Cyclization of *ortho*-Halogenated *N*-Acylbenzylamines: a Formal Synthesis of (±)-Cherylline[1]

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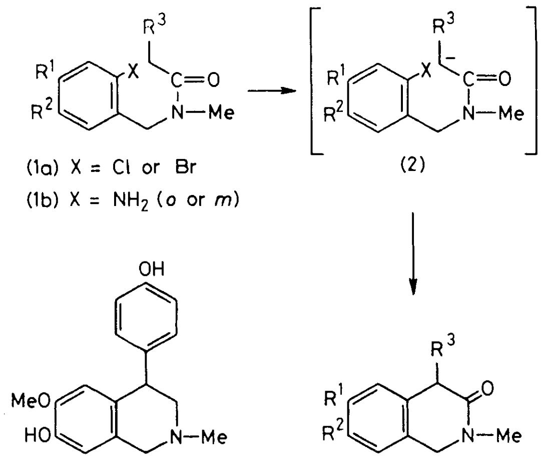
Summary *ortho*-Halogenated *N*-alkyl-*N*-acylbenzylamines can be cyclised to dihydroisoquinolones by reaction with KNH_2 in liquid NH_3 or lithium di-isopropylamide in tetrahydrofuran under photolytic and thermal conditions; the procedure has been employed to synthesize (±)-cherylline.

We have investigated the cyclization of α-carbanions derived from *ortho*-halogenated *N*-alkyl-*N*-acylbenzyl (**1a**) and phenethyl (**5**) amines as a route to heterocyclic systems, using the following conditions: (A) KNH_2 (8 mmol) in liq. NH_3 for 2 h; (B) KNH_2 (1 mmol) in liq. NH_3 under irradiation† for 8 min; (C) lithium di-isopropylamide (LDA, 4 mmol) in tetrahydrofuran (THF) under irradiation for 1·5 h; (D) LDA (4 mmol) in THF for 15 h at 25 °C. The results are presented in the Table.

It is clear that under typical aryne-generating conditions (A) cyclization is successful with the unsubstituted compound (**1a**) ($R^1 = R^2 = H$), but when alkoxy-substituents are present ($R^1 = R^2 =$ MeO) amination predominates.[2] With such substrates the desired ring closure can be brought about by irradiation (B). Remarkably, when LDA was used as a base, the cyclization proceeded smoothly under photolytic (C) as well as thermal[3] (D) conditions. Irradiation of (**1a**; $R^1 =$ MeO, $R^2 = PhCH_2O$, $R^3 = p\text{-}MeOC_6H_4$) in THF containing 4 mol. equiv. of LDA (C) gave the corresponding dihydroisoquinolone (**3**) in 48% yield, m.p. 163—165 °C; ^1H n.m.r. and mass spectral data were in conformity with the reported values[4] and the m.p. was not depressed on admixture with an authentic sample. It could be converted into (±)-cherylline (**4**) by the known procedure.[4]



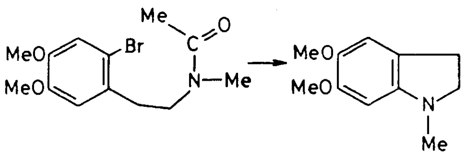
(1a) X = Cl or Br

(1b) X = NH_2 (*o* or *m*)

(2)

(4)

(3)



(5)

(6)

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† Medium-pressure mercury lamp (100 W) in a Pyrex immersion-type vessel.

TABLE. Cyclization of *ortho*-halogenated *N*-acylbenzylamines (**1a**).

Compound						
R^1	R_2	R^3	X	Reaction conditions	Major product[a]	% Yield[b]
H	H	H	Cl	A	(**3**)	51
MeO	MeO	H	Cl	A	(**1b**)	29
MeO	$PhCH_2O$	p-$PhCH_2OC_6H_4$	Br	A	(**1b**)	47
MeO	MeO	p-$MeOC_6H_4$	Br	B	(**3**)	48
MeO	MeO	p-$MeOC_6H_4$	Br	C	(**3**)	59
MeO	MeO	p-$MeOC_6H_4$	Br	D	(**3**)	51
MeO	MeO	H	Br	C	(**3**)	45
MeO	$PhCH_2O$	p-$MeOC_6H_4$	Br	C	(**3**)	48

[a] All new products were characterised by elemental analyses and n.m.r. and mass spectral data. [b] Reactions were carried out on a 1 mmol scale and products isolated by column or thick-layer chromatography.

Surprisingly, in the phenethyl system ring closure through the nitrogen atom is preferred. Thus, treatment of the amide (**5**) with LDA under conditions (C) or (D) gave the base (**6**) (42%) which was characterised by air oxidation to *N*-methyl-5,6-dimethoxyindole; ^{1}H n.m.r. ($CDCl_3$)[5] δ 3·80 (3H, s, $>$NMe), 4·0 and 4·05 (each 3H, s, OMe), 6·45 (1H, d, 3-H), 6·88 (1H, s, 7-H), 7·0 (1H, d, 2-H), and 7·2 (1H, s, 4-H); *m/e* 191·0948 (M^+) (calc. 191·0946). Additional studies on the synthetic scope and the mechanism of these reactions are in progress; depending on the reaction conditions and the substrate, both aryne and aryl radical intermediates ($S_{RN}1$ type mechanism) seem to be involved.

We thank Professor D. A. Evans and Dr. W. E. Scott for authentic samples of (**3**) and cherylline respectively.

(*Received*, 14*th July* 1981; *Com.* 833.)

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[1] Abstracted in part from M.Phil. dissertation of P. K., Panjab University, Chandigarh, India, 1979.

[2] A similar deleterious effect of 3,4-alkoxy-groups on a benzyne cyclization has been reported earlier; S. V. Kessar, D. Pal, and M. Singh, *Tetrahedron*, 1973, **29**, 177.

[3] This is in contrast with the recent findings with *N*-acyl-*o*-chloroanilines; J. F. Wolfe, M. C. Sleevi, and R. R. Goehring, *J. Am. Chem. Soc.*, 1980, **102**, 3646.

[4] For a recent synthesis of cherylline see D. J. Hart, P. A. Cain, and D. A. Evans, *J. Am. Chem. Soc.*, 1978, **100**, 1556.

[5] *Cf.* R. A. Heacock, O. Hutzinger, B. D. Scott, J. W. Daly, and B. Witkop, *J. Am. Chem. Soc.*, 1963, **85**, 1825.