Pyrrole Chemistry. Part XIII. New Syntheses of 3-Alkylpyrroles

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3-*n*-Alkylpyrroles are prepared in good yield by a combined Wolff–Kishner reduction and hydrolysis and decarboxylation of 4-acyl-2-pyrrolethiolcarboxylates. Methyl 4-isopropyl-2-pyrrolecarboxylate and 4-*t*-butyl-2-pyrrolecarbonitrile are prepared by alkylation of methyl 2-pyrrolecarboxylate and 2-pyrrolecarbonitrile respectively. Hydrolysis and decarboxylation of these disubstituted compounds afford the corresponding 3-alkylpyrroles. Mass spectral data for some 1-, 2-, and 3-alkylpyrroles are reported.

Les alkyl-3-*n* pyrroles sont préparés avec un bon rendement par réduction de Wolff–Kishner, hydrolyse et décarboxylation des acyl-4 pyrrolethiolcarboxylates-2. L'isopropyl-4 pyrrolecarboxylate-2 de méthyle et le *t*-butyl-4 pyrrolecarbonitrile-2 sont préparés par alkylation respectivement du pyrrolecarboxylate-2 de méthyle et du pyrrolecarbonitrile-2. L'hydrolyse et la décarboxylation de ces composés disubstitués conduit aux alkyl-3 pyrroles correspondants. On rapporte les données de spectrométrie de masse pour des alkyl-1, -2, et -3 pyrroles.

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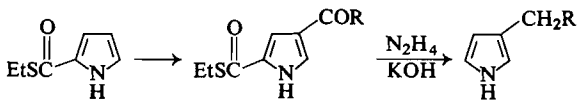
Although numerous monoalkylpyrroles are known good synthetic routes to the 3-alkylpyrroles, with the possible exception of 3-methylpyrrole (1–6), are notably absent. Skell and Bean (7) have prepared numerous 3-alkylpyrroles by the alkylation of pyrrylmagnesium bromide. The low yields of 3-isomer so obtained (5–18%) together with the necessity of effecting separation from relatively large amounts (10–32%) of 2-alkylpyrrole have prompted us to devise new synthetic routes to the former compounds.

We have previously shown (8) that a 2-ethylthiolcarboxylate substituent at the pyrrole nucleus directs Friedel–Crafts acylation and formylation almost exclusively to the 4-position. We now report that the resulting 2,4-substituted pyrroles are readily converted to the corresponding 3-alkylpyrroles by a combined Wolff–Kishner reduction of the acyl substituent and hydrolysis and decarboxylation of the thiolester group (Scheme 1). Yields for the reaction were



SCHEME 1

in the range 44–91% representing yields of 15–31% from pyrrole itself. The preparations of 3-methyl-, 3-ethyl-, and 3-benzylpyrrole are described but the method should prove to be quite general for the synthesis of 3-*n*-alkylpyrroles. A 2-methylcarboxylate substituent appears equally satisfactory in directing substitution to the 4-position thus methyl 2-pyrrolecarboxylate readily afforded 4-benzoyl-2-pyrrolecarboxylate which was subsequently converted to 3-benzylpyrrole by reduction and decarboxylation.

The aluminum chloride - catalyzed isopropylation (9) and *t*-butylation (10) of methyl 2-pyrrolecarboxylate afford the corresponding 4-alkyl-2-esters as the major kinetically controlled alkylation product. However these compounds exhibit a pronounced tendency to isomerize to the 5-alkyl-2-esters under these conditions preventing the use of these reactions as a convenient route to the corresponding 3-alkylpyrroles. Such rearrangement is largely avoided in the gallium trichloride - catalyzed isopropylation of the 2-ester (11) and by this method an 80% yield of methyl 4-isopropyl-2-pyrrolecarboxylate is obtained. This is readily separated from the small amount (*ca.* 8%) of 5-isopropyl-2-ester and hydrolysis and decarboxylation of the former affords 3-isopropylpyrrole in high yield (78%).

Rearrangement of the *t*-butyl group from the 4- to the 5-position of the alkylated 2-ester is more facile than for the corresponding isopropylated compound, thus the aluminum chloride - catalyzed *t*-butylation of methyl 2-pyrrolecarboxylate affords a 95:5 mixture of the 5- and 4-*t*-butyl-2-esters respectively (10). We find that the use of gallium trichloride as catalyst markedly increases the proportion of 4-*t*-butyl-2-ester (62% of the alkylation product) but still does not provide a sufficiently specific method

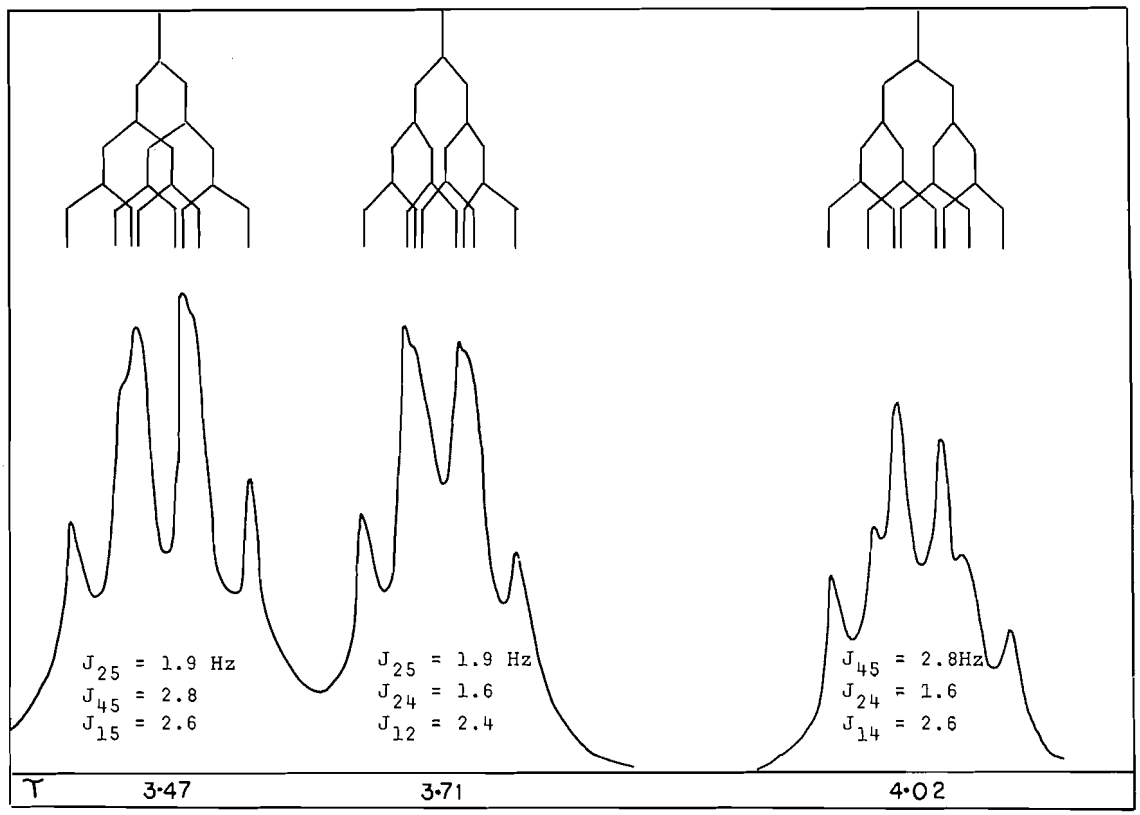


FIG. 1. Ring proton absorptions in the n.m.r. spectrum of 3-*t*-butylpyrrole.

of introducing a β-*t*-butyl substituent. A more strongly electron-withdrawing substituent at the 2-position should not only direct electrophilic attack more exclusively to the 4-position but should also suppress protonation of the product so obtained, hence reducing the extent of rearrangement. The cyano group might be expected to act in this way and should also permit a single stage hydrolysis and decarboxylation of the 4-*t*-butyl-2-pyrrolecarbonitrile to 3-*t*-butylpyrrole. Aluminum chloride - catalyzed *t*-butylation of 2-pyrrolecarbonitrile afforded a 13:87 mixture of the 5- and 4-alkylated products and the use of gallium trichloride as catalyst improved this ratio to 2:98. Purification and subsequent hydrolysis and decarboxylation of the 4-*t*-butylated product afforded pure 3-*t*-butylpyrrole (64%).

The structures of the alkylpyrroles were confirmed by their n.m.r. spectra. In all cases a separate signal was observed in the aromatic region for each of the three ring protons. Chemical shift data are given in Table 1. An analysis of the spectrum of 3-*t*-butylpyrrole is shown in Fig. 1. The various coupling constants were determined by deuteration and subsequent double irradiation. The spectra of the other 3-alkylpyrroles are further complicated by coupling between the ring protons and those of the alkyl substituent.

TABLE 1. The n.m.r. chemical shifts of 3-alkylpyrroles*

Substituent	H-2	H-4	H-5	3-Substituent
Me	3.71	4.12	3.57	8.93
Et	3.68	4.09	3.55	7.55 8.84
CH_2Ph	3.70	3.96	3.51	2.78 6.20
$CHMe_2$	3.65	4.05	3.53	7.21 8.82
CMe_3	3.71	4.02	3.47	8.79

*Values refer to *ca.* 10% solutions in CCl_4 and are quoted on the τ scale using TMS as an internal standard.

Mass spectral data for the 3-alkylpyrroles are reported in Table 2 along with those of some

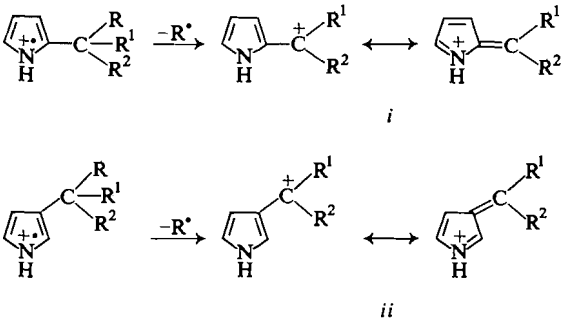
TABLE 2. Mass spectral data for substituted pyrroles

Substituent	1-Me	2-Me	3-Me	2-Et	3-Et	1-Pr^i	2-Pr^i	3-Pr^i	1-Bu^t	2-Bu^t	3-Bu^t	1-CH_2Ph	2-CH_2Ph	3-CH_2Ph
[Parent]$^+$	100	76	72	57	78	86	53	58	38	50	47	50	100	100
[P-H]$^+$	66	100	100	9	15	2	4	9	0*	2	0	6	92	67
[P-Me]$^+$	0	0	0	100	100	60	100	100	5	100	100	—	—	—
[P-Ph]$^+$	—	—	—	—	—	—	—	—	—	—	—	1	100	91
	0	0	0	0	0	100	24	23	100	5	5	0	0	0
	29	24	24	21	19	4	6	6	2	4	4	1	13	9
	4	2	1	5	7	35	17	16	17	9	8	2.0	0	0
	20	5	4	8	8	16	17	13	10	7	5	6	5	6
[Substituent]$^+$	4	0	0	0	0	10	0	0	10	0	0	100	8	5

*Ions of < 1% abundance are entered in the table as zero.

1- and 2-alkylpyrroles. High resolution mass spectrometry was not available and hence assignments of the fragment structures are tentative.

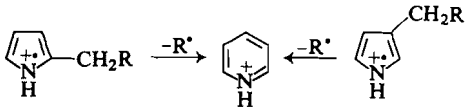
The base peak for all the *C*-alkylpyrroles involves loss of a hydrogen or methyl radical to afford the azafulvene ions (*i* or *ii*) or their rearrangement products (Scheme 2). Such fragmentation might proceed with concurrent rearrangement to a pyridinium ion (12, 13). The very marked similarity of the spectra of the *C*-methylpyrroles both with each other and with those of the *C*-ethylpyrroles are consistent with the involvement of a mutual stable ion of $m/e = 80$ (Scheme 3). In the formation of *i*, *ii*, or their rearrangement products from *C*-alkylpyrroles loss of methyl is preferred to loss of hydrogen. The *C*-benzylpyrroles differ in that loss of phenyl and hydrogen are about equally favorable, doubtless because of the extensive charge delocalization that can occur in the ions *iii* or *iv* or their rearrangement products.



i

ii

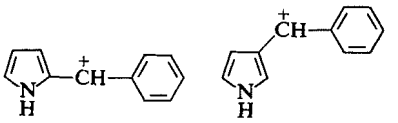
SCHEME 2



m/e 80

SCHEME 3

The mass spectra of the *C*-*t*-butylpyrroles also exhibit an ion of $m/e = 80$ of appreciable abundance (10%). Involvement of a cyclopropane intermediate, such as occurs in the fragmentation of *t*-butylbenzene (14), provides one possible explanation (Scheme 4).



iii *iv*

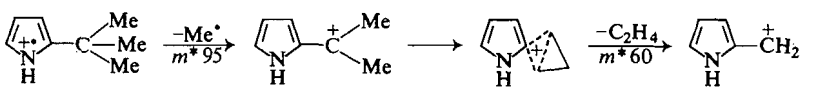
Whilst the mass spectra of the isomeric 2- and 3-substituted pyrroles are very similar those of the 1-substituted pyrroles differ substantially. The base peak in the spectrum of 1-benzylpyrrole arises by decomposition of the parent ion to a pyrrolyl radical and tropylium ion. Analogous but less abundant fragmentation occurs for the branched alkylpyrroles, however the major fragmentation for these compounds involves loss of a molecule of alkene with concurrent hydrogen transfer (*cf.* refs. 15 and 16) (Scheme 5). The extent of formation of immonium ions or their rearrangement products (*cf.* ref. 17) varies from being the major fragmentation process for 1-methylpyrrole to being relatively insignificant for 1-*t*-butylpyrrole.

Experimental

Melting points were determined on a Fisher–Johns m.p. block and are uncorrected. The n.m.r. spectra were determined on a Varian HA 100 spectrometer at 100 MHz and i.r. spectra were determined on a Perkin–Elmer 237B spectrophotometer. Mass spectra were determined on a Hitachi Perkin–Elmer RMU 6E instrument using an ionization energy of 70 eV. An indirect inlet system maintained at 60° was used throughout and total ion current variation was maintained at $< 5\%$. The g.l.c. analyses of 2,4-substituted pyrroles were carried out on a Beckman GC 2A chromatograph fitted with a 30″ column (no. 70007) packed with Carbowax 4000 dioleate on firebrick and operating at 190°. The 3-alkylpyrroles were purified by preparative g.l.c. on a Wilkens Aerograph 1520 fitted with an 8 ft column packed with OV17 (methyl phenyl silicone) on Chromosorb G and operating between 80–130°.

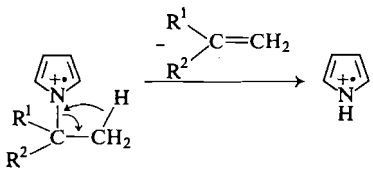
Benzoylation of Ethyl 2-Pyrrolethiolcarboxylate

Ethyl 2-pyrrolethiolcarboxylate (465 mg), aluminum chloride (800 mg), and dichloromethane (20 ml) were stirred and heated under reflux during the dropwise addition of benzoyl chloride (420 mg) in dichloromethane



m/e 123 *m/e* 108 *m/e* 80

SCHEME 4



SCHEME 5

(5 ml). After 3 h the mixture was poured onto ice–HCl and extracted with chloroform. The extracts were washed with $NaHCO_3$ solution, dried ($MgSO_4$), and the solvents removed to afford an oily solid. Recrystallization from CCl_4 afforded ethyl 4-benzoyl-2-pyrrolethiolcarboxylate (435 mg, 56%); m.p. 103.5°; n.m.r. bands at τ 1.9–2.7 (complex, Ar—H), 6.90 (q, CH_2CH_3, *J* 7Hz), 8.64 (t, CH_2CH_3, *J* 7Hz).

Anal. Calcd. for $C_{14}H_{13}NO_2S$: C, 64.9; H, 5.1. Found: C, 65.1; H, 5.2.

Benzoylation of Methyl 2-Pyrrolecarboxylate

Analogous reaction of methyl 2-pyrrolecarboxylate (500 mg) with aluminum chloride (1.68 g) and benzoyl chloride (843 mg) afforded methyl 4-benzoyl-2-pyrrolecarboxylate (430 mg, 48%), m.p. 145–146° (from aqueous 2-propanol); n.m.r. bands at τ 2.05–2.73 (complex, Ar—H) and 6.14 (s, CO_2CH_3).

Anal. Calcd. for $C_{13}H_{11}NO_3$: C, 68.1; H, 4.8. Found: C, 68.4; H, 4.8.

Hydrolysis in methanolic KOH gave the corresponding acid m.p. 223.5–224° (dec.) (lit. (18) 224–225° (dec.)).

General Procedure for Alkylations

The 2-substituted pyrrole, catalyst (1.1 equiv), and carbon disulfide (40 ml) were stirred and heated at 40° for 30 min prior to the rapid addition of alkyl halide (1.1 equiv). After further stirring at 40° for the set time the reaction mixture was poured onto ice–HCl and extracted with chloroform. The extracts were washed with $NaHCO_3$ solution, dried ($MgSO_4$), and the solvent removed.

The t-Butylation of Methyl 2-Pyrrolecarboxylate

Methyl 2-pyrrolecarboxylate (1.50 g), gallium chloride, and *t*-butyl chloride were allowed to react for 40 min prior to isolation of the product (2.18 g, 91%) which was shown (g.l.c.) to contain two components in 38:62 ratio. Chromatography on neutral activity I alumina using 1:1 petroleum – diethyl ether effected separation and the major component was shown to be methyl 4-*t*-butyl-2-pyrrolecarboxylate, m.p. and mixture m.p. 121–122°; n.m.r. bands ($CDCl_3$) at τ 7.10 (m, 3H and 5H), 6.10 (s, CO_2CH_3), and 8.72 (s, *t*-Bu). The minor component was methyl 5-*t*-butyl-2-pyrrolecarboxylate, m.p. and mixture m.p. 127–128°; n.m.r. bands ($CDCl_3$) at τ 3.08 (q, 3H, J_{34} 3.8, J_{13} 2.5 Hz), 3.90 (q, 4H, J_{34} 3.8, J_{14}, 2.5 Hz), 6.10 (s, CO_2CH_3), and 8.65 (s, *t*-Bu).

The t-Butylation of 2-Pyrrolecarbonitrile

(*A*) 2-Pyrrolecarbonitrile (19) (950 mg), aluminum chloride, and *t*-butyl chloride were allowed to react for 30 min prior to isolation of the product (1.407 g, 95%) which was shown (g.l.c.) to contain two components in 13:87 ratio. These were shown to be 5-*t*-butyl-2-pyrrolecarbonitrile and 4-*t*-butyl-2-pyrrolecarbonitrile respectively since hydrolysis and subsequent methylation (CH_2N_2) of the mixture afforded the corresponding alkylated 2-esters which were identified by g.l.c. comparison with the authentic esters.

(*B*) 2-Pyrrolecarbonitrile (1.12 g), gallium chloride, and *t*-butyl chloride were allowed to react for 30 min whilst the reaction mixture was flushed with nitrogen. Isolation gave a product (1.62 g, 93%) shown by g.l.c. to contain 4-*t*-butyl-2-pyrrolecarbonitrile contaminated by < 2% of the 5-*t*-butyl isomer. Distillation, b.p. 125–128°/0.05 mm and subsequent crystallization from petroleum afforded pure 4-*t*-butyl-2-pyrrolecarbonitrile m.p. 56–57°; n.m.r. bands (CCl_4) at τ 3.2 (d, 3H and 5H, $J_{13} \approx J_{15} = 2.6$), ν_{CN} (Nujol) 2220 cm^{-1}.

Anal. Calcd. for $C_9H_{12}N_2$: C, 73.0; H, 8.1; N, 18.9. Found: C, 72.9; H, 8.0; N 19.0.

3-Methylpyrrole

Ethyl 4-formyl-2-pyrrolethiolcarboxylate (8) (500 mg), potassium hydroxide (500 mg), hydrazine (500 mg of 64%), and triethylene glycol (5 ml) were stirred at 125° for 90 min. The temperature was then raised to 220° for 4 h prior to pouring into ice–water and extracting with ether. The extract was washed with water, dried ($MgSO_4$), and chromatographed on neutral activity I alumina to remove tarry material. Subsequent distillation afforded 3-methylpyrrole (122 mg, 44%), b.p. 142–144° (lit. (1) b.p. 143–143.5°).

3-Ethylpyrrole

Ethyl 4-acetyl-2-pyrrolethiolcarboxylate (8) (500 mg) was similarly converted into 3-ethylpyrrole (20) (135 mg, 53%), b.p. 86–88°/20 mm.

3-Benzylpyrrole

(*A*) Ethyl 4-benzoyl-2-pyrrolethiolcarboxylate (330 mg) was similarly converted to 3-benzylpyrrole (182 mg, 91%).

Anal. Calcd. for $C_{11}H_{11}N$: C, 84.0; H, 7.1. Found: C, 84.1; H, 7.2.

(*B*) Methyl 4-benzoyl-2-pyrrolecarboxylate (425 mg) similarly afforded 3-benzylpyrrole (270 mg, 92%).

3-Isopropylpyrrole

Methyl 4-isopropyl-2-pyrrolecarboxylate (200 mg), prepared by the gallium chloride - catalyzed isopropylation of methyl 2-pyrrolecarboxylate (11), was heated at 230° for 5 h with KOH (250 mg), water (250 mg), and triethylene glycol (3 ml). The mixture was then poured onto ice–HOAc, extracted with ether, washed with $NaHCO_3$ solution, and dried ($MgSO_4$). Removal of the solvent afforded 3-isopropylpyrrole (7) (101 mg, 78%).

3-t-Butylpyrrole

4-*t*-Butyl-2-pyrrolecarbonitrile (200 mg) was similarly hydrolyzed and decarboxylated to afford 3-*t*-butylpyrrole (7) (126 mg, 64%).

1-Alkylpyrroles

The 1-alkylpyrroles were prepared from 2,5-dimethoxytetrahydrofuran and the appropriate amine according to the method of Elming and Clauson–Kaas (21, 22).

2-Alkylpyrroles

The 2-*n*-alkylpyrroles (23) and 2-benzylpyrrole (24) were prepared by Wolff–Kishner reduction of the corresponding 2-acylpyrrole. 2-Isopropylpyrrole (7) and 2-*t*-

butylpyrrole (7) were prepared by hydrolysis and decarboxylation of the methyl 5-alkyl-2-pyrrolecarboxylates by the method described above for the preparation of the corresponding 3-alkylpyrroles.

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