Tetrahedron Letters 55 (2014) 2212–2216

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Facile functionalization at the C2 position of a highly substituted benzofuran

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ARTICLE INFO

Article history:
Received 25 January 2014
Revised 9 February 2014
Accepted 16 February 2014
Available online 24 February 2014

Keywords:
Benzofuran
Substituted 2-iodobenzofuran
Substituted benzofuran-2-ylboronic acid
Suzuki coupling

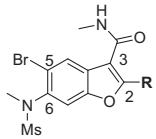
ABSTRACT

To expedite an SAR study of the C2 position of a highly substituted benzofuran ring system, we developed a method for the preparation of a key precursor, iodide **10**. From iodide **10**, a diverse set of compounds with different substituents at the C2 position were prepared efficiently.

The benzofuran motif appears in the structures of many biologically active natural products and pharmaceutical agents.[1] To explore structure activity relationships (SAR) during a medicinal chemistry program, we needed to access 5-bromo-*N*-methyl-6-(*N*-methyl-methylsulfonamido)benzofuran-3-carboxamide (**1**) with various substitutions at the C2 position (Fig. 1). It was desirable to maintain the C5 bromo substitution to allow for additional SAR development at this position.

Our chemistry effort began with the preparation of compound **1a**, which has a 4-F-phenyl at the C2 position (Scheme 1). Claisen condensation of 1-(4-fluorophenyl)ethanone (**2**) with diethyl carbonate provided ketoester **3** in high yield.[2] An iron-catalyzed, oxidative Pechmann condensation of ketoester **3** with 4-bromophenol formed the benzofuran **4** in moderate yield.[3] Nitration followed by reduction of the nitro group installed an amino group at the C6 position to give intermediate **6**.[4] The amino group was sulfonylated to provide compound **7**, which was converted to compound **9** in two steps. Selective methylation of the sulfonamide nitrogen afforded compound **1a**.[5] This synthetic route supplied **1a** for our initial SAR work, however, it would be tedious to apply this route to a series of compounds with different R-groups at the C2 position (Fig. 1) since this route required installing the C2 group (e.g., 4-fluoro-phenyl for **1a**) at the beginning of the synthetic sequence. It was desirable to obtain a common precursor which has the required substituents at C3, C5, and C6 positions with a handle at C2 that would allow for the late-stage installation of the C2 substituents.

We envisioned that intermediates **10** and **11** with an iodo or a boronic acid substitution at the C2 position would serve as the appropriate precursors (Fig. 2).[6–10] Compounds **10** and **11** could be derived from a C2 unsubstituted precursor **12**. Compound **12** itself could function as a potential precursor to install the C2 substituents since it has been well-known that the C2-position of the benzofuran ring can be readily metallated to give the organometallic species,[11] which could be employed in further transformations



Ms = methanesulfonyl

1

Figure 1. 5-Bromo-*N*-methyl-6-(*N*-methylmethylsulfonamido)benzofuran-3-carboxamide (**1**) with different substitutions at the C2 position.

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http://dx.doi.org/10.1016/j.tetlet.2014.02.051
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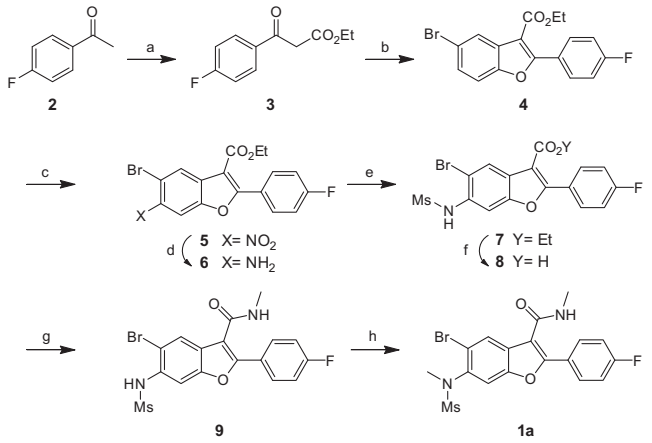


Scheme 1. Synthesis of compound **1a**. Reagents and conditions: (a) diethyl carbonate (1.0 equiv), NaH (1.2 equiv), THF, 70 °C, 3 h, 95%; (b) 4-bromophenol (3.0 equiv), $FeCl_3{\cdot}6H_2O$ (0.15 equiv), (*t*-BuO)$_2$ (2.2 equiv), reflux, 6 h, 14%; (c) fuming HNO_3 (8.1 equiv), $CHCl_3$, −15 °C, 30 min, 66%; (d) Iron filings (3.0 equiv), NH_4Cl (6.0 equiv), MeOH–THF–H_2O (2:2:1), reflux, 3 h, 82%; (e) MsCl (3.0 equiv), pyridine/CH_2Cl_2 (1:5), 0 °C to 25 °C, 82%; (f) LiOH·H_2O (5.1 equiv), dioxane–H_2O (5:1), 100 °C, 3 h, 96%; (g) HOBt (1.5 equiv), EDC (1.5 equiv), DMF, 25 °C, 2 h, Et_3N (4.7 equiv), CH_3NH_2·HCl (3.0 equiv), 94%; (h) MeI (3.0 equiv), K_2CO_3 (2.5 equiv), KI (0.02 equiv), DMF, 80–90 °C, overnight, 94%.

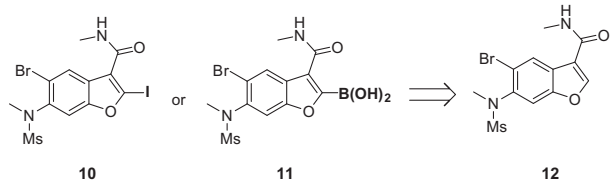


Figure 2. Possible precursors for installing C2 groups: **10** and **11**.

to install substituents at the C2-position.[12] However, for convenience, we desired a stable intermediate (such as **10**), which could be prepared and stored in bulk, to avoid preparing the organometallic species from **12** separately for each C2 substituent.

Preparation of C2 iodobenzofuran from C2 unsubstituted benzofuran has been well documented in the literature (Fig. 3). For example, the Larock group demonstrated that quenching of the lithium species derived from benzofuran with iodine provides the 2-iodobenzofuran in high yield.[7] In an example closely related to our work, Presidio scientists reported the preparation of a 2-iodobenzofuran compound with a carboethoxy group at C3 position and a methoxy group at C5 position.[13]

We set out to prepare the C2 unsubstituted substrate (**12**) for iodination/borylation (Scheme 2). The chemistry was similar to the preparation of compound **1a** (Scheme 1). However, when compound **12** was treated with LDA followed by I_2 according to the

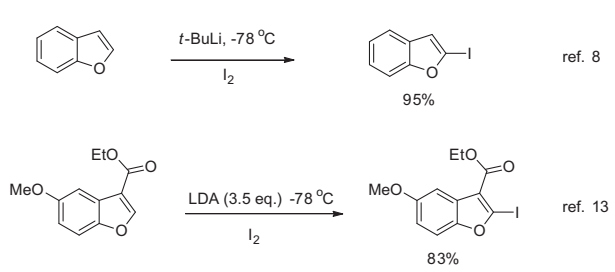
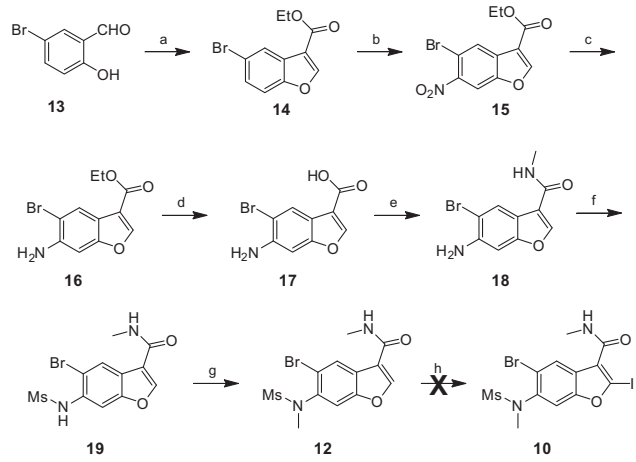
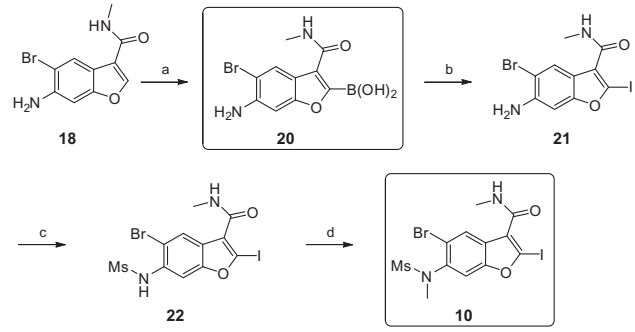


Figure 3. Representative examples known for the preparation of C2-iodo benzofuran ring system.



Scheme 2. Preparation of compound **12**. Reagents and conditions: (a) ethyl diazoacetate (1.43 equiv), $HBF_4{\cdot}Et_2O$ (0.1 equiv), CH_2Cl_2, <38 °C; then H_2SO_4 (concd, 1.3 equiv), followed by Na_2CO_3 (aq), 75%; (b) fuming HNO_3 (12.1 equiv), $CHCl_3$, −20 °C to 0 °C; 85%; (c) Fe filing (3.0 equiv), NH_4Cl (6.0 equiv), MeOH–THF–H_2O (2:2:1), 68%; (d) LiOH H_2O (5.0 equiv), dioxane–H_2O (5.6:1), reflux, 97%; (e) EDC (1.5 equiv), HOBt (1.5 equiv), DMF, 25 °C, 2 h; Et_3N (3.0 equiv), $MeNH_2$·HCl (3.0 equiv), 25 °C, 2 h, 71%; (f) MsCl (2.0 equiv), pyridine (3.0 equiv), CH_2Cl_2, 0 °C to 25 °C, 16 h, 70%; (g) K_2CO_3 (3.0 equiv), MeI (2.0 equiv), DMF, 80 °C, 3 h, 90%; (h) LDA (5.0 equiv), I_2 (6.0 equiv), THF, −78 °C, no required product was observed.



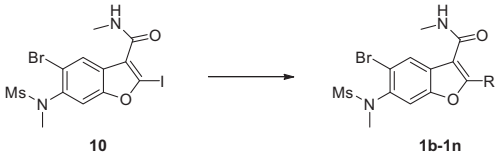
Scheme 3. Preparation of compounds **20** and **10**. Reagents and conditions: (a) LDA (4.2 equiv), THF,1 h; $B(OMe)_3$ (4.0 equiv), −78 °C, 1 h; 71%; (b) NIS(1.0 equiv), MeCN, 0 °C to 25 °C, 79%; (c) MsCl (2.0 equiv), pyridine, 0 °C to 25 °C, 1.5 h, LiOH·H_2O (7.9 equiv), 25 °C, 30 min, 59%; (d) K_2CO_3 (3.0 equiv), MeI (2.0 equiv), DMF, 0 °C, then 80 °C, 1 h, 91%.

procedure described in the literature,[13] the reaction failed to produce the required C2-iodo product **10**.

We suspected that the sulfonamide may have interfered with the metallation of **12**. To test this hypothesis, we decided to try the metallation on compound **18**, an intermediate without the sulfonamide group (Scheme 3). Unfortunately, treatment of amine **18** with LDA, followed by quenching with iodine produced many unidentified by-products and a poor yield of the required C2-iodide **21** (~6% after purification). On the other hand, when the lithium species was quenched with trimethylborate followed by hydrolysis of the boronate intermediate, boronic acid **20** was isolated in good yield.[14] Attempts to convert intermediate **20** to compound **11** were unsuccessful probably due to the limited stability of the boronic acid moiety. Instead, iododeboronation of boronic acid **20** with *N*-iodosucciimide afforded iodide **21** in good yield.[15] The methyl sulfonamide group was then installed according to the chemistry described above to provide the key intermediate **10**.

Once precursor **10** became available, a variety of substituents at C2 were installed via Suzuki coupling with the required boronic acids or boronates to afford compounds **1b**–**1n** (Table 1). Substituted phenylboronic acids participated well in the Suzuki coupling

Table 1
Preparation of **1b–1n** via the Suzuki coupling of iodide **10**



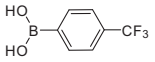
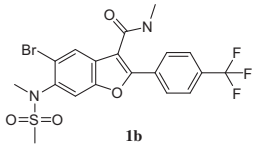
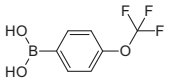
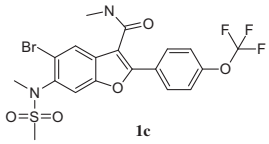
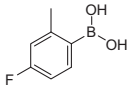
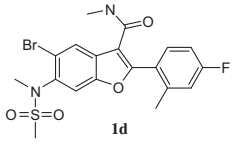
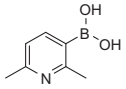
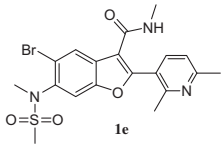
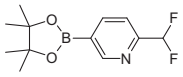
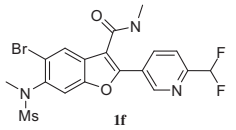
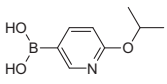
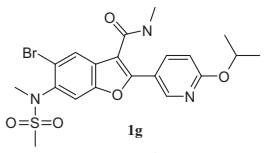
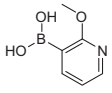
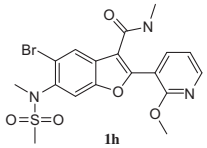
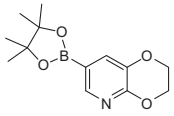
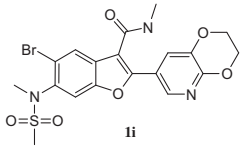
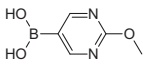
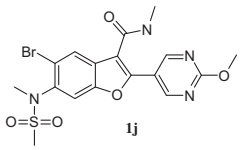
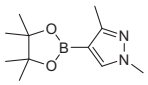
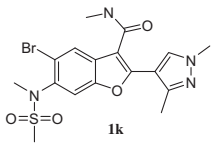
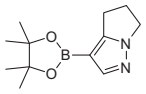
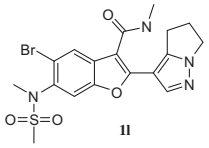
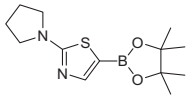
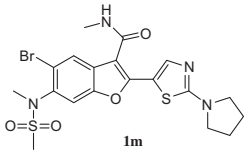
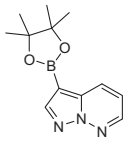
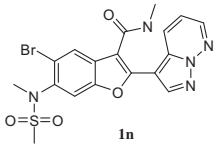
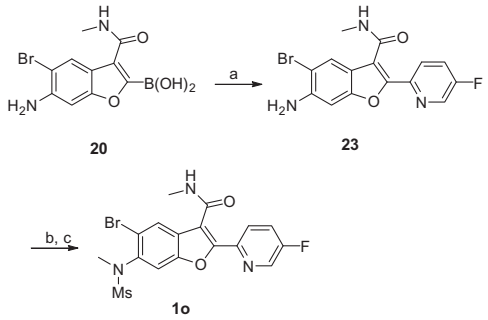
Entry	Boronic acid/boronate	Compound **1**	Coupling condition[a] (time)	Yield of **1** (%)
1		 **1b**	A	85
2		 **1c**	A	70
3		 **1d**	B	70
4		 **1e**	B	81
5		 **1f**	A	83
6		 **1g**	C	79
7		 **1h**	B	69
8		 **1i**	B	80
9		 **1j**	B	87
10		 **1k**	B	70

Table 1 (*continued*)

Entry	Boronic acid/boronate	Compound **1**	Coupling condition[a] (time)	Yield of **1** (%)
11		 **1l**	C	78
12		 **1m**	B	76
13		 **1n**	C	67

[a] Condition A: boronic acid or boronate, Na_2CO_3, Pd(dppf)Cl_2 (cat.), DMF, 50 °C, 12 h; Condition B: boronic acid or boronate, K_2CO_3, Pd(dppf)Cl_2 (cat.), DMF, 100 °C, 1 h; Condition C: boronic acid or boronate, Na_2CO_3, Pd(dppf)Cl_2 (cat.), DMF, 100 °C, 1 h.

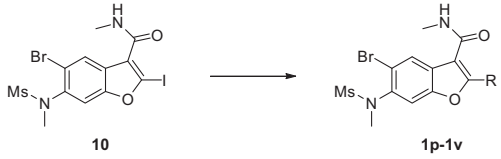


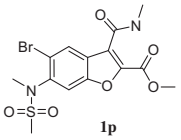
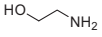
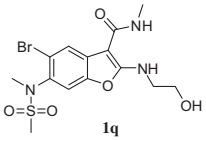
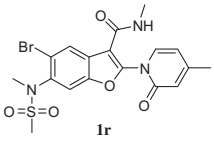
Scheme 4. Preparation of compound **1o**. Reagents and conditions: (a) 2-bromo-5-fluoropyridine, Pd(dppf)Cl_2 (cat.), $K_3PO_4{\cdot}3H_2O$, DMF, 25 °C, 3 h, 51%; (b) MsCl (2.0 equiv), pyridine, 0 °C to 25 °C, 1.5 h, LiOH·H_2O (7.9 equiv), 25 °C, 30 min, 66%; (c) K_2CO_3 (3.0 equiv), MeI (2.0 equiv), DMSO, 0 °C, then 25 °C, 1 h, 70%.

reaction to give the C2 phenyl substituted compounds **1b–1d**. Similarly, substituted pyridyl and pyrimidyl groups were installed at the C2 position (**1e–1j**). The Suzuki coupling reaction also proceeded in good yields for 5-membered heteroaryl boronic acids/boronates (**1k–1m**) as well as pyrazolo[1,5-*b*]pyridazine-3-boronate (**1n**). In all cases, the C5 bromo substituent survived the coupling conditions.

As a complementary method, for cases where the boronic acid/boronate of the desired C2 substituent was not commercially available, the Suzuki coupling reaction of boronic acid **20** and the corresponding halide could install the C2 group. For example, the coupling reaction of **20** with 2-bromo-5-fluoropyridine afforded **23** with 5-fluoropyridine-2-yl at C2 position (Scheme 4). The amino group at C6 was then converted to *N*-methylsulfonamide to provide compound **1o** according to the chemistry described above.

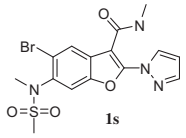
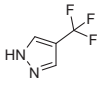
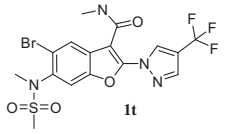
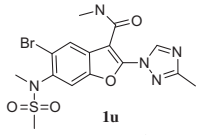
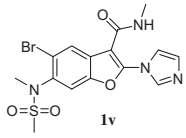
Table 2
Other transformations with iodide **10**



Entry	Reagents	Compound **1**	Coupling condition[a]	Yield of **1** (%)
1	CO, MeOH	 **1p**	D	84
2		 **1q**	E	60
3		 **1r**	F	83

(*continued on next page*)

Table 2 (*continued*)

Entry	Reagents	Compound **1**	Coupling condition[a]	Yield of **1** (%)
4		 **1s**	F	64
5		 **1t**	F	82
6		 **1u**	F	55
7		 **1v**	F	83

[a] Condition D: CO (50 psi), $Pd(PPh_3)_2Cl_2$, MeOH, DMSO, 50 °C, 16 h; Condition E: amine, pyridine, 60 °C, 3 h; Condition F: reagent, K_2CO_3, DMF, 80 °C, 10 h.

Beyond the Suzuki coupling, other reactions involving iodide **10** produced compounds with other C2 substituents (Table 2). Carbonylation of **10** gave the ester **1p**, which could be further derivatized. The reaction of 2-aminoethanol with **10** under basic conditions introduced a 2-hydroxyethylamino group at the C2 position (**1q**).[16] Heteroaryl C–N coupling afforded access to a variety of *N*-linked compounds (**1r**–**1v**). Again, in all cases, the C5 bromo substituent survived the coupling conditions.

In summary, we have developed a method to prepare a common precursor, iodide **10**, and demonstrated its utility in installing a variety of substituents at the C2 position of a highly substituted benzofuran ring system in a highly efficient fashion. This effort produced a diverse set of compounds to support the extensive SAR interrogation for this series. Further manipulation of these compounds into biologically active compounds as well as their activity on the biological target will be disclosed in due course.

Supplementary data

Supplementary data (the experimental procedures and characterization data for all new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.02.051.

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