Preparation of Halogenated Fluorescent Diaminophenazine Building Blocks

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5 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 reaction; this allows for formation of the desired 7,8-dihalo-2,3-diaminophenazines. Furthermore, we report a selective route under highly reducing conditions to monohydropyrimidinate the 2,3-di(methylamino)phenazine derivatives, which allows for further structural variations of these phenazine building blocks. All of these derivatives are luminescent and can 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,4 fluorescent or electroactive markers in biological systems,5,13 antibiotics and anticancer agents,6–9 electroactive materials for OFETs, OLEDs, and solar cells and for photocatalysis.5 The most popular route is based on direct condensation of adequately functionalized phenazines.5 The most popular methods for the preparation of functionalized phenazines are important and versatile building blocks for the preparation of polyfunctional phenazines and extended polyheteroacenes.29–31 This 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 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 hydroxylation, leading to a reaction involving the two adjacent unsubstituted positions (positions 5 and 6). This selectivity pattern suggested that the undesired hydroxylation byproducts, typically obtained in aqueous conditions, are completely suppressed by addition of a stoichiometric amount of acetone during the reaction; this allows for formation of the desired 7,8-dihalo-2,3-diaminophenazines. Furthermore, we report a selective route under highly reducing conditions to monohydropyrimidinate the 2,3-di(methylamino)phenazine derivatives, which allows for further structural variations of these phenazine building blocks. All of these derivatives are luminescent and can provide new fluorophores.

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 7,8-dihalo-2,3-diaminophenazines.28,32,33

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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

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X = F: 1a + 2a (97%)\(^\text{a}\), [1a 2a ~ 45:53]\(^\text{a}\)
X = Cl: 1b + 2b (99%)\(^\text{a}\), [1b 2b ~ 2:96]\(^\text{a}\)
X = Br: 1c + 2c (85%)\(^\text{a}\), [1c 2c ~ 2:94]\(^\text{a}\)
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\(^{\text{a}}\)On the basis of the isolated mixture of products. \(^{\text{b}}\)Ratio estimated using liquid chromatography mass spectrometry (LC–MS) analysis.

75 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-1H-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).

80 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 adds to the 4,5-dihalo-1,2-diaminobenzene starting material and is 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-2H-benzo[d]imidazoles.

87 This idea is consistent with previous studies showing that 2H-benzo[d]imidazoles can readily undergo nucleophilic attack on the S and 6 positions, due to their o-benzoquinone dinitrile character.\(^{37,38}\) Furthermore, highly efficient ipso substitution of chloro groups was reported upon treatment of 5,6-dichloro-2H-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-2H-benzo[d]imidazole with traces of 4,5-dichloro-1,2-diaminobenzene that were present after the in situ hydrolysis of the former.\(^{39}\)

110 The condensation of acetone on o-phenylenediamine to form 2,2-dimethyl-2,3-dihydro-1H-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-1H-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-1H-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-2H-benzo[d]imidazole intermediates.

117 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-2H-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).

124 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.

127 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 Me2C 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-1H-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-2H-benzo[d]imidazole intermediates.

128 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-2H-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).

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134 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 Me2C 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 Me2C 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.

154 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...
reduction to the corresponding \( N,N \)-dihydrophenazine might allow hydrolysis of the Me\(_2\)C 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.

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\(_2\)C protecting group. 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\(_2\)C 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.

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. In brief, the absorption spectra of the dichloro-phenazine derivatives 1b−f are shifted to longer wavelengths compared to the corresponding mono- and dihalo-derivatives. The rationalization of the selective monohydrodeamination of the bis- \( N \) \(-\)methylamino)phenazine derivatives is beyond the scope of this letter and will be the topic of further investigations.

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

<table>
<thead>
<tr>
<th>Phenazine</th>
<th>$\lambda_{\text{max, abs}}^{a}$ (nm)</th>
<th>$\epsilon_{\text{max, abs}}^{b}$ (M$^{-1}$ cm$^{-1} \times 10^3$)</th>
<th>$\lambda_{\text{max, emission}}^{b}$ (nm)</th>
<th>$E^0$ (eV)</th>
<th>$E^0_{\text{calc}}$ (eV)</th>
<th>$\Phi_{\text{fluor}}^{c,d}$</th>
<th>$E_{1/2}(0/-1)^{f}$ V vs NHE</th>
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<tr>
<td>1a</td>
<td>433</td>
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<td>n.d.</td>
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<tr>
<td>1b</td>
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<td>549</td>
<td>2.48</td>
<td>2.46</td>
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<td>1c</td>
<td>442</td>
<td>18.8</td>
<td>550</td>
<td>2.47</td>
<td>2.50</td>
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<td>n.d.</td>
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<tr>
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<td>440</td>
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<td>2.93</td>
<td>n.d.</td>
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<tr>
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<td>26.7</td>
<td>506</td>
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<td>2.86</td>
<td>0.42</td>
<td>n.d.</td>
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<tr>
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<td>473</td>
<td>27.0</td>
<td>508</td>
<td>2.56</td>
<td>2.85</td>
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<td>n.d.</td>
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<tr>
<td>4a</td>
<td>457</td>
<td>30.0</td>
<td>488</td>
<td>2.61</td>
<td>2.83</td>
<td>0.80</td>
<td>−1.34</td>
</tr>
<tr>
<td>4b</td>
<td>471</td>
<td>27.0</td>
<td>497</td>
<td>2.56</td>
<td>2.77</td>
<td>0.70</td>
<td>−1.27</td>
</tr>
<tr>
<td>4c</td>
<td>473</td>
<td>29.3</td>
<td>500</td>
<td>2.56</td>
<td>2.77</td>
<td>0.11</td>
<td>irreversible</td>
</tr>
<tr>
<td>5a</td>
<td>434</td>
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<td>529</td>
<td>2.58</td>
<td>2.58</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>5b</td>
<td>442</td>
<td>20.8</td>
<td>541</td>
<td>2.51</td>
<td>2.48</td>
<td>0.14</td>
<td>irreversible</td>
</tr>
<tr>
<td>5c</td>
<td>443</td>
<td>25.2</td>
<td>542</td>
<td>2.53</td>
<td>2.48</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>6a</td>
<td>490</td>
<td>11.4</td>
<td>599</td>
<td>2.25</td>
<td>2.11</td>
<td>0.06</td>
<td>−0.98</td>
</tr>
<tr>
<td>6b</td>
<td>421</td>
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<td>591</td>
<td>2.20</td>
<td>2.03</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

$^{a}$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. Estimated from the crossing point of the normalized experimental absorption and emission spectra.

$^{c}$Calculated at the CAM-B3LYP42/6-31G(d,p) level of theory using Gaussian09.

$^{d}$Excitation at 300 nm, under aerobic conditions; sample OD was adjusted to 0.049 using rhodamine-6G as the reference.

$^{e}$Emission at 300 nm, for samples with an optical density (OD) below 0.06; recorded in absolute ethanol at room temperature.

$^{f}$Emission at 300 nm, under aerobic conditions; sample OD was adjusted to 0.049 using rhodamine-6G as the reference.

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.
substituents, as well as inclusion of the latter substituents in the imidazolidine rings leads to a remarkable increase of fluorescence with Φ_f ≈ 0.10, 0.14, 0.42, and 0.70 for 1b, 3b, 3b, and 4b, respectively. The latter trend can be rationalized by the progressive suppression of the major nonradiative deactivation 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 Φ_f ≈ 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 TD-DFT calculations, performed at the CAM-B3LYP[5,6]31-31G(dp) level of theory, using the SMD continuum solvation model.[5,6,7] As shown in Table 1, the experimental and theoretical E° values are in good agreement, consistent with previous studies.[6,7] Variations, when comparing the E° values of the cyclized systems, might be due to the lack of specific solvent−solvent 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 alkyamine substituents. 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, 5b, and 6b, 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).

**EXPERIMENTAL SECTION**

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

**Instrumentation and Characterization.** 1H spectra were recorded at 400 MHz, 19F NMR at 376 MHz, and proton deuterated 13C NMR (13C{1H} NMR) at 101 MHz. Chemical shifts are reported as ppm from the internal reference tetramethylsilane (1H) or residual solvent peak (13C). High-resolution mass spectrometry (HRMS) was performed on a Q-Tof LC−MS with API by direct injection of a 1% 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 9 h the mixture was poured into brine (150 mL) and neutralized by the slow addition of sodium bicarbonate (~2 g). A solution of ethylenediamine tetracetate (0.5 M, 35 mL), prepared in 1 M aqueous sodium hydroxide, was added, and the aqueous phase was extracted with ethyl acetate containing 10 vol% 2-propanol (3 × 125 mL). The combined organic layer was washed with brine (1 × 150 mL) and water (1 × 40 mL), dried over Na2SO4, 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 (SiO2, EtOAc/hexanes = 3/2; dry loading).

7,8-Difluoro-2,2-dimethyl-2,3-dihydro-1H-imidazo[4,5-b]phenazine 3a. GP1 was carried out using the following quantities of 3a−c and solvents: 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, 2.16 mmol, 2.05 equiv) in water (2 mL). After filtration over a short plug of silica (SiO2, EtOAc/hexanes = 3/2, dry loading) the desired compound was obtained as a yellow powder. Yield: 77 mg, 0.27 mmol, 53%; 1H NMR (400 MHz, DMSO-d6, 25 °C) δ 8.22 (s, 2H), 7.74 (t, J = 10.3 Hz, 2H), 6.35 (s, 2H), 1.50 (s, 6H), 1.49 (s, 3H). 19F NMR (376 MHz, DMSO-d6) δ −157.7 (t, J = 10.4 Hz). 13C{1H} NMR (101 MHz, DMSO-d6) δ 149.4 (dd, J1 = 25 Hz, J2 = 18 Hz), 147.8, 145.2, 136.9 (dd, J1 = 7 Hz, J2 = 6 Hz), 113.0 (dd, J1 = 11 Hz, J2 = 7 Hz). UV/Vis in ethanol λmax (nm) [ε(Mol/L cm)−1] (10−3) 375 258 (71.7), 440 [29.1], 459 [28.5]. HRMS (m/z) 100% calc for C15H12F2N4+H2O 287.1105, found 287.1105.

7,8-Dichloro-2,2-dimethyl-2,3-dihydro-1H-imidazo[4,5-b]phenazine 3b. GP1 was carried out using the following quantities of 3b−c and solvents: 4,5-dichloro-1,2-diaminobenzene (178 mg, 1 mmol, 1 equiv) and acetone (85 μL, 58.5 mg, 1 mmol, 1 equiv) in 1.33 M aqueous HCl (9 mL), and iron trichloride hexahydrate (565 mg, 2.16 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%; 1H NMR (400 MHz, DMSO-d6, δ 8.50 (s, 2H), 8.00 (s, 2H), 6.34 (s, 2H), 1.51 (s, 6H), 13C{1H} NMR (101 MHz, DMSO-d6) δ 148.1, 146.0, 139.1, 128.2, 128.1, 93.1, 80.3, 30.3; UV/Vis in ethanol λmax (nm) [ε(Mol/L cm)−1] (10−3) 369 [67.9], 299 [19.3], 447 [25.9]. UV/Vis in ethanol λmax (nm) [ε(Mol/L cm)−1] (10−3) 471 [26.7]. HRMS (m/z) 100% calc for C15H12Cl2N4+H2O 319.0512, found 319.0512.
General Procedure 2 (GP2) for the Synthesis of Compounds 1a–c. 7,8-Dibromo-2,2-dimethyl-2,3-dihydro-1H-imidazo[4,5-b]-phenazine 1b.

7,8-Dibromo-2,2-dimethyl-2,3-dihydro-1H-imidazo[4,5-b]-phenazine 1c.

7,8-Dibromo-2,2-dimethyl-2,3-dihydro-1H-imidazo[4,5-b]-phenazine 1d.

7,8-Dibromo-2,2-dimethyl-2,3-dihydro-1H-imidazo[4,5-b]-phenazine 1e.

General Procedure 3 (GP3) for the Synthesis of Compounds 4a–c. 7,8-Dihalo-2,2-dimethyl-2,3-dihydro-1H-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 (SiO₂, EtOAc/Hexanes = 1/1) followed by recrystallization from CH₂Cl₂/hexanes yielded the desired compounds as light brown needles.

7,8-Difluoro-1,2,2,3-tetramethyl-2,3-dihydro-1H-imidazo[4,5-b]phenazine 4b.

7,8-Difluoro-1,2,2,3-tetramethyl-2,3-dihydro-1H-imidazo[4,5-b]phenazine 4c.

7,8-Difluoro-1,2,2,3-tetramethyl-2,3-dihydro-1H-imidazo[4,5-b]phenazine 4d.

7,8-Difluoro-1,2,2,3-tetramethyl-2,3-dihydro-1H-imidazo[4,5-b]phenazine 4e.

General Procedure 4 (GP4) for the Synthesis of Compounds 5a–c. 7,8-Dihalo-2,2,2,3-tetramethyl-2,3-dihydro-1H-imidazo[4,5-b]-phenazine 5a (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, 0.25 mmol, 2.5 equiv) was added, and the mixture was stirred under nitrogen at 40 °C.
After stirring for 30 min, TLC analysis (SiO₂, CH₂Cl₂/acetone = 8/2) indicated the presence of residual starting material. Zinc powder (140 μm particle size) (162 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 (SiO₂, CH₂Cl₂/acetone = 8/2). The mixture was filtered, and the solvent was evaporated. Column chromatography (SiO₂, CH₂Cl₂/acetone = 8/2) followed by precipitation from CH₂Cl₂/hexanes yielded the desired compound as a yellow powder.

7,8-Difluoro-1,2-dimethylamino phenazine 5a. GP 4 was carried out using the following quantities of reagents and solvents: 7,8-difluoro-1,2,3-tetramethyl-2,3-dihydro-1H-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%; 1H NMR (400 MHz, CDCl₃) δ 7.87 (t, J = 4.6 Hz, 2H), 6.64 (s, 2H), 6.52 (q, J = 4.4 Hz, 2H), 2.96 (d, J = 4.4 Hz, 6H), 13C[H] NMR (101 MHz, DMSO-d₅) δ 142.7, 137.5, 113.3 (dd, J₁ = 11 Hz, J₂ = 7 Hz), 98.3, 30.4; UV–vis in ethanol λmax (nm) [ε (L mol⁻¹ cm⁻¹)] × 10⁻¹ 261 [33.9], 434 [13.3]; HRMS (m/z 100%) calc for C₁₃H₁₃F₂N₃⁺H⁺ 276.0188, found 276.0189.

7,8-Dichloro-1,2-dimethylamino phenazine 5b. GP 4 was carried out using the following quantities of reagents and solvents: 7,8-dichloro-1,2,3-tetramethyl-2,3-dihydro-1H-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: 13 mg, 0.45 mmol, 71%; 1H NMR (400 MHz, DMSO-d₆) δ 7.56 (d, J = 4.5 Hz, 1H), 7.47 (d, J = 4.5 Hz, 1H), 7.41 (d, J = 4.5 Hz, 1H), 7.16 (t, J = 4.8 Hz, 1H), 6.58 (s, 2H), 3.58 (d, J = 9.4 Hz, 2H), 2.95 (d, J = 9.4 Hz, 2H), 2.86 (s, 3H), 2.80 (s, 3H), 2.78 (s, 3H), 13C[H] NMR (101 MHz, DMSO-d₆) δ 143.5, 143.5, 143.0, 139.4, 128.9, 128.6, 98.2, 30.4; UV–vis in ethanol λmax (nm) [ε (L mol⁻¹ cm⁻¹)] × 10⁻¹ 273 [57.1], 442 [20.8]; HRMS (m/z 100%) calc for C₁₃H₁₁Br₂N₃⁺H⁺ 366.9537, found 366.9540.

7,8-Dibromo-1,2-dimethylamino phenazine 5c. GP 4 was carried out using the following quantities of reagents and solvents: 7,8-dibromo-1,2,3-tetramethyl-2,3-dihydro-1H-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: 20 mg, 65 μmol, 57%; 1H NMR (400 MHz, DMSO-d₆) δ 8.13 (s, 2H), 6.66 (q, J = 4.6 Hz, 1H), 6.63 (s, 1H), 2.96 (d, J = 4.5 Hz, 3H), 13C[H] NMR (101 MHz, DMSO-d₆) δ 145.4, 143.5, 143.0, 139.4, 128.7, 128.7, 98.2, 30.4; UV–vis in ethanol λmax (nm) [ε (L mol⁻¹ cm⁻¹)] × 10⁻¹ 276 [64.7], 443 [25.2]; HRMS (m/z 100%) calc for C₁₃H₁₁Br₂N₃⁺H⁺ 370.0512, found 370.0512.

Synthesis of 7,8-Dichloro-1-methylaminophenazine 6b. 7,8-Dichloro-1,2,3-tetramethyl-2,3-dihydro-1H-imidazo[4,5-b]phenazine 4b (7.2 mg, 22 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 (SiO₂, CH₂Cl₂/acetone = 8/2) followed by precipitation from CH₂Cl₂/hexanes yielded the desired compound as a red powder. Yield: 4 mg, 14 μmol, 63%; 1H NMR (400 MHz, DMSO-d₆) δ 8.34 (s, 1H), 8.24 (s, 1H), 7.87 (d, J = 9.4 Hz, 1H), 7.50 (dd, J₁ = 6.05 9.5 Hz, J₂ = 2.5 Hz, 1H), 7.37 (q, J = 5.1 Hz, 1H), 6.65 (d, J = 2.4 Hz, 606 6.01 Hz, 1H), 2.90 (d, J = 4.9 Hz, 3H); 13C[H] NMR (101 MHz, DMSO-d₆) δ 152.3, 147.1, 142.3, 114.1, 138.6, 133.1, 130.2, 130.2, 129.5, 128.8, 128.6, 97.1, 29.9; UV–vis in ethanol λmax (nm) [ε (L mol⁻¹ cm⁻¹)] × 10⁻¹ 294 [52.6], 490 [11.4]; HRMS (m/z 100%) calc for C₁₃H₁₁Cl₂N₃⁺H⁺ 278.0246, found 278.0246.
after the purification was already present in the starting material.


The pH of the solution was determined to be very slightly acidic (pH < 6.5) at the end of the reaction.


In the case of the difluoro derivatives, the starting material was highly soluble, and the reaction mixture was fully homogeneous. Dichloro and especially dibromo derivatives were much less soluble in the reaction conditions, and the reaction proceeded under heterogeneous conditions.

Because of the high solubility of the difluoro derivatives, the product obtained after column chromatography was only washed with a minimum volume of hexanes.

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 obtained after column chromatography was only washed with a minimum volume of hexanes. 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.