Found	H Calcd./Found	N Calcd./Found
<b>7a</b> [2]	69	85-86.5 [a]	C <sub>12</sub> H <sub>11</sub> NO <sub>2</sub>	71.62/71.40	5.51/5.60	6.96/6.90
<b>7b</b>	89	63-66	C <sub>16</sub> H <sub>19</sub> NO <sub>2</sub>	74.68/74.31	7.44/7.73	5.44/5.68
<b>7c</b>	45 [b]	113-114.5	C <sub>18</sub> H <sub>23</sub> NO <sub>2</sub>	75.75/75.75	8.12/8.13	4.90/4.83
<b>7d</b>	63	oil	C <sub>18</sub> H <sub>15</sub> NO <sub>2</sub> ·0.3H <sub>2</sub> O	76.47/76.34	5.56/5.57	5.05/4.99
<b>7e</b>	76	oil	C <sub>20</sub> H <sub>17</sub> NO <sub>4</sub>	71.63/71.85	5.11/5.20	4.11/4.13
<b>7f</b>	67	86.5-89	C <sub>14</sub> H <sub>15</sub> NO <sub>4</sub>	64.35/64.30	5.79/5.91	5.36/5.22
<b>7g</b>	34 [c]	86-88	C <sub>12</sub> H <sub>10</sub> N <sub>2</sub> O <sub>4</sub>	58.53/58.48	4.09/4.40	11.38/11.64
<b>7h</b>	79	149.5-151	C <sub>12</sub> H <sub>9</sub> N <sub>3</sub> O <sub>6</sub> ·0.1H <sub>2</sub> O	49.18/49.14	3.16/3.21	14.34/13.95
<b>7i</b>	0	—	—	—	—	—
<b>7j</b>	0	—	—	—	—	—

[a] Lit mp 88-90°. [b] Second crop 14% yield. [c] Second crop 20% yield.

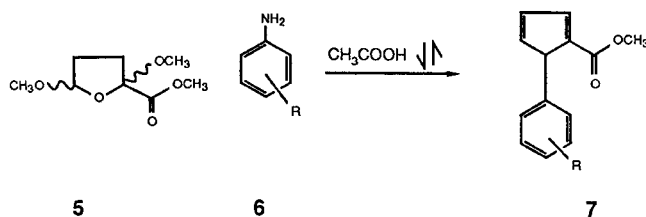
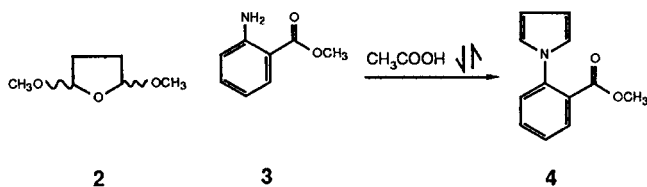
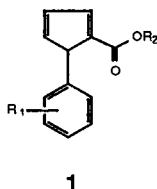
Table 2

Compound No.	IR (Potassium bromide, $\text{cm}^{-1}$ )	MS ( $m/z$ )	$^1\text{H-NMR}$ (Deuteriochloroform, ppm, $\delta$ )
<b>7a</b>	1710, 1599, 1273, 1127, 747, 696	201 ( $\text{P}^*$ ) 170 (base) 115	3.72 (s, 3H, $\text{OCH}_3$ ) 6.31 (m, 1H, pyrrole) 6.97 (m, 1H, pyrrole) 7.11 (m, 1H, pyrrole) 7.28-7.49 (m, 5H, phenyl)
<b>7b</b>	1715, 1528, 1273, 1133, 743	257 ( $\text{P}^*$ ) 198 (base) 168 154	1.08 (t, 6H, $\text{CH}_3$ ) $J = 7.6$ Hz 2.20 (m, 4H, $\text{CH}_2$ ) 3.66 (s, 3H, $\text{OCH}_3$ ) 6.36 (m, 1H, pyrrole) 6.78 (m, 1H, pyrrole) 7.01-7.40 (m, 4H, pyrrole and phenyl)
<b>7c</b>	3121, 2963 1709, 1274 1130, 752	285 ( $\text{P}^*$ ) 226 (base) 168	1.10 (m, 12H, $\text{CH}_3$ ) 2.29 (m, 1H, CH) 3.63 (s, 3H, $\text{OCH}_3$ ) 6.35 (m, 1H, pyrrole) 6.76 (m, 1H, pyrrole) 7.13 (m, 1H, pyrrole) 7.24 (m, 2H, phenyl) 7.41 (m, 1H, phenyl)
<b>7d</b>	2949, 1718 1276, 1134 738, 702	277 ( $\text{P}^*$ ) 246 2.17 (base) 189	3.60 (s, 3H, $\text{OCH}_3$ ) 6.15 (m, 1H, pyrrole) 6.77 (m, 1H, pyrrole) 6.90 (m, 1H, pyrrole) 7.03-7.08 (m, 2H, phenyl) 7.21-7.50 (m, 2H, phenyl)
<b>7e</b>	1717 (br), 1498, 1290 (br), 1124, 740, 700	335 ( $\text{P}^*$ ) 244 (base) 185 170 91	3.59 (s, 3H, $\text{OCH}_3$ ) 5.10 (m, 2H, $\text{OCH}_2$ ) 6.26 (m, 1H, pyrrole) 6.84 (m, 1H, pyrrole) 7.02 (m, 1H, pyrrole) 7.22-7.36 (m, 6H, phenyl) 7.46-7.61 (m, 2H, phenyl) 8.04 (m, 1H, phenyl)
<b>7f</b>	1717, 1517, 1230, 1118, 739	261 ( $\text{P}^*$ ) 230 202 (base) 187	3.70 (s, 3H, $\text{OCH}_3$ ) 3.71 (s, 3H, $\text{OCH}_3$ ) 3.79 (s, 3H, $\text{COOCH}_3$ ) 6.32 (m, 1H, pyrrole) 6.84-6.93 (m, 4H, pyrrole, phenyl) 7.08 (m, 1H, pyrrole)
<b>7g</b>	1700, 1523 1288, 1136 757	246 ( $\text{P}^*$ ) 187 (base) 169 157 143	3.69 (s, 3H, $\text{OCH}_3$ ) 6.40 (m, 1H, pyrrole) 6.93 (m, 1H, pyrrole) 7.13 (m, 1H, pyrrole) 7.43 (dd, 1H, $\text{CNO}_2\text{CH}$ ) $J = 1.5, 6.6$ Hz 7.68 (m, 2H, $\text{C}_6\text{H}_2$ ) 8.13 (dd, 1H, $\text{CNCH}$ ) $J = 1.7, 8.0$ Hz
<b>7h</b>	3110, 1708 1551, 1531 1361, 1278 1117, 767 730	291 ( $\text{P}^*$ , base) 260 232 213 168	3.77 (s, 3H, $\text{OCH}_3$ ) 6.45 (m, 1H, pyrrole) 7.05 (m, 1H, pyrrole) 7.21 (m, 1H, pyrrole) 8.54 (d, 2H, $\text{C}_6\text{H}_2$ ) $J = 2$ Hz 9.08 (m, 1H, $\text{CNO}_2\text{CHCNO}_2$ )

line nitrogen.

Although the yields have not been optimized for these conversions, in general this reaction will proceed in a moderate to excellent fashion for aromatic amines. In contrast

to an earlier conclusion [6], it appears that this type of pyrrole synthesis does have limitations. These limitations are only serious when the nucleophilicity of the amine is greatly diminished by delocalization.



6/7	R
a	H
b	2,6 - (CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub>
c	2,6 - (CH(CH <sub>3</sub> ) <sub>2</sub> ) <sub>2</sub>
d	2 - C <sub>6</sub> H <sub>5</sub>
e	2 - COOCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>
f	2,5 - (OCH <sub>3</sub> ) <sub>2</sub>

6/7	R
g	2 - NO <sub>2</sub>
h	3,5 - (NO <sub>2</sub> ) <sub>2</sub>
i	2,6 - (NO <sub>2</sub> ) <sub>2</sub>
j	2,4 - (NO <sub>2</sub> ) <sub>2</sub>

## EXPERIMENTAL

Melting points were determined on a Buchi 510 apparatus and are uncorrected. The <sup>1</sup>H-nmr spectra were recorded with a Varian XL-200 spectrometer in deuteriochloroform. Infrared spectra were recorded on a Nicolet MX-1 spectrophotometer as potassium bromide pellets. Mass spectral data was gathered using a VG Analytical 7070E/HF or a Finnegan 4500 spectrometer at 70eV by the direct insertion-electron impact method. All solvents and reagents were used as received from the supplier.

Methyl (1-(Phenyl)-1*H*-pyrrole-2-carboxylates (7a). Typical Procedure.

A mixture of methyl tetrahydro-2,5-dimethoxy-2-furancarboxylate [7] (0.76 g, 0.005 mole) and aniline (0.36 ml, 0.004 mole) in glacial acetic acid (10 ml) were refluxed under a nitrogen atmosphere for approximately 4-6 hours. Completion of the reaction was determined by the absence of the aniline by tlc (dichloromethane, silica gel). The reaction was cooled and the acetic acid removed by rotary-evaporation. The crude reaction products were filtered through a short column of silica gel with dichloromethane and the solvent removed to give an off-white solid, yield, 0.56 g (69%), mp 85-86.5°.

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