Mendeleev Communications

Mendeleev Commun., 2025, **35**, 645–647

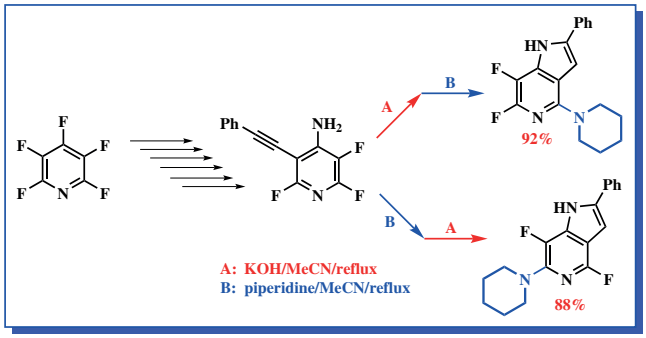
Regioselectivity of S_NAr reactions in the synthesis of isomeric difluorinated 4- and 6-piperidino-5-azaindoles

Larisa Yu. Gurskaya, Irina V. Beregovaya, Igor P. Chuikov, Boris A. Selivanov and Larisa V. Politanskaya*

N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 630090 Novosibirsk, Russian Federation. E-mail: plv@nioch.nsc.ru

DOI: 10.71267/mencom.7780

For the targeted synthesis of fluorinated analogues of 5-azaindoles used for the prevention and treatment of diabetes and obesity, the regioselectivity of fluorine replacement by piperidine residue in their precursors is explored. The reverse sequence of the S_NAr reaction and cyclization steps enables the selective preparation of isomeric 5-azaindoles containing substituents at positions 4 *vs.* 6, respectively. A quantum-chemical justification of the predominant positions of nucleophilic attack in polyfluoroarenes is given.

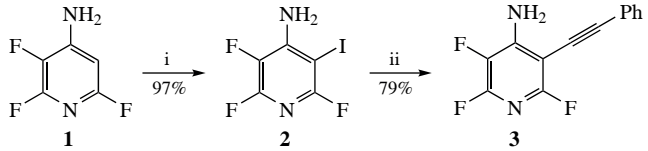


Keywords: electrophilic iodination, Sonogashira cross-coupling, heterocyclization, aminodefluorination, 5-azaindoles, organofluorine compounds, S_NAr reactions, regioselectivity, quantum chemical calculations.

Azaindoles are common scaffolds in biologically active natural and synthetic compounds. 5-Azaindole derivatives containing an amino group at positions 4 or 6 can be used to treat oncological,[1–5] autoimmune,[6,7] neurodegenerative,[5] ulcer,[8] parasitic[9] diseases, fibrotic disorders,[3] microbial infections,[10] as well as for the prevention of diabetes[5,11] and obesity.[11]

The main approach to amino substituted 5-azaindoles consists in the cross-coupling reactions of halogenated 4-amino pyridines with terminal acetylenes[11,12] or with (2-alkoxyvinyl)boronic acid ester[5–7] using the Sonogashira or Suzuki method, respectively, followed by closure of the pyrrole cycle. Subsequently, azaindoles, usually containing bromine[6] or chlorine[11] atoms, are involved in aminodehalogenation reactions, however no examples of aminodefluorination reactions in 5-azaindole derivatives have been found.

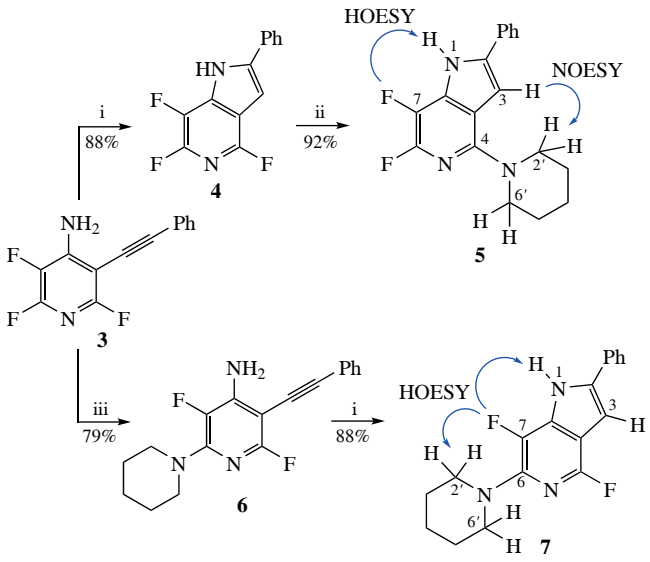
Fluorine is an important element in medicinal chemistry.[13] Its introduction into bioactive organic substances affects their lipophilicity, metabolic stability and bioavailability of compounds, which together leads to a change in the therapeutic effect of the molecules.[14–16] Previously, we have developed efficient strategies for the preparation of diverse potentially bioactive fluorinated azaheterocycles including indoles,[17,18] quinolines,[19,20] quinolinones[21–23] and phenanthridones.[24] Herein, we describe synthetic approach to difluorinated 4- and 6-piperidino-2-phenyl-5-azaindoles.



Scheme 1 *Reagents and conditions*: i, I_2, HIO_3, 1,4-dioxane, H_2O, reflux, 6 h; ii, $PhC{\equiv}CH$, $PdCl_2(PPh_3)_2$, CuI, NEt_3, Ar, 75 °C, 2 h.

The starting 4-amino-2,3,6-trifluoropyridine **1** was obtained by the transformations of commercially available pentafluoropyridine (see Online Supplementary Materials, Scheme S1). Compound **1** was converted into 5-iodo derivative **2** by its treatment with I_2/HIO_3 system in aqueous dioxane in high yield (Scheme 1) by analogy with previously published work.[25] The subsequent Sonogashira cross-coupling of **2** with phenylacetylene gave 2,3,6-trifluoro-5-(phenylethynyl)pyridin-4-amine **3**.

Amino alkyne **3** smoothly cyclized in the presence of KOH in MeCN to form trifluoroazaindole **4** (Scheme 2). The reaction of **4** with an excess of piperidine gave the product of fluorine



Scheme 2 *Reagents and conditions*: i, KOH, MeCN, reflux, 2 h; ii, piperidine, MeCN, reflux, 22 h; iii, piperidine, MeCN, reflux, 2 h.

substitution only at position 4, the target azaindole **5** in 92% yield. The reaction of amino alkyne **3** with an excess of piperidine prior to cyclization under the same conditions resulted in the selective substitution of fluorine atom *para*-positioned in respect to alkynyl group to afford product **6** (see Scheme 2). Its subsequent cyclization led to 6-(piperidin-1-yl)-2-phenyl-5-azaindole **7** in 88% yield. Thus, by the reverse sequence of nucleophile substitution of fluorine atom and cyclization steps, isomeric heterocycles **5** and **7** containing an amine substituent at positions 4 and 6, respectively, can be selectively obtained from the same precursor **3**. It is important that each of these heterocycles **5** and **7** contains two fluorine atoms in different positions of the pyridine fragment, which makes them promising objects for future biological tests.

The structures of compounds **2**–**7** were confirmed *via* the multinuclear NMR, IR spectroscopy and HRMS analysis. The assignment of signals in the NMR spectra was based on the analysis of chemical shifts and spin–spin interaction constants. The location of piperidine fragment at positions 4 and 6 of compounds **5** and **7** were additionally established on the basis of two-dimensional ^{1}H–^{1}H, ^{1}H–^{13}C, ^{19}F–^{1}H spectra (HOESY ^{19}F–^{1}H and NOESY) (see Scheme 2). In case of compound **7**, the presence of a cross peak for the 2- and 6-positioned protons of the piperidine moiety with C^{7}*F* nucleus confirms the location of the piperidine fragment in position C^{6} and, accordingly, fluorine atoms in positions 4 and 7. In addition, the HOESY spectrum also shows a cross peak for C^{7}*F* and N^{1}*H*, which helps to identify the signal of this fluorine atom. In the HOESY spectrum of compound **5**, signal for C^{7}*F* has a cross peak only with signal N^{1}*H*, but the cross peak is present in the NOESY spectrum for signals C^{3}*H* and 2- and 6-positioned protons of the piperidine moiety.

The experimentally observed regioselectivity of the fluorine substitution by the action of piperidine on compounds **3** and **4** can be interpreted on the basis of the calculated reaction pathways (Figure 1). In all cases, the concerted variant of S_NAr reactions is realized, and the transition states (TSs) of the reactions are unstable analogues of the Meisenheimer complexes.[26] Pre-reaction complexes (min$_i$, *i* is the position under consideration) are weakly bound associates of a substrate molecule and a piperidine molecule. Post-reaction complexes are the product of nucleophilic substitution and an HF molecule, which are linked by a hydrogen bond. The images and calculated characteristics of the located structures are given in Online Supplementary Materials.

Apparently, preferential substitution of fluorine atom at *para*-position to alkynyl group when compound **3** interacts with piperidine occurs due to the energetic stability of the corresponding pre-reaction complex and a lower energy barrier compared to the alternative channel [see Figure 1(*a*)]. In the case

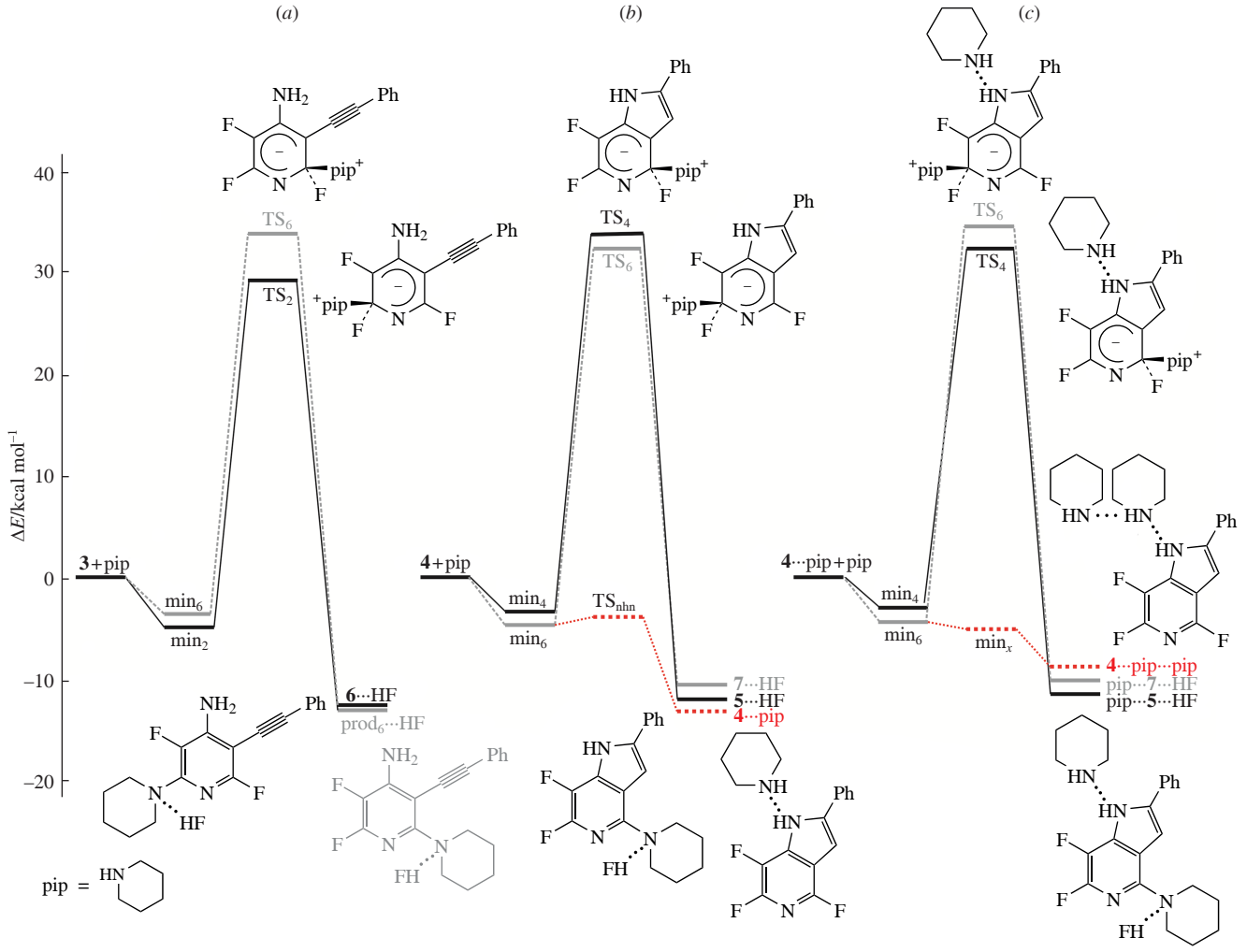


Figure 1 Interactions of compounds **3** and **4** with piperidine. Energy profiles were obtained at the CAMB3LYP/6-31G* level of calculations. The energy levels shown by the solid lines correspond to S_NAr reactions, those corresponding to the products isolated experimentally are shown in black. The red dotted lines correspond to the formation of hydrogen-bonded associates. The zero levels are the sums of energies of noninteracting molecular particles: (*a*) compound **3** and a piperidine molecule (pip); (*b*) compound **4** and pip; (*c*) hydrogen bonded complex **4**···pip and another piperidine molecule. The indices in the structure designations correspond to the position under consideration. Min$_x$ denotes an intermediate structure on the pathway of formation of a hydrogen bond N–H···N linking two piperidine molecules. We were unable to localize the transition states along this pathway.

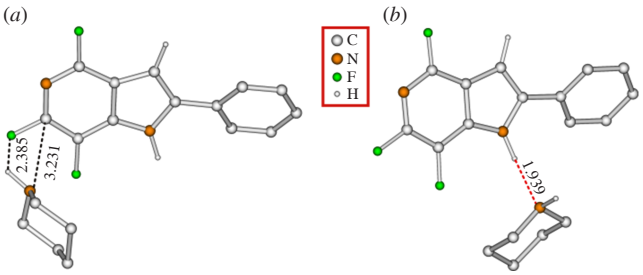


Figure 2 Strustures of (*a*) pre-reaction complex min_6 for **4**, (*b*) hydrogen bonded associate **4**···pip. C–H bonds are shown only in pyrrole rings.

of compound **4**, the same criteria are met by the substitution of the fluorine atom at position 6 [Figure 1(*b*)], but the corresponding product **7** has not been detected. We believe that this is due to the instability of the pre-reaction complex min_6 with respect to the transition to the structure with N–H···N hydrogen bonding (**4**···pip) (Figure 2). This structure is ~9 kcal mol^{-1} more stable than min_6, and the activation barrier of the transition is only 0.8 kcal mol^{-1}. The energy profile for the last process is shown in Figure 1(*b*) by dotted lines.

Since piperidine was used in excess (see Online Supplementary Materials), we also calculated the energy profiles [see Figure 1(*c*)] for the attack of piperidine on associate **4**···pip. In this case, the pre-reaction complex min_6 is also easily transformed into a structure with a hydrogen bond N–H···N. This bond links two piperidine molecules. The corresponding energy profile is shown by dotted lines. Thus, the presence of an NH group in the pyrrole ring of the substrate **4** capable of forming a hydrogen bond with a nucleophile, determines the advantage of substitution of the fluorine atom at position 4 (product **5**).

In conclusion, two isomeric mono-amino derivatives of 5-azaindole containing fluorine atoms in the pyridine fragment were selectively obtained by directed transformation of pentafluoropyridine. The reverse sequence of the reaction steps of diarylacetylene **3** with KOH and piperidine led to the 5-azaindoles **5** and **7** with different substitution pattern. The regioselectivity of fluorine substitution in polyfluoroarenes **3** and **4** was interpreted using quantum-chemically calculated potential energy surface profiles. The obtained 5-azaindole derivatives are promising objects of biological research.

This work was supported by the Ministry of Science and Higher Education of the Russian Federation (project no. 075-00365-25-00). The authors are grateful to the Multi-Access Chemical Research Center of SB RAS for spectral and analytical measurements.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7780.

References

1 H. Engelhardt, M. Petronczki, J. Ramharter, U. Reiser, H. Stadtmueller, D. Scharn and T. Wunberg, *Patent WO 2022090481 A1*, 2022; https://patents.google.com/patent/WO2022090481A1/zh.
2 Y. Shi and W. Ma, *Patent WO 2023186126 A1*, 2023; https://worldwide.espacenet.com/patent/search/family/088199502/publication/WO2023186126A1?q=WO%202023186126%20A1.
3 K. K. Sunil, D. M. Wallace, J. Cao, C. Chiruta and J. Hood, *Patent WO 2017024010 A1*, 2017; https://worldwide.espacenet.com/patent/search/family/057943709/publication/WO2017024010A1?q=WO%202017024010%20A1.
4 K. Vandyck, P. Raboisson, B. Jean-Marie, J. Deval, L. Beigelman, D. Mcgowan and Y. Debing, *Patent WO 2020205867 A1*, 2020; https://worldwide.espacenet.com/patent/search/family/072661994/publication/WO2020205867A1?q=WO%202020205867%20A1.
5 J. Axten, R. R. Kethiri, R. Kristam and C. Venkateshappa, *Patent WO 2018015879 A1*, 2018; https://worldwide.espacenet.com/patent/search/family/059631832/publication/WO2018015879A1?q=WO%202018015879%20A1.
6 A. Tasker, H. Maezaki, H. Hofland and W. Greenlee, *Patent WO 2024025896 A2*, 2024; https://worldwide.espacenet.com/patent/search/family/089707133/publication/WO2024025896A2?q=WO%202024025896%20A2.
7 M. Andrews, K. N. Dack and M. Larsen, *Patent WO 2021255085 A1*, 2021; https://worldwide.espacenet.com/patent/search/family/071108467/publication/WO2021255085A1?q=WO%202021255085%20A1.
8 J.-G. Kim, B.-N. Ahn, H.-W. Lee, S.-W. Yoon, Y.-A. Yoon, D.-H. Kim, S.-H. Keum, Y.-A. Shin, H.-I. Kang and R. Choi, *Patent WO 2006025714 A1*, 2006; https://worldwide.espacenet.com/patent/search/family/036000316/publication/WO2006025714A1?q=WO%202006025714%20A1.
9 D. E. Robinson, N. Hawryluk and S. Canan, *Patent WO 2022146920 A1*, 2022; https://worldwide.espacenet.com/patent/search/family/082261065/publication/WO2022146920A1?q=WO%202022146920%20A1.
10 B. Liu, J. Hu, Y. Zhang, Z. Chen and Y. Chen, *Patent CN 117683028 A*, 2024; https://worldwide.espacenet.com/patent/search/family/090132685/publication/CN117683028A?q=CN%20117683028%20A.
11 A. Ullrich and M. Falcenberg, *Patent WO 2014207260 A1*, 2014; https://patents.google.com/patent/WO2014207260A1/zh.
12 M. Andrés, M. A. Buil, M. Calbet, O. Casado, J. Castro, P. R. Eastwood, P. Eichhorn, M. Ferrer, P. Forns, I. Moreno, S. Petit and R. S. Roberts, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 5111; https://doi.org/10.1016/j.bmcl.2014.08.026.
13 D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308; https://doi.org/10.1039/B711844A.
14 E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly and N. A. Meanwell, *J. Med. Chem.*, 2015, **58**, 8315; https://doi.org/10.1021/acs.jmedchem.5b00258.
15 T. Fujiwara and D. O'Hagan, *J. Fluorine Chem.*, 2014, **167**, 16; https://doi.org/10.1016/j.jfluchem.2014.06.014.
16 C. Isanbor and D. O'Hagan, *J. Fluorine Chem.*, 2006, **127**, 303; https://doi.org/10.1016/j.jfluchem.2006.01.011.
17 L. V. Politanskaya, V. D. Shteingarts and E. V. Tretyakov, *J. Fluorine Chem.*, 2016, **188**, 85; https://doi.org/10.1016/j.jfluchem.2016.06.010.
18 L. V. Politanskaya, I. P. Chuikov and V. D. Shteingarts, *Tetrahedron*, 2013, **69**, 8477; https://doi.org/10.1016/j.tet.2013.07.037.
19 L. V. Politanskaya, L. A. Malysheva, I. V. Beregovaya, I. Yu. Bagryanskaya, Yu. V. Gatilov, E. V. Malykhin and V. D. Shteingarts, *J. Fluorine Chem.*, 2005, **126**, 1502; https://doi.org/10.1016/j.jfluchem.2005.08.010.
20 S. S. Laev, L. Yu. Gurskaya, G. A. Selivanova, I. V. Beregovaya, L. N. Shchegoleva, N. V. Vasil'eva, M. M. Shakirov and V. D. Shteingarts, *Eur. J. Org. Chem.*, 2007, 306; https://doi.org/10.1002/ejoc.200600684.
21 L. Yu. Safina, G. A. Selivanova, K. Yu. Koltunov and V. D. Shteingarts, *Tetrahedron Lett.*, 2009, **50**, 5245; https://doi.org/10.1016/j.tetlet.2009.07.013.
22 L. Politanskaya, T. Rybalova, O. Zakharova, G. Nevinsky and E. Tretyakov, *J. Fluorine Chem.*, 2018, **211**, 129; https://doi.org/10.1016/j.jfluchem.2018.04.005.
23 L. Politanskaya, E. Tretyakov and C. Xi, *J. Fluorine Chem.*, 2021, **242**, 109720; https://doi.org/10.1016/j.jfluchem.2020.109720.
24 L. Gurskaya, L. Politanskaya, J. Wang, P. Ilyina, A. Volobueva and V. Zarubaev, *J. Fluorine Chem.*, 2024, **274**, 110240; https://doi.org/10.1016/j.jfluchem.2024.110240.
25 L. V. Politanskaya, I. P. Chuikov, E. A. Kolodina, M. S. Shvartsberg and V. D. Shteingarts, *J. Fluorine Chem.*, 2012, **135**, 97; https://doi.org/10.1016/j.jfluchem.2011.09.008.
26 E. E. Kwan, Y. Zeng, H. A. Besser and E. N. Jacobsen, *Nat. Chem.*, 2018, **10**, 917; https://doi.org/10.1038/s41557-018-0079-7.

Received: 31st March 2025; Com. 25/7780