Tetrahedron Letters xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Efficient Suzuki-Miyaura mono-arylation of symmetrical diiodo(hetero)arenes

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ARTICLE INFO

Article history:
Received 17 March 2018
Revised 30 March 2018
Accepted 9 April 2018
Available online xxxx

Keywords:
Polyfluorinated aromatics
1,4-Diiodo-2,3,5,6-tetrafluorobenzene
Coupling reactions
Monocoupling
Halogen bond
Crystal engineering

ABSTRACT

A reliable protocol for converting 1,4-diiodo-2,3,5,6-tetrafluorobenzene into 1-(hetero)aryl-4-iodo-2,3,5,6-tetrafluorobenzene derivatives has been lacking in the literature. We have identified optimal conditions to achieve this conversion in good yields and have minimized formation of the bis-coupling product. The newly identified protocol involving the use of a syringe pump has been extended to other symmetrical diiodo(hetero)arenes.

1,4-Diiodo-2,3,5,6-tetrafluorobenzene (DITFB, **1**) is a building block of special significance for several reasons. Firstly, it is widely used in the construction of polyfluorinated organic compounds.[1] The latter have been employed as principal components of organic light-emitting diodes,[2] thin-film transistors,[3] and various supramolecular self-assembly systems.[4] The 2,3,5,6-tetrafluorophenyl moiety (which can be derived from DITFB) has been used as powerful tag for observing intermolecular interactions by ^{19}F NMR.[5] Oligomeric chains containing an array of 2,3,5,6-tetrafluoro-4-iodophenyl groups have been reported to efficiently transport anions across lipid bilayer membranes.[6] The most recent and perhaps the most exciting applications of DITFB and its derivatives is their use in the design and assembly of a special case of so-called molecular containers, namely, halogen-bonded supramolecular capsules with host-guest binding properties.[7] Halogen bonds (XB) in general have been receiving increasing attention in the last few years as a major non-covalent interaction that can complement or be viewed as an alternative to hydrogen bonds (HB).[8] Similar to the latter, XB can help form novel crystal structures[9] and be involved in forming specific interactions of small molecule ligands with their protein targets, which is particularly important from a medicinal chemistry and drug design perspective.[10] This, in turn, requires a wealth of validated approaches to prepare various derivatives of DITFB. However, as we recently demonstrated,[1] reliable methods to derivatize **1** *via* metal-catalyzed monocoupling reactions are surprisingly lacking in the current literature. For instance, Suzuki-Miyaura monocoupling reactions (yielding **2**) reported in the literature are always accompanied by the formation of a significant amount of bis-coupling product **3** (Fig. 1).[11]

Our recent interest in finding new 'tamed' solid forms of active pharmaceutical ingredients *via* co-crystallization with halogen bond donors such as DITFB and its derivatives drew our attention to this obvious void in the current synthetic methodology. Herein, we report an efficient protocol for a high-yielding Suzuki-Miyaura monocoupling of DITFB with (hetero)arene boronic acids and demonstrate its transferrability to other symmetrical diiodo (hetero)arene substrates.

Our initial experiments towards finding the optimal conditions for the Suzuki-Miyaura monocoupling were conducted with **1** and

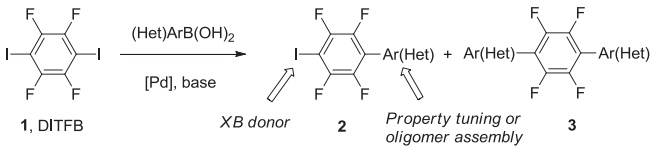

Fig. 1. DITFB and its derivatization *via* Suzuki-Miyaura coupling.

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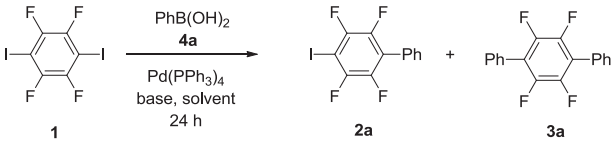
https://doi.org/10.1016/j.tetlet.2018.04.015
0040-4039/

Table 1
Screening of reaction conditions for the Suzuki-Miyaura coupling of DITFB.



Entry	Solvent	Base	T (°C)	**1**:**4a**	**2a**:**3a**	Yield **2a** (%)
1	MeCN	Na_2CO_3	77	2:1	10:1	5
2	MeCN	K_2CO_3	77	2:1	10:1	8
3	MeCN	Cs_2CO_3	77	2:1	5:1	16
4	MeCN/H_2O (2:1)	Na_2CO_3	77	2:1	10:1	30
5	MeCN/H_2O (2:1)	K_2CO_3	77	2:1	5:1	44
6	MeCN/H_2O (2:1)	Cs_2CO_3	77	2:1	5:1	40
7	MeCN/H_2O (2:1)	K_3PO_4	77	2:1	10:0.8	23
8	MeCN/H_2O (2:1)	LiOH	77	2:1	10:3	51
9	MeCN/H_2O (2:1)	NaOH	77	2:1	10:4.2	33
10	THF	K_2CO_3	70	2:1	5:1	10
11	THF	Cs_2CO_3	70	2:1	10:2.3	27
12	THF	LiOH	70	2:1	2:1	37
13	THF	*t*-BuOK	55	2:1	2:1	18
14	MeOH	Na_2CO_3	70	2:1	10:1	19
15	MeOH	K_2CO_3	70	2:1	10:1	9
16	MeOH	Cs_2CO_3	70	2:1	10:1.5	30
17	MeOH	LiOH	70	2:1	2:1	75
18	*i*-PrOH	LiOH	82	2:1	10:0.7	13
19	Toluene	Cs_2CO_3	110	2:1	–	No reaction
20	Toluene/MeOH	Cs_2CO_3	110[a]	2:1	–	No reaction
21	1,4-Dioxane	Na_2CO_3	100	2:1	–	No reaction
22	1,4-Dioxane	K_2CO_3	100	2:1	10:1	23
23	1,4-Dioxane	Cs_2CO_3	100	2:1	2:1	26
24	1,4-Dioxane/H_2O (2:1)	K_2CO_3	100	2:1	5:1	54
25	1,4-Dioxane/MeOH (2:1)	K_2CO_3	95	2:1	10:1	79
26	1,4-Dioxane/MeOH (2:1)	K_2CO_3	95	1.5:1	10:3	54
27	1,4-Dioxane/MeOH (2:1)	K_2CO_3	95	1.25:1	5:2	41
28	1,4-Dioxane/MeOH (2:1)	K_2CO_3	95	1.1:1	5:2	37
29	1,4-Dioxane/MeOH (2:1)	K_2CO_3	95[b]	1.1:1	10:1	74

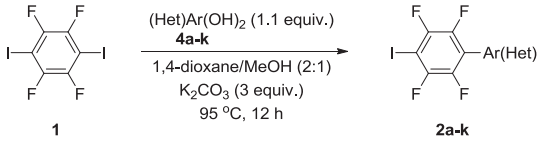
[a] Reaction conducted in a microwave reactor.
[b] Solution of **4a** in 1,4-dioxane added to the reaction mixture over 10 h using a syringe pump.

phenylboronic acid (**4a**) using 0.05 equiv. of $Pd(PPh_3)_4$ and 3 equiv. of base. The influence of solvent, base and temperature were investigated using a 2-fold excess of **4a** over **1** (Table 1, entries 1–25). The use of aprotic solvents (MeCN, THF, 1,4-dioxane, toluene) led to low conversions or no reaction at all. In the case of toluene, addition of MeOH did not improve the situation (Entry 20). The best results were achieved in MeOH (Entry 17), aqueous MeCN (Entry 8), aqueous 1,4-dioxane (Entry 24) or 1,4-dioxane/MeOH (Entry 25). The latter experiment gave the best result and was further optimized with the aim of lowering the excess of **1** used in the reaction (Table 1, entries 26–29). Gradual lowering of the **1**:**4a** ratio, unfortunately, led to a similar drop in the **2a**:**3a** ratio and the isolated yield of **2a**. However, when we chose to add a solution of **4a** in 1,4-dioxane to the reaction mixture slowly over 10 h using a syringe pump, both the **2a**:**3a** ratio and the isolated yield of **2a** improved. This approach only utilized a 10% excess of **1** (Entry 29). These conditions were considered optimal and were employed to prepare other monoaryl derivatives of **1** while the reaction time was shortened to 12 h (Table 2).[12]

The monocoupling reaction was largely unaffected by electronic or steric effects as electron-rich (e.g., **4d**) and electron-poor (e.g., **4i**) boronic acids as well as the ones possessing *ortho*-substituents (**4g** and **4h**) gave comparable results.

Encouraged by these results, we wondered if the same protocol would be applicable to other symmetrical diiodo(hetero)arene templates **5a**–**c**. The results of these experiments are provided in

Table 2
1-(Hetero)aryl-4-iodo-2,3,5,6-tetrafluorobenzenes **4a**–**4k** prepared in this work.[a,b]



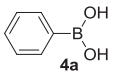
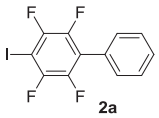
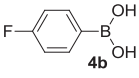
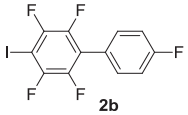
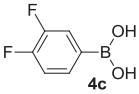
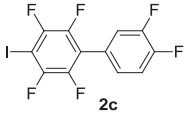
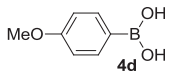
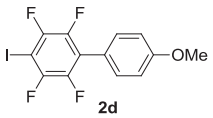
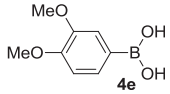
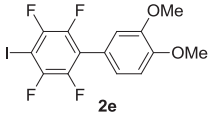
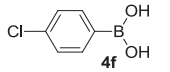
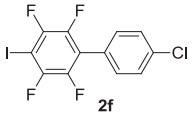
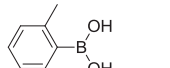
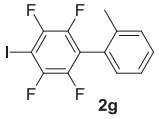
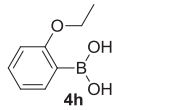
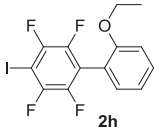
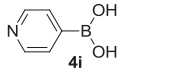
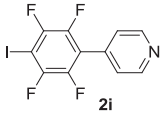
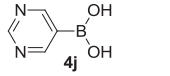
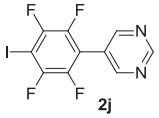
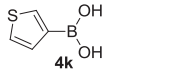
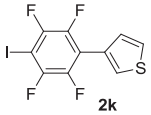
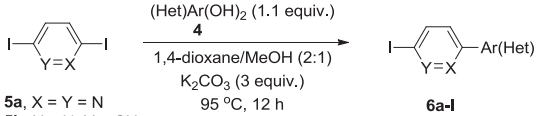
Entry	$Ar(OH)_2$	Compound	Isolated yield (%)
1			74
2			79
3			61

Table 2 (*continued*)

Entry	$Ar(OH)_2$	Compound	Isolated yield (%)
4	 **4d**	 **2d**	77
5	 **4e**	 **2e**	54
6	 **4f**	 **2f**	54
7	 **4g**	 **2g**	50
8	 **4h**	 **2h**	62
9	 **4i**	 **2i**	73
10	 **4j**	 **2j**	59
11	 **4k**	 **2k**	57

[a] Boronic acid was added *via* a syringe pump over 10 h.
[b] <10% of the bis-coupling product formed in each reaction as judged by crude ^{1}H NMR spectroscopy.

Table 3
1-(Hetero)aryl-4-iodo-2,3,5,6-tetrafluorobenzenes **4a**–**4k** prepared in this work.[a,b]



5a, X = Y = N
5b, X = N, Y = CH
5c, X = Y = CH

6a-l

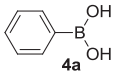
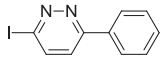
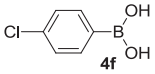
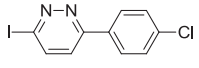
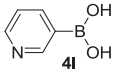
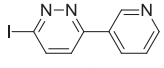
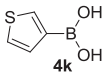
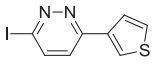
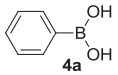
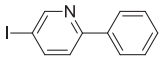
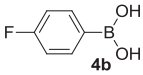
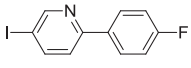
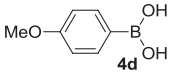
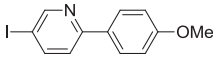
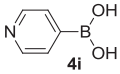
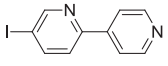
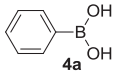
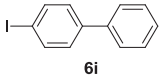
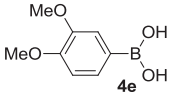
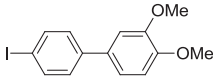
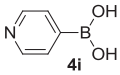
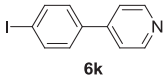
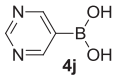
Entry	Substrate	$Ar(OH)_2$	Compound	Isolated yield (%)
1	5a	 **4a**	 **6a**	79
2	5a	 **4f**	 **6b**	68
3	5a	 **4l**	 **6c**	51

Table 3 (*continued*)

Entry	Substrate	$Ar(OH)_2$	Compound	Isolated yield (%)
4	5a	 **4k**	 **6d**	70
5	5b	 **4a**	 **6e**	83
6	5b	 **4b**	 **6f**	77
7	5b	 **4d**	 **6g**	80
8	5b	 **4i**	 **6h**	69
9	5c	 **4a**	 **6i**	64
10	5c	 **4e**	 **6j**	67
11	5c	 **4i**	 **6k**	51
12	5c	 **4j**	**6l**	42

[a] Boronic acid was added *via* a syringe pump over 10 h.
[b] <10% of the bis-coupling product formed in each reaction as judged by crude ^{1}H NMR spectroscopy.

Table 3 and demonstrate the universal nature of this method, involving the use of a syringe pump, for carrying out the Suzuki-Miyaura monocoupling.

In summary, we have reported a practical method to conduct the Suzuki-Miyaura reaction of (hetero)arene boronic acids and DITFB which provided good yields of the desired monocoupling product and minimized (<10% by crude ^{1}H NMR spectroscopy) formation of the undesired bis-coupling by-product. These conditions appear to be widely applicable as they provided good monocoupling product yields in case of other symmetrical diiodo (hetero) arenes. The synthesized iodo-substituted biaryls will be tested as halogen bond donors; the results of these studies will be reported in due course.

Acknowledgement

This work was supported by the Russian Science Foundation (project grant 17-73-20185).

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.04.015.

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(b) Vanderkooy A, Pfefferkorn P, Taylor MS. *Macromolecules*. 2017;50:3807–3817.
12. *General procedure for the preparation of compounds **2a–k** and **6a–l**:* To a solution of diiodarene **1** or **5a–c** (0.306 mmol) in 1,4-dioxane/MeOH (2:1, 10 mL) K_2CO_3 (126 mg, 0.918 mmol) was added. The mixture was degassed by bubbling nitrogen gas through it for 15 min. $Pd(PPh_3)_4$ (17 mg, 0.015 mmol) was added and the solution was heated to 95 °C. A solution of the boronic acid (0.275 mmol) in 1,4-dioxane (5 mL) was added dropwise to the reaction mixture for 10 h using a syringe pump. After the addition was complete, the reaction mixture was stirred at 95 °C for an additional 2 h. It was then allowed to cool to room temperature, the solvent was removed under reduced pressure, the residue dispersed in CH_2Cl_2 (10 mL). This suspension was washed with water, upon which the organic phase cleared up. It was dried dried over anhydrous $CaCl_2$, filtered and concentrated to dryness. The desired product was purified by chromatography on silica gel using 0 → 5% CH_2Cl_2 in cyclohexane as eluent.

Please cite this article in press as: Sapegin A., Krasavin M. Tetrahedron Lett. (2018), https://doi.org/10.1016/j.tetlet.2018.04.015