

A New Synthesis of 4-Aryl-2-benzazepine-1,5-diones

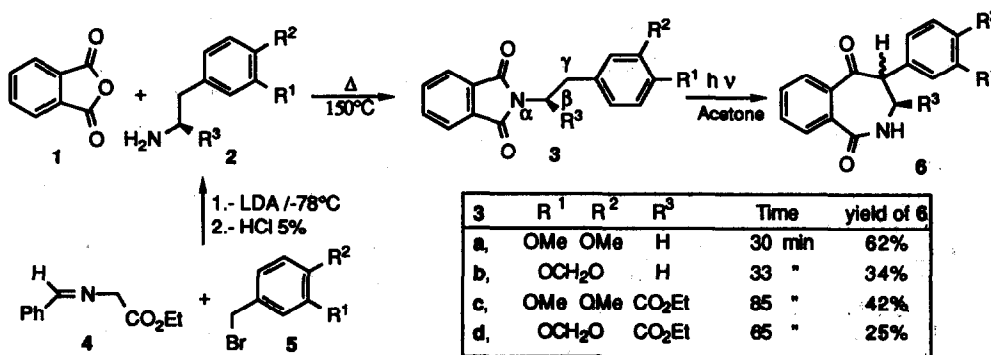
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Abstract: 4-Aryl-2-benzazepine-1,5-diones were prepared by photocyclization of *N*-(2-arylethyl)phthalimides.

There is much current interest in the preparation of phenylbenzazepines as they have considerable medical interest;¹ 2-benzazepines have shown antihypertensive, adrenoceptor-blocking and cholinesterase inhibiting activities.² The 4-aryl-2-benzazepine unit is present in the skeleton of ribasine alkaloids.³

The only known method for the preparation of 4-aryl-2-benzazepine-1,5-diones is based on [2+2] cycloaddition between *N*-methylphthalimide and styrene.^{4,5} Because of the lack of generality of this method,⁶ we decided to investigate a new approach based on photocyclization of *N*-(2-arylethyl)phthalimides. It is known that simple *N*-alkylphthalimides undergo photocyclization to 2-benzazepinediones by way of γ -hydrogen abstraction, although in low yield;⁷ however, the corresponding photoprocess for *N*-(2-phenylethyl)phthalimide (**3**; R¹=R²=R³=H) results in the formation of complex mixture of minor products.⁸ Nevertheless, we found that the presence of electron-donating substituents on the aryl ring of phthalimides **3** favours photocyclization, thus allowing the preparation of benzazepinediones **6**.



Phthalimides **3a-d** were prepared by fusing a mixture of phthalic anhydride (**1**) and the corresponding phenethylamine **2** at 150°C. Compounds **2a** and **2b** are commercially available, while the ethyl 2-amino-3-aryl

propanoates **2c** and **2d** were prepared by condensation of the lithium enolate derived from ethyl benzylidene glycinate (**4**) with the corresponding benzyl bromide **5**, followed by imine hydrolysis with 5% HCl.⁹

Photolysis of **3a-d** was carried out at room temperature for 30-85 min in various solvents (acetonitrile, dichloromethane, acetone); the best results were obtained with acetone. Photolysis of **3a** for 30 min afforded the benzazepinone lactam **6a** in 62% isolated yield. Starting material **3a** was still observed when irradiation was terminated but longer exposure to light produced a complex mixture because **6a** is photochemically reactive.¹⁰ Photolysis of **3b** for 33 min gave **6b** in 34% yield. These results, when compared with those obtained with the unsubstituted phthalimide **3** ($R^1=R^2=R^3=H$), show that photocyclization is favoured by the presence of donor substituents on the aryl ring, probably due to stabilization of the intermediate radical resulting from the γ -abstraction process.

The presence of a β -carboxylate group does not hinder photocyclization, as irradiation of **3c** and **3d** afforded the corresponding lactams **6c** and **6d** in 42 and 25% yield respectively. The photocyclization process is not stereoselective; a 1:1 mixture of diastereomers was obtained in these reactions.

More research is being carried out to further extend the potential of this new method for synthesis of 4-aryl-2-benzazepine-1,5-diones.

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References and notes

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- General procedure for irradiation of phthalimides 3.** A solution of the phthalimide (0.2 g) in acetone (200 mL) was irradiated under Ar using a Hanovia 450 w medium-pressure lamp in a Pyrex jacket at room temperature. The solution was degassed by bubbling Ar through it for a period of 10 min prior to irradiation. Solvent was removed in vacuo and the residue purified by preparative TLC (silica gel, 97:3, CH₂Cl₂-MeOH).
4-(3,4-Dimethoxyphenyl)-2-benzazepine-1,5-dione (6a). M.p.: 166-167°C (CH₂Cl₂-hexane). IR (CHCl₃) 1670, 1690 cm⁻¹. UV (CH₃OH) λ_{max} : 208, 280 nm. ¹H NMR δ (CDCl₃): 3.68 (m, 1H), 3.82 (m, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 4.12 (dd, 1H, J = 4.1, 10.2 Hz), 6.65 (m, 2H), 6.80 (d, 1H, J = 8.0 Hz), 6.95 (t, 1H, J = 6.2 Hz), 7.56 (m, 1H), 7.6-7.8 (m, 2H), 7.96 (m, 1H). ¹H NMR δ (CDCl₃-D₂O): 3.66 (dd, 1H, J = 4.1, 14.9 Hz), 3.82 (dd, 1H, J = 14.9, 10.2 Hz), 3.83 (s, 3H), 3.84 (s, 3H), 4.14 (dd, 2H, J = 4.1, 10.2 Hz), 6.65 (m, 2H), 6.80 (d, 1H, J = 8.0 Hz), 7.56 (m, 1H), 7.6-7.8 (m, 2H), 7.94 (m, 1H). ¹³C NMR δ (CDCl₃): 44.25, 55.94, 61.32, 111.78, 120.08, 128.53, 129.79, 130.01, 131.52, 132.33, 132.60, 137.30, 148.95, 149.51, 170.86, 204.32. Anal. Calc. for C₁₈H₁₇NO₄: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.42; H, 5.86; N, 4.60.