



Facile functionalization at the C2 position of a highly substituted benzofuran

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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.

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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

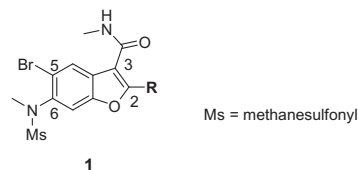
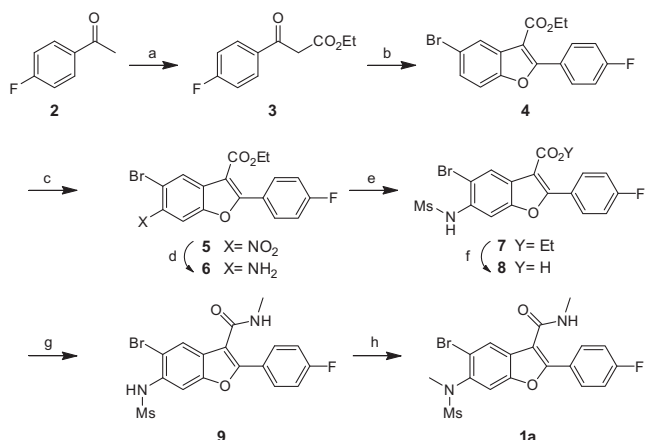


Figure 1. 5-Bromo-*N*-methyl-6-(*N*-methylmethylsulfonamido)benzofuran-3-carboxamide (**1**) with different substitutions at the C2 position.

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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), FeCl₃·6H₂O (0.15 equiv), (t-BuO)₂ (2.2 equiv), reflux, 6 h, 14%; (c) fuming HNO₃ (8.1 equiv), CHCl₃, −15 °C, 30 min, 66%; (d) Iron filings (3.0 equiv), NH₄Cl (6.0 equiv), MeOH–THF–H₂O (2:2:1), reflux, 3 h, 82%; (e) MsCl (3.0 equiv), pyridine/CH₂Cl₂ (1:5), 0 °C to 25 °C, 82%; (f) LiOH·H₂O (5.1 equiv), dioxane–H₂O (5:1), 100 °C, 3 h, 96%; (g) HOBT (1.5 equiv), EDC (1.5 equiv), DMF, 25 °C, 2 h, Et₃N (4.7 equiv), CH₃NH₂·HCl (3.0 equiv), 94%; (h) MeI (3.0 equiv), K₂CO₃ (2.5 equiv), KI (0.02 equiv), DMF, 80–90 °C, overnight, 94%.

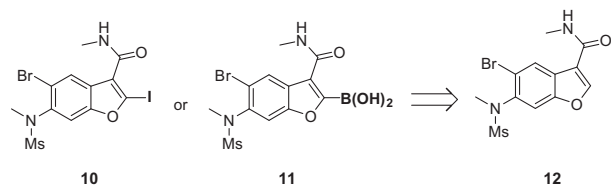


Figure 2. Possible precursors for installing C2 groups: **10** and **11**.

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 carboxy 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 I₂ according to the

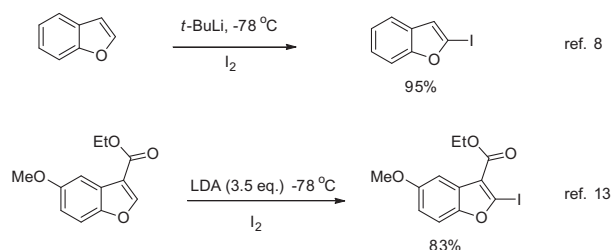
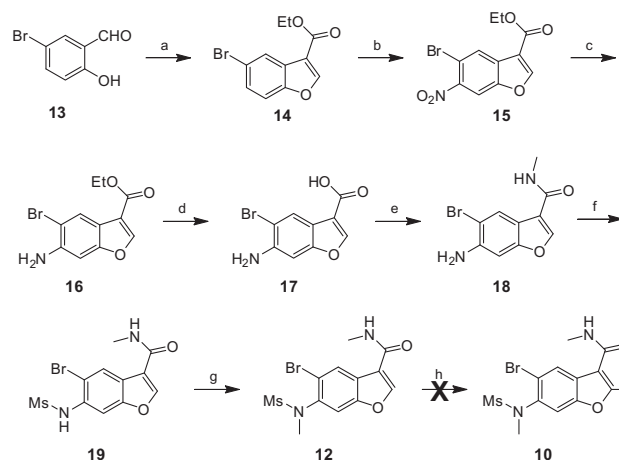
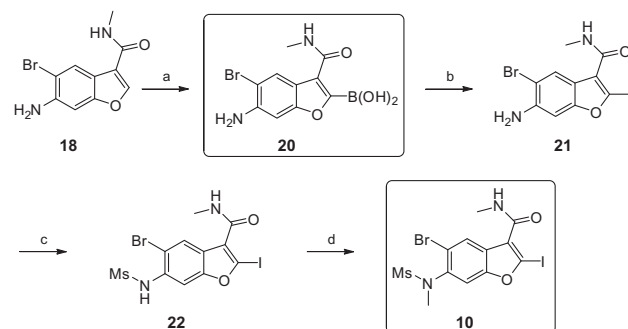


Figure 3. Representative examples known for the preparation of C2-iodo benzofuran ring system.



Scheme 2. Preparation of compound **12**. Reagents and conditions: (a) ethyl diazoacetate (1.43 equiv), HBF₄·Et₂O (0.1 equiv), CH₂Cl₂, <38 °C; then H₂SO₄ (concd, 1.3 equiv), followed by Na₂CO₃ (aq), 75%; (b) fuming HNO₃ (12.1 equiv), CHCl₃, −20 °C to 0 °C, 85%; (c) Fe filing (3.0 equiv), NH₄Cl (6.0 equiv), MeOH–THF–H₂O (2:2:1), 68%; (d) LiOH·H₂O (5.0 equiv), dioxane–H₂O (5.6:1), reflux, 97%; (e) EDC (1.5 equiv), HOBT (1.5 equiv), DMF, 25 °C, 2 h; Et₃N (3.0 equiv), MeNH₂·HCl (3.0 equiv), 25 °C, 2 h, 71%; (f) MsCl (2.0 equiv), pyridine (3.0 equiv), CH₂Cl₂, 0 °C to 25 °C, 16 h, 70%; (g) K₂CO₃ (3.0 equiv), MeI (2.0 equiv), DMF, 80 °C, 3 h, 90%; (h) LDA (5.0 equiv), I₂ (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·H₂O (7.9 equiv), 25 °C, 30 min, 59%; (d) K₂CO₃ (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, iododeboration of boronic acid **20** with *N*-iodosuccinimide 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

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