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# Novel synthesis of ketocyanine dyes

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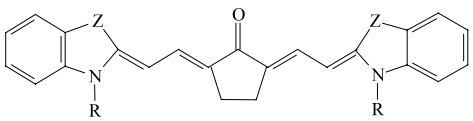
**Abstract**—New one-step synthesis of ketocyanine dyes is presented. The dyes obtained expose spectral changes in pH range from 1.7 to 4.3 and their protonated forms absorb at 715–750 nm. © 2001 Published by Elsevier Science Ltd.

The development of optical sensors working in the near-infrared (NIR) region of the spectra causes growing interest in design and synthesis of NIR-absorbing pH-sensitive dyes.[1]

In that sense poorly examined ketocyanine dyes of general structure **1** (Fig. 1) seem to be promising chromophores for using in optical fibre techniques.

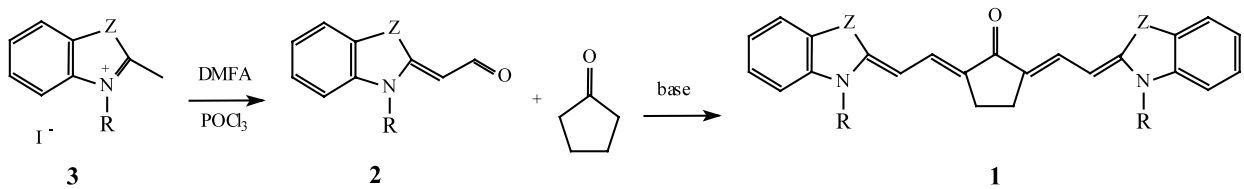


**1**

**Figure 1.**

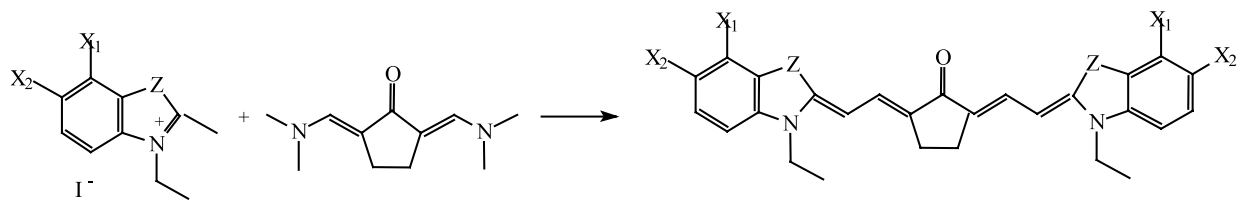
Some of these dyes with unsubstituted benzene rings were synthesised by condensation of heterocyclic aldehydes **2** with cyclic ketones.[2] This route requires prepreparation of aldehydes **2** by Vilsmeier–Haak formylation of quaternary salts of the corresponding heterocycles **1** (Scheme 1), which is rather troublesome in the presence of some substituents, namely hydroxy- or acetylamino groups in benzene rings. Dyes containing such functional groups are of special interest because they can be covalently attached to a suitable matrix.

We found that ketocyanines of this type can be synthesised directly from salts **3** by their coupling with easily available 2,3-bis(dimethylaminomethylene)cyclopentanone[3] **4** in boiling pyridine[4] (Scheme 2).[4]




**3** **2** **1**

**Scheme 1.**



**3a-f** **4** **5aa-ff**

**Scheme 2.**

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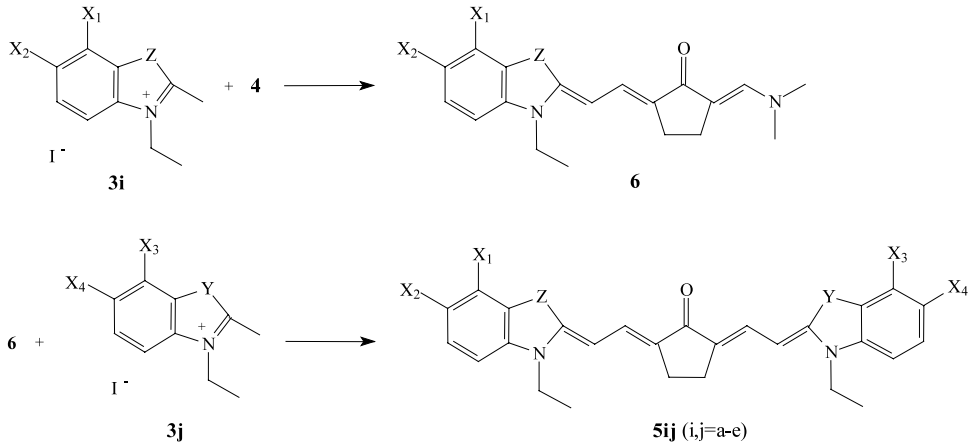


**Scheme 3.**

**Table 1.** Synthesised dyes, maximum absorbance wavelengths, p$K_a$ values and yields

| Dye | Z | Y | $X_1$ | $X_2$ | $X_3$ | $X_4$ | $\lambda_{max}$ (nm) | p$K_a$ | Yield (%) |
|---|---|---|---|---|---|---|---|---|---|
| **5aa** | $C(CH_3)_2$ | $C(CH_3)_2$ | H | H | H | H | 717.0 | 3.0 | 73 |
| **5bb** | $C(CH_3)_2$ | $C(CH_3)_2$ | H | OH | H | OH | 747.0 | 2.0 | 72 |
| **5cc** | $C(CH_3)_2$ | $C(CH_3)_2$ | H | $NHCOCH_3$ | H | $NHCOCH_3$ | 742.0 | 3.5 | 75 |
| **5dd** | S | S | H | H | H | H | 743.0 | 4.3 | 65 |
| **5ee** | $C(CH_3)_2$ | $C(CH_3)_2$ | $-(CH=CH)_2-$ | | $-(CH=CH)_2-$ | | 750.0 | 2.9 | 73 |
| **5ff** | $C(CH_3)_2$ | $C(CH_3)_2$ | OH | $COOC_2H_5$ | OH | $COOC_2H_5$ | 717.0 | 2.0 | 58 |
| **5ab** | $C(CH_3)_2$ | $C(CH_3)_2$ | H | H | H | OH | 731.5 | 3.4 | 52 |
| **5ac** | $C(CH_3)_2$ | $C(CH_3)_2$ | H | H | H | $NHCOCH_3$ | 729.5 | 2.7 | 56 |
| **5ad** | $C(CH_3)_2$ | S | H | H | H | H | 725.5 | 3.8 | 62 |
| **5ae** | $C(CH_3)_2$ | $C(CH_3)_2$ | H | H | $-(CH=CH)_2-$ | | 733.0 | 2.9 | 61 |
| **5bc** | $C(CH_3)_2$ | $C(CH_3)_2$ | H | OH | H | $NHCOCH_3$ | 744.0 | 1.7 | 75 |
| **5bd** | $C(CH_3)_2$ | S | H | OH | H | H | 745.5 | 3.4 | 52 |
| **5be** | $C(CH_3)_2$ | $C(CH_3)_2$ | H | OH | $-(CH=CH)_2-$ | | 748.5 | 3.8 | 68 |
| **5cd** | $C(CH_3)_2$ | S | H | $NHCOCH_3$ | H | H | 741.0 | 2.9 | 67 |
| **5ce** | $C(CH_3)_2$ | $C(CH_3)_2$ | H | $NHCOCH_3$ | $-(CH=CH)_2-$ | | 745.5 | 3.6 | 62 |
| **5de** | $C(CH_3)_2$ | S | $-(CH=CH)_2-$ | | H | H | 744.0 | 3.3 | 61 |

Furthermore, we observed that our method allows us to obtain unsymmetrical dyes with different terminating nuclei by consequent addition of corresponding salts **3** to reagent **4** avoiding isolation of intermediate product **6**[5] (Scheme 3). Yields, spectral characteristics and p$K_a$ values in ethanol are presented in Table 1.

The protonated form of dyes **5** have highly intensive absorbances in the NIR region. Fig. 2 shows the vis–NIR spectrum of dye **3a** as the pH is changed from 2.4 to 7.3.

Experiments showed complete reversibility of spectral changes that should enable future use of these dyes as pH-sensitive components of optical sensors.

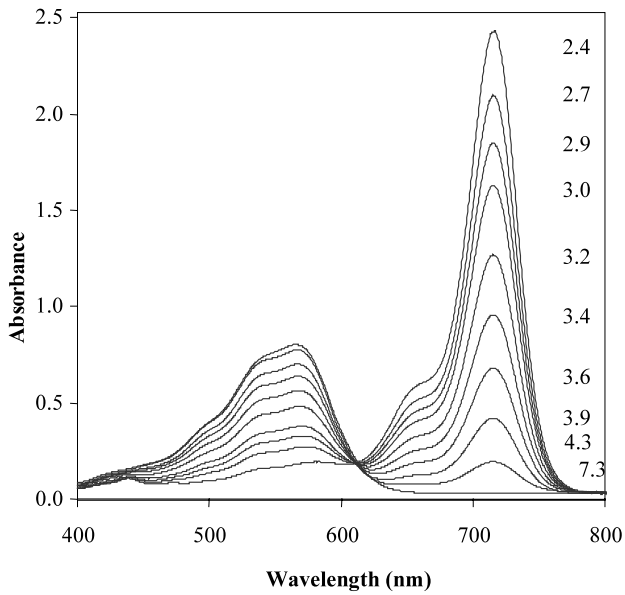


**Figure 2.** Absorbance spectra of dye **5aa** at indicated pH values.

## Acknowledgements

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4. Representative procedure for **5aa**: 630 mg (2 mmol) of **3a** and 194 mg (1 mmol) of **4** in 10 ml of pyridine were heated at reflux for 1 hour. After cooling, the mixture was diluted with 100 ml of water and the solid separated was filtered out, dried and recrystallized from methanol. Yield 384 mg (73%). $\varepsilon$ acid $=2.52\times10^5$, $^1$H NMR (250 MHz, DMSO-$d_6$): $\delta$ pm, $J$ Hz; 1.22 (t, $J=7.0$ Hz, 6H), 1.58 (s, 12H), 2.68 (s, 4H), 3.79 (q, $J=7.0$ Hz, 4H), 5.37 (d, $J=13.2$ Hz, 2H), 6.83–7.28 (m, 8H), 7.52 (d, $J=13.2$ Hz, 2H). Anal. calcd for $C_{33}H_{38}N_2O$; C, 82.80; H, 8.00; N, 5.85. Found: C, 82.28; H, 8.06; N, 5.86. MALDI $m/z$ 478.3 ($M^+$, 100), 479.3 ($M^+$+H, 57).
5. Representative procedure for **5ad**: 305 mg (1 mmol) of **3d** and 194 mg (1 mmol) of **4** in 10 ml of pyridine were heated at reflux for 1 hour. After addition of 315 mg of **3a**, heating was continued for a further hour. The reaction mixture was worked up as for dye **3aa**. Yield 290 mg (62%). $\varepsilon$ acid $=2.51\times10^5$, $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ pm, $J$ Hz; 1.16 (t, $J=7.0$ Hz, 3H), 1.22 (t, $J=7.0$ Hz, 3H), 1.55 (s, 6H), 2.64 (br s, 4H), 3.79 (q, $J=7.0$ Hz, 2H), 4.02 (q, $J=7.0$ Hz, 2H) 5.38 (d, $J=12.5$ Hz, 1H), 5.53 (d, $J=13.0$ Hz, 1H), 6.91–6.93 (m, 2H), 6.99 (d, $J=12.6$ Hz, 1H), 7.05–7.35 (m, 5H), 7.47 (d, $J=13.0$ Hz, 1H), 7.62 (d, $J=7.6$ Hz, 1H). Anal. calcd for $C_{30}H_{32}N_2OS$; C, 76.89; H, 6.88; N, 5.98; S, 6.84. Found: C, 75.93; H, 6.66; N, 5.94; S, 6.70. MALDI $m/z$ 468.2 ($M^+$, 100), 469.2 ($M^+$+H, 83).