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Synthesis of Substituted Phenothiazines Analogous to Methylene Blue by Electrophilic and Nucleophilic Aromatic Substitutions in Tandem. A Mechanistic Perspective.

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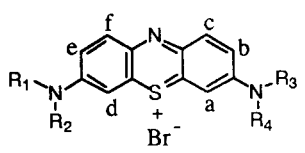
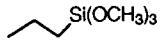
Abstract: 3,7-Disubstituted phenothiazines analogous to methylene blue (**1**) were synthesized from phenothiazine (**6**) reacting first with an excess of bromine in acetic acid to give 3,7-dibromophenothiazin-5-ium bromide (**8**), according to a reaction sequence that involves two electrophilic aromatic substitutions and one oxidation. Subsequently, **8** reacting with diallylamine or allylmethylamine via two nucleophilic aromatic substitution steps gave 3,7-bis[di(2-propenyl)amino]phenothiazin-5-ium bromide (**3**) or 3,7-bis[methyl, (2-propenyl)amino]phenothiazin-5-ium bromide (**4**), compounds analogous to methylene blue. The choice of solvent for the second step is critically important as 3,7-dibromophenothiazin-5-ium bromide is very reactive and prone to irreversible oxidation, reduction, and *ipso* attack at the 3- and 7- positions. The best yields (~63%) for the methylene blue analogues **3** and **4** were obtained when $CHCl_3$ or CH_2Cl_2 were employed as solvents for the nucleophilic aromatic substitution step. These solvents dissolve the methylene blue analogue products, but not 3,7-dibromophenothiazin-5-ium bromide.

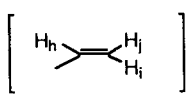
Methylene blue, **1**, perhaps the most well-known phenothiazine dye,[1] and redox indicator,[2] was first described in a German Patent of 1877.[3] More recently it has been used as an optical probe of biophysical systems,[4a] as an intercalator in nanoporous materials,[4b] as a redox mediator,[4c] and in photoelectrochromic imaging.[4d] It is synthesized commercially by oxidation of *N,N*-dimethyl-*p*-phenylene diamine with $Na_2Cr_2O_7$ in the presence of $Na_2S_2O_3$, followed by further oxidation in the presence of *N,N*-dimethylaniline.



1. $R_1 = R_2 = R_3 = R_4 = CH_3$

2. $R_1 = R_2 = R_3 = R_4 =$ 

3. $R_1 = R_2 = R_3 = R_4 =$ 



4. $R_1 = R_3 =$  , $R_2 = R_4 = CH_3$

5. $R_1 = R_2 = CH_3$, $R_3 = R_4 =$ 

For our studies of charge and ion percolation in dye-doped zerogels[5] we designed monomer

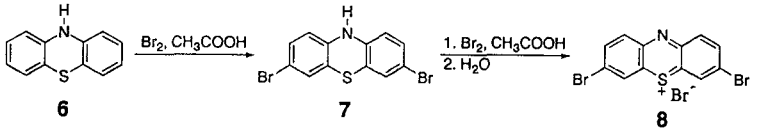
2 which cross-links via hydrolysis and condensation of the -$Si(OCH_3)_3$ groups[6] leading to a glass-like material that incorporates the redox-active methylene blue chromophore. (Monomer **2** was prepared from **3** via a H_2PtCl_6-catalyzed hydrosilylation reaction.[7])

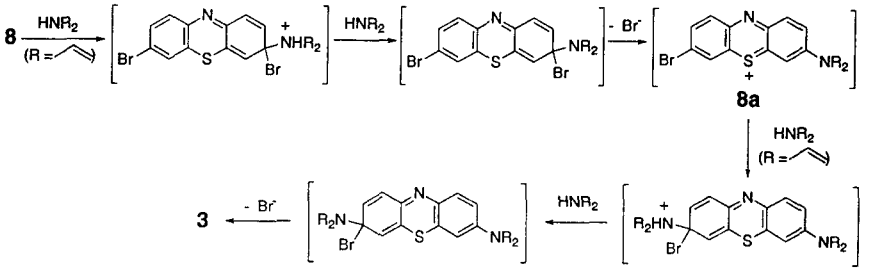
Preparation of **3** via the conventional route of methylene blue synthesis[1] would not only be lengthier than synthesis of **1** itself as it requires preparation of special *N*-substituted *p*-phenylene diamine and aniline, but also involves oxidation steps potentially incompatible with aliphatic double bonds.[8] An alternative two-step synthesis, reported by F. Kehrmann in 1916,[9] employing phenothiazine (**6**) as starting material reacting with bromine in acetic acid and the product with dimethylamine in ethanol, remains largely overlooked despite its potential utility for the synthesis of methylene blue analogues, and the great advances made in the synthesis of substituted phenothiazines since Kehrmann's work.[10] In this paper we report the results of a mechanistic investigation of Kehrmann's method prompted by the fact that our initial attempts to adopt it for the synthesis of **3** and **4** produced only trace amounts of the desired compounds. In turn, the obtained mechanistic insight led to the preparation of the methylene blue analogues **3**-**5** in good yields.

RESULTS AND DISCUSSION

Scheme I summarizes our understanding of the mechanism for the formation of **3** from phenothiazine, **6**, according to our modification of Kehrmann's procedure. The first step (Eq.[1])

Scheme I. Synthetic route for **3**.





is a sequence of two electrophilic aromatic substitutions followed by an oxidation. Bromine provides the electrophile (Br^+) that converts phenothiazine (**6**) to 3,7-dibromophenothiazine (**7**), and subsequently excess of Br_2 oxidizes **7** to the isolated brick-red 3,7-dibromophenothiazin-5-ium bromide (**8**), which is precipitated by addition of water. If only a 4-molar excess of Br_2 is used for the first step,[9a] both elemental analysis,[11] and FAB mass spectrometric analysis (see

Figure 1) indicate that the product is a mixture of **7** and **8**, where the reduced form **7** is the major

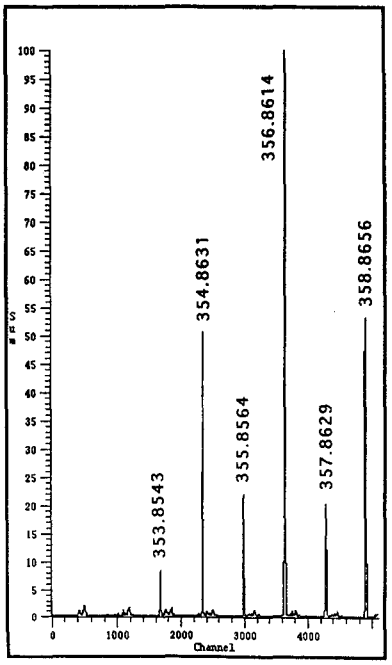
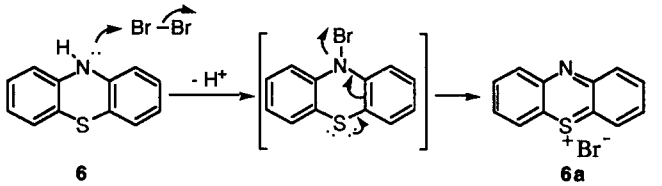


Figure 1. High resolution FAB-MS (matrix: 3-NBA/Gly/TFA) of the product from Eq.[1] using a 4:1 molar ratio of Br_2 over phenothiazine. Peaks at 354.8631, 356.8614 and 358.8656 correspond to **7**, and peaks at 353.8543, 355.8564, and 357.8629 correspond to the cation of **8**.

component. On the other hand, by using a 20-molar excess of Br_2 the precipitated product is pure **8** (see experimental section). These results suggest that a typical electrophilic substitution takes place first,[12] (so that **8** is formed via **7**) and seem to render alternative schemes that call for an oxidation[9,10a,10b] followed by nucleophilic aromatic substitutions[13] improbable. It should be noted that the sequence of events, namely substitution vs. oxidation, is a point that could not have been decided *a priori*, as Br_2 (aq.) ($E^{o'}$=1.087 V vs. NHE)[14] seems to have the redox potential to oxidize either **6** (for which we measured $E^{o'}$=0.55 V and $E^{o'}$=0.95 V vs. aq. Ag/AgCl in glacial acetic acid/0.25 M TBAP), or **7** (for which it has been reported $E^{o'}$=0.41 V and $E^{o'}$=0.82 V vs. Ag/Ag^+, 10^{-2} M in aq. $HClO_4$).[15] In fact, if the latter scenario -namely oxidation followed by substitution- was correct, a 4-molar excess of Br_2 would have been stoichiometrically enough to oxidize all **6** (presumably to the phenothiazinium cation), in which case no **7** would have been

observed. Furthermore, oxidation of any phenothiazine, e.g., **6**, to the corresponding phenothiazin-5-ium cation, **6a**, involves loss of two electrons, and if it is carried out using Br_2 as the oxidizing agent, it most probably proceeds according to Eq.[3]; therefore, oxidation should be inhibited in highly acidic media, (and/or by cations coordinating strongly to nitrogen),



6 **6a** Eq.[3]

probably becoming a slower process than electrophilic aromatic substitution, which was carried out in acetic acid. Finally, the nuclear polybromination described by Bodea *et al.*,[10b,16] which also requires an excess of Br_2, takes place in boiling acetic acid, and was not observed under our room temperature conditions.

For the second step (Eq.[2]), initially we chose the same solvent as in Kehrmann's procedure, i.e., ethanol.[9a] In our modification of that procedure (e.g., synthesis of **3**), solid **8** was added to a stirred ethanolic solution of diallylamine which turned immediately to deep blue (Fig. 2)

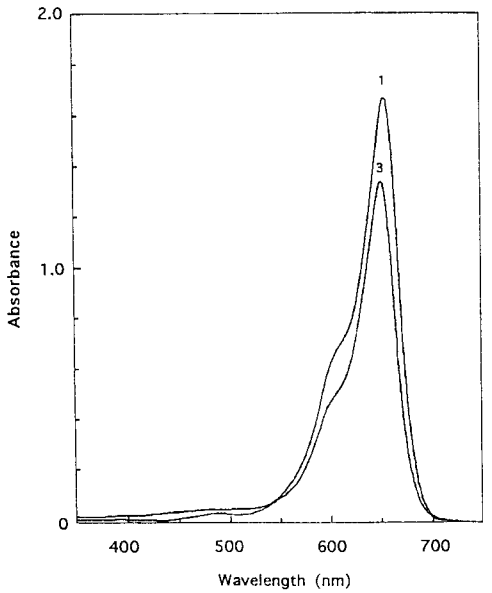


Figure 2. Comparison of visible absorption spectra of methylene blue (Aldrich) ([**1**]=1.92x10^{-5} M; ε_{652}=8.7x10^4 M^{-1}cm^{-1}),[17] and **3** ([**3**]=1.47x10^{-5} M; ε_{648}=9.1x10^4 M^{-1}cm^{-1}) in CH_3OH.

as **8** was dissolved. A bimolecular rate constant for the appearance of **3** is calculated from the data shown as an inset of Fig. 3A, and is found equal to 1.0x10^{-1} M^{-1}s^{-1}.[18] In this step, two amine molecules replace both bromine atoms via a postulated sequence of two addition-elimination type

nucleophilic aromatic substitutions (Eq.[2]). In agreement with Shine,[13b] it is suggested that the positive charge on sulfur activates by conjugation the 3-, and 7- positions for nucleophilic attack, thereby its presence is critical for the conversion of **8** to **3** (**4** or **5**). Indeed, if a smaller amount of Br_2 is used for the reaction sequence of Eq.[1] (e.g., a 4-molar excess over **6**), O_2 (air) must be passed (~ 0.5 h) through the ethanolic solution of the mixture of **7**, **8** (*vide ante*), and diallylamine

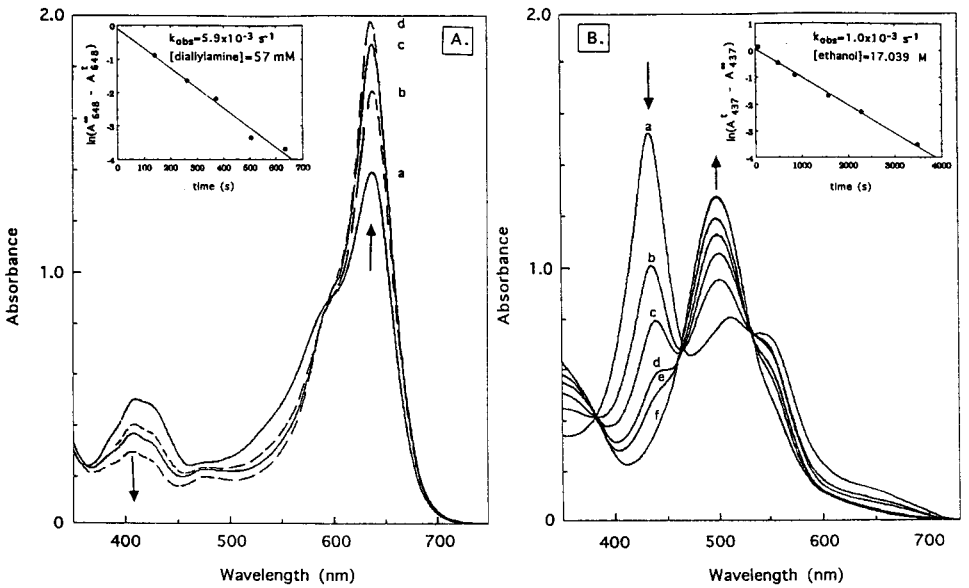
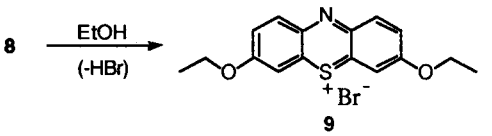


Figure 3. A. Visible absorption spectra of 0.03 mg of **8** upon mixing with 3 ml of ethanol containing diallylamine (47.4 mM), [**8**]=2.0x10^{-5} M. Curves; a: 2 min; b: 5 min; c: 7 min; d: 9 min. (Inset: kinetic plot for the calculation[20] of the pseudounimolecular rate constant, [k_{obs}= -(slope)], for the appearance of **3**; r^2=0.979)

B. Visible absorption spectra of **8** ([**8**]=2.7x10^{-5} M) in ethanol. Curves; a: 1 min; b: 8 min; c: 14 min; d: 26 min; e: 38 min; f: 110 min (t_∞). (Inset: kinetic plot for the calculation[20] of the pseudounimolecular rate constant, [k_{obs}=-(slope)], for the disappearance of **8** according to Eq.[4]; r^2=0.995).

for the blue color of **3** (Fig. 2) to appear. It could be argued at this point that air, a cheaper alternative to bromine, should be used to complete the oxidation of **7** to **8** in order for the latter to react with diallylamine. However, this approach for the synthesis of **3**-**5** might be complicated by the fact that **8** is prone to irreversible oxidation.[21] Nevertheless, the main potential source of complication for the second step is that, in direct competition with its reaction with the amine, **8** reacts also with ethanol itself (see Fig. 3B) with a pseudounimolecular rate constant k_{obs}=1.0x10^{-3} s^{-1} (calculated from data shown as an inset of Fig. 3B) producing 3,7-diethoxyphenothiazin-5-ium

bromide (**9**)[22] presumably via a sequence of two nucleophilic aromatic substitutions as well (Eq.[4]). Compound **9** is analogous, and its spectra are similar to those reported for the electro-



Eq.[4]

9

chemically generated[15] two-electron oxidation product of 3,7-dimethoxyphenothiazine.[23] At this point our results suggest conclusively that the residency of **8** in solution should be kept as short as possible, and justify why we have chosen to add solid **8** directly into the amine solution.

The complications imposed by the parallel process of Eq.[4] notwithstanding, methanol or ethanol are logical choices of solvents for the second step because they offer excellent solubility for the product (**3**, **4** or **5**), and their reaction with **8** is slower than the reaction of the latter with amines (compare Figures 3A and 3B). In any event, formation of **3** is under kinetic control, and the ratio of k_{obs} of Eq.[2] vs. Eq.[4] under our preparative conditions ([diallylamine] = 0.41 M; see experimental section) sets the maximum theoretical yield of **3** in ethanol at about 98%. However, formation of **9** (and the cross coupling product from **8** reacting with both ethanol and the amine) must be accelerated in the presence of the amine because the reaction of Eq.[4] is probably base-catalyzed,[19] and therefore the actual rate-ratio of the process of Eq.[2] vs. the process of Eq.[4] should be significantly less than the one calculated by a simple division of the k_{obs} of those two processes measured independently. Our best yield of **3** in ethanol was 27%.

On the other hand, it is difficult to identify other more convenient solvents for the nucleophilic aromatic substitution reaction, because **8** is generally unstable in solution: surprisingly, it reacts even with seemingly innocuous solvents such as acetone (the solution decolorizes - similar behavior was observed by Biehl with the one electron oxidation product of 3,7-dibromo-*N*-methylphenothiazine and acetone, and was attributed to reduction),[12] or acetonitrile (the solution turns green), but we made no attempt to isolate products from these reactions. Even reaction of **8** with neat diallylamine is also complicated: the solution turns immediately to blue as **8** is dissolved, but then it quickly decolorizes completely as **3** is presumably reduced by the amine to its leuco form. (Decolorization was also observed independently by dissolving **3** in diallylamine.)

All our observations seem to suggest that probably the best yields of methylene blue analogues via our modification of Kehrmann's procedure would be obtained if we could employ a non-nucleophilic solvent that dissolves the product (e.g., **3**) but not the reactant (**8**). Such solvents are chloroform and methylene chloride. In these solvents, the reaction takes significantly longer for completion than in ethanol, but the maximum yield of the purified product (**3**) was increased to 63% (see experimental section).

Despite the uncomplicated plots of Figures 3A and 3B, and the steady yield improvements via the rational steps above, still a large percentage of **8** remains unaccounted for, both in ethanol and in $CHCl_3$. A likely yield-compromising parallel process in ethanol, where the concentration of **8** is higher than in $CHCl_3$, is dimerization of **8**[10b,13b,15] via an *ipso* attack from the 10-*N*

position of one molecule at the 3- and 7- positions of another. Furthermore, the fact that the yield of methylene blue itself according to our procedure (see experimental) was 70% in ethanol and 85% in $CHCl_3$, indicates that probably the vinyl groups of **3** are involved in lowering its yield, perhaps via acid (HBr) catalyzed polymerization.

CONCLUSIONS

The reaction sequence of Scheme I turns out to be a fast, convenient and inexpensive method for the preparation of phenothiazinium salts analogous to methylene blue in good yields. Non-symmetric methylene blue analogues (e.g., **5**: see experimental section) may be also prepared by using a mixture of amines. Even though the original impetus for this work was synthesis of **2** and polymers thereof, at this point it seems that a new kind of polymers could be possible via the step-growth polymerization of **8** with diamines.

EXPERIMENTAL

NMR spectra were obtained at Washington University in St. Louis with either a Unity-Plus 500 or a Unity-Plus 300 NMR spectrometer both of Varian Corporation (Palo Alto, CA). FAB-Mass Spectra we obtained with a VG ZAB-T four sector tandem mass spectrometer also at Washington University in St. Louis. Elemental analyses were performed by Oneida Research Services, Inc., Whiteboro, N.Y. Infra red spectra were obtained with a Perkin Elmer 1750 FTIR Spectrometer. UV-Vis. Spectra were obtained with a Beckman Model 35 Spectrophotometer. Redox potentials were measured in Ar purged solutions using a EG&G 263A potentiostat and a Kipp & Zonen Y-Y-Y' recorder. The aq. Ag/AgCl reference electrode was purchased from Bioanalytical Systems, Inc. (West Lafayette, Indiana).

All kinetic experiments were performed at 23 °C, using a two-tube (10 ml each, parallel to each other, and fused at the bottom of a 100 ml round bottom flask), one-cuvette (UV-Vis, at right angle with the tubes) tonometer degassed with three freeze-pump-thaw cycles at 10^{-5} Torr while the correct amount of solid **8** and the appropriate solvent (EtOH) or solution (diallylamine in EtOH) were placed in separate tubes. The time t=0 is set at the point of dissolving **8**.

Synthesis of 3,7-dibromophenothiazin-5-ium bromide (8): phenothiazine, **6**, (2 g, 10.0 mmol, Aldrich) was dissolved in oxygen-free glacial acetic acid (120 ml), and a solution of bromine also in acetic acid (100 ml, 10% v/v, 195 mmol) was added to it all at once with vigorous stirring; stirring was continued for about one minute, then water (400 ml) was added to the mixture, the red precipitate was filtered, washed with diethylether, dried under vacuum, and identified as 3,7-dibromophenothiazin-5-ium bromide (**8**). Yield: 4.35 g (9.98 mmol), (~100%); mp ~95°C (dec.); ^{1}H NMR (CD_3COCD_3, 300 MHz) δ 6.66 (2H, d, J_{bc}=8.2 Hz), 7.10 (2H, dd, J_{bc}=8.2 Hz, J_{ab}=2.2 Hz), 7.14 (2H, d, J_{ab}=2.2 Hz); IR (KBr): 734(s), 771(s), 1256(w), 1328(w), 1374(s), 1446(s), 1510(w), 1554(w), 1588(w), 3020-3080(w) cm^{-1}; elemental analysis (Cal. for $C_{12}H_6Br_3NS$: C, 33.06; H, 1.39; N, 3.21; S, 7.36; Br, 54.99. Found: C, 33.12; H, 1.89; N, 3.26; S, 7.33; Br, 54.49).

Synthesis of 3,7-bis[di(2-propenyl)amino]phenothiazin-5-ium bromide (3): to a solution of diallylamine (3.148 g, 32.4 mmol) in absolute ethanol (80 ml; [diallylamine]=0.41 M) kept under N_2, 2.011 g (4.6 mmol) of **8** was added all at once with vigorous stirring. Half hour later, ethanol was removed under vacuum, the crude product was dissolved in chloroform (200 ml) and extracted once with aq. HBr (75 ml, 1% w/v) and once with H_2O (75 ml). The organic layer was dried (Na_2SO_4), concentrated, and the product was purified chromatographically with a short column packed with silica gel, eluting first with $CHCl_3$, and then with $CHCl_3/CH_3OH$ 98:2 v/v, followed by recrystallization ($CHCl_3$/ether), and vacuum drying. Yield: 0.58 g (27%). (Chloroform elutes a cherry-red band which was identified with visible absorption as **9**.[22] The $CHCl_3/CH_3OH$ mixture first elutes a green-blue impurity, presumably the cross-coupling product of **8** with diallylamine and ethanol. A blue impurity that remains at the top of the column is probably composed of dimerization and polymerization products.) The yield of **3** is improved dramatically by using $CHCl_3$ (or CH_2Cl_2) as solvent for the reaction of **8** with diallylamine: **8** (0.998 g, 2.3 mmol) was added under N_2 to $CHCl_3$ (250 ml) containing diallylamine (1.14 g, 11.7 mmol). The mixture was stirred for 3 h, and was worked up as above. (In chromatographic purification chloroform elutes a mixture (by TLC, $CHCl_3$, R_f~0.9) of impurities as a pale-green band which quickly turns to an intractable blue-black mixture of pigments upon exposure to air. A blue impurity still remains at the top of the column.) Yield: 0.68 g (63 %); mp ~165°C (dec.); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.34 (8H, br s), 5.26 (4H, d, J_{hi}=16.8 Hz), 5.33 (4H, d, J_{hj}=10.1 Hz), 5.86-6.08 (4H, m), 7.25 (2H, d, J_{bc}=8.7 Hz), 7.74 (2H, s), 7.93 (2H, d, J_{bc}=8.7 Hz); IR (KBr): 877(m), 1138(m), 1225(s), 1326(m), 1392(m), 1486(w), 1593(s), 2930-3050(w) cm^{-1}; Vis. (methanol) λ_{max}, nm (ε, M^{-1}cm^{-1}): 648 (91,000); elemental analysis (Cal. for $C_{24}H_{26}BrN_3S$: C, 61.54; H, 5.59; Br, 17.06; N, 8.97; S, 6.84. Found: C, 60.85; H, 5.56; Br, 16.54; N, 9.01, S, 6.99.)

Synthesis of 3,7-bis[methyl,(2-propenyl)amino]phenothiazin-5-ium bromide (4) was carried out in a similar fashion to the synthesis of **3**. mp ~140°C (dec.); ^{1}H NMR (CD_3OD, 500 MHz) δ 2.1 (6H, s), 3.10 (4H, d, J_{gh}=2.0 Hz), 3.97 (2H, dd, J_{ij}=0.98 Hz, J_{hi}=15 Hz), 4.05 (2H, dd, J_{ij}=0.98, J_{hj}=10 Hz), 4.67-4.74 (2H, m), 6.09 (2H, d, J_{ab}=2.4 Hz), 6.19 (2H, dd, J_{ab}=2.4 Hz, J_{ef}=9.6 Hz), 6.645 (2H, d, J_{ef}=9.6 Hz); IR (KBr): 532(w), 687(m), 797(m), 837(w), 881(s), 941(w), 994(w), 1037(m), 1141(s), 1196(s), 1249(s), 1348(s), 1396(s), 1450(w), 1489(m), 1520(w), 1597(s), 2927-3100(w) cm^{-1}; Low resolution FAB (3-NBA/Gly/TFA) m/z 336.2 (cation).

For the synthesis of 3-(dimethylamino),7-[di-(2-propenyl)amino]phenothiazin-5-ium bromide (5), diallylamine (2 ml, 16.2 mmol) and dimethylamine (8.1 ml of a 2 M solution in methanol -Aldrich-, 16.2 mmol) were diluted to 500 ml with chloroform; **8** (2.0 g, 4.59 mmol) was added, and the mixture was stirred under N_2 for 3 h. The cross-coupling product, **5**, was separated from the side products (**1** and **3**) with a sequence of three extractions with CH_2Cl_2/aq.HBr, followed by column chromatography with silica gel eluting first with $CHCl_3$, and then with $CHCl_3/CH_3OH$ 99:1 v/v, and recrystallization from CH_2Cl_2/hexane. Yield: 0.67 g (35 %); mp ~82°C (dec.); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.47 (6H, br s), 4.27 (4H, br s), 5.25 (2H, d, J_{hi}=17.3 Hz), 5.34 (2H, d, J_{hj}=10.3 Hz), 5.91-5.97 (2H, m), 6.66 (1H, d, J_{bc}=8.4

Hz), 6.836 (1H, d, J_{ab}=2.0 Hz), 6.88 (1H, dd, J_{bc}=8.4 Hz, J_{ab}=2.0 Hz), 7.19 (1H, dd, J_{ef}=9.6 Hz, J_{ed}=2.7 Hz), 7.31 (1H, d, J_{ed}=2.7 Hz), 7.39 (1H, d, J_{ef}=9.6 Hz); Low resolution FAB (Gly) m/z 336.2 (cation).

The preparation of 3,7-bis[dimethylamino]phenothiazin-5-ium bromide (methylene blue: 1) was carried out in ethanol and in $CHCl_3$ using in both cases 1.0 g (2.29 mmol) of **8**, and 6 ml of a 2 M solution of dimethylamine in methanol (Aldrich) (12 mmol), following the conditions for the preparation of **3** above. Because **1** is soluble in water, extractions were omitted from purification, and **1** was eluted from the column when the $CHCl_3/CH_3OH$ mixture was 95:5 (v/v). Yield in ethanol: 0.58 g (70 %), and in $CHCl_3$: 0.71 g (85%). ^1H NMR ($CDCl_3$, 300 MHz) δ 3.49 (12H, s), 7.29 (2H, dd, J_{ab}=3.0 Hz, J_{bc}=7.9 Hz), 7.55 (2H, d, J_{ab}=3.0 Hz), 7.95 (2H, d, J_{bc}=7.9 Hz); Low resolution FAB (3-NBA) m/z 284.1 (cation).

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11. Found: C: 39.10; H, 1.90; N, 3.97; S, 8.76; Br, 46.52. Calculated for **7**: C, 40.37; H, 1.98; N, 3.92; S, 8.98; Br, 44.75. The calculated values for **8** are given in the experimental section.
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18. It is noteworthy that despite the multistep mechanisms, Fig. 3A and 3B show no sign of intermediates (such as **8a**, Eq.[2]) and no loss of isosbestic points: the spectrum of **8** evolves directly into the spectra of **3** or **9** respectively, suggesting that the corresponding rate determining step occurs early, and is followed by a fast cascade of events leading to the product. By analogy to what is known on nucleophilic aromatic substitutions of bromine atoms with secondary amines,[19] we expect at least for Eq.[2] simple bimolecular kinetics where the slow step is the coordination of the amine to carbon. From this perspective, the first order kinetics of Fig.s 3A and 3B are interpreted as pseudounimolecular, and second order rate constants can be calculated.
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21. In contact with air **8** turns to an insoluble purple-black material over a period of 2-3 days, while in DMF/0.1 M TBAP **8** shows an irreversible oxidation wave above 0.8 V vs. Ag/AgCl.
22. For identification purposes, compound **9** was prepared by stirring **8** in ethanol at room temperature under continuous N_2 purge, overnight. The cherry red product was purified with TLC (silica gel; $CHCl_3$; R_f~0.8). mp 203-206°C (dec.); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.48 (6H, t, J=7.0 Hz), 4.14 (4H, q, J=7.0 Hz), 6.73 (2H, d, J_{ab}=2.5 Hz), 7.03 (2H, dd, J_{bc}=8.7 Hz, J_{ab}=2.5 Hz), 7.82 (2H, d, J_{bc}=8.7 Hz); IR (KBr): 828(m), 849(w), 863(m), 1114(w), 1132(w), 1211(m), 1249(m), 1278(m), 1349(m), 1496(m), 1529(m), 1605(s), 1620(s), 2978(w), 3057(w) cm^{-1}; UV-Vis. (ethanol) λ_{max}, nm (ε, $M^{-1}cm^{-1}$): 498 (46,300), 284 (62,300), 252 (81,000);[15] low resolution FAB (3-NBA/Gly/TFA) m/z 286.0 (cation).
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