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Novel environmentally benign procedures for the synthesis of styryl dyes

Aleksey Vasilev [a], Todor Deligeorgiev [a,*], Nikolai Gadjev [a], Stefka Kaloyanova [a], Juan J. Vaquero [b], Julio Alvarez-Builla [b], Alejandro G. Baeza [b]

[a] University of Sofia, Faculty of Chemistry, 1, James Bourchier Avenue, 1164 Sofia, Bulgaria
[b] University of Alcalá, Faculty of Pharmacy, 28871 Alcalá de Henares, Madrid, Spain

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Abstract

A series of styrylpyridinium, styrylquinolinium and styrylbenzothiazolium dyes have been synthesized by novel environmentally benign procedures. The condensation of 4-methylpyridinium methosulphate, 2- or 4-methylquinolinium methosulphate or 2-methylbenzothiazolium methosulphate with aromatic aldehydes was performed under solvent-free conditions or microwave irradiation in the presence of different basic or acidic reagents. The chemical structures of the derived styrylcyanine dyes were confirmed by ^{1}H NMR and UV–vis spectroscopies and elemental analysis.

Keywords: Styryl dyes; Synthesis; Solvent-free; Microwave; Green chemistry

1. Introduction

Styryl dyes are widely used as sensitizers and other additives in the photographic industry [1–4]. These materials also represent an important group of biologically active compounds and are widely applied in the pharmaceutical industry [5]. In recent years, interest in the application of styrylcyanines as novel and successful fluorescent probes in numerous bioanalytical methods has grown – especially in RNA and DNA analyses [6–10]. On the other hand, the development of Green Chemistry [11–13] and the search for new environmentally friendly synthetic methods are of general importance in Organic Chemistry, especially for the chemical industry. Enhancing the efficiency of organic synthesis constitutes one of the most exciting challenges for synthetic chemists. A great deal of attention has been paid to the applications of sonochemistry and microwave dielectric heating in organic synthesis because of the enhanced reaction rates, simplified manipulation and work-up procedures and higher purity of final products. To date, however, there are a few reports in the literature that refer to the microwave acceleration of the synthesis of styryl dyes [9,14,15]. The classical synthesis of such dyes is often carried out by the reaction of 2- or 4-methyl quaternary salts and aromatic aldehydes at high temperature for a relatively longer reaction time [2] (Scheme 1), which usually leads to the formation of undesired side products, low yields and considerable power consumption.

Our previous experience [16,17] in the field of styrylcyanine synthesis and the aforementioned disadvantages of the conventional methods [2] encouraged us to devise and develop novel green, rapid and convenient procedures for the preparation of styryl dyes.

2. Results and discussion

In brief, Green Chemistry can be comprehensively defined by a set of 12 principles, which were proposed by Anastas and

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* Corresponding author. Tel.: +359 2 8161 269; fax: +359 2 9625 439.
E-mail address: toddel@chem.uni-sofia.bg (T. Deligeorgiev).

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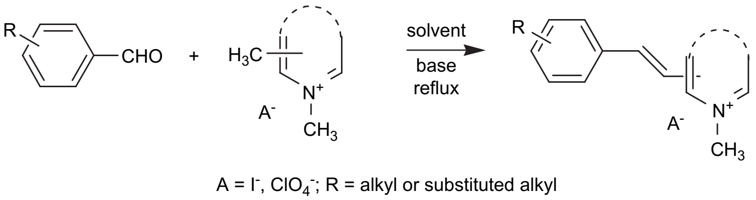


Scheme 1.

Warner [11–13]. These principles include guidelines for professional chemists concerning the creation of new substances, new syntheses and new technological processes.

In this paper, we demonstrate that some principles of Green Chemistry can be applied to the synthesis of styryl dyes using solvent-free or microwave-accelerated reaction conditions.

The synthesis of dyes **3a–3i** was carried out in solvent-free conditions (except procedure C, Section 3) by condensation of the respective aldehydes and quaternary salts in the presence of different basic reagents (or *p*-TsOH) (Scheme 2, Tables 1 and 4).

In the first reaction procedure we used sodium hydroxide as the basic reagent. The reaction proceeded at room temperature with good to moderate yields (Section 3) in solvent-free conditions with simple grinding of the initial compounds. However, attempts to react 4-methylpyridinium methosulphate **1a** with 4-(dimethylamino)-benzaldehyde **2a** to synthesize the target dye **3d**, 4-methylpyridinium methosulphate **1a** with 4-morpholinobenzaldehyde **2d** to afford the target dye **3e** and 4-methylquinolinium methosulphate **1d** with julolidinecarbaldehyde **2c** to obtain dye **3i** (see Table 1) in this manner failed. The reaction time was extended to 8 h, even then only the formation of the appropriate aldol derivative was observed (Scheme 3). It was previously reported [18] that the formation of condensation products in the synthesis of styryl dyes is highly dependent on the electron-donating properties of the appropriate substituents in the benzaldehyde moiety and on the CH-acidity of the derivatives with activated methyl groups.

In all the procedures with microwave acceleration, the reactions leading to the formation of the styryl dyes proceeded efficiently and gave excellent yields in extremely short reaction times (Tables 2–4). The conversion of the starting materials and the progress of the reactions were followed by TLC. All derived dyes were recrystallized from methanol:water = 2:1.

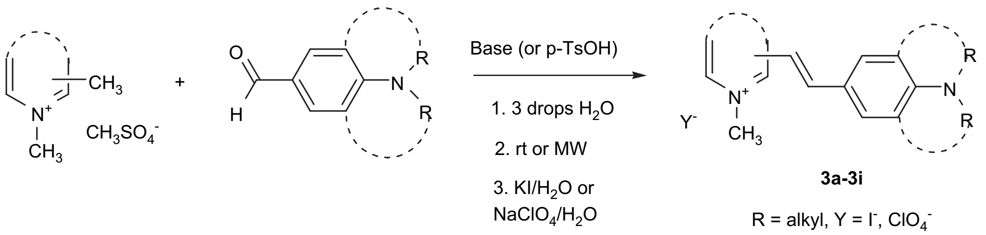
According to us the most effective catalysts are NaOH, NH_4HCO_3, $NaHCO_3$ and PPh_3, and the most ineffective one is K_2CO_3 (Tables 4 and 5). Additionally it could be pointed out that procedures B–D are more effective in comparison with procedure A, where in some cases the aldol form is the main product.

All of the synthetic procedures described here are fully consistent with the aforementioned principles of Green Chemistry.

All of the styryl dyes (**3a–3i**) synthesized are well known [2] and their structures and purities were confirmed by ^{1}H NMR and UV–vis spectroscopies, elemental analysis and melting points (Tables 2 and 3). The melting points for all the target dyes were sharp, indicating a high level of purity and a crystalline phase of the resulting salts. The ^{1}H NMR spectra of the styryl dyes **3a–3i** display two characteristic doublets in the range 7.1–8.1 ppm with coupling constants between 15 and 18 Hz. These coupling constants indicate the *trans* forms of the dyes in their ground states. It is known that each of the products can be transformed into the corresponding *cis* isomer by photolysis of their acidic solutions [19], but the *cis* styryl dye forms are not stable and readily undergo thermal isomerization to the *trans* form [19]. In addition, it has been reported that significant differences can be observed between the UV–vis spectra of the *cis* and *trans* isomers [19].

3. Experimental part

Melting points were determined on a Kofler apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a Varian UNITY 300 instrument in DMSO-d_6. Elemental analyses were performed on a LECO CHNS-932 instrument. All starting compounds were commercially available and were used as supplied. Intermediates **1a–1d** (Table 1) were prepared according to a modified literature procedure [20] by simple melting of the starting compounds with dimethyl sulphate. 4-Pyrrolidinylbenzaldehyde and 4-morpholinobenzaldehyde were synthesized according to the method of Gale and Wilshire [21] by the reaction of 4-fluorobenzaldehyde with pyrrolidine or morpholine in



Scheme 2.

Table 1
Chemical structures of the starting compounds and styryl dyes **3a–3i**

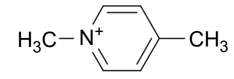
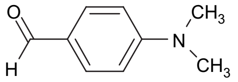
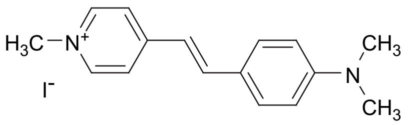
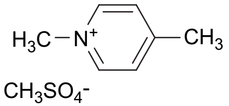
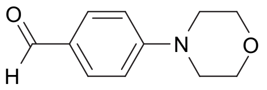
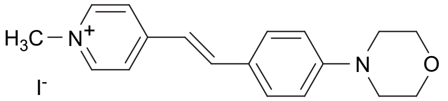
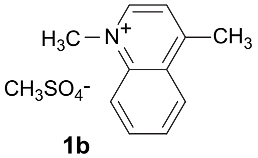
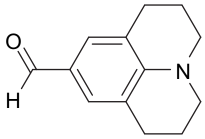
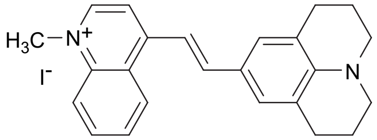
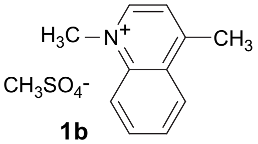
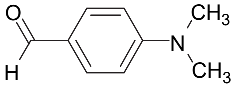
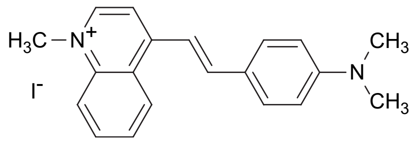
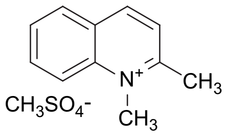
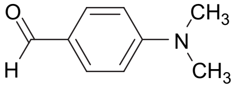
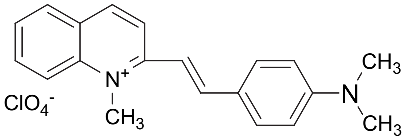
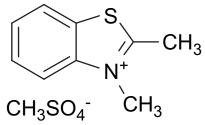
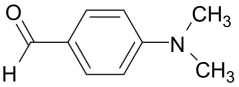
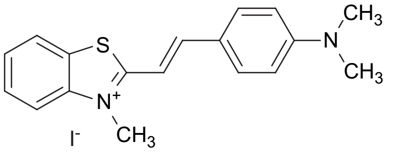
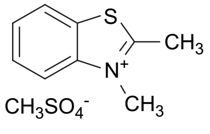
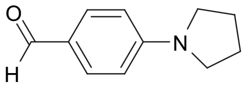
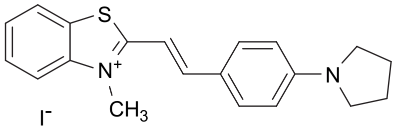
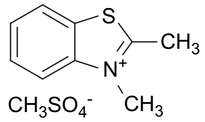
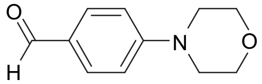
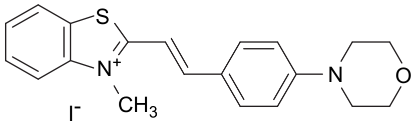
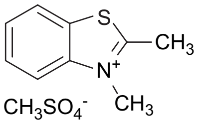
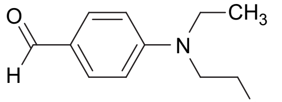
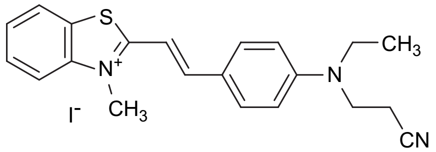
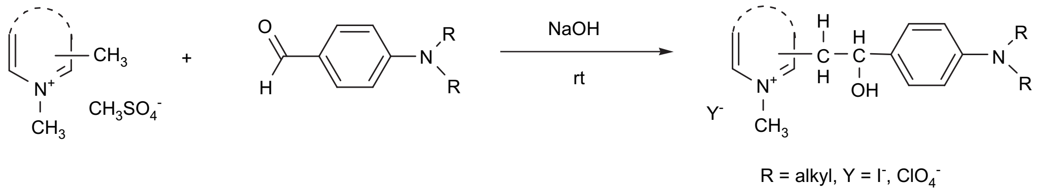
Starting azinium salt	Starting aldehyde	Styryl dye
 **1a**	 **2e**	 4-[(4-Dimethylamino)styryl]-1-methylpyridinium iodide **3a**
 **1a**	 **2b**	 1-Methyl-4-(4-morpholinostyryl)pyridinium iodide **3b**
 **1b**	 **2c**	 4-((Julolidino)styryl)-1-methylquinolinium iodide **3c**
 **1b**	 **2e**	 4-(4-(Dimethylamino)styryl)-1-methylquinolinium iodide **3d**
 **1c**	 **2e**	 2-(4-(Dimethylamino)styryl)-1-methylquinolinium perchlorate **3e**
 **1d**	 **2e**	 2-(4-(Dimethylamino)styryl)-3-methylbenzo[*d*]thiazol-3-ium iodide **3f**
 **1d**	 **2a**	 3-Methyl-2-(4-(pyrolidin-1-yl)styrylbenzo[*d*]thiazol-3-ium iodide **3g**
 **1d**	 **2b**	 3-Methyl-2-(4-morpholinostyryl)benzo[*d*]thiazol-3-ium iodide **3h**

Table 1 (*continued*)

Starting azinium salt	Starting aldehyde	Styryl dye
 **1d**	 **2d**	 2-(4-((2-Cyanoethyl)(ethyl)amino)styryl)-3-methylbenzo[*d*]thiazol-3-ium iodide **3i**



Scheme 3.

Table 2
Melting points, molecular formulae and elemental analysis of styryl dyes **3a**–**3i**

Dye no.	M.p. (°C) from MeOH	Molecular formula (MW)	Analysis (%) calc/found			
			C	H	N	S
3a	278–280	$C_{16}H_{19}IN_2\cdot MeOH$ (398.24)	51.21/51.48	5.82/5.82	7.03/6.81	–
3b	267–269	$C_{18}H_{21}IN_2O$ (408.28)	52.95/52.90	5.18/5.22	6.86/6.80	–
3c	258–260	$C_{24}H_{25}IN_2$ (468.37)	61.54/61.37	5.38/5.16	5.98/6.37	–
3d	241–243	$C_{20}H_{21}IN_2\cdot MeOH$ (448.3)	56.26/56.54	5.62/5.19	6.25/6.01	–
3e	261–263	$C_{20}H_{21}ClN_2O_4$ (388.84)	61.78/61.46	5.44/5.49	7.20/7.12	–
3f	264–265	$C_{18}H_{19}IN_2\cdot H_2O\cdot MeOH$ (472.33)	48.31/48.24	5.33/4.96	5.93/6.16	–
3g	244–245	$C_{20}H_{21}IN_2S\cdot 2H_2O$ (484.36)	49.59/49.73	5.20/5.11	5.78/5.74	6.62/6.45
3h	235–237	$C_{20}H_{21}IN_2OS\cdot H_2O$ (482.36)	49.80/49.40	4.81/4.83	5.81/5.72	6.65/6.38
3i	254–256	$C_{20}H_{22}IN_3S\cdot H_2O$ (493.40)	51.12/51.39	4.90/5.07	8.52/8.40	6.50/6.27

Table 3
Photo-physical characteristics and ^{1}H NMR data of the styryl dyes **3a**–**3i**

Dye no.	λ_{max} (nm, MeOH) (ε (L mol^{-1} cm^{-1}))	^{1}H NMR [DMSO-d_6 δ (ppm)]
3a	498 (22 100)	2.82 s (6H, $N(CH_3)_2$), 3.63 s (3H, N^+CH_3), 6.76–7.98 m (8H, Ar), 7.14 d (1H, $J_{HH} = 16.3$ Hz, CH=), 7.55 d (1H, $J_{HH} = 15.4$ Hz, CH=).
3b	442 (33 720)	3.28 t (4H, $O(CH_2)_2$), 3.73 t (4H, $N(CH_2)_2$), 4.18 s (3H, N^+CH_3), 7.08–8.66 m (8H, Ar), 7.26 d (1H, $J_{HH} = 16.2$ Hz, CH=), 7.92 d (1H, $J_{HH} = 16.2$ Hz, CH=).
3c	554 (144 700)	2.42–2.56 m (8H, CH_2), 2.62 br s (4H, $N(CH_2)_2$), 4.02 s (3H, N^+CH_3), 6.45–8.53 m (8H, Ar), 7.54 d (1H, $J_{HH} = 15$ Hz, CH=), 7.83 s (1H, $J_{HH} = 17.7$ Hz, CH=).
3d	555 (57 960)	2.62 s (6H, $N(CH_3)_2$), 4.01 s (3H, N^+CH_3), 6.45–8.52 m (10H, Ar), 7.56 d (1H, $J_{HH} = 15.1$ Hz, CH=), 7.95 d (1H, $J_{HH} = 14.7$ Hz, CH=).
3e	553 (58 780)	3.03 s (6H, $N(CH_3)_2$), 3.99 s (3H, N^+CH_3), 6.37–8.54 m (10H, Ar), 7.43 d (1H, $J_{HH} = 14$ Hz, CH=), 7.91 s (1H, $J_{HH} = 17.1$ Hz, CH=).
3f	522 (83 450)	3.09 s (6H, $N(CH_3)_2$), 4.21 s (3H, N^+CH_3), 6.80–8.31 m (8H, Ar), 7.61 d (1H, $J_{HH} = 15.5$ Hz, CH=), 8.05 s (1H, $J_{HH} = 15.3$ Hz, CH=).
3g	534 (74 670)	1.99 m (4H, CH_2CH_2), 3.42 t (4H, $N(CH_2)_2$), 4.20 s (3H, N^+CH_3), 6.68–8.29 m (8H, Ar), 7.58 d (1H, $J_{HH} = 15.2$ Hz, CH=), 8.05 d (1H, $J_{HH} = 15.2$ Hz, CH=).
3h	493 (49 890)	3.40 t (4H, $O(CH_2)_2$), 3.74 t (4H, $N(CH_2)_2$), 4.26 s (3H, N^+CH_3), 7.06–8.34 m (8H, Ar), 7.71 d (1H, $J_{HH} = 15.0$ Hz, CH=), 8.09 d (1H, $J_{HH} = 15.0$ Hz, CH=).
3i	507 (61 850)	1.15 t (3H, CH_3), 2.82 t (2H, CH_2CN), 3.54–3.75 q (2H, $N\mathit{CH}_2CH_2$), 3.79 t ($N\mathit{CH}_2CH_3$), 4.23 s (3H, N^+CH_3), 6.90–8.32 m (8H, Ar), 7.66 s (1H, $J_{HH} = 15.5$ Hz, CH=), 8.08 s (1H, $J_{HH} = 15.5$ Hz, CH=).

Table 4
Different catalysts and times for MW preparations of styryl dyes **3a–3i**

Dye no.	NaOH (MW,[a] min)	NH_4HCO_3 (MW, min)	$NaHCO_3$ (MW, min)	NaH_2PO_4 (MW, min)	*p*-TsOH (MW, min)	NH_4OOCCH_3 (MW, min)	PPh_3 (MW, min)	K_2CO_3 (MW, min)
3a	2 (2 × 1)	2 (2 × 1)	2	2	3 (2 × 1.5)	3 (2 × 1.5)	2	5 (2 × 2.5)
3b	2 (2 × 1)	2 (2 × 1)	2	2	4 (2 × 2)	3 (2 × 1.5)	2	6 (3 × 2)
3c	2 (2 × 1)	2 (2 × 1)	2	2	3 (2 × 1.5)	2	3	4 (2 × 2)
3d	2 (2 × 1)	2 (2 × 1)	2	3 (2 × 1.5)	4 (2 × 2)	2.5	3 (2 × 1.5)	5 (2 × 2.5)
3e	3 (2 × 1.5)	3 (2 × 1.5)	4 (2 × 2)	4 (2 × 2)	5 (2 × 2.5)	4 (2 × 2)	3 (2 × 1.5)	6 (3 × 2)
3f	1.5	1.5	2	2	3 (2 × 1.5)	3 (2 × 1.5)	3 (2 × 1.5)	5 (2 × 2.5)
3g	1.5	1.5	2	3 (2 × 1.5)	4 (2 × 2)	3 (2 × 1.5)	3 (2 × 1.5)	5 (2 × 2.5)
3h	2 (2 × 2)	3 (3 × 1)	2 (2 × 1)	2	4 (2 × 2)	4 (2 × 2)	3 (2 × 1.5)	5 (2 × 2.5)
3i	3 (3 × 1)	3 (3 × 1)	3 (3 × 1)	3 (2 × 1.5)	3 (2 × 1.5)	3 (3 × 1)	3 (3 × 1)	5 (2 × 2.5)

[a] MW = 460 W. For all microwave-accelerated reactions the yields are in the range 93–99%.

Table 5
Yields (%) of dyes **3a–3i**

Dye no.	NaOH (rt)	NaOH (MW)	NH_4HCO_3 (MW)	$NaHCO_3$ (MW)	NaH_2PO_4 (MW)	*p*-TsOH (MW)	NH_4OOCCH_3 (MW)	PPh_3 (MW)	K_2CO_3 (MW)
3a	68	99	95	94	93	94	93	96	93
3b	70	97	96	98	98	93	99	98	94
3c	67	97	98	94	98	96	98	99	95
3d	72 (Aldol)	96	100	96	96	95	99	97	94
3e	38 (Aldol)	95	99	98	94	95	93	99	94
3f	72	96	93	94	97	96	95	94	97
3g	81	98	98	95	93	95	93	95	99
3h	74	96	94	97	95	94	94	94	93
3i	47 (Aldol)	93	95	96	94	97	95	98	94

dimethyl sulphoxide in the presence of potassium carbonate. Julolidine was formylated by the Vilsmeier procedure [22], which led to the formation of julolidine-carbaldehyde **2c**. A mixture of *N*-ethylaniline and acrylonitrile was heated in acetic acid and this reaction afforded 3-(ethyl(phenyl)amino)propanenitrile, which was subsequently formylated by the aforementioned Vilsmeier method [22].

3.1. Procedure A

A mixture of the appropriate compounds **1a–1d** (0.001 mol), compounds **2a–2d** (0.001 mol), NaOH (0.0011 mol) and 3–4 drops of H_2O was ground in a porcelain mortar for a period of 30 min. Hot methanol (30 ml) was added and the resulting solution was poured into saturated aqueous KI (30 ml). The resulting precipitate was filtered off under reduced pressure and air-dried. Yields (%): **3a**, 68; **3b**, 70; **3c**, 67; **3f**, 72; **3g**, 81; **3h**, 74.

3.2. Procedure B

A mixture of the appropriate compounds **1a–1d** (0.001 mol), compounds **2a–2e** (0.001 mol), the appropriate base or *p*-TsOH (0.0011 mol) (see Table 4) and 3–4 drops of H_2O was ground in a porcelain mortar for 1 min. The mixture was subjected to microwave irradiation at 460 W for the appropriate reaction time (see Table 4) and was then allowed to cool down to room temperature. Hot methanol (30 ml) was added to the mixture. The resulting solution was worked up as described in the procedure described above. The precipitate was filtered under reduced pressure and air-dried.

3.3. Procedure C

The appropriate compounds **1a–1d** (0.001 mol), compounds **2a–2e** (0.001 mol), 1 drop of *N*-ethyldiisopropylamine and PEG 400 (3 ml) were mixed in 25 ml reaction vessel. The mixture was subjected to microwave irradiation for 3 min (2 × 1.5 min) at 460 W and was cooled down to room temperature. Saturated aqueous KI or $NaClO_4$ (30 ml) was added to the reaction mixture (Table 1). The precipitated dyes were filtered off under reduced pressure and air dried. The reaction yields were in the range 96–100%.

4. Conclusions

- The synthetic procedures reported here are simple, reliable and highly reproducible;
- The procedures are environmentally benign and energy efficient (short reaction times up to several minutes);
- The use of solvent-free conditions lead to smaller reaction volumes;
- The reaction products are obtained in high yields and with high purity.

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