Synthesis of Some Substituted Pyrrolidines from Cyclopropyl Carbonyl Compounds

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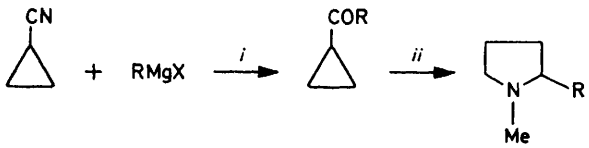
A series of alkyl and aryl cyclopropyl carbonyl compounds, when refluxed in *N*-methylformamide in the presence of magnesium chloride, gave variously substituted pyrrolidines.

In connection with some current research, we required, as starting materials, a series of 1-methyl-2-alkyl(aryl)-pyrrolidines. The most generally used synthetic routes for the preparation of such compounds are: (i) the Hoffmann–Loffler reaction [1] which involves the rearrangement of *N*-halogeno-secondary amines, and has generally been used for the preparation of 2-alkylpyrrolidines, (ii) from 3-aroylpropiononitriles by sequential reduction,[2] and more recently (iii) by alkylation of 2-lithio-1-nitroso-pyrrolidines.[3]

We were attracted by the simplicity of a pyrrolidine synthesis which involves the interaction of aryl cyclopropyl ketones with either formamide,[4] to give 1-formyl-2-arylpyrrolidines, or *N*-methylformamide,[5] to give directly 1-methyl-2-arylpyrrolidines. By analogy we

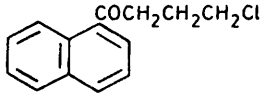


SCHEME 1 *Reagents: i*, reflux, Et_2O; aq HCl; *ii*, reflux, $MeNHCHO–MgCl_2$

anticipated that alkyl cyclopropyl ketones would give 2-alkylpyrrolidines by this method. Since the various cyclopropyl ketones were readily available by the action of Grignard reagents on cyclopropyl cyanide, this procedure offered a two-step synthesis of 1-methyl-2-alkyl-(aryl)pyrrolidines (Scheme 1).

RESULTS

A number of alkyl and aryl cyclopropyl ketones (see Table) were prepared according to Scheme 1. In the case of 1-naphthyl cyclopropyl ketone (7) the product from the Grignard reaction, after hydrolysis with aqueous hydrochloric acid, was found to be the chloro-ketone (A). Treat-

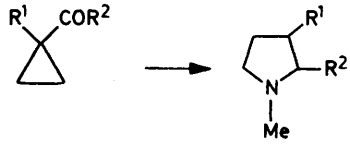


(A)

ment of this compound with potassium t-butoxide in tetrahydrofuran effected ring closure to the desired cyclopropyl ketone (7).

To test the generality of the pyrrolidine-forming reaction 1-phenylcyclopropyl cyanide was converted into a 1-phenylcyclopropyl ketone and also reduced to 1-phenylcyclopropanecarbaldehyde. When these cyclopropyl ketones and the aldehyde were subjected to the rearrangement conditions [5] with *N*-methylformamide the substituted pyrrolidines (see Table) were formed. Although the molar ratio

Conversion of cyclopropyl carbonyl compounds to substituted pyrrolidines



Carbonyl compound	R^1	R^2	Pyrrolidine [a]	Yield (%) Crude	Yield (%) After distillation
(1)	H	Me	(10)	73	31
(2)	H	Pr^i	(11)	56	40
(3)	H	cyclohexyl	(12)	73	50
(4)	H	CH_2Ph	(13)	72	57
(5)	H	Ph	(14)	79	59
(6)	H	3-C_6H_4F	(15)	83	59
(7)	H	1-naphthyl	(16)	97	72
(8)	C_6H_5	H	(17)	68	—
(9)	C_6H_5	Bu^n	(18) [b]	85	68

[a] All pyrrolidines were, after distillation, at least 90% pure by g.l.c. [b] *ca.* 1 : 1 mixture of stereoisomers (g.l.c., n.m.r.)

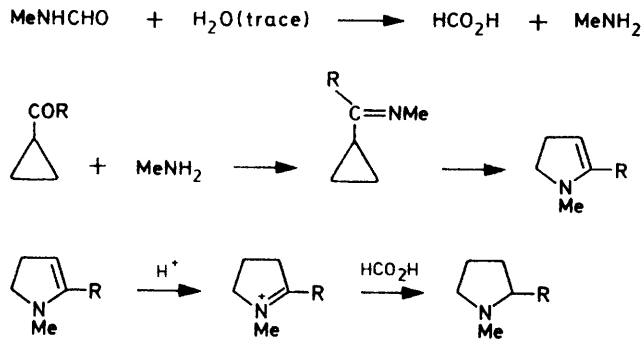
of magnesium chloride (0.1 mol per mol of ketone) originally used [5] was satisfactory in most cases, it was found that larger amounts (up to 1 mol) were necessary to effect satisfactory rearrangement of isopropyl cyclopropyl ketone in particular. Various amounts of magnesium chloride (0.1—0.5 mol) were used for other ketones, larger amounts being used when steric hindrance was anticipated.

Although in general the ^1H n.m.r. spectra of these pyrrolidines were unexceptional, the spectrum of 1-methyl-2-(1-naphthyl)pyrrolidine (7) was of interest in that it was the only one which showed a complete separation of the 2-proton and the 3-*cis*-proton due to the large anisotropic ring-current effect of the naphthyl group.

DISCUSSION

The rearrangement reaction gave rise in all cases to quite reasonable yields of the substituted pyrrolidines. This procedure therefore offers a two-step synthesis of both alkyl and aryl substituted pyrrolidines. The mechanism of the cyclopropyl ketone rearrangement (Scheme 2) presumably proceeds *via* an intermediate cyclopropylimine which undergoes bond reorganisation

to a pyrroline [6,7] which is reduced *in situ* by formic acid [8] to the pyrrolidine.



SCHEME 2

EXPERIMENTAL

M.p.s were taken on an Electrothermal melting-point apparatus. ^{1}H N.m.r. spectra were taken on a Varian EM-360 spectrometer. I.r. spectra were taken on a Perkin-Elmer 157G instrument. G.l.c. was carried out on a Pye-Unicam GCD system using a 5% OV-210 Chromosorb W-Hp column. *N*-Methylformamide, cyclopropyl cyanide, 1-phenylcyclopropyl cyanide, 3-fluorobromobenzene, 1-bromonaphthalene, methyl cyclopropyl ketone, and phenyl cyclopropyl ketone were obtained from Aldrich Chem. Co.

Preparation of the Cyclopropyl Carbonyl Compounds.—The general experimental procedure is illustrated by the preparation of 3-fluorophenyl cyclopropyl ketone (6). Dry magnesium turnings (3.48 g, 0.145 mol) were treated with 3-fluorobromobenzene (25.0 g, 0.143 mol) in dry ether (60 ml) in the usual manner employing a final reflux period of 1 h. To the ice-cooled solution of the Grignard reagent was gradually added with stirring a solution of cyclopropyl cyanide (7.70 g, 0.114 mol) in dry ether (60 ml). The mixture was then refluxed for 1.5 h, cooled in ice, and decomposed by the gradual addition of 10% aqueous hydrochloric acid (80 ml), and the mixture was stirred at room temperature until two clear layers resulted. After separation of the phases the aqueous layer was extracted with ether (2 × 150 ml) and the combined ether extracts washed with water (2 × 100 ml) and saturated sodium chloride (70 ml) and dried over sodium sulphate. Filtration and removal of the solvent under reduced pressure gave the crude ketone (16.1 g, 80%) which was distilled to give pure *3-fluorophenyl cyclopropyl ketone* (6) (13.0 g, 70%) b.p. 62 °C at 0.1 mmHg, $\nu_{max.}$ (film) 1 675 cm^{-1}, τ ($CDCl_3$) 2.0—3.0 (4 H, m, Ar-H), 7.1—7.6 (1 H, m, ring-H), and 8.6—9.0 (4 H, m, ring-H) (Found: C, 72.6; H, 5.5. $C_{10}H_9FO$ requires C, 73.2; H, 5.5%). The following ketones were prepared in an analogous manner: cyclopropyl isopropyl ketone [9] (2), 47% after distillation, b.p. 44—47 °C at 20 mmHg (lit.,[9] 141.0—141.4 °C at 761 mmHg), $\nu_{max.}$ (film) 1 695 cm^{-1}, τ ($CDCl_3$) 7.20 (1 H, septet, *J* 7 Hz, C*H*Me), 7.6—8.3 (1 H, m, ring-H), 8.85 (6 H, d, *J* 7 Hz, CH*Me*$_2$), and 8.8—9.3 (4 H, m, ring-H); *cyclohexyl cyclopropyl ketone* (3), 71% after distillation, b.p. 98 °C at 11 mmHg, $\nu_{max.}$ (film) 1 695 cm^{-1}, τ ($CDCl_3$) 7.0—7.8 (2 H, m, 2 × CHCO), 7.7—9.0 (10 H, m, cyclohexyl), and 8.9—9.3 (4 H, m, cyclopropyl) (Found: C, 78.4; H, 10.9. $C_{10}H_{16}O$ requires C, 78.9; H, 10.5); *benzyl cyclopropyl ketone* [9] (4), 67% after distillation, b.p. 80 °C at 0.5 mmHg (lit.,[10] 90—96 °C at 0.75—1 mmHg), $\nu_{max.}$ (film) 1 695 cm^{-1}, τ ($CDCl_3$) 2.80 (5 H, s, phenyl), 6.20 (2 H, s, CHCO), 7.8—8.4 (1 H, m, ring-H), and 8.8—9.5 (4 H, m, ring-H). 1-*Phenyl-1-valerylcyclopropane* (9) was obtained (a reflux period of 18 h was used in this case) in 69% yield after distillation, b.p. 92.5 °C at 0.25 mmHg, $\nu_{max.}$ (film) 1 695 cm^{-1}, τ ($CDCl_3$) 2.60 (5 H, s, phenyl), 7.5—7.9 (2 H, t, *J* 7 Hz, CH_2CO), 8.2—9.5 (11 H, complex, ring and chain), and characterised as its *2,4-dinitrophenylhydrazone*, m.p. 110 °C (from ethanol–ether) (Found: C, 63.3; H, 5.4; N, 15.1. $C_{20}H_{21}N_4O_4$ requires C, 62.8; H, 5.8; N, 14.7%), and its *semicarbazone*, m.p. 138 °C (from ethanol—ether) (Found: C, 69.2; H, 8.8; N, 16.1. $C_{15}H_{21}N_3O$ requires C, 69.0; H, 8.8; N, 16.1%).

In the case of cyclopropyl 1-naphthyl ketone (7) the following procedure was used. The Grignard reagent (0.193 mol) was formed in the normal way from 1-bromonaphthalene (40.0 g, 0.193 mol) and magnesium (4.68 g, 0.195 mol) in ether (150 ml). Addition of cyclopropyl cyanide (12.98 g, 0.194 mol) was followed by a reflux period of 2.5 h. The cooled solution was then treated with concentrated hydrochloric acid (130 ml) and extra ether (200 ml) was added. After gently refluxing the mixture for 3.5 h the ether phase was decanted off and toluene (150 ml) added. The mixture was then refluxed for 9 h and diluted with water (100 ml) to give two clear layers. The toluene layer was separated and combined with the ether layer from above and the aqueous phase was extracted with ether (2 × 100 ml). The combined toluene–ether extracts were washed with water, dried, filtered, and concentrated under reduced pressure to give, in quantitative yield (45 g), crude 4-chloro-1-(1-naphthyl)butanone, $\nu_{max.}$ (film) 1 680 cm^{-1}, τ ($CDCl_3$) 1.23—1.50 (1 H, m, H-8), 2.0—2.9 (6 H, m, ArH), 6.2—6.6 (2 H, t, *J* 7 Hz, CH_2Cl), 6.75—7.10 (2 H, t, *J* 7 Hz, CH_2CO), and 7.40—8.15 (2 H, m, $CH_2CH_2CH_2$). To a stirred and ice-cooled solution of the chloro-ketone (44.99 g, 0.194 mol) in dry tetrahydrofuran (130 ml) was gradually added potassium t-butoxide (21.88 g, 0.195 mol) and the mixture was stirred at room temperature for 1.5 h. The whole was then poured with cooling into 1.5M-aqueous hydrochloric acid (200 ml) and the mixture extracted with ether (4 × 200 ml). The combined extracts were washed with water (6 × 200 ml), dried, and concentrated under reduced pressure to give an oil (34.66 g) which was distilled to give *cyclopropyl 1-naphthyl ketone* (7) (27.78 g, 74%), b.p. 130 °C at 0.04 mmHg, which crystallised, m.p. 50—52 °C, $\nu_{max.}$ (film) 1 655 cm^{-1}, τ ($CDCl_3$) 1.48—1.77 (1 H, m, H-8), 2.23—3.30 (6 H, m, ArH), 7.47—7.90 (1 H, m, ring-H), 8.55—8.90 (2 H, m, *cis* ring-H), and 8.9—9.35 (2 H, m, *trans* ring-H) (Found: C, 85.1; H, 6.2. $C_{14}H_{12}O$ requires C, 85.7; H, 6.2%). 1-*Phenylcyclopropanecarbaldehyde* [11] (8) was prepared by reduction of 1-phenylcyclopropyl cyanide with lithium diethoxyaluminium hydride (the triethoxy-reagent [12] was ineffective) in diethyl ether, the crude product being purified *via* its sodium hydrogensulphite addition compound, $\nu_{max.}$ (film) 1 710 cm^{-1}, τ ($CDCl_3$) 0.77 (1 H, s, CHO), 2.68 (5 H, s, phenyl), and 8.2—8.9 (4 H, m, ring-H).

Preparation of the Pyrrolidines.—A mixture of the cyclopropyl carbonyl compound (1 mol), *N*-methylformamide (6 mol), and anhydrous magnesium chloride (0.5 mol) was refluxed under nitrogen for 24 h. The cooled mixture was then repeatedly extracted with portions of ether and the combined extracts washed with water (to remove *N*-methylformamide) and dried. Filtration and removal of the ether under reduced pressure gave the crude pyrrolidine which was purified by distillation. In this manner the following pyrrolidines were prepared: 2-isopropyl-1-methylpyrrolidine [8]

(11), b.p. 37 °C at 5.5 mmHg, 99.7% (g.l.c.), $\nu_{max.}$ (film) 2 770 cm^{-1} (NMe), τ ($CDCl_3$) 6.6—7.2 (1 H, m, 2-H), 7.73 (3 H, s, NMe), 7.6—8.6 (7 H, complex, ring-H and $CHMe_2$), and 9.16 (H, dd, J 3 and 7 Hz, $CHMe_2$), was characterised as its methiodide, m.p. 243 °C (from methanol–ether) (lit.,[13] 240—40.5 °C) (*note:* in this case 1 mol equiv. of $MgCl_2$ was used and a reflux period of 48 h); *2-cyclohexyl-1-methylpyrrolidine* (12), b.p. 45 °C at 0.25 mmHg 96% (g.l.c.), $\nu_{max.}$ (film) 2 770 cm^{-1} (N–Me), τ ($CDCl_3$) 6.7—7.2 (1 H, m, 2-H), 7.70 (3 H, s, NMe), 7.8—9.3 (17 H, complex, ring-H) was characterised as its *methiodide* m.p. 171 °C (from methanol–ether) (Found: C, 46.9; H, 8.4; N, 4.5. $C_{12}H_{24}IN$ requires C, 46.6; H, 7.8; N, 4.5%) (*note:* in this case 0.2 mol equiv. of $MgCl_2$ was used); 2-benzyl-1-methylpyrrolidine (13), b.p. 70 °C at 0.1 mmHg (lit.,[2] 69—70 °C at 0.3 mmHg), 93% (g.l.c.), $\nu_{max.}$ (film) 2 780 cm^{-1}, τ ($CDCl_3$) 2.88 (5 H, s, phenyl), 6.6—7.2 (2 H, m, CH_2Ph), 7.68 (3 H, s, N-Me), and 7.2—8.6 (7 H, complex, ring-H) was characterised as its *methiodide*, m.p. 199—200 °C (from methanol–ether) (Found: C, 48.6; H, 6.6; N, 4.2. $C_{13}H_{20}IN$ requires C, 49.2; H, 6.3; N, 4.4%) (*note:* in this case 0.1 mol equiv. of $MgCl_2$ was used); *1-methyl-2-phenylpyrrolidine* [2,5] (14), b.p. 52—54 °C at 0.7 mmHg, 90% (g.l.c.), $\nu_{max.}$ (film) 2 765 cm^{-1}, τ ($CDCl_3$) (2.4—2.9, 5 H, m, phenyl), 6.5—7.1 [2 H, m, 2- and 3(*cis*)-H], 7.4—8.4 (5 H, complex, ring-H), and 7.83 (3 H, s, N-Me) (*note:* in this case 0.1 mol equiv. of $MgCl_2$ was used); *2-(3-fluorophenyl)-1-methylpyrrolidine* (15), b.p. 54 °C at 0.47 mmHg, 99% (g.l.c.), $\nu_{max.}$ (film) 2 790 cm^{-1} (N–Me), τ ($CDCl_3$) 2.5—3.3 (4 H, m, ArH), 6.5—7.2 [2 H, m, 2- and 3(*cis*)-H], 7.82 (3 H, s, NMe), 7.3—8.5 (5 H, m, ring-H), was characterised as its *methiodide*, m.p. 169 °C (from methanol–ether) (Found: C, 45.8; H, 5.3; N, 4.3. $C_{12}H_{17}FIN$ requires C, 44.9; H, 5.3; N, 4.4%); *1-methyl-2-(1-naphthyl)pyrrolidine* (16), b.p. 99—100 °C at 0.04 mmHg, 96% (g.l.c.), $\nu_{max.}$ (film) 2 777 cm^{-1} (N–Me), τ ($CDCl_3$) 1.6—1.9 (1 H, m, 8′-H), 2.1—2.8 (6 H, m, ArH), 6.0—6.4 (1 H, m, 2-H), 6.55—6.95 (1 H, m, *cis* 3-H), 7.4—8.6 (5 H, complex, ring-H), and 7.80 (3 H, s, NMe) (Found: C, 84.8; H, 7.7; N, 6.7. $C_{15}H_{17}N$ requires: C, 85.3; H, 8.1; N, 6.6%); it was also characterised as its *picrate*, m.p. 148—149 °C (from ethanol) (Found: C, 56.6; H, 4.6; N, 12.3. $C_{21}H_{20}N_4O_7$ requires C, 57.3; H, 4.6; N, 12.7%); 1-methyl-3-phenylpyrrolidine (17), $\nu_{max.}$ (film) 2 775 cm^{-1} (N–Me), τ ($CDCl_3$) 2.80 (5 H, s, phenyl), 6.0—8.4 (7 H, complex, ring-H), and 7.68 (3 H, s, NMe), was characterised as its picrate, m.p. 155—156 °C (from ethanol) (lit.,[14] 155—158 °C); *2-butyl-1-methyl-3-phenylpyrrolidine* (18), b.p. 77.5 °C at 0.1 mmHg, 98% (g.l.c.), $\nu_{max.}$ (film) 2 780 cm^{-1} (N–Me), τ ($CDCl_3$) 2.68 (5 H, s, phenyl), 6.5—7.2 (2 H, complex, 2- and 3-H), 7.62 and 7.65 (3 H, 2 s, NMe of isomers), 7.3—9.6 (13 H, complex, ring-H and n-butyl), was characterised as its *picrate*, m.p. 111—112 °C (from ethanol) (Found: C, 56.6; H, 5.9; N, 12.4. $C_{21}H_{21}N_4O_7$ requires C, 56.6; H, 5.6; N, 12.6%). Due to its high solubillity in water 1,2-dimethylpyrrolidine (10) was isolated by direct distillation from the reaction mixture (using in this case 0.1 mol equiv. of $MgCl_2$) and the crude product was redistilled, b.p. 96 °C at atmospheric pressure (lit.,[13] b.p. 93—96 °C at 760 mmHg), 92% (g.l.c.), $\nu_{max.}$ (film) 2 780 cm^{-1} (N–Me), τ ($CDCl_3$) 6.7—7.1 (1 H, m, 2-H), 7.4—8.6 (6 H, complex, ring-H), 7.70 (3 H, s, NMe), 8.90 (3 H, d, J 7 Hz, 2-Me), and was characterised as its *methiodide*, m.p. 244 °C (from methanol–ether) (Found: C, 34.9; H, 6.7; N, 5.8. $C_7H_{16}IN$ requires C, 34.9; H, 6.6; N, 5.8%).

Microanalytical determinations were carried out by Mr. P. Baker and the staff of the microanalytical laboratory, and the 80-MHz ^1H n.m.r. spectrum was run by Dr. J. C. Lindon of the Physical Chemistry Department of the Wellcome Research Laboratories, Beckenham, Kent.

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