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A ONE-STEP ROUTE TO 4-HYDROXY-2,3-DIARYL-3,4-DIHYDRO-1(2*H*)-ISOQUINOLONES

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Summary: A new procedure for the synthesis of 2,3-diaryl-3,4-dihydro-4-hydroxy-1(2*H*)-isoquinolones is described in which the *cis*-isomer predominates. Dehydration leads to 2,4-diarylisocarbostyrils.

The synthetic utility of metallated phthalide derivatives has recently received considerable attention for the preparation of polycyclic systems such as quinones, naphthols, and anthraquinones.[1-3] In these procedures, the use of substituted phthalides and substrates permits the regioselective formation of products, under mild conditions, in moderate to good yields. Herein we describe the reaction of lithium phthalides with Schiff's bases, which results in the formation of isoquinolones. Recently reports on alternative methods for generating these and related systems have appeared.[4,5]

The reaction of organo-lithium and organo-magnesium reagents[6] with imines provides a well established method for the preparation of substituted amines and it was considered that the addition of lithium phthalides to a Schiff's base would provide a simple method for the preparation of phthalide-isoquinoline alkaloids such as β-hydrastine and β-norhydrastine.[7] Instead, however, the reaction has been shown to give the 4-hydroxy-3,4-dihydro-1(2*H*)-isoquinolone system as shown in Scheme 1.

The highly coloured lithium phthalide (2a) was generated by the reaction of phthalide (1a) with lithium di-isopropylamide in tetrahydrofuran. Reaction of (2a) with the Schiff's base (3a) proceeded at *ca*. 60°, probably *via* the intermediate (4), directly followed by intramolecular nucleophilic attack on the lactone carbonyl group leading to the cyclic amides (6a) and (7a). No evidence for the intermediacy of the free amino-phthalide (5) was obtained in this reaction. (The base catalysed cyclisation of 3-aminomethyl-phthalide has been reported[8] and gives 4-hydroxy-3,4-dihydro-1(2*H*)-isoquinolone.)

Formation of the cyclic amide in this way generates two chiral centres at positions 3- and 4- and thus the reaction product is obtained as a mixture of the enantiomeric pairs (6) and (7), which are readily separable by preparative layer chromatography on silica gel. The less polar components show the expected AB system (after chemical exchange with deuterium oxide), J_{AB} 6-6.6 Hz, while the more polar pair show an AB system with J_{AB} 2-2.2 Hz (again after chemical exchange with D_2O). Dreiding models indicate that, for the enantiomers with a trans-configuration of the C-3 and C-4 hydrogens, the most favourable conformation is the one in which the C-3 phenyl group is pseudo-axial. In this case the dihedral angle between the hydrogens approaches 90° and thus a small coupling constant would be expected.[9] Similarly, for the isomers with a cis-configuration of the C-3 and C-4 hydrogens (7), molecular models indicate a dihedral angle of ca. 55° for each of the two possible conformations, thus a larger coupling constant would be expected. A similar interpretation has been reported for the cis- and trans-isomers of 2-methyl-3-aryl-4-carboxyl-3,4-dihydro-1(2H)-isoquinolones and our coupling constants are in agreement with the reported values, assuming similar conformational effects.[10]

Accordingly, the trans structure, (6), is assigned to the more polar components of the reaction mixtures and the cis structure (7), to the less polar isomers. Reaction of (6) and (7) with acetic anhydride in pyridine gives the corresponding O-acetyl derivatives (8) and (9) respectively and dehydration of the isomeric alcohols with trifluoroacetic acid gives not the 2,3-[11] but the 2,4-diaryl-1(2H)-isoquinolones (10) in good yield, by concomitant migration of the aryl group from position 3 to 4 (see Table).

TABLE[a]

Phthalide (3)	Schiff's base (5)	trans- 3,4-Dihydro-1(2H)-isoquinolone (8) %;	m.p.;	acetate m.p.	cis- 3,4-Dihydro-1(2H)-isoquinolone (9) %;	m.p.;	acetate m.p.	m.p. Derived isocarbostyril[c]
a, R = H	a, Y = Z = H	a, 22,	281-3	162-4	a, 51,	200-2	166-7	132-3 (73%)[d]
	b, Y = H; Z = p-Me	b, 18,	251-3	-	b, 33,	240-2	156-8	-
	c, Y = H; Z = p-MeO	c, 15,	189	-	c, 26,	164-5	143-5	119-21 (90%)
	d, Y = Z = p-MeO	d, 16,	111-8	192-9	d, 31,	110-2	78-80	-
	e, Y = p-MeO; Z = H	e, 20,	216-8	197-8	e, 39,	154	149-51	151-3 (97%)
b, R = 5,6-$(MeO)_2$	c,	f, 23,	-[b]	179-81	f, 34,	235-6	-	-
	N-(benzylidene)-benzylamine, 5f	-			g, 41,	142-5	99-100	145-6 (54%)

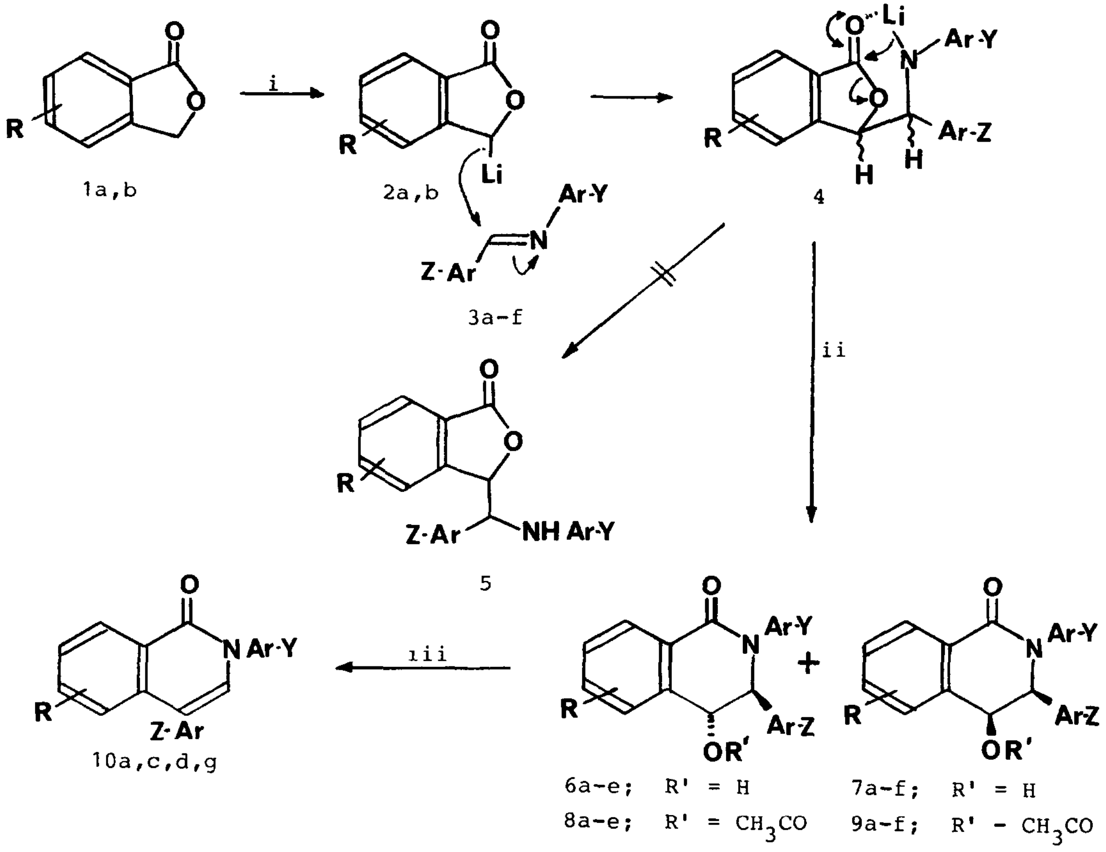
[a] All new compounds gave correct microanalytical data.

[b] Could not be obtained in crystalline state (amorphous) ∴ acetate prepared for characterisation.

[c] Isolated yields from mixture of (8) and (9)

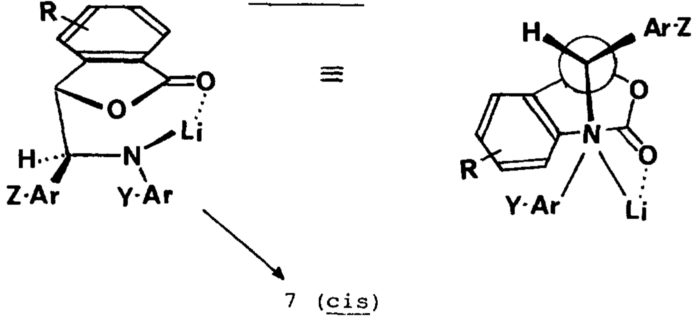
[d] G. Berti, P. Corti and F. Mancini, Ann.Chim. (Rome), 1959, 49, 1253, quote m.p. 134-136°.

Scheme 1



i, lithium di-isopropylamide/THF; ii, H_3O^+; iii, CF_3CO_2H, Δ

Scheme 2



Ar = substituted phenyl, see Table

Although yields have not been optimised, the relative proportion of *cis*- and *trans*-isomers isolated (*ca*. 2:1) requires explanation. The present system is formally analogous to the condensation of enolates with carbonyl compounds in which the product distribution is determined by internal asymmetric induction.[12] Thus the *cis*-isomer may be presumed to form from a transition state in which the gauche interaction between the C-3 aryl group and the aromatic residue of the phthalide species is minimised (Scheme 2). Similarly, the isolation of a high proportion of the *cis*-isomer in the reaction of lithium phthalide with N-(benzylidene)benzylamine (3f) may be explained in these terms. (The relatively low yield of product obtained in this case may be due to the formation of the lithium derivative of the Schiff's base under the conditions employed.[13])

The factors which affect the stereochemical consequences of this reaction together with a parallel study of the reaction of lithium phthalides with iminium salts are presently being studied and the results will be published elsewhere.

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