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Heterocycles

Palladium-Catalyzed Amination of C-5 Bromoimidazo[2,1-*b*]-[1,3,4]thiadiazoles

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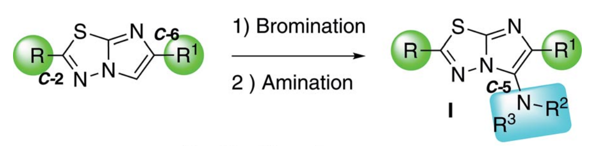
Abstract: A new and efficient palladium-catalyzed amination of imidazo[2,1-*b*][1,3,4]thiadiazole at the C-5 position under microwave irradiation is reported. The reactivity toward bromine release at the C-5 position was investigated, and palladium-catalyzed cross-coupling conditions were optimized. A wide range of amines was employed to examine the scope and limitations of the method. To complete this methodological study, the influence of the nature and the positions of additional imidazo[2,1-*b*][1,3,4]thiadiazole substitutions was investigated.

Introduction

In the last few years, imidazo[2,1-*b*][1,3,4]thiadiazole, a bicyclic [5-5]-fused system with one bridgehead nitrogen atom, has been widely used to design many bioactive compounds.[1] This scaffold has proven applicable to the discovery of a wide variety of biologically active molecules and antitumor,[2] antitubercular,[3] and analgesic agents.[4]

Current strategies for preparing imidazo[2,1-*b*][1,3,4]thiadiazole derivatives generally consist of building imidazothiadiazole by condensation of 2-amino-5-substituted[1,3,4]thiadiazoles with various α-haloketones or acetophenones.[5] Although compounds with well-positioned substituents are obtained, the major limitations of these strategies are the necessity of unavailable polyfunctionalized reagents and harsh conditions. These drawbacks constitute a major hindrance to the development of medicinal chemistry programs or exploration of the corresponding chemical space. It is therefore of interest to propose alternative methods.

For several years, our group has been developing efficient methodologies to selectively functionalize heterocycles such as azaindoles,[6] pyridopyrimidines,[7] and, more recently, bicyclic heterocycles that have two five-membered fused rings, such as triazolothiadiazoles,[8] thiazolotriazoles,[9] or imidazothiadiazoles.[10] In the latter series, our latest challenge is to directly access a variety of original C-5-aminated compounds. To the best of our knowledge, the sole route for the synthesis of C-5-aminated imidazo[2,1-*b*][1,3,4]thiadiazoles consists of using a three-component Groebke–Blackburn–Bienaymé reaction.[11] However, only secondary amines are generated by using this strategy with the chosen isocyanide. This paper reports a tandem sequence including bromination and halogen displacement under Buchwald–Hartwig cross-coupling strategies[10,12] to synthesize compounds of type **I** (Scheme 1). We proved the versatility of the approach and its efficiency toward primary or secondary benzyl, alkyl, aromatic, and heteroaromatic amines in the presence of various C-2 and C-6 substituents.



Scheme 1. C-5 amination program.

Results and Discussion

First, 5-bromoimidazo[2,1-*b*][1,3,4]thiadiazole derivatives **11**–**20** were prepared by using a two-step cyclization/bromination sequence involving commercially available 2-amino-5-methyl or 5-aryl[1,3,4]thiadiazoles and a variety of α-halogenoketones in boiling ethanol (Table 1).[13] At the C-2 and C-6 positions, methyl or phenyl systems with or without electron-donating or electron-withdrawing groups were used. At the C-6 position, we additionally prepared hydrogenated derivative **1** and ethyl ester **2**. Cyclization step 1 and bromination step 2 occurred smoothly in most cases. Obtaining **1** and its bromination remained difficult even if step 2 appeared to be fully regioselective. Bromination of **4** and **5** led to polyhalogenated derivatives. Fortunately, derivatives **14** and **15** could be separated from the complex mixture. This representative C-5 bromoimidazothiadiazole library (Table 1) contains enough diversity to find general conditions during amination studies.

At the beginning of this study, we tried the simple displacement of the C-5 bromine atom under S_NAr conditions, but all attempts remained unsuccessful, regardless of the temperature

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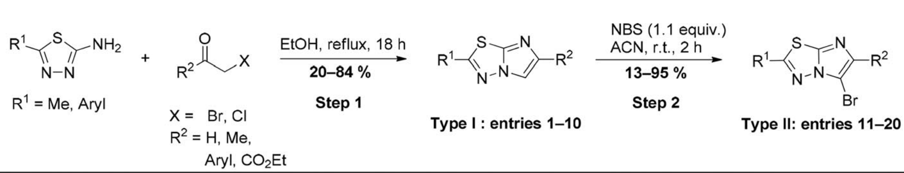
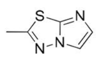
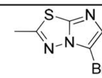
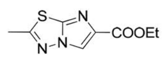
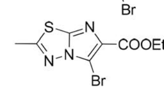
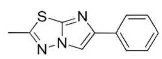
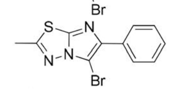
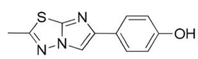
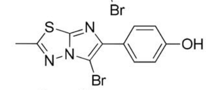
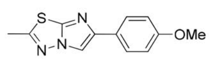
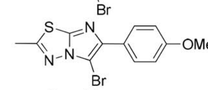
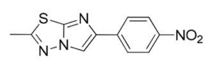
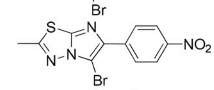
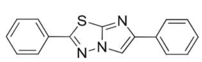
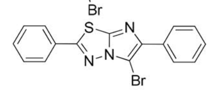
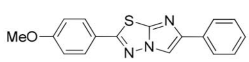
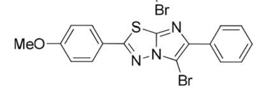
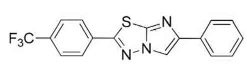
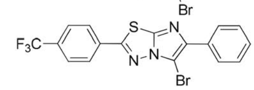
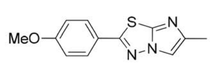
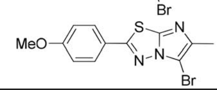
Table 1. Synthesis of type **I** derivatives and their C-5 brominated analogs.



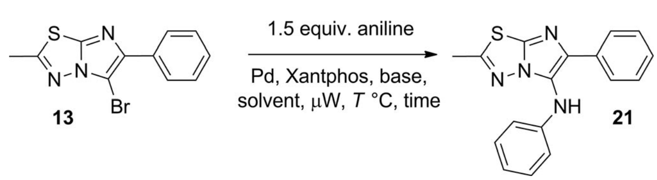
Entry	Compound of type I		Step 1, Yield[a]	Entry	Compound of type II		Step 2, Yield[a]
1		**1**	20 %	11		**11**	44 %
2		**2**	28 %	12		**12**	84 %
3		**3**	61 %	13		**13**	92 %
4		**4**	84 %	14		**14**	13 %
5		**5**	74 %	15		**15**	15 %
6		**6**	47 %	16		**16**	89 %
7		**7**	82 %	17		**17**	92 %
8		**8**	74 %	19		**18**	95 %
9		**9**	43 %	20		**19**	95 %
10		**10**	57 %	18		**20**	85 %

[a] Yields are indicated for isolated compounds.

and the activation mode (thermal or microwave irradiation) used. This lack of reactivity prompted us to quickly switch to palladium-catalyzed reactions (Table 2).

We started with conditions that had proved their efficiency in the imidazotriazole series,[14] but in this case, all attempts failed and only starting material was recovered (Table 2, entry 1). However, increasing the amount of base, the catalytic system, as well as the reaction time and temperature, partially restored the reactivity, and the desired compound **21** was formed in an encouraging 11 % yield (entry 2).

Table 2. Optimization of the palladium-catalyzed reaction to synthesize **21**.



Entry	Pd_2dba_3	Xantphos	Base	Solvent, Heating, Temp., Time	Yield of **21**[a]
1	5.0 mol-%	10.0 mol-%	K_2CO_3 (2.0 equiv.)	Dioxane, µW, 130 °C, 15 min	ND[b]
2	10.0 mol-%	20.0 mol-%	K_2CO_3 (3.0 equiv.)	Dioxane, µW, 140 °C, 30 min	11 %
3	10.0 mol-%	20.0 mol-%	Cs_2CO_3 (3.0 equiv.)	Dioxane, µW, 140 °C, 30 min	91 %
4	5.0 mol-%	10.0 mol-%	Cs_2CO_3 (3.0 equiv.)	Dioxane, µW, 140 °C, 30 min	92 %
5	2.5 mol-%	5.0 mol-%	Cs_2CO_3 (3.0 equiv.)	Dioxane, µW, 140 °C, 30 min	87 %
6	5.0 mol-%	10.0 mol-%	Cs_2CO_3 (3.0 equiv.)	DME, µW, 140 °C, 30 min	86 %
7	5.0 mol-%	10.0 mol-%	Cs_2CO_3 (3.0 equiv.)	Toluene, µW, 140 °C, 30 min	34 %
8	–	10.0 mol-%	Cs_2CO_3 (3.0 equiv.)	Dioxane, µW, 140 °C, 30 min	ND[b]

[a] Yields are indicated for isolated compounds. [b] ND: not detected, only starting material was recovered.

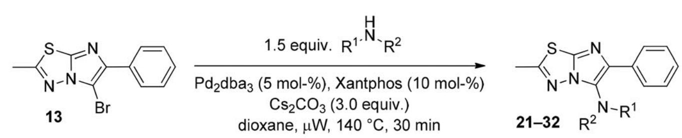
The nature of the base was investigated next. Surprisingly, Cs_2CO_3 led to a full conversion in only 30 min, and the targeted product **21** was isolated in a very good yield of 91 % (entry 3). A further catalyst charge adjustment to 5.0 mol-% proved to be a good compromise as 2.5 mol-% led to a slight decrease in the yield (entries 4, 5). It is noteworthy that all attempts to change the solvent led to a decrease in yield (entries 6–7), and DMF imparted a strong instability to the catalytic system, which quickly stopped working. Finally, suppression of the catalyst (entry 8) confirmed that the amine introduction is due to a Buchwald type reaction and not by an S_NAr pathway.

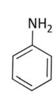
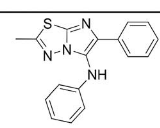
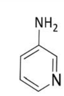
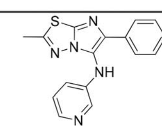
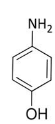
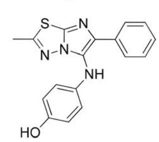
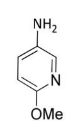
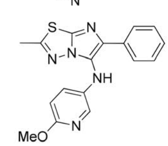
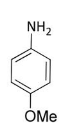
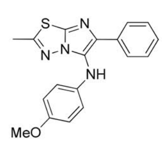
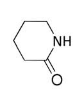
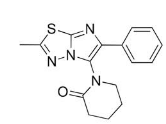
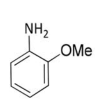
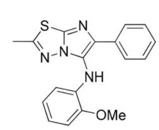
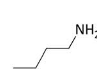
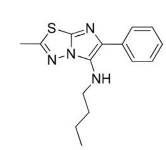
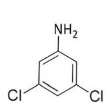
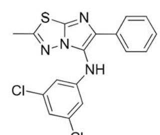
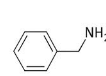
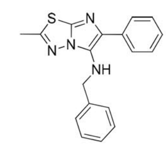
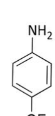
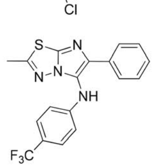
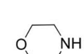
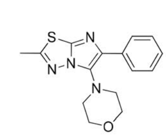
To prove the usefulness of this novel cross-coupling reaction, we then studied the reactivity of **13**, which was prepared on a large scale with a representative aminated derivative panel (Table 3). While aniline gave satisfactory yields, anisidine and 4-aminophenol were less efficient (entries 2, 3). Isomerization of the OMe group to the *ortho* position did not interfere with the efficiency of the reaction. This result seems to indicate the low impact of steric effects (entries 3, 4). 3,5-Dichloroaniline remained suitable for the synthesis of **25**, which was again obtained in a very good yield (entry 5).

There appeared to be an electronic dependence of the amination given the condensation of the 4-CF_3 aniline or 3-aminopyridine, which led to **26** in only 49 % yield, while **27** was never detected (entries 6, 7). To confirm this hypothesis, we used the 2-OMe-5-aminopyridine. The addition of an electron-donating group restored the reactivity, and **28** was isolated in a 65 % yield (entries 7, 8). Finally, the amination was not efficient with lactams or primary aliphatic amines, but the condensation of bromo derivative **13** with the morpholine, a highly reactive cyclic secondary amine, led to the desired product **32** in moderate yield (entry 12).

To study the scope and limitation of this reaction, we then investigated the influence of the nature of the C-6 and C-2 substituents on the efficiency of the reaction with aniline as partner (Table 4). A sensitive but less bulky ester substituent at position

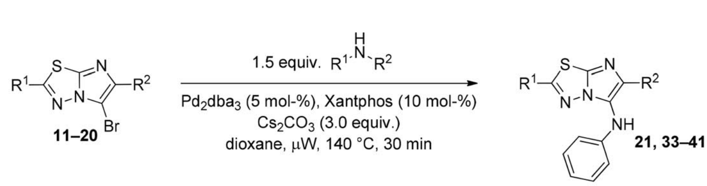
Table 3. Library of aminated compounds **21**–**32**.

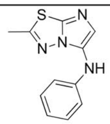
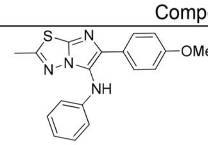
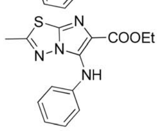
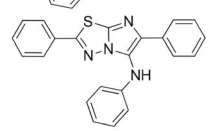
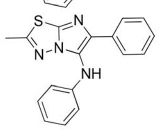
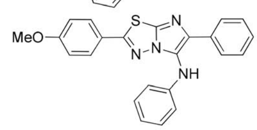
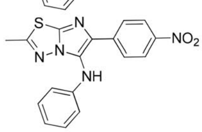
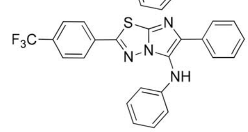
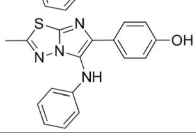
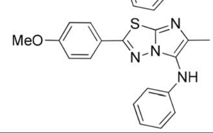


Entry	Amine	Compound		Yield[a]	Entry	Amine	Compound		Yield[a]
1			**21**	92 %	7			**27**	ND[b]
2			**22**	78 %	8			**28**	65 %
3			**23**	76 %	9			**29**	ND[b]
4			**24**	77 %	10			**30**	ND[b]
5			**25**	92 %	11			**31**	ND[b]
6			**26**	49 %	12			**32**	31 %

[a] Yields are indicated for isolated compounds. [b] ND: not detected.

Table 4. Synthesis of compounds **21**, **33**–**41**.



Entry	Compound		Yield[a]	Entry	Compound		Yield[a]
1		**33**	ND[b]	6		**37**	47 %
2		**34**	95 %	7		**38**	76 %
3		**21**	92 %	8		**39**	74 %
4		**35**	59 %	9		**40**	38 %
5		**36**	traces[c]	10		**41**	ND[b]

[a] Yields are indicated for isolated compounds. [b] ND: not detected, only starting material was recovered. [c] Detected by ^{1}H NMR spectroscopy.

C-6 was fully compatible with the palladium-catalyzed reaction, and **34** was isolated in an excellent 95 % yield (entry 2).

When the bromothiadiazole derivative was substituted by a methyl group at the C-2 position and an aryl group at the C-6 position, the reaction gave trisubstituted derivatives **21**, **35**, and **37** in satisfying yields (entries 3, 4, 6). Nevertheless, the absence of a C-6 substituent or inversion of the substituent positions (i.e. aryl at C-2 and methyl at C-6) led to inactivation of the system (entries 1, 10). The real sensitivity to the presence of a labile proton is shown by the results obtained for derivatives **36** and **37** (entries 5, 6).

No reaction occurred in the presence of a phenol derivative, whereas oxygen methylation restored the reactivity and **37** was isolated in a satisfying yield. Finally, when two aryl groups were placed at the C-2 and C-6 positions, the desired products were obtained in good yields (entries 7–9), albeit with a slightly lower yield of isolated product **40** because of the purification step.

Conclusions

This study offers chemists an alternative and more practical method to directly introduce aminated groups at the C-5 position in the imidazo[2,1-*b*][1,3,4]thiadiazole series. The Buchwald–Hartwig cross-coupling reaction was performed, and the palladium-catalyzed system was optimized. An efficient, low-catalyst-loading procedure was employed under microwave-assisted activation and gave the desired C-5 aminated derivatives. The nature and the positions of additional imidazothiadiazole substitutions or aniline derivatives had a great influence on the efficiency. In contrast to the other reported strategies, this synthesis enabled the easy introduction of aniline derivatives or secondary amines at the C-5 position. We are currently designing these scaffolds in order to synthesize new biologically active compounds.

Experimental Section

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures, characterization data, and spectra of the compounds.

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