Synthesis of different classes of five/six membered heterocyclic cyanine dyes: A review

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In this paper, synthesis of different classes of five/six membered heterocyclic cyanine dyes has been reviewed. In this paper review detailed synthesis steps were represented via equations. The synthesis covers, monomethine cyanine dyes (simple cyanine dyes), dimethine cyanine dyes, trimethine cyanine dyes (carbocyanine dyes), styryl cyanine dyes (hemicyanine dyes), azastylr cyanine dyes (aza-hemicyanine dyes and/or aza-cyanine dyes), merocyanine dyes (acyclic merocyanine dyes and cyclic merocyanine dyes) and apocyanine dyes. Besides, in the introduction section of this review paper some light is focused on the uses, applications and properties of cyanine dyes. This review paper is informative, useful and very readable for synthetic dye chemists, researchers and students who look for the different methods in the synthesis and preparation of various classes of five/six membered heterocyclic cyanine dyes with special emphasize in the field of heterocyclic and/or cyanine dyes chemistry. This specific type of collective review in the synthesis of different classes of only five/six membered heterocyclic cyanine dyes has been paid little attention and has great importance in the chemistry literature.

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Capsule Summary: Synthesis of different classes of five/six membered heterocyclic cyanine dyes have been reviewed.


INTRODUCTION

Much and much attention and have been paid to the chemistry of cyanine dyes (Shindy, 2014; Shindy, 2015; shindy, 2015a; Shindy, 2012; Yagupolski et al., 2008; Volkova et al., 2008; Volkova et al., 2007; Xu et al., 2007; Yashchuk et al., 2007; Boto et al., 2008; Gadjev et al., 1999; Fasiulla et al., 2008; Deligeorliev et al., 1998; Shindy, 2016; Shindy, 2017; Kovalska et al., 2010; Kabac et al., 2010; Yakubovskiy et al., 2010; Klochko et al., 2010; Matsuoka, 1990). This is because the extraordinarily uses and applications of these dyes in a broad and diverse area, such as biology, biotechnology, biochemistry, physics, engineering, pharmacology and medicine. In more than one century's time (In 1873) Vogel discovered that dye had spectrum sensitization added function (Hamer, 1964). From this time, the synthesis, development and application of the spectrum sensitization additive dyes (mainly refers to cyanine dyes) have made the important contribution to the photosensitize material industry. Now, the spectrum sensitization additive dyes was still one essential photography organic matter of kinds new variety photosensitive material.
Scheme 1: Synthesis of dimethine cyanine dyes and their cyclocondensation reactions with urea.

Substituents in Scheme 1: 
{(1a-g): (2a-g): Y = O; X = H (a), ρ.OCH₃ (b), ρ.NO₂ (c), o.NO₂ (d), m.NO₂ (e), OH (f); Y = NH; X = H (g). (3a-h): Y = O; X = H, A = H-2yl salt (a); X = H, A = C₆H₄-2-yl salt (b); X = ρ.OCH₃, A = C₆H₄-2yl salt(c); X = ρ.NO₂, A = C₆H₄-2-yl salt(d); X = o.NO₂, A = C₆H₄-2-yl salt (e); X = m.NO₂, A = C₆H₄-2-yl salt (f); X = ρ.OH, A = C₆H₄-2-yl salt (g); Y = NH; X = H, A = C₆H₄-2-yl salt (h). (5a-d): Y= O; X = H (a), ρ.OCH₃ (b), m.NO₂ (c); Y = NH; X = H (d). (4a-e): Y = O; X = H, A = H-2yl salt (a), X = H, A = C₆H₄-2-yl salt (b), X = ρ.OCH₃, A = C₆H₄-2-yl salt(c), X = m.NO₂, A = C₆H₄-2-yl salt (d); Y = NH, X = H, A = C₆H₄-2-yl salt (e)}
Scheme 2: Synthesis of monomethine and trimethine cyanine dyes.

Substituents in Scheme 2: (6a-c); (8a-c); (9a-c); (11a-c): R = H (a), OCH₃ (b), NO₂ (c). (10a-e): R = H, A = H-4-yl (a); R = H, A = C₆H₄-4-yl (b); R = H, A = C₆H₄-1-yl (c); R = OCH₃, A = C₆H₄-4-yl (d); R = NO₂, A = C₆H₄-4-yl (e). (12a-e): R = H, A = H-2yl (a); R = H, A = C₆H₄-2-yl (b); R = H, A = H-4-yl (c); R = OCH₃, A = C₆H₄-2-yl (d); R = NO₂, A = C₆H₄-2-yl (e).
Scheme 3: Synthesis of dimethine, dimethine/aza-styryl mixed and styryl/aza-styryl mixed cyanine dyes.

Substituents in Scheme 3: (13a – c), (14a – c), (17a – c): X = ρ.Cl (a), ρ.NO2 (b), ρ.N(CH3)2 (c). (15a – f): X = ρ.Cl, A = 1-ethyl quinolinium-2-yl salt (a); X = ρ.Cl, A = 1-ethyl pyridinium-2-yl salt (b); X = ρ.N(CH3)2, A = 1-ethyl quinolinium-2-yl salt (c); X = ρ.N(CH3)2, A = 1-ethyl pyridinium-2-yl salt (d); X = ρ.NO2, A = 1-ethyl quinolinium-2-yl salt (e); X = ρ.NO2, A = 1-ethyl pyridinium-2-yl salt (f); (16a – f): X = ρ.Cl, A = 1-ethyl quinolinium-2-yl salt (a); X = ρ.NO2, A = 1-ethyl quinolinium-2-yl salt (b); X = ρ.OH, A = 1-ethyl quinolinium-2-yl salt (c); X = ρ.OCH3, A = 1-ethyl quinolinium-2-yl salt (d); X = ρ.OCH3, A = 1-ethyl quinolinium-2-yl salt (e); X = ρ.NO2, A = 1-ethyl pyridinium-2-yl salt (f). (18a – f): X = ρ.Cl, R = ρ.NO2 (a); X = ρ.Cl, R = ρ.N(CH3)2 (b); X = ρ.NO2, R = ρ.NO2 (c); X = ρ.NO2, R = ρ.N(CH3)2 (d); X = ρ.N(CH3)2, R = ρ.NO2 (e); X = ρ.N(CH3)2, R = ρ.N(CH3)2 (f).
Scheme 4: Synthesis of monomethine, trimethine and aza-styryl cyanine dyes.

Substituents in Scheme 4: (21a-c), (22a-c), (25a-c): \( R = H \) (a); \( \text{OCH}_3 \) (b); \( \text{NO}_2 \) (c). (23a-d): \( R = H, \alpha \)-nitroso-\( \beta \)-2327naphthol (a); \( R = \text{OCH}_3, \alpha \)-nitroso-\( \beta \)-naphthol (b); \( R = \text{NO}_2, \alpha \)-nitroso-\( \beta \)-naphthol (c); \( R = \text{OCH}_3, \beta \)-nitroso-\( \alpha \)-naphthol (d); (24a-e): \( R = H, A = \text{N-ethyl quinolin-4-iium salt} \) (a); \( R = \text{OCH}_3, A = \text{N-ethyl quinolin-4-iium salt} \) (b); \( R = \text{NO}_2, A = \text{N-ethyl quinolin-4-iium salt} \) (c); \( R = \text{OCH}_3, A = \text{N-ethyl isoquinolin-1-iium salt} \) (d); \( R = \text{NO}_2, A = \text{N-ethyl quinolin-4-iium salt} \) (e). (26a-e): \( R = H, A = \text{1-ethyl quinolin-2-iium salt} \) (a); \( R = \text{OCH}_3, A = \text{1-ethyl pyridin-2-iium salt} \) (b); \( R = \text{OCH}_3, 23\text{s} \) \( A = \text{1-ethyl quinolin-4-iium salt} \) (c); \( R = \text{OCH}_3, A = 27 \text{1-ethyl pyridin-4-iium salt} \) (d); \( R = \text{NO}_2, A = \text{1-ethyl quinolin-2-iium salt} \) (e).
Therefore, it continuously received the attention in the research of the synthesis and applications both in domestic and in a broad. In addition, cyanine dyes have been used on new techniques in molecular imaging because of their usefulness in biological, medical and clinical research. Fluorescence imaging methods are generally superior in terms of sensitivity, selectivity and ease of use. Cyanine dyes have been employed as fluorescent labels in fluorescence imaging studies of biological mechanism, as important signaling molecule involved in the regulation of a wide range of physiological and pathophysiological mechanisms and many disorders. Besides, polymethine cyanine dyes have many technology application areas such as forgery prevention, photoresists, spectrally sensitized photographic materials, thermal transfer printing and heat shielding materials. A number of publications published recently are also highlighting the importance of cyanine dyes.
Scheme 6: Continue...
Scheme 7: Synthesis of monomethine cyanine dyes.

Substituents in Scheme 7: (41a – e); (42a – e); (44a – e); (45a – e); (46a – e): X(A): N-ethyl-1-H-pyrazoline, R = H (a), \( \rho \text{OCH}_3 \) (b), \( \rho \text{NO}_2 \) (c), N-ethyl-1-phenyl-pyrazoline, \( R = \rho \text{OCH}_3 \) (d); N-ethyl-oxazoline, \( R = H \) (e). (43a – g): X(A): N-ethyl-1-phenyl pyrazoline, \( R = H \) (a), \( \rho \text{OCH}_3 \) (b), \( \rho \text{NO}_2 \) (c); o.OH (d), p.OH (e); N-ethyl-1-H-pyrazoline, \( R = H \) (f); N-ethyl oxazoline, \( R = H \) (g).

The synthesis, properties and applications of cyanine dyes reflect the important and vital position of these dyes in the chemistry of dyes and pigments (Shindy et al., 2015; Soriano et al., 2016; Shindy 2017a; Shindy et al., 2017; Shindy 2016a; Shindy et al., 2016; Shindy et al., 2016a; Shindy et al., 2016b; Shindy et al., 2016c; Shindy et al., 2017a; Komljenovic et al., 2016; Zhang et al., 2016; Chen et al., 2016; Arjona et al., 2016; Shindy 2018; Shindy 2018a; Shindy et al., 2018a; Shindy et al., 2019; Shindy et al., 2020).

Synthesis of different classes of five/six membered heterocyclic cyanine dyes

Dimethine cyanine dyes were prepared by the condensation of 4-benzylideno-oxazol- / imidazol-5-one-2-carboxaldehyde derivatives with 2-methyl pyridinium (quinolinium)-2-yl salts. Cyclocondensation reaction of these dyes with urea gave new asymmetrical oxazolo(imidazo)[4,5-d]-pyrimidine-2(2H)-dimethine cyanines (Koraieim, et al., 1991), Scheme (1).

Derivatives of 6-amino-5-cyano-3-methyl-1,4-diarylpymaro[2,3-c]pyrazole were prepared via the reaction of \( \alpha \)-\( \beta \)-unsaturated nitriles with 3-methyl-1-phenyl-pyrazole-5-one as starting materials in the synthesis of new asymmetrical mono-(tri-)methylene cyanine dyes (Abd El Aal et al., 1998), Scheme (2).

A number of photosensitizers asymmetrical dimethine and styryl cyanine dyes having pyrazolo pyran nucleus were synthesized (Hassan et al., 1991), Scheme (3).

Oxazolo[1,2-a]quinoline derivatives were used to synthesis novel bridgehead cyanine dyes such as azamethine, monomethine and trimethine cyanines (Abd El Eal et al, 1999), Scheme (4).

A series of cyclic merocyanine dyes (27), (28) \( R_1 = H \) or lower alkyl, \( X = H \), halo, OH, alkoxyl, alkyl, \( \text{NO}_2 \). \( R_2 = \text{OH, alkoxyl, Cl} \), useful for dyeing polyester fibres orange shades, are manufactured by reaction of the corresponding 3-methyl-1-(6-methyl-2-pyrimidinyl)-5-pyrazolines with 5-methyl-2-phenyl-oxazolo-4-carboxaldehyde or aldehydes (Ioan et al., 1998), Scheme (5).
Scheme 8: Synthesis of monomethine, dimethine, dimethine base, and trimethine cyanine dyes.

Substituents in Scheme 8: (47a, b); (49a, b); (50a, b); (51a, b); (54, b); (55a, b); (56a, b): X = O (a); N-ph (b). (52a – d): X = O, Z = N+Me (a); X = N-ph, Z = N+Me (c); X = O, Z = N+Me (d). (57a – d): X = O, A = 1-methyl quinolinium-2-yl salt (a); X = N-ph, A = 1-methyl pyridinium-2-yl salt (b); X = N-ph, A = 1-methyl quinolinium-2-yl salt (c); X = N-ph, A = 1-methyl pyridinium-4-yl salt (d).
4-Aryl-1,2,3,4,5,6-hexahydroimidazo[4,5-d]pyrimidine-2,6-diones were prepared and used to obtain (with quinaldine or picoline ethiodides) 6-mononmethine, 2,6-bis mononmethine, 6-trimethine and 2,6-bis trimethine cyanine dyes (Koraiem et al., 1998), Scheme (6).

A number of photosensitizers mononmethine cyanine dyes incorporating pyrazolino and/or oxazolino nuclei were synthesized (Koraiem et al., 1990), Scheme (7). Different types of 2(3)-oxazolino(pyrazolino)-[4,3-d] quinoline-2(4)-methine cyanine dyes including mononmethine, dimethine and trimethine cyanines were prepared (El-Hamad et al., 1994), Scheme (8). 4,5-dioxo-3-methyl-1-phenyl-pyrazoline is condensed with α-picoline-EtI, quinaldine-EtI or 2-methyl benzoazole-EtI to form mononmethine derivatives, which is then brominated and finally cycondensed with hydrazines, hydroxylamine or with thiourea to give apocyanine dyes (Koraiem, 1984), Scheme (9).

Monomethine, B-substituted dimethine and styryl cyanine dyes were synthesized using oxonium salts (Abd El Aal, et al., 2005), Scheme (10).

A series of dimethine cyanine dyes, acyclic merocyanine dyes and cyclic merocyanine dyes containing pyrazine and/or oxazine nucleus were synthesized (Abu El Hamd and Koraiem, 1990), Scheme (11). A series of different mononmetnine cyanine dyes containing thiazole and/or pyridine nucleus were prepared (Koraiem et al., 1995), Scheme (12).

Dimethine cyanine dyes (Koraiem et al., 1996) containing thiazole and/or pyridine nucleus were synthesized (Scheme 13). A series of mononmethine cyanine dyes and trimethine cyanine dyes having pyrazolo/

oxadiazine nucleus were prepared (Eissa, 2009) (Scheme 14).

**CONCLUSIONS**

The structures of any cyanine dyes are characterized by the presence of at least two essential centers. The first one is the basic center which have the responsibility of pushing electrons across the conjugated chromophoric group system of the dyes molecules, and the second one is the acidic center which have the responsibility of pulling electrons across the conjugated chromophoric group system of the dyes structures, and vice versa, Scheme (15). These push-pull system in the dyes structures have the reason and/ or the responsibility for the intensity of the colour of cyanine dyes, where they leads to the formation of two mesomeric electronic transitions structures (two resonance forms) (A) and (B) inside the dyes molecules producing a delocalized positive charge over the conjugated chromophoric group system of the dyes structures, Scheme (15).

The synthesis and/or the preparation methods of cyanine dyes usually carried out through using a number of active heterocyclic quaternary salts residue, Scheme (16).

The most common active heterocyclic quaternary salts used in the preparation of cyanine dyes (Scheme 16) are as follows:

- a-N-iodomethane and/or N-idoethane quaternary salts of 2-picoline, quinaldine, 4-picoline and/or lepidine,
- b- N-iodomethane and/or N-idoethane quaternary salts of 2-methylthiazole, 2-methyl benzothiazole, 2-methyl oxazole, 2-methyl benzoazole, 2-methyl selenazole, 2-methyl benzoselenazole, 2-methyl imidazole and/or 2-methyl benzoimidazole.
Scheme 10: Synthesis of monomethine, styryl and dimethine cyanine dyes.

Substituents in Scheme 10: (62a, b); (63a, b): Z = 1-methyl-4(2-propenyl)cyclohexen-1,5-diene (a); cyclohexene (b). (64a, b): Z = 1-methyl-4(2-propenyl)cyclohexen-1,5-diene, X = CH3 (a); Z = cyclohexene, X = CH3 (b). (65a, b): Z = 1-methyl-4(2-propenyl)cyclohexen-1,5-diene, R = OH (a); Z = cyclohexene, R = OH (b). (66a-d): Z = 1-methyl-4(2-propenyl)cyclohexen-1,5-diene, X = CH3, A = 1-ethylpyridine-2-ium (a); Z = 1-methyl-4(2-propenyl)cyclohexen-1,5-diene, X = CH3, A = 1-ethylpyridine-2-ium (b); Z = 1-methyl-4(2-propenyl)cyclohexen-1,5-diene, X = CH3, A = 1-ethylpyridine-4-ium (c); Z = 5-cyclohexene, X = CH3, A = 1-ethylquinolin-2-ium (d). (67a, b): Z = 1-methyl-4(2-propenyl)cyclohexen-1,5-diene, R = OH (a); Z = cyclohexene, R = OH (b).
Scheme 11: Synthesis of dimethine, acyclic merocyanine and cyclic merocyanine dyes.

Substituents in Scheme 11: (69a, b); (70a, b): X = O (a); NH (b). (72a – e): X = O, Z = N, A = 1-ethyl pyridinium-2yl salt (a); X = O, Z = N, A = 1-ethyl quinolinium-2yl salt (b); X = O, Z = N, A = 1-ethyl pyridinium-4yl salt (c); X = NH, Z = N, A = 1-ethyl quinolinium-2yl salt (d); X = NH, Z = N, A = 1-ethyl quinolinium-2yl salt (e). (74a – i): X = CH₃, R = C₆H₅ (a); X = CH, R = C₆H₄-p.OCH₃ (b); X = CH, R = C₆H₄-p.OH (c); X = CH, R = C₆H₄-p.N(NH)₂ (d); X = CH, R = C₆H₄-o.OH (e); X = CH, R = C₆H₄-p.OH.m.OCH₃ (f); X = CH, R = C₆H₄O (g); X = N, R = C₆H₄-p.OH (h); X = N, R = C₆H₄-p.N(CH₃)₂ (i). (75a, b): R = COCH₃ (a); COOEt (b).
c- N-iodomethane and/or N-iodoethane quaternary salts of pyridine, quinoline and/or isoquinoline,
d-N-iodomethane and/or N-iodoethane quaternary salts of thiazole, benzothiazole, oxazole, benoxazole, selenazole, benzoselenazole, imidazole and/or benzoimidazole.

4-The quaternary salts in a and b characterized by the presence of active (acidic) methyl group at 2 and/or 4 positions, while the quaternary salts in c and d characterized by the presence of active (acidic) hydrogen atom in 4, 1 and/or 2 positions, Scheme (16).

5-The activity (acidity) of the 2 (4)-methyl group in the quaternary salts of 2-picoline, quinaldine, 4-picoline and/or lepedine is related to the presence of the highly electron attracting positive charge on the quaternary nitrogen atom at position 1 of these compounds, Scheme (16).
Scheme 14: Synthesis of monomethine and trimethine cyanine dyes.

Substituents in Scheme 14: (83a, b); (84a, b); (85a, b); (86a, b); (87a, b); (88a, b): X = H (a); Ph (b).

Scheme 15: Structure and colour intensity illustration of cyanine dyes.
The activity ( acidity) of the 2-methyl group in the quaternary salts of 2-methyl thiazole, 2-methyl oxazole, 2-methyl selenazole and/or 2-methyl imidazole is related to the presence of the highly electron attracting positive charge on the quaternary nitrogen atom at position 3 of these compounds in addition to the electron pulling characters of the hetero atom present, Scheme (16).

7-The activity ( acidity) of the 2-methyl group in the quaternary salts of 2-methyl benzothiazole, 2-methyl benzoxazole, 2-methyl benzoselenazole and/or 2-methyl imidazole is related to the presence of the highly electron attracting positive charge on the quaternary nitrogen atom at position 3 of these compounds in addition to the electron pulling characters of the hetero atom present and the electron attracting character of the condensed benzene ring system, Scheme (16).

8-The activity ( acidity) of the 4 (1)-hydrogen atom in the quaternary salts of pyridine, quinoline and/or isoquinoline is related to the presence of positive charge on the quaternary nitrogen atom at positions 1 and/or 2 of these compounds, Scheme (16).

9-The activity ( acidity) of the 2-hydrogen atom in the quaternary salts of thiazole, oxazole, selenazole and/or imidazole is related to the presence of the highly electron attracting positive charge on the quaternary nitrogen atom at position 3 of these compounds in addition to the electron pulling characters of the hetero atom present, Scheme (16).

10- The activity ( acidity) of the 2-hydrogen atom in the quaternary salts of benzothiazole, benzoxazole, benzoselenazole and/or benzoimidazole is related to the presence of the highly electron attracting positive charge on the quaternary nitrogen atom at position 3 of these compounds in addition to the electron pulling characters of the hetero atom present and the electron attracting character of the condensed benzene ring system (Scheme 16). Cyanine dyes also might have enhanced biological properties, which need to be tested evaluated (Abate et al., 2019; Ayare et al., 2019; Karci et al., 2013; Manjunatha et al., 2019; Mishra et al., 2019; Negm et al., 2016; Rizk et al., 2015; Rizk et al., 2017; Sadeghi-Kiakhani et al., 2019; Şener et al., 2018; Silva et al., 2018; Sun et al., 2019; Zhang et al., 2019).

**Scheme 16:** Most common active heterocyclic quaternary salts residue used in the preparation of cyanine dyes.
FUTURE PROSPECTS

The current and the future research developments aim to provide novel synthetic methods for the preparation of different classes of highly antimicrobial (antibacterial and anti-fungl) active, anti-tumor, anti-cancer, pH sensitive, highly photogaphic sensitizers, non-toxic, high stability, light fastness, near IR (Infrared), fluorescent, anti-corrosion, strong labeled DNA and extra conjugated cyanine dyes. Such as oxadiazine cyanine dyes, thiazole cyanine dyes, metal stabilized cyanine dyes, pentamethine cyanine dyes, heptamethine cyanine dyes, nonamethine cyanine dyes, undecamethine cyanine dyes and tridecamethine cyanine dyes.

Also, the current and/or the future research developments aimed to provide new, novel and/or patent review papers in the field of color, dyes and pigments chemistry. The aimed review papers will covers and/or includes topics like the origin of color, the relation between color and constitutions, synthesis of dyes, properties of dyes, classification of dyes, uses and/or applications of dyes. Also, additional important topics for the current and/or the future research developments for the aimed review papers will includes methine cyanine dyes, hemicyanine dyes (styril cyanine dyes), merocyanine dyes, apocyanine dyes, monoheterocyclic cyanine dyes, biheterocyclic cyanine dyes, polyheterocyclic cyanine dyes, six membered heterocyclic cyanine dyes, five/six membered heterocyclic cyanine dyes, five membered heterocyclic cyanine dyes and benz(naphth)/five membered heterocyclic cyanine dyes.

A very bright future for cyanine dyes chemistry can be expected through joint efforts (collaboration) of a large heterogenous community groups composed of synthetic dyes chemists, biologists, physicists, biotechnologists, pharmacologists, technological engineerists and medical scientists.

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