Facile One-Pot Assembly of Push–Pull Imines by a Selective C–F Substitution Process in Aryl Fluorides

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Abstract: Herein, we report the synthesis of a series of push–pull imines by considering cyclic diamino substituent at the C-centre and fluoroaryl substituent at the N-centre. This has been achieved by a selective aromatic nucleophilic substitution of different fluoroarenes by N-H-substituted N-heterocyclic imines (NHIs) at ambient conditions without any additional reagent. Solid-state molecular structure analysis reveals the elongation of the central C–N bond of the imine functionality, which is consistent with the push–pull nature of these imines. The push–pull nature of these imines is further validated by computational studies.

Compounds involving imine functionality (C=N) play an important role in different fields of research ranging from covalent organic frameworks (COF) to dynamic chemistry.[1] Imines of the type I, possessing various types of R groups are known (Scheme 1).[2] The difference in electronegativity between carbon and nitrogen makes the imine group inherently polar unlike an alkene moiety. This inherent polarity of the C–N group can be augmented by incorporating an electron-donating group (EDG) at the C-centre and an electron-withdrawing group (EWG) at the N-centre. Such imines with a polar C=N bond constitute a family of push–pull imines. It must be noted that push–pull alkenes having EDG and EWG at the vicinal positions have attracted interest because of their distinct properties in comparison to non-polarized alkenes.[3] In view of the general interest in such push–pull systems,[4] we were interested in finding ready synthetic routes for assembling push–pull imines of the type II (Scheme 1). This design considered cyclic diamino group as electron donating group (EDG) at the C-centre and fluoroaryl group as electron withdrawing group (EWG) at the N-centre of the imine moiety. Accordingly, herein, we have considered N-H-substituted N-heterocyclic imines (NHIs) as an appropriate precursor for reaction with fluoroarenes for the synthesis of N-(per)-fluoroaryl-substituted N-heterocyclic imines. The idea was to examine if push–pull imines can be prepared by such an aromatic nucleophilic substitution[5] without using any other catalyst or activating reagent. Hexafluoroacetone imine is known to replace the p-C–F bonds of pentafluoropyridine and octafluorotoluene in presence of excess CsF at 70–90 °C, thus lending credence to our design.[6] Moreover, to address

Scheme 1. Chemical structures of I and II (R = organic substituents, EDG = electron donating group, and EWG = electron withdrawing group).
the push–pull nature of \(N\)-(per)-fluoroaryl-substituted \(N\)-heterocyclic imines we have computed several bond parameters and compared the values against their corresponding non-fluorinated analogues and a reference imine with no push–pull character.

\(N\)-aryl-substituted \(N\)-heterocyclic imines were prepared previously (i) by a reaction of an NHC with aryl azide,[7] (ii) by reacting 2-chloro-imidazolium chloride with arylamine,[8] or (iii) by Pd-catalyzed reaction of \(N\)-H-substituted \(N\)-heterocyclic imine and aryl bromide.[9] \(N\)-H-substituted \(N\)-heterocyclic imines (NHIs) were used previously as mono-anionic ligands for main-group as well as transition metal complexes.[10] Recently, cyclic(alkyl)(amino)carbene (CAAC) derived imino ligand has also been introduced for the synthesis of both main-group as well as transition metal complexes.[11] In this study, we have chosen \(N\)-alkyl and \(N\)-aryl-substituted \(N\)-heterocyclic carbene-derived \(N\)-H-substituted \(N\)-heterocyclic imines (NHIs) 1[13] and 2[13] to explore the variation in steric and electronic factors (Scheme 2). The individual 1:2 reactions of 1 and 2 with pentfluoropyridine led to the selective formation of 4-tetrafluoropyridyl-substituted \(N\)-heterocyclic imines 1a and 2a, respectively, in good yields (Scheme 2).[14] In the course of the reaction, \(N\)-H-substituted NHIs 1 and 2 also act as HF-scavengers; we were able to obtain the corresponding guanidinium cations and in the case of 1 we isolated 1·HF\(_2\) with bifluoride (HF\(_2^–\)) as the counter anion (Figure S45 in SI).[15]

Compound 1 was treated with pentfluoropyridine at room temperature. \(\textsuperscript{1}H/\textsuperscript{19}F\) \((\textsuperscript{1}H)\) NMR measurements showed the reaction to be completed within 30 minutes. In contrast to this, compound 2 reacted with pentfluoropyridine at 60 °C and required about 2 hours for completion. 1a and 2a were characterized by \(\textsuperscript{1}H\), \(\textsuperscript{13}C\)\((\textsuperscript{1}H)\), and \(\textsuperscript{19}F\)\((\textsuperscript{1}H)\) NMR studies as well as single-crystal X-ray crystallography (Figure 1 and Figure 2).[15] The C1–N3 bond lengths in 1a and 2a are 1.356(2) Å and 1.309(2) Å, respectively which are both longer than those found in \(N\)-H substituted \(N\)-heterocyclic imines, 1 (1.294 Å)[16] and 2 (1.289 Å).[17] A notable feature of 1a and 2a is the dihedral angle of 72.4° and 22.2°, respectively between the two planes (N1–C1–N2 and C28–N3–C1 for 1a; N1–C1–N2 and C28–N3–C1 for 2a) around the central carbon–nitrogen double bond.

Based on these observations, a set of distinct fluorooarenes were then investigated in the reactions with 1 and 2. Compound 1 regioselectively reacts with a variety of fluorooarenes such as octafluorotoluene, pentafluorobezonitrile, pentafluoro- benzene, hexafluorobenzene, bromopentafluorobenzene, octafluoro naphthalene, and decafluorobiphenyl under the formation of \(N\)-(per)-fluorooaryl-substituted \(N\)-heterocyclic imines, 1b–1h, respectively (Scheme 3).[14] In case of bromopentafluorobenzene, we obtained exclusively C–F replacement product over C–Br, despite the fact that the C–F bond strength is higher than C–Br. This indicates that the reaction most likely proceeds through the nucleophilic attack of NHI at the most electrophilic carbon centre of the fluorooarenes.

The outcome of the reactions indicate that compound 1 tolerates aryl–CF\(_3\), –Br, and –CN functional groups in the course of the transformations. The formation of all these compounds was confirmed by multinuclear-NMR spectroscopy. In the case of compounds 1b and 1g, we were able to obtain their solid state molecular structures by single-crystal X-ray diffraction studies (Figure S44 in SI for 1b and Figure 3 for 1g).[15] The C1–N3 bond length of 1b [1.347(2) Å] is comparable with that of 1a [1.347(2) Å] and 1g [1.351(2) Å]. The dihedral angle of 1b between the two planes (N1–C1–N2 and C12–N3–C1) around the central carbon–nitrogen double bond is 77.5°, which is similar to that of 1a (72.4°). Due to the presence of structural disorder in 1g, we are not discussing any metrical parameters of it. We have also tested the reaction

![Figure 1](https://example.com/image1)

![Figure 2](https://example.com/image2)

**Scheme 2. Reactions of 1 and 2 with pentfluoropyridine.**

**Figure 1.** Solid state molecular structure of 1a with thermal ellipsoids at 50 %.

**Figure 2.** Solid state molecular structure of 2a with thermal ellipsoids at 50 %.

Scheme 3. Reactions of 1 with different fluoroarenes (isolated yields are in the parenthesis).

Scheme 4. Reactions of 2 with different fluoroarenes (isolated yields are in the parenthesis).

The notable feature of 2c is the smaller dihedral angle of 17.6° between the two planes (N1–C1–N2 and C16–N3–C1) around the central carbon–nitrogen double bond.

Figure 4. Solid state molecular structure of product 2c with thermal ellipsoids at 50 %. All H-atoms were omitted for clarity. Selected bond lengths [Å] and bond angles [°]: N1–C1 1.379(1), N2–C1 1.367(1), N3–C1 1.308(1), N3–C16 1.365(2), N1–C1–N2 105.67(8), N1–C1–N3 132.31(10), N2–C1–N3 121.71(9), C1–N3–C16 121.47(9).

Figure 4. Solid state molecular structure of product 2c with thermal ellipsoids at 50 %. All H-atoms were omitted for clarity. Selected bond lengths [Å] and bond angles [°]: N1–C1 1.379(1), N2–C1 1.367(1), N3–C1 1.308(1), N3–C16 1.365(2), N1–C1–N2 105.67(8), N1–C1–N3 132.31(10), N2–C1–N3 121.71(9), C1–N3–C16 121.47(9).

The observed dihedral angles between the two planes around the central carbon–nitrogen double bond in 1a (72.4°), 1b (77.5°), 2a (22.2°), and 2c (17.6°) are quite different. This is most likely due to the steric hindrance at N-substituents. These suggestions, however, are tentative and further study is needed for a better understanding. The consequence of the dihedral angle is also reflected in the imine C–N bond lengths {1a [1.356(2) Å], 1b [1.347(2) Å], 2a [1.309(2) Å], and 2c [1.308(1) Å]}. Thus, larger dihedral angles seem to result in a less-effective \( \pi \)-overlap between the C- and N-centres of the central imine moiety, resulting in an increased bond length.

To gain theoretical insight into the reaction mechanism, we carried out DFT computations using NHIEtMe, 3 and penta-
fluoropyridine, C₅F₅N as the model imine and the fluoro substrate respectively (Scheme 5). We considered the following. A nucleophilic attack of 3 at the most electrophilic p-C-centre (p-C–F bond) of the C₅F₅N, leading to the formation of an intermediate, Int1 through TS1. A direct HF elimination (pathway-a) from Int1, in which the leaving fluoride anion itself assists in the proton abstraction, yields the desired product 3a through the involvement of TS2 (Figure 5). Alternatively, 3 can also assist in the proton abstraction from Int1 (pathway-b), leading to the final product via TS3 (see Figure S46 in SI). The HF-elimination proceeds with a much lower free energy activation barrier than the initial nucleophilic attack (14.2 kcal/mol vs. 2.2 kcal/mol for Int1 → 3a) and it is a highly exergonic step as the pyridine moiety regains its aromaticity back. As a result, the formation of 3a is thermodynamically favored by 26.3 kcal/mol with respect to the staring materials. The overall free energy activation barrier in the computed mechanism is 14.2 kcal/mol (corresponding to TS1) which is consistent with the observed reactivity at room temperature.

Finally, the newly synthesized push–pull imines (PPlims), 1a, 1b, 2a, and 2b were subjected to computational analysis to address their push–pull nature. The computed structural parameters for 1a, 1b, and 2a are fairly consistent with the crystallographic data. For example, the imine C=N bond length in 2a is found to be 1.309 Å which is in excellent agreement with the experimentally measured value 1.305 Å. The push–pull nature of these imines are addressed in terms of several bond parameters for the central imine C–N bond including bond length (d), Wiberg bond index (WBI), NPA charge difference between the C and the N atom (Δq), electron density (ρ) obtained from QTAIM analysis and finally, the rotational barrier across the central imine C–N bond. These results are compared against the bond parameters for a reference imine, Me₂C=NMe (rim), which is expected to have no push–pull character. Additionally, we have also considered four non-fluorinated analogues (NFA), 1a-H, 1b-H, 2a-H, 2b-H, designed from the structures of 1a, 1b, 2a, and 2b, respectively, by replacing the F-substituents with H atoms. Such a comparative analysis would further highlight the push–pull characteristics of the imines considered in this study. All computed bond parameters are listed in Table 1. The reference imine Me₂C=NMe (rim) shows a C–N bond length of 1.267 Å along with a corresponding WBI of 1.874 and an energy barrier of imine C–N bond rotation of 26.2 kcal/mol. The push–pull effect tends to weaken the C–N bond and consequently, this is reflected on all computed bond parameters. All push–pull imines exhibit a more elongated C–N bond length and a lower WBI compared to Me₂C=NMe, suggesting push–pull nature present in them. The non-fluorinated analogues exhibit an intermediate push–pull effect as expected from the relatively lower electronegativity of H atom in comparison to F; for a particular pair of PPlim and its NFA, the C–N bond length varies following the trend, PPlim > NFA > rim. The Δq values in PPlims are higher than that in rim, suggesting a more charge-separated central C–N bond due to a significant push–pull character (Table 1). The computed ρ values are also consistent with the higher push–pull character in 1a, 1b, 2a, 2b compared to their corresponding non-fluorinated analogues and rim.

![Scheme 5. Proposed mechanism of aromatic nucleophilic substitution of C–F bond of pentafluoropyridine by 3.](Image)

**Figure 5.** The relative Gibbs free energy profile for reaction of 3 with pentafluoro-pyridine. Solvent-corrected Gibbs free energy (kcal/mol) values are given in parenthesis. All distances are given in angstrom.

**Table 1.** Calculated parameters of 1a, 1b, 2a, and 2b and their non-fluorinated analogue 1a-H, 1b-H, 2a-H, and 2b-H.

<table>
<thead>
<tr>
<th>Compounds/Parameters</th>
<th>1a</th>
<th>1a-H</th>
<th>1b</th>
<th>1b-H</th>
<th>2a</th>
<th>2a-H</th>
<th>2b</th>
<th>2b-H</th>
<th>Me₂C=NMe</th>
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<tr>
<td>(1.356)</td>
<td>(1.347)</td>
<td></td>
<td></td>
<td>(1.309)</td>
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<td>WBI</td>
<td>1.35</td>
<td>1.45</td>
<td>1.37</td>
<td>1.51</td>
<td>1.45</td>
<td>1.51</td>
<td>1.46</td>
<td>1.55</td>
<td>1.87</td>
</tr>
<tr>
<td>NPA charges</td>
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<td>C:0.65</td>
<td>C:0.66</td>
<td>C:0.64</td>
<td>C:0.65</td>
<td>C:0.64</td>
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<td>C:0.63</td>
<td>C:0.30</td>
</tr>
<tr>
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<td>N:0.63</td>
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<td>N:0.63</td>
<td>N:0.61</td>
<td>N:0.61</td>
<td>N:0.46</td>
</tr>
<tr>
<td>Electron Density (e/Å³)</td>
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<td>2.49</td>
<td>2.43</td>
<td>2.52</td>
<td>2.48</td>
<td>2.53</td>
<td>2.48</td>
<td>2.55</td>
<td>2.59</td>
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<tr>
<td>Barrier of Imine C–N Rotation (kcal/mol)</td>
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<td>3.5</td>
<td>3.9</td>
<td>4.7</td>
<td>5.1</td>
<td>7.1</td>
<td>5.6</td>
<td>9.9</td>
<td>26.2</td>
</tr>
</tbody>
</table>

[a] Bond length obtained from single-crystal X-ray diffraction study.
proof for the push–pull character comes from the computed rotational barriers around the central imine C–N bond which are much lower in push pull imines owing to a weakened C–N bond with respect to Me2C=NMe (Table 1). However, one anomalous result concerns the reverse trend in 1a/1a-H pair. The reasons for this are not clear at the moment.

In conclusion, we demonstrate a facile, one-step assembly of a new family of push–pull imines. This was accomplished by a selective aromatic nucleophilic substitution of C–F bonds of various types of fluoroarenes by N-H-substituted N-heterocyclic imines (NHI)s. Remarkably, the reactions occur at ambient conditions and also do not need any additional catalyst/reagent. Our synthetic paradigm reveals a facile C–F cleavage even in the presence of functional substituents/groups such as –CF3, –Br and –CN. The push–pull nature of these N-(per)-fluoroaryl-substituted N-heterocyclic imines are further confirmed by a detailed computational analysis. The properties of these novel systems are currently under investigation in our laboratory.

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Keywords: Aryl fluorides · One-pot reaction · Nucleophilic substitution · Push–pull imines · Synthetic design

[14] See the Supplementary Information for the experimental and computational details.
[15] Deposition Numbers 1949537 (1a), 1949540 (1b), 1949543 (1g), 1949542 (2a), 1949542 (2c), and 1949539 (1-HF2) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the Joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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