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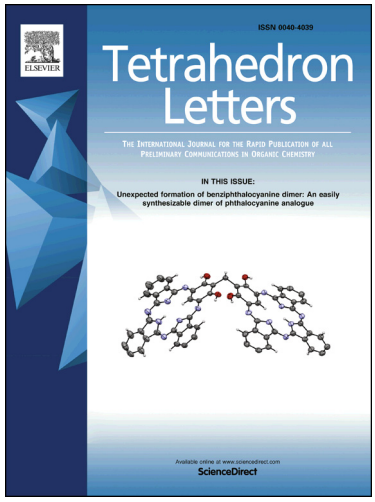

Synthesis of 5-Pentafluorosulfanyl Indazoles

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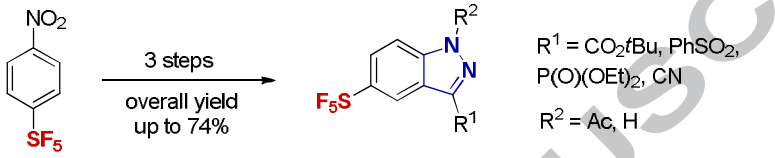

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ABSTRACT

An efficient method for the synthesis of 5-SF_5 substituted indazoles from commercially available 4-nitro-(pentafluorosulfanyl)benzene through vicarious nucleophilic substitution of hydrogen (VNS) reaction, reduction of nitro group and cyclization of resulting anilines were described. Transformations of 5-SF_5-indazoles led to a variety of SF_5-substiuted heteroarenes that can serve as a versatile building block for diversity-oriented organic synthesis.

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The demand for discovering new pharmaceuticals, agrochemicals and advanced functional materials has triggered continuing endeavors in preparation of novel fluorinated compounds.[1] Recently, the pentafluorosulfanyl (SF_5) group containing molecules have received increasing attention because of the unique properties of such a "super-trifluoromethyl" group,[2] such as high lipophilicity, remarkable stability, large steric bulk, and strong electron-withdrawing ability, which can dramatically improve both the pharmacokinetic and pharmacodynamic properties of biologically active molecules. For example, incorporation of SF_5 into the triazolopyrimidine led to the discovery of the first dihydroorotate dehydrogenase (DHODH) inhibitor **I** for the treatment of malaria with improved oral bioavailability and metabolic stability (Figure 1).[3] The improved pharmacokinetic and pharmacodynamic of selective COX-2 inhibitor **II**, used for the treatment of inflammation and associated pain, has also resulted from the introduction of SF_5 into the benzopyrans (Figure 1).[4] Despite of the important applications of SF_5-containing (hetero)aromatic compounds [(Het)Ar-SF_5] in medicinal chemistry, efficient methods for preparation of such a valuable structural motif are very limited,[5] which significantly impeded the use of (Het)Ar-SF_5 as a potential core-structure for drug discovery and development.

Generally, there are two strategies to access (Het)Ar-SF_5. One is based on arene disulfides through direct oxidative fluorination[6] or via a stepwise oxidative chlorotetrafluorination and chloride/fluoride exchange[7] to prepare simple pentafluorosulfanyl(hetero)arenes; the other is the utilization of pentafluorosulanylated building blocks to prepare relatively more complex molecules.[5b] Among these methods, the preparation of SF_5-containing heteroaromatic compounds has received increasing attention due to the important application of heteroarenes in medicinal chemistry.[5b] Recently, Dolbier[7c] and Shibata[7d] reported the efficient synthesis of SF_5-substituted pyridines from pyridine disulfides, separately, however, the synthesis of other HetAr-SF_5 are not applicable to this method. An alternative strategy to address this issue is based on the SF_5-containing building blocks. In this regard, other types of SF_5-substituted *N*-heteroarenes were prepared, including pyrazoles,[8] pyrroles,[9] indoles,[10] quinolonines[11], triazoles[8b] and isoxazoles[12]. However, to the best of our knowledge, the synthesis of SF_5-substituted indazoles has not been reported yet.

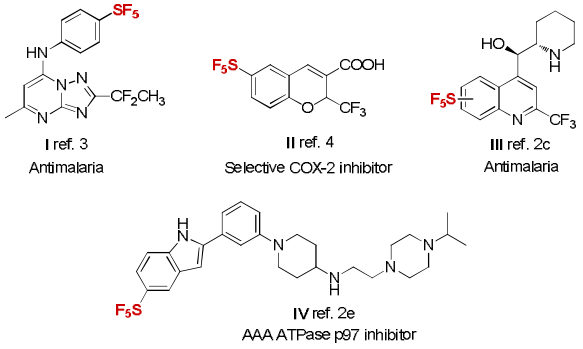

Figure 1. Representative SF_5-Containing Biologically Active Molecules.

Indazoles is an important class of heteroarenes found in many pharmaceuticals and agrochemicals.[13] Conceptually, the introduction of SF_5 into indazoles would provide good opportunities to discover interesting new bioactive molecules. In 2013, we have developed a cross-coupling reaction through palladium-catalyzed direct arylation of nitro-

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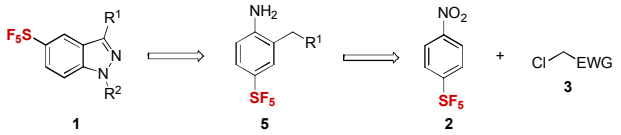
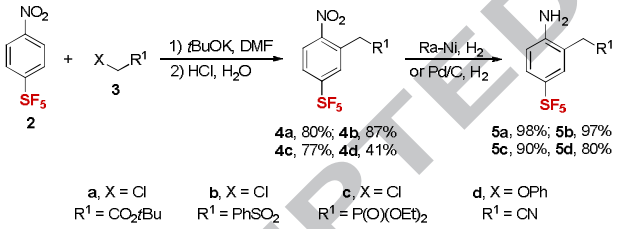
(pentafluorosulfanyl)benzenes.[14] To continue our interests in efficient preparation of pentafluorosulfanylated compounds, herein, we report an efficient method to prepare 5-SF_5 substituted indazoles from readily available 4-nitro-(pentafluorosulfanyl)benzene. The resulting heteroaromatics can serve as a versatile building block for various transformations. We envisioned that the preparation of 5-SF_5 substituted indazoles **1** could be derived from SF_5-substituted anilines **5**, which could be readily prepared from 4-nitro-(pentafluorosulfanyl)benzene **2** through vicarious nucleophilic substitution of hydrogen (VNS) reaction with electron-withdrawing groups substituted chloromethane **3**, followed by reduction of nitro group.



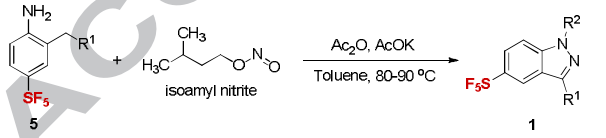
Scheme 1. Retrosynthesis of 5-SF_5 Substituted Indazoles.

Accordingly, a variety of alkylated arenes by reaction of (pentafluorosulfanyl)benzene **2** with nucleophiles, which was generated *in situ* by treatment of compounds **3** with *t*BuOK, were prepared through VNS reaction according to the literature[15] (Scheme 2). Generally, high yields of compounds **4** were obtained with exclusive alkyl substitution *ortho* to the nitro group. However, in the case of 2-phenoxyacetonitrile **3d**, a synthetic reasonable yield (41%) was obtained. Hydrogenation of compounds **4** with Raney nickel as a catalyst underwent smoothly, providing anilines **5** with high efficiency.[15] While, for the compound **4d**, 10% Pd/C was used and the reaction was conducted under 10 atm H_2 with 80% yield obtained.



Scheme 2. Synthesis of Anilines **5**.

Table 1. Synthesis of Pentafluorosulfanyl Indazoles **1**.[a]



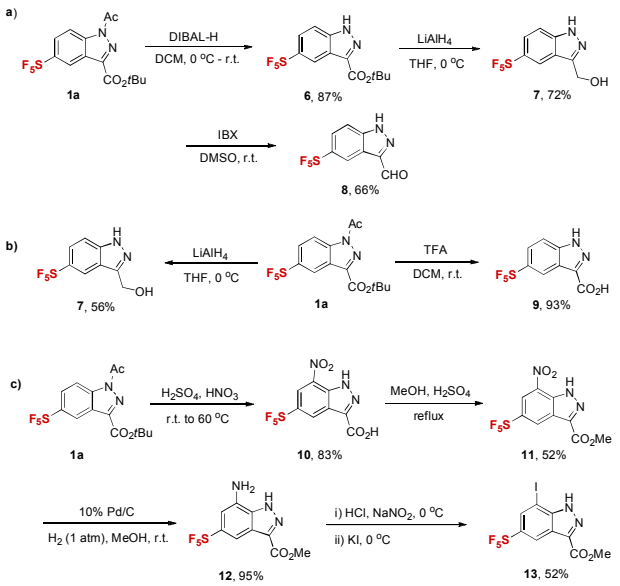
Entry	5	R^1	R^2	Yield[b] (%)
1	**5a**	CO_2tBu	$C(O)CH_3$	**1a**, 94
2	**5b**	$PhSO_2$	$C(O)CH_3$	**1b**, 56
3	**5c**	$P(O)(OEt)_2$	$C(O)CH_3$	**1c**, 81
4[c]	**5d**	CN	H	**1d**, 68

[a]Reactions were carried out using **5** (1.0 mmol), Ac_2O (7.0 mmol), isoamyl nitrite (7.0 mmol) and AcOK (1.3 mmol) in toluene (5 mL). [b]Isolated yields. [c]Reaction was carried out with **5d** (0.52 mmol), Ac_2O (3.64 mmol), isoamyl nitrite (3.64 mmol) and AcOK (0.68 mmol) in toluene (5 mL).

With the alkylated 4-(pentafluorosulfanyl)anilines in hand, the cyclization of **5** to construct the 5-SF_5-substituted indazoles were investigated. The strong electron withdrawing group SF_5 and other versatile functional groups, such as ester, sulfonyl, phosphonate and cyano, did not interfere with the reaction efficiency. As shown in Table 1, treatment of **5a** with acetic anhydride and isoamyl nitrite in the presence of potassium acetate afforded an excellent yield of product **1a** (entry 1).[16] Moderate to good yields of **1b** and **1c** were also obtained under same reaction conditions (entries 2-3). While in the case of **1d**, 68% yield of indazole without protection by acyl group was provided (entry 4).

In order to demonstrate the versatility of these SF_5-substituted indazoles, several transformations of compound **1a** were conducted (Scheme 3). The acyl group could be selectively removed with intact CO_2tBu group by treatment of **1a** with DIBAL-H. While, the acyl and *tert*-butyl groups could be readily deprotected in one pot when compound **1a** was treated with TFA. Reduction of indazole **6** with $LiAlH_4$ led to alcohol **7**, which was oxidized by IBX to afford another versatile building block **8**. Since aldehyde is a good functional group for a wide range of transformations, this method provides a good platform for structural diversity synthesis. Alternatively, compound **7** could also be directly obtained by reduction of **1a** with $LiAlH_4$.

Furthermore, the functionalization of **1a** could be conducted on the indazole skeleton. As shown in Scheme 3c, nitration of **1a** exclusively provided 7-nitro-substituted indazole **10**, which was further reduced under 1 atm H_2 in the presence of 10% Pd/C to afford amine **12** with high efficiency. Conversion of amine group into iodide through two-step synthetic procedure also proceeded smoothly. In light of the importance of amine group and aryl-iodide in organic synthesis, these transformations provide a useful tool for applications in medicinal chemistry.



Scheme 3. Transformations of 5-SF_5 Substituted Indazole **1a**.

In conclusion, we have developed an efficient method for the synthesis of 5-SF_5-indazoles from commercially available 4-nitro-(pentafluorosulfanyl)benzene. Transformations of 5-SF_5-indazoles showed that this type of novel SF_5-substiuted

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heteroarenes can serve as a versatile building block for diversity-oriented organic synthesis, thus providing a useful tool for applications in drug discovery and development.

Acknowledgments

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References and notes

1. For reviews, see: (a) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3; (b) Maienfisch, P.; Hall, R. G. *Chimia.* **2004**, *58*, 93; (c) Special issue on "Fluorine in the Life Sciences", *ChemBioChem* **2004**, *5*, 557; (d) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881; (e) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.
2. (a) Altomonte, S.; Zanda, M. *J. Fluorine Chem.* **2012**, *143*, 57; (b) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 2832; For selected paper, see: (c) Wipf, P.; Mo, T.; Geib, S. J.; Caridha, D.; Dow, G. S.; Gerena, L.; Roncal, N.; Milner, E. E. *Org. Biomol. Chem.* **2009**, *7*, 4163; (d) Welch, J. T.; Lim, D. S. *Bioorg. Med. Chem.* **2007**, *15*, 6659; (e) Alverez, C.; Arkin, M. R.; Bulfer, S. L.; Colombo, R.; Kovalio, M.; LaPorte, M. G.; Lim, C.; Liang, M.; Moore, W. J.; Neitz, R. J.; Yan, Y.; Yue, Z.; Huryn, D. M.; Wipf, P. *ACS Med. Chem. Lett.,* **2015**, *6*, 1225.
3. (a) Coteron, J. M.; Marco, M.; Esquivias, J.; Deng, X.; White, K. L.; White, J.; Koltun, M.; El Mazouni, F.; Kokkonda, S.; Katneni, K.; Bhamidipati, R.; Shackleford, D. M.; Angulo-Barturen, I.; Ferrer, S. B.; Jimenez-Diaz, M. B.; Gamo, F. J.; Goldsmith, E. J.; Charman, W. N.; Bathurst, I.; Floyd, D.; Matthews, D.; Burrows, J. N.; Rathod, P. K.; Charman, S. A.; Phillips, M. A. *J. Med. Chem.* **2011**, *54*, 5540; (b) Phillips, M. A.; Lotharius, J.; Marsh, K.; White, J.; Dayan, A.; White, K. L.; Njoroge, J. W.; El Mazouni, F.; Lao, Y.; Kokkonda, S.; Tomchick, D. R.; Deng, X.; Laird, T.; Bhatia, S. N.; March, S.; Ng, C. L.; Fidock, D. A.; Wittlin, S.; Lafuente-Monasterio, M.; Benito, F. J.; Alonso, L. M.; Martinez, M. S.; Jimenez-Diaz, M. B.; Bazaga, S. F.; Angulo-Barturen, I.; Haselden, J. N.; Louttit, J.; Cui, Y.; Sridhar, A.; Zeeman, A. M.; Kocken, C.; Sauerwein, R.; Dechering, K.; Avery, V. M.; Duffy, S.; Delves, M.; Sinden, R.; Ruecker, A.; Wickham, K. S.; Rochford, R.; Gahagen, J.; Iyer, L.; Riccio, E.; Mirsalis, J.; Bathhurst, I.; Rueckle, T.; Ding, X.; Campo, B.; Leroy, D.; Rogers, M. J.; Rathod, P. K.; Burrows, J. N.; Charman, S. A. *Sci. Transl. Med.* **2015**, *7*, 296ra111; (c) Kokkonda, S.; Deng, X.; White, K. L.; Coteron, J. M.; Marco, M.; de las Heras, L.; White, J.; El Mazouni, F.; Tomchick, D. R.; Manjalanagara, K.; Rudra, K. R.; Chen, G.; Morizzi, J.; Ryan, E.; Kaminsky, W.; Leroy, D.; Martínez-Martínez, M. S.; Jimenez-Diaz, M. H.; Bazaga, S. F.; Angulo-Barturen, I.; Waterson, D.; Burrows, J. N.; Matthews, D.; Charman, S. A.; Phillips, M. A.; Rathod, P. K. *J. Med. Chem.* **2016**, *59*, 5416.
4. Zhang, Y.; Wang, Y.; He, C.; Liu, X.; Lu, Y.; Chen, T.; Pan, Q.; Xiong, J.; She, M.; Tu, Z.; Qin, X.; Li, M.; Tortorella, M. D.; Talley, J. J. *J. Med. Chem.* **2017**, *60*, 4135.
5. (a) Savoie, P. R.; Welch, J. T. *Chem. Rev.* **2015**, *115*, 1130; (b) Kanishchev, O. S.; Dolbier Jr, W. R. Chapter 1, In Advances in Heterocyclic Chemistry Heterocyclic- Chemistry in the 21st Century A Tribute to Alan Katritzky; Eric F. V. Scriven, E. F. V.; Ramsden, C. A. Eds.; Academic Press: Salt Lake City, UT, **2016**.
6. (a) Sheppard, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 3072; (b) Sipyagin, A. M.; Pomytkin, I. A.; Paltsun, S. V.; Aleinikov, N. N.; Kartsev, V. G. *J Fluorine Chem*., **1991**, *54*, 115; (c) Williams, A. G.; Foster, N. R. Patent WO9422817.
7. (a) Umemoto, T.; Garrick, L. M.; Saito, N. *Beilstein J. Org. Chem.* **2012**, *8*, 461; (b) Lummer, K.; Ponomarenko, M. V.; Röschenthaler, G.-V.; Bremer, M.; Beier, P. *J. Fluorine Chem.* **2014**, *157*, 79; (c) Kanishchev, O. S.; Dolbier Jr., W. R. *Angew. Chem. Int. Ed.* **2015**, *54*, 280; (d) Kosobokov, M; Cui, B.; Balia, A.; Matsuzaki, K.; Tokunaga, E.; Saito, N.; Shibata, N. *Angew. Chem. Int. Ed.* **2016**, *55*, 10781; (e) Das, P.; Takada, M.; Matsuzaki, K.; Saito, N.; Shibata, N. *Chem. Commun.* **2017**, *53*, 3850.
8. (a) Hoover, F. W.; Coffmann, D. D. *J. Org. Chem.***1964**, *29*, 3567; (b) Ye, C.; Gard, G. L.; Winter, R. W.; Syvret, R. G.; Twamley, B. Shreeve, J. M. *Org. Lett.*, **2007**, *9*, 3841.
9. (a) Dolbier Jr., W. R.; Zheng, Z. *J. Org. Chem.* **2009**, *74*, 5626; (b) Dolbier Jr. W. R.; Zheng, Z. *J. Fluorine Chem.* **2011**, *132*, 389.
10. (a) Frischmuth, A.; Unsinn, A.; Groll, K.; Stadtmüller, H.; Knochel, P. *Chem. Eur. J.* **2012**, *18*, 10234; (b) Iakobson, G.; Posta, M.; Beier, P. *Synlett* **2013**, *24*, 855.
11. (a) Wipf, P.; Mo, T.; Geib, S. J.; Caridha, D.; Dow, G. S.; Gerena, L.; Roncal, N.; Milner, E. E. *Org. Biomol. Chem.*, **2009**, *7*, 4163; (b) Mo, T.; Mi, X.; Milner, E. E.; Dow, G. S.; Wipf, P. *Tetrahedron Lett.* **2010**, *51*, 5137; (c) Pastyrikova, T.; Iakobson, G.; Vida, N.; Pohl, R.; Beier, P. *Eur. J. Org. Chem.* **2012**, 2123; (d) Joliton, A.; Plancher, J.-M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2016**, *55*, 2113.
12. Lopez, S. E.; Mitani, A.; Pena, P.; Ghiviriga, I.; Dolbier Jr., W. R. *J. Fluorine Chem.* **2015**, *176*, 121; (b) Emamian, S. *J. Fluorine Chem.* **2015**, *178*, 165.
13. (a) Gaikwad, D. D.; Chapolikar, A. D.; Devkate, C. G.; Warad, K. D.; Tayade, A. P.; Pawar, R. P.; Domb, A. J. *Eur. J. Med. Chem.* **2015**, *90*, 707; (b) Cerecetto, H.; Gerpe, A.; Gonzalez, M.; Aran, V. J.; Ocariz, C. O. *Mini-Rev. in Med. Chem.,* **2005**, *5,* 869.
14. Wang, C.; Yu, Y. –B.; Fan, S.; Zhang. X. *Org. Lett.* **2013**, *15*, 5004.
15. Beier, P.; Pastyrikova, T.; Iakobson, G. *J. Org. Chem.* **2011**, 76, 4781.
16. Rooney, L.; Vidal, A.; D'Souza, A. –M.; Devereux, N.; Masick, B.; Boissel, V.; West, R.; Head, V.; Stringer, R.; Lao, J.; Petrus, M. J.; Patapoutian, A.; Nash, M.; Stoakley, N.; Panesar, M.; Verkuyl, J. M.; Schumacher, A. M.; Petrassi, H. M.; Trully, D. C. *J. Med. Chem.* **2014**, *57*, 5129.

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Highlights

- Readily available starting material
- Facile access to 5-pentafluorosulfanyl indazoles
- Versatile building block for medicinal chemistry

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