

Novel Base-induced Ring Transformation of 1,2-Benzisoxazole-3-acetic Acid Esters into 2*H*-Azirines or Benzofurans

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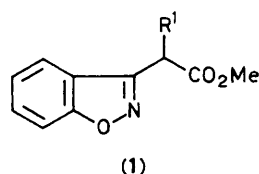
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Treatment of α -mono-substituted 1,2-benzisoxazole-3-acetic acid esters (**1**) with strong bases caused a ring transformation to afford 2*H*-azirines (**2**) or 3-imino-2,3-dihydrobenzofurans (**3**).

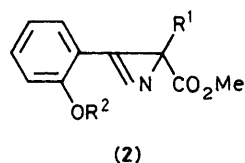
During our studies, we have paid much attention to the high nucleophilicity of the α -methylene carbon of 1,2-benzisoxazole-3-acetic acid derivatives.¹ As an extension of these studies, we now report the novel ring transformation of α -mono-substituted 1,2-benzisoxazole-3-acetic acid esters (**1**) with strong bases to give 2*H*-azirines (**2**) or 3-imino-2,3-dihydrobenzofurans (**3**).

The esters (**1**) were treated with an equimolar amount of NaH or Bu^tOK in dimethylformamide for 30 min at room temperature. An aqueous solution of ammonium chloride was added to the reaction solution at 0 °C, and the mixture was

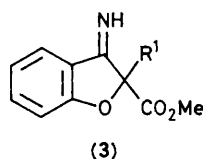
extracted with diethyl ether. After evaporation of the solvent, the residue was purified by means of recrystallization or column chromatography. Compounds (**1a–d**) having an alkyl, benzyl, phenylthio, or phenoxy group as an α -substituent gave 2*H*-azirine derivatives [(**2a**):† 90% yield, m.p. 107–109 °C; (**2b**): 65%, m.p. 74–77 °C; (**2c**): 60%, m.p. 112–114 °C; (**2d**): 91%, oil]. On the other hand, α -amino-substituted compounds (**1e**) and (**1f**) gave 3-imino-2,3-



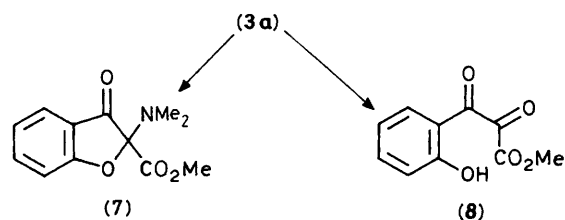
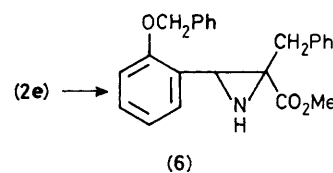
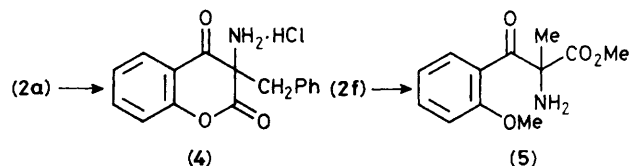
- a; R¹ = CH₂Ph
b; R¹ = Me
c; R¹ = SPh
d; R¹ = OPh
e; R¹ = NMe₂
f; R¹ = morpholino



- a; R¹ = CH₂Ph, R² = H
b; R¹ = Me, R² = H
c; R¹ = SPh, R² = H
d; R¹ = OPh, R² = H
e; R¹ = R² = CH₂Ph
f; R¹ = R² = Me



- a; R¹ = NMe₂
b; R¹ = morpholino



† All new compounds described in this paper gave satisfactory spectral (¹H n.m.r., i.r., and mass) and analytical data.

dihydrobenzofuran derivatives [(3a): 76%, m.p. 119–121 °C; (3b): 66%, m.p. 136–137 °C]. The structures of compounds (2) and (3) were deduced from elemental and spectral analyses and chemical transformations.

I.r. spectra of compounds (2) showed the characteristic band due to the azirine C=N bond² at around 1760 cm⁻¹ [e.g., (2a): $\nu(\text{KBr})$ 3250 (OH), 1760 (C=N), 1725 cm⁻¹ (C=O)].

Acid catalysed hydrolysis of azirines to α -amino ketones is well established. Treatment of compound (2a) with hydrochloric acid in methanol gave 3-amino-3-benzylchroman-2,4-dione hydrochloride (4) (m.p. 143–145 °C) which was considered to be formed by recyclisation of the initially formed amino keto ester. Under similar conditions, compound (2f) which was prepared by methylation of the phenolic OH of (2b) gave the expected amino keto ester (5) in quantitative yield as an oily product [$\nu(\text{film})$: 3400 and 3330 (NH₂), 1740 and 1680 cm⁻¹ (C=O)].

Furthermore, reduction of (2e), which was prepared by benzylation of (2a), with NaBH₄ gave the corresponding dihydro derivative (6) (m.p. 110–112 °C) in 60% yield.

Meanwhile, mild hydrolysis of (3a) with oxalic acid in methanol–water gave the corresponding 3(2H)-benzofuranone (7) (m.p. 120–121 °C) in quantitative yield. The ¹³C n.m.r. spectral data of (7) [$\delta(\text{CDCl}_3)$: 103.8 (2-C), 192.9 (3-C), 119.0 (3a-C), 122.4 and 125.2 (4-C, 5-C), 139.4 (6-C), 113.4 (7-C), 164.7 (7a-C), 39.0 (N-CH₃), 53.9 (O-CH₃), 172.3 (-CO-O)] are similar to the reported data³ for 2-methoxy-2-(4-methoxybenzoyl)-3(2H)-benzofuranone.

Furthermore, hydrolysis of (3a) with hydrochloric acid in methanol at room temperature afforded the diketo ester (8) (m.p. 109 °C) in 40% yield. Thus the evidence described above substantiates the structures of compounds (2) and (3).

A plausible mechanism for the ring transformation of compounds (1) to 2H-azirines (2) may involve the Neber-like rearrangement of the initially formed α -carbanion of (1). In the case of the α -amino derivatives (1e), (1f), it is assumed that the initially formed azirines, which could not be isolated, may undergo further cleavage of the azirine C–N bond followed by recyclisation to give benzofurans (3).

The present azirine formation from (1) is the first example of the Neber-like rearrangement which involves a phenoxide as a leaving group.

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