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PYRROLE STUDIES. PART. 44.[1] SYNTHESIS OF POTENTIALLY BIOLOGICALLY ACTIVE PYRROLOYLANILINES

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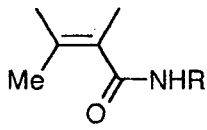
Abstract: The direct reaction of acid labile pyrrolecarboxylic acids with anilines in the presence of N,N'-dicyclohexylcarbodiimide provides an efficient general synthesis of pyrroloylanilines.

A wide range of carboxamides have been shown to have fungicidal activity. It has been suggested that the presence of the partial structure **1**, which may or may not be incorporated in a ring system, is an important in their activity and, for example, several (N-furoyl)- and (N-thenoyl)- anilines have been shown to be fungicidal.[3-5] However, virtually no examples have been recorded of the biological activity of the corresponding pyrroloylanilines[6] and this may be a result of the lack of an efficient mild general synthesis of pyrrolylcarboxamides from the acid-labile pyrrolecarboxylic acids.[7,8]



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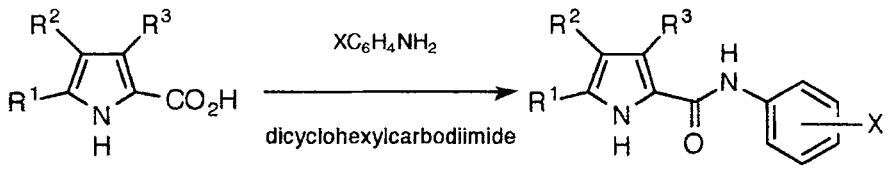

2 $R^1 = R^3 = Me$; $R^2 = CO_2Et$ **4** $R^1 = R^3 = Me$; $R^2 = CO_2Et$

3 $R^1 = R^3 = CO_2Et$; $R^2 = Me$ **5** $R^1 = R^3 = CO_2Et$; $R^2 = Me$

a X = H; **b** X = 4-Me; **c** X = 3-Me; **d** X = 4-OMe; **e** X = 3-OMe; **f** X = 4-OEt; **g** X = 4-F; **h** X = 4-Cl; **i** X = 3-Cl; **j** X = 4-Br; **k** X = 3-Br; **l** X = CO_2Et; **m** X = 4-NO_2; **n** X = 3-NO_2

We report here the simple conversion in good yields of pyrrolecarboxylic acids **2** and **3** into the respective anilides **4** and **5**. *via* the addition of N,N'-dicyclohexylcarbodiimide in tetrahydrofuran to the pyrrolecarboxylic acid and appropriate aniline in tetrahydrofuran or dichloromethane at 50 - 60°C. This procedure, which can be readily extended to the pyrroloyl derivatives of aliphatic amines,[9] is easier to control and produces superior yields of the pure anilides, compared with the reaction of the pyrroloyl chloride with the aniline, which tended to give extremely crude products needing repeated recrystallisation, or by a direct Knorr pyrrole synthesis from the acetoacetanilide which, when applied to the synthesis of **4b**, **4d**, and **4j**, respectively, from (N-acetoacetyl)-4-methylaniline, (N-acetoacetyl)-4-methoxyaniline, and (N-acetoacetyl)-4-bromoaniline, gave not only the expected pyrroloylanilines in *ca.* 45% yields, but also diethyl 3,5-dimethylpyrrole-2,4-dicarboxylate, the separation of which was tedious and resulted in a considerable reduction in the final yields of the anilides.

The fungicidal activity of the anilides showed no systematic pattern. The 4-methyl-, 4-methoxy- and 4-fluoro- derivatives **4b**, **4d** and **4g** and the 4-methyl-, 4-ethoxy- and 4-chloro- compounds **5b**, **5f** and **5h** showed significant activity against grape downy mildew, while the other anilides were totally inactive, and the 4-fluoro- and 4-chloro-derivatives **4g** and **5h** were the only compounds active against venticillium wilt. The 4-ethoxy- and 3-chloro-anilides **4f**, **5f**, **4i** and **5i**

were active against apple scab; **5f** was also active against rice blast, as was the 4-chloroanilide **5h**. Only the 3-chloroanilide **4i** showed any activity against apple mildew and virtually no activity was recorded for any of the anilides against barley mildew, tobacco black shank, wheat leaf rust, or black root rot. The lack of any structure-activity correlation suggests that there is only a minimal electronic effect of the N-aryl rings on the basic pyrrolylcarboxamide system. This proposition is well supported by infrared and ^{13}C NMR spectral data. Thus, the amidic νC=O frequencies of the anilides, measured for *ca.* 10^{-4}M solutions in carbon tetrachloride, are almost constant for the monoester anilides **4** at 1661 ± 2 cm^{-1}, while the corresponding band for the diester anilides **5** occurs at the predictably higher and virtually fixed frequency of *ca.* 1683 ± 1 cm^{-1}. These data, together with the almost constant ^{13}C NMR chemical shifts for the pyrrole ring and the carboxamido carbon atoms for both series of compounds, indicate that the 2-carboxamido group conjugates predominantly with the π-electron excessive pyrrole ring (even for the pyrrole systems having two other electron-withdrawing substituents), rather than with the aniline system.

Experimental

General Procedure for the Conversion of Pyrrolecarboxylic Acids into Pyrroloylanilines:

Method A: N,N'-Dicyclohexylcarbodiimide (2.88 g, 0.014 mol) in tetrahydrofuran (50 ml) was added dropwise slowly with stirring at room temperature to the pyrrolecarboxylic acid **2** or **3** (2.6 g, 0.014 mol) and the appropriate the aniline (0.013 mol) in tetrahydrofuran (50 ml). The mixture was allowed to stand at room temperature for 1 h and a few drops of acetic acid were then added. The precipitated N,N'-dicyclohexylurea was removed by filtration and the filtrate was evaporated to give the crude anilide, which was taken up in hot ethyl acetate; the solution was filtered and petroleum ether (b.p. 40 - 60°C) was added. The precipitated anilide was recrystallised from ethanol.

Method B: N,N'-Dicyclohexylcarbodiimide (5.75 g, 0.028 mol) in dichloromethane (50 ml) was added dropwise slowly with stirring at room temperature to

the pyrrolecarboxylic acid **2** or **3** (5.27 g, 0.025 mol) and the appropriate the aniline (0.025 mol) in dichloromethane (50 ml). The reaction mixture was worked up and the product isolated using the procedure given in Method A.

N-(4-Ethoxycarbonyl-3,5-dimethyl-2-pyrroloyl)aniline **4a** (Method A, 50%) had m.p. 180 - 182°C (lit., [10] m.p. 180°C).

N-(4-Ethoxycarbonyl-3,5-dimethyl-2-pyrroloyl)-4-methylaniline **4b** (Method A, 42%) had m.p. 181 - 183°C (Found: C, 67.6; H, 6.5; N, 9.3 $C_{17}H_{20}N_2O_3$ requires C, 68.0; H, 6.7; N, 9.3%)..

N-(4-Ethoxycarbonyl-3,5-dimethyl-2-pyrroloyl)-3-methylaniline **4c** (Method B, 91%) had m.p. 143 - 144°C (Found: C, 68.1; H, 6.9; N, 9.7; $C_{17}H_{20}N_2O_3$ requires C, 68.0; H, 6.7; N, 9.3%).

N-(4-Ethoxycarbonyl-3,5-dimethyl-2-pyrroloyl)-4-methoxyaniline **4d** (Method A, 43%) had m.p. 192 - 194°C (Found: C, 64.7; H, 6.4; N, 8.7 $C_{17}H_{20}N_2O_4$ requires C, 64.5; H, 6.4; N, 8.9%).

N-(4-Ethoxycarbonyl-3,5-dimethyl-2-pyrroloyl)-3-methoxyaniline **4e** (Method B, 64%) had m.p. 141 - 143°C (Found: C, 64.8; H, 6.6; N, 9.1; $C_{17}H_{20}N_2O_4$ requires C, 64.5; H, 6.4; N, 8.9%).

N-(4-Ethoxycarbonyl-3,5-dimethyl-2-pyrroloyl)-4-ethoxyaniline **4f** (Method B, 60%) had m.p. 166 - 168°C (Found: C, 65.8; H, 6.7; N, 8.4 $C_{18}H_{22}N_2O_4$ requires C, 65.4; H, 6.7; N, 8.5%).

N-(4-Ethoxycarbonyl-3,5-dimethyl-2-pyrroloyl)-4-fluoroaniline **4g** (Method A, 63%) had m.p. 191 - 193°C (Found: C, 62.8; H, 5.5; N, 9.0 $C_{16}H_{17}N_2FO_3$ requires C, 63.15; H, 5.6; N, 9.2%).

N-(4-Ethoxycarbonyl-3,5-dimethyl-2-pyrroloyl)-4-chloroaniline **4h** (Method A, 15%) had m.p. 250 - 251°C (Found: C, 59.8; H, 5.1; N, 8.6; Cl, 10.4 $C_{16}H_{17}N_2ClO_3$ requires C, 59.9; H, 5.3; N, 8.7; Cl, 11.0%).

N-(4-Ethoxycarbonyl-3,5-dimethyl-2-pyrroloyl)-3-chloroaniline **4i** (Method B, 44%) had m.p. 168 - 170°C (Found: C, 59.8; H, 5.0; N, 8.9; Cl, 10.9 $C_{16}H_{17}N_2ClO_3$ requires C, 59.9; H, 5.3; N, 8.7; Cl, 11.0%).

N-(4-Ethoxycarbonyl-3,5-dimethyl-2-pyrroloyl)-4-bromoaniline **4j** (Method B, 44%) had m.p. 190 - 191°C (Found: C, 52.8; H, 4.7; N, 7.5; Br 22.0 $C_{16}H_{17}N_2BrO_3$ requires C, 52.8; H, 4.7; N, 7.7; Br, 21.8%).

N-(4-Ethoxycarbonyl-3,5-dimethyl-2-pyrroloyl)-3-bromoaniline **4k** (Method B, 54%) had m.p. 173 - 175°C (Found: C, 52.7; H, 5.1; N, 7.7; Br 21.9 $C_{16}H_{17}N_2BrO_3$ requires C, 52.8; H, 4.7; N, 7.7; Br, 21.8%).

N-(4-Ethoxycarbonyl-3,5-dimethyl-2-pyrroloyl)-4-ethoxycarbonylaniline **4l** (Method B, 48%) had m.p. 209 - 211°C (Found: C, 63.5; H, 6.2; N, 8.0 $C_{19}H_{22}N_2O_5$ requires C, 63.7; H, 6.2; N, 7.8%).

N-(3,5-Bisethoxycarbonyl-4-methyl-2-pyrrolyl)aniline **5a** (Method B, 48%), m.p. 137 - 139°C (Found: C, 62.8; H, 6.0; N, 7.8 $C_{18}H_{20}N_2O_5$ requires C, 62.8; H, 5.85; N, 8.1%).

N-(3,5-Bisethoxycarbonyl-4-methyl-2-pyrrolyl)-4-methylaniline **5b** (Method B, 51%), m.p. 161 - 163°C (Found: C, 63.9; H, 6.1; N, 7.9; $C_{19}H_{22}N_2O_5$ requires C, 63.7; H, 6.2; N, 7.8%).

N-(3,5-Bisethoxycarbonyl-4-methyl-2-pyrrolyl)-3-methylaniline **5c** (Method B, 66%), m.p. 145 - 147°C (Found: C, 63.8; H, 6.1; N, 7.5; $C_{19}H_{22}N_2O_5$ requires C, 63.7; H, 6.2; N, 7.8%).

N-(3,5-Bisethoxycarbonyl-4-methyl-2-pyrrolyl)-4-methoxyaniline **5d** (Method B, 64%), m.p. 148.5 - 150.5°C (Found: C, 61.0; H, 6.1; N, 7.3; $C_{19}H_{22}N_2O_6$ requires C, 60.95; H, 5.9; N, 7.5%).

N-(3,5-Bisethoxycarbonyl-4-methyl-2-pyrrolyl)-3-methoxyaniline **5e** (Method B, 64%), m.p. 133 - 135°C (Found: C, 60.8; H, 6.0; N, 7.4; $C_{19}H_{22}N_2O_6$ requires C, 60.95; H, 5.9; N, 7.5%).

N-(3,5-Bisethoxycarbonyl-4-methyl-2-pyrrolyl)-4-ethoxyaniline **5f** (Method B, 62%), m.p. 119 - 120°C (Found: C, 61.8; H, 6.2; N, 7.1; $C_{20}H_{24}N_2O_6$ requires C, 61.85; H, 6.2; N, 7.2%).

N-(3,5-Bisethoxycarbonyl-4-methyl-2-pyrrolyl)-4-chloroaniline **5h** (Method B, 61%), m.p. 153 - 155°C (Found: C, 57.2; H, 5.2; N, 7.2; Cl, 9.3 $C_{18}H_{19}N_2ClO_5$ requires C, 57.1; H, 5.1; N, 7.4; Cl, 9.4%).

N-(3,5-Bisethoxycarbonyl-4-methyl-2-pyrrolyl)-3-chloroaniline **5i** (Method B, 61%), m.p. 141 - 143°C (Found: C, 56.9; H, 5.3; N, 7.2; Cl, 9.4 $C_{18}H_{19}N_2ClO_5$ requires C, 57.1; H, 5.1; N, 7.4; Cl, 9.4%).

N-(3,5-Bisethoxycarbonyl-4-methyl-2-pyrrolyl)-4-bromoaniline **5j** (Method B, 70%), m.p. 156.5 - 158.5°C (Found: C, 50.8; H, 4.6; N, 6.6; Br, 19.1 $C_{18}H_{19}N_2BrO_5$ requires C, 51.1; H, 4.5; N, 6.6; Br, 18.9%).

N-(3,5-Bisethoxycarbonyl-4-methyl-2-pyrrolyl)-3-bromoaniline **5k** (Method B, 72%), m.p. 155 - 156°C (Found: C, 50.9; H, 4.6; N, 6.7; Br, 18.7 $C_{18}H_{19}N_2BrO_5$ requires C, 51.1; H, 4.5; N ,6.6; Br, 18.9%).

N-(3,5-Bisethoxycarbonyl-4-methyl-2-pyrrolyl)-4-ethoxycarbonylaniline **5l** (Method B, 66%), m.p. 167 - 169°C (Found: C, 60.8; H, 5.8; N, 7.0; $C_{21}H_{24}N_2O_7$ requires C, 60.6; H, 5.8; N, 6.7%).

N-(3,5-Bisethoxycarbonyl-4-methyl-2-pyrrolyl)-4-nitroaniline **5m** (Method B, 37%), m.p. 192 - 194°C (Found: C, 55.2; H, 5.0; N, 11.0; $C_{18}H_{19}N_3O_7$ requires C, 55.5; H,4.9; N, 10.8%).

N-(3,5-Bisethoxycarbonyl-4-methyl-2-pyrrolyl)-3-nitroaniline **5n** (Method B, 73%), m.p. 163 - 165°C (Found: C, 55.3; H, 5.0; N, 10.4; $C_{18}H_{19}N_3O_7$ requires C, 55.5; H,4.9; N, 10.8%).

Attempted Conversion of Pyrroloyl chlorides into Pyrroloyl anilines:

An excess of the appropriate aniline was added dropwise with stirring to the crude pyrroloyl chloride (*ca*. 0.02 mol) in xylene (10 ml), prepared from the reaction of the 4-ethoxycarbonyl-3,5-dimethylpyrrole-2-carboxylic acid with thionyl chloride, and the mixture was stirred at room temperature for 1 h. The precipitated crude anilide was collected, washed well with water, and recrystallised from ethanol. Analytical samples of **4b**, **4d**, **4g**, **4h**, **4j**, and **4l** were obtained only after repeated recrystallisations.

Attempted Knorr synthesis of N-(4-Ethoxycarbonyl-3,5-dimethyl-2-pyrroloyl) -anilines:

Sodium nitrite (0.69 g, 0.01 mol) in water (5 ml) was added dropwise to the appropriate N-acetoacetanilide (0.01 mol) in acetic acid at 5°C. The solution was stirred for 30 min and then allowed to come to room temperature. Ethyl acetoacetate (1.3 g, 0.01 mol) was added, followed by zinc powder (1.4 g) added in portions at such a rate to maintain a gentle reflux. After the addition of the zinc, the mixture was refluxed for a further 1 h and the mixture was then poured into water (150 ml). The precipitate was collected, washed well with water and recrystallised from ethanol. Analytical samples of the anilides **4b**, **4d**, and **4j** were obtained only after repeated recrystallisation or by column chromatography.

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