Light-induced Reactions of Heteroaryl *N*-Methylanilinomethyl Ketones: Formation of 3-Heteroaryl-1-phenylazetidin-3-ols

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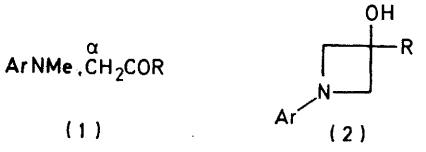
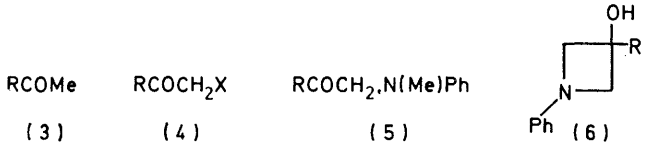
A series of heteroaryl *N*-methylanilinomethyl ketones, $PhNMe{\cdot}CH_2COR$ (R = heteroaryl), were irradiated with ether as the solvent. The corresponding 3-heteroaryl-1-phenylazetidin-3-ols (type II cyclisation products) were formed when R was 2-furyl, benzo[*b*]furan-2-yl, 2-thienyl, 1-methylpyrrol-2-yl, and 2,4-dimethylthiazol-5-yl, but such products were not isolated when R was pyrrol-2-yl or 3-pyridyl. In some cases, products formed *via* type II fission were obtained.

IRRADIATION of α-*N*-methylarylamino-ketones (1; R = alkyl) derived from aliphatic ketones led to fission of the $N{-}C_\alpha$ bond, the major photoproducts being the *N*-methylarylamine, ArNHMe, and products formed *via* combination of the fragments in an alternative manner.[1] In contrast, irradiation (with ether as the solvent) of α-*N*-methylarylamino-ketones (1; R = aryl) derived



(1) (2)

from aromatic ketones resulted in a type II photoreaction, the major photoproduct being the azetidinol (2).[2] In view of the pronounced influence of group R (alkyl or aryl) on the photoreactivity of (1), a series of amino-ketones (1), in which the group R is a heterocyclic ring, were irradiated. By using different heteroaromatic



(3) (4) (5) (6)

(3), (4), (5), and (6)
a; R = 2-furyl
b; R = benzo[*b*]furan-2-yl
c; R = 2-thienyl
d; R = pyrrol-2-yl
e; R = 1-methylpyrrol-2-yl
f; R = 2,4-dimethylthiazol-5-yl
g; R = 3-pyridyl

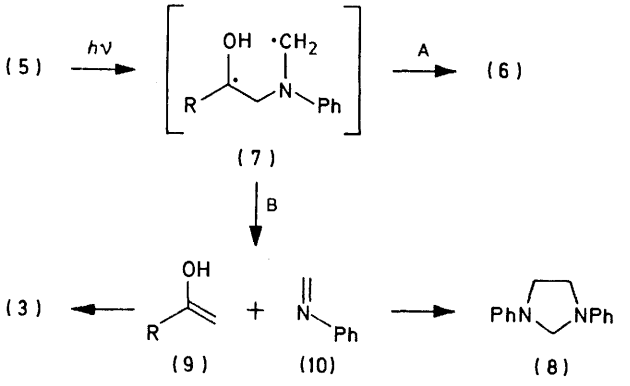
(4)
a; X = Br
b; X = Br
c; X = Br
d; X = Cl
e; X = Cl
f; X = Br
g; X = Br

groups, the effect on the photoreaction of varying the aromatic character of group R may be studied.

A series of heteroaryl *N*-methylanilinomethyl ketones (5a—g) were prepared by treating the appropriate α-halogeno-ketone (4), or its hydrobromide salt in the case of the basic ketones (4f) and (4g), with an excess of *N*-methylaniline.

The heterocyclic amino-ketones (5a—g) were irradiated using a medium-pressure mercury-vapour lamp with ether or tetrahydrofuran as the solvent (see Table). Ketones (5a—c, e, and f) yielded the corresponding 3-heteroaryl-1-phenylazetidin-3-ol (6), generally as the major photoproduct. Irradiation of the pyrrolylamino-ketone (5d) gave a crude product, for which the acetidinol structure (11) is suggested, which could not be purified. A complex mixture was obtained from the pyridylamino-ketone (5g) after irradiation in tetrahydrofuran, and no photoproduct was isolated.

The azetidinols (6) are cyclisation products (Scheme, path A) resulting from the biradical (7) produced by a type II reaction of the amino-ketone (5). An alternative



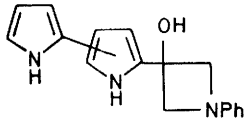
SCHEME

reaction of the biradical is type II fission (Scheme, path B) to the enol (9), isolated as the tautomeric ketone (3), and the unstable imine (10). Ketones (3a—d) were obtained from the corresponding amino-ketones (5a—d). In several cases, from the amino-ketones (5a—c) and (5f), 1,3-diphenylimidazolidine (8) was isolated from the photoreaction mixture. This product is probably formed by further reaction of the imine (10) and the

possible mechanism of this process has been discussed previously.[2]

With the exception of the amino-ketones (5d) and (5g), the heterocyclic amino-ketones (5) behave photochemically in a manner similar to that of the aromatic *amino-ketones* (1; Ar and R = phenyl or a substituted phenyl group). Any differences in aromatic character of the heterocyclic rings in the amino-ketones (5a—c, e, and f) are not significantly reflected in their photoreactions. Irradiation of the amino-ketones (1; R = aryl or heteroaryl) provides a general and reasonable synthetic route to 1,3-disubstituted azetidin-3-ols.

Characterisation of the Photoproducts.—The azetidinols (6a—c, e, and f) were characterised by their i.r. (ν_{OH} 3 240—3 330 cm^{-1} and the absence of absorption for a carbonyl group), n.m.r., and mass spectra. In the n.m.r. spectra, the CH_2 and N–Me singlets of the original



(11)

amino-ketone are replaced by the two doublets of the ring methylene groups. In general, the major peaks in the mass spectra correspond to fragment ions formed by cleavage across the azetidine ring, in some cases with transfer of hydrogen, as described previously for 1,3-diarylazetidi n-3-ols.[3]

Attempts to purify the major product from the pyrrolyl-amino-ketone (5d) resulted in partial decomposition. The proposed structure (11) is consistent with its spectroscopic properties (see Experimental section).

The ketones (3) and imidazolidine (8) were identical with authentic samples.

Irradiation of α-*N*-methylanilinomethyl heteroaryl ketones (5)

Amino-ketone	Reaction time (h)	Yield (%) Azetidinol	Other products
(5a)	3	45 (6a)	13 (3a),[a] 9 (8),[b] 4.5 (5a)
(5b)	10	20 (6b)	37 (3b), 8 (8)[b]
(5c)[c]	6	32 (6c)	8(3c), trace (8), 18 (5c)
(5d)	4	48 (11)[d]	15 (3d), 4 (5d)
(5e)	1.5	44 (6e)	13 (5e)
(5f)[e]	2	34 (6f)	39 (8),[b] 12 (5f)

Products are shown in parentheses. Unless otherwise stated, a 75-W medium-pressure mercury-vapour lamp was used and the solvent was ether. [a] Isolated as its 2,4-dinitrophenylhydrazone. [b] Assuming 3 mol equiv. of (5) yield 1 mol equiv. of (8). [c] Ether–THF (9 : 1) as solvent. [d] Crude product for which structure (11) is suggested. [e] A 125-W medium-pressure mercury-vapour lamp, Thorn Electric Kolorlux MBF with the outer glass envelope removed, was used.

EXPERIMENTAL

All irradiations were carried out with stirring, in dried and distilled solvents, under nitrogen at room temperature. The light source, a 75-W medium-pressure mercury-vapour lamp type Q81 Quarzlampen GMBH Hanau (unless otherwise stated), was centrally situated in a water-cooled Pyrex cold-finger. The silica gel used for column chromatography was Hopkin and Williams M.F.C. Light petroleum had b.p. 60—80 °C. I.r. spectra were recorded as Nujol mulls (solids) or liquid films. N.m.r. spectra were recorded with deuteriochloroform as the solvent (s = singlet, d = doublet, dd = doublet of doublets, m = multiplet, and *J* in Hz). Figures in parentheses following *m/e* values show abundance as a percentage of the base peak.

Preparation of Heteroaryl α-N-*Methylanilinomethyl Ketones* (5).—A solution of the appropriate α-halogenoketone (4), or its hydrobromide salt for (5f) and (5g), in ethanol was heated under reflux with *N*-methylaniline (2.5 equiv.) [or 3.5 equiv. for (5f) and (5g)]. On addition of a little water and cooling, the amino-ketones (5a) and (5b) crystallised from the reaction mixture. Other amino-ketones were isolated by column chromatography over silica gel. Work-up procedure, reaction time, and yield are given below.

2-N-*Methylanilinoacetylfuran* (5a), 2 h (80%), m.p. 106—108 °C (ethanol) (Found: C, 72.7; H, 6.2; N, 6.4. $C_{13}H_{13}NO_2$ requires C, 72.5; H, 6.1; N, 6.5%); $\nu_{max.}$ 1 680 cm^{-1}; τ 2.4—3.5 (m, ArH), 5.43 (s, CH_2), and 6.91 (s, NMe); *m/e* 215 (M^+, 6), 120 (base), 105 (12), 104 (10), 95 (3), 91 (3), and 77 (5).

2-N-*Methylanilinoacetylbenzo*[b]*furan* (5b), 3 h (75%), m.p. 135—136 °C (ethanol) (Found: C, 76.6; H, 5.7; N, 5.2. $C_{17}H_{15}NO_2$ requires C, 77.0; H, 5.7; N, 5.3%); $\nu_{max.}$ 1 700 cm^{-1}; τ 2.45—3.35 (m, ArH), 5.33 (s, CH_2), and 6.9 (s, NMe); *m/e* 265 (M^+, 67), 121 (42), 120 (base), 106 (14), 105 (25), 104 (22), and 77 (33).

2-N-*Methylanilinoacetylthiophen* (5c), 1 h (75%), eluted with 5% ethyl acetate in toluene, m.p. 112—114 °C (ethanol) (Found: C, 67.2; H, 5.6; N, 5.9. $C_{13}H_{13}NOS$ requires C, 67.5; H, 5.7; N, 6.1%); $\nu_{max.}$ 1 670 cm^{-1}; τ 2.26—3.35 (m, ArH), 5.5 (s, CH_2), and 6.92 (s, NMe); *m/e* 231 (M^+, 29), 121 (30), 120 (base), 111 (36), 105 (43), 104 (43), 91 (17), 83 (14), and 77 (67).

2-N-*Methylanilinoacetylpyrrole* (5d), 18 h (43%). Ether was added to the reaction mixture and the product was extracted into 4M-hydrochloric acid. Basification gave a solid which was purified by elution with 1% ethyl acetate in toluene over silica gel; m.p. 73—74 °C (ethanol) (Found: C, 72.6; H, 6.5; N, 13.1. $C_{13}H_{14}N_2O$ requires C, 72.9; H, 6.6; N, 13.1%); $\nu_{max.}$ 1 625 cm^{-1}; τ −0.4 (s, NH), 2.7—3.82 (m, ArH), 5.58 (s, CH_2), and 6.9 (s, NMe); *m/e* 214 (M^+, 7), 120 (base), 105 (7), 104 (7), 94 (3), 91 (3), and 77 (15).

1-*Methyl*-2-N-*methylanilinoacetylpyrrole* (5e), 5 h (28%). Work-up as for (5d) but with toluene elution, m.p. 51—52 °C (ethanol) (Found: C, 73.35; H, 7.1; N, 12.6. $C_{14}H_{16}N_2O$ requires C, 73.7; H, 7.1; N, 12.3%); $\nu_{max.}$ 1 630 cm^{-1}; τ 2.6—3.9 (m, ArH), 5.4 (s, CH_2), 6.1 (s, 1-Me), 6.9 (s, NMe); *m/e* 228 (M^+, 38), 123 (17), 121 (28), 120 (base), 108 (13), 105 (17), 104 (16), 91 (10), and 77 (37).

2,4-*Dimethyl*-5-N-*methylanilinoacetylthiazole* (5f), 5 h (51%). The solvent was evaporated and the residue was chromatographed over silica gel, with 5% ethyl acetate in toluene elution; m.p. 68—69 °C (light petroleum) (Found: C, 64.2; H, 6.3; N, 10.5. $C_{14}H_{16}N_2OS$ requires C, 64.6; H, 6.2; N, 10.8%); $\nu_{max.}$ 1 670 cm^{-1}; τ 2.32—3.32 (m, ArH), 5.68 (s, CH_2), 6.84 (s, NMe), 7.16 (s, Me), and 7.32 (s, Me); *m/e* 260 (M^+, 25), 121 (32), 120 (base), 105 (19), 104 (17), 91 (6), and 77 (24).

3-N-*Methylanilinoacetylpyridine* (5 g), 2 h (14%), eluted with 5% methanol in chloroform; m.p. 90—92 °C (methanol) (Found: C, 73.6; H, 6.2; N, 12.4. $C_{14}H_{14}N_2O$

requires C, 74.3; H, 6.2; N, 12.4%); $\nu_{max.}$ 1 705 cm^{-1}; τ 0.8—3.4 (m, ArH), 5.3 (s, CH_2), and 6.9 (s, NMe); *m/e* 226 (M^+, 14), 120 (base), 105 (21), 91 (8), 78 (13), and 77 (37).

Literature methods were used to prepare the following α-halogenoketones; 2-bromoacetylfuran (4a),[4] 2-bromoacetylbenzo[*b*]furan (4b),[5] 2-bromoacetylthiophen (4c),[6] 2-chloroacetylpyrrole (4d),[7] 2-chloroacetyl-1-methylpyrrole (4e),[7] the hydrobromide salt of 5-bromoacetyl-2,4-dimethylthiazole (4f),[8] and the hydrobromide salt of 3-bromoacetylpyridine (4g).[9]

Irradiation of Heteroaryl N-Methylanilinomethyl Ketones (5).—A 1—2% solution of the amino-ketone was irradiated, after which the solvent was evaporated off and the residue chromatographed over silica gel (60—100 g for each g of photoproduct). Reaction time, lamp used, solvent, and yields of photoproducts are given in the Table. Generally toluene [preceded by light petroleum after irradiation of (5a)] and then toluene containing ethyl acetate in progressively increasing concentrations were used to elute the products.

1,3-Diphenylimidazolidine (8) was eluted with toluene, or with light petroleum [after irradiation of (5a)].

The starting amino-ketone (5) was eluted with ethyl acetate in toluene, 1—2% for (5a), (5c), and (5e) and 5% for (5d).

The ketone (3b) was eluted with toluene, and ethyl acetate in toluene was used to elute the other ketones, 1—2% for (3a) and (3c), and 9% for (3d). The ketone (3a) was isolated as its 2,4-dinitrophenylhydrazone.

The azetidinols were eluted with ethyl acetate in toluene, 5—6% for (6a), (6c), and (6f), and 10% for (6b) and (6e).

The crude product from amino-ketone (5d), for which structure (11) is suggested, was eluted with 15% ethyl acetate in toluene.

Identification of the Photoproducts.—The photoproducts were compared (i.r. spectra) with authentic samples or characterised by their i.r., n.m.r., and mass spectra in the case of the azetidinols (6).

3-(2-*Furyl*)-1-*phenylazetidin*-3-*ol* (6a), m.p. 129—130 °C (benzene) (Found: C, 72.2; H, 6.0; N, 6.3. $C_{13}H_{13}NO_2$ requires C, 72,5; H, 6.1; N, 6.5%); $\nu_{max.}$ 3 240 cm^{-1}; τ 2.5—3.7 (m, ArH), 5.73 (d, *J ca.* 8) and 6.01 (d, *J ca.* 8) (2 × CH_2), and 7.15br (OH); *m/e* 215 (M^+, 26), 120 (4), 110 (82), 106 (88), 105 (95), 104 (base), 95 (36), 91 (20), 81 (33), and 77 (78).

3-(*Benzo*[b]*furan*-2-*yl*)-1-*phenylazetidin*-3-*ol* (6b), m.p. 110—111 °C (light petroleum) (Found: C, 76.2; H, 5.6; N, 5.0. $C_{17}H_{15}NO_2$ requires C, 77.0; H, 5.7; N, 5.3%); $\nu_{max.}$ 3 310 cm^{-1}; τ 2.3—3.6 (m, ArH), 5.67 (d, *J* 8) and 5.95 (d, *J* 8) (2 × CH_2), and 6.8 (s, OH); *m/e* 265 (M^+, 17), 160 (base), 145 (17), 131 (42), 105 (29), 104 (34), 89 (19), and 77 (37).

1-*Phenyl*-3-(2-*thienyl*)*azetidin*-3-*ol* (6c), m.p. 75 °C (light petroleum) (Found: C, 67.2; H, 5.7; N, 5.9. $C_{13}H_{13}NOS$ requires C, 67.5; H, 5.7; N, 6.1%); $\nu_{max.}$ 3 330 cm^{-1}; τ 2.6—3.6 (m, ArH), 5.78 (d, *J ca.* 7) and 5.93 (d, *J ca.* 7) (2 × CH_2), and 7.1br (OH); *m/e* 231 (M^+, 7), 126 (86), 120 (10), 111 (41), 106 (99), 105 (base), 104 (83), 97 (39), 91 (23), and 77 (98).

3-(1-*Methylpyrrol*-2-*yl*)-1-*phenylazetidin*-3-*ol* (6e), m.p. 94—95 °C (light petroleum) (Found: C, 73.25; H, 7.25; N, 12.6. $C_{14}H_{16}N_2O$ requires C, 73.7; H, 7.1; N, 12.3%); $\nu_{max.}$ 3 325 cm^{-1}; τ 2.7—4.0 (m, ArH), 5.7—6.0 (dd, 2 × CH_2), 6.4 (s, Me), and 7.3 (s, OH); *m/e* 228 (M^+, 19), 210 (17), 124 (98), 120 (21), 108 (base), 106 (24), 105 (14), 104 (13), 94 (17), 91 (14), 80 (24), and 77 (36).

3-(2,4-*Dimethylthiazol*-5-*yl*)-1-*phenylazetidin*-3-*ol* (6f), m.p. 139.5—141.5 °C (ethanol) (Found: C, 64.8; H, 5.9; N, 10.3. $C_{14}H_{16}N_2OS$ requires C, 64.6; H, 6.2; N, 10.8%); $\nu_{max.}$ 3 250 cm^{-1}; τ 2.65—3.52 (m, ArH), 5.65—5.9 (dd, 2 × CH_2), 7.0 (s, OH), 7.4 (s, Me), and 7.6 (s, Me); *m/e* 260 (M^+, 10), 155 (base), 140 (80), 120 (8), 106 (75), 105 (50), 104 (35), 91 (15), and 77 (55).

1,3-Diphenylimidazolidine (8) was identical with an authentic sample.[10] Similarly, the heterocyclic ketones (3a),[11] (3b),[12] (3c),[13] and (3d) [14] were identical with samples prepared according to literature methods. Ketone (3a) was isolated as its 2,4-dinitrophenylhydrazone.[15]

The major photoproduct from the amino-ketone (5d), for which structure (11) is suggested, was obtained as a crude material which partly decomposed on attempted purification (thick-layer chromatography). It had m.p. 138—144 °C (decomp.); $\nu_{max.}$ 3 300 cm^{-1}; τ 2.6—2.9 (m, ArH), 5.6 (s, 2 × CH_2), 6.0 (s) and 8.3 (s) (OH and NH); *m/e* 279 (M^+), 212 (loss of pyrrole), 167, 149 (base), 120, 113, 106, 104, 94, 93, 91, and 77.

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