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Synthesis of Internal Alkynes through the Pd-Catalyzed Coupling of Heteroaryl Halides with Terminal Alkynes

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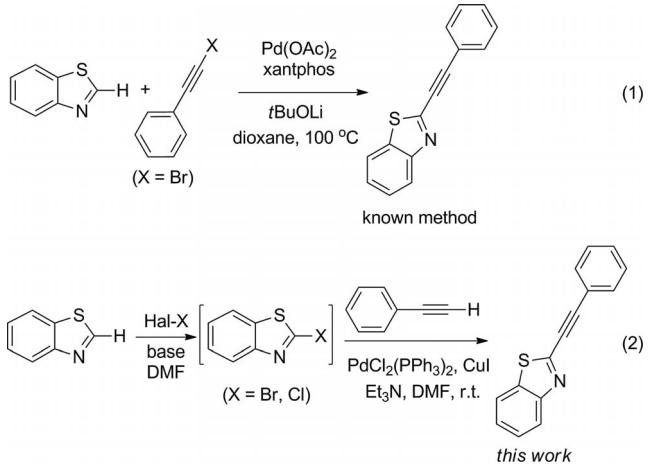
Sonogashira-type cross-couplings of functionalized heterocyclic halides with terminal alkynes were performed efficiently at room temperature. The heteroaryl halides were easily prepared from the corresponding heterocyclic compounds. The catalytic system tolerated a very broad scope of substrates; oxazoles, thiazoles, and furans participate in this type of reaction for the first time. This reaction provides an efficient method for the direct functionalization of heterocycles.

Introduction

Substituted alkynes are recurring units in numerous natural products, bioactive molecules, and organic materials,[1] and they are also versatile synthetic intermediates.[2] Among them, alkynyl-substituted azoles have gained much attention owing to both industrial and academic values.[3] Over the last several decades, Sonogashira coupling has become one of the most widely used methods for the incorporation of the alkynyl functional group into organic compounds.[4] It enables the efficient coupling of an organic halide or pseudohalide with a terminal alkyne, typically by using a Pd catalyst together with a Cu co-catalyst. Aryl bromides and aryl iodides are well known to undergo this coupling reaction in the presence of suitable catalysts. Aryl alkynes are easily prepared in this way; however, there are few examples of Sonogashira reactions to synthesize the heteroaryl alkynes. Fortunately, new synthetic methods to prepare heteroaryl alkynes have been developed recently.[5] A significant step forward in the development of the Sonogashira reaction to synthesize heteroaryl alkynes was achieved by Chang et al. who treated various alkynyl bromides with heterocyclic compounds in the presence of $Pd(OAc)_2$ (2.5 mol-%), xantphos ligand (2.8 mol-%), and *t*BuOLi (2 equiv.) at 100 °C to produce the coupling products in good yields [Scheme 1, Equation (1)].[6] Apart from this work, state-of-the-art catalysts are based on the $Pd(PPh_3)_4$/Et_3N/CuI system, which was described by Panek et al.[7] as well as by Lautens et al.,[8] and this system allowed the coupling of heteroaryl bromides with various alkynes. However, examples of efficient palladium catalyst systems for the Sonogashira coupling of heteroaryl chlorides with various alkynes are rare. In this paper, based on our interest in coupling reactions,[9] we herein report our preliminary trials and results. We describe here a high-yielding catalyst system based on $PdCl_2(PPh_3)_2$/Et_3N/CuI for the Sonogashira coupling of heteroaryl bromides and chlorides with terminal alkynes **2** [Scheme 1, Equation (2)]. It is noteworthy that these heteroaryl halides could be easily prepared from the corresponding heterocyclic compounds.[10] Furthermore, the substrate scope of this reaction is very broad, and heterocycles such as oxazoles, thiazoles, and furans are, for the first time, shown to participate in this type of coupling reaction.



Scheme 1. Synthesis of 2-(2-phenylethynyl)benzo[*d*]thiazoles by different approaches.

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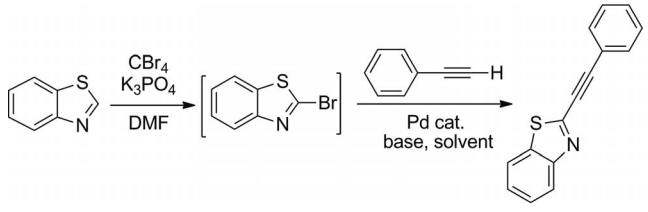
Results and Discussion

2-Bromobenzothiazole could be synthesized from benzothiazole in one step in 82% yield.[10] Thus, initial studies were carried out by treating 2-bromobenzothiazole with phenylacetylene. In our initial screening of the reaction, two catalytic systems were examined[11] (Table 1, entries 1 and 2), and the $PdCl_2(PPh_3)_2$/CuI system gave better results than $PdCl_2(PCy_3)_2$ alone (Table 1, entry 2). The effects of different solvents were then studied (Table 1, entries 3–5). The results show that dimethylformamide (DMF) is well suited for this reaction. Further experiments proved that the yield of the product could reach 99% in less than 4 h. Another control experiment was performed in the absence of CuI, and the corresponding product was obtained in 67% yield (Table 1, entry 6). Obviously, CuI in combination with $PdCl_2(PPh_3)_2$ led to an enhancement in the catalytic efficiency. However, when the copper loading was reduced to 6 mol-%, a decrease in the yield of the desired product was observed after increasing the reaction time (Table 1, entry 7). Furthermore, to our delight, when we reduced both $PdCl_2(PPh_3)_2$ to 2 mol-% and CuI to 7 mol-%, we achieved a yield of 99% after 11 h at room temperature (Table 1, entry 8), and these conditions were deemed optimal.

Table 1. Screening of the catalytic conditions in the coupling of 2-bromobenzo[*d*]thiazole with phenylacetylene.[a]

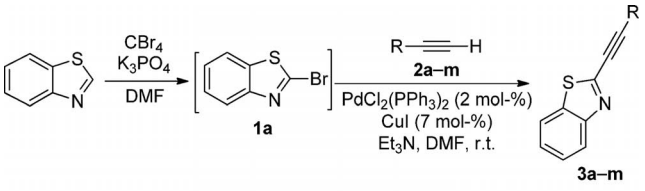


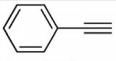
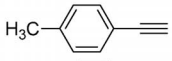
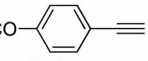
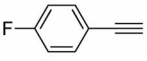
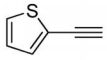
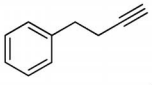
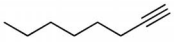
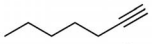
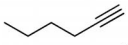
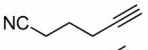
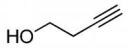
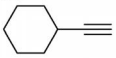
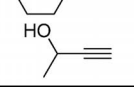
Entry	Pd. cat. (mol-%)	Base	Solvent	*T* [°C] /*t* [h]	Yield [%][b]
1	$PdCl_2(PCy_3)_2$ (3)	Cs_2CO_3	DMSO	120/24	trace
2	$PdCl_2(PPh_3)_2$ (3)/CuI (10)	Pr_2NH	DMF	120/24	62
3	$PdCl_2(PPh_3)_2$ (3)/CuI (10)	Et_3N	THF	r.t./10	85
4	$PdCl_2(PPh_3)_2$ (3)/CuI (10)	Et_3N	dioxane	r.t./10	73
5	$PdCl_2(PPh_3)_2$ (3)/CuI (10)	Et_3N	DMF	r.t./4	>99
6	$PdCl_2(PPh_3)_2$ (3)	Et_3N	DMF	r.t./43	67
7	$PdCl_2(PPh_3)_2$ (3)/CuI (6)	Et_3N	DMF	r.t./24	95
8	$PdCl_2$ $(PPh_3)_2$ (2)/CuI (7)	Et_3N	DMF	r.t./11	>99

[a] Reaction conditions: 2-bromobenzo[*d*]thiazole (0.2 mmol), phenylacetylene (0.4 mmol), base (0.4 mmol), solvent (1.5 mL), Ar. [b] Isolated yield (based on 2-bromobenzo[*d*]thiazole).

With the optimized protocol in hand, the scope of the coupling was investigated. Coupling reactions of 2-bromobenzothiazole with both aromatic and aliphatic alkynes furnished the desired products in 76–99% isolated yields (Table 2). We monitored the remaining amount of 2-bromobenzothiazole by TLC to control the reaction time at room temperature. For aryl alkynes with electron-donating groups, the reaction time could be reduced to 4–5 h, and the coupling products were obtained in yields of 87 and 76% under the standard conditions (Table 2, entries 2 and 3). Unfortunately, we observed the formation of the homocoupling dimer of 4-methoxyphenylacetylene, which led to a decrease in the yield of the desired product. Relative to aromatic alkynes with electron-donating groups, an aromatic alkyne with an electron-withdrawing group needed a longer reaction time, and the yield of the product was 90% (Table 2, entry 4). Interestingly, a 99% yield could be obtained for 2-ethynylthiophene (Table 2, entry 5). Furthermore, the Sonogashira coupling reaction of 2-bromobenzothiazole with aliphatic alkynes also gave good to excellent results of 80–95%, whereas the reaction time should be extended to complete the coupling (Table 2, entries 6–13). Therefore, one can conclude that Sonogashira coupling reactions of aromatic alkynes are more favorable than those of aliphatic alkynes.

Table 2. Scope of the Pd-catalyzed couplings of various terminal alkynes with 2-bromobenzo[*d*]thiazole.[a]

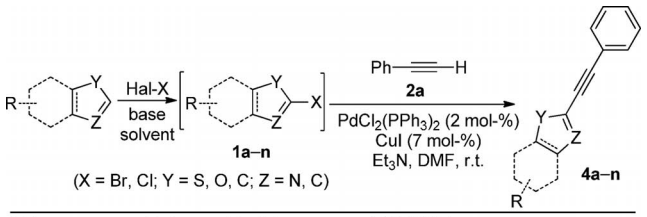


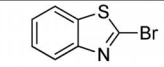
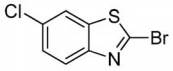
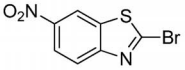
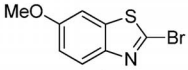
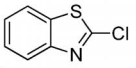
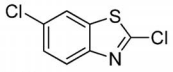
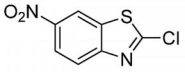
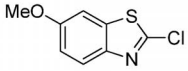
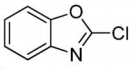
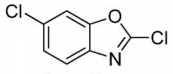
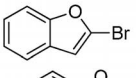
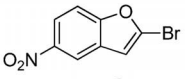
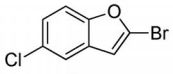
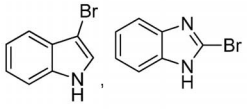
Entry	RC≡CH	*t* [h]	Product, yield [%][b]
1		12	**3a**, >99
2		5	**3b**, 87
3		4	**3c**, 76
4		26	**3d**, 90
5		9	**3e**, >99
6		45	**3f**, 85
7		45	**3g**, 82
8		45	**3h**, 80
9		90	**3i**, 93
10		20	**3j**, 93
11		27	**3k**, 95
12		90	**3l**, 80
13		72	**3m**, 90

[a] Reaction conditions: 2-bromobenzo[*d*]thiazole (0.2 mmol), alkyne (0.4 mmol), Et_3N (0.4 mmol), DMF (1.5 mL), r.t., Ar. [b] Isolated yield (based on 2-bromobenzo[*d*]thiazole, average of two runs).

To extend the range of substrates further, we intended to apply our method to a wide range of different halides, such as heteroaryl bromides and chlorides.[10] Table 3 shows the experimental results performed under standard conditions. 6-Substituted heteroaryl halides with electron-withdrawing groups needed shorter reaction times than heteroaryl halides with electron-donating groups, but both afforded good to excellent yields of the products (80–99%; Table 3, entries 1–8). However, when 2-chlorobenzoxazoles were examined as substrates, a longer reaction time and a higher temperature was needed, and decreased yields of the desired products were observed (44, 40%; Table 3, entries 9 and 10). Also, 2-bromobenzofurans proceed smoothly by using this sequence (Table 3, entries 11–13). X-ray structural analysis proved the structure of **4g** (Figure 1). 5-Bromo-2-bromobenzofuran was then involved to test the regioselectivity of the reaction, and the bromine in the 5-position remained intact under these gentle conditions, which demonstrates that our catalytic system is regiospecific for substrates of this type. Furthermore, 2-bromothiazole was transformed into the desired product in 77% yield at 40 °C (Table 3, entry 14). From an experimental point of view, it is found that the coupling products of heteroaryl bromides were obtained in good yields within shorter reaction times, and the coupling reactions of heteroaryl chlorides were conducted with moderate results because of their poor reactivity, which can be attributed to the greater strength of the C–Cl bond.[12] Finally, the couplings of bromides of indole and benzo[*d*]-imidazole were fruitless, and many sides reactions occurred, which was indicated by TLC. This may be attributed to the influence of the secondary amine from the heterocyclic molecules. Further research is underway.

Table 3. Scope of the Pd-catalyzed couplings of various heteroaryl halides with phenylacetylene.[a]



Entry	Heteroaryl halide	*T* [°C]/*t* [h]	Product, yield [%][b]
1		r.t./12	**4a**, >99
2		r.t./24	**4b**, 99
3		r.t./4	**4c**, 91
4		r.t./33	**4d**, 80
5		r.t./40	**4a**, >99
6		r.t./30	**4b**, 91
7		r.t./26	**4c**, 81
8		r.t./33	**4d**, 87
9		40/24	**4e**, 44
10		40/72	**4f**, 40
11		r.t./6.5	**4g**, 50
12		r.t./4	**4h**, 98
13		r.t./4	**4i**, 87
14		40/24	**4j**, 77
15		40/24	(intractable)

[a] Reaction conditions: Heteroaryl halide (0.2 mmol), phenylacetylene (0.4 mmol), Et_3N (0.4 mmol), DMF (1.5 mL), r.t. to 40 °C, Ar. [b] Isolated yield (based on heteroaryl halide, average of two runs).

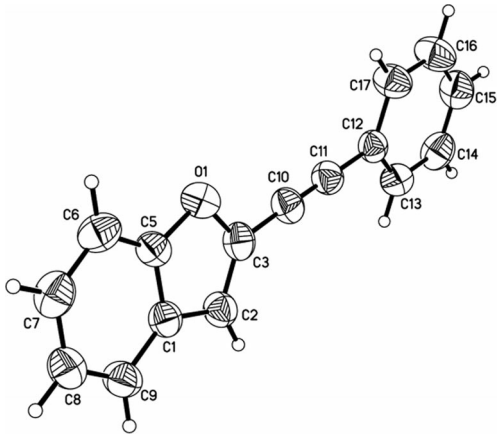
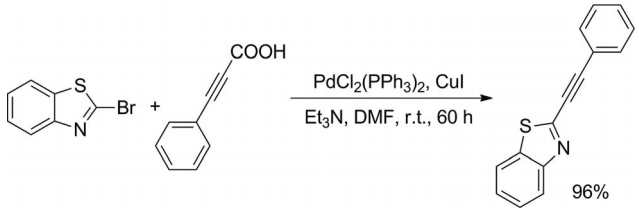


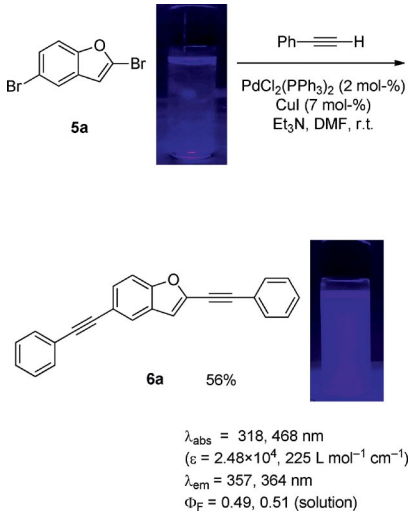
Figure 1. X-ray crystal structure of product **4g**.

To test the reactivity of 2-bromobenzothiazole further, an experiment involving the reaction of 2-bromobenzothiazole with phenylpropiolic acid was carried out. As shown in Scheme 2, under the optimized conditions, the desired heteroaryl alkyne was obtained in 96% yield, which broadened the scope of our method.



Scheme 2. Pd-catalyzed coupling of **1a** with phenylpropiolic acid.

In addition, when using 2,5-dibromobenzofuran as a substrate, to our surprise, another undesired product could be obtained after a prolonged reaction time. As shown in Scheme 3, we finally achieved a 56% yield of **6a**. Interestingly, this compounds showed strong blue fluorescence (357, 364 nm) in solution (Φ_F = 0.49, 0.51). It cannot only be used as a potential fluorescent material but also apply to industrial production.



Scheme 3. The fluorescence of 2,5-bis(2-phenylethynyl)benzofuran.

Conclusions

In summary, we have developed an effective and promising Pd/Cu co-catalyzed system for the coupling of heteroaryl halides, including heteroaryl bromides and chlorides, with various alkynes. Furthermore, these heteroaryl halides were easily prepared from the corresponding heterocyclic compounds. Notably, for the first time, it was shown that the substrate scope of the reaction was very broad and included oxazoles, thiazoles, and furans, which offers an important advance in the direct functionalization of heterocycles. Practical application of the products is underway in our laboratory. Thus, these products are potentially useful in the synthesis of biologically active molecules. Further investigations in this direction are in progress.

Experimental Section

General Procedure for Pd-Catalyzed Coupling between Heteroaryl Halides and Terminal Alkynes: A mixture of the heteroaryl halide (0.2 mmol), terminal alkyne (0.4 mmol), Et_3N (0.4 mmol), $PdCl_2(PPh_3)_2$ (2 mol-%), CuI (7 mol-%), and DMF (1.5 mL) in a Schlenk tube was stirred under an argon atmosphere at room temperature to 40 °C for the desired time until complete consumption of the starting material (monitored by TLC). The mixture was then poured into ethyl acetate, washed with water, extracted with ethyl acetate, dried with anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography (petroleum ether or petroleum ether/ethyl acetate) to afford the corresponding coupling products.

Supporting Information (see footnote on the first page of this article): Experimental details, fluorescence experiments, characterization data of the products, and copies of the HRMS and NMR spectra for the products.

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