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Facile preparative redox chemistry of bis(4-dialkylaminophenyl)squaraine dyes

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Abstract—Bis(4-dialkylaminophenyl)squaraine dyes are readily reduced in solution by borohydride to give alkali soluble *leuco* compounds, which exist in the 3-hydroxy-2,4-(4-dialkylaminophenyl)cyclobutenone tautomeric form. The *leuco* dyes can be oxidised rapidly back to the squaraine dye, thus providing a means of temporarily solubilising the squaraine dye in water. The *leuco* compounds undergo substitution reactions typical of vinylogous carboxylic acids.

It is well known that certain classes of dye are reducible to stable colourless *leuco* compounds, which can be oxidised in air quantitatively back to the coloured species. This reversible behaviour is made use of in textile dyeing, photoimaging, redox indicators, and enzyme assays.[1] Carbonyl-based dye chromophores that show such behaviour generally require at least two mutually conjugated carbonyl groups, and the most familiar of these are the quinone and indigoid dyes. It is surprising that another important class of carbonyl dye, namely the ubiquitous bis(4-dialkylaminophenyl)-squaraine dyes, has not been investigated in this respect. These dyes have many technical applications, e.g. in xerography,[2] solar cells,[3] optical recording media,[4] and non-linear optics,[5] but studies of their redox properties have been confined to electrochemical,[6] pulse-radiolytic and photochemical[7] processes, and in these studies, no attempts have been made to isolate and characterise reduction products. We now report that bis(4-dialkylaminophenyl)-squaraines **1** are readily decolourised in solution by sodium borohydride to give 3-hydroxy-2,4-bis(4-dialkylaminophenyl)cyclobuten-one *leuco* compounds **2**,[8] which can be air-oxidised back to the squaraine dye in high yield. The *leuco* products are easily isolated and undergo a range of reactions which may be regarded as typical of vinylogous carboxylic acids. The reduction—oxidation sequence is simple and efficient, and extends synthetic possibilities in this class of dye. Because the *leuco* compounds are soluble in water at alkaline pH (in marked contrast to the parent dye), this affords many new opportunities for extending the chemistry and applications of squaraine dyes. Examples would include their purification, morphological modification, and incorporation into polymeric substrates from an aqueous phase.

When an intense blue solution of **1a** (3.7 mmol) in a mixture of dichloromethane (30 cm^3) and methanol (5 cm^3) was treated with sodium borohydride (7.4 mmol), complete decolourisation occurred after stirring for 30 minutes at room temperature. Neutralisation with acetic acid followed by evaporation of the solvent gave a colourless solid, which was extracted into dichloromethane and chromatographed rapidly over a short column of silica gel in the same solvent. The isolated colourless *leuco* compound **2a** (45%) was characterised by elemental analysis, mass spectrometry, and NMR. It was converted in high yield (>98%) back to **1a** by air oxidation in solution. The sequence is summarised in Scheme 1. The tautomeric structure **1a**, rather than the alternative 2,3-diaryl-1,3-cyclobutanone structure, was assigned to the *leuco* dye on the basis of its NMR spectrum[9] and IR spectrum. Thus the two 1,4-disubstituted benzene rings were non-equivalent, and the cyclobutenone H-4 was evident as a 1H singlet at δ 4.30.

The reduction–oxidation sequence observed for **1a** proved to be general for other dyes of this class, and similar results were obtained for squaraines **1b**–**g**. Their *leuco* forms were isolated in yields of 45–80% after purification. Typically 10^{-5} M solutions of these *leuco* dyes in dichloromethane containing a little methanol would take less than one hour to oxidise fully back to the squaraine dye in air at room temperature, and

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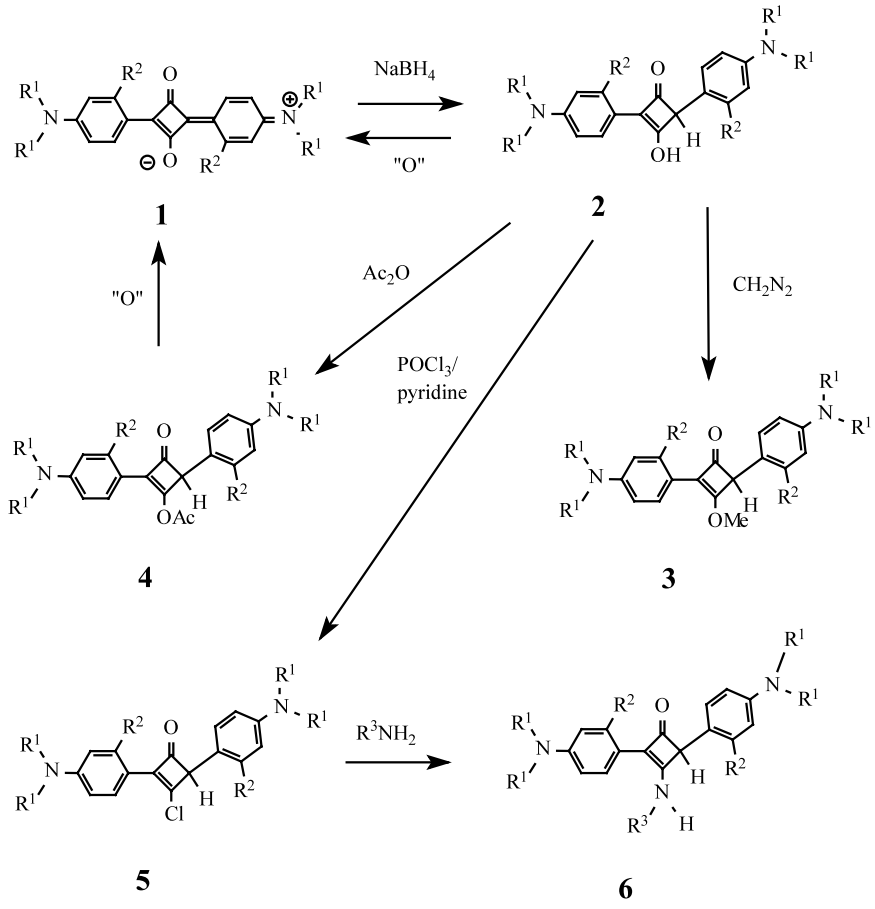


a R^1 = Et R^2 = H, **b** R^1 = Me R^2 = H, **c** R^1 = *n*-Bu R^2 = H, **d** R^1 = Et R^2 = OH
e R^1 = *n*-Bu R^2 = OH, **f** R^1 = Et R^2 = NHAc, **g** R^1 = *n*-Pr R^2 = OH **h** R^1 = R^3 = Et, R^2 = H,
i R^1 = Et, R^2 = H, R^3 = Me, **j** R^1 = Et, R^2 = H, R^3 = *n*-Bu, **k** R^1 = *n*-Bu , R^2 = H, R^3 = Me,
l R^1 = *n*-Bu , R^2 = H, R^3 = Et, **m** R^1 = R^3 = *n*-Bu, R^2 = H

Scheme 1.

reaction efficiencies for the oxidative reversion were higher than 80% in all cases, as determined spectrophotometrically. Oxidation could be effected more rapidly with chloranil, ferric chloride, lead dioxide and iodine.

Solutions of the *leuco* species in organic solvents or water can be applied to polymeric substrates, e.g. paper, and dried to give a colourless layer that develops the colour of the squaraine dye on standing. The development process is greatly accelerated by heating.

Another potential application of the *leuco*-squaraines is as fluorogenic substrates for peroxidase enzyme assays. For example, squaraine dye **1d** is strongly red fluorescent in solution,[10] and after reduction to the *leuco* compound **2d** this fluorescence naturally disappears. In aqueous dilute hydrogen peroxide solution at ca. pH 9 containing horse-radish peroxidase, oxidation of **2d** back to **1d** occurred much more rapidly than in the absence of the enzyme, with the concomitant appearance of the red emission from **1d**. Although the usefulness of this reaction as an assay is restricted by the poor solubility of **1d** in water, resulting in its gradual precipitation, derivatives of **1d** with water solubilising groups could be used more effectively.

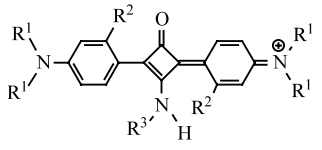
The ease of air-oxidation of the *leuco* derivatives is in part due to the acidic hydroxy group present in the structure, and by analogy with *leuco*-quinones and *leuco*-indigoids, *O*-alkylation or acylation should increase the resistance of the system towards oxidation. Treatment of **2a** in dichloromethane with diazomethane followed by column chromatography (silica gel 60/CH_2Cl_2) afforded **3a** as a colourless gum in 20% yield. The NMR data[11] were consistent with the enol ether structure, and the MeO protons evident as a 3H singlet at δ 3.93, and the isolated cyclobutenone proton as a 1H singlet at δ 4.70. As expected, **3a** proved stable to air oxidation in solution. Similar observations were made for the *O*-methyl derivative **3c**, which was obtained in 44% yield from **2c**.

Treatment of **2a** with acetic anhydride gave the enol acetate **4a**, isolated in 45% yield after purification by column chromatography. The NMR spectrum showed the MeCO protons as a 3H singlet at δ 2.10. The ester

was not as susceptible to air oxidation as **2a**, but was more reactive than **3a** in this respect. This may be due to the ease of hydrolysis of the enol acetate residue. Nevertheless, acetylation provided a convenient means of converting the *leuco* squaraines to derivatives that were sufficiently stable for purification and storage, and which, when required, could easily be converted back to the squaraine dye by mild hydrolysis and air oxidation. The *leuco* esters **4a**–**g** were isolated in yields of 45–70% after purification Interestingly, the derivative **4d** proved to be a fluorogenic substrate for horseradish peroxidase in the same way that **2d** did, but with the advantage that competitive air oxidation was greatly reduced in this case.

Further substitution of the *leuco* squaraine system proved possible by converting **2a** to the vinylogous acid chloride **5a**. This was most conveniently achieved by reaction of **2a** with phosphorous oxychloride and a catalytic amount of pyridine in dichloromethane at room temperature for 4 h. The chloride was obtained as a colourless oil in 48% yield after column chromatography, and the structure was confirmed by mass spectrometry and NMR. The chlorine atom in **5a** proved labile, and for example could be replaced by amines. Thus reaction with 2 equiv. of ethylamine in dichloromethane at room temperature for 4 h, followed by purification by column chromatography gave the vinylogous *N*-ethyl amide **6h** in 63% yield. The analogous methylamino- and *n*-butylamino- derivatives **6i** and **6j** were similarly prepared from **5a**, in yields of 62 and 67%, respectively. The amino compounds **6k**–**m** were also prepared from the *leuco* squaraine **2c** via the chloride **5c**.

Interestingly, each amino derivative **6** could be oxidised in solution with chloranil or lead dioxide to give an unstable coloured product with an absorption peak of similar intensity and bandwidth to that of the parent squaraine dye, but at longer *wavelengths*. For example, oxidation of **6h** in dichloromethane gave a product with $\lambda_{max} = 690$ nm, which may be compared to the value of 630 nm for **1a**. It is probable that the oxidised species is the aminosquaraine derivative **7**, but this has yet to be confirmed. Analogous aminosquaraine systems with heterocyclic terminal groups have also been reported to absorb at longer wavelengths than the corresponding squaraine dye.[12]



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Oxidation of the *leuco* ester **4a**, with lead dioxide gave only the original squaraine dye **1a**, whereas similar oxidation of the methyl ether **3a** and chloro derivative **5a** gave new coloured products absorbing at longer wavelengths than **1a**, which were unstable under these reaction conditions. These were presumably the methoxy- and chloro-substituted cationic dyes, respectively, analogous to **7**, and these reactions are currently under investigation, with a view to improving their efficiency for preparative purposes.

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11. Spectral data for **3a**: δ_H (300 MHz; $CDCl_3$) 7.62 (d, *J* 8.5, 2H), 7.11 (d, *J* 8.5, 2H), 6.65 (d, *J* 7.4, 4H), 4.70 (s, H), 3.93 (s, 3H), 3.35 (m, 8H), 1.15 (m, 12H).
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