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SHORT COMMUNICATION

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Synthesis of 2,6-Disubstituted Imidazo[2,1-*b*][1,3,4]thiadiazoles through Cyclization and Suzuki–Miyaura Cross-Coupling Reactions

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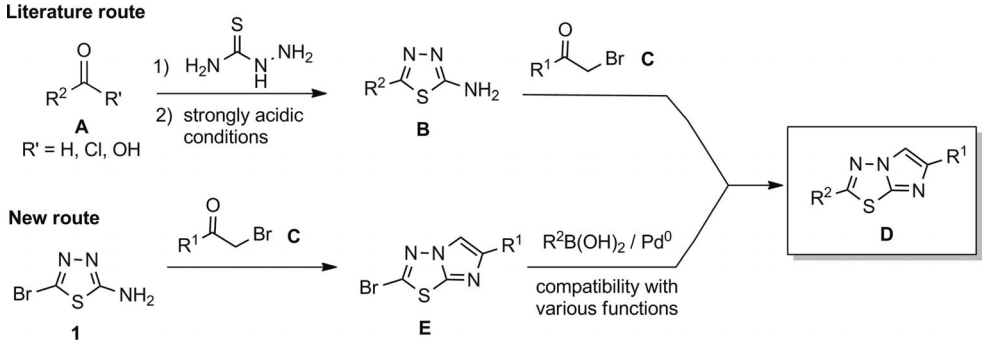
Highly substituted imidazo[2,1-*b*][1,3,4]thiadiazole derivatives were synthesized through successive cyclization and Suzuki–Miyaura cross-coupling reactions. The palladium-catalyzed coupling reaction was optimized and a wide range of boronic acids was used to evaluate the scope and limitations of the methodology. The final compounds were obtained in fair to very good yields and high compatibility with various chemical functions or (hetero)cycles was observed.

Introduction

The interest in the imidazo[2,1-*b*][1,3,4]thiadiazole moiety for use in pharmaceutical products makes this scaffold a highly useful building block for organic chemistry.[1] These derivatives have found applications in various areas of medicine including in their use in anticancer,[2] antitubercular,[3] and analgesic treatments.[4] There has therefore been tremendous interest in developing efficient synthetic methodologies for the regioselective synthesis of polysubstituted imidazo[2,1-*b*][1,3,4]thiadiazoles. Extensive research has been conducted to develop preparative methods to reach this goal.

Investigations have focused on the synthesis of 2,6-disubstituted-imidazo[2,1-*b*][1,3,4]thiadiazole derivatives **D** as key intermediates for further developments (Scheme 1).[5] The classic and almost only method available to date to obtain these derivatives involves the use of 2-amino[1,3,4]-thiadiazole derivatives **B** with the appropriate α-haloketones **C**.[6] Although useful, these reactions require, for each C-2 modulation on **D**, the synthesis of the appropriately substituted 2-amino[1,3,4]thiadiazole derivatives **B** by condensation of **A**, an aroyl chloride,[7] and an arylcarboxylic acid[8] or an aryl carboxaldehyde[9] with the thiosemicarbazide under strongly acidic conditions such as H_2SO_4, $POCl_3$, and $FeCl_3$ as reagents.

Acid-sensitive chemical groups cannot be easily introduced under this previously described method. In order to introduce a wide range of functional groups, a promising solution is to find an efficient alternative to selectively functionalize imidazo[2,1-*b*][1,3,4]thiadiazoles at the C-2 position. Our expertise in heterocyclic synthesis[10] prompted us to envision the use of a Suzuki–Miyaura cross-coupling protocol that seems to be particularly powerful in this novel challenge.[11]



Scheme 1. Routes to 2,6-disubstituted imidazo[2,1-*b*][1,3,4]thiadiazole derivatives.

As an interesting alternative, we propose a simple and flexible method that can easily access 2-substituted imidazo[2,1-*b*][1,3,4]thiadiazole derivatives **D** from commercial 2-amino-5-bromo[1,3,4]thiadiazole (**1**) and several α-halo ketones **C** (Scheme 1). Our new route thus offers a wide library of **D** compounds in only two soft steps.

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Results and Discussion

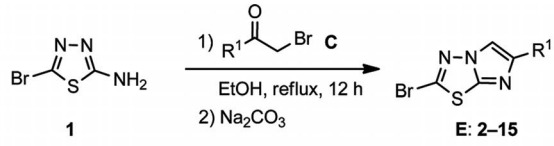
To perform the required Suzuki–Miyaura cross-coupling reaction, some 2-bromo-imidazo[2,1-*b*][1,3,4]thiadiazole derivatives **E** were first prepared. Rare 2-bromo-imidazothiadiazoles **2**–**15** were obtained by treating commercially available 2-amino-5-bromo[1,3,4]thiadiazole (**1**) with a variety of α-bromo ketones **C** in boiling ethanol (Table 1).[6] Aryl α-bromo ketones **C** were the most efficient substrates, and they provided the products in yields ranging from 67 to 85% (Table 1, Entries 2, 4–6, 8–12). The presence of substituent in the *ortho* position of the aryl group lowered the yields, probably because of steric hindrance (Table 1, Entries 3 and 7). In order to have a representative **E** library, methyl, ethyl ester, and 4-pyridinyl α-bromo ketones were additionally treated with **1** to afford desired products **2**, **14**, and **15** in only 20, 31, and 29% yield, respectively (Table 1, Entries 1, 13, 14). The instability of these α-halogeno ketone derivatives could explain the lack of reactivity.

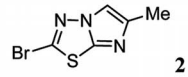
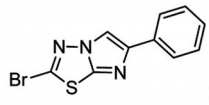
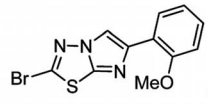
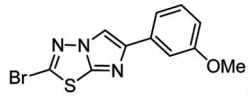
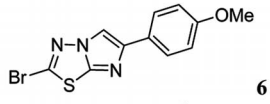
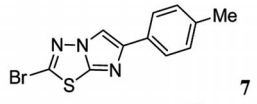
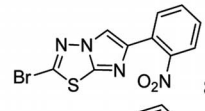
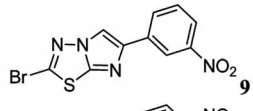
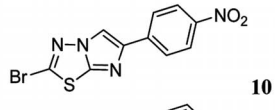
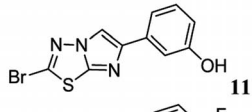
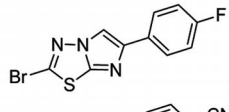
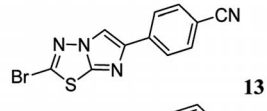
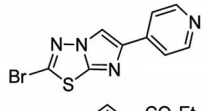
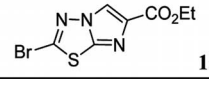
With these compounds in hand, we then tried to achieve the bromine displacement of compounds **2**–**15**. At the beginning of our program, the sole reaction involving a C-2 halogen atom in the imidazo[2,1-*b*][1,3,4]thiadiazole series was a S_NAr.[15] Consequently, we decided to find a general and efficient catalytic system by optimizing all the reaction parameters, that is, palladium source, ligand, base, solvent, and thermal activation (Table 2).

First of all, we decided to use $Pd_2(dba)_3$ as palladium source, and K_2CO_3 and DME as laboratory conditions, but only starting material was recovered (Table 2, Entry 1). $Pd(PPh_3)_4$ led to a very low amount of product **16** (^1H NMR spectrum of the crude material: 5% estimated) but after the purification step we mostly isolated starting material (88%; Table 2, Entry 2). Using Cs_2CO_3 (2.0 equiv.) as base and dioxane as solvent, desired compound **16** was fortunately formed, in an encouraging isolated yield of 10% (Table 2, Entry 3). In the following experiment, we tried to catalyze the reaction with a bidentate palladium complex, which was formed by using $Pd(OAc)_2$ (10 mol-%) and Xantphos (20 mol-%). Under these effective catalytic conditions, the reaction was complete in 1 h and product **16** was isolated in a very good yield of 92% (Table 2, Entry 4).

Once the efficient catalytic system had thus been determined, the following assays concerned the optimization of other parameters. The replacement of Cs_2CO_3 by K_2CO_3 improved the yield up to 96% (Table 2, Entry 5), whereas changing the reaction solvent to toluene or DME conversely decreased the yield to 80 and 76% respectively (Table 2, Entries 6 and 7). However, starting material **6** was unstable in DMF, which was revealed by a dramatic decrease in the yield (Table 2, Entry 8). This degradation could be explained by the instability of DMF under microwave heating in the presence of base to release dimethylamine, which could react with **6**. In addition, the use of classical heating led to degradation and reduced the yield to 68% after a reaction time of 12 h (Table 2, Entry 9). Only 5% conversion to **16** was observed after 1 h under thermal conditions. Finally, after adjusting the irradiation time, we observed that after only 30 min, a complete conversion occurred and **6** was isolated in an excellent yield of 96% (Table 2, Entry 10).

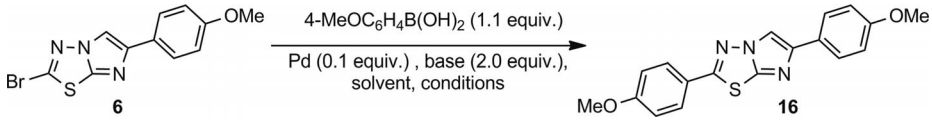
Table 1. Library of type **E**.



Entry	R^1COCH_2Br (**C**)	Product **E**	Yield[a] [%]
1	Me	 **2**	20[12]
2	Ph	 **3**	69[13]
3	2-$MeOC_6H_4$	 **4**	41
4	3-$MeOC_6H_4$	 **5**	78
5	4-$MeOC_6H_4$	 **6**	77
6	4-MeC_6H_4	 **7**	71
7	2-$NO_2C_6H_4$	 **8**	24
8	3-$NO_2C_6H_4$	 **9**	67
9	4-$NO_2C_6H_4$	 **10**	84
10	3-OHC_6H_4	 **11**	78
11	4-FC_6H_4	 **12**	73[14]
12	4-CNC_6H_4	 **13**	85
13	4-pyridinyl	 **14**	31
14	CO_2Et	 **15**	29

[a] Yield is given for the isolated compound.

Table 2. Library of type **E**.



Entry	Catalyst[a]	Ligand[b]	Base	Solvent	Conditions	Yield[c] [%]
1	$Pd_2(dba)_3$	–	K_2CO_3	dioxane	MW, 150 °C, 1 h	–
2	$Pd(PPh_3)_4$	–	K_2CO_3	dioxane	MW, 150 °C, 1 h	trace
3	$Pd(PPh_3)_4$	–	Cs_2CO_3	dioxane	MW, 150 °C, 1 h	10
4	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	dioxane	MW, 150 °C, 1 h	92
5	$Pd(OAc)_2$	Xantphos	K_2CO_3	dioxane	MW, 150 °C, 1 h	96
6	$Pd(OAc)_2$	Xantphos	K_2CO_3	toluene	MW, 150 °C, 1 h	80
7	$Pd(OAc)_2$	Xantphos	K_2CO_3	DME	MW, 150 °C, 1 h	76
8	$Pd(OAc)_2$	Xantphos	K_2CO_3	DMF	MW, 150 °C, 1 h	21
9	$Pd(OAc)_2$	Xantphos	K_2CO_3	dioxane	Δ, reflux, 12 h	68
10	$Pd(OAc)_2$	Xantphos	K_2CO_3	dioxane	MW, 150 °C, 30 min	96

[a] 0.1 equiv. of catalyst was used. [b] If a ligand was required, 0.2 equiv. was used. [c] Yield is given for the isolated compound.

In conclusion, we clearly showed that the success of the Suzuki–Miyaura reaction in the imidazo[2,1-*b*][1,3,4]thiazole series mainly depends on the choice of catalyst, activation method (i.e., thermal or microwave), and solvent. In order to explore the scope and limitations of this cross-coupling reaction, we then used previously synthesized C-2 bromo derivative **E** with various boronic acids (Table 3).

To evaluate the effect of the substituents in the R^1 position, we first performed the reaction using a near stoichiometric amount of a simple phenylboronic acid to prevent any alteration of the results by interference of an additional reactive function. The displacement of the methoxy phenyl group on derivative **E** from the *para* to the *ortho* position (Table 3, Entries 1–3) gave a slight but no significant variation in yield and **17**–**19** were obtained in 78–82% yield. Replacement of the methoxy group by a strong electron-withdrawing group of the NO_2-type gave the same behavior (Table 3, Entries 4–6).

Other assays with Me, F, and CN substituents led to compounds **24**–**26** (Table 3, Entries 8–10), and the best results were obtained with the fluoro and cyano groups, which afforded **25** and **26** in yields up to 90%. In the latter two cases, the purification step was considerably easier than in the other assays. Afterwards, we successfully performed our reaction with other R^1 substituents such as methyl, pyridinyl, and base-sensitive ethyl ester groups (Table 3, Entries 11–14). Compatibility of the cross-coupling conditions with major acid/base-sensitive functions encountered in R^1 was also demonstrated during the assays. During our investigation, we found one patent reporting such a Suzuki–Miyaura cross-coupling reaction with $Pd(dppf)Cl_2$–DCM, K_2CO_3, and DME as the reaction system to synthesize a related compound of **30**, but in our hands, these conditions failed.[16]

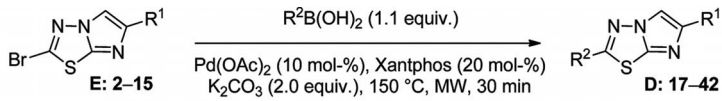
To complete our study, we determined the influence of the nature of the boronic acid on the reaction. This goal was achieved by starting only from 2-bromo derivative **10**. The use of 2-, 3-, or 4-methoxyphenyl boronic acids (Table 3, Entries 15–17) showed that steric hindrance had no real impact on the reaction yields. Nevertheless, diminishing the strength of the electron-donating group slowly decreased the yield. However, final compound **34** was always isolated in an acceptable 80% yield (Table 3, Entry 18). The presence of a small and weakly electron-withdrawing fluorine atom restored the efficiency of the reaction, but the increase in the electron-withdrawing character exhibited a major impact. The cyano-, trifluoromethyl-, and aldehyde-containing adducts **36**, **37**, and **41** were isolated in 67, 57, and 91% yield, respectively, whereas the reaction with 4-(dimethylcarbamoyl)phenylboronic acid led to **38** in only 32% yield (Table 3, Entries 20–22, 26). To finish our investigation, we attempted the cross-coupling reaction with the 3-furylboronic acid or methylboronic acid. Fortunately, the switch to a heterocyclic or alkyl series was successful, and the efficiency of the reaction was partially restored, leading to **39** and **42** in satisfactory yield of 70 and 65% respectively (Table 3, Entries 23 and 27).

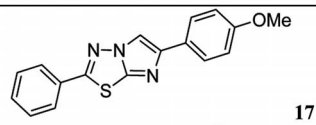
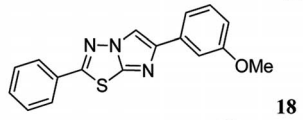
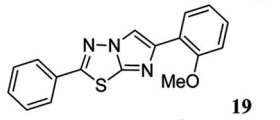
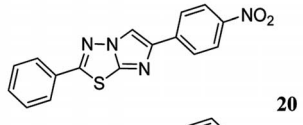
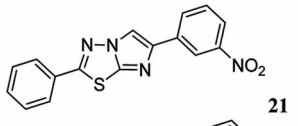
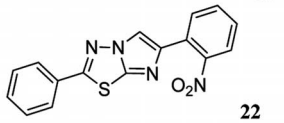
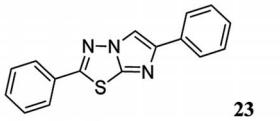
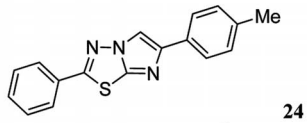
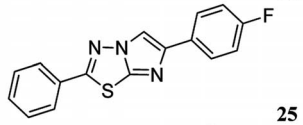
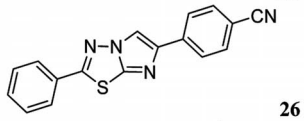
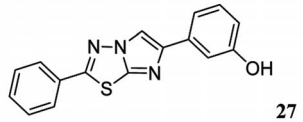
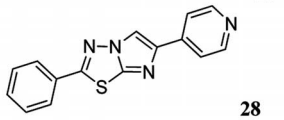
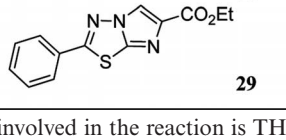
During this library design, the sole limitation we found concerned the use of 4-hydroxyphenylboronic acid, which totally inhibited the reaction, but the reactivity could be fully restored by using a THP-protected 4-hydroxyphenylboronic acid to give, after hydrochloric acid deprotection, **40** in 84% overall yield (Table 3, Entries 24 and 25).

Conclusions

In this paper, we reported the synthesis of 2-bromoimidazo[2,1-*b*][1,3,4]thiadiazole derivatives substituted in the 6-position by various substituted groups. This series of molecules has allowed to us to develop a Suzuki–Miyaura cross-coupling reaction and to obtain a new class of imidazo[2,1-*b*][1,3,4]thiadiazole derivatives substituted in the 2- and 6-positions by alkyl, ester, or substituted aryl groups. This new strategy is efficient and successfully yielded the desired products in the presence of electron-withdrawing, electron-donating, and acid-sensitive chemical groups. This route will have a major impact on the synthesis of new bioactive

Table 3. Synthesis of compounds **17**–**42**.



Entry	Starting material **E**	R^1	R^2	Product **D**	Yield [%][a]
1	**6**	4-$MeOC_6H_4$	C_6H_5	 **17**	78
2	**5**	3-$MeOC_6H_4$	C_6H_5	 **18**	73
3	**4**	2-$MeOC_6H_4$	C_6H_5	 **19**	82
4	**10**	4-$NO_2C_6H_4$	C_6H_5	 **20**	83
5	**9**	3-$NO_2C_6H_4$	C_6H_5	 **21**	73
6	**8**	2-$NO_2C_6H_4$	C_6H_5	 **22**	82
7	**3**	C_6H_5	C_6H_5	 **23**	90[13]
8	**7**	4-MeC_6H_4	C_6H_5	 **24**	79
9	**12**	4-FC_6H_4	C_6H_5	 **25**	94
10	**13**	4-NCC_6H_4	C_6H_5	 **26**	91
11	**11**	3-HOC_6H_4	C_6H_5	 **27**	92
12	**14**	4-pyridinyl	C_6H_5	 **28**	76
13	**15**	CO_2Et	C_6H_5	 **29**	81

[a] Yield is given for the isolated compound. ND: Not detected. [b] The compound involved in the reaction is THP protected. Additional treatment with 20% HCl was required to isolate **40**.

compounds containing the rare imidazo[2,1-*b*][1,3,4]thiadiazole central skeleton.

Experimental Section

General Procedure A for the Synthesis of 2-Bromo-(6-substituted)-imidazo[2,1-*b*][1,3,4]thiadiazoles E: A mixture of 2-amino-5-bromo-1,3,4-thiadiazole (**1**, 1.0 equiv.) and α-bromo ketone **C** (1.1 equiv.) in ethanol was heated at reflux for 18 h. The mixture was then cooled to room temperature and slightly concentrated under vacuum. If a salt precipitated (procedure A1), it was filtered and then suspended in water, and the solution was neutralized with a saturated solution of sodium carbonate under vigorous stirring. Finally, the precipitate was washed with ethanol and the product fully characterized without any further purification. If homogeneity occurred after cooling the reaction (procedure A2), the solution was concentrated in vacuo, then diluted with dichloromethane, and washed with a saturated solution of sodium carbonate. The organic layers were dried with magnesium sulfate, filtered, and then concentrated before purification by silica gel flash chromatography.

General Procedure B for the Synthesis of 2,6-Disubstituted Imidazo[2,1-*b*][1,3,4]thiadiazoles D Under Suzuki–Miyaura Cross-Coupling Conditions: Bromide derivative **E** (1.0 equiv.), K_2CO_3 (2.0 equiv.), the boronic acid (1.1 equiv.), Xantphos (0.2 equiv.), $Pd(OAc)_2$ (0.1 equiv.), and degassed 1,4-dioxane were subsequently added into a 2–5-mL microwave vial. The resulting mixture was subjected to microwave irradiation at 150 °C for 30 min. Once the heating cycle was completed, the solvent was evaporated under reduced pressure, and the residue was diluted in CH_2Cl_2. The organic layers were washed with water, dried with anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was then washed successively with acetone, methanol, and diethyl ether. After drying under vacuum, the obtained product was pure enough to be fully characterized.

Supporting Information (see footnote on the first page of this article): Characterization data and copies of ^1H NMR and ^{13}C NMR spectra for all new compounds.

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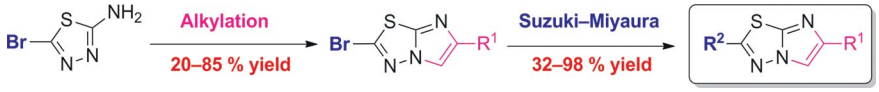
SHORT COMMUNICATION

Heterocyclic Chemistry



The synthesis of 2,6-disubstituted imidazo-[2,1-*b*][1,3,4]thiadiazoles obtained through the cyclization of 2-amino-5-bromo[1,3,4]-thiadiazole and several α-halo ketones followed by Suzuki–Miyaura cross-coupling with a variety of boronic acids was developed. The products were obtained in fair to very good yields.

Keywords: Palladium / Microwave chemistry / Fused-ring systems / Cross-coupling

