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Dibutyl 2-(trifluoromethyl)cyclopropylboronate as a useful (trifluoromethyl)-cyclopropyl donor: application to antagonists of TRPV1

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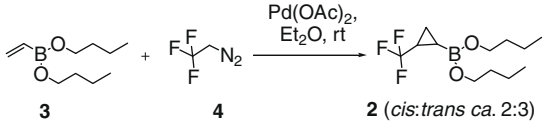
ABSTRACT

Dibutyl-2-(trifluoromethyl)cyclopropylboronate 2, available in one step from commercially available reagents, serves as a useful (trifluoromethyl)cyclopropylating reagent by participating in a palladium-catalyzed Suzuki coupling. The use of boronate ester **2** in medicinal chemistry was exemplified by preparation of TRPV1 receptor antagonists.

The introduction of small privileged motifs into compounds with biological activity is an increasingly popular tactic within medicinal chemistry.[1] The cyclopropyl group, which can have beneficial effects upon biological activity and metabolic stability, is one such privileged motif, whose use has become increasingly popular within the drug discovery community.[2] The trifluoromethyl group is another privileged sub-structure within medicinal chemistry. This group utilizes the beneficial effect of fluorine substitution in order to improve numerous characteristics important to drug molecules.[3] Although conceptually attractive, a (trifluoromethyl)cyclopropyl substituent **1** (Fig. 1) is a relatively rare occurrence within drug discovery programs, especially when 1,2-disubstituted variants are considered.[4] In part, this may be due to a limited number of methods to prepare such compounds.[5] Beyond the realm of medicinal chemistry, the (trifluoromethyl)cyclopropyl group is also useful to agrochemical and materials scientists, where its unique electronic structure can also be used advantageously. In this Letter, we detail a preparation of dibutyl 2-(trifluoromethyl)cyclopropylboronate **2**, and demonstrate its ability to serve as a (trifluoromethyl)cyclopropyl donor, by reaction in a palladium-catalyzed Suzuki coupling. The ability of **2** to provide final compounds with biological activity was exemplified by preparing a number of molecules with antagonist activity at the TRPV1 (VR1) receptor.[6]

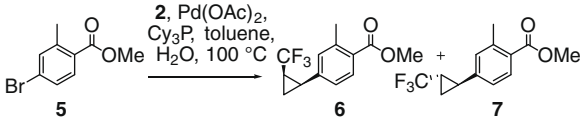
Our synthesis of compound **2** began by examining the cyclopropanation of dibutyl vinylboronate **3** with (2,2,2-trifluoromethyl)diazomethane **4** under the influence of palladium(II) acetate catalysis (Scheme 1). Such conditions for forming cyclopropylboronate derivatives have been employed previously by other research groups, using alternative diazo compounds as reacting partners.[7] Additionally, the use of (2,2,2-trifluoromethyl)diazomethane **4** in cyclopropanation reactions is well-known.[5a,b,6,8] The reaction of **3** and **4** progressed smoothly, providing the boronate **2** as an approximate 2:3 mixture of cis- and trans-isomers by ^{19}F NMR.[9] Compound **2**, a non-viscous liquid, was then used without further purification, and usually within a short timeframe. However, **2** could be stored for prolonged periods before use, in a fridge or freezer, if necessary.

Figure 1. (Trifluoromethyl)cyclopropyl group **1** and dibutyl 2-(trifluoromethyl)cyclopropylboronate **2**.



Scheme 1. Synthesis of dibutyl 2-(trifluoromethyl)cyclopropylboronate **2**.

Next, we examined the use of **2** in a Suzuki reaction (Scheme 2). For our studies, we used the conditions reported by Wallace and Chen, which were optimized for couplings with cyclopropylboronic acid.[10] Reaction of compound **2** (mixture of cis- and trans-iso-



Scheme 2. Suzuki reaction with dibutyl 2-(trifluoromethyl)cyclopropylboronate **2**.

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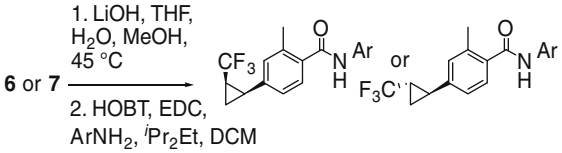
mers) with methyl 4-bromo-2-methylbenzoate **5** under the influence of $Pd(OAc)_2$/tricyclohexylphosphine catalysis proceeded smoothly to produce the *cis*- and *trans*-cylopropane products **6** and **7**. Compounds **6** and **7** were readily separable by high-performance liquid chromatography to provide stereochemically pure cis- and trans-isomers (as racemic mixtures).[9] The stereochemistry of compounds **6** and **7** was confirmed by proton NMR studies.[11]

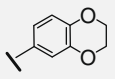
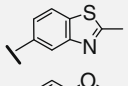
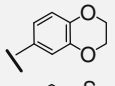
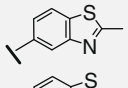
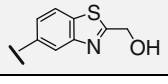
In order to demonstrate utility to the field of medicinal chemistry, the Suzuki products **6** and **7** were reacted further to provide antagonists of the transient receptor potential vanilloid 1 (TRPV1), also known as vanilloid receptor 1 (VR1). Antagonists of TRPV1 have been highlighted as potential next-generation pain therapeutics.[12] Additionally, TRPV1 receptor antagonists may be useful against other conditions, such as urinary incontinence, cough, asthma and diabetes, amongst others.[13] In order to provide target molecules, compounds **6** and **7** were hydrolyzed, and the resulting acids were coupled with a range of anilines to provide amide products.[6,14] As can be seen from Table 1, potent antagonists could be obtained. Interestingly, both the cis- and trans-stereoisomers of final compounds were active. For example, the *N*-(2-methylbenzo[*d*]thiazol-5-yl) amides (compounds **9** and **11**) appeared to be approximately equipotent at the TRPV1 receptor, with each compound giving an IC_{50} of around 40 nM against human TRPV1.[9]

In recent years, potassium trifluoroborates have become increasingly popular as easily-handled, air-stable equivalents of boronic acids or boronic esters.[15] Thus, we also undertook a preliminary investigation into the synthesis of potassium 2-(trifluoromethyl)cyclopropyl trifluoroborate **13**, from boronate ester **2**, using aqueous KHF_2 in MeOH. Unfortunately, our initial experiments did not yield significant quantities of the desired product (Scheme 3).[16] At this time it is unclear why **13** was not produced, since other cyclopropyl trifluoroborates have been prepared previously.[17] Thus, future studies may attempt a more thorough investigation into the synthesis of **13**, since the successful preparation of a solid trifluoroborate salt of compound **2** would be attractive.[18]

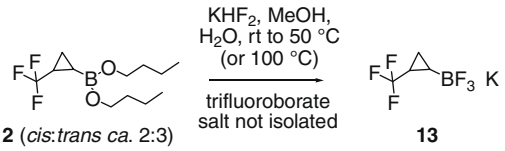
In addition to Suzuki reactions, boronic acids, boronic esters, and trifluoroborates have also been utilized in a multitude of synthetically valuable transformations, such as Petasis–Mannich reactions[19] and copper-mediated alkylations of phenols, thiols, amides,

Table 1
TRPV1 antagonist activity of (trifluoromethyl)cyclopropyl amide derivatives



Compound	Relative stereochemistry	Ar	hTRPV1 IC_{50}[a] (nM)
8	*cis*-		283
9	*cis*-		40
10	*trans*-		529
11	*trans*-		43
12	*trans*-		26

[a] IC_{50} against human TRPV1 receptor (agonist = capsaicin at an EC_{50} concentration).



Scheme 3. Attempted synthesis of potassium (trifluoromethyl)cyclopropyl trifluoroborate **13** from compound **2**.

sulfonamides and nitrogenous heterocycles (both aromatic and non-aromatic).[20,21] Unfortunately, time constraints did not allow us to examine the use of boronic ester **2** in these reactions. Thus, future work may also attempt to evaluate the performance of compound **2**, or an equivalent, beyond the realm of Suzuki coupling reactions.

In conclusion, this Letter describes the preparation of butyl (trifluoromethyl)cyclopropylboronate **2** and its use in a Suzuki coupling reaction. The ability of compound **2** to act as a (trifluoromethyl)cyclopropyl donor was demonstrated by preparing the compounds with antagonist activity at the human TRPV1 receptor. The results of our investigations will be of interest to medicinal, agrochemical and materials scientists alike, where the unique properties of the (trifluoromethyl)cyclopropyl group can be used advantageously.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.073.

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