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PYRROLE STUDIES. PART 36.[1] THE SYNTHESIS OF 2,2'-BIPYRROLES AND RELATED COMPOUNDS

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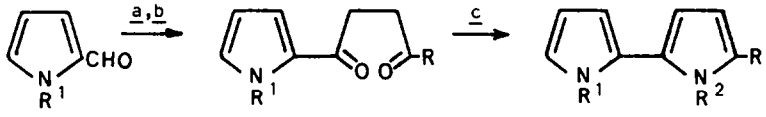
Abstract: Nucleophilic addition to but-1-en-3-one by the acyl anion equivalent of 2-formylpyrroles, generated by reaction with thiazolium salts, yields 1-(2-pyrrolyl)pent-1,4-diones, which undergo the Paal-Knorr reaction with ammonia and primary amines to give the 2,2'-bipyrroles. Alternatively, the 2,2'-bipyrrole system can be obtained by pyrolysis of 2-azido-5-(2-pyrrolyl)penta-2,4-dienoic esters.

During the course of our investigations[2] of possible routes for the synthesis of 10a,21-didehydro-10a-homocorrole,† we required a simple and an efficient synthesis of 2,2'-bipyrroles. Standard procedures, including the Ullmann reaction of iodopyrroles and the Vilsmeier-Haack reaction of pyrrolid-2-one with pyrroles unsubstituted at the 2-position, generally either proceed in low yield or require precursors, which are not readily available.[3] Recent developments in the synthesis of 1,4-diketones, via the nucleophilic addition of acyl anion equivalents to α,β-unsaturated ketones,[4] presented the possibility of a novel and versatile route to 2,2'-bipyrroles from 2-formylpyrroles (Scheme 1).



(1) (2)

a CN^- or 1,3-thiazolium salts b CH_2=CH.CO.R c R^2NH_2/H^+

Scheme 1

In previous work, the synthesis of several 1-aryl- and 1-heteroaryl-pentan-1,4-diones, using either thiazolium salts or cyanide anions, as catalysts for the formation of the acyl anion equivalent, has been described.[5] There are no reports, however, for the preparation of the analogous 2-pyrrolyl derivatives (1,

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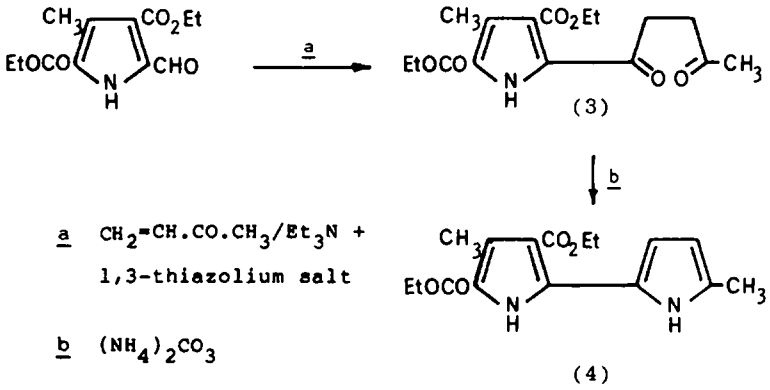
† Systematic name: 6,8,:16,18-bisetheno-1,4:11,14-bisimino-7,17-diazacycloocta-deca-1,3,5,7,9,11,13,15,17-nonaene

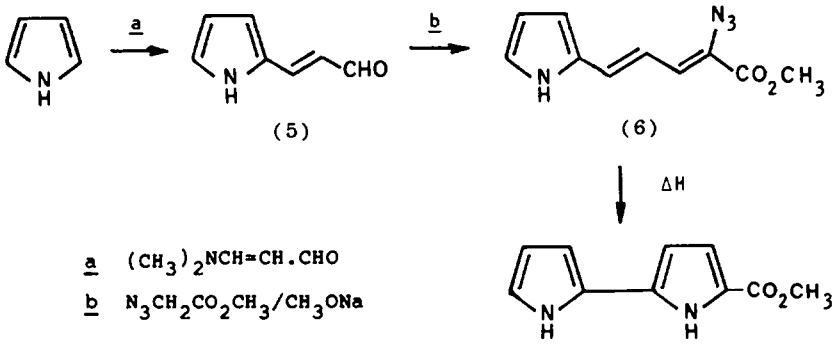
= Me). Cyclisation of the 1-aryl- and 1-heteroarylpentan-1,4-diones, upon treatment with sulphuric acid and acetic anhydride, has been shown to provide a viable route to 2-aryl and 2-heteroarylfurans[6] and, although in isolated cases the diones have been characterised by conversion into 1-methyl- and 1-phenylpyrroles by the Paal-Knorr reaction with methylamine and aniline, respectively,[5d,5b] the method has not been exploited as a route to 2,2'-bipyrroles.

We have found that 5-(2-furyl)-2-methyl- and 2-methyl-5-phenylpyrroles and their N-substituted derivatives can be readily obtained from furfural and benzaldehyde, respectively, using 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3--thiazolium chloride as the catalyst, in overall yields in excess of 60%. The procedure was not suitable for the preparation of the corresponding 2-methyl--5-(2-thienyl)pyrroles, owing to the poor yields in the preparation of 1-(2-thienyl)pentan-1,4-dione (*cf.* ref. 5c) and an extension of the method to the synthesis of simple 2,2'-bipyrroles from 2-formylpyrrole and 2-formyl-1--methylpyrrole failed completely. The fickleness of formylpyrroles towards attack by carbanionic nucleophiles is well established.[3] The lack of reactivity is caused, in the main, by strong interaction between the π-electron excessive ring and the formyl group and it has been recorded that, for example, neither 2-formylpyrrole nor its 1-methyl derivative will undergo a "benzoin" type condensation with potassium cyanide.[7] The ease of formation of the acyl anion equivalent of 2-formyl pyrrole can be enhanced, however, by the presence of electron-withdrawing substituents at either the carbon or nitrogen atoms of the ring,[8] and we have found that the thiazolium ion catalysed reaction of 1-benzenesulphonyl-2-formylpyrrole and of diethyl 2-formyl-4-methylpyrrole-3,5--dicarboxylate with but-1-en-3-one gave the 1,4-diketones (1, R = Me, R^1 = $PhSO_2$) and (3), respectively, in yields of 64% and 80%. The diketones were converted into the 2,2'-bipyrroles (2, R = Me, R^1 = $PhSO_2$, R^2 = H, n-Bu, Ph) and (4, R = H, n-Bu, Ph) in moderate to good yields.



The 5-aryl-2-methylpyrroles are well characterized by their ^1H and ^{13}C NMR spectra. The resonance signals for the β-carbon atoms appear at 106.6 ± 1.0 and at 109.3 ± 2.0 p.p.m. and are relatively insensitive to the nature of the 5-aryl group, whereas the position of the resonance signals for the α-carbon atoms at 127.8 ± 4.0 and 131.2 ± 2.5 p.p.m. are dependent both upon the electronic character of the 5-aryl group and upon the steric interaction between the 1-substituent and the 5-aryl group. A β-CH signal at 5.85 ± 0.3 p.p.m. is readily discernible in the ^1H NMR spectra of all of the compounds, but the second signal near 6.30 p.p.m. is frequently obscured by other aromatic signals.

In an alternative approach to the synthesis of 2,2'-bipyrroles, pyrrole was converted into 3-(2-pyrrolyl)propenal (5). Subsequent reaction with ethyl 2-azidoethanoate gave the thermally unstable azido ester (6) which, when heated to 70°C, gave the 2,2'-bipyrrole (62%). A similar procedure has been used previously for the synthesis of 2-phenylpyrrole[9], but the method has not been extended to the preparation of the bipyrroles.



The formation of the propenal (5) from pyrrole occurs in only moderate yield, but (5) can also be obtained *via* the Wittig reaction with 2-formylpyrrole (*cf.* ref. 10) and therefore compliments the pentan-1,4-dione method. Both procedures are versatile and simple, and generally produce consistently higher yields than the current literature methods.

EXPERIMENTAL

Unless stated otherwise, ^{1}H and ^{13}C NMR spectra were measured for *ca.* 35% solutions in $CDCl_3$ at 100MHz and 25MHz, respectively, using a JEOL JMN-100FT spectrometer. All chemical shifts are recorded with respect to the internal standard (Me_4Si)

General procedure for the preparation of 1-arylpentan-1,4-diones:- 3-Benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (1.63 g, 0.006 mol), obtained from the reaction of 5-(2-hydroxyethyl)-4-methyl-1,3-thiazole with benzyl chloride according to the procedure described in the literature,[11] but-1-en-3-one (10.5 g, 0.15 mol), triethylamine (7.6 g, 0.075 mol), anhydrous sodium acetate (0.45 g, 0.006 mol) and the appropriate aryl aldehyde (0.05 mol) in ethanol (150 ml) were heated under reflux until t.l.c. analysis failed to show the presence of starting material. The ethanolic solution was cooled to 0°C, poured into water (100 ml), and the aqueous mixture was extracted with dichloromethane (4 x 100 ml). The organic extracts were dried (Na_2SO_4) and evaporated. The crude product was purified by elution from Merck Kieselgel 60 with dichloromethane:ethyl acetate (10:1) to give the analytically pure diones.

Benzaldehyde gave 1-phenylpentan-1,4-dione (64%), b.p. 95 - 96°C at 0.1 mm Hg (lit.,[5a] b.p. 93 - 94°C at 0.1 mm Hg), after 4 days at reflux temperature. δ_H 2.20 (3H,s), 2.83 (2H, t), 3.23 (2H, t), 7.18 - 7.60 (3H, m), 7.87 - 8.14 (2H, m); δ_C 29.9 (q), 32.4 (t), 37.0 (t), 127.9 (d), 128.5 (d), 133.0 (d), 136.7 (s), 198.3 (s), 207.0 (s).

Furfural gave 1-(2-furyl)pentan-1,4-dione (66%), m.p. 45 - 46°C (lit.,[6] m.p. 45 - 46°C), after 3h at reflux temperature. δ_H 2.18 (3H, s), 2.83 (2H, t), 3.08 (2H, t), 6.46 (1H, dd), 7.13 (1H, dd), 7.45 - 7.61 (1H, m); δ_C 29.8 (q), 32.1 (t), 36.6 (t), 112.1 (d), 117.0 (d), 146.3 (d), 152.4 (s), 187.5 (s), 206.7 (s).

1-Benzenesulphonyl-2-formylpyrrole[12] gave 1-(1-benzenesulphonyl-2-pyrrolyl)pentan-1,4-dione (64%) m.p. 115 - 117°C (Found: C, 59.1; H, 4.9; N, 4.5; S, 10.4

$C_{15}H_{15}NO_4S$ requires C, 59.0; H, 4.9; N, 4.6; S, 10.5%). δ_H 2.28 (3H, s), 2.68 - 3.32 (4H, m), 6. 52 (1H, t), 7.28 (1H, dd), 7.43 - 8.24 (6H, m); δ_C 29.6 (q), 32.7 (t), 37.0 (t), 110.1 (d), 123.1 (d), 127.9 (d), 128.2 (s), 128.6 (d), 130.2 (d), 133.6 (d), 138.7 (s), 186.7 (s), 207.0 (s).

Diethyl 2-formyl-4-methylpyrrole-3,5-dicarboxylate[13] gave 1-(3,5-bisethoxycarbonyl-4-methyl-2-pyrrolyl)pentan-1,4-dione (80%) m.p. 58.5 - 59.5°C (Found: C, 59.7; H, 6.6; N, 4.25 $C_{16}H_{21}NO_6$ requires C, 59.4; H, 6.5; N, 4.3%). δ_H 1.37 (3H, t), 1.41 (3H, t), 2.21 (3H, s), 2.46 (3H, s), 2.85 (2H, t), 3.23 (2H, t), 4.35 (2H, q), 4.39 (2H, q), 9.96 (1H, s); δ_C 11.3 (q), 14.2 (q), 14.3 (q), 29.8 (t), 34.6 (t), 37.3 (t), 61.0 (t), 61.8 (t), 120.0 (s), 122.1 (s), 129.3 (s), 131.8 (s), 160.4 (s), 164.9 (s), 190.9 (s), 206.8 (s).

Typical conversion of 1-Arylpentan-1,4-diones into 2-Arylpyrroles:- The 1,4-dione (0.2 mol) and ammonium carbonate (0.5 mol) were heated at 100°C for between 2 and 5h. Water was added and the mixture heated under reflux for 30 min and then cooled to room temperature. The aqueous mixture was extracted with dichloromethane (3 x 30 ml) and the extracts were dried (Na_2SO_4) and evaporated to give the crude 2-arylpyrroles, which were purified by chromatography on Merck Kieselgel 60, using dichloromethane:petroleum ether (1:2) as the eluant.

2-Methyl-5-phenylpyrrole (57%), Rf 0.77, had m.p. 101 - 103°C (lit.,[14] m.p. 101°C). δ_H 2.32 (3H, s), 5.96 (1H, m), 6.38 (1H, t), 7.10 - 7.58 (5H, m), 8.23 (1H, br s); δ_C 13.1 (q), 106.1 (d), 107.9 (d), 123.3 (d), 125.6 (d), 128.7 (s), 128.8 (d), 130.7 (s), 132.9 (s).

2-(2-Furyl)-5-methylpyrrole (37%) , Rf 0.43, had m.p. 48 - 50°C (Found: C, 73.8; H, 6.2; N, 9.4 C_9H_9NO requires C, 73.4; H, 6.2; N, 9.5%). δ_H 2.26 (3H, s), 5.84 (1H, t), 6.12 - 6.44 (3H, m), 7.23 (1H, m), 8.16 (1H, br s); δ_C 12.9 (q), 101.3 (d), 105.6 (d), 107.5 (d), 111.4 (d), 122.6 (s), 128.3 (s), 139.8 (d), 148.5 (s).

1-Benzenesulphonyl-2-(5-methyl-2-pyrrolyl)pyrrole (25%), Rf 0.48, was isolated as a viscous oil (Found: C, 63.2; H, 5.0; N, 9.9 $C_{15}H_{14}N_2O_2S$ requires C, 62.9; H, 4.9; N, 9.8%). δ_H 2.34 (3H, s), 5.83 (1H, m), 5.99 (1H, t), 6.21 (2H, m), 7.26 - 7.58 (6H, m), 8.60 (1H, br s); δ_C 13.1 (q), 106.7 (d), 111.8 (d), 112.0 (d), 115.1 (d), 119.7 (s), 123.3 (d), 127.3 (d), 128.5 (s), 128.9 (d), 129.2 (s), 133.6 (d), 138.4 (s).

Diethyl 4-methyl-2-(2-methyl-5-pyrrolyl)pyrrole-3,5-dicarboxylate (40%), Rf 0.80, had m.p. 160 - 162°C (Found: C, 63.2; H, 6.5; N, 8.9 $C_{16}H_{20}N_2O_4$ requires C, 63.1; H, 6.6; N,9.2%). δ_H 1.37 (3H, t), 1.39 (3H, t), 2.34 (3H, s), 2.57 (3H, s), 4.35 (4H, q), 5.96 (1H, t), 6.48 (1H, t), 8.99 (1H, br s), 11.66 (1H, br s); δ_C 12.7 (q), 13.3 (q), 14.3 (q), 14.5 (q), 60.4 (t), 60.5 (t), 107.8* (d), 110.3 (s), 118.2 (s), 121.4 (s), 130.1 (s), 130.9 (s), 134.0 (s), 161.3 (s), 167.3 (s).

Typical Conversion of the 1-Arylpentan-1,4-diones into 1-Phenyl- and 1-n-Butyl--2-arylpyrroles:- Method A. Titanium tetrachloride (1.05 g, 0.006 mol) in toluene (10 ml) was added dropwise to the 1,4-dione (0.005 mol) and the appropriate primary amine (0.003 mol) in toluene (55 ml) under nitrogen at 5°C. The reaction mixture was stirred at 15°C for 15h and then filtered and evaporated. Chromatography of the crude product on Merck Kieselgel 60, using petroleum ether:dichloromethane (2:1) as the eluant, gave an analytically pure sample of the pyrrole.
Method B. The 1,4-dione (0.003 mol) and the appropriate primary amine (0.003 mol) and a catalytic amount of p-toluenesulphonic acid (ca. 10 mg) in toluene (60 ml) were heated under reflux for 4h. The solvent was removed under reduced pressure and the crude product was purified by chromatography, as described in Method A.

1-n-Butyl-2-methyl-5-phenylpyrrole (64%), Rf 0.76, had b.p. 90 - 92°C at 0.1 mm Hg (Found: C, 84.4; H, 9.0; N, 6.5 $C_{15}H_{19}N$ requires C, 84.5; H, 9.0; N, 6.6%). δ_H 0.76 (3H, t), 0.80 - 1.76 (4H, m), 2.23 (3H, s), 3.86 (2H, t), 5.92 (1H, d), 6.06 (1H, d), 7.04 - 7.40 (5H, m); δ_C 12.7 (q), 13.6 (q), 19.8 (t), 33.2 (t), 43.9 (t), 106.7 (d), 107.7 (d), 126.5 (s), 128.2 (d), 128.9 (d), 129.6 (s), 133.9 (s), 134.4 (s).

1-n-Butyl-2-furyl-5-methylpyrrole (47%), Rf 0.58, had b.p. 90 - 95°C at 0.1mm Hg (Found: C, 77.1, H, 8.5; N, 7.0 $C_{13}H_{17}NO$ requires C, 76.8; H, 8.4; N, 6.9%). δ_H 0.84 (3H, t), 1.10 - 1.88 (4H, m), 2.11 (3H, s), 3.90 (2H, t), 5.82 (1H, d), 6.14 - 6.38 (3H, m), 7.30 (1H, m); δ_C 12.3 (q), 13.6 (q), 20.0 (t), 33.3 (t), 44.7 (t), 105.6 (d), 107.3 (d), 108.9 (d), 110.9 (d), 123.8 (s), 130.3 (s), 140.8 (d), 149.1(s).

1-Benzenesulphonyl-2-(1-n-butyl-2-methyl-5-pyrrolyl)pyrrole (46%), Rf 0.43, had b.p. 190 - 195°C at 0.1mm Hg (Found: C, 67.0; H, 6.6; N, 8.2; S, 9.0 $C_{19}H_{22}N_2O_2S$ requires C, 66.6; H, 6.5; N, 8.2; S, 9.4%). δ_H 0.86 (3H, t), 1.00 - 1.60 (4H, m),

* peak considered to result from the superimposition of two resonance signals

2.21 (3H, s), 3.39 (2H, t), 5.75 (2H, m), 6.22 (2H, m), 7.18 - 7.60 (6H, m); δ_C 12.6 (q), 13.6 (q), 19.9 (t), 32.9 (t), 44.2 (t), 105.9 (d), 111.3 (d), 112.3 (d), 118.4 (d), 119.9 (s), 123.3 (d), 126.6 (s), 127.6 (d), 128.6 (d), 129.6 (s), 133.3 (d), 138.4 (s).

Diethyl 2-(1-n-butyl-2-methyl-5-pyrrolyl)-4-methylpyrrole-3,5-carboxylate (58%), Rf 0.76, had m.p. 80°C (Found: C, 66.9; H, 7.8; N, 7.8 $C_{20}H_{28}N_2O_4$ requires C, 66.6; H, 7.8; N, 7.8%). δ_H 0.74 (3H, t), 1.14 (3H, t), 1.36 (3H, t), 1.28 (3H, s), 2.63 (3H, s), 3.74 (2H, t), 4.14 (2H, q), 4.30 (2H, q), 5.91 (1H, s), 9.21 (1H, s); δ_C 11.9 (q), 12.6 (q), 13.6 (q), 14.0 (q), 14.4 (q), 19.8 (t), 33.1 (t), 44.3 (t), 59.5 (t), 60.5 (t), 106.6 (d), 109.9 (d), 115.5 (s), 119.5 (s), 122.6 (s), 130.4 (s), 130.6 (s), 132.6 (s), 161.4 (s), 164.5 (s).

5-Methyl-1,2-diphenylpyrrole (50.5%), Rf 0.80, had m.p. 81 - 82°C (lit.,[15] m.p 84°C). δ_H 2.14 (3H, s), 6.06 (1H, d), 6.32 (1H, d), 7.00 - 7.36 (10H, m); δ_C 13.3 (q), 107.5 (d), 108.7 (d), 125.6 (d), 127.3 (d), 127.8 (d), 127.9 (d), 128.5 (d), 128.9 (d), 131.6 (s), 133.5 (s), 134.1 (s), 139.4 (s).

2-(2-Furyl)-5-methyl-1-phenylpyrrole (74%), Rf 0.54, had b.p. 120°C at 0.1 mm Hg (Found: C, 80.7; H, 5.8; N, 6.5 $C_{15}H_{13}NO$ requires C, 80.7; H, 5.9; N, 6.3%) δ_H 2.06 (3H, s), 5.28 (1H, d), 6.00 - 6.20 (2H, m), 6.49 (1H, d), 7.10 - 7.50 (6H, m); δ_C 12.7 (q), 103.3 (d), 107.3 (d),* 110.5 (d), 125.4 (s), 128.2 (d), 128.5 (d), 129.0 (d), 131.6 (s), 139.1 (s), 140.0 (d), 148.0 (s).

2-(1-Benzenesulphonyl-2-pyrrolyl)-5-methyl-1-phenylpyrrole (53%), Rf 0.21, had m.p. 151.5 - 154°C (Found: 69.6; H, 5.0; N, 7.65 $C_{21}H_{18}N_2O_2S$ requires C, 69.6; H, 5.0; N, 7.7%) δ_H 2.12 (3H, s), 5.84 - 6.19 (4H, m), 6.66 - 7.00 (2H, m), 7.10 - 7.34 (4H, m); δ_C 13.2 (q), 106.5 (d), 111.2 (d), 113.0 (d), 118.4 (d), 121.8 (s), 123.1 (d), 126.5 (s), 127.2 (d), 127.6 (d), 128.2 (d), 128.3 (d), 128.7 (d), 131.3 (s), 133.6 (d), 138.5 (s), 139.2 (s).

Diethyl 4-methyl-2-(2-methyl-1-phenyl-5-pyrrolyl)pyrrole-3,5-dicarboxylate (42%), Rf 0.75, had m.p. 135 - 136°C (Found: C,69.55, H, 6.1, N, 7.2 $C_{22}H_{24}N_2O_4$ requires C, 69.45; H, 6.4; N, 7.4%). δ_H 1.18 (3H, t), 1.24 (3H, t), 2.02 (3H, s), 2.44 (3H, s), 3.95 - 4.35 (4H, overlapping q), 6.06 (1H, d), 6.42 (1H, d), 7.02 - 7.50 (5H, m), 9.10 (1H, br s); δ_C 11.7 (q), 13.2 (q), 14.1 (q), 14.3 (q), 59.5 (t), 60.2 (t), 107.6 (d), 111.8 (d), 115.6 (s), 118.9 (s), 123.4 (s), 127.6 (d), 128.5* (d), 129.2 (s), 131.7 (s), 131.9 (s), 138.4 (s), 161.3 (s), 164.4 (s).

Methyl 2,2'-bipyrrole-5-carboxylate:- Phosphorus oxychloride (13.8 g, 0.09 mol) in dichloromethane (30 ml) was added dropwise to pyrrole (7.0 g, 0.1 mol), 3-dimethylaminopropenal (8.8 g, 0.089 mol) in dichloromethane (30 ml) at -10°C. The mixture was stirred for 1h at -10°C and the volatile material was then removed under vacuum. Aqueous potassium hydroxide (5% w/v, 50 ml) was added to the residue and the aqueous mixture was extracted with dichloromethane (3 x 25 ml). The organic extracts were dried and evaporated to give 3-(2-pyrrolyl)propenal (1.8 g, 17%), m.p. 114 - 115°C (Found: C, 69.6; H, 5.8; N, 11.5 C_7H_7NO requires C, 69.4; H, 5.8; N, 11.6%). δ_H 6.33 (1H, s), 6.54 (1H, dd), 6.66 (1H, s), 7.06 (1H, s), 7.35 (1H, d), 9.51 (1H, d), 9.73 (1H, s); δ_C 111.6 (d) 117.6 (d), 121.7 (d), 124.9 (d), 128.4 (s), 142.6 (d), 193.6 (d). 3-(2-Pyrrolyl)propenal (0.121 g, 0.001 mol) was added to methyl 2-azidoethanoate (0.69 g, 0.006 mol) and sodium methoxide (3.24 g, 0.06 mol) in methanol (10 ml) at -10°C and stirred at ca. -5°C for 9h. Water (20 ml) was added to the reaction mixture at room temperature and the yellow thermally labile methyl 2-azido-5-(2-pyrrolyl)penta-2,4-dienoate was collected. δ_H (DMSO-d6) 3.79 (3H, s), 6.11 (1H, s), 6.36 (1H, s), 6.82 (3H, s), 6.93 (1H, s), 11.42 (1H, s); δ_C (DMSO-d_6) 62.4 (q), 109.7 (d), 112.8 (d), 115.7 (d), 121.0 (s), 122.4 (d), 128.7 (d), 129.9 (s), 130.6 (d), 163.0 (s).
The azido ester was heated, without further purification, in toluene (10 ml) at 70°C for 3h. The solvent was removed under vacuum and the product was purified by chromatographic elution from Merck Kieselgel 60 with dichloromethane to give methyl 2,2'-bipyrrole-5-carboxylate (0.118 g, 62%), m.p. 216 - 218°C (lit.,[16] m.p. 231 - 232°C) (Found: N, 14.6% Calc. for $C_{10}H_{10}N_2O_2$ N, 14.7%) δ_H (DMSO-d_6) 3.75 (3H, s), 6.07 (1H, s), 6.39 (1H, s), 6.62 (1H, s), 6.80 (2H, s), 11.09 (1H, s), 11.71 (1H, s); δ_C (DMSO-d_6) 50.8 (q), 104.9 (d), 106.0 (d), 108.7 (d), 116.5 (d), 118.6 (d), 120.3 (s), 123.9 (s), 131.8 (s), 160.6 (s).

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* peak considered to result from the superimposition of two resonance signals

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