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Advanced Synthesis & Catalysis

Palladium(0)-catalyzed Domino C–N Coupling/Hydroamination/C–H Arylation: Efficient Synthesis of Benzothieno[2′,3′:4,5]pyrrolo[1,2-*f*]phenanthridines

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Abstract: Two new and efficient routes to benzothieno[2′,3′:4,5]pyrrolo[1,2-*f*]phenanthridines have been developed. Alkynylated benzothiophenes reacted with various anilines to the target compounds in a domino reaction consisting of a C–N coupling-, hydroamination- followed by a final, ring-closing C–H arylation step. Products were isolated in moderate to good yields.

Keywords: heterocycles; palladium; cyclization; homogeneous catalysis; domino reaction

Introduction

Phenanthridine is a tricyclic heterocycle which has received increasing attention in medicinal science. Previously, it has been explored to be incorporated in the chemical structure of sanguinarine[1] (Figure 1) in *Sanguinaria Canadensis*. Further medicinal studies related to sanguinarine have revealed its potential for the treatment of cancer.[2] Given its medicinal importance, synthetic chemists were devoted to efficient syntheses of this skeleton.[3] Consequently, a number of further phenanthridine derivatives has been discovered with promising biological properties, for example, compound NK109 with antitumor activity (Figure 1).[4] Beyond medicinal applications, phenanthridine possesses great potential to be employed in material science, for example as fluorescent dyes.[5] In order to explore even more promising candidates, synthetic chemists have recently attempted to establish the preparation of phenanthridine-fused heterocycles including coumarin, pyrrole, purine, indole, imidazole, benzoimidazole and quinazoline (cf. Figure 1).[6,7]

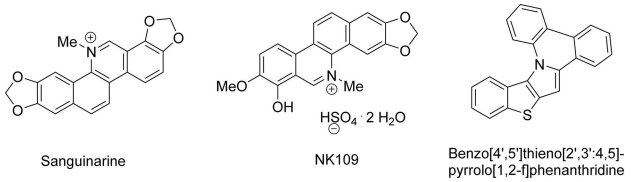


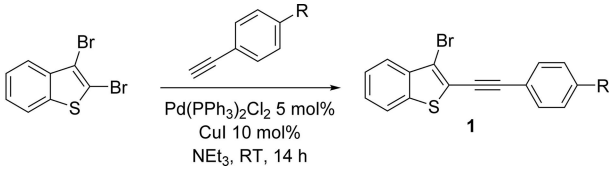
Figure 1. Relevant phenanthridine- and benzothiophene-derivatives.

Despite a wide range of synthetically available polycycles of phenanthridine fused with *O*- and *N*-heterocycles, those fused with S-heterocycles have still remained thus far unexplored. Their syntheses have been considered to be difficult and tedious. Fortunately, with the development of innovative palladium–catalyzed cross–coupling reactions, new C–C and C–N bonds can be created in more elegant and atom-economic fashion. Utilizing palladium catalysts, we have synthesized several complex fused phenanthridines from 1,2-dihalobenzene and 2,3-dihalopyridine by sequential regioselective Sonogashira and domino C–N coupling/hydroamination/C–H arylation.[8,9] These results have tempted us to undertake a further investigation of the synthesis of benzothieno [2′,3′:4,5]pyrrolo-[1,2-*f*]phenanthridines from 2,3-dibromobenzothiophene.

Results and Discussion

At first, we attempted to obtain 3-bromo-2-(arylethynyl)benzo[*b*]thiophenes **1a–c** as precursors for the domino C–N coupling/hydroamination/C–H arylation. These compounds were synthesized by applying site–selective Sonogashira coupling of 2,3-dibromobenzothiophene with corresponding arylacetylenes in high yields using previously reported reaction conditions (Table 1).[10]

Table 1. Synthesis of 3-bromo-2-(arylethynyl)benzo[*b*]thiophenes **1a–c.**

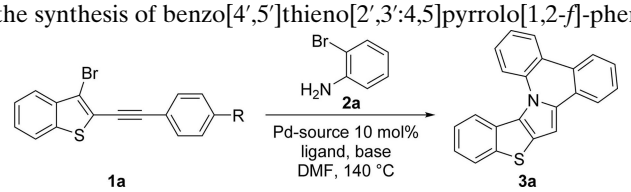


R	1	Yield[a]
H	**1a**	80%
–Me	**1b**	85%
–OMe	**1c**	87%

[a] Isolated yield

Next, we optimized the domino C–N coupling/hydroamination/C–H arylation reaction of 3-bromo-2-(phenylethynyl)benzo[*b*]thiophene (**1a**) and 2-bromoaniline (**2a**). Initially, our previously reported conditions for the synthesis of indolo[1,2-*f*]phenanthridines and azaindolo[1,2-*f*]phenanthridines were applied (Entry 1–2, Table 2).[8] Unfortunately, these two conditions led to the formation of the corresponding product in only 30% yield. Subsequently, we tested other monodentate (Entry 3–7, Table 2) and bidentate ligands (Entry 8–10, Table 2) in the presence of the palladium source $Pd(OAc)_2$. We found that the monodentate ligand $PtBu_3{\cdot}HBF_4$ gave rise to the formation of the desired product **3a** in highest yield (65%, Entry 10, Table 2). Afterwards, we checked the robustness of these reaction conditions by varying the palladium source, base, solvent and temperature. From the experimental results, it became obvious that nearly no product was formed by employing Pd $(PPh_3)_4$ instead of $Pd(OAc)_2$ (Entry 11, Table 2) or by using other bases (Entry 13–14, Table 2). On the other hand, raising the reaction temperature to more than 140 °C did not improve the reaction while reducing the temperature to 120 °C led to sluggish conversion to the desired product (Entry 15, 16, Table 2) and uncyclized product **4** was observed as a major product

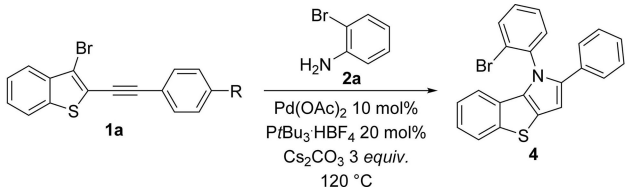
Table 2. Optimization study for the synthesis of benzo[4′,5′]thieno[2′,3′:4,5]pyrrolo[1,2-*f*]-phenanthridine 3a.



Entry	Pd-source	Ligand	Base	Yield[a]
1	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	30%
2	$Pd(PPh_3)_4$	Xantphos	Cs_2CO_3	trace
3	$Pd(OAc)_2$	dppf	Cs_2CO_3	35%
4	$Pd(OAc)_2$	dppe	Cs_2CO_3	42%
5	$Pd(OAc)_2$	XPhos	Cs_2CO_3	38%
6	$Pd(OAc)_2$	DavePhos	Cs_2CO_3	40%
7	$Pd(OAc)_2$	(*S*)-BINAP	Cs_2CO_3	34%
8	$Pd(OAc)_2$	SPhos	Cs_2CO_3	30%
9	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	30%
10	**$Pd(OAc)_2$**	**$PtBu_3{\cdot}HBF_4$**	**Cs_2CO_3**	**65%**
11	$Pd(PPh_3)_4$	$PtBu_3{\cdot}HBF_4$	Cs_2CO_3	trace
12	Pd_2dba_3	$PtBu_3{\cdot}HBF_4$	Cs_2CO_3	55%
13	$Pd(OAc)_2$	$PtBu_3{\cdot}HBF_4$	K_2CO_3	trace
14	$Pd(OAc)_2$	$PtBu_3{\cdot}HBF_4$	KO*t*Bu	trace
15[b]	$Pd(OAc)_2$	$PtBu_3{\cdot}HBF_4$	Cs_2CO_3	60%
16[c]	$Pd(OAc)_2$	$PtBu_3{\cdot}HBF_4$	Cs_2CO_3	trace

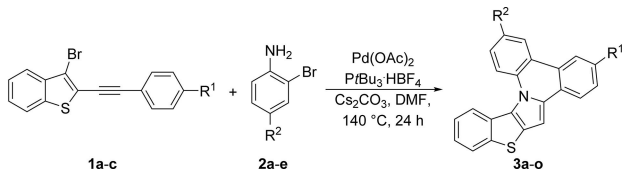
Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), Pd-source 10 mol%, ligand (0.02 mmol for monodentate ligands and 0.01 mmol for bidentate ligands), base (0.3 mmol), DMF (3 ml), 140 °C, 24 h;
[a] Isolated yield;
[b] reaction was carried out at 160 °C;
[c] reaction was carried out at 120 °C

(detected by GC/MS) (Scheme 1). This means that a temperature of 140 °C is essential for the final C–H arylation step. Interestingly, these conditions involve identical catalysts, base and solvent compared to those used in the synthesis of 1*H*-benzo[4,5]thieno[3,2-*b*] pyrrole in our previous report, despite at a higher temperature (140 versus 105 °C).[10]



Scheme 1. Formation of uncyclized intermediate **4.**

Table 3. Synthesis of benzothieno[2′,3′:4,5]pyrrolo[1,2-*f*]phenanthridines **3a–o.**

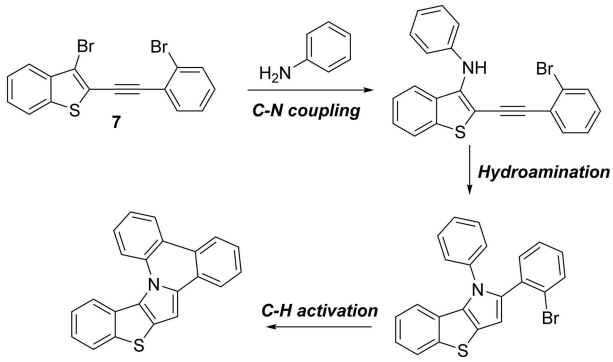


Entry	R^1	R^2	**3**	Yield (%)[a]
1	H	H	**a**	65
2	H	Me	**b**	68
3	H	Cl	**c**	58
4	H	F	**d**	60
5	H	*i*Pr	**e**	70
6	Me	H	**f**	55
7	Me	Me	**g**	62
8	Me	F	**h**	57
9	Me	Cl	**i**	58
10	Me	*i*Pr	**j**	75
11	OMe	Me	**k**	77
12	OMe	*i*Pr	**l**	80
13	OMe	Cl	**m**	66
14	OMe	F	**n**	60
15	OMe	H	**o**	58

Reaction conditions: **1** (0.3 mmol), **2** (0.38 mmol), $Pd(OAc)_2$ (0.03 mmol), $PtBu_3{\cdot}HBF_4$ (0.06 mmol), Cs_2CO_3 (0.9 mmol), DMF (4.0 mL), 140 °C, 24 h.
[a] Isolated yield.

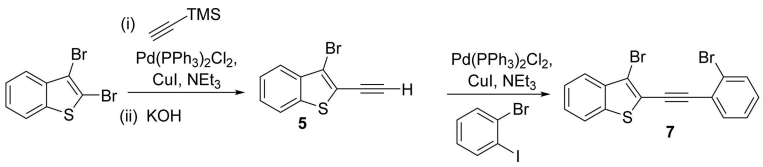
Applying the above optimized conditions in the reaction of 3-bromo-2-(arylethynyl)benzo[*b*]-thiophenes **1a–c** with 2-bromoaryl amines **2a–c**, corresponding benzothieno[2′,3′:4,5]pyrrolo-[1,2-*f*]phenanthridines **3a–o** were afforded in 55% to 80% yield (Table 3). The highest yield was observed for the electron-rich system **3l** (Table 3). However, there was no clear trend observed for a relation between chemical structure and yield.

In another context, we envisaged an alternative pathway to obtain benzothieno[2′,3′:4,5]pyrrolo-[1,2-*f*] phenanthridines, in which further options to install substituents on the products are available (Scheme 2, 3). Hence, we synthesized alkynyl-benzothiophene **7** by site-selective Sonogashira reaction.



Scheme 3. Proposed reaction pathway to benzothieno [2′,3′:4,5]pyrrolo[1,2-*f*] phenanthridines.

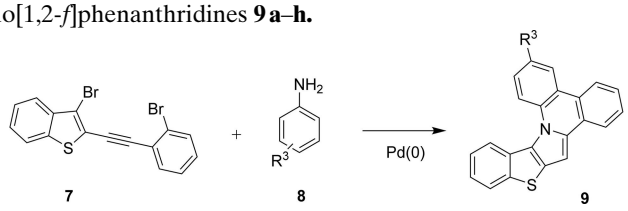
Starting from 3-bromo-2-((2-bromophenyl) ethynyl)benzo[*b*]thiophene **7**, we tested the above reaction conditions with three different amines to compare the results with those obtained from the previous synthesis (Entry 1–3, Table 3 vs. Entry 1–3, Table 4). To our delight, identical products were afforded in comparable yields. Encouraged by these results, we examined the scope of the reaction with several other amines (Entry 4–8, Table 4). Benzothieno[2′,3′:4,5]pyrrolo[1,2-*f*]phenanthridines **9d–h** were furnished in moderate yields. The lowest yield was observed by applying 4-(methylthio)aniline (Entry 8, Table 4). Both electron-withdrawing and -donating substituents were tolerated. The reaction performed well even with the sterically hindered and electron-



Scheme 2. Synthesis of 3-bromo-2-((2-bromophenyl)ethynyl)benzo[*b*]thiophene **7.**

poor 2-fluoroaniline (Entry 7, Table 4). However, there is no correlation between the chemical structure and the reaction yield.

Table 4. Alternative synthesis of benzothieno[2′,3′:4,5]pyrrolo[1,2-*f*]phenanthridines **9a–h.**



7 8 9

Entry	R^3	9	Yield[a]
1	H	**9a=3a**	60% (vs. 65%)
2	4-Me	**9b=3b**	65% (vs. 68%)
3	4-Cl	**9c=3c**	50% (vs. 58%)
4	4-*t*Bu	**9d**	65%
5	4-OMe	**9e**	60%
6	2-OMe	**9f**	52%
7	2-F	**9g**	55%
8	4-SMe	**9h**	48%

Reaction conditions: **7** (0.3 mmol), **8** (0.38 mmol), $Pd(OAc)_2$ (0.03 mmol), $P(tBu)_3.HBF_4$ (0.06 mmol), Cs_2CO_3 (0.9 mmol), DMF (4 mL), 140 °C, 24 h.
[a] Isolated yield.

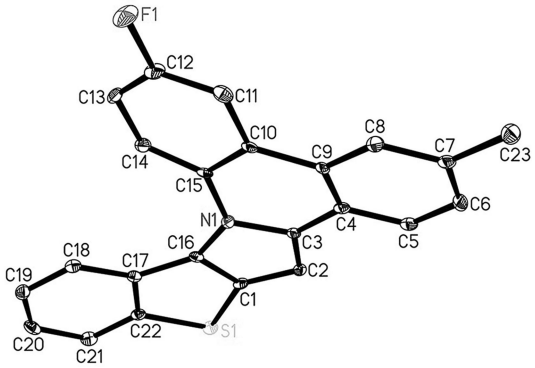


Figure 2. Crystal structure of 3 h.[11].

Finally, the structure of benzothieno[2′,3′:4,5]pyrrolo[1,2-*f*]phenanthridine **3h** was independently confirmed by X-Ray crystal structure analysis (Figure 2). Noticeably, the compound displays a distorted helical instead of a planar structure, possibly due to the steric repulsion between the rings (C10-C15) and (C17-C22).

Conclusion

In summary, we have developed a convenient synthesis of benzothieno[2′,3′:4,5]pyrrolo[1,2-*f*]phenanthridines. The protocol involves a site-selective Sonogashira reaction followed by a cascade C–N coupling/hydroamination/C–H arylation. The synthesis can also be carried out in a complementary pathway wherein further choices of amines are available. Overall, these methods are amendable to the generation of a large product library for further biological- and material applications.

Experimental Section

General. All chemicals used are commercially available and were used without further purification. Column chromatography was performed using Merck Silicagel 60 (0.043–0.06 mm). NMR data were recorded on Bruker AC 250, Bruker ARX 300 and Bruker ARX 500 spectrometers.

Gas chromatography-mass analysis was carried out on an AgilentHP-5890 instrument with an Agilent HP-5973 Mass Selective Detector (EI) and HP-5 capillary column using helium carrier gas. ESI HR-MS measurements were performed on an Agilent 1969 A TOF mass–spectrometer. For High Resolution MS (HRMS), a Finnigan MAT95 XP was used. Only the measurements with an average deviation from the theoretical mass of ±2mDa were accounted as correct.

X-Ray crystallography was collected on a Bruker-Nonius Apex X8 diffractometer. Infrared Spectra were recorded on a Nicolet 550 FT-IR spectrometer with ATR sampling technique.

Characterization data for the compounds can be found in the electronic Supporting Information.

General Experimental Procedure. 3-Bromo-2-(phenylethynyl)benzo[*b*]thiophene **1** (0.32 mmole), 2-bromoaniline **2** (1.2 equiv., 0.38 mmol), $Pd(OAc)_2$ (10 mol%, 0.03 mmol), $P(tBu)_3{\cdot}HBF_4$ (20%, 0.06 mmol), and Cs_2CO_3 (3 *equiv.*, 0.96 mmol) were placed in a dried pressure tube equipped with septum. Subsequently, dried and degassed DMF (4 mL) was added under argon. The reaction was evacuated and back-filled with argon three times and sealed by a Teflon cap. The reaction mixture was allowed to stir at 140 °C for 24 h. The reaction mixture was cooled to 20 °C, poured into H_2O and extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (flash silica gel, heptanes/EtOAc) to obtain compound **3.** On the other hand, compounds **1a, 1b, 1c, 7** were prepared according to procedure described in literature.[12,13]

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[11] CCDC 1517900 containing supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www. Ccdc.cam.ac.uk/data_request/cif.

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UPDATES

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