Anthraquinone-photocatalysed addition of amines to α,β-unsaturated esters: a novel route to indolizidone, pyrrolizidone and related ring systems

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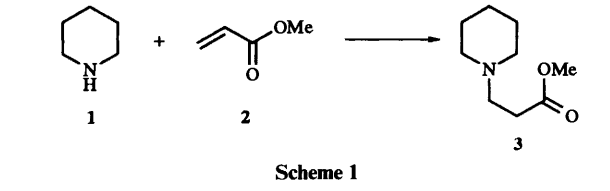
The indolizidone **9**, the pyrrolizidone **14**, a mixture of heliotridone **15a** and pseudoheliotridone **15b** and the lactam **19** have been synthesized in a one-step anthraquinone-photocatalysed reaction of the corresponding amines, piperidine **1**, pyrrolidine **10** and morpholine **16**, with α,β-unsaturated esters.

Syntheses of indolizidine and pyrrolizidine-containing systems continue to attract attention because of the ubiquity of such compounds in natural products.[1] Electrophilic addition to the α-carbanion of amines,[2] the reactions of iminimum derivatives[3,4] and, more recently, carbon-carbon bond-forming reactions of α-aminoalkyl radicals have been used to prepare such compounds.[5-7] In this connection the photoelectron-transfer catalysed reactions of α-silylamines using sensitizers such as dicyanonaphthalene (DCN) and dicyanoanthracene (DCA), for the generation of α-aminoalkyl radicals have been extensively explored.[8-10] We have recently observed that α-aminoalkyl radicals, which are generated efficiently in anthraquinone-photocatalysed reactions of underivatized amines, undergo multiple additions with electron deficient olefinic substrates.[11] In the course of these studies we had observed that the reactions of primary and secondary amines with methyl methacrylate led to the formation of spirocyclic and bicylic amides, respectively. A major limitation in these reactions, however, was that apart from methyl methacrylate, α,β-unsaturated esters undergo facile Michael-type additions to yield the N-adducts, quantitatively. This difficulty could be overcome by carrying out these reactions at low temperatures, where the Michael adduct formation is minimized and the photoinduced free-radical reactions remain unaffected. Here we report on the one-step anthraquinone-photocatalysed reactions of piperidine **1**, pyrrolidine **10** and morpholine **16** with α,β-unsaturated esters to form the indolizidone **9**, the pyrrolizidone **14**, a mixture of heliotridone **15a** and pseudoheliotridone **15b** and the lactam **19**, which are precursors of naturally occurring alkaloids. The effect of temperature on these reactions has also been examined.

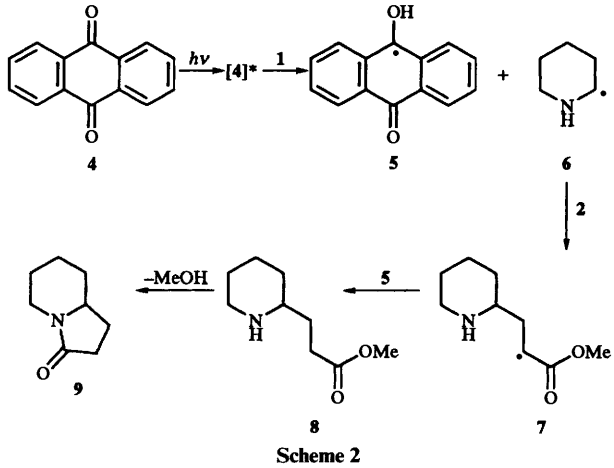
Results and discussion

The photosensitized addition of piperidine **1** to methyl acrylate **2** was studied by irradiating argon-saturated solutions of piperidine and methyl acrylate in acetonitrile containing catalytic amounts of anthraquinone, under Pyrex-filtered light ($\lambda > 290$ nm). Two products, **3** and **9** were isolated from the reaction mixture (Schemes 1 and 2) and characterized on the basis of spectral information. The percentage distribution of the products is shown in Table 1. At normal temperatures (30 °C), nearly quantitative formation of **3** was observed along with traces of **9**. Piperidine undergoes an efficient Michael-type addition with methyl acrylate, which could account for the formation of **3** in the reaction mixture (Scheme 1). Compound **9** could arise through the pathways shown in Scheme 2. Excitation of the reaction mixture with Pyrex-filtered light would lead to the selective excitation of anthraquinone, since piperidine and methyl acrylate do not have significant



1 2 3

Scheme 1



4 5 6 9 8 7

Scheme 2

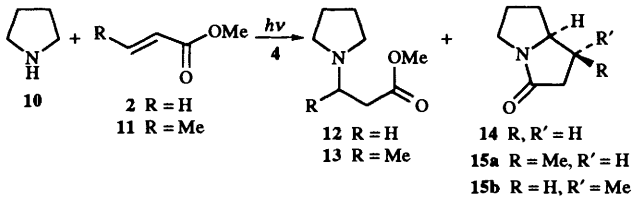
absorbance at wavelengths >290 nm. The triplet state of anthraquinone ($\Phi_T = 0.93$),[12] formed in the excitation process can undergo electron-transfer reactions with piperidine, which, followed by rapid proton transfer between the radical ion pairs, can lead to efficient generation of the α-aminoalkyl radical **6**.[11,13-15] Reaction of **6** with methyl acrylate will lead to the adduct radical **7**, which can presumably be quenched by the anthraquinone ketyl radical to give rise to **8**. The amine–olefin adduct **8** formed in the process can undergo cyclization during work up to yield indolizidone **9**. Such cyclizations are known to be very efficient.[6] Indolizidone can be easily reduced to give the naturally occurring compound δ-coniceine.[16]

Table 1 shows the effect of temperature on these reactions. At lower temperatures, the yield of the Michael-adduct **3** is significantly reduced, whereas the yield of **9** increases, indicating that the photochemically induced free-radical reactions are not significantly affected by lowering of the temperature. Similarly, the anthraquinone-photosensitized reaction of pyrrolidine **10** with methyl acrylate **2** gave the pyrrolizidone **14**, along with the Michael-type adduct **12** (Scheme 3). Lowering of the temperature of the reaction medium led to the reduction in the yield of the *N*-adduct **12** and an increase in the yield of **14** (Table 1). The reaction of pyrrolidine **10** with methyl crotonate **11** yielded a diastereoiso-

Table 1 Temperature dependence of the anthraquinone (3×10^{-4} mol dm^{-3}) photosensitized addition of amines (15 mmol) to α,β-unsaturated esters (15 mmol) in degassed acetonitrile solutions (300 cm^3)

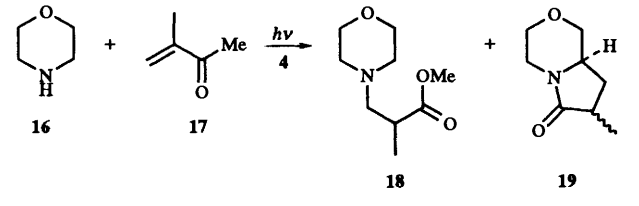
Amine	Ester	Temp (T/°C)	Period of irrdn. (t/h)	% Conversion of ester	Product (%)*
1	**2**	30	2	95	**3** (93%), **9** (< 1%)
		5	2	40	**3** (30%), **9** (8%)
		0	1	25	**3** (15%), **9** (5%)
		0	2	25	**3** (15%), **9** (8%)
10	**2**	30	2	98	**12** (96%), **14** (< 1%)
		5	2	60	**12** (50%), **14** (5%)
		0	1	35	**12** (25%), **14** (5.5%)
		0	2	40	**12** (28%), **14** (8%)
10	**11**	30	2	40	**13** (16%), **15** (10%)
		5	2	30	**13** (9%), **15** (10.5%)
		0	2	20	**13** (4%), **15** (10%)
16	**17**	30	2	35	**18** (9%), **19** (10%)
		5	2	25	**18** (2.5%), **19** (10%)
		0	2	20	**18** (1%), **19** (9%)

* The reported yields are based on the total amount of ester used in any reaction and not on the amount of ester consumed in the reaction.



Scheme 3

meric mixture of heliotridone **15a** and pseudoheliotridone **15b**. A diastereoisomeric ratio of 3:7 (**15a**:**15b**) was estimated by gas chromatography (OV101, fused silica capillary column) using a pure sample of **15b** as reference. The stereochemistry of **15a** and **15b** were also established by comparing the ^{13}C NMR chemical shifts of the diastereoisomers. The ^{13}C NMR signals due to **15a** appear upfield in comparison to **15b**. It is well documented that diastereoisomers having axial substitution always appear upfield.[17,18] The assignment was further supported by comparing the ^{1}H NMR values of **15a** and **15b** with reported values.[19] Heliotridones can be reduced easily to heliotridanes.[19] The anthraquinone-photocatalysed addition of morpholine **16** to methyl methacrylate **17** yielded the Michael adduct **18** and a diastereoisomeric mixture (3:2, as evidenced from the capillary GC analysis) of the cyclized product **19**.



Scheme 4

These studies indicate that the anthraquinone-photocatalysed addition of secondary amines to α,β-unsaturated esters can form a convenient route to the synthesis of azabicyclic ring systems. None of the above reactions could be photocatalysed using DCA. Although the yields of the cyclic amides in these reactions are modest, the simple one-step process for obtaining such products from underivatized amines could make this the preferred route for their synthesis.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a JEOL EX 90 NMR spectrometer. ^{13}C NMR (22.5 MHz) resonances were assigned using QUART and DEPT programs to determine the number of hydrogen attachments. Mass spectra were recorded on a Finnegan MAT Model 8430 or Hewlett Packard 5971 series mass selective detector. HPLC analysis and purification were carried out in a Shimadzu LC-8A liquid chromatograph. Gas chromatographic analysis was carried out using a Hewlett-Packard 5890 series II, gas chromatograph. IR spectra were recorded on a Perkin-Elmer model 882 IR spectrometer and the UV–visible spectra on a Shimadzu 2100 spectrometer. Anthraquinone was purified by vacuum sublimation. All other reagents were purified by distillation before use.

Preparative photochemical reactions were carried out under irradiation from a 450 W medium-pressure mercury vapour lamp in a Pyrex-jacketted, water-cooled immersion well. The photolysis mixture, typically consisting of the amine (15 mmol) and olefinic substrate (15 mmol) in acetonitrile (300 cm^3) containing anthraquinone (3×10^{-4} mol dm^{-3}) was purged with nitrogen before irradiation (2–3 h). The reaction vessel was immersed in a temperature-controlled bath and the temperature of the reaction vessel was monitored continuously. The solvent and unchanged reactants were removed under reduced pressure and the product mixture was chromatographed (flash column) on silica gel (230–400 mesh) or using a Harrison Chromatotron employing a mixture (3:7) of ethyl acetate and light petroleum. All the photoproducts were finally purified using semi-preparative HPLC (ODS-semipreparative column 20 mm i.d. × 25 cm length, methanol eluent). The yields reported are based on the olefenic substrates consumed, which were estimated by HPLC before removal of the solvent from the reaction mixture. Anthraquinone was recovered quantitatively (> 90%) under all the irradiation conditions.

The Michael-type adducts formed in the reactions mixtures (**3**, **12**, **13**, **18**) were characterized by comparing their spectral data with the compounds obtained in the thermal reactions between the corresponding amine and α,β-unsaturated ester. The indolizidone and pyrrolizidone derivatives (**9**, **14**, **15**) were characterized by comparing their spectral data with those reported in the literature.[16,19] The lactam **19** obtained from morpholine was characterized on the basis of spectral data and a high resolution mass measurement.

Photosensitized addition of piperidine 1 to methyl acrylate 2

Irradiation of a solution, through which nitrogen was bubbled, of **1** (1.3 g, 15 mmol) and **2** (1.3 g 15 mmol) in acetonitrile (300 cm^3) containing anthraquinone (3×10^{-4} mol dm^{-3}) for 2 h at 0 °C and separation of the photoproducts by column chromatography gave **9** (120 mg, 30%) and **3** (400 mg, 60%).

These yields are based on the amount of **2** that had reacted (25%), as estimated by HPLC. The reaction was repeated at different temperatures and the percentage conversion and product yields are shown in Table 1. Compound **9**: ν_{max}(neat)/cm^{-1} 2987, 2880 (CH) and 1680 (C=O); δ_H($CDCl_3$) 1.4–2.1 (6 H, m, 3 CH_2), 2.15–2.9 (4 H, m, 2 CH_2), 3.3–3.9 (2 H, m, CH_2) and 4.1–4.4 (1 H, m, CH); δ_C($CDCl_3$) 23.38, 24.16, 25.02, 29.98, 33.29, 39.91 (CH_2), 56.98 (CH) and 173.24 (C=O, lactam); *m/z* (rel. inten) 139 (M^+, 82), 138 (100), 124 (20), 111 (15), 98 (25), 83 (60), 68 (25) and 55 (50). Compound **3**: ν_{max}(neat)/cm^{-1} 2980, 2870 (CH) and 1744 (C=O); δ_H($CDCl_3$) 1.3–1.7 (6 H, m, 3 CH_2), 2.2–2.8 (8 H, m, 4 CH_2) and 3.5–3.7 (3 H, s, OCH_3); δ_C($CDCl_3$) 23.93, 25.60, 31.72, 50.90, 53.88 and 172.45 (C=O, ester); *m/z* (rel. inten.) 171 (M^+, 10), 143 (20), 114 (30), 98 (100), 88 (10), 73 (10) and 55 (30).

Photosensitized addition of pyrrolidine 10 to methyl acrylate 2

Irradiation of a solution, through which nitrogen was bubbled, of **10** (1.06 g, 15 mmol) and **2** (1.3 g, 15 mmol) in acetonitrile (300 cm^3) containing anthraquinone (3×10^{-4} mol dm^{-3}) for 2 h at 0 °C and separation of the products by column chromatography gave **14** (100 mg, 15%) and **12** (800 mg, 70%). These yields are based on the amount of methyl acrylate that had reacted (40%) as estimated by HPLC. The percentage conversion and product yields when the reaction was carried out at different temperatures are shown in Table 1. Compound **14**: ν_{max}/cm^{-1} 2980, 2880 (CH) and 1682 (C=O); δ_H($CDCl_3$) 1.8–2.1 (4 H, m, 2 CH_2) 2.15–2.6 (4 H, m, 2 CH_2), 3.2–3.6 (2 H, m, CH_2) and 4.2–4.6 (1 H, m, CH); δ_C($CDCl_3$) 26.75, 26.93, 31.94, 35.11, 40.78 (CH_2), 61.87 (CH) and 174.62 (C=O, lactam); *m/z* (rel. inten.) 125 (M^+, 80), 110 (2), 97 (100), 80 (4), 69 (44) and 55 (18). Compound **12**: ν_{max}(neat)/cm^{-1} 2975, 2868 (CH) and 1742 (C=O); δ_H($CDCl_3$) 1.65–1.85 (4 H, m, 2 CH_2), 2.4–2.9 (8 H, m, 4 CH_2) and 3.6–3.75 (3 H, s, OCH_3); δ_C($CDCl_3$) 22.93, 33.38, 50.62, 50.83, 53.34 and 171.93 (C=O, ester); *m/z* (rel. inten.) 157 (M^+, 5), 129 (15), 98 (25), 83 (100), 68 (10) and 55 (20).

Photosensitized addition of pyrrolidine 10 to methyl crotonate 11

Irradiation of a solution, through which nitrogen was bubbled, of **10** (1.06 g, 15 mmol) and **11** (1.5 g, 15 mmol) acetonitrile (300 cm^3) containing anthraquinone (3×10^{-4} mol dm^{-3}) for 2 h at 0 °C and chromatographic separation of the product mixture gave an isomeric mixture of **15a** and **15b** (130 mg, 40%) and of **13** (70 mg, 15%). The yields reported are based on the amount of methyl crotonate that had reacted (20%). The percentage conversion and product yields at different temperatures are shown in Table 1. Compounds **15a, 15b**: ν_{max}/cm^{-1} 2970, 2876 (CH) and 1688 (C=O); δ_H($CDCl_3$) 0.9–0.98 (3 H, d, CH_3, *J* 7, **15a**), 1.0–1.15 (3 H, d, CH_3, *J* 6, **15b**), 1.8–2.2 (8 H, m, 4 CH_2), 2.25–2.6 (4 H, m, 2 CH_2), 2.8–3.2 (2 H, m, 2 CH) and 3.25–3.8 (6 H, m, 2 CH_2, 2 CH); δ_C($CDCl_3$) **15a** 15.77 (CH_3), 24.96, 29.50, 41.07, 42.95 (CH_2), 35.05, 64.97 (CH) and 174.05 (C=O, lactam); δ_C($CDCl_3$) **15b** 17.89 (CH_3), 26.84, 30.64, 41.28, 43.70 (CH_2), 37.85, 68.85 (CH) and 174.23 (C=O, lactam); *m/z* (rel. inten.) 139 (M^+, 23), 124 (4), 111 (18), 96 (6), 85 (6), 70 (80) and 56 (4). Compound **13**: ν_{max}/cm^{-1} 2980, 2872 (CH) and 1744 (C=O); δ_H($CDCl_3$) 1.1–1.3 (3 H, d, CH_3), 1.7–1.9 (4 H, m, 2 CH_2), 2.1–3.2 (7 H, m, 3 CH_2, CH) and 3.6–3.8 (3 H, s, OCH_3); δ_C($CDCl_3$) 17.92, 22.96, 39.58, 49.99, 50.77, 54.83 and 172.11 (C=O, ester); *m/z* (rel. inten.) 171 (M^+, 5), 156 (15), 124 (5), 98 (100), 70 (5) and 56 (10).

Photosensitized addition of morpholine 16 to methyl methacrylate 17

Irradiation of a nitrogen degassed solution of **16** (1.3 g, .15 mmol) and **17** (1.5 g, 15 mmol) in acetonitrile (300 cm^3) containing catalytic amounts of anthraquinone (3×10^{-4} mol dm^{-3}) for 2 h at 5 °C and separation of the product mixture by column chromatography gave **19** (100 mg, 40%) and **18** (40 mg, 10%). Yields are based on the amount of methyl methacrylate that had reacted (25%). The percentage conversion and product yields at 30 and 0 °C are shown in Table 1. Compound **19**: ν_{max}/cm^{-1} 2976, 2878 (CH) and 1692 (C=O); λ_{max}(MeCN)/nm 205 (ε/dm^3 mol^{-1} cm^{-1}, 3620) and 254, 510 sh; δ_H($CDCl_3$) 1.0–1.2 (3 H, d, CH_3), 1.6–2.0 (2 H, m, CH_2), 2.1–2.6 (1 H, m, CH), 2.8–3.2 (2 H, m, CH_2) and 3.2–4.1 (5 H, m, 2 CH_2, CH); δ_C($CDCl_3$) 15.80, 16.79 (CH_3), 28.19, 29.95 (CH_2), 35.44 (CH), 39.58, 39.97 (CH_2), 52.41, 52.98 (CH), 65.48, 71.83, 72.67 (CH_2), 175.06 and 175.63 (C=O, lactam); *m/z* (rel. inten.) 155 (M^+, 80), 125 (65), 110 (7), 97 (100), 82 (86), 69 (42) and 54 (84) [Found (HRMS): M, 154.0866. Calc. for $C_8H_{13}NO_2$: *M*, 154.0868]. Compound **18**: ν_{max}/cm^{-1} 2985, 2870 (CH) and 1740 (C=O); δ_H($CDCl_3$) 0.9–1.0 (3 H, d, CH_3), 2.4–3.2 (7 H, 3 CH_2, CH) and 3.4–3.8 (7 H, m, 2 CH_2, OCH_3); δ_C($CDCl_3$) 18.02, 41.28, 43.54, 45.76, 52.80, 70.80 and 172.45 (C=O, ester); *m/z* (rel. inten.) 187 (M^+, 2), 156 (5), 142 (5), 114 (5), 100 (100), 86 (5), 76 (10) and 56 (15).

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