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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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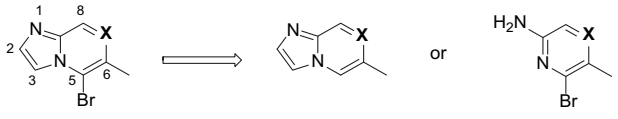
ABSTRACT

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.

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

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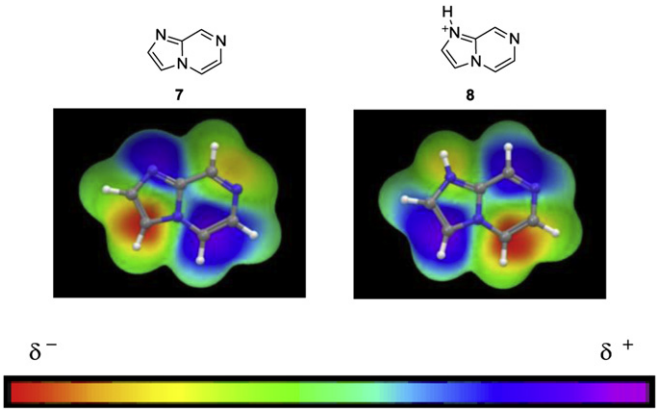
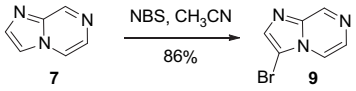
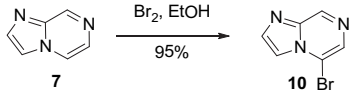


Fig. 1. Electrophilic frontier density map for **7** and **8**.



Equation 2.



Equation 3.

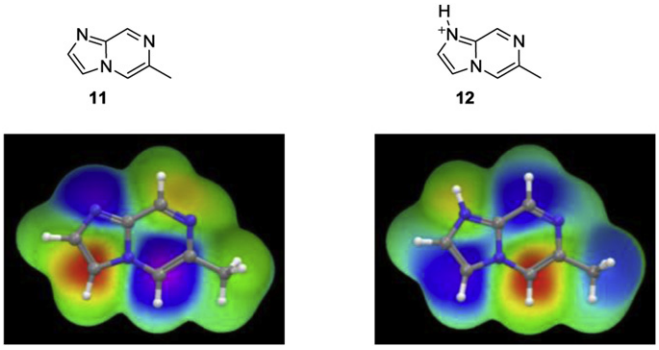
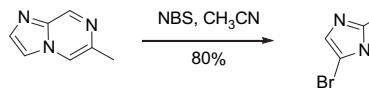
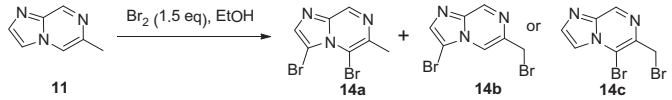


Fig. 2. Electrophilic frontier density map for **11** and **12**.

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 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.

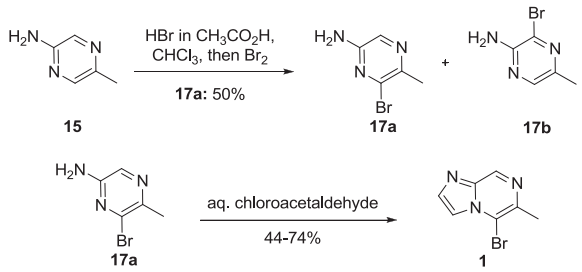


Equation 4.



Equation 5.

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.

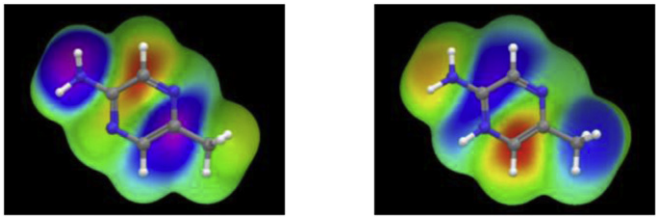
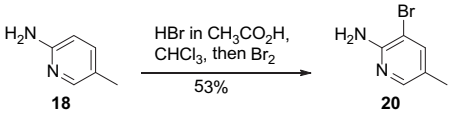


Fig. 3. Electrophilic frontier density map for **15** and **16**.

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 predominately 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.