

Push–Pull Imines | Very Important Paper |

VIP 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.

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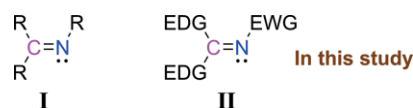
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available on the WWW under <https://doi.org/10.1002/ejoc.202001344>.

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tions or adaptations are made.

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

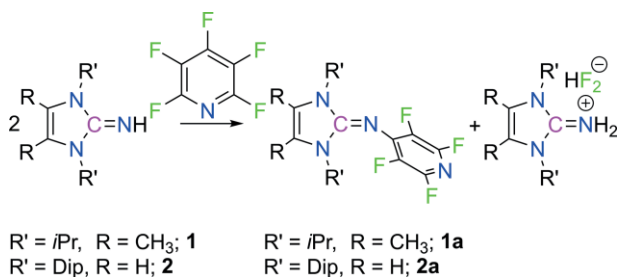


Scheme 1. Chemical structures of **I** and **II** (R = organic substituents, EDG = electron donating group, and EWG = electron withdrawing group).

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 the synthesis of transition metal as well as lanthanide metal complexes^[10] and low-valent low-coordinate main group compounds.^[11] 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.^[12]

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 pentafluoropyridine 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·HF₂** with bifluoride (HF₂[−]) as the counter anion (Figure S45 in SI).^[15]



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

Compound **1** was treated with pentafluoropyridine at room temperature. ¹H/¹⁹F{¹H} NMR measurements showed the reaction to be completed within 30 minutes. In contrast to this, compound **2** reacted with pentafluoropyridine at 60 °C and required about 2 hours for completion. **1a** and **2a** were characterized by ¹H, ¹³C{¹H}, and ¹⁹F{¹H} 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).^[16] 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 C12–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 fluoroarenes were then investigated in the reactions with **1** and **2**. Compound **1** regioselectively reacts with a variety of fluoroarenes such as octafluorotoluene, pentafluorobenzonitrile, pentafluorobenzene, hexafluorobenzene, bromopentafluorobenzene, oc-

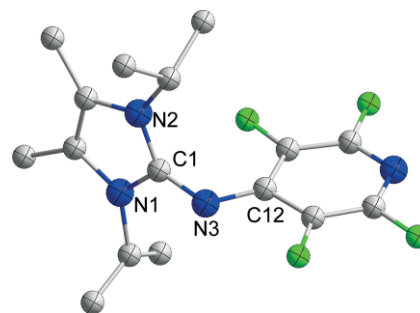


Figure 1. Solid state molecular structure of **1a** with thermal ellipsoids at 50 %. All H-atoms were omitted for clarity. Selected bond lengths [Å] and bond angles [°]: N1–C1 1.339(2), N2–C1 1.345(2), N3–C1 1.356(2), N3–C12 1.335(2); N1–C1–N2 107.70(13), N1–C1–N3 124.22(15), N2–C1–N3 127.74(15), C1–N3–C12 120.582(13).

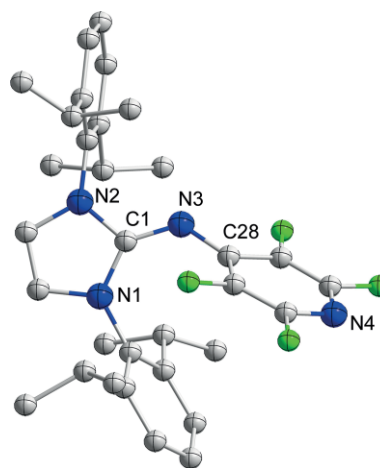
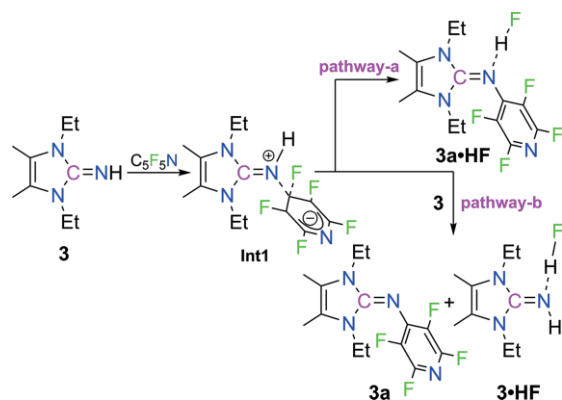


Figure 2. Solid state molecular structure of **2a** with thermal ellipsoids at 50 %. All H-atoms were omitted for clarity. Selected bond lengths [Å] and bond angles [°]: N1–C1 1.375(2), N2–C1 1.366(2), N3–C1 1.309(2), N3–C28 1.358(2); N1–C1–N2 105.81(10), N1–C1–N3 132.14(11), N2–C1–N3 121.50(10), C1–N3–C28 124.58(10).

tafluoro naphthalene, and decafluorobiphenyl under the formation of *N*-(per)-fluoroaryl-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 fluoroarenes.

The outcome of the reactions indicate that compound **1** tolerates aryl–CF₃, –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** 1.356(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

fluoropyridine, C_5F_5N as the model imine and the fluoro substrate respectively (Scheme 5).^[14] We considered the following. A nucleophilic attack of **3** at the most electrophilic *p*-C-centre (*p*-C–F bond) of the C_5F_5N , 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).^[14] 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 starting materials.^[14] 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.



Scheme 5. Proposed mechanism of aromatic nucleophilic substitution of C–F bond of pentafluoropyridine by **3**.

Finally, the newly synthesized push–pull imines (**PPIms**), **1a**, **1b**, **2a**, and **2b** were subjected to computational analysis to address their push–pull nature.^[14] 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

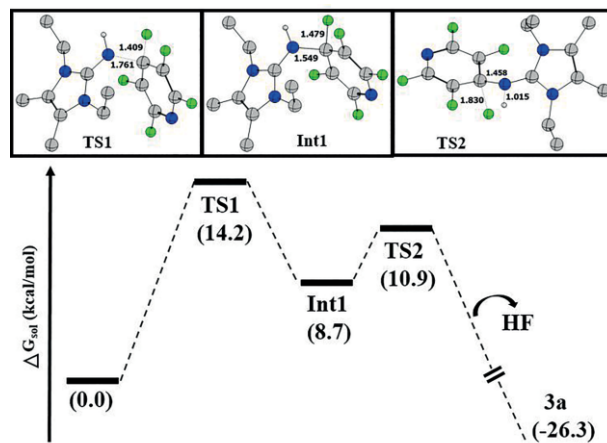


Figure 5. The relative Gibbs free energy profile for reaction of **3** with pentafluoropyridine. Solvent-corrected Gibbs free energy (kcal/mol) values are given in parenthesis. All distances are given in angstrom.

QTAIM analysis and finally, the rotational barrier across the central imine C–N bond. These results are compared against the bond parameters from a reference imine, $Me_2C=NMe$ (**rlm**), which is expected to have no push–pull character. Additionally, we have also considered four non-fluorinated analogues (**NFAs**), **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 $Me_2C=NMe$ (**rlm**) 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 $Me_2C=NMe$, 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 PPIm and its NFA, the C–N bond length varies following the trend, **PPIm** > **NFA** > **rlm**. The Δq values in **PPIms** are higher than that in **rlm**, 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 **rlm**. Final

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

Compounds/Parameters	1a	1a-H	1b	1b-H	2a	2a-H	2b	2b-H	$Me_2C=NMe$
Imine C–N Bond Length [Å]	1.323 (1.356) ^[a]	1.307	1.320 (1.347) ^[a]	1.300	1.305 (1.309) ^[a]	1.296	1.306	1.292	1.270
WBI	1.35	1.45	1.37	1.51	1.45	1.51	1.46	1.55	1.87
NPA charges	C 0.66 N –0.63	C 0.65 N –0.63	C 0.66 N –0.63	C 0.64 N –0.63	C 0.65 N –0.61	C 0.64 N –0.61	C 0.65 N –0.61	C 0.63 N –0.61	C 0.30 N –0.46
Electron Density ($e/\text{Å}^3$)	2.42	2.49	2.43	2.52	2.48	2.53	2.48	2.55	2.59
Barrier of Imine C–N Rotation (kcal/mol)	4.3	3.5	3.9	4.7	5.1	7.1	5.6	9.9	26.2

[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 (NHIs). 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.

Acknowledgments

This project was funded by intramural funds at TIFR Hyderabad from the Department of Atomic Energy (DAE), Government of India and SERB (CRG/2019/003415) India. The National Facility for High-Field NMR, TIFR-Hyderabad, is highly acknowledged for the very convenient access to the NMR spectrometers. PS thanks Council of Scientific and Industrial Research (CSIR), New Delhi, India for Senior Research Fellowship (SRF) and SD thanks JNCASR for fellowship. S.K.P. and V.C. are thankful to the Department of Science and Technology, New Delhi, India, for National J.C. Bose fellowships. Funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation)–Project-ID 387284271–SFB 1349 Fluorine-Specific Interactions: Fundamentals and Applications.

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

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Received: October 8, 2020