An Unexpected Rearrangement of 2-(2-Benzofuranyl)-benzonitriles: a New Route to Phenylmethylene-dihydro-isoindolinones

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Depending on the solvent used, the alkaline hydrolysis of 2-(2-benzofuranyl)-benzonitriles leads to the expected amide or acid, or to isoindolinones by rearrangement.

Alkaline rearrangements of acyl-3 furans[1] and benzofurans[2,3] into nitrogen containing heterocycles have already been reported. These transformations, which involve the opening of oxygen heterocycles under alkaline conditions followed by ring closure in an acidic medium, provide nitrogen heterocycles whose nitrogen atoms arise from the amino-bases used in the first step of the reaction. This procedure has allowed the development of new approaches to nitrogen containing heterocycles such as pyrroles,[1] isoxazoles,[2,4] pyrazoles,[2] and pyrimidines.[2]

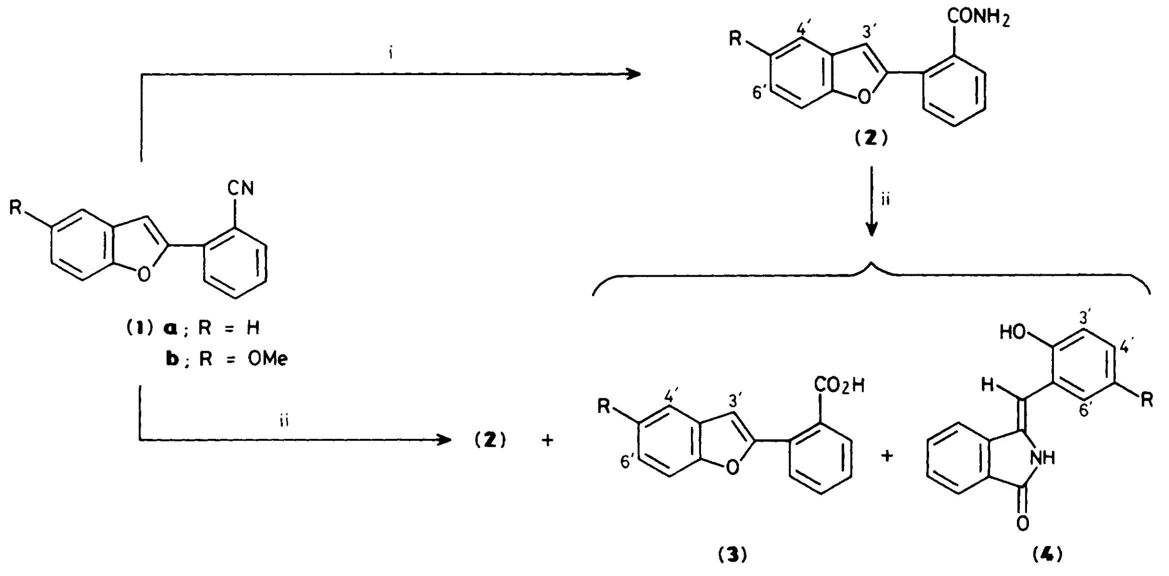
We describe herein a novel rearrangement of 2-(2-benzofuranyl)-benzonitriles (**1**) and 2-(2-benzofuranyl)-benzamides (**2**) where the electron-withdrawing group is not on the β-position of the oxygen containing heterocycle.

The nitriles (**1**) have been synthesized, in an usual way, by the reaction between 2-bromomethyl-benzonitriles and *ortho*-hydroxy-benzaldehydes followed by cyclization.[5,6]

The hydrolysis of the nitriles (**1**) by potassium hydroxide in ethanol does not go to completion and stops at the intermediate stage to provide the amides (**2**). That is why the

Table 1.

			% Yield							
Solvent	Time	Temp./°C	a	b	a	b	a	b	a	b
EtOH	72 h	80		6		81				
$MeOCH_2CH_2OH$	1 h	125	7	12	78	58	Traces	3	14	15
	16 h	—			5	Traces	Traces	6	92	85
$HOCH_2CH_2OH$	5 min	198		31		45		2		3
	15 min	—	3	2	28	25	32	26	25	26
	1 h	—			5	Traces	52	39	42	45



Scheme 1. *Reagents and conditions*: i, (**1**) (1 equiv.), KOH (3.2 equiv.), ethanol, reflux; ii, (**1**) or (**2**) (1 equiv.), KOH (3.2 equiv.), ethylene-glycol or methoxy-ethanol, reflux.

transformation of these cyano-derivatives into the corresponding acids (**3**) has been carried out by modification of the experimental conditions. The use of solvents such as ethylene-glycol allows the required acids (**3**) to be obtained, as well as important amounts of other compounds characterized as (*Z*)-2,3-dihydro-3-(2-hydroxy-phenylmethylene)-(1*H*)-isoindolinones (**4a**)[7] and (**4b**), whereas the use of methoxy-ethanol provides the isoindolinones (**4**) in markedly improved yields (up to 85—92%) (Table 1).

Under identical conditions, the isolated amides (**2**) lead to the same products (**3**) and (**4**).

The structures of isoindolinones (**4**) have been elucidated on the basis of microanalysis, mass spectrometry, ^1H n.m.r.,† and i.r. spectroscopy. Moreover, the compounds (**4a**) and the previously unknown (**4b**) have been unequivocally prepared by an alternative method,[7] for comparison of their physico-chemical and spectral data. Their (*Z*)-configuration is unambiguously assigned by n.O.e. difference spectroscopy.

To our knowledge, the reaction reported in the present paper is the sole example of an oxygen to nitrogen heterocycle rearrangement of a benzofuran structure devoid of an electron-withdrawing group in the β-position.

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† *Selected spectroscopic data* for (**4a**): (m.p. 242 °C) ^1H n.m.r. ($^2H_6$-Me_2SO, 400 MHz) δ 6.80 (1H, s, H_{benzyl}), 6.84—6.95 (2H, m, $H_{3'}$ and $H_{5'}$), 7.12—7.18 (1H, m, $H_{4'}$), 7.55—7.58 (2H, m, H_6 and $H_{6'}$), 7.67—7.74 (1H, m, H_5), 7.76 (1H, dd, H_7, *J* 7.5 Hz), 8.02 (1H, d, H_4, *J* 8.5 Hz), 10.04 (1H, b.s., OH), 10.45 (1H, b.s., NH).

For (**4b**): (m.p. 232 °C) ^1H n.m.r. ($^2H_6$-Me_2SO, 400 MHz) δ 3.78 (3H, s, OCH_3), 6.70 (1H, dd, $H_{4'}$, *J* 8.75, 2.9 Hz), 6.76 (1H, s, H_{benzyl}), 6.85 (1H, d, $H_{3'}$, *J* 8.8 Hz), 7.05 (1H, d, $H_{6'}$, *J* 2.9 Hz), 7.52—7.59 (1H, m, H_6); 7.67—7.78 (2H, m, H_5 and H_7), 8.00 (1H, d, H_4, *J* 7.8 Hz), 9.58 (1H, b.s., OH), 10.53 (1H, b.s., NH).

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