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Preparation of Halogenated Fluorescent Diaminophenazine Building Blocks

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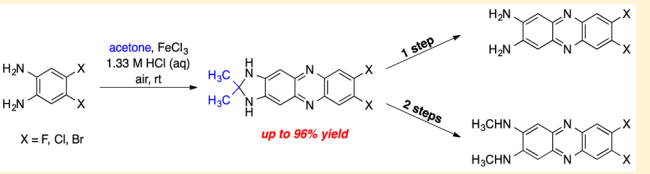
Supporting Information

ABSTRACT: A short, convenient, and scalable protocol for the one-pot synthesis of a series of fluorescent 7,8-dihalo-2,3-diaminophenazines is introduced. The synthetic route is based on the oxidative condensation of 4,5-dihalo-1,2-diaminobenzenes in aqueous conditions. The resulting diaminophenazines could be attractive intermediates for the preparation of polyfunctional phenazines and extended polyheteroacenes. We find that the undesired hydroxylation byproducts, typically obtained in aqueous conditions, are completely suppressed by addition of a stoichiometric amount of acetone during the oxidation step allowing for selective formation of 7,8-dihalo-2,2-dimethyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]phenazine derivatives with good to excellent yields. Under reductive conditions, the imidazolidine ring can be hydrolyzed into the desired 7,8-dihalo-2,3-diaminophenazines. Furthermore, we report a selective route under highly reducing conditions to monohydrodeaminate the 2,3-di(methylamino) phenazine derivatives, which allows for further structural variations of these phenazine building blocks. All of these derivatives are luminescent, with measured fluorescence quantum-yields of up to 80% in ethanol for the more rigid structures, highlighting the potential of such materials to provide new fluorophores.



INTRODUCTION

Phenazines, (i.e., 5,9-diazaanthracenes) and their derivatives are important and versatile building blocks for the preparation of industrial dyes,[1] fluorescent or electroactive markers in biological systems,[2,3] antibiotics and anticancer agents,[4−6] electroactive materials for OFETs, OLEDs, and solid state memories,[7,8] as well as photoactive materials for dye sensitized solar cells and for photocatalysis.[9−12] There is, therefore, a great need to develop efficient protocols for synthesis of these important building blocks. In this paper, we introduce a convenient and very short synthetic route to 7,8-dihalo-2,3-diaminophenazines based on oxidative condensation of 4,5-dihalo-1,2-diaminobenzenes in aqueous conditions. The products are suitable for further functionalization to adapt them for a variety of potential applications.

Several well-established methods are available for the preparation of functionalized phenazines.[5] The most popular route is based on direct condensation of adequately functionalized *o*-quinone or catechol with *o*-phenylenediamine derivatives.[13−15] This method permits the preparation of a variety of extended polyazaacene cores in modest to high yields from readily available starting materials. Other methods feature the intramolecular cyclization of substituted diphenylamines such as 2,2′-diaminodiphenylamines and 2-aminodiphenylamines,[16,17] 2-nitrodiphenylamines,[18] or 2-fluoro-2′-nitrodiphenylamines;[19] the Pd-catalyzed cyclization of 2-amino-2′-bromodiphenylamines;[20] the chemical[21−23] or electrochemical[24−26] oxidative cyclization of fluorinated aniline derivatives; and the oxidative condensation of *o*-phenylenediamines.[27,28] We investigate the latter strategy and present an expeditious protocol for the synthesis of 7,8-dihalo-2,3-diaminophenazines, where the halogen substituents can be F, Cl, or Br.

Our work fills a gap in the literature pertaining to strategies for the preparation of 7,8-dihalo-2,3-diaminophenazines, which appear to be appealing building blocks for the preparation of larger heteroacenes and polyfunctional materials.[29−31] This gap is surprising, considering that the synthesis of 7-chloro- and 7-bromo-2,3-diaminophenazines has been previously described from oxidative coupling of 4-chloro- and 4-bromo-1,2-diaminobenzene in the presence of iron trichloride or hydrogen peroxide.[28,32,33] In these examples, the cyclization systematically led to the elimination of the halide substituent rather than leading to a reaction involving the two adjacent unsubstituted positions (positions 5 and 6). This selectivity pattern suggested dihalogenated *o*-phenylenediamines as judicious starting materials for the preparation of the corresponding 7,8-dihalo-2,3-diaminophenazines.

RESULTS AND DISCUSSION

As previously observed in the case of monohalogenated and halogen free 1,2-diaminobenzenes,[28,34,35] the direct treatment of 4,5-dihalo-1,2-diaminobenzene with aqueous iron trichloride, under acidic conditions, leads to the formation of a mixture of

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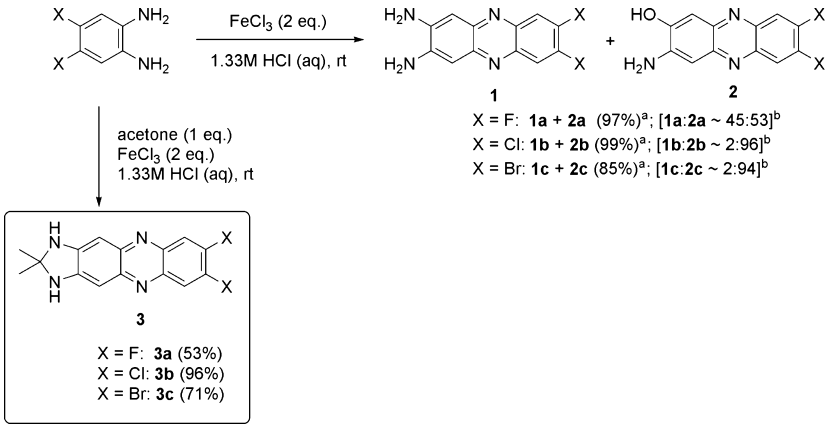
Scheme 1. Chemically Driven Oxidative Condensation of 4,5-Dihalo-1,2-diaminobenzene Derivatives in Aqueous Conditions, in Absence (Right) Or Presence (Bottom Left) of Acetone



[a]On the basis of the isolated mixture of products. [b]Ratio estimated using liquid chromatography mass spectrometry (LC−MS) analysis.

products that include monohydroxylated 7,8-dihalo-phenazine derivatives (Scheme 1 and Supporting Information). We find that the presence of an equimolar amount of acetone allows for the oxidation of 4,5-dihalo-1,2-diaminobenzene derivatives selectively, yielding the corresponding 7,8-dihalo-2,2-dimethyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]phenazine, with good to excellent yields (Scheme 1). Moreover, formation of both 2,3-diaminophenazines and hydroxylated derivatives can be completely suppressed under optimized conditions.[36] In the case of the halogen-free *o*-phenylenediamine starting material, however, hydroxylation of the phenazine could not be entirely suppressed, even upon addition of a large excess of acetone (see SI).

The selective formation of the imidazolidine derivatives **3a−c** from the halogenated *o*-phenylenediamines is remarkable. In test reactions, the direct condensation of acetone with 7,8-dichloro-1,2-diaminophenazine was not observed under simple acid catalysis. It is, therefore, likely that cyclic acetone adducts of the 4,5-dihalo-1,2-diaminobenzene starting material are formed prior to condensation of the phenazine backbone. Plausible intermediates that could lead to the imidazolidine derivatives are the corresponding 5,6-dihalo-2,2-dimethyl-2*H*-benzo[*d*]imidazoles.

This idea is consistent with previous studies showing that 2*H*-benzo[*d*]imidazoles can readily undergo nucleophilic attack on the 5 and 6 positions, due to their o-benzoquinone diimine character.[37,38] Furthermore, highly efficient *ipso* substitution of chloro groups was reported upon treatment of 5,6-dichloro-2*H*-benzo[*d*]imidazole with N, O, or S nucleophiles.[39] In the latter study, the authors identified a phenazine derivative as the major byproduct of the reaction. The formation of the phenazine derivative was explained by the reaction of 5,6-dichloro-2*H*-benzo[*d*]imidazole with traces of 4,5-dichloro-1,2-diaminobenzene that were present after the in situ hydrolysis of the former.[39]

The condensation of acetone on *o*-phenylenediamine to form 2,2-dimethyl-2,3-dihydro-1*H*-benzo[*d*]imidazole is known to have very fast kinetics under mild acid catalysis.[40] Therefore, it is likely that under the strongly acidic conditions used in the present work, the starting 4,5-dihalo-1,2-diaminobenzenes equilibrate with the corresponding 5,6-dihalo-2,2-dimethyl-2,3-dihydro-1*H*-benzo[*d*]imidazole derivatives. In the latter derivatives, the inclusion of the two amino groups in a five membered ring increases their conjugation with the adjacent phenyl ring. This may explain the selective oxidation of the 5,6-dihalo-2,2-dimethyl-2,3-dihydro-1*H*-benzo[*d*]imidazole derivatives by iron trichloride over the noncyclized 4,5-dihalo-1,2-diaminobenzenes and, thus, the formation of the 5,6-dihalo-2,2-dimethyl-2*H*-benzo[*d*]imidazole intermediates.

In the proposed reaction scheme (cf. to SI), the formation of the phenazines **3a−c** results from the *ipso* substitution of the halogen groups in the 5,6-dihalo-2,2-dimethyl-2*H*-benzo[*d*]-imidazoles by the remaining *o*-phenylenediamines, followed by the tautomerization into the final imidazolidine products. Because of the complex sequence of reactions required for formation of the latter compounds in a one-pot approach, a strict control of the stoichiometry of the reagents is crucial to achieve high yields. Importantly, this strategy is readily scalable to gram-scale synthesis as shown for compound **3b** (see Experimental Section).

The assignment of **3a−c** as having a fully oxidized phenazine core fused to a dihydro-imidazole (imidazolidine) ring is supported by extensive NMR characterization (see SI). In particular, the observation of through-space spin polarization transfer (NOE), between the protons of the methyl groups and those of the amine groups, unambiguously permitted the assignment of the secondary amine groups to the five membered rings rather than to the pyrazine cycle.

Next, we investigated ways to obtain the desired 7,8-dihalo-2,3-diaminophenazine cores by opening the imidazolidine ring. First, we examined the acid-catalyzed hydrolysis of the Me_2C protecting group using **3b** as a model compound. Negligible hydrolysis to **1b** occurred under any of the following conditions: concentrated HCl; TFA or sulfuric acid in the presence of 5−10% of water between room temperature and 60 °C. Upon treatment of **3b** with 5−10% water in concentrated sulfuric acid (or TFA), at temperatures higher than 70 °C, slow hydrolysis of the Me_2C protecting group occurred over the course of several days, yielding the desired phenazine **1b** concurrently with the formation of the undesired monohydroxylated derivative **2b**. Unfortunately, the latter process could not be avoided and it hampered the use of acid hydrolysis as a direct way to obtain the targeted diaminophenazine derivatives.

Noting that the electron withdrawing character of the phenazine core may impede deprotection by greatly increasing the acidity of the amino substituents, we thought that its

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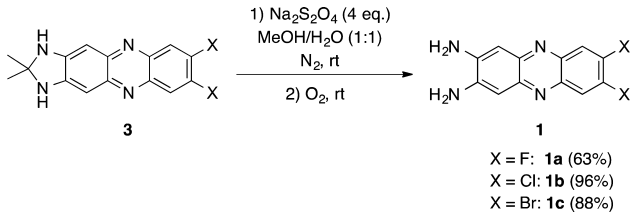
reduction to the corresponding *N*,*N*-dihydrophenazine might allow hydrolysis of the Me_2C protecting group under mild conditions. Indeed, we find that the treatment of **3b** with an aqueous solution of sodium dithionite at room temperature, under an inert atmosphere, directly leads to the very clean deprotection of the amines. After completion of the hydrolysis, simple exposure to air led to the spontaneous oxidation of the *N*,*N*-dihydrophenazine intermediate to give **1b** in excellent yields (Scheme 2). This approach was very efficient for all three imidazolidine derivatives **3a**−**c**, with no noticeable side reactions.

Scheme 2. Hydrolysis of the Me_2C Protecting Group under Reductive Conditions



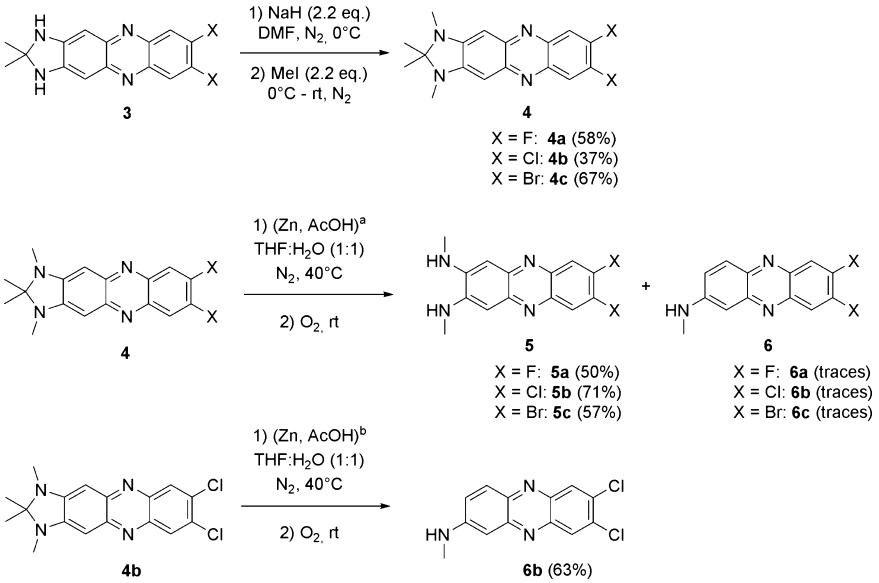
Interestingly, no additional acid catalyst was required to promote the reaction; after the reduction of the phenazine core, the weakly acidic solution resulting from the decomposition of sodium dithionite was sufficient to fully hydrolyze the Me_2C protecting group.[41] This simple protocol thus provides a very convenient way to deprotect the 7,8-dihalo-2,2-dimethyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]phenazine series, and permits the preparation of a variety of 7,8-dihalo-1,2-diaminophenazines in high yields.

The imidazolidine series was expanded via alkylation of **3a**−**c** with MeI to obtain the very soluble derivatives **4a**−**c** (Scheme 3). The latter failed to undergo hydrolysis of the Me_2C protecting group under the conditions used for the parent **3a**−**c** derivatives. After treatment with sodium dithionite and reoxidation in air, most of the starting material was recovered; no traces of the desired 7,8-dihalo-2,3-di(methylamino)-phenazines could be detected. Neither the addition of catalytic amounts of strong acid (trifluoroacetic acid, hydrochloric acid, or *p*-toluenesulfonic acid) after full reduction of the starting material nor the direct treatment of **4b** with $SnCl_2$ in hydrochloric acid provided the desired products. Treatment with zinc powder in aqueous conditions in the presence of acetic acid, however, permitted the isolation of the desired 7,8-dihalo-2,3-di(methylamino)phenazines **5a**−**c** in good yields (Scheme 3).

Monohydrodeamination of the desired phenazines to give **6a**−**c** was identified as a major side reaction. The product distribution was found to be highly sensitive to the rate of addition and amount of zinc powder and acetic acid. In the case of fast addition of a large excess of the latter reagents, 7,8-dichloro-2-methylaminophenazine **6b** could be obtained as the main product in good yield (Scheme 3). Under the conditions tested, the hydrodeamination reaction is selective for *N*-methylated derivatives; treatment of the parent imidazolidine derivative **3b** under the same conditions led to the isolation of the 7,8-dichloro-2,3-diaminophenazine **1b** as the major product of the reaction, with no noticeable hydrodeamination observed. This provides an alternative route for the hydrolysis of the Me_2C protecting group of **3a**−**c** derivatives. The rationalization of the selective monohydrodeamination of the bis-(methylamino)phenazine derivatives is beyond the scope of this letter and will be the topic of further investigations.

Having access to a variety of hitherto unknown phenazine building blocks, we next investigated the fundamental physicochemical properties of a few representative analogues (Table 1). Overall, the photophysical properties of the newly synthesized aminophenazines are comparable with data reported previously for related compounds.[42,43] In brief, the absorption spectra of the dichloro-phenazine derivatives **1b**,

Scheme 3. *N*-Methylation of Compounds 3a−c, Hydrolysis of the Me_2C Protecting Group under Reductive Conditions, and Hydrodeamination



[a]Portion-wise addition of the reagents; addition of 7.5−15 equiv of zinc. [b]Direct addition of a large excess of the reagents; addition of 25−50 equiv of zinc. See SI for detailed procedures.

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Table 1. Comparison of Experimental and Theoretical Properties of Phenazines Derivatives

phenazine	$\lambda_{max,\ abs}$ [a] (nm)	$\varepsilon_{max,\ abs}$ [a] ($M^{-1}\ cm^{-1} \times 10^3$)	$\lambda_{max,\ emission}$ [b] (nm)	E^{0-0} [c] (eV)	E^{0-0}_{calc} [c,d] (eV)	Φ_{fluor} [e]	$E_{1/2}(0/-1)$ [f] V vs NHE
1a	433	17.5	537	2.52	2.57	n.d.	n.d.
1b	442	20.8	549	2.48	2.46	0.10	n.d.
1c	442	18.8	550	2.47	2.50	n.d.	n.d.
3a	440	29.1	496	2.62	2.93	n.d.	n.d.
3b	471	26.7	506	2.56	2.86	0.42	n.d.
3c	473	27.0	508	2.56	2.85	n.d.	n.d.
4a	457	30.0	488	2.61	2.83	0.80	−1.34
4b	471	27.0	497	2.56	2.77	0.70	−1.27
4c	473	29.3	500	2.56	2.77	0.11	irreversible
5a	434	13.3	529	2.58	2.58	n.d.	n.d.
5b	442	20.8	541	2.51	2.48	0.14	irreversible
5c	443	25.2	542	2.53	2.48	n.d.	n.d.
6b	490	11.4	599	2.25	2.11	0.06	−0.98

[a]Reported for the wavelength with the highest extinction coefficient in the visible range; spectra recorded in absolute ethanol at room temperature. [b]Excitation at 300 nm, for samples with an optical density (OD) below 0.06; recorded in absolute ethanol at room temperature. [c]Estimated from the crossing point of the normalized experimental absorption and emission spectra. [d]Calculations performed at the CAM-B3LYP42/6-31G(d,p) level of theory using Gaussian09. [e]Excitation at 300 nm, under aerobic conditions; sample OD was adjusted to 0.049 using rhodamine-6G as the reference (Φ_{fluor} Rhodamine-6G ∼ 0.95); spectra collected in absolute ethanol at room temperature. [f]Measured in dichloromethane using 0.1 M tetra-*n*-butylammonium hexafluorophosphate as supporting electrolyte, using platinum as working and counter electrodes and ferrocene (Fc) as the internal reference, with $E_{1/2}$ (Fc^+/Fc) = 0.72 V vs NHE. n.d. = not determined.

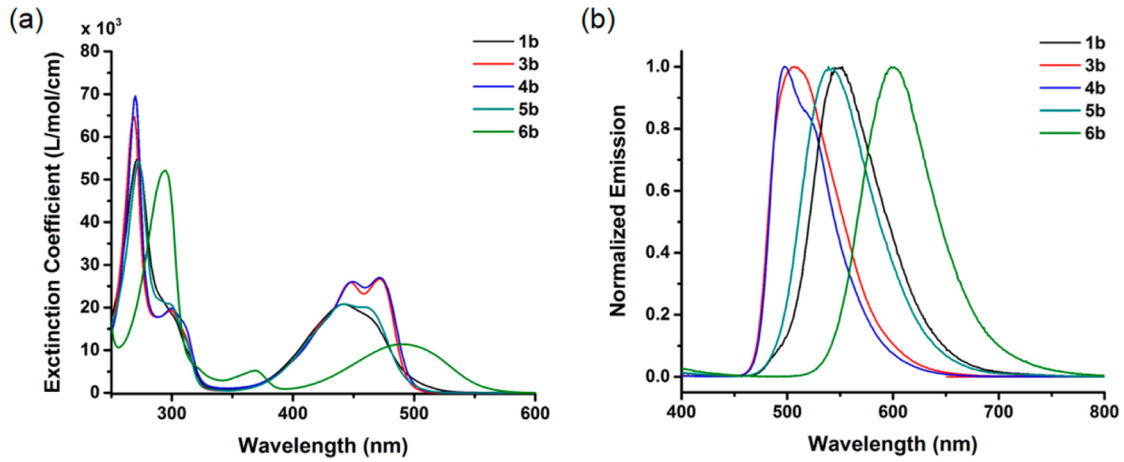

Figure 1. Absorption (a) and normalized emission (b) spectra of the dichloro-phenazine derivatives **1b**, **3b**−**6b**, collected in absolute ethanol at room temperature. The emission spectra were recorded with excitation at 300 nm.

3b−**6b** are depicted in Figure 1a. As can be observed, the imidazolidine derivatives **3b** and **4b** exhibit slightly red-shifted visible absorption bands compared to those of the corresponding uncyclized diamines **1b** and **5b**. Furthermore, the vibronic fine structure of the absorption band is better resolved in the case of the imidazolidine derivatives, and the latter generally possess higher extinction coefficients. Methylation of the amino substituents does not induce any marked shift of the absorption bands; however, it does lead to slight variations in the extinction coefficients. Finally, the monoamino derivative **6b** exhibits a very distinct spectrum with a large red-shift and significant broadening of the main visible bands, as was reported for the unhalogenated bis- and monoaminophenazines.[43]

Similar trends apply to the fluorinated and brominated series (see SI for the full spectra). A more substantial variation of the extinction coefficients is observed after the methylation of the amine substituents in the latter series. Across the phenazine spectra, a systematic blue shift is noticeable on going from the fluorinated derivatives to the chlorinated and brominated analogues (Table 1). This is consistent with the slightly greater π-donating character of the fluorine substituents, as compared to the Cl or Br substituents. The inductive effects of the three halogens are comparable, which are indicated by the Swain−Lupton parameters: F: F = +0.45, R = −0.39; Cl: F = +0.42, R = −0.19; Br: F = +0.45, R = −0.22 (where F is the field effect parameter, and R is the resonance parameter).[44]

All of the derivatives are luminescent in ethanol. Their main emission peaks are reported in Table 1 (see Figure 1b and SI for full emission spectra). Likely due to their increased rigidity, the imidazolidine derivatives show a smaller Stokes shift as compared to the acyclic derivatives, with typical values of 40 nm for the former as compared to 100 nm for the latter. Furthermore, methylation of the amines resulted in a minor decrease in the Stokes shift (<10 nm). The fluorescence quantum yields (Φ_{fluor}, Table 1) for **1b**, **3b**−**6b**, **4a** and **4c** were measured at room temperature in air-saturated ethanol. As shown by the chlorinated aminophenazines **1b** and **3b**−**6b**, two main factors appear to modulate the quantum yield of fluorescence of the derivatives. The alkylation of the amino

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substituents, as well as inclusion of the latter substituents in the imidazolidine rings leads to a remarkable increase of fluorescence with $\Phi_{fluor} \sim 0.10$, 0.14, 0.42, and 0.70 for **1b**, **5b**, **3b** and **4b**, respectively. The latter trend can be rationalized by the progressive suppression of the major nonradiative de-excitation pathways associated with vibrational and rotational degrees of freedom of the amino groups. Finally, the change in the fluorescence quantum yields for the methylated imidazolidine series **4a–c** follows the expected trend with $\Phi_{fluor} \sim 0.80$, 0.70, and 0.11 for **4a**, **4b**, and **4c**. The decrease in fluorescence from the fluorinated to the brominated derivatives is likely due to the increasing heavy atom effect of the halogen substituents.

The main trends in the absorption and emission properties of the phenazine derivatives were captured by DFT and TDDFT calculations, performed at the CAM-B3LYP[45]/6-31G(d,p) level of theory, using the SMD continuum solvation model.[46,47] As shown in Table 1, the experimental and theoretical E^{0-0} energies are in good agreement, consistent with previous studies.[48] Deviations, when comparing the E^{0-0} energies of the cyclized systems, might be due to the lack of specific solvent–solute interactions, including hydrogen bonds in ethanol. An extended computational analysis of the photophysical properties of phenazine derivatives, including more detailed solvents effects, will be the topic of a forthcoming report.

Finally, the electrochemical properties of **4a–c**, **5b**, and **6b** were investigated in dichloromethane with 0.1 M tetra-*n*-butylammonium hexafluorophosphate. All of the compounds featured irreversible oxidation waves, above 1.15 V vs NHE, as expected for the oxidation of alkylamino substituents.[49] In addition, **4a**, **4b** and **6b** exhibited a reversible one-electron redox couple at −1.34 V, −1.27 V and −0.98 V vs NHE, respectively. The latter can be assigned to the reduction of the phenazine to its radical anion. Compounds **4c**, and **5b**, in contrast, featured irreversible cathodic waves. The presence of bromine substituents may explain this behavior in the case of **4c**; however, the irreversible cathodic current associated with **5b** was not expected. It could be related to the selective hydrodeamination reaction observed for the di(methylamino)-phenazines derivatives under reductive conditions (see above).

CONCLUSION

Our straightforward and scalable synthetic strategy allows for the preparation of a variety of potentially useful amino-phenazine motifs, featuring halogen-substituents as synthetic handles for further modification. We have shown that the in situ protection of the halogenated *o*-phenylenediamine starting material by direct condensation with acetone is critical to suppress the monohydroxylation of the phenazine products, otherwise occurring under oxidative treatment in aqueous conditions. The resulting imidazolidine derivatives were particularly robust toward hydrolysis and upon methylation exhibited a strong fluorescence in protic media, making these derivatives promising candidates for further development as fluorophores. The reduction of the phenazine core was required to permit the hydrolysis of the imidazolidine ring and isolation of the targeted 7,8-dihalo-2,3-diaminophenazines. Interestingly, we found that the use of zinc/acetic acid not only permits the deprotection of both the methylated and parent imidazolidine derivatives, but under specific reaction conditions can also lead to the selective monohydrodeamination of the di-(methylamine)phenazine derivatives. Our results taken together suggest multiple ways to increase the structural variety of the synthetically accessible halogenated aminophenazines, and allow the preparation of versatile building blocks that appear suitable for obtaining extended and highly functionalized heteroacene materials. In that sense, we note several recent examples that demonstrate the potential of chloro,[50] fluoro[42] and amino substituents[35,51−53] in phenazine derivatives to lead to further modification of 7,8-dihalo-2,3-diaminophenazines.

EXPERIMENTAL SECTION

Materials. All chemicals and solvents were commercially available and used as obtained, without further purification.

Instrumentation and Characterization. ^{1}H spectra were recorded at 400 MHz, ^{19}F NMR at 376 MHz, and proton decoupled ^{13}C NMR (^{13}C{^{1}H} NMR) at 101 MHz. Chemical shifts are reported as ppm from the internal reference tetramethylsilane (^{1}H) or residual solvent peak (^{13}C). High-resolution mass spectrometry (HRMS) was performed on a Q-TOF LC–MS with API by direct injection of a methanolic solution at ∼0.5 mg/mL concentration. Analytical LC–MS analysis was performed on a system equipped with a C18 column (1.8 μm, 4.6 × 50 mm).

General Procedure 1 (GP1) for the Synthesis of Compounds 3a–c. The 4,5-dihalo-1,2-diamino benzene (1 mmol, 1 equiv) was dispersed in 1.33 M HCl (9 mL). Acetone (74 μL, 58.5 mg, 1 mmol, 1 equiv) was added, and the mixture was stirred at room temperature for 5 min. A solution of iron trichloride hexahydrate (561 mg, 2.05 mmol, 2 equiv) in 2 mL of water was added, and the mixture was stirred at room temperature in the dark. After 8 h the mixture was poured into brine (150 mL) and neutralized by the slow addition of sodium bicarbonate (∼2 g). A solution of ethylenediamine tetraacetate (0.5 M, 25 mL), prepared in 1 M aqueous sodium hydroxide, was added, and the aqueous phase was extracted with ethyl acetate containing 10 volume% of 2-propanol (3 × 125 mL). The combined organic layer was washed with brine (1 × 150 mL) and water (1 × 40 mL), dried over Na_2SO_4, filtered, and the solvent was evaporated. In the case of dichloro and dibromo derivatives **3b** and **3c**, the solid was suspended in dichloromethane (15 mL), sonicated (1–2 min) and filtered. It was washed with dichloromethane until the filtrate appeared pale yellow (25–50 mL dichloromethane). The solid was dried and used without further purification. In the case of the difluoro derivatives **3a**, due to the high solubility of the material, it was purified by a short plug filtration (SiO_2, EtOAc/hexanes = 3/2; dry loading).

7,8-Difluoro-2,2-dimethyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]-phenazine 3a. GP1 was carried out using the following quantities of solvents and reagents: 4,5-difluoro-1,2-diaminobenzene (145 mg, 1 mmol, 1 equiv) and acetone (74 μL, 58.5 mg, 1 mmol, 1 equiv) in 1.33 M aqueous HCl (9 mL), and iron trichloride hexahydrate (565 mg, 2.1 mmol, 2.05 equiv) in water (2 mL). After filtration over a short plug of silica (SiO_2, EtOAc/hexanes = 3/2, dry loading) the desired compound was obtained as a yellow powder. Yield: 77 mg, 0.27 mmol, 53%; ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 8.22 (s, 2H), 7.74 (t, J = 10.3 Hz, 2H), 6.35 (s, 2H), 1.50 (s, 6H); ^{19}F NMR (376 MHz, DMSO-d_6) δ −137.7 (t, J = 10.4 Hz); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d6) δ 149.4 (dd, J_1 = 250 Hz, J_2 = 18 Hz), 147.8, 145.2, 136.9 (dd; J_1 = 7 Hz, J_2 = 6 Hz), 113.0 (dd; J_1 = 11 Hz, J_2 = 7 Hz), 93.2, 80.0, 30.4; UV–vis in ethanol λ_{max}(nm) [ε(L mol^{-1} cm^{-1}) × 10^3] 258 [71.7], 440 [29.1], 459 [25.8]; HRMS (m/z 100%) calc for $C_{15}H_{12}F_2N_4$+H$^+$ 287.1103, found 287.1105.

7,8-Dichloro-2,2-dimethyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]-phenazines 3b. GP1 was carried out using the following quantities of reagents and solvents: 4,5-dichloro-1,2-diaminobenzene (178 mg, 1 mmol, 1 equiv) and acetone (74 μL, 58.5 mg, 1 mmol, 1 equiv) in 1.33 M aqueous HCl (9 mL), and iron trichloride hexahydrate (565 mg, 2.1 mmol, 2.05 equiv) in water (2 mL). The desired compound was obtained as a yellow-brown powder. Yield: 153 mg, 0.48 mmol, 96%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (s, 2H), 8.00 (s, 2H), 6.34 (s, 2H), 1.51 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 148.1, 146.0, 139.1, 128.2, 128.1, 93.1, 80.3, 30.3; UV–vis in ethanol λ_{max}(nm) [ε(L mol^{-1} cm^{-1}) × 10^3] 269 [67.9], 299 [19.3], 447 [25.9] 471 [26.7]; HRMS (m/z 100%) calc for $C_{15}H_{12}Cl_2N_4$+H$^+$ 319.0512, found 319.0512.

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7,8-Dibromo-2,2-dimethyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]-phenazine 3c. GP1 was carried out using the following quantities of reagents and solvents: 4,5-dibromo-1,2-diaminobenzene (267 mg, 1 mmol, 1 equiv) and acetone (76 μL, 60.1 mg, 1.03 mmol, 1.03 equiv) in 1.33 M aqueous HCl (9 mL), and iron trichloride hexahydrate (562 mg, 2 mmol, 2 equiv) in water (2 mL). The desired compound was obtained as a yellow-brown powder. Yield: 144 mg, 0.35 mmol, 71%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 2H), 8.14 (s, 2H), 6.34 (s, 2H), 1.51 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 148.2, 146.0, 139.7, 131.5, 120.4, 93.1, 80.3, 30.3; UV−vis in ethanol λ_{max}(nm) [ε(L mol^{-1} cm^{-1}) × 10^3] 271 [72.4], 301 [22.4], 448 [30.4] 473 [27.0]; HRMS (*m*/*z* 100%) calc for $C_{15}H_{12}Br_2N_4$+H$^+$ 408.9481, found 408.9484.

Scale-up Synthesis of 7,8-Dichloro-2,2-dimethyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]phenazines 3b. 4,5-Dichloro-1,2-diamino benzene (1.068 g, 6 mmol, 1 equiv) was sonicated for 2 min in 1.33 M HCl (60 mL). Acetone (444 μL, 351 mg, 6 mmol, 1 equiv) was added, and the mixture was stirred at room temperature for 10 min. A solution of iron trichloride hexahydrate (3.32 g, 12.3 mmol, 2.05 equiv) in 8 mL of water was added, and the mixture was stirred at room temperature in the dark for 8 h. The mixture was then treated as described in GP1, with the appropriate quantity of solvents and reagents (scaled up six times). Yield: 0.68 g, 2.13 mmol, 71%.

General Procedure 2 (GP2) for the Synthesis of Compounds 1a−c. 7,8-Halo-2,2-dimethyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]-phenazine **3** (0.1 mmol) was suspended in methanol (15 mL), and the suspension was purged with nitrogen for 10 min. A solution of sodium dithionite (0.4 mmol, 4 equiv) dissolved in nitrogen-purged water (purging time: 10 min; 15 mL) was added slowly to the suspension, and the mixture was stirred under nitrogen at room temperature in the dark. The reaction was followed by TLC analysis (SiO_2, EtOAc). When all the starting material was converted, the mixture was poured into brine (100 mL) and aqueous sodium bicarbonate (5%, 10 mL) was added. The aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and the solvent was evaporated. The crude material was filtered over a silica short plug (SiO_2, 5% MeOH in EtOAc). Precipitation from CH_2Cl_2−10% MeOH/Hexanes yield the desired product as a light yellow solid.[54]

7,8-Difluoro-1,2-diaminophenazine 1a. GP2 was carried out using the following quantities of reagents and solvents: 7,8-difluoro-2,2-dimethyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]phenazine **3a** (29 mg, 0.1 mmol), $Na_2S_2O_4$ (70 mg, 0.4 mmol), MeOH (15 mL), and water (15 mL). Full conversion was observed after 2 h. The desired compound was obtained as a light yellow powder. Yield: 16 mg, 65 μmol, 65%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (t, *J* = 10.3 Hz, 2H), 6.88 (s, 2H), 6.36 (s, 4H); ^{19}F NMR (376 MHz, DMSO-d_6) δ −136.5 (t, *J* = 10.5 Hz); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) 149.9 (dd, J_1 = 252 Hz, J_2 = 18 Hz), 144.9, 142.4, 137.5 (m), 113.3 (dd, J_1 = 11 Hz, J_2 = 7 Hz), 102.2; UV−vis in ethanol λ_{max}(nm) [ε(L mol^{-1} cm^{-1}) × 10^3] 276 [49.1], 433 [17.5]; HRMS (*m*/*z* 100%) calc for $C_{12}H_8F_2N_4$+H$^+$ 247.0790, found 247.0791.

7,8-Dichloro-1,2-diaminophenazine 1b. GP2 was carried out using the following quantities of reagents and solvents: 7,8-dichloro-2,2-dimethyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]phenazine **3b** (32 mg, 0.1 mmol), $Na_2S_2O_4$ (70 mg, 0.4 mmol), MeOH (15 mL), and water (15 mL). Full conversion of the starting material was observed after 4 h. The desired compound was obtained as a light yellow powder. Yield: 27 mg, 97 μmol, 97%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (s, 2H), 6.87 (s, 2H), 6.53 (s, 4H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 145.6, 143.2, 139.4, 128.8, 128.7, 102.0; UV−vis in ethanol λ_{max}(nm) [ε(L mol^{-1} cm^{-1}) × 10^3] 272 [54.3], 442 [20.8]; HRMS (*m*/*z* 100%) calc for $C_{12}H_8Cl_2N_4$+H$^+$ 279.0199, found 279.0195.

7,8-Dibromo-1,2-diaminophenazine 1c. GP2 was carried out using the following quantities of reagents and solvents: 7,8-dibromo-2,2-dimethyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]phenazine **3c** (41 mg, 0.1 mmol), $Na_2S_2O_4$ (70 mg, 0.4 mmol), MeOH (15 mL), and water (15 mL). Full conversion of the starting material was observed after 8 h. The desired compound was obtained as a light yellow powder. Yield: 33 mg, 90 μmol, 90%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (s, 2H), 6.87 (s, 2H), 6.55 (s, 4H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 145.7, 143.2, 140.0, 132.0, 121.0, 102.0; UV−vis in ethanol λ_{max}(nm) [ε(L mol^{-1} cm^{-1}) × 10^3] 276 [50.7], 442 [18.8]; HRMS (*m*/*z* 100%) calc for $C_{12}H_8Br_2N_4$+H$^+$ 368.9168, found 368.9166.

General Procedure 3 (GP3) for the Synthesis of Compounds 4a−c. 7,8-Dihalo-2,2-dimethyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]-phenazine **3** (0.16 mmol) was dissolved in anhydrous DMF (10 mL). The solution was purged with nitrogen (vacuum/nitrogen cycles, 3×) and cooled down to 0 °C under nitrogen. Sodium hydride (60%-w/w dispersion in mineral oil, 13.6 mg, 0.35 mmol, 2.2 equiv) was added, and the mixture was stirred under nitrogen at 0 °C for 15 min. Methyl iodide (21 μL, 48 mg, 0.33 mmol, 2.1 equiv) was added, and the mixture was further stirred at 0 °C for 30 min under nitrogen, then was allowed to warm up to room temperature. After 30 min, a saturated aqueous ammonium chloride solution (1 mL) was added, and the mixture was poured into brine (50 mL). The aqueous phase was extracted with ethyl acetate (3 × 25 mL), and the combined organic layers were further washed with brine (1 × 50 mL) and water (2 × 50 mL). The organic layer was dried with sodium sulfate, filtered, and the solvent was evaporated. Column chromatography (SiO_2, EtOAc/Hexanes = 1/1) followed by recrystallization from CH_2Cl_2/hexanes yielded the desired compounds as light brown needles.[55]

7,8-Difluoro-1,2,2,3-tetramethyl-2,3-dihydro-1*H*-imidazo-[4,5-*b*]phenazine 4a. GP3 was carried out using the following quantities of reagents and solvent: 7,8-difluoro-2,2-dimethyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]phenazine **3a** (44.3 mg, 0.16 mmol), sodium hydride (60%-w/w dispersion in mineral oil, 13.6 mg, 0.35 mmol), methyl iodide (21 μL, 48 mg, 0.33 mmol), and DMF (10 mL). The desired compound was obtained as a light yellow powder. Yield: 17.1 mg, 55 μmol, 35%; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.63 (t, *J* = 9.9 Hz, 2H), 6.36 (s, 2H), 3.00 (s, 6H), 1.52 (s, 6H); ^{19}F NMR (376 MHz, DMSO-d_6) δ −137.6 (t, *J* = 10.3 Hz); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 150.4 (dd, J_1 = 252.5 Hz, J_2= 18.3 Hz), 146.3, 145.1, 137.1 (t, *J* = 5.7 Hz), 112.81 (dd, J_1 = 12.1 Hz, J_1 = 6.5 Hz), 92.7, 85.7, 27.8, 23.4; UV−vis in ethanol λ_{max}(nm) [ε(L mol^{-1} cm^{-1}) × 10^3] 443 [29.5], 457 [30.0]; HRMS (*m*/*z* 100%) calc for $C_{17}H_{16}F_2N_4$+H$^+$ 315.1416, found 315.1417.

7,8-Dichloro-1,2,2,3-tetramethyl-2,3-dihydro-1*H*-imidazo-[4,5-*b*]phenazine 4b. GP3 was carried out using the following quantities of reagents and solvent: 7,8-dichloro-2,2-dimethyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]phenazine **3b** (49.8 mg, 0.16 mmol), sodium hydride (60%-w/w dispersion in mineral oil, 13.6 mg, 0.35 mmol), methyl iodide (21 μL, 48 mg, 0.33 mmol), and DMF (10 mL). The desired compound was obtained as light brown needles. Yield: 18.8 mg, 54 μmol, 35%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 2H), 6.34 (s, 2H), 3.01 (s, 6H), 1.54 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 146.6, 145.8, 139.1, 130.1, 128.1, 92.7, 85.8, 27.8, 23.5; UV−vis in ethanol λ_{max}(nm) [ε(L mol^{-1} cm^{-1}) × 10^3] 270 [65.8], 300 [19.9], 449 [26.4], 471 [27.0]; HRMS (*m*/*z* 100%) calc for $C_{17}H_{16}Cl_2N_4$+H$^+$ 347.0825, found 347.0827.

7,8-Dibromo-1,2,2,3-tetramethyl-2,3-dihydro-1*H*-imidazo-[4,5-*b*]phenazine 4c. GP3 was carried out using the following quantities of reagents and solvent: 7,8-dibromo-2,2-dimethyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]phenazine **3c** (63.2 mg, 0.16 mmol), sodium hydride (60%-w/w dispersion in mineral oil, 13.6 mg, 0.35 mmol), methyl iodide (21 μL, 48 mg, 0.33 mmol), and DMF (10 mL). The desired compound was obtained as brown needles. Yield: 45.6 mg, 105 μmol, 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 2H), 6.35 (s, 2H), 3.04 (s, 6H), 1.52 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 147.4, 146.3, 139.2, 128.3, 128.2, 91.9, 28.1, 23.5; UV−vis in ethanol λ_{max}(nm) [ε(L mol^{-1} cm^{-1}) × 10^3] 273 [71.1], 301 [20.1], 451[27.5], 473 [29.3]; HRMS (*m*/*z* 100%) calc for $C_{17}H_{16}Br_2N_4$+H$^+$ 436.9794, found 436.9794.

General Procedure 4 (GP4) for the Synthesis of Compounds 5a−c. 7,8-Dihalo-1,2,2,3-tetramethyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]-phenazine **4** (0.1 mmol) was dissolved in a tetrahydrofuran-water 1−1 mixture (10 mL). The solution was purged with nitrogen (vacuum/nitrogen cycles, 3×) and zinc powder (16.2 mg, 0.25 mmol, 2.5 equiv) was added. Glacial acetic acid (14.3 μL, 15 mg, 0.25 mmol, 2.5 equiv) was added, and the mixture stirred under nitrogen at 40 °C.

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After stirring for 30 min, TLC analysis (SiO_2, CH_2Cl_2/acetone = 8/2) indicated the presence of residual starting material. Zinc powder (<140 μm particles size) (16.2 mg, 0.25 mmol, 2.5 equiv) was added, the mixture purged with nitrogen (vacuum/nitrogen cycles 3×), and glacial acetic acid (14.3 μL, 15 mg, 0.25 mmol) was added. The mixture was further stirred at 40 °C under nitrogen for 30 min, and the reaction progression was determined by TLC analysis (SiO_2, CH_2Cl_2/acetone = 8/2). Zinc portions and glacial acetic aliquots were added as previously described, until most of the staring material was converted. After the last zinc/glacial acetic acid addition, the mixture was stirred for 30 min, the residual zinc was filtered out, and then the mixture was poured into aqueous sodium bicarbonate (5%, 50 mL). The aqueous phase was extracted with ethyl acetate (2 × 25 mL), and the combined organic layer was dried over sodium sulfate, filtered, and the solvent was evaporated. Column chromatography (SiO_2, CH_2Cl_2/acetone = 8/2) followed by precipitation from CH_2Cl_2/hexanes yield the desired compound as an orange powder.[56]

7,8-Difluoro-1,2-di(methylamino)phenazine 5a. GP4 was carried out using the following quantities of reagents and solvents: 7,8-difluoro-1,2,2,3-tetramethyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]-phenazine **4a** (10 mg, 32 μmol), zinc powder (5.2 mg, 80 μmol), glacial acetic acid (4.5 μL, 4.8 mg, 80 μmol), and tetrahydrofuran/water 1/1 (10 mL). Additional zinc (3 × 5.2 mg) and glacial acetic acid (3 × 4.5 μL) were introduced, with an interval of 30 min between each addition. The desired compound was obtained as a yellow powder. Yield: 4.5 mg, 16 μmol, 50%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (t, J = 10.3 Hz, 2H), 6.64 (s, 2H), 6.52 (q, J = 4.4 Hz, 2H), 2.96 (d, J = 4.4 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) 144.9, 142.7, 137.5, 113.3 (dd; J_1 = 11 Hz, J_2 = 7 Hz), 98.3, 30.4; UV−vis in ethanol λ_{max}(nm) [ε(L mol^{-1} cm^{-1}) × 10^3] 261 [33.9], 434 [13.3]; HRMS (m/z 100%) calc for $C_{14}H_{12}F_2N_4$+H$^+$ 275.1103, found 275.1101.

7,8-Dichloro-1,2-di(methylamino)phenazine 5b. GP4 was carried out using the following quantities of reagents and solvents: 7,8-dichloro-1,2,2,3-tetramethyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]-phenazine **4b** (32 mg, 0.92 mmol), zinc powder (15 mg, 0.23 mmol), glacial acetic acid (13 μL, 13.7 mg, 0.23 mmol), and tetrahydrofuran/water 1/1 (10 mL). Additional zinc (3 × 15 mg) and glacial acetic acid (3 × 13 μL) were introduced, with an interval of 30 min between each addition. The desired compound was obtained as an orange powder. Yield: 20 mg, 65 μmol, 71%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (s, 2H), 6.66 (q, J = 4.6 Hz, 1H), 6.63 (s, 1H), 2.96 (d, J = 4.5 Hz, 4H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 145.4, 143.5, 139.4, 128.9, 128.6, 98.2, 30.4; UV−vis in ethanol λ_{max}(nm) [ε(L mol^{-1} cm^{-1}) × 10^3] 273 [57.1], 442 [20.8]; HRMS (m/z 100%) calc for $C_{14}H_{12}Cl_2N_4$+H$^+$ 307.0512, found 307.0512.

7,8-Dibromo-1,2-di(methylamino)phenazine 5c. GP4 was carried out using the following quantities of reagents and solvents: 7,8-dibromo-1,2,2,3-tetramethyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]-phenazine **4c** (36 mg, 0.83 mmol), zinc powder (15 mg, 0.23 mmol), glacial acetic acid (13 μL, 13.7 mg, 0.23 mmol), and tetrahydrofuran/water 1/1 (10 mL). Additional zinc (3 × 15 mg) and glacial acetic acid (3 × 13 μL) were added, with an interval of 30 min between each addition. The desired compound was obtained as an orange powder. Yield: 18.4 mg, 47 μmol, 57%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (s, 2H), 6.68 (q, J = 4.5 Hz, 2H), 6.63 (s, 2H), 2.96 (d, J = 4.5 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 145.5, 143.5, 140.0, 131.8, 121.2, 98.2, 30.4; UV−vis in ethanol λ_{max}(nm) [ε(L mol^{-1} cm^{-1}) × 10^3] 276 [64.7], 443 [25.2]; HRMS (m/z 100%) calc for $C_{14}H_{12}Br_2N_4$+H$^+$ 396.9481, found 396.9470.

Synthesis of 7,8-Dichloro-1-methylaminophenazine 6b. 7,8-Dichloro-1,2,2,3-tetramethyl-2,3-dihydro-1*H*-imidazo[4,5-*b*]phenazine **4b** (7.2 mg, 22.4 μmol) was dissolved in a tetrahydrofuran-water 1−1 mixture (4 mL). The solution was purged with nitrogen (vacuum/nitrogen cycles, 3×) and zinc powder (30 mg, 0.5 mmol, 23 equiv) was added. Water/acetic acid 2/1 mixture (1 mL) was added, and then the mixture was stirred under nitrogen at 40 °C. After stirring for 1 h the residual zinc was filtered out, and the mixture was poured into aqueous sodium bicarbonate (5%, 50 mL). The aqueous phase was extracted with ethyl acetate (2 × 25 mL), and the combined organic layer was dried over sodium sulfate, filtered, and the solvent was evaporated. Column chromatography (SiO_2, CH_2Cl_2/acetone = 8/2) followed by precipitation from CH_2Cl_2/hexanes yield the desired compound as a red powder. Yield: 4 mg, 14 μmol, 63%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (s, 1H), 8.24 (s, 1H), 7.87 (d, J = 9.4 Hz, 1H), 7.50 (dd, J_1 = 9.5 Hz, J_2 = 2.5 Hz, 1H), 7.37 (q, J = 5.1 Hz, 1H), 6.65 (d, J = 2.4 Hz, 1H), 2.90 (d, J = 4.9 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 152.3, 147.1, 142.3, 141.1, 138.6, 133.1, 130.2, 130.2, 129.5, 128.8, 128.6, 97.1, 29.9; UV−vis in ethanol λ_{max}(nm) [ε(L mol^{-1} cm^{-1}) × 10^3] 294 [52.6], 490 [11.4]; HRMS (m/z 100%) calc for $C_{13}H_9Cl_2N_3$+H$^+$ 278.0246, found 278.0246.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01339.

Additional details of the synthetic procedures, ^{1}H, ^{13}C and ^{19}F NMR spectra, LC−MS analysis, absorption and emission spectra, details of quantum yield measurements, and details of computational analysis of the different phenazine derivatives. (PDF)

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Notes

The authors declare no competing financial interest.

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(36) In the case of the 4,5-bisfluoro-1,2-diaminobenzene starting material, 7,8-difluoro-1,2-diaminophenazine was present as a minor impurity in the commercially available compound. The latter diaminophenazine was recovered after the treatment with iron chloride and acetone; however, we found no indications for the competitive formation of this product during the reaction (no hydroxylated derivative was observed in LC−MS analysis). We therefore assume that the 7,8-difluoro-1,2-diaminophenazine collected after the purification was already present in the starting material.
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(55) Because of the high solubility of the difluoro derivatives, the product obtained after column chromatography was only washed with a minimum volume of hexanes.
(56) A total of 3 to 4 additions of zinc/acetic acid was usually necessary to convert most of the starting material into the desired product. Sequential addition of the zinc and acetic acid is required to minimize the hydrodeamination side reaction that is observed during the synthesis. Addition of a large excess of zinc directly followed by a large excess of acetic acid leads to the rapid conversion of the starting material into the corresponding 1-methylaminophenazine derivative.

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