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A SYNTHESIS OF ISOINDOLES AND ISOINDOLINES VIA ARYNE INTERMEDIATES

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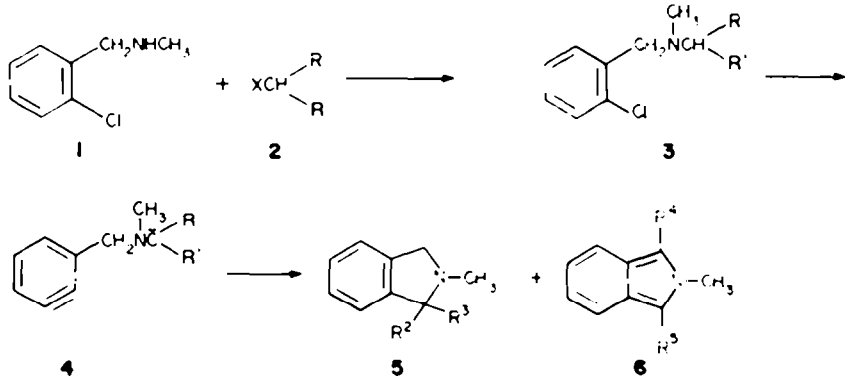
Abstract—The intramolecular cyclization of the tertiary amines (3) with potassium amide in liquid ammonia affords a variety of unsymmetrical isoindolines (5) and isoindoles (6).

It has recently been shown that the reaction of N - 2 - chlorobenzyl - N - methylaminoacetonitrile with potassium amide in liquid ammonia gives 2-methylisoindole in 89% yield.[1] The scope of this reaction has now been investigated and the extension of this method to one of more generality is described in this report.

The isoindolines (5) and isoindoles (6) have been synthesised in two steps from N - 2 - chlorobenzyl - N - methylamine (1).[2,3] In the first stage a tertiary amine (3) was prepared (Table 1) and this was subsequently cyclised by treatment with potassium amide (4 equiv) in liquid ammonia for 0.5 hr.[4] In view of the heat and air sensitivity of the products (5 and 6) it was clearly advantageous to generate the aryne intermediates (4) at a low temperature (- 33°) and to form the products in an atmosphere of ammonia. These factors contributed to the reduced degree of decomposition and oxidation of the unstable products and thus to the comparatively good yields. In this respect it was observed that the isoindolines and isoindoles were relatively difficult to preserve even under a blanket of purified nitrogen. The cyclisations were carried out on a 0.020–0.025 M scale and the different isoindolines (5) or isoindoles (6) were prepared in substantial quantities as compared to existing methods.[5]

The results of the potassium amide-liquid ammonia reactions are summarised in Table 2. It will be seen that cyclic products were obtained from compounds **3a**, **3b**, **3d**, **3f** and **3g**, but not with compounds **3c** and **3e**. We suggest that **3c** failed to cyclise because the presence of acidic hydrogens on the nitrogen of the amide group prevented carbanion formation; **3e** yielded an unidentified polymeric product.

Reaction with the ester (**3a**) gave a complex mixture of the cyclised esters (**5a** and **6a**) and the amides (**5b** and **6b**) and with the ester (**3b**) a mixture of the amides (**5b**, **5c** and **6b**) was obtained. Evidently under the reaction conditions ammonolysis of the cyclised esters was occuring. Complete ammonolysis of **5a** and **6a** was accomplished by treatment of the mixture after cyclisation with n-butyl lithium; the latter was known to be an effective reagent for promoting the conversion of esters to amides in liquid ammonia.[6] The yield of the isoindole (**6a**) was substantially improved by oxidation of **5a** in the



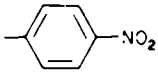
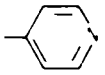
2a R H R' COOEt, X Br
2b R R' COOEt, X Br
2c R H, R' $CONH_2$, X Cl
2d R H, R' COPh, X Br
2e R H, R' $C_4H_4NO_2p$; X Br
2f R H, R' 4-C_5H_4N, X Cl
2g R Ph, R' CN X Cl

3a R H, R COOEt
3b R R' COOEt
3c R H, R' $CONH_2$
3d R H, R' COPh
3e R H, R' $C_4H_4NO_2p$
3f R H, R' 4-C_5H_4N
3g R Ph, R' CN

5a R' H, R' COOEt
5b R' H, R' $CONH_2$
5c R' R' $CONH_2$
5d R' H, R' 4-C_5H_4N
5e R' Ph, R' C(NH)NH_2

6a R' H, R' COOEt
6b R' H, R' $CONH_2$
6c R' H, R' COPh
6d R' R' COPh

Table 1. Preparation of substituted 2-Chlorobenzylamines (3)†

Compound	R	R¹	b.p./torr m.p. (solvent)	Starting material	Yield	Reaction conditions
3a	H	COOEt	106–109/0.1	2a	90	Ethanol, 1 hr reflux
3b	COOEt	COOEt	129–131/0.1	2b	82	Ethanol, 1 hr reflux
3c	H	$CONH_2$	77–78 (ethanol)	2c	84	Methanol, 3 hr reflux
3d	H	COPh	decomposes on heating	2d	88	Methanol, 1 hr reflux
3e	H		164–168/0.1	2e	84	Methanol, 1 hr reflux
3f	H		118–120/0.1	2f	80	Methanol, 1 hr reflux
3g	Ph	CN	44.5–45.5 (pet.-ether 60–80)	2g	79	Methanol, 4 hr reflux

†Compounds 3a–g all gave satisfactory elemental analyses for C, H and N except 3d and all had spectroscopic (IR, UV, NMR) properties consistent with their assigned structures.

Table 2. Reaction of potassium amide in liquid ammonia with compounds 3a–g

Substrate	No.	Cyclised product Isoindoline 5 R²	Isoindoline 5 R³	Isoindole 6 R⁴	Isoindole 6 R⁵	Other product	Yield (%)	m.p. (solvent)
3a	5a	H	COOEt	—	—	—	9.6	—
	5b	H	$CONH_2$	—	—	—	0.9	185–187 (ethanol)
	6a	—	—	H	COOEt	—	6.7	56–56.5 (n-pentane–ether)
	6b	—	—	H	$CONH_2$	—	11	215–217 (methanol)
3b	5b	H	$CONH_2$	—	—	—	11	185–187 (ethanol)
	5c	$CONH_2$	$CONH_2$	—	—	—	22	196–198 (ethanol)
	6b	—	—	H	$CONH_2$	—	9	215–217 (methanol)
3c	—	—	—	—	—	Aminated‡ product	5.6	172–174 (ethylacetate)
3d§	6c	—	—	H	COPh	—	27	102 (n-pentane–ether)
	6d	—	—	COPh	COPh	—	8	185–186 (n-pentane–ether)
3e	—	—	—	—	—	Unidentified polymeric product	—	—
3f	5d	H		—	—	—	75	70–72 (pet–ether 60–80)
3g	5e	Ph		—	—	—	92	176–178 (ethanol–ether)

†All the isoindolines and isoindoles give a green colour with Erhlich's reagent except 6d.

‡Probably N-o-aminobenzyl-N-methylaminoacetamide, isolated as its acetyl derivative, which gave satisfactory spectroscopic and elemental analysis.

§Together with 6c and 6d, benzamide and N-methylphthalimide were also isolated.

mixed ester fraction with chloranil.[7] However similar treatment of the 4-pyridyl isoindoline (5d), formed in high yield by cyclisation of 3f, failed to give the corresponding isoindole. Autoxidation of the benzoylisoindole (6c) resulted in the formation of the 1,3-dibenzoylisoindole (6d) and N-methylphthalimide[8,9] and 1,3 - dicarbethoxy - 2 - methylisoindole was detected by mass spectrometry among the autoxidation products of 5a.

It is noteworthy that the cyano group of **3g** was not eliminated after cyclisation, as in the formation of 2-methylisoindole, but was aminated affording the amidine (**5e**) in excellent yield.

EXPERIMENTAL

M.ps were determined on a Gallenkamp m.p. apparatus and are uncorrected. IR spectra were recorded on a Unicam SP200 spectrometer. UV spectra in 96% EtOH solns were recorded on a Unicam SP800A spectrometer. Mass spectral measurements were performed by PCMU, Harwell U.K. PMR spectra were recorded on a Perkin-Elmer R12 B spectrometer, using TMS as an internal standard; chemical shifts are reported in δ units (ppm downfield from TMS). Ether or dichloromethane extracts of mixtures were dried over $MgSO_4$.

N - 2 - *Chlorobenzyl* - N - *methylamine* (**1**) was prepared by the method of Lutz *et al.*[2] reduction of the Schiff's base was carried out with sodium borohydride in MeOH.[3]

General method for the preparation of the tertiary amines (**3a-3g**). To a soln of **2** (0.10 mol) in MeOH or EtOH (40 ml) was added dropwise N - 2 - chlorobenzyl - N - methylamine (0.2 mol). The mixture was maintained at reflux temp for 1-4 hr, the solvent was evaporated under reduced pressure and ether was added to precipitate N - 2 - chlorobenzyl - N - methylamine hydrochloride or hydrobromide. The ppt was recovered by filtration and washed with ether. The combined ethereal washings and filtrate were concentrated and the residue obtained was purified by distillation (**3a**, **3b**, **3e** and **3f**) or chromatography (**3d**) on silica gel, eluting with ether-pet. ether 60-80 (4:1) or crystallization (**3c**, **3g**). The yields, m.ps or b.ps and reaction conditions are recorded in Table 1.

Reaction of **3** *with potassium amide in liquid ammonia*

General procedure. A mixture of potassium amide (4 equiv) and the substrate **3** (1 equiv) in dry liquid ammonia (600 ml) was stirred for 0.5 hr. After quenching the mixture with ammonium nitrate (4.5 equiv), the liquid ammonia was allowed to evaporate. Water and ether were added and insoluble material, if present, removed by filtration. The filtrate was separated into two layers and the aqueous layer repeatedly extracted with ether and/or dichloromethane. The combined organic extracts were washed with brine, dried and evaporated to give an oil or a solid. The crude products were purified by sublimation (**5b**, **6b** and **5d**) or chromatography (**5a**, **6a**, **6c** and **6d**) or crystallization (**5e**), followed by recrystallization from a suitable solvent. Table 2 shows the products isolated in each reaction, their yields and m.ps. Their isolation, analytical data and spectroscopic properties are given below.

Isolation of the reaction products from **3a**

Following the general procedure, the water and ether insoluble solid recovered was fractionally sublimed to give **5b**, subliming at 110-120/0.1 mm and **6b**, subliming at 165-175/0.1 mm, in 1% and 11% yields. The aqueous filtrate was extracted with ether and the combined ethereal extracts and washings were washed with brine, dried, concentrated and the residue obtained was chromatographed on a silica gel column (1:30 w/w) eluting with n-hexane–ether (4:1) and n-hexane–ether (7:3) to give **6a** and **5a** in 7% and 10% yields respectively. The yield of **6a** was improved to 40% by treating the ethereal extract and washings with chloranil and refluxing in xylene for 3 hr before chromatography. In another experiment the mixture was treated with n-BuLi (1.06 equiv) before adding ammonium nitrate. This resulted in improved yields, 32.5% and 20% of **5b** and **6b**.

1-*Carbethoxy*-2-*methylisoindoline* (**5a**). An unstable liquid, highly sensitive to air. IR (film): 1760 (C=O), 1730 (C=O), 750 (=CH) cm^{-1}; NMR (CCl_4): 1.27 (t, 3, J = 7.5 Hz, CH_3), 2.6 (s, 3, N-Me), 3.7-4.6 (m, 5, CH_2; CH_2–N–CH), 7.2-7.5 (m, 4, aromatic); (M^+-2) at *m/e* 203.

1-*Carbethoxy*-2-*methylisoindole* (**6a**) A light-yellow crystalline compound, slightly darkens in air. IR (Nujol): 1685 (C=O), 805 (=CH), 772 (=CH), 729 (=CH) cm^{-1}; UV: λ_{max} (96% EtOH): 230, 234 sh, 255, 262.5, 277.5, 284, 296, 321 sh, 335, 359 nm; NMR (CCl_4): 1.45 (t, 3, J = 7.5 Hz, CH_3), 4.45 (q, 2, J = 7.5 Hz, CH_2), 4.2 (s, 3, N-Me), 7.0-8.25 (m, 5, aromatic); M^+ at *m/e* 203. (Found: C, 71.07; H, 6.45; N, 6.69. $C_{12}H_{13}NO_2$ (203.29) requires: C, 70.91; H, 6.44; N, 6.89%).

2-*Methylisoindoline*-1-*carboxamide* (**5b**). A white crystalline compound, IR (Nujol): 3390 (NH), 3200 (NH), 1665 (C=O), 745 (=CH) cm^{-1}; UV: λ_{max} (96% EtOH): 258, 264.5, 271.5 nm; NMR (acetone-d_6): 2.6 (s, 3, N-Me), 3.5-4.5 (m, 3, CH_2–N–CH), 7.2-7.4 (m, 4, aromatic; 2, $CONH_2$; exchangeable); (M^+–$CONH_2$) at *m/e* 132 (Found: C, 68.16; H, 6.82; N, 15.99. $C_{10}H_{12}N_2O$ (176.22) requires: C, 68.15; H, 6.86; N, 15.90%).

2-*Methylisoindole*-1-*carboxamide* (**6b**). A stable yellow crystalline solid, IR (Nujol): 3325 (NH), 3135 (NH), 1636 (C=O), 1603 (C=C), 764 (=CH), 730 (=CH) cm^{-1}; UV: λ_{max} (96% EtOH): 230, 234 sh, 258, 264.5, 285, 321 sh, 335.5, 349 nm; NMR (DMSO-d_6): 4.15 (s, 3, N-Me), 6.87-7.90 (m, 5, aromatic; 2, $CONH_2$, exchangeable); M^+ at *m/e* 174. (Found: C, 68.97; H, 5.90; N, 16.02. $C_{10}H_{10}N_2O$ (174.20) requires: C, 68.94; H, 5.79; N, 16.08%).

Isolation of the reaction products from **3b**

After separation of **5b** and **6b** by filtration and extraction with ether, the aqueous phase was extracted continuously with dichloromethane for 4 hr. The extract was dried and concentrated to give white crystals of **5c** in 22% yield.

2-*Methylisoindoline*-1,1-*dicarboxamide* (**5c**). A stable white crystalline compound, IR (Nujol): 3390 (NH); 3180 (NH), 1690 (C=O), 735 (=CH) cm^{-1}; UV: λ_{max} (96% EtOH): 258 sh, 265, 272 nm; NMR ($CDCl_3$): 2.71 (s, 3, N-Me), 4.34 (s, 2, CH_2), 5.80 (s, 2, $CONH_2$, exchangeable), 7.2-7.5 (m, 4, aromatic), 8.00 (s, 2, $CONH_2$, exchangeable); M^+ at *m/e* 219. (Found: C, 60.23; H, 5.99; N, 19.37. $C_{11}H_{13}N_3O_2$ (219.23) requires: C, 60.26; H, 5.97; N, 19.17%).

Isolation of the reaction products from **3d**

Following the general procedure, the aqueous phase was extracted with ether. The ethereal extract was chromatographed on a silica gel column (1:30 w/w) eluting with ether-pet.ether 60-80 (1:4) to give **6c**, which was found to be air-sensitive. Further elution of the column with ether-pet.ether 60-80 (3:2) gave **6d** which resulted from the autoxidation of **6c**.

1-*Benzoyl*-2-*methylisoindole* (**6c**). A yellow compound, undergoes autoxidation to **6d** and N-methylphthalimide. IR (Nujol): 1600 (C=O), 1590 (C=C), 795 (=CH), 755 (=CH), 740 (=CH), 720 (=CH), 700 (=CH), 670 (=CH) cm^{-1}; UV: λ_{max} (96% EtOH): 237, 253 sh, 285, 371.5 nm; NMR (CCl_4): 4.14 (s, 3, N-Me), 6.8-7.9 (m, 10, aromatic); M^+ at *m/e* 235. (Found: C, 80.62; H, 5.73; N, 5.96. $C_{16}H_{13}NO$ (235.27) requires: C, 81.67; H, 5.57; N, 5.95%).

1,3-*Dibenzoyl*-2-*methylisoindole* (**6d**). A yellow solid, oxidises rapidly in air to N-methylphthalimide. IR (Nujol): 1718 (C=O), 750 (=CH), 710 (=CH) cm^{-1}; NMR (CCl_4) 4.41 (s, 3, N-Me), 6.8 (s, 4, aromatic), 7.3-8.1 (m, 10, aromatic); M^+ at *m/e* 339.

1-(4-*Pyridyl*)-2-*methylisoindoline* (**5d**). The residue obtained from the ethereal extract was sublimed to give **5d** a white crystalline solid, which changed to yellow when exposed to air. IR (Nujol): 1600 (C=N), 803 (=CH), 755 (=CH) cm^{-1}; UV λ_{max} (96% EtOH): 251 sh, 257, 264, 271.5 nm; NMR (CCl_4): 2.4 (s, 3, N-Me); 3.5-4.6 (m, 3, CH-N-CH_2), 6.6-7.7 (m, 6, aromatic), 8.5 (d, 2, J = 5.5 Hz, aromatic); (M^+-1) at *m/e* 209. (Found: C, 80.03; H, 6.59; N, 13.25. $C_{14}H_{14}N_2$ (210.27) requires C, 79.96; H, 6.71; N, 13.32%).

1-*Phenyl*-2-*methylisoindoline*-1-*carboximidamide* (**5e**)

A white solid, isolated as water and ether insoluble material, IR (Nujol): 3480 (NH), 3420 (NH), 3240 (NH), 1680 (C=N), 765 (=CH), 755 (=CH), 705 (=CH) cm^{-1}; UV: λ_{max} (96% EtOH): 264 271.5 nm; NMR ($CDCl_3$): 2.12 (s, 3, N-Me), 3.35-4.45 (dd, 2, J = 14 Hz, CH_2), 5.3 (s, 3, HN=C-NH_2), exchangeable), 6.8-7.5 (m, 9, aromatic); (M^+-CH_3N_2) at *m/e* 208; analysed as its picrate (Found: C, 55.05; H, 4.18; N, 17.66. $C_{22}H_{20}N_6O_7$ requires: C, 54.99; H, 4.195; H, 17.49%).

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