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Syntheses of cyanines: a review

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1. Introduction

Cyanine dyes came to the limelight during 1856 for their application in the field of photography and have now received wide attention due to their applications in photodynamic therapy.[1] *Cyanine dyes* (a class of *polymethine dyes*) are planar, conjugated, open-chain (sometimes ring) systems of sp^2-hybridized carbon atoms with an odd number of methine groups and an even number of π electrons according to the general formula:

$$X-(CR)_n-X'$$

with n=1, 3, 5, …; R=H or substituents;

Abbreviations: BSA, bovine serum albumin; α-CD, α-cyclodextrin; DBF, di-*n*-butylformamide; DBHT, di-*O*-benzoyl hydrogen tartrate; DCC, dicyclohexylcarbodiimide; DIEA, diisopropyl ethylamine; DMF, dimethyl formamide; DMSO, dimethyl sulphoxide; DPFA, *N*,*N*′-diphenylformamidine; DSSC, dye-sensitized solar cell; DVD-R, recordable digital versatile disk; IPCE, incident photon-to-current conversion efficiencies; NHS, *N*-hydroxysuccinamide; NIR, near-infrared; NMR, nuclear magnetic resonance; PEG, polyethylene glycol; pip, piperidine; rt, room temperature; TO, thiazole orange; UV–vis, ultra violet-visible.

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X and X′=terminal chain atoms (e.g., N, O, P, S) or atom groups (e.g., NR_2, CH=O).

These are usually called *cyanine dyes* with X=X′=N and represented by vinylogous amidinium salts; *oxonol dyes* with X=X′=O and represented by vinylogous carboxylate salts; and *merocyanine dyes* with X=N and X′=O and represented by vinylogous carboxamides.

Together with *aromatics* and *polyenes*, *polymethines* (cyanines) belong to a particular group or organic compounds with conjugated π-systems, which can be advantageously classified by the *triad system*, introduced by Dänhe et al.,[2] which describes the common and the different electronic properties, such as delocalization energy and polarizability, as well as π-electron densities and bond-length alternation along the polymethine chain of these three archetypal π-systems. The chromophoric stereochemical alignment is usually *transoid*, which leads to stability due to attenuation of steric hindrance. However, cis–trans isomerization has also been observed, under some specific conditions.[3]

This class of dyes, besides having applications in photography and photodynamic therapy, possesses versatile applications in inorganic large band-gap semiconductor materials,[4–6] laser materials,[7] light harvesting systems of photosynthesis[8] and photovoltaics,[9] photorefractive materials,[10–13] as fluorescence probes for monitoring photochemically initiated polymerization,[14] as antitumor agents,[15–19] in optical data storage,[20] in organic solar cells,[21] proteomics,[22] and biomolecular labeling.[23–27] Of particular interest are molecules that can reversibly switch between a nonemissive and an emissive state. Some representative examples are fluorogenic unsymmetrical cyanine dyes, which become fluorescent upon interaction with specific proteins,[28] and photochromic compounds,[29] which can undergo a reversible change in their optical properties under illumination. Such dynamic systems can find valuable applications as fluorescent supramolecular devices, for the design of smart materials.[30]

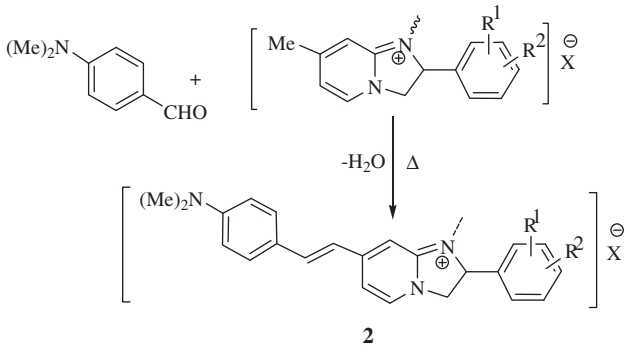
2. Synthesis of cyanine dyes

A number of synthetic procedures for polymethine dyes of diverse molecular structure have been reported in the literature.[31–34] Synthetic processes have been proposed extensively for monomethines,[35–41] dimethines,[42–46] trimethines,[47–50] tetramethines,[51] pentamethines,[52–56] heptamethines,[57–59] squarylium cyanines,[60–64] and various other cyanine dyes.[65–67]

2.1. Synthesis of non-chiral polymethine cyanine dyes

2.1.1. Synthesis in organic medium. Generally, for the generation of a methine dye, the prestruct has a synthon component containing a methylene group activated by a quaternized nitrogen atom and another component having a carbonyl group with an auxochrome. By using this strategy, large numbers of styryl pyridinium dyes (**1**) have been synthesized with varying alkyl chains R and electron-donating groups Y. (Scheme 1).[68]

Fused pyridinium ring systems, such as substituted quaternary imidazo[1,2-*a*]pyridinium salts were condensed with 4-(dimethylamino)benzaldehyde in the presence of 1-butanol and piperidine (pip) as base at reflux temperature by Yarmoulk et al.[69] to obtain a fluorophore probe (**2**) for the study of the behavior of nucleic acid and bovine albumin serum (BSA) proteins (Scheme 2).



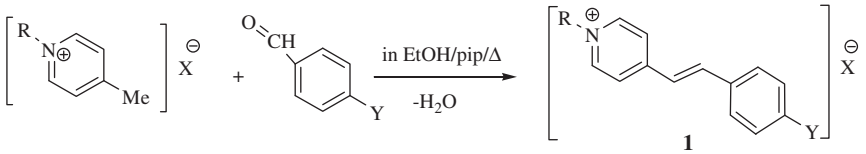
2

Scheme 2.

An extended series of mono- and bis-cyanine dyes with mono- and trimethine chains were prepared by Shindy et al. (Scheme 3).[70] The synthon components were *p*-chloranil (**3**) and 4-amino-5-(hydroxy, mercapto, or imino)-3-methyl-1-phenylpyrazole (**4a**–**c**), taken in 1:2 molar ratios to afford (**5a**–**c**) as the stationary material for all the dyes. To introduce heterocyclic auxochromes, methylene groups are activated in (**5a**–**c**) by quaternizing the molecule with iodoethane to produce (**6a**–**c**) and (**7a**–**c**). The reactions were carried out using piperidine as the base and iodoethane quaternary salts of pyridine, quinoline and isoquinoline (**8**) in ethanol at suitable places to yield monomethine dyes (**9a**–**e**), bismonomethine dyes (**10a**–**e**) and (**11a**–**e**), trimethine dyes (**12a**–**e**) and bis-trimethine dyes (**13a**–**e**).

An isoxazole unit was fused to the pyrazolidinone (**14**) to afford a biheterocyclic compound (**16**) through (**15**). The pyrazolo-isooxazole derivative has been used as a starting material for the synthesis of some photosensitizer trimethines (**17a**–**e**), monomethine mixed cyanines (**18a**–**c**), monomethines (**19a**–**c** and **20a**–**c**), and azamethine cyanines (**21a**–**c**) (Scheme 4).[71]

Imide functional groups are important structural constituents in pigment dyestuffs because these functional groups form hydrogen-bonded networks, which contribute to the high lattice energies, providing the desired insolubility of pigment particles. Some monomethine dyes, (**24**–**27**) and (**30**–**32**), with these characteristics have been prepared by condensation of the CH acidic heterocycles, 4-alkyl-2,6-dioxo-1,2,5,6-tetrahydropyridine-3-carbonitrile (**22**), and barbituric acid (**29**), with electron-rich thiophene aldehydes (**23a**–**c**) and benzaldehyde derivatives.[72] The formylation of (**22**) and (**29**) with *N*,*N*′-diphenylformamidine or *N*,*N*-di-*n*-butylformamide in acetic anhydride and further reaction with 4-picolinium salts engendered the dimethine dyes (**28**) and (**33a**,**b**) (Schemes 5 and 6).



1

pip = piperidine

Scheme 1.