ORGANIC
LETTERS

2013
Vol. 15, No. 20
5147–5149

Ir-Catalyzed Preparation of SF_5-Substituted Potassium Aryl Trifluoroborates via C−H Borylation and Their Application in the Suzuki−Miyaura Reaction

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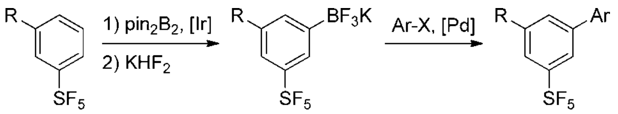
Received September 5, 2013

ABSTRACT



The preparation of new pentafluorosulfanyl-substituted potassium aryltrifluoroborates via Ir-catalyzed C−H borylation is reported. The utility of these novel building blocks was demonstrated in the Suzuki−Miyaura cross-coupling reaction, giving access to 3,5-disubstituted pentafluorosulfanylbenzenes.

In recent years, the pentafluorosulfanyl group has gained increasing attention because of its particular combination of properties. The SF_5 is often compared to trifluoromethyl; however it is more electronegative (Hammett substituent constants: for SF_5 $\sigma_I = 0.55$, for CF_3 $\sigma_I = 0.39$)[1] and possesses higher intrinsic lipophilicity (Hansch hydrophobicity constants: for SF_5 $\pi = 1.51$, for CF_3 $\pi = 1.09$).[2] Moreover, the SF_5 displays higher chemical and thermal stability.[3] These assets make the pentafluorosulfanyl group increasingly attractive, and several examples of its potential for various applications have been reported, such as for agrochemicals and pharmaceuticals, and also in material sciences, including polymers, liquid crystals, and energetic materials.[4]

The first synthesis of pentafluorosulfanylbenzene was reported by Sheppard 50 years ago by oxidative fluorination of aryl disulfides with silver difluoride.[5] However, yields were low and the substrate scope was limited to a few nitro-substituted phenylsulfur pentafluorides. Improvements in the preparation of SF_5-aryl compounds were achieved recently. Notably, Umemoto developed an efficient two-step procedure, involving the synthesis of SF_4Cl-substituted aromatics, which were treated with a fluoride source, such as zinc difluoride or even hydrofluoric acid in pyridine to give $ArSF_5$.[6]

More expansive applications of the pentafluorosulfanyl group are limited by the paucity of building blocks that are generally available. Herein, we document the implementation of the Ir-catalyzed C−H borylation reaction of Hartwig, Ishiyama, and Miyaura with simple pentafluorosulfanylarenes to provide access to an expanded set of SF_5-building blocks from the parent hydrocarbon. Given that the chemistry of SF_5-substituted arenes is relatively unexplored, we showcase that they can be subjected to Suzuki−Miyaura cross-coupling reactions (Scheme 1).

Using the electron withdrawing effect of the pentafluorosulfanyl group, nucleophilic substitutions of halogens,[7]

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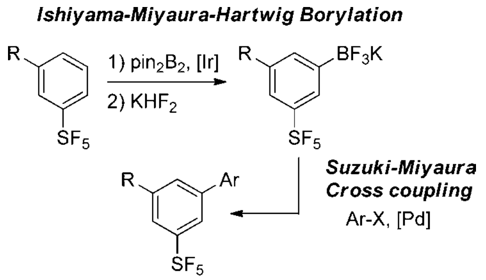
10.1021/ol4025666

Scheme 1. Access to SF_5-ArBF_3K via C−H Borylation



nitro group,[8] or hydrogen[9] have been described. Despite the increasing interest in exploring and diversifying the chemistry of aryl-SF_5 compounds, their utility as substrates in a number of modern metal-catalyzed transformations remains underexplored. Knochel prepared magnesium reagents, by Br/Mg exchange using *i*PrMgCl·LiCl and by directed metalation using $TMP_2Mg·2LiCl$. The handful of examples underwent further transformations, such as cross-coupling reactions.[10] However, the current portfolio of basic building blocks incorporating SF_5 remains limited. Indeed, in most of the synthesis work, the routes can be traced back to the same set of starting materials: *para*- or *meta*-(pentafluorosulfanyl)nitrobenzene. Because of our interest in providing greater access to novel building blocks for drug discovery,[11] we have been exploring ways of developing new approaches to SF_5 compounds.

Hartwig, Ishiyama, and Miyaura developed a powerful catalytic system for the *meta*-directed C−H borylation of 1,3-disubstituted arenes using $[\{Ir(OMe)(cod)\}_2]$ and 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy).[12] This reaction allowed the access to various functionalities via one-pot sequences, such as halogenation, cyanation, alkylation, hydroxylation, or amination.[13] Additionally, one-pot synthesis of 3,5-disubstituted potassium aryltrifluoroborates via Ir-catalalyzed C−H borylation followed by treatment with KHF_2 has been reported, but not for SF_5-aryl substrates.[14]

Compared to other boron reagents, organotrifluoroborate salts are exceptionally stable toward air and moisture. Moreover, they are easily isolated, usually by simple precipitation or recrystallization from acetone with diethyl ether, and they show comparable reactivity to boronic acids in many reactions, such as Suzuki−Miyaura cross-coupling.[15,16] Consequently, we decided to examine the borylation reaction for the introduction of trifluoroborates onto SF_5-containing scaffolds.

In prospecting experiments we were delighted to note that the pentafluorosulfanyl group displayed excellent compatibility with Ir-catalyzed C−H borylation conditions of Hartwig, Ishiyama, and Miyaura. After complete conversion of the precursor, direct addition of water and KHF_2 to the reaction mixture converted the resulting boronic ester into the corresponding aryltrifluoroborate (Table 1). To the best of our knowledge, this is the first example of the C−H activation reaction with a pentafluorosulfanyl-containing aryl system. Thus, from readily available *meta*-substituted SF_5-aryl compounds,[17] we were able to provide access to this novel class of buildings blocks. Several examples with various substituents in *meta*-position of the SF_5-group were obtained in good to high yields, such as methoxy, methyl ester, or halogens. Interestingly, contrary to most of the potassium organotrifluoroborates, SF_5-ArBF_3K are soluble in diethyl ether, emphasizing the lipophilicity of the pentafluorosulfanyl group. Therefore, isolation was achieved by precipitation from acetone with chloroform or dichloromethane. The pinacol coproduct could be removed by additional washing of the solids to afford the SF_5-substituted potassium aryltrifluoroborates in high purity, according to ^{19}F and ^1H NMR *spectra*. The simplicity of the approach is underscored in a preparative scale reaction that was conducted to give more than 3 g of **2a** from a *meta*-methoxy precursor in 92% yield.

In order to demonstrate the usefulness of these SF_5-building blocks, we set out to explore their reactivity in the

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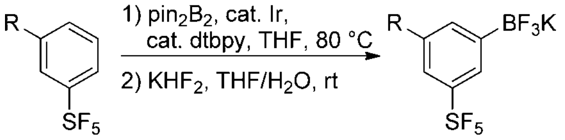
(17) Most of these starting materials are commercially available, but in the present case, they were prepared in our laboratory. See Supporting Information for detailed preparations.

Table 1. One-Pot Synthesis of SF_5-Substituted Potassium Aryltrifluoroborates[a]

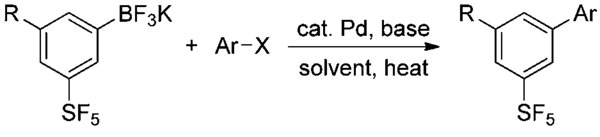


1 **2**

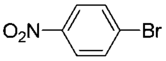
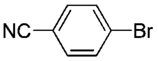
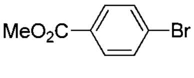
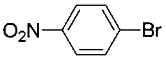
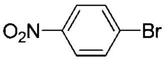
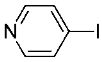
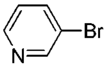
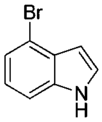
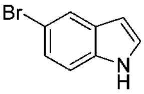
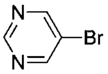
entry	R	**2**	yield (%)
1	OMe	**2a**	94
2	CN	**2b**	88
3	CO_2Me	**2c**	65
4	NMe_2	**2d**	81
5	Cl	**2e**	89
6	Br	**2f**	76
7	I	**2g**	72[b]

[a] Reaction conditions: **1**, pin_2B_2 (0.7 equiv), $\{[Ir(OMe)(cod)]_2\}$ (0.75 mol %), dtbpy (1.5 mol %), THF, 80 °C, 24 h. Then KHF_2 (5.7 equiv), THF/H_2O (5:3), rt, 6 h. [b] 48 h were needed for the C−H borylation.

Table 2. Cross-Coupling Reactions of SF_5−$ArBF_3K$ with Aryl Halides



2 **3**

entry	R	Ar-X	**3**	method[a]	yield (%)
1	OMe		**3a**	A	93
2	OMe		**3b**	A	81
3	OMe		**3c**	A	85
4	CN		**3d**	A	41
5	CO_2Me		**3e**	A	57
6	OMe		**3f**	B	54
7	OMe		**3g**	B	83
8	OMe		**3h**	B	42
9	OMe		**3i**	B	46
10	OMe		**3j**	B	95

[a] Method A: Ar−X, **2** (1.2 equiv), Et_3N (3.0 equiv), $PdCl_2(dppf)\cdot CH_2Cl_2$ (2 mol %), EtOH, 85 °C, 12−16 h. Method B: Ar−X, **2** (2.0 equiv), K_2CO_3 (3.0 equiv), $Pd(OAc)_2$ (5 mol %), MeOH, 80 °C, 16 h.

Suzuki−Miyaura reaction. After screening of conditions for the cross-coupling of aryl halides and organotrifluoroborates, we identified those of Molander as promising.[18] In our case, slight modifications of these conditions were necessary in order to obtain satisfying yields. The choice of the method was dependent on the aryl halide used (Table 2). Thus, employing 2 mol % of $PdCl_2(dppf)\cdot CH_2Cl_2$ with 3 equivalents of triethylamine in EtOH at 85 °C (Method A) allowed cross-coupling of the *meta*-methoxy derivative of SF_5−$ArBF_3K$ **2a** with various functionalized aryl halides (Table 2, entries 1−3). The use of substrates bearing electron withdrawing groups under conditions A resulted in a decrease in yield of product (Table 2, entries 4−5). Attempts to improve the reaction by using $Pd(OAc)_2$ with K_2CO_3 in MeOH at 80 °C (Method B) failed with only traces of the biaryl product being observed. However, with heteroaryl halides, the conditions of method A were not effective, whereas using method B afforded the desired cross-coupling product. For example, when 3-bromopyridine was submitted to reaction conditions B, the corresponding biaryl was obtained in excellent yield (Table 2, entry 7), whereas method A afforded less than 20% conversion. Reaction of **2a** with unprotected 4- and 5-bromoindoles could be achieved in modest yield (Table 2, entries 8−9). Diheteroaryl halide 5-bromopyrimidine also participated in the reaction and gave the corresponding cross-coupling product in excellent yield (Table 2, entry 10).

In conclusion, we have described the preparation of new stable and versatile 3,5-disubstituted potassium aryltrifluoroborates bearing a pentafluorosulfanyl group. These new compounds are potential important building blocks for drug discovery and agrochemicals. Their synthesis was achieved in one-pot, involving Hartwig, Ishiyama, and Miyaura Ir-catalyzed C−H borylation. We also showed their compatibility in the Suzuki−Miyaura cross-coupling reaction with aryl and heteroaryl halides, allowing the access to a library of unprecedented 3,5-disubstituted SF_5-aryl compounds.

Acknowledgment. We gratefully acknowledge financial support from the ETH Zürich (ETH-23-11-1) and Spirochem for supplying *meta*-(pentafluorosulfanyl)nitrobenzene. We are also grateful to F. Hofmann-La Roche for generous support of our research program and to Dr. Jean-Marc Plancher, senior scientist at F. Hofmann-La Roche, for fruitful discussions.

Supporting Information Available. Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet http://pubs.acs.org.

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The authors declare no competing financial interest.