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Convenient synthesis of 2-alkynylbenzazoles through Sonogashira cross-coupling reaction between thioethers and terminal alkynes

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ABSTRACT

We describe herein the synthesis of 2-alkynylbenzoxazole and 2-alkynylbenzothiazole derivatives through the Sonogashira cross-coupling reaction of the corresponding thioethers and terminal alkynes under aerobic conditions, using CuI and Pd(dppf)Cl_2 as catalysts. The synthetic methodology allows the convenient cross-coupling of heteroaromatic substrates with a wide variety of aromatic and aliphatic alkynes, in moderate to good yields. The behavior of mercapto benzoxazoles and benzothiazoles were also investigated in the desulfitative Sonogashira cross-coupling reaction. It is noteworthy that the reaction occurred better under aerobic conditions rather than an inert atmosphere, although with increased amounts of the diyne side-product.

Introduction

Transition metal-catalyzed carbon–carbon cross-coupling reactions have revolutionized the art and practice of organic synthesis in the last two decades.[1] The development of generalized mild reaction conditions, high functional group tolerance and broad availability of the starting materials have contributed to the growing success of palladium-catalyzed carbon–carbon bond formation methods.[2] The cross-coupling reactions usually occur between organometallic or boronic reagents and organic halides (mostly iodides and bromides, rarely chlorides) or pseudohalides (e.g., triflates) as electrophilic partners.[1b] The variety of the electrophilic partner has been extensively screened and, recently, protocols involving sulfur compounds as electrophiles were reported as convenient alternatives to halides.[3] Notably, this holds true in the cross-coupling of heteroaromatics which has not been developed to its full extent due to the limited availability of the corresponding heteroaromatic halides. Heteroaryl thioethers have been less explored as substrates in coupling reactions (i.e., Suzuki[4] or Stille[5]) although they are stable, readily accessible and exhibit good compatibility with various transformations. Due to the continued interest in developing new organic molecules with biological relevance[6] and functional materials containing ethynylene-bridged π-conjugated systems,[7] the Sonogashira reaction has proved to be an excellent tool for the synthesis of alkyne heteroaromatic motifs. The literature reported on the Sonogashira reaction has witnessed tremendous development in terms of the examined electrophilic substrates, catalysts, solvents and bases, demonstrating its utility in various fields of chemistry.[8] We therefore focused our attention on extending the scope of the Sonogashira cross-coupling by using heteroaromatic methylthioethers as electrophilic partners, which have been less explored in alkynylation procedures via Sonogashira conditions.[3,9] In this work we report a new and convenient method for the preparation of 2-alkynyl benzoxazoles and 2-alkynyl benzothiazoles (Fig. 1) through the aerobic, copper(I)-promoted, palladium-catalyzed desulfitative Sonogashira coupling of (2-methylthio)benzazoles with terminal alkynes. Interest in the synthesis of compounds containing the benzoxazole[10a–c] and benzothiazole[10d,e] moieties has lately increased due to their presence in recently discovered biologically active molecules, which act as natural antibiotics, modulators for various receptors and antitumor compounds. This is also apparent from the growing number of publications reporting the direct oxidative coupling in position 2 of such benzazoles using various reaction conditions.[11]

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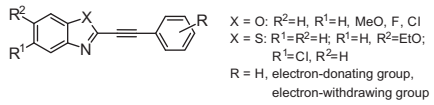


Figure 1. Structure of the synthesized compounds.

Results and discussions

To the best of our knowledge, use of 2-(thioether)benzoxazoles or 2-mercaptobenzoxazole derivatives in the Sonogashira coupling reaction has not been reported.[11,12] Thus, our work began with an exploration of the reaction conditions for the model coupling of (2-methylthio)benzoxazole **1a**[13] with phenylacetylene **2a**, in presence of copper(I) iodide, using $Pd(dppf)Cl_2$ as the palladium source (Table 1), which was in line with previous reports using this catalytic system with various heteroaromatics.[9b] Solvents, bases, alkyne equivalents as well as temperature and reaction times were varied in order to find the optimum reaction conditions for the preparation of compound **3a** (Table 1). Since most classical Sonogashira conditions use polar solvents,[8a,9b,c] we initially utilized THF and 1,4-dioxane, under an inert atmosphere (entries 1 and 2), with very poor results (traces of **3a** using THF and 32% yield using 1,4-dioxane). The coupling reaction was found to provide better yields (47%) when toluene was used (entry 5). Performing the same reactions under aerobic conditions (entries 3 and 6) significantly increased the yield of **3a**. This result suggested that oxygen was not innocent in this reaction. A possible role could be to preserve the effective oxidation state of the catalyst in order to enhance the reaction yield.[14] Further studies to elucidate this aspect are currently in progress.

The highest yields for the coupling reaction were obtained after 24 h in refluxing 1,4-dioxane or toluene (Table 1, entries 4 and 7). The Sonogashira coupling reaction was found to be influenced by the base used,[15] and among the investigated bases, triethylamine led to the best results for this particular substrate. In addition, the amount of the alkyne was screened, which showed that three equivalents of alkyne in 1,4-dioxane or toluene gave similar results (Table 1, entries 4 and 7).

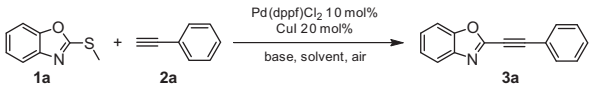
Expectedly, all reactions gave the homocoupling side-product, 1,4-diphenyl-1,3-butadiyne, as a combined result of the aerobic atmosphere,[16] and the excess alkyne. A larger amount of the acetylene was thus required for effective cross-coupling to occur.

Having established the optimum reaction conditions (Table 1, entry 7), we further investigated the scope of our reaction using a wide variety of substituted acetylenes (Table 2). Reasonable to good yields were obtained in each case and varied according to the nature of the alkyne partner. In the case of aryl acetylenes with electron-donating substituents (**2b**–**g**), the yields differed according to the position of the substituent on the benzene ring. The following pattern was observed: *para*-substituted aryl acetylenes gave the lowest yields (60% for **3b** and 52% for **3e**) followed by the *meta*-substituted (73% for **3c** and 62% for **3f**) and *ortho*-substituted (92% for **3d** and 90% for **3g**) arylalkynes. Excellent yields were obtained for compounds **3d** and **3g**, and was consistent with studies performed in classical Sonogashira cross-coupling reactions[17] which showed that bulky substituents in the *ortho* position of the aryl ring of the alkyne enhance the cross-coupling reaction rate. When aryl acetylenes with electron-withdrawing substituents were used, the overall yields of the cross-coupling reaction were significantly lower than those involving electron-rich alkynes (Table 2). However, using this protocol we were able to prepare new ethylene bridged benzoxazole compounds containing electron-withdrawing-substituted aryl rings (see ESI for the spectra of new compounds). In this series, it was also noted that for the *para*-substituted acetylenes, fluorine-substituted coupling product **3h** was obtained in higher yields than the cyano-substituted product **3j** and the trifluoromethyl derivative **3k**, respectively. As far as the *meta*-substituted acetylenes were concerned, we observed that the yields of the resultant products **3i** and **3l** were lower than the corresponding *para*-substituted arylalkynes (**3i** vs **3h**), which was in contrast to the electron-donating substituted arylalkynes (**3c** vs **3b** and **3f** vs **3e**). Use of aliphatic alkynes in the cross-coupling reaction[18] led to very good yields using only 1.5 equiv of the alkyne (Table 2, entries 12 and 13).

An attempt (Scheme 1) to selectively perform the cross-coupling reaction of compound **1h** with phenylacetylene via the classical Sonogashira protocol (under inert atmosphere at room temperature) surprisingly yielded the 2-alkynylated product **5**, with preservation of the bromine substituent (see ESI). The main side-product was found to be diphenyl-1,3-butadiyne. Although the obtained yield was modest, one can note that by performing the reaction at room temperature, 2-alkynylated-5-bromobenzoxazole could selectively be obtained, thus, allowing the possibility to further increase the molecular diversity through reactions of the C–Br bond.

We further investigated the coupling reaction of 2-mercaptobenzoxazole with alkynes, beginning with the reaction between 2-mercaptobenzoxazole **6a** and alkyne **2a** (Table 3). Attempts to utilize the reaction conditions reported by Tatibouet and co-workers[19] (Table 3, entry 1) gave the coupling product **3a** in

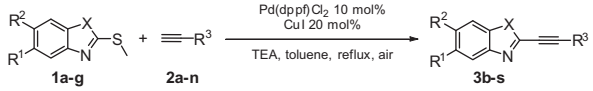
Table 1
Optimization of the cross-coupling reaction conditions between 2-(methylthio)benzoxazole **1a** and phenylacetylene **2a**



Entry	Solvent	Temp (°C)	Equivalents of **2a**	Co-catalyst	Base	Reaction time (h)	Yields (%)
1[a]	THF	66	2	CuI	TEA	6	Traces
2[a]	1,4-Dioxane	100	2	CuI	TEA	6	32
3	1,4-Dioxane	100	2	CuI	TEA	6	52
4	1,4-Dioxane	100	3	CuI	TEA	24	69
5[a]	Toluene	110	2	CuI	TEA	6	47
6	Toluene	110	2	CuI	TEA	6	67
7	Toluene	110	3	CuI	TEA	24	72
8	Toluene	110	3.5	CuI	TEA	24	70
9	DMF	130	3	CuI	TEA	24	Traces
10	DMF	130	2	CuI	Cs_2CO_3	24	Traces
11	—	106	2	—	Piperidine	24	Traces

[a] Reaction performed under Ar.

Table 2
Cross-coupling reactions between methylthioethers **1a–g** and phenylacetylenes **2a–n**

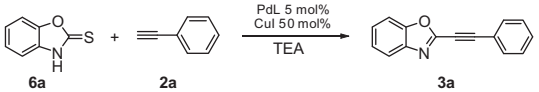


1a-g 2a-n 3b-s

Entry	Reactant	X	R^1	R^2	Alkyne	R^3	Alkyne equiv	Reaction time (h)	Product[a]	Yields[b] (%)
1	**1a**	O	H	H	**2b**	4-Me-C_6H_4	1.5/2/3	24/24/24	**3b**[11a]	57/59/60
2	**1a**	O	H	H	**2c**	3-Me-C_6H_4	1.5/2/3	24/48/24	**3c**[11e]	30/57/73
3	**1a**	O	H	H	**2d**	2-Me-C_6H_4	1.5/3	24/24	**3d**[11c]	27/92
4	**1a**	O	H	H	**2e**	4-MeO-C_6H_4	2/3	24/24	**3e**[11a]	47/52
5	**1a**	O	H	H	**2f**	3-MeO-C_6H_4	3	24	**3f**	62
6	**1a**	O	H	H	**2g**	2-MeO-C_6H_4	3	24	**3g**	90
7	**1a**	O	H	H	**2h**	4-F-C_6H_4	3	24	**3h**[11f]	56
8	**1a**	O	H	H	**2i**	3-F-C_6H_4	3	24	**3i**	45
9	**1a**	O	H	H	**2j**	4-CN-C_6H_4	1.5/2/3	36/36/24	**3j**	14/17/29
10	**1a**	O	H	H	**2k**	4-CF_3-C_6H_4	3	24	**3k**[11c]	19
11	**1a**	O	H	H	**2l**	3-Cl-C_6H_4	1.5/2/3	36/36/24	**3l**	48/52/54
12	**1a**	O	H	H	**2m**	C_5H_{11}	1.5	24	**3m**[11e]	62
13	**1a**	O	H	H	**2n**	C_6H_{11}	1.5	24	**3n**	77
14	**1b**	O	MeO	H	**2a**	C_6H_5	3	24	**3o**[11d]	75
15	**1c**	O	F	H	**2a**	C_6H_5	3	24	**3p**	67
16	**1d**	O	Cl	H	**2a**	C_6H_5	3	24	—[c]	—
17	**1e**	S	H	H	**2a**	C_6H_5	3	24	**3q**[12]	53
18	**1f**	S	H	EtO	**2a**	C_6H_5	3	24	**3r**	60
19	**1g**	S	Cl	H	**2a**	C_6H_5	3	24	**3s**[12]	40

[a] The spectral analysis of the reported compounds were identical with those described in the indicated references.
[b] Yield after purification by flash column chromatography.
[c] Degradation indicated by TLC.

Table 3
Optimization of the cross-coupling reaction conditions between 2-mercaptobenzoxazole 6a and phenylacetylene **2a**



6a 2a 3a

Entry	Ligand (L)	Additive (equiv)	Solvent/temp (°C)	Atmosphere	Reaction time (h)	Alkyne equiv	Yield[a] (%)
1	$(PPh_3)_4$	CuTC (0.1)	DMF/130	Ar	2	1.5	15
2	$(PPh_3)_4$	CuTC (3)	1,4-Dioxane/100	Ar	1	1.2	Traces
3	$(PPh_3)_4$	CuMeSal (0.5)	DMF/25	Ar	3	3	24
4	$(PPh_3)_4$	CuMeSal (1)	DMF/130	air	1	3	50
5	$(dppf)Cl_2$	CuMeSal (1)	DMF/130	air	24	3	60

[a] Yield after purification by flash column chromatography.

low yield (15%). Use of 1,4-dioxane as solvent and 3 equiv of Cu(I) thiophene-2-carboxylate (CuTC) did not furnish any product (Table 3, entry 2) and attempts to perform the reaction in toluene failed due to the low solubility of the substrate. However, replacement of catalytic CuTC with one equivalent of Cu(I)-3-methylsalycilate (CuMeSal) along with performing the reaction under air and increasing the alkyne equivalents had a positive effect (Table 3, entries 3 and 4). Finally, optimum results were obtained when $Pd(PPh_3)_4$ was replaced by $Pd(dppf)Cl_2$, yielding the desired product in 60% yield (Table 3, entry 5) (see ESI for experimental procedure).

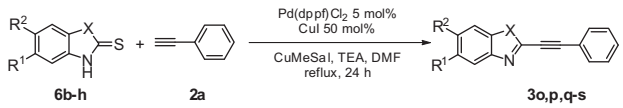
Encouraged by these results, we attempted the cross-coupling reactions of compounds **6b–e** with phenylacetylene **2a** (Table 4, entries 1–4). We observed that successful coupling was only achieved for methoxy-substituted benzoxazole **6b** (Table 4, entry 1), proceeding in modest yield (30%), while for fluorine derivative **6c** (Table 4, entry 2) only traces of the product were observed by TLC. No coupling product was detected for the chlorine and bromine derivatives **6d** and **6e** (Table 4, entries 3 and 4).

Therefore, we transformed the mercaptobenzoxazoles **6b–e** into their corresponding methylthioethers **1b–d**,**h** (see Table 2, entries 14–16 for compounds **1b–d** and Scheme 1 for compound **1h**) and performed the coupling reactions with phenylacetylene using the optimized reaction conditions. Gratifyingly, we obtained very good results for the coupling reactions of **1b** (75%, Table 2, entry 14) and **1c** (67%, Table 2, entry 15). However, for halogenated methylthiobenzoxazoles **1d** and **1h**, we observed that the chloroderivative **1d** yielded only degradation products (Table 2, entry 16), while the brominated analog **1h** gave compound **4** in 54% yield (Scheme 1). Increasing the alkyne equivalents did not improve the coupling reaction yield.

To further broaden the scope of the alkynylation procedure, we also examined the use of 2-(methylthio)benzothiazoles **1e–g** as substrates (Table 2, entries 17–19). The yields of the cross-coupling reactions were similar to their corresponding benzoxazole derivatives for compounds **3q** (53%) and **3r** (60%), while the chlorine product **3s** was obtained in 40% yield, which was higher than its benzoxazole derivative which was not formed (see ESI for the spectral analysis of the compounds).

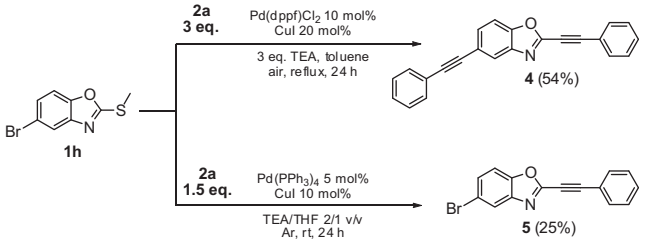
Finally, we used 2-mercaptobenzothiazoles **6f–h** (Table 4, entries 5–7) as substrates in the reaction with phenylacetylene **2a**. Very good yields were obtained for compounds **3q** (70%) and **3r** (75%) while **3s** was obtained in a lower yield (38%). We observed enhanced reactivity compared to their corresponding mercaptobenzoxazole derivatives (Table 4, entries 5 and 7 vs Table 1, entry 7 and Table 2, entry 16) as well as to their corresponding

Table 4
Cross-coupling reactions between compounds **6b–h** and phenylacetylene **2a**



Entry	Reactant	X	R^1	R^2	Alkyne equiv	Product[a]	Yield[b] (%)
1	**6b**	O	MeO	H	3	**3o** [11d]	30
2	**6c**	O	F	H	3	**3p**	Traces
3	**6d**	O	Cl	H	3	—	—
4	**6e**	O	Br	H	3	—	—
5	**6f**	S	H	H	3	**3q** [12]	70
6	**6g**	S	H	EtO	3	**3r**	75
7	**6h**	S	Cl	H	3	**3s** [12]	38

[a] The spectral analysis of the reported compounds were identical with those described in the indicated references.
[b] Yield after purification by flash column chromatography.



Scheme 1. Cross-coupling reactions between 5-bromo-2-(methylthio)benzoxazole **1h** and phenylacetylene **2a**.

benzothiazole thioethers in the case of products **3q** and **3r** (Table 4, entries 5 and 6 vs Table 2, entries 17 and 18).

Conclusions

In conclusion, we have shown that benzoxazole and benzothiazole methylthioethers can be efficiently used as electrophilic substrates in the Sonogashira reaction, enlarging, thus, the variety of alternative reagents that can be used in cross-couplings.[4,5,9] The reactions with terminal alkynes were performed using palladium and copper(I)-catalysis under aerobic conditions. The synthetic approach allowed preparation of 2-alkynyl benzoxazole derivatives containing aliphatic and substituted electron-donating and electron-withdrawing aromatic moieties in moderate to good yields. In addition, the reactions proceeded well when various benzothiazole methylthioethers, as well as mercaptobenzothiazoles were used, providing the coupling products in very good yields. Moreover, the mercaptobenzothiazoles appear to perform better than the corresponding mercaptobenzoxazoles. Our work showed that the reaction proceeded better under aerobic conditions rather than an inert atmosphere. Use of 5-bromo-2-(methylthio)benzoxazole in our aerobic coupling conditions occurred with concomitant C–Br and C–S coupling of the alkyne. Surprisingly, the C–S cross-coupling reaction occurred selectively under an inert atmosphere, at room temperature, albeit in modest yield, allowing the possibility to further functionalize the benzoxazole core using the C–Br bond and therefore, extending the scope of the reaction.

Acknowledgment

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Supplementary data

Supplementary data (experimental procedures for the cross-coupling reactions as well as ^{1}H, ^{13}C NMR and HRMS spectra of the new compounds are described) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.08.001.

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