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Dynamic exchange of heterocyclic subunits during halogen substitution in chloroheptamethinecyanine dyes by benzoazolium salts

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Abstract—The chlorine atom present in the exocyclic conjugated bridge incorporated in the polymethine chain of heptamethine-cyanine dyes can be easily replaced by a substituted 2-methylbenzoazolium salt. This reaction is promoted by residual water present in the reaction medium. This strategy was applied to the synthesis of a heptamethinecyanine dye possessing a vinyl group in the substituting heterocycle. Surprisingly, the expected monovinyl substituted dye was obtained along with di- and trisubstituted vinyl dyes. Such mixture can be, in principle, incorporated into an organic polymer monolith and used for affinity chromatography. This substitution reaction was investigated varying the nature of the benzoazole moiety of the chloroheptamethinecyanine dye and the substituting 2-methylbenzoazolium salt. A mechanism rationalizing the substitution pattern observed is proposed.
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Chloroheptamethinecyanines incorporating a cyclohexane ring in the polymethine chain have found extensive use for a wide range of technological applications, having been prepared by a variety of methods.[1] The most common heteroaromatic nuclei present in this class of functional dyes belong to the indole type, while those bearing other benzoazole terminal groups remain scarcely explored.

We have recently described the synthesis of several chloroheptamethinecyanines alike **1**, derived from quinoline, benzoxazole, benzothiazole and benzoselenazole[2] (Fig. 1). The synthetic route devised was shown to be efficient provided that the newly formed **1** was insoluble in the reaction solvent. Otherwise, it led to the formation of triheterocyclic dye **2**, which could be obtained as the exclusive product under certain conditions. The formation of **2** was thought to be originated by the inclusion of an oxygen atom from the water produced in the con-
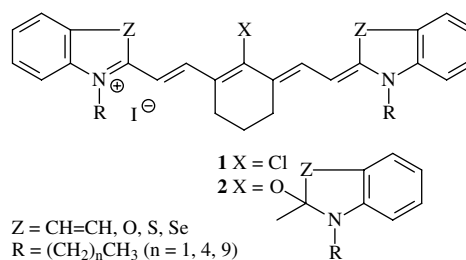

Figure 1. Chloro- and triheterocyclic heptamethinecyanine dyes **1** and **2**.

densation step and/or residually present in the solvent. Consistently, the synthesis of chloro dyes **1** could be accomplished efficiently using the same method under anhydrous conditions.[3]

The observation that some 2-methylbenzoazole iodides are converted quantitatively into the corresponding 2-methylbenzoazol-2-ol derivatives,[4] in non-anhydrous DMSO-d_6, has reinforced their role in the mechanistic route earlier proposed for triheterocyclic dyes **2**.[3]

The presence of the chlorine atom in the exocyclic conjugated bridge of these dyes is a very important

structural characteristic to achieve desirable features for several applications requiring its substitution by different nucleophiles. Traditionally, this has been performed employing phenolates,[5] arylthiolates/thiophenolates,[5a–c,f–i,6] alcoxydes,[5i,7] alkylamines,[5i,6a,8] anilines,[9] diphenylphosphines,[7] morpholines,[7] pyridines,[10] imidazoles,[10] piperidines[6a] and mercaptans.[9]

When compared to their indolenine analogues, chlorobenzothiazole, benzoxazole and benzoselenazole dyes somewhat lack structural versatility, due to a generally less efficient nucleophilic substitution of the chlorine atom.[5b] Therefore, while inconvenient during the targeting of chloroheptamethinecyanines **1**, the formation of dyes **2**, when intentionally carried out from 2-methylheteroaromatic quaternary salts possessing a suitable functional group, appears to offer an attractive alternative to classical methods of functionalization.
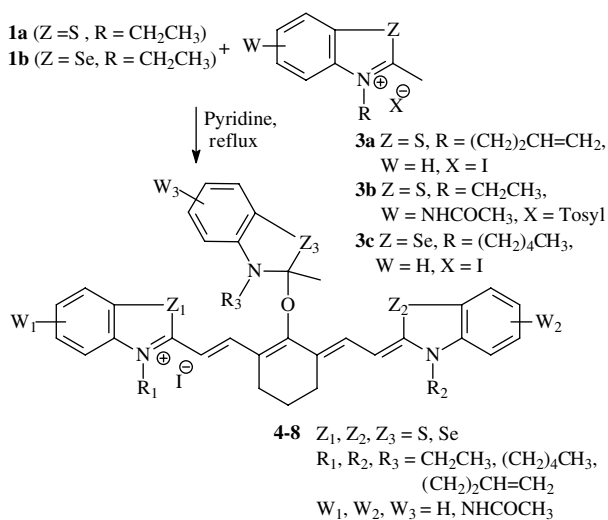
The halogen substitution by a third heterocyclic ring bearing a pendent vinylic group would yield dyes that can, in principle, be incorporated into an organic polymer monolith[11] of potential usefulness for cyanine-affinity chromatography.[12]

In order to assess the viability of the derivatization of chloroheptamethinecyanines with quaternary benzoazolium salts possessing a pendent vinyl group, an equimolar mixture of dye **1a**[2,3] and vinylbenzothiazolium iodide **3a**,[13] in pyridine, was heated under reflux, under non-anhydrous conditions, until complete consumption of the starting materials (60 min)[14] (Scheme 1).

Unexpectedly, the corresponding ordinary FAB mass spectrum of the isolated product revealed the presence of a mixture of compounds constituted by the expected monovinyl substituted dye **5a** (m/z 676) (and/or its constitutional isomer **5a′**), together with other four possible substituted dyes: $N,N′,N″$-triethyl cyanine **4** (m/s 650), the divinyl substituted dye **5b** (and/or its constitutional isomer **5b′**) (m/s 702) and $N,N′,N″$-trivinyl cyanine **5c** (Fig. 2).

To assess the influence of the nature of the benzoazolium salt and of the chloro dye's heterocycle, the reactions of **1a** with 5-acetamide-N-ethylbenzothiazolium tosylate (**3b**) and N-pentylbenzoselenazolium iodide (**3c**),[13] as well as between chloroheptamethineselenacyanine **1b**[3] and vinylbenzothiazolium iodide **3a** were also carried out.

The identity of the substituted dyes **4–8**, resulting from the reaction of chloroheptamethinecyanines **1a,b** with benzoazolium salts **3a–c**, was established by FAB-HRMS. Their proportion in each isolated reaction product was determined from the ordinary FAB mass spectrum, by the ratio between the sum of the relative intensities of the peaks of all isotopic specimens of each

1a (Z = S , R = CH₂CH₃)
1b (Z = Se, R = CH₂CH₃)

Pyridine, reflux

3a Z = S, R = (CH₂)₂CH=CH₂, W = H, X = I
3b Z = S, R = CH₂CH₃, W = NHCOCH₃, X = Tosyl
3c Z = Se, R = (CH₂)₄CH₃, W = H, X = I

4-8 Z₁, Z₂, Z₃ = S, Se
R₁, R₂, R₃ = CH₂CH₃, (CH₂)₄CH₃, (CH₂)₂CH=CH₂
W₁, W₂, W₃ = H, NHCOCH₃

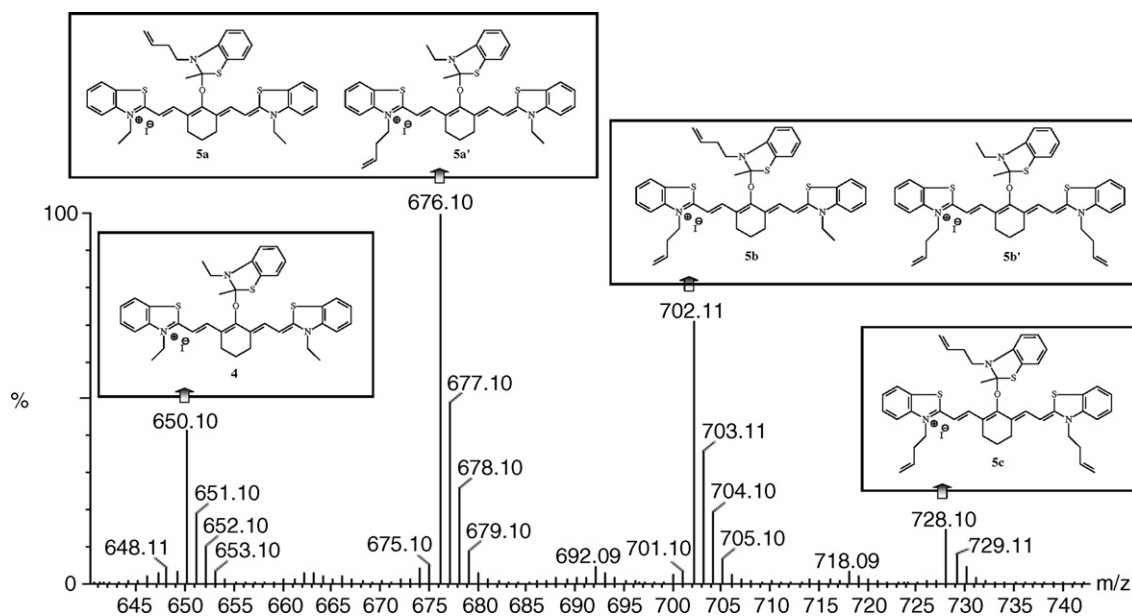**Scheme 1.** Synthesis of triheterocyclic heptamethinecyanine dyes **4–8**.

Figure 2. FAB mass spectrum of the mixture isolated from the reaction of chloroheptamethinecyanine **1a** with benzothiazolium salt **3a**.

Table 1. Triheterocyclic cyanines **4**–**8** formed in the reaction of chloroheptamethinecyanines **1a**–**b** with 2-methylbenzoazolium iodides **3a**–**c** in refluxing pyridine for 60 min

Precursors		Substituted heptamethinecyanine dyes			
		Z_1–Z_3, R_1–R_3, W_1–W_3	Proportion (%)	FABHRMS (3-NBA)	
				Molecular formula	Found (required)
1a + 3a	**4**	Z_1–Z_3 = S, W_1–W_3 = H, R_1–R_3 = Et,	16	$C_{38}H_{40}N_3S_3O$	650.2329 (650.2334)
	5a	Z_1–Z_3 = S, W_1–W_3 = H, R_1 = R_2 = Et, R_3 = $(CH_2)_2CH=CH_2$	42	$C_{40}H_{42}N_3S_3O$	676.2493 (676.2490)
	5a′	Z_1-Z_3 = S, W_1–W_3 = H, R_1 = R_3 = Et, R_2 = $(CH_2)_2CH=CH_2$			
	5b	Z_1-Z_3 = S, W_1–W_3 = H, R_1 = R_3 = $(CH_2)_2CH=CH_2$, R_2 = Et	33	$C_{42}H_{44}N_3S_3O$	702.2648 (702.2647)
	5b′	Z_1-Z_3 = S, W_1–W_3 = H, R_1 = R_2 = $(CH_2)_2CH=CH_2$, R_3 = Et			
	5c	Z_1-Z_3 = S, W_1–W_3 = H, R_1–R_3 = $(CH_2)_2CH=CH_2$	9	$C_{44}H_{46}N_3S_3O$	728.2834 (728.2803)
1a + 3b	**4**	Z_1–Z_3 = S, W_1–W_3 = H, R_1–R_3 = Et	33	$C_{38}H_{40}N_3S_3O$	650.2349 (650.2334)
	6a	Z_1–Z_3 = S, W_1 = W_2 = H, W_3 = $NHCOCH_3$, R_1–R_3 = Et	46	$C_{40}H_{43}N_4S_3O_2$	707.2550 (707.2548)
	6a′	Z_1–Z_3 = S, W_1 = $NHCOCH_3$, W_2 = W_3 = H R_1–R_3 = Et			
	6b	Z_1–Z_3 = S, W_1 = W_2 = $NHCOCH_3$, W_3 = H, R_1–R_3 = Et	21	$C_{42}H_{46}N_5S_3O_3$	764.2750 (764.2763)
	6b′	Z_1–Z_3 = S, W_1 = W_3 = $NHCOCH_3$, W_2 = H, R_1–R_3 = Et			
1a + 3c	**4**	Z_1–Z_3 = S, W_1–W_3 = H, R_1–R_3 = Et,	14	$C_{38}H_{40}N_3S_3O$	650.2346 (650.2334)
	7a	Z_1 = Z_2 = S, Z_3 = Se, W_1–W_3 = H, R_1 = R_2 = Et, R_3 = Pt	80	$C_{41}H_{46}N_3S_2{}^{78}SeO$	738.2240 (738.2255)
	7a′	Z_1 = Z_3 = S, Z_2 = Se, W_1–W_3 = H, R_1 = R_3 = Et, R_2 = Pt		$C_{41}H_{46}N_3S_2{}^{80}SeO$	740.2247 (740.2248)
			6	$C_{44}H_{52}N_3S{}^{78}Se_2O$	826.2176 (826.2177)
	7b	Z_1 = Z_3 = Se, Z_2 = S, W_1–W_3 = H, R_1 = R_3 = Pt, R_2 = Et		$C_{44}H_{52}N_3S{}^{78}Se{}^{80}SeO$	828.2202 (828.2169)
	7b′	Z_1 = Z_2 = Se, Z_3 = S, W_1–W_3 = H, R_1 = R_2 = Pt, R_3 = Et		$C_{44}H_{52}N_3S{}^{80}Se_2O$	830.2203 (830.2171)
1b + 3a	**5c**	Z_1–Z_3 = S, W_1–W_3 = H, R_1–R_3 = $(CH_2)_2CH=CH_2$	21	$C_{44}H_{46}N_3S_3O$	728.2786 (728.2803)
	8a	Z_1 = Z_2 = S, Z_3 = Se, W_1–W_3 = H, R_1 = R_2 = $(CH_2)_2CH=CH_2$, R_3 = Et	40	$C_{42}H_{44}N_3S_2{}^{78}SeO$	748.2080 (748.2099)
	8a′	Z_1 = Z_3 = S, Z_2 = Se, W_1–W_3 = H, R_1 = R_3 = $(CH_2)_2CH=CH_2$, R_2 = Et		$C_{42}H_{44}N_3S_2{}^{80}SeO$	750.2064 (750.2091)
	8b	Z_1 = Z_3 = Se, Z_2 = S, W_1–W_3 = H, R_1 = R_3 = Et, R_2 = $(CH_2)_2CH=CH_2$	30	$C_{40}H_{42}N_3S{}^{78}Se_2O$	768.1398 (768.1395)
	8b′	Z_1 = Z_2 = Se, Z_3 = S, W_1–W_3 = H, R_1 = R_2 = Et, R_3 = $(CH_2)_2CH=CH_2$		$C_{40}H_{42}N_3S{}^{78}Se{}^{80}SeO$	770.1392 (770.1387)
				$C_{40}H_{42}N_3S{}^{80}Se_2O$	772.1378 (772.1379)
	8c	Z_1–Z_3 = Se, W_1–W_3 = H, R_1–R_3 = Et	9	$C_{38}H_{40}N_3{}^{78}Se_3O$	788.0723 (788.0723)
				$C_{38}H_{40}N_3{}^{78}Se_2{}^{80}SeO$	790.0696 (790.0683)
				$C_{38}H_{40}N_3{}^{78}Se{}^{80}Se_2O$	792.0692 (792.0675)
				$C_{38}H_{40}N_3{}^{80}Se_3O$	794.0636 (794.0667)

dye and the sum of the relative intensities of the isotopic peaks of all dyes, assuming that all cationic dyes display similar response from the MS detector (Table 1). Compounds **4**–**8** arise, in a formal sense, from the substitution of one or both *N*-ethyl residues of the starting chloro cyanine by *N*-but-3-enyl groups.

The reaction between chloro dye **1a** and vinylbenzothiazolium iodide **3a** was additionally repeated in times shorter (5 and 10 min) than necessary for the reaction to be completed (60 min) and at a lower temperature (90 °C) than that of refluxing pyridine. The FAB spectrum of the isolated products revealed, apart from unreacted **1a**, the presence of the substituted cyanines **4** and **5**, as before, and of chloroheptamethinecyanine dyes **1c**–**d** (Table 2).

Table 2. Chloroheptamethinecyanine dyes **1a**,**d** and triheterocyclic dyes **4** and **5** obtained by reaction of chloroheptamethinecyanine **1a** with 2-methylbenzothiazolium iodide **3a** in refluxing pyridine (5, 10, 60 and 150 min) and at 90 °C (60 min)

1a $Z_1=Z_2=S$, $R_1=R_2=Et$, $W_1=W_2=H$
1c $Z_1=Z_2=S$, $R_1=Et$, $R_2=(CH_2)_2CH=CH_2$, $W_1=W_2=H$
1d $Z_1=Z_2=S$, $R_1=R_2=(CH_2)_2CH=CH_2$, $W_1=W_2=H$

Reaction time (min)	Reaction products relative proportion						
	Chloro dyes (%)			Trisubstituted dyes (%)			
	1a	**1c**	**1d**	**4**	**5a,a′**	**5b,b′**	**5c**
5	19	8	0	10	29	26	8
10	7	6	0	14	40	26	7
60	0	0	0	16	42	33	9
150	0	0	0	17	44	32	7
60 (90 °C)	15	17	3	5	19	28	13

The surprising formation of substituted heptamethinecyanine dyes **4**–**8**, other than the expected **5a**–**7a** and **8b**, as that of the transient chlorocyanines **1c**–**d**, seems to point to an exchange reaction between benzoazole nuclei or between *N*-alkyl (or *N*-alkylvinyl) pendent substituents. However, the absence of dyes bearing *N*-pentylbenzothiazole or *N*-ethylbenzoselenazole moieties, resulting from the reaction between **1a** and **3c**, as well as that of dyes possessing *N*-(but-3-enyl)benzoselenazole or *N*-ethylbenzothiazole groups from the reaction of **1b** with **3a**, clearly excludes any mechanism involving a simple exchange of *N*-alkyl (or *N*-alkylvinyl) groups between quaternary benzoazolium moieties.

The observed exchange reactions can be rationalized in terms of the mechanism depicted in Scheme 2, exemplified for the synthesis of the intermediate chloroheptamethinecyanine **1c** and triheterocyclic dye **5b**, arising from the reaction of dye **1a** with iodide **3a**. This mechanistic route is essentially the reverse of the one accepted for the base-catalyzed formation of chloroheptamethinecyanine dyes from 2-chloro-1-formyl-3-(hydroxymethylene)cyclohex-1-ene and benzoazolium iodides. The first step is the addition of a residual water molecule to the electrophilic β position of the polymethine chain of **1a**. The resulting hydroxylated compound **9** affords, upon C_α–C_β cleavage, the methylenic base **3d*** and the intermediary aldehyde **10**, which then undergoes condensation with the methylenic base **3a***, generated in situ from the corresponding iodide **3a**, to yield the asymmetric chlorocyanine **1c**. Finally, the formation of **5b** would result from the nucleophilic substitution of the central chlorine atom of **1c** by the 2-hydroxy derivative of **3a**, which is likely to be formed from the latter under non-anhydrous conditions.[2] The synthesis of the triheterocyclic substituted cyanine **5b** can also proceed by an inverse order of events, comprising firstly the formation of **5a**, via the 2-hydroxy derivative of **3a**, followed by substitution of a terminal *N*-ethylbenzothiazole nucleus by an exogenous methylenic base **3a***. The formation of
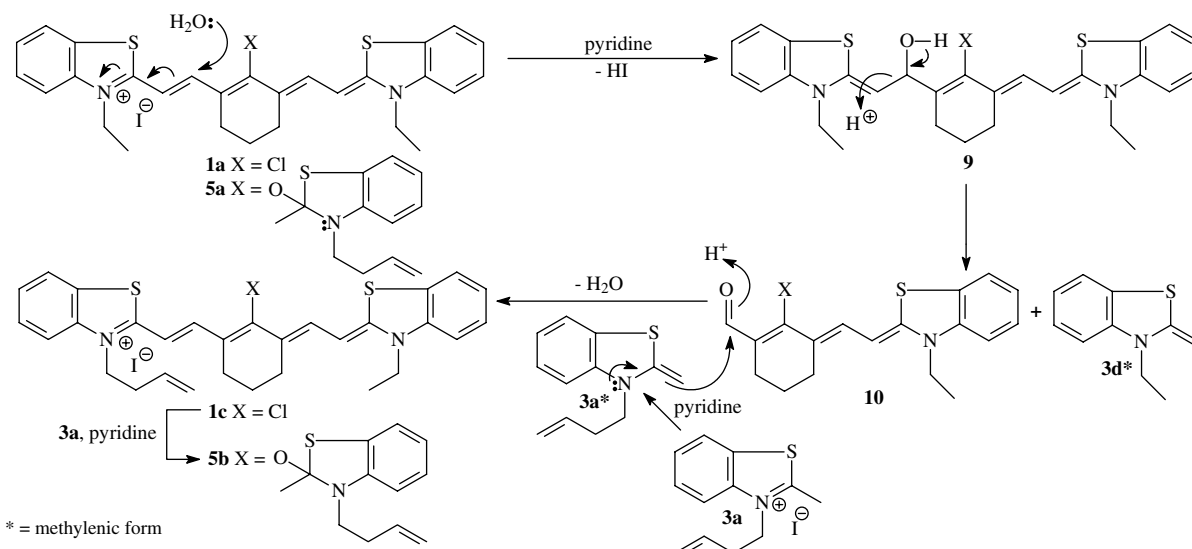
Scheme 2. Proposed mechanism for the formation of transient chloro dye **1c** and trisubstituted cyanine dye **5b** in the reaction of chloro dye **1a** with benzoazolium salt **3a**.

the remaining compounds in the reaction of **1a** with vinyl benzothiazolium iodide **3a**, as well of those which were found in the other reactions carried out, may be understood on the basis of the main mechanistic steps described above by changing the order and/or the nature of the intervenient benzoazole groups.

The proportion of the different triheterocyclic dyes formed in each of the reactions between heptamethinecyanines **1** and benzoazolium salts **3** seems to be dependent on the number of consecutive exchange/substitution steps involved in their formation. Accordingly, dyes bearing simultaneously the three heteroaromatic nuclei different from those of the starting chloro dye **1** are among the minor components of the mixtures. Cyanines **5a,a′**, **6a,a′**, **7a,a′** and **8b,b′** are invariably the main components of each isolated mixture. Since the formation of dyes **5a**–**7a** and **8b** requires one single substitution step, while their constitutional isomers (**5a′**–**7a′**, **8b′**) arise after two consecutive exchange steps, it is reasonable to presume that the former are truly the main products of each reaction. Nevertheless dyes **4** and **8c** also result from one single substitution, their less significant presence in each isolated mixture reflects the obvious reduced availability of benzoazolium residues identical to those of the framework of the starting chloroheptamethinecyanine in the reaction medium.

The nature of the benzoazole nuclei of the starting chloroheptamethinecyanine seems to have a negligible influence on the proportion of the products of the isolated mixtures, as seen in the reactions of **3a** with **1a** and **1b**.

Besides the formation of the transient symmetric and asymmetric chloroheptamethinecyanines **1c** and **1d**, it is noticeable that the distribution of triheterocyclic dyes formed at 5, 10, 60 and 150 min follows the same pattern (Table 2). In reaction times less than 1 h, the starting chloro dye **1a** was always in majority in relation to the other resulting chloro dyes, which can, at least partially, explain the final proportion of the triheterocyclic dyes. Symmetric chloro dye **1d** is always the minor component since it results from two consecutive external exchanges. Both TLC and MS analyses revealed the total consumption of all chloro dyes after 1 h.

In conclusion, chloroheptamethinecyanine dyes incorporating a rigidifyng cyclohexane ring in the polymethine chain were functionalized by replacing the central chlorine atom by a 2-methylbenzoazole group, through an ether linkage. The expected substituted cyanines were obtained together with some other related triheterocyclic dyes, resulting from the replacement of terminal heterocyclic moieties of the starting chloro dye or of an already substituted dye, by an exogenous benzoazolium salt. A possible mechanism involving transient aldehydes and/or exchange reactions between terminal heterocyclic moieties was proposed, based on the ordinary and high resolution FAB mass spectra of the products obtained in a set of experiments. The exchange of heterocyclic subunits may occur in any of the cyanine dyes present in the reaction mixture, following or before chlorine substitution. As a representative example of the usefulness of this functionalization reaction, the synthesis of a mixture of triheterocyclic heptamethinecyanine dyes mono-, di- and trisubstituted with a vinylic group was carried out. The mixtures of vinylic dyes so formed are expected to copolymerize with traditional vinylic monomers to afford reticulated monoliths, which can potentially be used for AC.

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14. *Typical procedure:* A solution of chloro dye **1** (1.0 mmol) and benzoazolium salt **3** (1.0 mmol), in pyridine (25 mL), was heated under reflux for 1 h. After being cooled at room temperature, Et_2O was added and the resulting residue was collected by filtration under reduced pressure and recrystallized from $MeOH/Et_2O$.