

BASE-INDUCED INTRAMOLECULAR CYCLISATION OF o-AZIDOPHENYL SEC-ALKYL KETONES.

A NEW SYNTHESIS OF 2,2-DIALKYLINDOXYLS

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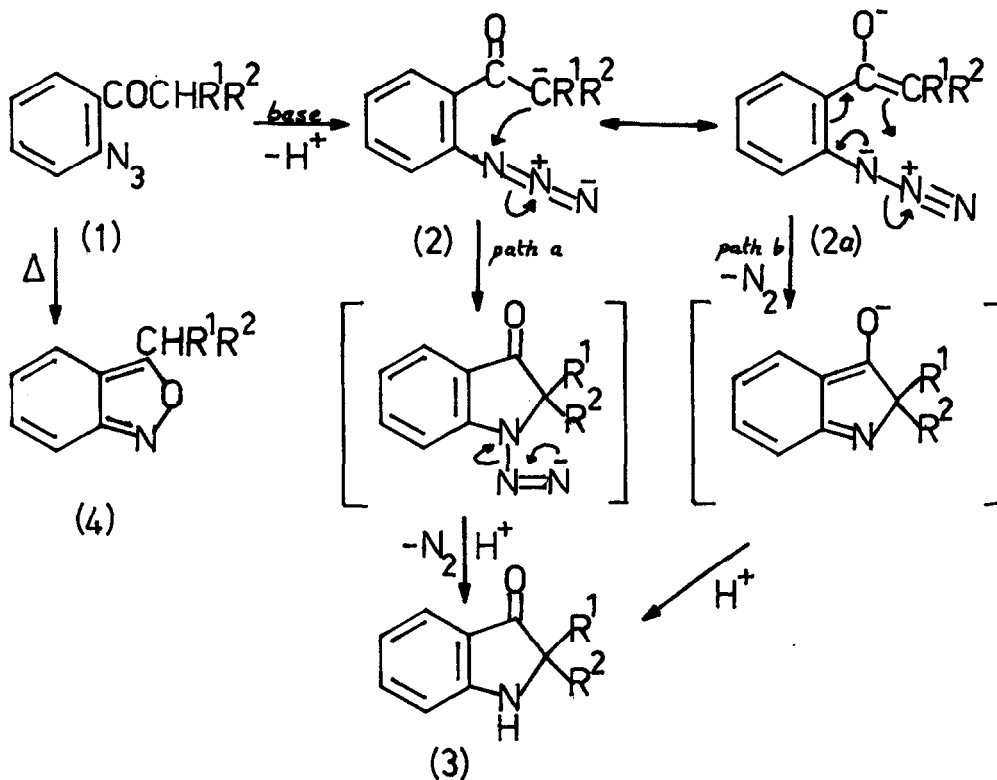
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Summary o-Azidophenyl sec-alkyl ketones in ethanolic potassium hydroxide at room temperature cyclise in high yield to 2,2-dialkylindoxyls.

In the preceding letter¹ we described the base-induced cyclisation of o-azidoanilides to 2-aryl-1,2-dihydro-3H-indazolin-3-ones. The main feature of these reactions is the loss of the amide proton followed by electrocyclic ring-closure of the resulting mesomeric anion in a manner analogous to the formation of benzofuroxans from o-nitrophenyl azides². The success and novelty of this reaction prompted us to investigate the effect of base on other systems possessing an 'acidic' hydrogen in a side-chain ortho to an azide function. Of particular interest are o-azidoaryl ketones as they undergo cyclisation, either by a concerted pericyclic process³ or by an intramolecular 1,3-dipolar cycloaddition,⁴ to 2,1-benzisoxazoles under relatively mild conditions.⁵ However, on the basis of the reaction sequence proposed for the cyclisation of azidoanilides to indazolin-3-ones¹ an alternative cyclisation (Scheme; path a or b) to indoxyls via the mesomeric anion ($2\leftrightarrow 2a$) appears possible in base solution. This has been found to be the case and preliminary results on these novel azido-ketone reactions are reported here.

In order to avoid thermolysis of the azides to 2,1-benzisoxazoles the reactions were carried out at room temperature.⁶ In addition, it is known⁷ that under basic conditions indoxyl and 2-substituted indoxyls undergo rapid condensation and oxidation reactions. Therefore, in order to avoid troublesome by-products investigations so far have been with o-azidophenyl sec-alkyl ketones.⁸ These ketones [1 ; $R^1 = \text{Me}$, $R^2 = \text{Me}$, Et , or Ph ; and $R^1R^2 =$

$(\text{CH}_2)_4$ and $(\text{CH}_2)_5$] were prepared⁹ by treating *o*-azidobenzonitrile with the appropriate Grignard reagent ($\text{R}^1\text{R}^2\text{CHMgX}$), followed by diazotisation and then azidolysis with sodium azide in buffered sodium acetate solution.



Scheme

As with the *o*-azidoanilides¹ we found that cyclisation of the azido-ketones could be effected by sodium hydride in dimethylformamide. However, better yields were obtained using ethanolic potassium hydroxide; a typical experiment being as follows. Addition of *o*-azidophenyl isopropyl ketone (1; $\text{R}^1 = \text{R}^2 = \text{Me}$) (0.5 g) to ethanolic potassium hydroxide (1 g of KOH in 15 ml of EtOH) at room temperature resulted in immediate darkening of the solution and the slow evolution of nitrogen. When gas evolution ceased (ca. 3 hours) the residue obtained after removal of solvent was triturated with water, extracted with the diethyl ether, and the extracts chromatographed on an alumina column [diethyl ether-light petrol (b.p. 40-60°) as eluant] to give 2,2-dimethylindoxyl (3; $\text{R}^1 = \text{R}^2 = \text{Me}$) as yellow needles (0.4 g), m.p. 89°C [λ_{max} 395 nm, $\log \epsilon$ 3.61; $\nu(\text{NH})$ 3140, $\nu(\text{C=O})$ 1675 cm^{-1}]¹⁰. Cyclisations were equally successful

with the other sec-alkyl ketones and details of the 2,2-disubstituted indoxyls obtained are listed in the Table.

Table

2,2-Dialkylindoxyls (3)

R ¹	R ²	Yield (%)	m.p. (°C)	Lit. m.p.	Ref.
Me	Me	89	89	89	11
Me	Et	87	64	-	12
Me	Ph	67	113	113	13
	(CH ₂) ₄	87	79	79	14
	(CH ₂) ₅	96	135	136	15

As expected, decomposition of the azido-ketones in neutral solution (boiling xylene) yielded the corresponding 3-alkyl-2,1-benzisoxazoles (4; R¹ and R² as in the Table).

The possibility that the indoxyls had been produced by base-catalysed rearrangement¹⁶ of initially formed 2,1-benzisoxazoles, rather than as outlined in the Scheme, was excluded by allowing the 2,1-benzisoxazole [4; R¹R² = (CH₂)₅] to react with ethanolic potassium hydroxide at room temperature for several hours. Careful investigation of the reaction mixture by t.l.c. failed to detect any of the spiro-indoxyl [3; R¹R² = (CH₂)₅].

The reactions described herein provide a useful new method for the synthesis of 2,2-dialkylindoxyls which, previously, appear to have been obtained only as by-products from an assortment of diverse reactions (see Table for references).

Further work is in progress to extend the scope of this reaction.

References and notes.

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