Pd/phenanthroline-catalyzed arylation cyclization of *o*-(1-alkynyl)thioanisoles: synthesis of 3-arylated benzo[*b*]thiophenes

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ABSTRACT

The arylation cyclization of *o*-(1-alkynyl)thioanisoles with aryl iodides in the presence of catalytic amounts of [Pd(phen)₂][PF₆]₂ resulted in the efficient formation of 3-arylated benzo[*b*]thiophenes, and a range of aryl iodides with electron-donating or -withdrawing groups could be used. While this reaction proceeded in the presence of aromatic and aliphatic groups on the terminal alkynyl carbon atom, silyl and alkoxycarbonyl groups hampered the reaction. Furthermore, this method could be extended to the synthesis of 3-arylated indoles from *N,N*-dimethyl-*o*-(1-alkynyl)aniline. All these reactions proceeded smoothly via cleavage of the carbon-heteroatom bond. In addition to the desired cyclization products, the use of a *o*-(hydroxypropyl)phenylmethyl substituent on the sulfur atom afforded isochroman, which should be formed by the intramolecular attack of a hydroxy group onto the benzylic carbon atom.

Introduction

Multi-substituted benzo-fused heterocycles, such as benzo[*b*]thiophenes, exhibit a diverse range of biological activity¹ and have been applied in functional materials.² Accordingly, various efficient and selective methods for the generation of such functionalized benzo-fused heterocycles have been developed over the last decades. For the construction of benzo-fused heterocycles, π -acidic transition metal-mediated intramolecular cyclizations of 1-alkynylarenes with tethered heteroatom nucleophiles at the *o*-position proved to be very efficient.³ In the context of these cyclization reactions, Cacchi *et al.*, Larock *et al.*, and others reported that Pd-catalyzed arylation cyclizations of alkynylarenes, containing nucleophilic groups in close proximity with e.g. nitrogen and oxygen atoms, represent powerful tools for the formation of 3-arylated benzofurans and indoles (eq. 1).⁴ These reactions can be carried out using readily available *o*-alkynylarenes as starting materials in the presence of a wide variety of Pd catalysts. As these reactions are widely applicable and compatible with a broad range of functional groups, a wide variety of substituted benzo-fused heterocycles can thus be obtained. However, this method is not suitable for the synthesis of 3-arylated benzo[*b*]thiophenes, as sulfur atoms often deactivate transition metal catalysts.⁵ Therefore, a two step synthesis of 3-arylated benzo[*b*]thiophenes, including halo-cyclization of *o*-(1-alkynyl)thioanisoles and a cross-coupling reaction of 3-halogenated benzothio[*b*]phenes with metalated arenes is utilized (eq. 2).⁶ Recently, we reported that [Pd(phen)₂][PF₆]₂ is

able to mediate the direct arylation of heteroarenes with thiocarbonyl groups, even though the latter may act as a strong catalyst poison.⁷ During the course of this study, 3-arylated benzo[*b*]thiophenes were obtained in 23% yield unexpectedly from the reaction of heteroaryl-substituted *o*-(1-alkynyl)thioanisole and aryl halides under direct arylation conditions using [Pd(phen)₂][PF₆]₂ (eq. 3). This reaction proceeded via an arylation cyclization involving the cleavage of the C-S bond. We envisioned that such arylation cyclizations should represent a more efficient synthetic route to 3-arylated benzo[*b*]thiophenes compared to the corresponding halo-cyclization/cross-coupling methods, and consequently carried out further investigations. Herein, we report the first examples for a Pd/phenanthroline-catalyzed arylation cyclization of *o*-(1-alkynyl)thioanisoles and aryl iodides to afford 3-arylated benzo[*b*]thiophenes (eq. 4).

Results and Discussions

Initially, we treated *o*-(1-alkynyl)thioanisole **1a** with aryl iodide **2a** using the arylation cyclization conditions reported for *N,N*-dialkyl-*o*-(1-alkynyl)anilines^{4c,d} and *o*-(1-alkynyl)anisoles.⁸ However, these conditions did not furnish the desired product **3** (Table 1, entries 1 and 2). In contrast, the use of [Pd(phen)₂][PF₆]₂ (5 mol%) as a catalyst yielded the desired product **3aa**, which was confirmed by GC-MS, albeit in fairly low yield (entry 2). The addition of Na₂CO₃ furnished **3aa** in higher yield (entry 4), and further tests of other inorganic salts

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revealed that Cs_2CO_3 provided the best results (entry 6). Also, other Pd-catalyzed systems (e.g. Pd(0)/1,10-phenanthroline) gave poor yield (see Supporting Information).

Table 1. Arylative cyclization of *o*-(1-alkynyl)thioanisole **1a**

entry	conditions	yield ^a
1	Pd(PPh) ₂ Cl ₂ (10 mol%), <i>n</i> -Bu ₄ NI (10 mol%) CH ₃ CN, 90 °C (MW), 1 h	n.d.
2 ^b	Cu(OTf) ₂ (10 mol%), DCE, 60 °C, 10 h	n.d.
3	[Pd(phen) ₂][PF ₆] ₂ (5 mol%) DMA, 150 °C, 20 h	trace
4	[Pd(phen) ₂][PF ₆] ₂ (5 mol%) Na ₂ CO ₃ (1.1 equiv) DMA, 150 °C, 20 h	24%
5	[Pd(phen) ₂][PF ₆] ₂ (5 mol%) K ₂ CO ₃ (1.1 equiv) DMA, 150 °C, 20 h	24%
6	[Pd(phen) ₂][PF ₆] ₂ (5 mol%) Cs ₂ CO ₃ (1.1 equiv) DMA, 150 °C, 20 h	46% ^c

^a Yields determined by GC analysis using *n*-heptadecane as an internal standard; ^b Ph₂IPF₆ was used instead of I-Ar; ^c isolated yield; ^d n.d. = not detected.

Table 2. Optimization of reaction conditions

Reaction scheme showing the conversion of **1a** to **3aa** under the following conditions:

- 1-Ar 2a** (1.1 equiv)
- $[\text{Pd}(\text{phen})_2][\text{PF}_6]_2$ (5 mol%)
- Cs_2CO_3 (1.1 equiv)
- DMA, T, 20 h
- (Ar = 4- $\text{CF}_3\text{C}_6\text{H}_4$)

1a **3aa**

entry	T (°C)	yield ^a	conv.
1	150	46% ^b	100%
2	120	78% (66% ^b)	72%
3	110	33%	33%
4	90	5%	7%
5 ^c	120	60%	89%

^a Yields determined by GC analysis using *n*-heptadecane as an internal standard; ^b isolated yield; ^c *t* = 31 h.

Subsequently, we tried to optimize the reaction temperature, as starting material **1a** was completely consumed at 150 °C, but the

yield of **3aa** was only moderate (Table 2, entry 1). Decreasing the reaction temperature to 120 °C increased the yield of **3aa** to 66% (entry 2), whereas lower yields were obtained at 110 °C (entry 3) and 90 °C (entry 4). Prolonging the reaction time did not increase the yield of **3aa** (entry 5). Instead, several products including a benzothiophene were observed by GC-MS.

Scheme 1. Substrate scope of the arylation of *o*-(1-alkynyl)thioanisoles **1** and I-Ar **2**

^a Isolated yield; ^b K₂CO₃ was used instead of Cs₂CO₃; ^c relative to the amount of I-Ar.

With optimized conditions in hand, we examined the scope of this arylation with respect to *o*-(1-alkynyl)thioanisoles **1** and aryl iodides **2** (Scheme 1). We observed that the electronic properties of the aromatic rings in **2** had a strong impact on the yield of **3** (entries 1-6). For instance, reactions with **2a-d**, which contain electron-withdrawing -CF₃, -CN, -COOEt, and -NO₂ groups, afforded the arylation products **3aa-3ad** in good yield (entries 1-4). In contrast, low yields were obtained when 4-iodoanisole (**2e**) and iodobenzene (**2f**) were used (entries 5 and 6). The reaction of various *o*-(1-alkynyl)thioanisoles **1a-f** with **2a** furnished the corresponding benzo[*b*]thiophenes **3ba-3fa** in good yield, regardless of the electronic character and steric hindrance of the aromatic groups (R) attached to the alkyne

carbon atoms (entries 7-11). Substrate **1g**, which carried an alkyl group on the alkynyl carbon atom, also afforded the arylyative cyclization product **3ga** in 47% yield (entry 12). Silyl **1h** and alkoxy carbonyl groups **1i** were not compatible with these arylyative cyclization conditions, and yielded 2,3-diarylated benzo[*b*]thiophene **3ba** in 44% and 39%, respectively (entries 13 and 14).

We then turned our attention to the reaction of other nucleophilic heteroatom-containing *o*-(1-alkynyl)arenes. Initially, the arylyative cyclization of *N,N*-dimethyl-*o*-(1-alkynyl)aniline **4** proceeded smoothly to afford the corresponding 3-arylated indoles **5** in excellent yield, regardless of the electronic character of the aryl iodides (**2**), albeit that higher reaction temperatures were required (eq. 5). However, when [Pd(phen)]₂[BARF]₂ (BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) was used as a catalyst, a reaction using *o*-(1-alkynyl)anisole **6** produced merely trace amounts of 3-arylated benzofuran **7** (eq. 6).

We previously reported that [Pd(phen)₂][PF₆]₂ exhibits catalytic activity towards the C-H bond arylation of heteroarenes.⁹ Based on these reports, it became clear that the following question requires answering: does the intramolecular cyclization of *o*-(1-alkynyl)thioanisoles **1** initially generates a 3-unsubstituted benzo[*b*]thiophene, which is subsequently transformed into 3-arylated benzo[*b*]thiophene **3** via C-H bond arylation. When the preformed 3-unsubstituted benzo[*b*]thiophene **8** was treated with aryl iodide **2a** under arylyative cyclization conditions, 3-arylated benzo[*b*]thiophene **3da** was obtained (eq. 7). However, the yield was substantially lower than in the reaction with the corresponding alkyne **1d** (cf. Scheme 1, entry 9). Furthermore, the reaction of *o*-(1-alkynyl)thioanisoles **1** in the absence of aryl iodides **2** under arylyative cyclization conditions did not proceed at all. These results indicate that the present reaction should be a tandem, rather than a one-pot reaction.

In order to gain insight into the reaction mechanism of the cleavage of the C-S bond during the arylyative cyclization of **1**, further examinations were carried out. For similar transition metal-catalyzed intramolecular cyclizations of *o*-(1-alkynyl)arenes, usually an S_N2-type cleavage of the carbon-heteroatom bond is proposed.¹⁰ Alternatively, the involvement of radical species is conceivable.¹¹ However, the addition of radical inhibitors such as Galvinoxyl, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), or dibutylhydroxytoluene (BHT) did not hamper the arylyative cyclization (see SI).

In order to capture the substituents eliminated from the sulfur atom, we prepared a substrate with a bulky substituent on the

sulfur atom, and treated it with aryl iodide **2a** under identical cyclization conditions. Using (*o*-alkynylphenyl)sulfide **1j** as a substrate furnished, in addition to the arylyative cyclization product **3aa**, benzaldehyde (**8**) in 7% yield, even though the mass balance of the reaction was low (eq. 8). The low yield of the products derived from the benzyl group on the sulfur atom may be due to several follow-up reactions of the initially formed products. To efficiently trap the substituents of the sulfur atom, we envisioned an approach, in which the substituents within the starting material trap themselves. Accordingly, we carried out the [Pd(phen)₂][PF₆]₂-catalyzed reaction between **1k** and **2a** (eq. 9). In this case, the intramolecular S_N2 cyclization of the substituent on the sulfur atom occurred readily and generated isochroman (**9**) in 38% yield in addition to **3ka** (66%). On the basis of these results, the cleavage of the carbon-sulfur bonds in a catalytic cycle may be suggested to involve ionic processes. Additionally, catalytic cycles involving Pd(II) and Pd(IV) species appears to be involved.

In conclusion, we developed an arylyative cyclization between *o*-(1-alkynyl)thioanisoles **1** and aryl iodides **2**, involving a demethylation and subsequent coupling reaction with aryl halides. To the best of our knowledge, this study presents the first examples of arylyative cyclizations via the cleavage of the C-S bonds in *o*-(1-alkynyl)thioanisoles **1**. The addition of inorganic salts such as Cs₂CO₃ was essential for this arylyative cyclization, although its role in the reaction still remains to be ascertained. Nevertheless, a range of aromatic substituents could be incorporated into the products **3**. Further studies on the use of [Pd(phen)₂][PF₆]₂ as an arylyative cyclization catalyst for other substrates such as alkynyl sulfides and alkenes are in currently in progress in our laboratories.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at XX.

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