Synthesis of 5-bromo-6-methyl imidazopyrazine, 5-bromo and 5-chloro-6-methyl imidazopyridine using electron density surface maps to guide synthetic strategy

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ABSTRACT

Small heteroaromatic rings are valuable monomers in drug discovery that can enable rapid access to novel and desirable chemical space. Installation of a synthetic handle on a heteroaromatic core may be difficult if steric and electronic factors are not in alignment with the desired transformation. Described are practical routes for the construction of 5-bromo-6-methyl imidazopyrazine (1) as well as 5-bromo and 5-chloro-6-methyl imidazopyridines (2a and 2b), which were developed using electron density surface maps encoded with ionization potential to guide synthetic strategy.

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1. Introduction

Small halogenated heteroaromatic ring systems are valuable monomers because of their ability to participate in established cross-couplings including the Heck, Stille, and Suzuki reactions.[1] As part of a chemistry initiative to increase the diversity of our available low molecular weight heteroaryl monomer set, we were interested in developing a practical construction of the novel heterocycles imidazopyrazine 1 and imidazopyridines 2a and 2b (Eq. 1). Formation of the fused imidazole ring was planned by reaction of chloroacetaldehyde with a 2-amino pyrazine or pyridine, such as in 5 or 6. One anticipated challenge with this approach was regioselective installation of the requisite halogen handle at the sterically and electronically disfavored C(5) position.

1: X=N
2a: X=CH

3: X=N
4: X=CH

5: X=N
6: X=CH
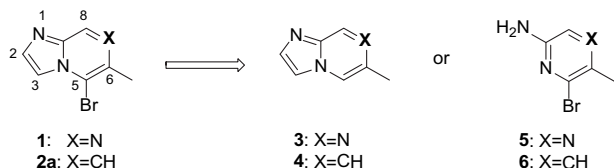
Equation 1.

2. Results and Discussion

Brominating reagents, such as N-bromosuccinimide (NBS) and bromine, react with heterocycles via electrophilic aromatic halogenation (EAH) at the site of greatest electron density.[2] The electronic properties of a ring system are dictated by the heteroatom substitution pattern and pendant electron donating or withdrawing functionality. Protonated or hydrogen-bonded heterocycles can have vastly different charge distributions and orbital energies relative to their neutral counterparts. Imidazo[1,2-a]pyrazine 7 is an interesting example of this phenomenon (Fig. 1).[3] The electron density surface map encoded with ionization potential predicts that neutral reactant 7 will preferentially undergo electrophilic attack at C(3) while its protonated counterpart 8 would likely substitute at C(5).[4]

The calculations on this system are in agreement with published experimental data which we have reproduced in our laboratories. When 7 is treated with NBS under neutral conditions 3-bromoimidazo[1,2-a]pyrazine 9 is obtained exclusively,[5] while treatment with bromine provides 5-bromoimidazo[1,2-a]pyrazine 10 as the major adduct (Eqs. 2 and 3).[6] We believe in the latter case that the HBr generated during the course of the reaction protonates the parent heterocycle at N(1) and is responsible for the altered reactivity, although we stipulate that hydrogen bonding to ethanol might also be responsible.

The electronic properties of related 6-methylimidazo[1,2-a]pyrazine 11 are predicted to be similar to 7 (Fig. 2) with C(3) being

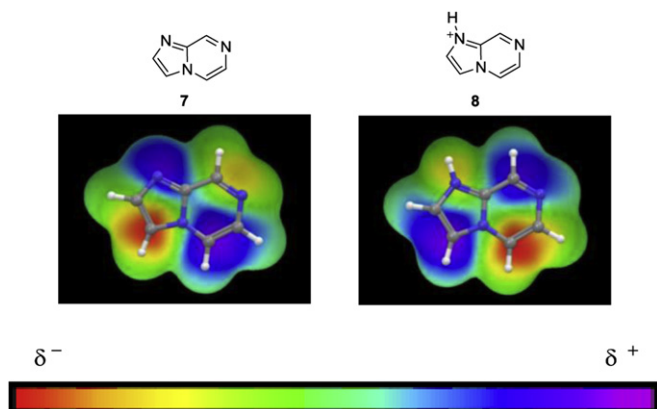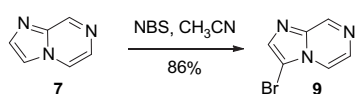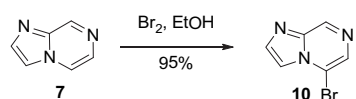* Corresponding author. Fax: +1 (860) 686 7444; e-mail address: jennifer.e.davoren@pfizer.com (J.E. Davoren).

Fig. 1. Electrophilic frontier density map for **7** and **8**.

Equation 2.
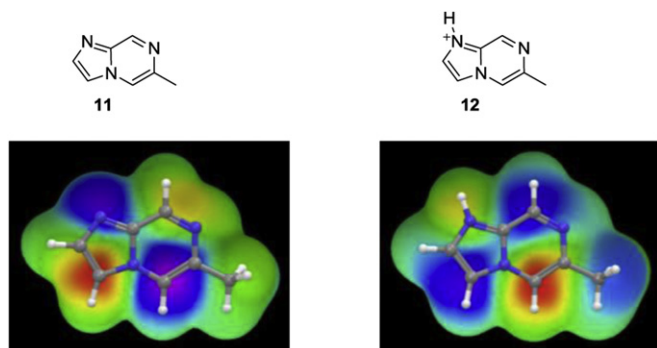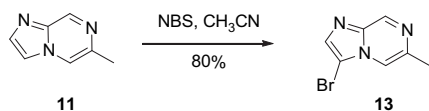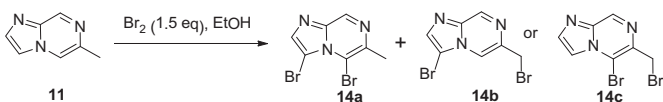

Equation 3.

Fig. 2. Electrophilic frontier density map for **11** and **12**.

the preferential site of electrophilic attack on the neutral reactant and C(5) on its protonated form. As expected bromination of **11** with NBS exclusively furnished the C(3) brominated adduct **13** in 80% yield. Treatment with bromine, however, under conditions identical to those used on **7** yielded a mixture of brominated


Equation 4.

Equation 5.

species (Eqs. 4 and 5). GC–MS of the crude reaction mixture identified two major dibrominated products. ^{1}H NMR data suggests that one of the dibromo species was brominated on the 6-methyl group while the other had only aromatic bromides. In addition, a minor amount of **13** (ca. 10%), but no **1**, was present. Taken together, we conclude that the two major products from this reaction were **14a** and either **14b** or **14c**. With the steric effect of the methyl group apparently overriding any electronic bias for bromination at C(5), an alternate approach to 5-bromo-6-methyl imidazopyrazine **1** was investigated.

Our second approach to 5-bromo-6-methyl imidazopyrazine **1** commenced with commercial 2-amino-5-methyl pyrazine **15** (Scheme 1). Due to the strong directing effect of the amino substituent, EAH of **15** with either Br$_2$ or NBS exclusively led to the formation of undesired regioisomer **17b**. The key to at least partially mitigating the amine's directing effect was to form the HBr salt of **15** prior to bromination (Fig. 3).[7] With C(3) sufficiently deactivated, bromination of **15** ortho to the weakly activating methyl group at C(6) was accomplished in moderate yield and selectivity (~3:2). We noted that when the crude reaction mixture was heated to 50 °C, the undesired isomer **17b** was converted to a highly polar material, which simplified the purification of **17a** by silica gel chromatography. Cyclization of **17a** with aqueous chloroacetaldehyde furnished the target 5-bromo-6-methylimidazo[1,2-a]pyrazine **1** in moderate to good yield[8] making the overall efficiency ≥22% over the two steps.
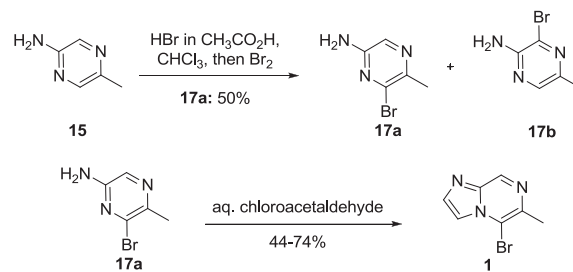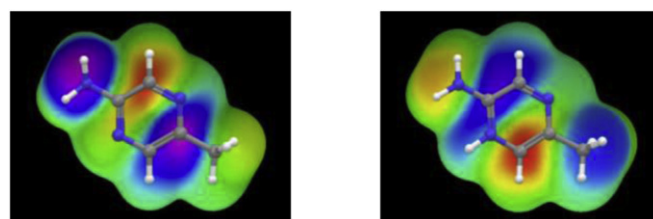

Scheme 1.

Fig. 3. Electrophilic frontier density map for **15** and **16**.

Although it would have been convenient to prepare 5-bromo-6-methylimidazo[1,2-a]pyridine **2** via an analogous route, direct bromination of commercial 2-amino-5-methyl pyridine **18** under the described acidic conditions led exclusively to 3-bromo-5-methylpyridin-2-amine **20** (Eq. 6). This is not surprising since as a pyridine, **18**, is more polarized than pyrazine **15**. Protonation of **18** should predominantly occur on the more basic pyridine nitrogen **19**, further deactivating the ortho-position towards electrophilic attack (Fig. 4).

Facing this combination of electronic and steric factors, we focused our attention on work done by Wachi and Terada.[9]
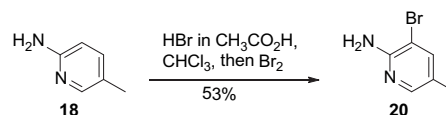
Equation 6.

Fig. 4. Electrophilic frontier density map for **18** and **19**.

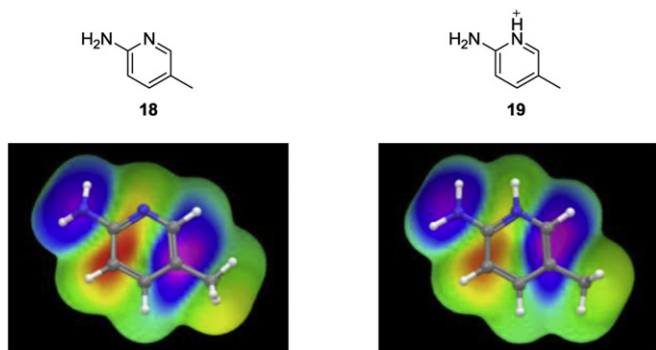Accordingly, when *N*-oxide **21**[10] was refluxed with benzoxazine **22**,[11] the intermediate addition product cyclized to an oxadiazolidine and eliminated HCl to give a mixture (1:1) of bromo- and chloro-pyridinium oxazines **23a** and **23b** in moderate yield (Scheme 2). The ratio of **23a** to **23b** could be determined by ^{1}H NMR. We believe that the bromide is extremely labile to displacement by chloride generated during the reaction. Hydrolysis of the mixture with concentrated HCl furnished 2-aminopyridines **24a** and **24b** (1:1). Formation of the imidazole ring was accomplished by refluxing the mixture with 2-chloroacetaldehyde in ethanol to give 5-bromo and 5-chloro-6-methylimidazo[1,2-*a*]pyridines **2a** and **2b** in high yield but with further erosion of the bromo/chloro ratio in some batches. The individual bromo- and chloro components could either be separated by HPLC or used as a mixture. Although chloroimidazopyrazine **2b** is presumably less reactive than its bromo-substituted counterpart **2a**, we found no practical disadvantage to using a mixture of these halogenated heterocycles in subsequent Suzuki couplings.
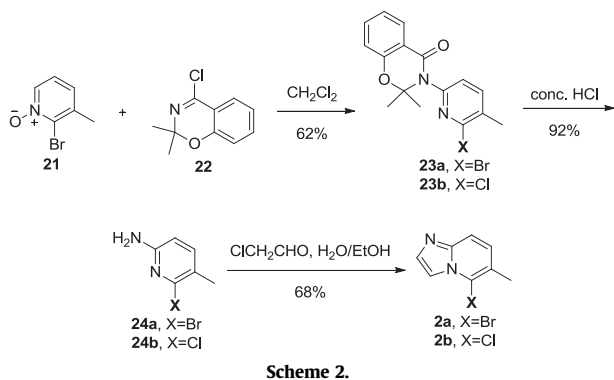
Scheme 2.

In summary, described herein is a practical and scalable route for the synthesis of previously unknown heterocycles 5-bromo-6-methyl imidazopyrazine **1**, 5-bromo- and 5-chloro-6-methyl imidazopyridines **2a** and **2b**. The challenge in constructing these architectures was the regioselective installation of the bromine or chlorine functionality at the sterically and electronically disfavored C(5) position. Electron density surface maps encoded with ionization potential were used to guide synthetic strategy. In our hands, both heterocycles readily underwent Suzuki reactions in a parallel format with a diverse set of boronic esters with average yields ranging from 50 to 80%.

3. Experimental

3.1. General

NMR spectra were recorded on a Bruker Avance II spectrometer (^{1}H: 400 MHz, ^{13}C: 100 MHz) at 25 °C, using CDCl$_3$, CD$_3$OD or DMSO-d_6 as the solvent. Chemical shifts are reported in parts per million (ppm) relative to solvent (CDCl$_3$: 7.27 and 77.0 ppm; DMSO-d_6: 2.50 and 39.51 ppm; CD$_3$OD: 3.31 and 49.2 ppm in ^{1}H and ^{13}C NMR, respectively). IR spectra were recorded on an FT-IR type Nicolet 380 spectrometer and are reported in cm^{-1}. Mass spectra were recorded using the ESI$^+$ method on an Agilent G1969A LC/MSD TOF mass spectrometer. Melting points were measured on a WRS-2A apparatus and are uncorrected. Petroleum ether (PE) used refers to the fraction boiling in the range 30–60 °C.

*3.1.1. 3-Bromo-6-methylimidazo[1,2-a]pyrazine (**13**).* NBS (26 mg, 0.15 mmol) was added to a solution of 6-methylimidazo[1,2-*a*] pyrazine (**11**) (20 mg, 0.15 mmol) in anhydrous acetonitrile at 0 °C. The ice bath was removed and after 1.5 h the reaction was concentrated under reduced pressure. The residue was purified by preparative TLC eluting with petroleum ether/EtOAc (1:2) to give 3-bromo-6-methylimidazo[1,2-*a*]pyrazine (**13**) (25 mg, 80%) as a yellow solid. mp 80–83 °C; IR (KBr): 3430, 2923, 1618, 1502, 1436, 1320, 923 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ=8.99 (s, 1H), 7.88 (s, 1H), 7.74 (s, 1H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ=142.7, 140.4, 139.5, 135.6, 113.6, 100.0, 20.9; HRMS-ESI: calcd for C$_7$H$_7$BrN$_3$ (M+H)$^+$: 211.9823 and 213.9803; found: 211.9818 and 213.9794.

*3.1.2. 6-Bromo-5-methylpyrazin-2-amine (**17a**) and 3-bromo-5-methylpyrazin-2-amine (**17b**).* A solution of HBr/CH$_3$CO$_2$H (360 g (260 mL), 1.50 mol, 33% HBr in CH$_3$CO$_2$H) in anhydrous CHCl$_3$ (300 mL) was added over 15 min to a solution of 5-methylpyrazin-2-amine **15** (42 g, 0.38 mmol) in CHCl$_3$ (1 L). The reaction flask was wrapped in aluminum foil and heated to 50 °C for 30 min in the dark whereupon a solution of Br$_2$ (68 g, 0.42 mmol) in CHCl$_3$ (500 mL) was added dropwise over 3 h during which time the internal temperature of the reaction never exceeded 55 °C. After 18 h at 55 °C the solvent was evaporated under reduced pressure. The crude mixture was diluted with water (200 mL) and the pH was adjusted to pH=9 by the addition of solid Na$_2$CO$_3$. The suspension was filtered under vacuum and the filtrate was extracted with EtOAc (1 L×5). The combined organic extracts were concentrated under reduced pressure and purified by flash silica gel chromatography eluting with petroleum ether/EtOAc (5:1→1:1) to give compound 6-bromo-5-methylpyrazin-2-amine **17a** (36 g, 50%) as a light orange solid; mp 154–157 °C; IR (KBr): 3315, 3188, 1744, 1638, 1575, 1482, 1375, 1308, 1051 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ=7.84 (s, 1H), 4.55 (br s, 2H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ=152.2, 141.8, 138.4, 129.2, 22.2; HRMS-ESI: calcd for C$_5$H$_7$BrN$_3$ (M+H)$^+$: 187.9823 and 189.9803; found: 187.9816 and 189.9796. An analytical sample of 3-bromo-5-methylpyrazin-2-amine (**17b**) was also isolated for spectroscopic analysis; mp 56–57 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ=7.80 (s, 1H), 4.95 (br s, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ=150.6, 142.8, 139.9, 125.2, 19.7; HRMS-ESI: calcd for C$_5$H$_7$BrN$_3$ (M+H)$^+$: 187.9823 and 189.9803; found: 187.9817 and 189.9796.

*3.1.3. 5-Bromo-6-methylimidazo[1,2-a]pyrazine (**1**).* A mixture of compound **15a** (100 g, 0.53 mol) and ClCH$_2$CHO (500 g (400 mL), 3.20 mol, 50 wt % aqueous solution) in H$_2$O (600 mL) was refluxed for 5 h. The reaction mixture was concentrated to remove ClCH$_2$CHO then extracted with EtOAc (600 mL×3). The combined organic layers were concentrated and recrystallized from EtOAc and petroleum ether. The mother liquor was purified by column chromatography eluted with petroleum ether/EtOAc (2:1→1:1) to give 5-bromo-6-methylimidazo[1,2-*a*]pyrazine **1** (50 g, 44%) as a yellow solid; mp 145–148 °C; IR (KBr): 3100, 1495, 1324, 1295, 1145, 771 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ=8.99 (s, 1H), 7.87–7.84 (m, 2H), 7.69 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ=140.0

(2C), 139.0, 134.8, 115.0, 110.4, 22; HRMS-ESI: calcd for $C_7H_7BrN_3$ $(M+H)^+$: 211.9823 and 213.9803; found: 211.9817 and 213.9797.

3.1.4. 3-(6-Bromo-5-methylpyridin-2-yl)-2,2-dimethyl-2H-benzo[e] [1,3]oxazin-4(3H)-one (23a) and 3-(6-chloro-5-methylpyridin-2-yl)-2,2-dimethyl-2H-benzo[e][1,3]oxazin-4(3H)-one (23b).

A solution of 2-bromo-3-methylpyridine 1-oxide **21** (10 g, 54 mmol) and 4-chloro-2,2-dimethyl-2*H*-benzo[*e*][1,3]oxazine **22** (5.3 g, 27 mmol) in anhydrous CH_2Cl_2 (250 mL) was refluxed for 18 h under an inert atmosphere. The reaction was cooled to rt, then concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography eluting with CH_2Cl_2/heptane (1:1→1:0) to give a mixture (1:1) of **23a** and **23b** (5.4 g, ~17 mmol, 62%) as a yellow solid. A sample was separated by HPLC and the individual heterocycles were characterized as follows: for **23a**: mp 106–109 °C; IR (KBr): 1672, 1469, 1342, 1067, 765 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ=7.98 (d, *J*=6.8 Hz, 1H), 7.60 (d, *J*=7.6 Hz, 1H), 7.50 (t, *J*=7.8 Hz, 1H), 7.23 (d, *J*=7.6 Hz, 1H), 7.10 (t, *J*=7.4 Hz, 1H), 6.97 (d, *J*=8.4 Hz, 1H), 2.42 (s, 3H), 1.78 (s, 6H); ^{13}C NMR (100 MHz, CDCl$_3$): δ=161.8, 155.5, 148.8, 142.1, 139.9, 134.8, 134.2, 128.4, 123.3, 122.1, 117.6, 117.1, 93.1, 26.8, 21.5; HRMS-ESI: calcd for $C_{16}H_{16}BrN_2O_2$ $(M+H)^+$: 347.0395 and 349.0375; found: 347.0390 and 349.0371. For **23b**: mp 99–103 °C; IR (KBr): 1672, 1453, 1345, 1073, 766 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ=7.98 (dd, *J*=7.6, 1.6 Hz, 1H), 7.64 (d, *J*=8.0 Hz, 1H), 7.50 (td, *J*=8.0, 1.2 Hz, 1H), 7.20 (d, *J*=7.6 Hz, 1H), 7.11 (td, *J*=7.6, 1.2 Hz, 1H), 6.98 (d, *J*=8.0 Hz, 1H), 2.42 (s, 3H), 1.77 (s, 6H); ^{13}C NMR (100 MHz, CDCl$_3$): δ=161.9, 155.5, 149.7, 148.7, 140.6, 134.8, 131.6, 128.3, 123.1, 122.1, 117.6, 117.1, 93.0, 26.8, 19.2; HRMS-ESI: calcd for $C_{16}H_{16}ClN_2O_2$ $(M+H)^+$: 303.0900; found: 303.0890.

3.1.5. 6-Bromo-5-methylpyridin-2-amine (24a) and 6-chloro-5-methylpyridin-2-amine (24b).

A solution of **20a** and **20b** (5.4 g, ~17 mmol) in concentrated HCl (35 mL) was refluxed for 45 h whereupon it was concentrated under reduced pressure. The residue was adjusted to pH 8 by the addition of satd aqueous NaHCO$_3$ and extracted with CH_2Cl_2 (3×80 mL). The combined organic extracts were washed with brine, dried (Na$_2$SO$_4$), and concentrated under reduced pressure to give a mixture (1:1) of **24a** and **25b** (2.5 g, ~15 mmol, 92%) as a white solid. A sample was separated by HPLC and the individual heterocycles were characterized as follows: for **24a**: mp 96–98 °C; IR (KBr): 3364, 3200, 1600, 1475, 1373, 819 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ=7.25 (d, *J*=8.0 Hz, 1H), 6.38 (d, *J*=8.0 Hz, 1H), 4.48 (br s, 2H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ=156.4, 141.7, 140.5, 123.3, 107.3, 20.7; HRMS-ESI: calcd for $C_6H_8BrN_2$ $(M+H)^+$: 186.9871 and 188.9850; found: 186.9865 and 188.9845. For **24b**: mp 90–92 °C; IR (KBr): 3362, 1639, 1479, 1378, 820 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ=7.29 (d, *J*=8.0 Hz, 1H), 6.36 (d, *J*=8.0 Hz, 1H), 4.41 (br s, 2H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ=156.4, 148.8, 141.2, 120.7, 106.9, 18.3; HRMS-ESI: calcd for $C_6H_8ClN_2$ $(M+H)^+$: 143.0376; found:143.0371.

3.1.6. 5-Bromo-6-methylimidazo[1,2-a]pyridine (2a) and 5-chloro-6-methylimidazo[1,2-a]pyridine (2b).

2-Chloroacetaldehyde (9.5 g, 61 mmol, 50% aqueous solution) was added to a solution of **23a** and **23b** (2.3 g, ~14 mmol) in EtOH (50 mL). The mixture was heated to reflux for 4 h whereupon the solution was cooled to rt and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography eluting with CH_2Cl_2/MeOH (100:0→95:5) to give a mixture (1:1) of **2a** and **2b** (1.8 g, ~9.6 mmol, 68%). A sample was separated by HPLC and the individual heterocycles were characterized as follows: for **2a**: IR (KBr): 3154, 1482, 1289, 1142, 801, 602 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ=7.79 (s, 1H), 7.65 (d, *J*=1.2 Hz, 1H), 7.54 (d, *J*=9.2 Hz, 1H), 7.10 (d, *J*=9.2 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ=144.9, 132.9, 127.7, 122.8, 115.7, 114.4, 113.7, 20.5; HRMS-ESI: calcd for $C_8H_8BrN_2$ $(M+H)^+$: 210.9871 and 212.9850; found: 210.9865 and 212.9845. For **2b**: IR (KBr): 3377, 1488, 1288, 1146, 800, 700 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ=7.68 (s, 1H), 7.61 (d, *J*=1.2 Hz, 1H), 7.46 (d, *J*=9.0 Hz, 1H), 7.04 (d, *J*=9.0 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ=145.2, 133.4, 127.7, 123.9, 119.3, 115.2, 111.3, 17.7. HRMS-ESI: calcd for $C_8H_8ClN_2$ $(M+H)^+$: 167.0376; found: 166.0298.

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3. In color map figures the HOMO is mapped onto an electron density isosurface. Colors toward red predict where electrophilic attack would likely occur.
4. All computational studies were performed using the Density Functional Theory (DFT) methods implemented in the Jaguar version 7.7 suite of programs. Molecular geometries were optimized using the 6-31G** basis set. The electronic properties calculated from these structures were the HOMO and LUMO energies. The distribution of the electron density in the HOMO is highlighted as the principal factor governing the selective behavior of substrate to reagent.
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