The Direct Knorr Synthesis of 2-Pyrrolecarboxamides

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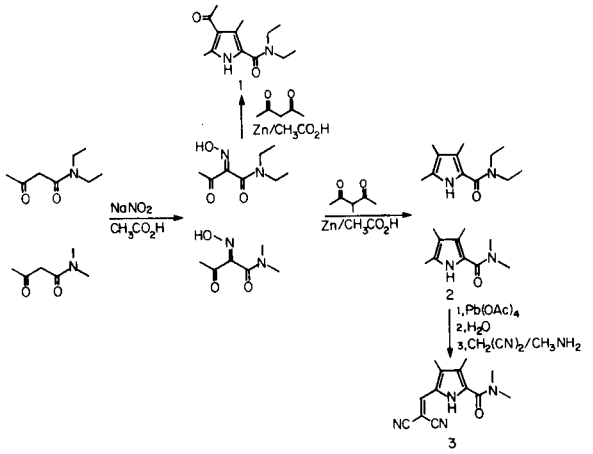
Dipyrroketones are important intermediates for the synthesis of porphyrins *via* oxobilanes (3,4). The principal route to dipyrroketones used by Kenner (5) in such syntheses involved the Vilsmeier reaction (6) of an α-pyrrylcarboxamide with an α-free pyrrole. At the time of the initiation of this study the only report of the direct synthesis of pyrrole amides was that of the α- and β-carboxanilides by Knorr himself (7) who prepared such derivatives of *Knorr's pyrrole* (2,4-dimethylpyrrole-3,5-dicarboxylic acid) from acetoacetanilide which nitrosated to give the oximinoacetoacetanilide, rather than the *N*-nitrosoamide. Treibs (8) had also reported the synthesis of several β-pyrrylcorboxamides by the reaction of acetoacetamides with oximinoketoesters, but this work had not been extended to the synthesis of the α-amides, which would require nitrosation of the acetoacetamides themselves. Instead the α-pyrrylcarboxamides have been prepared from α-free pyrroles with phosgene and dimethylamine, or from α-methylpyrroles by trichlorination followed by aminolysis.

More recently Kenner's group (9) have reported the synthesis of pyrrole α-carboxamides by the classical Knorr procedure. We wish to report here that the Johnson (10) modification of the Knorr synthesis employing 3-alkylated-2,4-pentanediones can be employed thus eliminating, in many cases, the need for the phosgene dialkylamine route.

Only tertiary amides can be used in the Vilsmeier condensation. The synthesis of tertiary pyrrylcarboxamides by a direct Knorr condensation would require the use of tertiary acetoacetamides, which is convenient since the nitrosation of non-tertiary amides might be expected to be complicated.

Both *N,N*-dimethyl and *N,N*-diethylacetamides (11) undergo smooth nitrosation (with sodium nitrite in acetic acid), and the resulting oximinoacetoacetamides reacted under the Knorr conditions (zinc dust and acetic acid) with 2,4-pentanedione to give the expected pyrroles. The yields from these reactions were entirely comparable with those obtained from β-ketoesters, and in the case of the



acetylpyrrole carboxamide (**1**) a higher yield (70%) than usual was obtained.

Pyrrylcarboxaldehydes are widely used in the syntheses of dipyrromethenes and porphyrins (12) and we have shown (13) that such aldehydes can be conveniently protected as their dicyanovinyl derivatives by reaction with malononitrile. In order to prepare similar derivatives the pyrrylamide (**2**) was oxidized to the aldehyde with two equivalents of lead tetraacetate. Unexpectedly the reaction mixture turned black (pyrrylcarboxylate esters remain light colored under such conditions and give high yields of the corresponding aldehyde) and no crystalline aldehyde could be precipitated from solution. Scavenging a methylene chloride extract with malononitrile afforded the desired dicyanovinyl derivative (**3**). These observations suggest that the expected lower electronegativity of the amide function, compared to that of an ester, provides less stabilization for the pyrrole nucleus, and that the initially formed acetoxymethylpyrrole amide may have a low barrier to ionisation to the pyrrylcarbinyl cation which would solvolyse to dipyrromethanes and other side products.

EXPERIMENTAL

Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ir spectra

(potassium bromide) were determined on a Perkin Elmer 137 spectrophotometer. The pmr spectra were obtained on a Varian Associates A-60 spectrometer with tetramethylsilane as internal standard and deuteriochloroform as solvent. Chemical shifts are expressed in the δ scale. Combustion analyses were carried out by Scandanavian Microanalytical Laboratories, Herlev, Denmark.

N,N-Dimethyl 3,4,5-Trimethylpyrrole-2-carboxamide (**2**).

A stirred, ice-cooled solution of *N,N*-dimethylacetoacetamide (129 g., 1 mole, Fluka Prakt.) in acetic acid (200 ml.) was treated rapidly and dropwise with a solution of sodium nitrite (70.1 g., ~ 1 mole) in water (80 ml.). Despite the ice-cooling, the internal temperature reached 45°. The resulting solution of *N,N*-dimethyloximinoacetoacetamide was added dropwise, along with an excess of zinc dust (290 g., 4.44 moles), to a well-stirred solution of 3-methyl-2,4-pentanedione (130 g., 1.14 moles) in acetic acid (400 ml.), contained in a two-liter flask. The addition of reactants was completed in about 40 minutes, and after stirring for 20 minutes longer, the solution was decanted from the remaining zinc sludge, and slowly diluted with water (2500 ml.), causing the product to crystallize out as shiny white needles. The product was collected by filtration and dissolved in methylene chloride. This solution was filtered to remove inorganic contaminants, separated from the aqueous phase and the methylene chloride removed, by heating in a steam bath, and replaced with methanol. The product crystallized from methanol (170 ml.). The crystals were collected by filtration, washed with methanol and then hexane to give 60.9 g. (33.8%). A second crop gave 21.1 g. (11.7%) for a combined yield of 82 g. (45.5%). An analytical sample was recrystallized from methylene chloride-methanol to give enormous chunky prisms, m.p. 167.5-168.5°; ν: 3150 (NH), 1580 (C=O) cm^{-1}; pmr: 1.88 (s, 3H), 2.01 (s, 3H), 2.13 (s, 3H), 3.04 (s, 6H), 9.92 (bs, 1H).

Anal. Calcd. for $C_{10}H_{16}N_2O$: C, 66.63; H, 8.95; N, 15.54. Found: C, 66.54; H, 8.91; N, 15.46.

N,N-Diethyl 3,4,5-Trimethylpyrrole-2-carboxamide.

N,N-Diethylacetoacetamide (62.8 g., 0.4 mole, Fluka Purum), in acetic acid (150 ml.), was treated dropwise with a solution of sodium nitrite (28 g., ~ 0.4 mole) in water (35 ml.). Zinc dust (113.5 g., 1.74 moles) and the above solution of *N,N*-diethyloximinoacetoacetamide were added to a stirred solution of 3-methyl-2,4-pentanedione (49 g., 0.43 mole) in acetic acid (350 ml.) over a 20 minute period. After an additional ten minutes of stirring, the solution was decanted from the zinc, and diluted with water. After workup as above, the methylene chloride was boiled away and replaced with hexane. The product crystallized in snow-white dense granules; first crop: 30.4 g. (36.5%), and second crop: 7.3 g. (8.8%), for total yield of 37.7 g. (45.4%). An analytical sample was recrystallized from methanol, m.p. 116.5-118.0°; ν: 3240 (NH), 1585 (C=O) cm^{-1}; pmr: 1.13 (t, 6H, J = 7.0 Hz), 1.87 (s, 3H), 2.00 (s, 3H), 2.11 (s, 3H), 3.52 (q, 4H, J = 7.0 Hz), 9.93 (bs, 1H).

Anal. Calcd. for $C_{12}H_{20}N_2O$: C, 69.19; H, 9.68; N, 13.45. Found: C, 69.14; H, 9.75; N, 13.36.

N,N-Diethyl 4-Acetyl-3,5-dimethylpyrrole-2-carboxamide (**1**).

N,N-Diethylacetoacetamide (31.4 g., 0.2 mole, Fluka Purum), in acetic acid (80 ml.) was nitrosated as above with a solution of sodium nitrite (14.1 g., ~ 0.2 mole) in water (20 ml.). The resulting solution of *N,N*-diethyloximinoacetoacetamide was added, with zinc dust (50 g., 0.77 mole), to a vigorously stirred solution of 2,4-pentanedione (22 g., 0.22 mole) in acetic acid (100 ml.). The reaction mixture reached reflux despite the small scale, and was ready to work up after only 20 minutes. Addition of water to the decanted solution caused separation of product as colorless sparkling granular crystals. After filtration and a thorough washing with water, the solids were dissolved in methylene chloride, filtered, and recrystallized from hexane. The yield was impressive, for a Knorr reaction, first crop: 30.1 g., second crop: 3.1 g., total: 33.2 g. (70.2%). An analytical sample was recrystallized from methanol to give clear colorless chunky diamonds, m.p. 173.0-174.0°; ν: 3150 (NH), 1630, 1590 (C=O) cm^{-1}; pmr: 1.18 (t, 6H, J = 7.5 Hz), 2.28 (s, 3H), 2.39 (s, 3H), 2.41 (s, 3H), 3.53 (q, 4H, J = 7.5 Hz), 11.05 (bs, 1H).

Anal. Calcd. for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.86. Found: C, 66.02; H, 8.49; N, 11.78.

N,N-Dimethyl 5-(2,2-Dicyanovinyl)-3,4-dimethylpyrrole-2-carboxamide (**3**).

N,N-Dimethyl 3,4,5-trimethylpyrrole-2-carboxamide (9.1 g., 0.05 mole) in glacial acetic acid (50 ml.) was treated with lead tetraacetate (49.1 g., of moist material, 0.1 mole) in one portion, with ice-cooling. Only half of the oxidant reacted until the solution was warmed, whereupon the lead tetraacetate dissolved completely and the solution became very dark. The addition of water caused no precipitation from a test sample, so that methylene chloride (250 ml.) was added, followed by water (250 ml.). The dark methylene chloride extracts were shaken with aqueous sodium carbonate to remove acetic acid, and then boiled down to give 9.9 g. of a brownish-black oil The oil was diluted with methanol (several volumes) and treated with malononitrile (3.5 g., 0.053 mole) and methylamine catalyst, on a steam bath. The hot solution almost immediately went solid with product, pale lemon-yellow silvery flakes. These were collected by filtration and washed with methanol until the rinsings were pale, then with hexane, yield, 4.02 g. (32.9%). An analytical sample was crystallized twice from methylene chloride methanol and then from methanol, m.p. 223.0-224.5° dec.; ν: 3360 (NH), 2210 (C=N), 1640 (C=O), 1580 (C=C) cm^{-1}; pmr: 2.07 (s, 3H), 2.17 (s, 3H), 3.08 (s, 6H), 7.52 (s, 1H), 9.58 (bs, 1H).

Anal. Calcd. for $C_{13}H_{14}N_4O$: C, 64.44; H, 5.82; N, 23.13. Found: C, 64.32; H, 5.82; N, 22.82.

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