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〈Research Paper〉

The Synthesis of New Leuco Squarylium Dyes

Sooyoul Park*, Kun Jun, Seungrim Shin and Jongil Shin

Bio Fine Chemical Research Center, Korea Research Institute of Chemical Technology, Yuseong, Daejeon, 305-600, Korea

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Abstract— It is well known that certain classes of dye are reducible to stable colorless leuco compounds, which can be oxidized in air back to the colored species. We now reported that bis(4-dialkylaminophenyl)squaraine dyes are readily reduced in solution by borohydride to give alkali soluble leuco compound, which exists in the 3-hydroxy 2,4-bis(4-dialkylaminophenyl)cyclobuten-one. New alkylamine leuco compounds were synthesized by the reaction of leuco chloro-squaraine with alkylamine derivatives. The leuco compounds are easily isolated and can be air oxidized back to the squaraine dyes. These dyes have many technical application. e.g. in xerography, solar cell, optical recording material, redox indicators, and enzyme assays.

Keywords: *Leuco compound, squaraine dye, optical recording materials, redox indicators, enzyme assay*

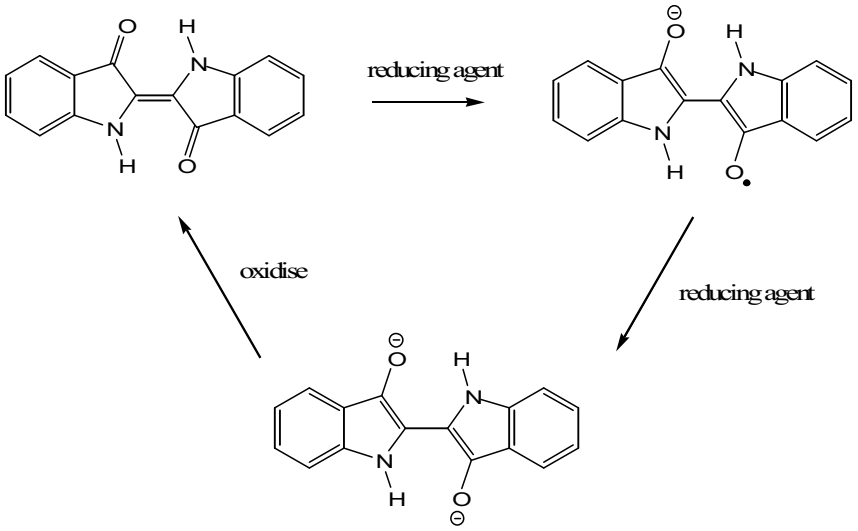
1. Introduction

Squaraine dyes are 1,3-disubstituted compounds synthesized from squaric acid and two equivalents of various types of electron donating carbocycles or heterocycles. The structural modification of squaraine dyes has been an active area on account of their advantageous properties such as photo-conductivity and high fluorescence quantum yields in the visible and near-infrared regions[1,6].

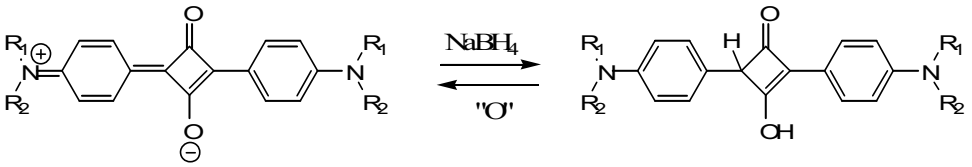
Because of these properties, squaraines are suited for application in optical data storage, xerography, lasers and medical probe application[7,8]. Carbonyl-based dyes that show such behavior generally require at least two mutually conjugated carbonyl groups, and the most familiar of these are the quinine and indigoid dyes. indigoid-type dyes can be reduced in a two-stage process to the so-called "*leuco dianions*", which unlike the original dyes are readily soluble in water and have a high affinity for cellulosic fiber. Thus in this *leuco* form the dyes can be exhausted efficiently onto cotton, and then by means of a re-oxidation process, the original insoluble dye can be formed within the fibre. In recent years this redox behavior has also found use in the area of functional dyes, particularly where the colour change associated with reduction/oxidation can be employed in sensors and indicators, *e.g.* in enzyme assay and diagnostic systems[9,10].

Alkali is generally incorporated with the reducing agent to ensure that the substantive ionized leuco species is formed, since the acid leuco form is generally insoluble. The reduction rate is critically dependent on the physical form of the dye as characterized by its crystal form and particle size distribution. The stability of the leuco dye in solution is also a function of the concentrations of dye and reducing agent, temperature, pH and liquor ratio. Also, the leuco compounds are soluble in water at alkaline pH contrast to the parent dye, this affords may new opportunities for extending the chemistry and applications of squaraine dyes, e.g. electro-chemical[11,12]and photochemical processes[13].

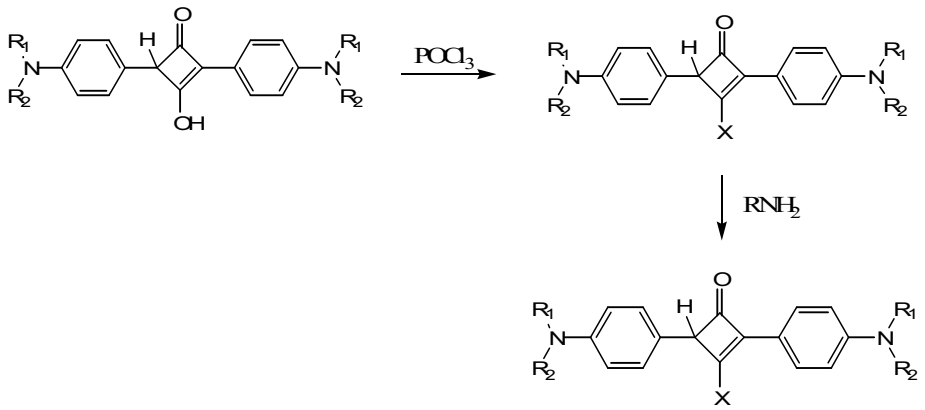
*Corresponding author. Tel: +82-42-860-7660; Fax: +82-42-860-7669; e-mail: sypark@krict.re.kr



Scheme 1. Oxidation / reduction of indigo.



Scheme 2. Formation of leuco 1,3-squaraines.



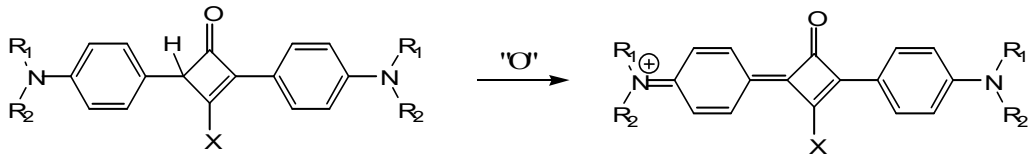
Scheme 3. The synthesis route of leuco amino-squarylium.

2. Experimental

2.1 The experimental synthesis of leuco squarylium dyes

Leuco chloro-sqauarylium was obtained by reaction of leuco squarilium and phosphrous oxychloro in dichloromethane with added pyridine for 4 hours at room temperature. Target product was obtained as a liquid. The crude product was reacted with alkylamine in dichloromethane at room temperature for 4 hours. The leuco amino-squarylium dye was purified by column chromatography (silica; in dichloromethane) and was obtained as a liquid (Scheme 3).

We have shown that oxidation of the parent *leuco*-squaraines gives the neutral squaraine system. Initial observations indicated that the derivatives where X = Cl and NHAlkyl gave new long-wavelength absorbing chromophores.



X = Cl, NHAlkyl, R_1, R_2 = Et, Bu

However, closer investigation revealed that oxidation of the latter did initially produce a species absorbing at longer wavelengths than the parent squaraine dye, but this was unstable and readily converted to the squaraine dye in a short period of time.

The 1-alkylamino *leuco* squaraines after oxidation should give the alkylamino cationic dye system which may then undergo deprotonation to give the neutral 1-amino squaraine system which is isoelectronic with the parent squaraine system. Oxidation of the 1-alkylamino *leuco* squaraines could be effected with ferric chloride, chloranil or lead dioxide, and gave cationic dyes.

3. Results and Discussion

These cationic dyes absorbed at even longer wavelengths and furthermore the bathochromic shift increased with increasing electron donating strength of the alkylamine. Thus in the *N,N*-diethylamino series (**2-4**), the λ_{max} values were 643, 660 and 680 nm for the methylamino, ethylamino and n-butyamino derivatives respectively. For the *N,N*-dibutylamino series (**6-8**) the corresponding λ_{max} values were 663, 670 and 690 nm. A typical absorption spectrum of an oxidized amino leuco squaraine dye solution compared to the parent squaraine dye is shown in Table 1.

Unfortunately the amino cationic dyes were relatively labile, and their solutions were become colorless or pale yellow after 3-4 days. Initial attempts to isolate the cations, *e.g.* as their perchlorate salts, were unsuccessful. Some evidence for deprotonation of the cations to the neutral imino-squaraine system was obtained spectroscopically – thus addition of dilute methanolic potassium hydroxide to a solution of the cation resulted in a hypsochromic shift, which could be reversed by addition of hydrochloric acid.

The most difficult part of the synthesis was the purification after the amination, since the product from the amination have unstable and easily back to change to the colour form.

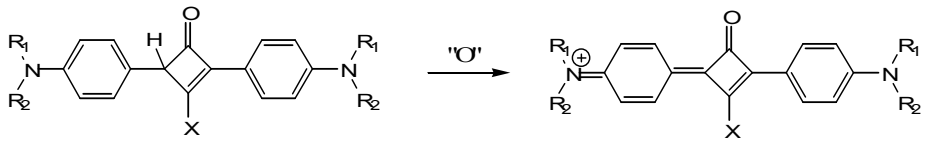
Interestingly, each amino squaraine derivative could be oxidized in solution with chloranil or lead dioxide to give an unstable colored product with an absorption peak of similar intensity and bandwidth to that of the parent squaraine dye, but at longer wavelengths. For example, oxidation of dye (**8**) in dichloromethane gave a product with λ_{max} = 690 nm, which may be compared to the value of 630 nm for parent dye. Their yields and visible absorption spectra properties were summarized in Table 1.

3.1 General Methods

All the chemicals and solvents used during the reactions were purchased from Aldrich, Acros, and Junsei. Before being used, some of them were purified using normal procedures. All reactions were monitored by thin layer chromatography (TLC). Ultraviolet and visible spectra were determined on a Perkin-Elmer Lambda 15 Spectrophotometer. Melting points were measured on an electro-thermal melting point apparatus. Nuclear magnetic resonance spectra (^{1}H-NMR) were performed on Bruker 300 spectra at 300.13 MHz in deuterio chloroform and chemical shift were referenced to tetramethylsilane as internal standard.

Synthesis of leuco 2,4-bis-(4-diethylaminophenyl) -3-chloride-cyclobutenone(1) : 2,4-bis-(4-diethylaminophenyl)-3-hydroxy-cyclobutenone(380 mg, 1 mmole) was dissolved in dichloromethane (5 ml). Phosphrous oxychloride (153 mg, 1 mmole) and pyridine (6 drops) were dropped to the reaction mixture. (Extreme care should be taken in this operation, which should be conducted

Table 1. Yields and their visible absorption spectra for leuco amino-squarylium dyes synthesized



No	X	R_1, R_2	Yield (%)	Leuco dye	After oxidation (λ_{max} in DCM*)
1	Cl	Et	48	Colorless	592
2	$NHCH_3$	Et	62	Colorless	643
3	$NHCH_2CH_3$	Et	63	Colorless	660
4	$NHCH_2CH_2CH_2CH_3$	Et	67	Colorless	680
5	Cl	Bu	50	Colorless	600
6	$NHCH_3$	Bu	55	Colorless	663
7	$NHCH_2CH_3$	Bu	60	Colorless	670
8	$NHCH_2CH_2CH_2CH_3$	Bu	60	Colorless	690

* DCM : Dichloromethane

in an efficient fume cupboard because of the poisonous properties of phosphrous oxychloride).

The reaction mixture was stirred at room temperature for 4 hours and the solvent was removed on a rotary evaporator. The residue was chromatographed over silica gel in dichloromethane. The product was obtained as a liquid (0.19 g, 48 %, Oily). Mass Spectrum (FAB): found M= 396; required for $C_{24}H_{29}N_2OCl$, M = 396. ^{1}NMR (300 MHz, $CDCl_3$): 1.18 (m, 12H), 3.34 (m, 8H), 4.75 (s, H), 6.60 (d, 2H, J=8.5 Hz), 6.69 (d, 2H, J=8.6 Hz), 7.20 (d, 2H, J=8.6 Hz), 7.85 (d, 2H, J=8.9 Hz).

Synthesis of leuco 2,4-bis-(4-diethylaminophenyl)-3-methylamine-cyclobutenone (2):
2,4-Bis-(4-diethylaminophenyl)-3-chloride-cyclobutenone (158 mg, 0.4 mmole) and *n*-methylamine (62 mg, purity. 40%, 0.8 mmole) were dissolved in dichloromethane (7 ml). The reaction mixture was stirred at room temperature for 4 hours and the same experimental procedure was followed to synthesis 1. The product was obtained as a liquid (97 mg, 62 %, Oily). Mass Spectrum (FAB): found M = 391; required for $C_{25}H_{33}N_3O$, M = 391.

Synthesis of leuco 2,4-bis-(4-diethylaminophenyl)-3-ethylamine-cyclobutenone (3):
2,4-Bis-(4-diethylaminophenyl)-3-chloride-cyclobutenone (158 mg, 0.4 mmole) and n-ethylamine (50 mg, purity. 70 %, 0.8 mmole) were dissolved in dichloromethane (7 ml). The reaction mixture was stirred at room temperature for 4 hours and the same experimental procedure was followed to synthesis 1. The product was obtained as a liquid (0.1 g, 63 %, Oily). Mass Spectrum (FAB): found M = 405; required for $C_{26}H_{35}N_3O$, M = 405. ^{1}H NMR (300 MHz, $CDCl_3$): 1.14 (m, 12H), 1.21(m, 6H), 3.33 (m, 8H), 4.62 (s, H), 6.60 (d, 2H, J=8.4 Hz), 6.65 (d, 2H, J=8.3 Hz), 7.25 (d, 2H, J=8.5 Hz), 7.71 (d, 2H, J=8.9 Hz).

Synthesis of leuco 2,4-bis-(4-diethylaminophenyl)-3-butylamine-cyclobutenone (4):
2,4-Bis-(4-diethylaminophenyl)-3-chloride-cyclobutenone (400 mg, 1 mmole) and n-butylamine (146 mg, 2 mmole) were dissolved in dichloromethane (7 ml). The reaction mixture was stirred at room temperature for 4 hours and the same experimental procedure was followed to synthesis 1. The product was obtained as a liquid (0.29 g, 67 %, Oily) Mass Spectrum (FAB): found M = 433; required for $C_{28}H_{39}N_3O$, M =433. ^{1}H NMR (300 MHz, $CDCl_3$): 0.84 (t, 3H, J=7.2 Hz), 1.15 (t, 12H, J=7.9 Hz), 1.35 (m, 6H), 3.33 (t, 8H, J=7.1 Hz), 4.53 (s, H), 5.75 (s, H), 6.65 (d, 2H, J=8.4 Hz), 6.71 (d, 2H, J=8.2 Hz), 7.12 (d, 2H, J=8.7 Hz), 7.42 (d, 2H, J=8.8 Hz).

Synthesis of leuco 2,4-bis-(4-dibutylaminophenyl)-3-chloride-cyclobutenone (5):
2,4-Bis-(4-dibutylaminophenyl)-3-hydroxy-cyclobutenone (1.2 g, 2.5 mmole) was dissolved in ethanol (5 ml) and phosphrous oxychloride (765 mg, 5 mmole)was dropped to the reaction mixture. (Extreme care should be taken in this operation, which should be conducted in an efficient fume cupboard because of the poisonous properties of phosphrous oxychloride). The reaction mixture was stirred at room temperature for 4 hours and the same experimental procedure was followed to synthesis 1. The product was obtained as a liquid (0.64 g, 50 %, Oily). Mass Spectrum (FAB): found M = 509; required for $C_{32}H_{45}N_2OCl$, M = 509. ^1H NMR (300 MHz, $CDCl_3$): 0.96 (t, 12H, J=7.1 Hz), 1.34 (m, 8H), 1.56 (m, 8H), 3.28 (m, 8H), 4.70 (s, H), 6.62 (d, 2H, J=8.8Hz), 6.64 (d, 2H, J=9.8 Hz), 7.21 (d,2H, J=8.7 Hz), 7.84 (d, 2H, J=8.9 Hz).

Synthesis of leuco 2,4-bis-(4-dibutylaminophenyl)-3-methylamine-cyclobutenone (6):
2,4-Bis-(4-dibutylaminophenyl)-3-chloride-cyclobutenone (153 mg, 0.3 mmole) and ***n***-methylamine (46.6 mg, purity. 40 %, 0.6 mmole) were dissolved in dichloromethane (7 ml). The reaction mixture was stirred at room temperature for 4 hours and the same experimental procedure was followed to synthesis 1. The product was obtained as a liquid (83 mg, 55 %, Oily). Mass Spectrum (FAB): found M = 503; required for $C_{33}H_{49}N_3O$, M = 503. ^1H NMR (300 MHz, $CDCl_3$): 0.97 (t, 12H, J=7.3 Hz), 1.25 (m, 8H), 1.60 (quint, 8H, J=7.2 Hz), 3.32 (t, 8H, J=7.5 Hz), 3.49 (s, 3H), 4.30 (s, H), 5.30 (s, H), 6.67 (dd, 4H, J=9.5 Hz), 7.47 (dd, 4H, J=9.5 Hz).

Synthesis of leuco 2,4-bis-(4-dibutylaminophenyl)-3-ethylamine-cyclobutenone (7):
2,4-Bis-(4-dibutylaminophenyl)-3-chloride-cyclobutenone (100 mg, 0.2 mmole) squaraine and n-ethylamine (26 mg, purity. 70 %, 0.4 mmole) was dissolved in dichloromethane (5 ml). The reaction mixture was stirred at room temperature for 4 hours and the same experimental procedure was followed to synthesis 1. The product was obtained as a liquid (62 mg, 60 %, Oily). Mass Spectrum (FAB): found M = 517; required for $C_{34}H_{51}N_3O$, M = 517. ^1H NMR (300 MHz, $CDCl_3$): 0.93 (m, 12H,), 1.11(t, 3H, J=7.2 Hz), 1.32 (m, 8H), 1.53 (m, 8H), 3.24 (m, 10H), 4.51 (s, H), 5.45 (s, H), 6.59 (d, 2H, J=8.7 Hz), 6.63 (d, 2H, J=8.6 Hz), 7.10 (d, 2H, J=8.7 Hz), 7.37 (d, 2H, J=8.6 Hz).

Synthesis of leuco 2,4-bis-(4-dibutylaminophenyl)-3-butylamine-cyclobutenone (8):
2,4-Bis-(4-dibutylaminophenyl)-3-chloride-cyclobutenone (760 mg, 1.5 mmole) and butylamine (220 mg, 3 mmole) were dissolved in dichloromethane. Reaction mixture was stirred in dichloromethane for 4 hours and the same experimental procedure was followed to synthesis 1. The product was obtained as a liquid (0.49 g, 60 %, Oily). Mass Spectrum (FAB): found M = 546; required for $C_{36}H_{55}N_3O$, M = 546.^1H NMR (300 MHz, $CDCl_3$): 0.82 (t, 3H, J=7.2 Hz), 0.93 (t, 12H, J=7.2 Hz), 1.35(m, 10H), 1.53 (m, 10H), 3.23 (quart, 10H, J=7.9 Hz), 4.50 (s, H), 5.30 (s, H), 6.58 (d, 2H, J=8.6 Hz), 6.63 (d, 2H, J=8.6 Hz), 7.1 (d, 2H, J=8.6 Hz), 7.38 (d, 2H, J=8.1 Hz).

4. Conclusions

Although the 1,3-bis(4-aminoaryl)squaraines showed no pH-induced color change behavior, they were found to undergo reduction with sodium borohydride in solution to give colorless leuco compounds, which oxidized readily in air back to the colored squaraine dye. This color-change redox behavior has potential in the area of peroxidase-based bioassays. Thus the hydroxy group could be reacted with phosphorous oxychloride or thionyl chloride to give chloro-leuco derivatives. The susceptibility of the chorine atom towards nucleophilic substitution in the last group of compounds was demonstrated by their facile reaction with alkylamines to give amino-leuco squaraines. The discovery of the facile synthesis of the leuco squaraine system and the demonstration that the leuco

compounds can undergo a wide range of chemical inter-conversions and then be oxidized back to a squaraine system, opens up many possibilities for synthesing new types of squaraine dye not accessible by existing chemical routes.

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