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Diazaphenoxazines and Diazaphenothiazines: Synthesis of the "Correct" Isomers Reveals They Are Highly Reactive Radical-Trapping Antioxidants

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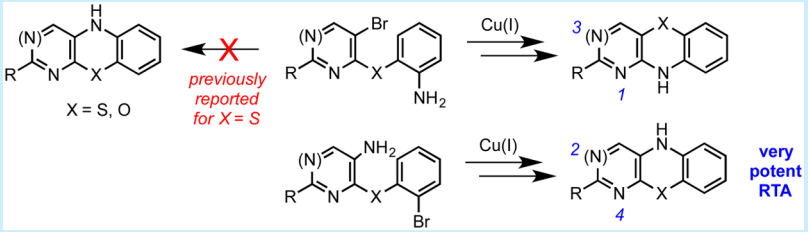
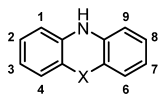
Supporting Information



ABSTRACT: The preparation of 2,4-diazaphenothiazines and 2,4-diazaphenoxazines via a copper-catalyzed intramolecular amination is described. Literature approaches which utilize easily accessed (2′-aminophenyl) 4-pyri(mi)dyl sulfides undergo a Smiles rearrangement that gives rise to the 1,3-diaza derivatives instead, confirmed by X-ray crystallography. Inversion of the polarity of the cyclization avoids the rearrangement and affords the desired products. Preliminary kinetic studies suggest that 2,4-diazaphenothiazines and diazaphenoxazines, but not the 1,3-diaza isomers, are remarkably potent radical-trapping antioxidants.

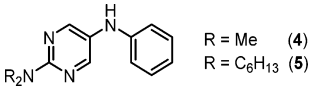
Phenoxazines and phenothiazines (i.e., **1** and **2**, Figure 1) figure prominently in medicinal chemistry,[1−5] and their photophysical properties have enabled their use in dye-sensitized solar cells,[6−8] organic light emitting diodes,[9−11] and as photoredox catalysts.[12] Phenothiazines have also long been known to possess potent antioxidant activity[13] and have been pursued as additives to protect petroleum-derived products, including lubricants, rubber, and fuels from (peroxyl) radical-mediated autoxidation. At ambient temperatures, phenothiazine is 440-fold more reactive to peroxyl radicals than diphenylamine (**3**),[14] the base structure of the industry-standard alkylated diphenylamine (DPA) radical-trapping antioxidants (RTAs).[15,16] Phenoxazine is a further 3-fold more reactive under the same conditions.[14,17]



X	k_{inh}^{PhCl} ($M^{-1}s^{-1}$)	
O	2.9×10^7	(**1**)
S	8.8×10^6	(**2**)
H,H′	2.0×10^4	(**3**)

Figure 1. General structures of phenoxazine (**1**), phenothiazine (**2**), and diphenylamine (**3**) and the rate constants for their reactions with peroxyl radicals (k_{inh}, in chlorobenzene).

Previous work by our group has shown that incorporation of heteroatoms at the 3- and/or 5-position of one or both of the aromatic rings of diarylamines greatly stabilizes them toward one electron oxidation.[18,19] This modification enables ring substitution with strongly electron-donating groups, which weaken the N−H bond and increases the rate of H atom transfer to peroxyl radicals without compromising stability to one-electron oxidation. For example, diarylamine **4** is ∼20-fold more reactive than the industry-standard alkylated DPA at ambient temperatures,[18,19] a difference that translates to the inhibition of high temperature autoxidations of heavy hydrocarbons by **5**.[20] Reasoning that phenoxazine and phenothiazine would present a better scaffold for further optimization, we sought to incorporate oxygen and sulfur into the structures of **4**, **5**, and related heterocyclic diarylamines.



Although there has been some interest in aza-analogues of phenoxazine and phenothiazine,[21−29] 2-aza, 4-aza-, and 2,4-diaza derivatives have received little attention.[30,31] Of particular relevance, Bakavoli and co-workers reported the preparation of phenothiazine analogs of **4**/**5** (Scheme 1) and their study as inhibitors of 15-lipoxygenase catalysis.[31−34] When we attempted to reproduce Bakavoli's synthesis of a representative 2,4-diazaphenothiazine (the 3-pyrrolidine-substituted derivative **6**), the crude material contained only trace amounts of the product.[33] However, upon recrystallization (as reported), a significant quantity of the major product was converted to the initially trace (reported) product. We surmised that our crude material may have undergone oxidation during recrystallization. Indeed, when the reaction was repeated and the crude material was treated with a basic methanolic solution of iodine, the reported product was obtained. This product was characterized by us to be disulfide **7**

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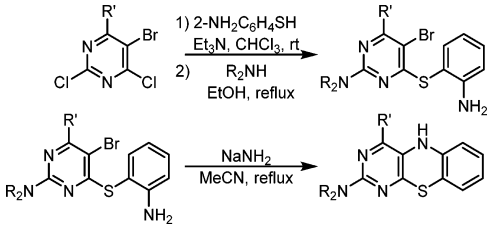
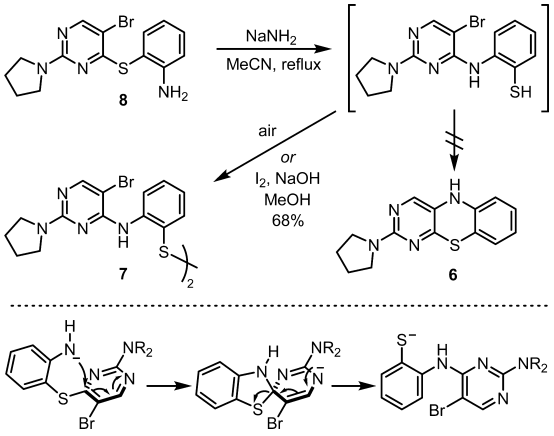
Scheme 1. Reported Synthesis of 3-Amino-2,4-diazaphenothiazines Analogous to 4/5



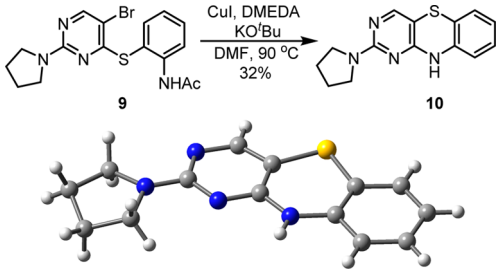
(see Supporting Information (SI)), implying that the initial product was the corresponding thiol, and the difference between our experiment and that of Bakavoli was simply that *in situ* oxidation of the thiol(ate) was minimized in our hands. Thus, **8** undergoes a Smiles rearrangement under these conditions,[35] with the amide displacing the thiolate as in Scheme 2.

Scheme 2. Literature Conditions for Cyclization of 8 to 6 Yields the Rearranged Thiol and Corresponding Disulfide 7



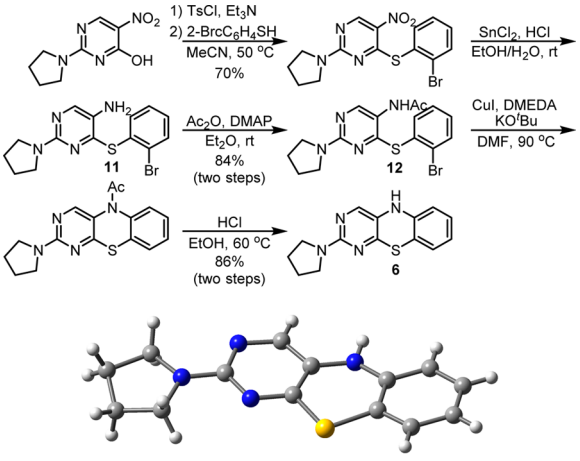
In an attempt to favor cyclization over the Smiles rearrangement, we converted the amine to the less nucleophilic acetamide (**9**) and subjected it to Ullmann-type conditions (Scheme 3). This afforded a new product whose structure was determined unambiguously by single-crystal X-ray diffraction to be the 1,3-diazaphenothiazine **10**. Thus, although the cyclization proceeded (in good conversion, but poor yield after chromatography), it *follows* the Smiles rearrangement. Unfortunately, the same was true when the bromide was exchanged with an iodide. Evidently, these substrates are too activated to the Smiles rearrangement, which copper may even promote.[36]

Scheme 3. Preparation of 1,3-Diazaphenothiazine 10 and Its Structure As Determined by Single Crystal X-ray Diffraction



To suppress the Smiles rearrangement, the polarity of the reaction was reversed; that is, the positions of the amine and bromide substituents on the pyrimidyl and phenyl rings were exchanged (i.e., **11** in Scheme 4).[37] Following acetylation to give

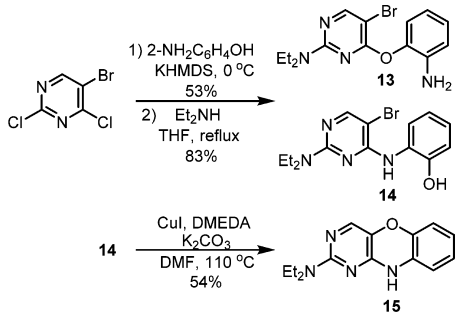
Scheme 4. Preparation of 2,4-Diazaphenothiazine 6 and Its Structure As Determined by Single Crystal X-ray Diffraction



12, the cyclization proceeded with excellent conversion, and subsequent deprotection provided the desired 2,4-diazaphenothiazine **6** in 86% (isolated) yield. Given that our ^{1}H and ^{13}C NMR spectral data were significantly different than those reported by Bakavoli et al. (which we have now shown correspond to disulfide **7**),[33] we determined the structure of our product unambiguously by single-crystal X-ray diffraction in order to confirm that it was indeed **6**.

The synthesis of the corresponding 2,4-diazaphenoxazine derivative was similarly problematic. The preparation of **13**, the diaryl ether analogous to diaryl thioether **8** (Scheme 2), required explicit prior formation of the phenolate, and despite the poorer leaving group, the Smiles rearrangement proceeded readily upon installation of the diethylamino substitutent to give an ~1:1 mixture of **13** and **14** (Scheme 5). Subsequent cyclization of **14**

Scheme 5. Preparation of 1,3-Diazaphenoxazine 15



gave the 1,3-diazaphenoxazine **15**. However, as was the case with the sulfur analog, exchanging the amine and halide substituents provided the desired 2,4-diazaphenoxazine **16** (Scheme 6). To the best of our knowledge, **16** is the first reported 2,4-diazaphenoxazine.

With the two isomers of representative diazaphenothiazines and diazaphenoxazines in hand, the RTA activity of each was measured by the inhibited autoxidation of 1,4-dioxane. The autoxidations were monitored by following the consumption of

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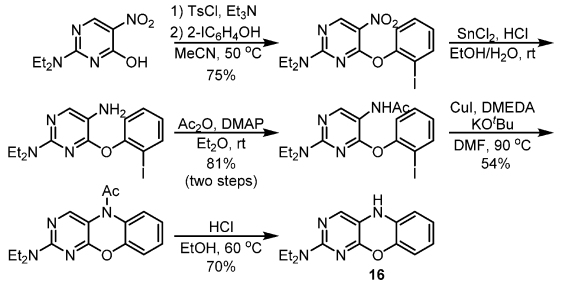
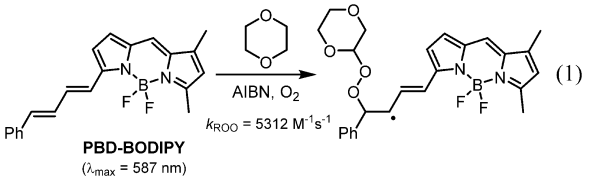
Scheme 6. Preparation of 2,4-Diazaphenoxazine 16



PBD-BODIPY, a highly oxidizable and highly absorbing substrate which is added to the autoxidation to enable reaction monitoring by conventional spectrophotometry (eq 1).[38,39] The rate



(1)

constants for the reaction of the amines with chain-carrying peroxyl radicals and the reaction stoichiometry (k_{inh} and n, respectively) can be calculated from the initial rate and inhibited period of PBD-BODIPY consumption through the use of eqs 2 and 3, respectively. Representative autoxidation traces for **6**, **10**, **15**, and **16** are shown in Figure 2.

$$\frac{-\mathrm{d}[\text{PBD-BODIPY}]}{\mathrm{d}t} = \frac{k_{ROO}[\text{PBD-BODIPY}]R_i}{nk_{inh}[\text{RTA}]} \quad (2)$$

$$t_{inh} = \frac{n[\text{RTA}]}{R_i} \quad (3)$$

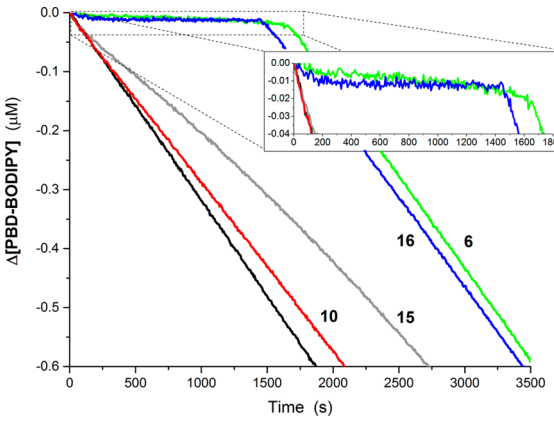
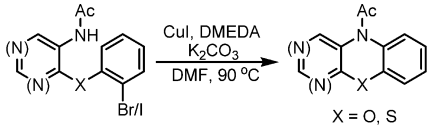


Figure 2. Co-autoxidation of 1,4-dioxane (2.9 M) and PBD-BODIPY (10 μM) initiated by AIBN (6 mM) in PhCl at 37 °C (black) and inhibited by 2 μM of **6** (green), **10** (red), **15** (gray), and **16** (blue). Reaction progress was monitored by absorbance at 587 nm (ε = 123 023 M^{-1} cm^{-1}).

Although the 1,3-diazaphenothiazine **10** barely inhibits the autoxidation and the 1,3-diazaphenoxazine **15** only retards it, the corresponding 2,4-diaza isomers **6** and **16** are remarkably effective. The stark difference in reactivity between the isomers is consistent with the trends we have observed in the simpler diarylamines, where nitrogen incorporation at tautomerizable positions is highly detrimental.[18] The inhibited periods (of *ca.* 1600 s) observed for the 2,4-diaza isomers correspond to the trapping of two chain-carrying peroxyl radicals—as is typical for diarylamine RTAs at ambient temperatures.[16,18,19] The very slight initial rate of the autoxidation inhibited by the 2,4-diazaphenothiazine **6** corresponds to a rate constant for its reaction with chain-carrying peroxyl radicals of $k_{inh}^{dioxane}$ = 5.0 × 10^6 M^{-1} s^{-1}; while the 2,4-diazaphenoxazine **16** is so reactive that it completely suppresses the autoxidation, precluding determination of a rate constant. To enable comparison of the reactivity of **6** with other diarylamines, its inhibition rate constant was corrected for the retarding effect of H-bonding of the aminic H-atom to dioxane using the Ingold-Abraham relationship (eq 4, where $\Delta\beta_2^H = 0.26$ is the difference in the H-bond basicity of the solvents and $\alpha_2^H = 0.44$ is the H-bond acidity of the H-atom donor; see SI).[40,41] The corresponding value of k_{inh}^{PhCl} = 4.5 × 10^7 M^{-1} s^{-1} exceeds that of any diarylamine RTA ever reported.[19] Given that the 2,4-diazaphenoxazine **16** is an even better inhibitor than **6** (consistent with the difference between phenoxazine and phenothiazine, see Figure 1),[14] its rate constant must be >10^8 M^{-1} s^{-1}, suggesting $E_a \approx 0$ since log A for this H-atom transfer is likely to be around 8.[42]

$$\log(k_{inh}^{PhCl}) = \log(k_{inh}^{dioxane}) + 8.3\alpha_2^H\Delta\beta_2^H \quad (4)$$

The 2-aza and 4-aza phenothiazines and phenoxazines can also be prepared using the approach described above.



Although compounds of these types have previously been reported,[21,43] the conditions under which they have been prepared are often significantly harsher than those described above (e.g., 10 equiv of activated Cu, 160 °C).[21,44] Moreover, many of the reported routes are vulnerable to the Smiles rearrangement, leading to the incorrect (undesired) isomer. For example, we have found that recent reports of the syntheses of substituted 4-azaphenothiazines[45] and 4-azaphenoxazines[46] lead to 1-azaphenothiazines and 1-azaphenoxazines, respectively (see SI for complete details). Not unexpectedly, it is difficult to assign the structures of these molecules simply from their NMR spectra, examples of which are included in Figure 3 (see the SI for ^{13}C NMR spectra).[47] This underscores the need for multiple modes of characterization for structural elucidation.

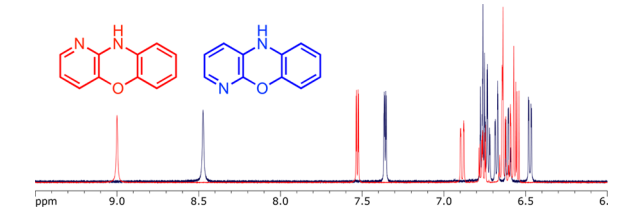


Figure 3. ^{1}H NMR spectra of 1-azaphenoxazine and 4-azaphenoxazine in d_6-DMSO at 25 °C.

In summary, we have developed a successful strategy to synthesize 2,4-diazaphenothiazine and 2,4-diazaphenoxazine derivatives. Some previously reported syntheses of these compounds have been mischaracterized because of a favorable Smiles rearrangement. Reversing the polarity of the intramolecular cross-coupling reaction suppresses the rearrangement and allows successful construction of the central oxazine or

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thiazine ring. 1,3-Diazaphenoxazine and diazaphenothiazine derivatives have moderate reactivity as radical-trapping antioxidants, while the corresponding 2,4-diaza derivatives are some of the fastest RTAs ever reported, trapping peroxyl radicals at rates approaching diffusion. Given these results, we anticipate more detailed studies on the synthesis and properties of azaphenoxazine and phenothiazine derivatives as RTAs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00615.

Crystallographic information (CIF, CIF)
Synthetic schemes and procedures, characterization data, inhibited autoxidation procedures (PDF)

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Notes

The authors declare no competing financial interest.

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(47) It should be noted that although the original NMR characterization for these compounds is often incomplete, melting points for 1- and 4-azaphenoxazine and azaphenothiazine have been reported and are consistent with those measured by our group.

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