Synthesis of Sulfur Heterocycles *via* Domino Metal-Mediated Reactions

Thomas Castanheiro, Jean Suffert, Morgan Donnard,* and Mihaela Gulea*

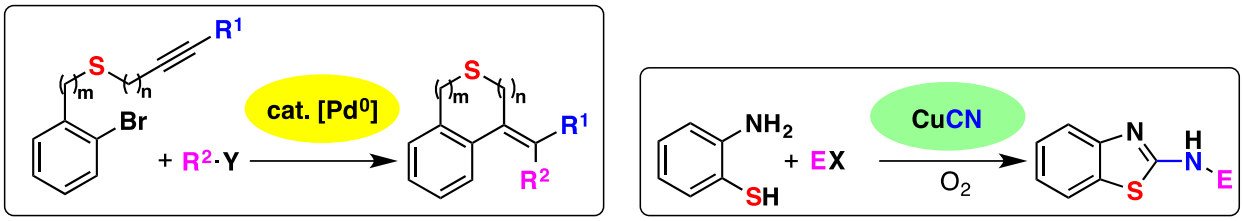
Laboratoire d'Innovation Thérapeutique, UMR 7200 CNRS, Université de Strasbourg, Faculté de Pharmacie, 74 route du Rhin, 67401 Illkirch Cedex, France

Address correspondence to Morgan Donnard or Mihaela Gulea, Laboratoire d'Innovation Thérapeutique, UMR 7200 CNRS, Université de Strasbourg, Faculté de Pharmacie, 74 route du Rhin, 67401 Illkirch Cedex, France. Email: donnard@unistra.fr, gulea@unistra.fr

Abstract

Two methodologies to access S-heterocycles and mixed N,S-heterocycles via metal-mediated domino reactions are described. One involves a cyclocarbopalladation / cross-coupling domino process and leads to benzene-fused five- or six-membered sulfur heterocycles with a stereodefined tetrasubstituted exocyclic double bond. The other consists in a three-component domino reaction between 2-aminophenyl disulfide, copper cyanide, and an electrophile to access N-substituted 2-amino benzothiazoles. Preliminary results in the use of the second method to access N-substituted 2-imino benzothiazoles are also reported.

GRAPHICAL ABSTRACT



Keywords

Sulfur heterocycles; domino reactions; palladium catalysis; copper-mediated reaction; sulfides, thiocyanates

INTRODUCTION

Domino reactions involving transition metal catalysts or reagents represent a powerful tool in the synthesis of heterocyclic molecules. They provide a step-economic access to complex molecules from simple starting materials.[1] The impact of S-heterocyclic compounds in pharmaceutical industry is significant,[2] therefore the search for efficient diversity-oriented syntheses to provide this type of compounds represents a topical subject.

One of the objectives of our laboratory is to develop new efficient syntheses of small and medium sulfur heterocycles based on metal-mediated domino reactions, starting from readily accessible pre-organized sulfur-containing substrates. This communication summarizes our recent results in this topic. We have developed two types of metal-mediated domino processes for the synthesis of *S*- or mixed *N,S*-heterocycles from simple acyclic substrates containing a sulfur function. The first one involves a palladium-catalyzed reactions in sulfides series and the second one a copper-mediated S-cyanation of 2-amino-benzene disulfide.

RESULTS AND DISCUSSION

Synthesis of *S*-heterocycles *via* Pd-catalyzed domino reactions

Original benzene-fused 5- or 6-membered S-heterocycles **2-12** bearing a stereodefined tetrasubstituted exocyclic double bond have been obtained *via* the cyclocarbopalladation/cross-coupling (Stille or Suzuki-Miyaura) domino reaction starting from propargyl sulfides **1a-d** or ynethioethers **1e** (Scheme 1, Table 1).[3] The different precursors **1a-d** have been reacted in the presence of $Pd(PPh_3)_4$ catalyst with 2-furyl, 2-thienyl, allyl, and vinyl tributylstannanes as Stille coupling partners, and led to the desired products **2a-e**, **3a**, **4a**, and **5a**, respectively (Table 1,

entries 1-8). The yields were moderate due in particular to the difficulty in the product isolation using stannanes. Cyclocarbopalladation/Suzuki-Miyaura cascade reaction was then investigated. By using electron-rich or electron-poor arylboronic acids, as well as vinyl, allyl, and cyclopropyl derivatives as coupling partners, the reaction worked well, and sulfur heterocycles **3b-e** and **4d-12d** have been obtained in good yields (Table 1, entries 9-21).

To illustrate the interest of our method for the synthesis of biologically active molecules, we have decided to prepare compound **13** as a potential selective estrogen-receptor modulator (SERM), due to its structural similitudes with the anticancer agent Tamoxifen (Scheme 2). Two routes have been attempted starting from *S*-(2-bromo-5-methoxybenzyl) thioacetate: **route 1** involved the transformation of OMe into OH group (**12e** into **12f**) after the domino reaction, but the desired product **12f** was isomerized into isothiochromene **12f'** under the acidic conditions due to the use of BBr_3; **route 2** consisted in a three-steps sequence (OMe into OH transformation, *S*-alkylation, and *O*-alkylation) to obtain the appropriate precursor for the Pd-catalyzed cyclization/Suzuki domino process. Targeted product **13** was thus obtained in 42% overall yield.

Synthesis of *N,S*-heterocycles *via* Cu-mediated domino reactions involving thiocyanates

Diversely *N*-substituted 2-amino-benzothiazole derivatives have been synthesized *via* a domino sequence involving an oxidative copper-mediated S-cyanation of 2-amino-benzene disulfides **14** as the key-step. First we developed an efficient access to aromatic thiocyanates by using copper cyanide (CuCN) as the cyanating agent of thiols/disulfides.[4,5] We then integrated this transformation in a domino three-component process involving aromatic disulfides bearing an amino group at the ortho position.[6] The reactions have been performed between a 2,2′-

diaminodiphenyl disulfide **14a-c**, CuCN, and an electrophile, under air, in acetonitrile, and with the use of TMEDA as the copper ligand (Scheme 3, Table 2). Aromatic and aliphatic acyl chlorides (Table 2, entries 1-13), Boc anhydride, menthyl chloroformate, and phenyl isocyanate (entries 14-17) have been successfully used as electrophiles to access variously *N*-substituted 2-amino-benzothiazoles **15-28**.

We proposed two mechanisms to describe this domino process: one consisted in *S*-cyanation by CuCN at first, then cyclization *via* nitrogen nucleophilic attack of the thiocyanate carbon, and final N-acylation of the exocyclic nitrogen, and the second consisted at first in the *N*-acylation of the 2-aminoaryl disulfide, then *S*-cyanation followed by cyclization, and finally an acyl transfer from the endocyclic nitrogen to the exocyclic nitrogen. Several experiments[6] let us conclude that the transformation takes place *via* the second mechanism and that the final nitrogen-to-nitrogen acyl transfer is intermolecular (Scheme 4).

To extend the synthetic applicability of our method we also have envisioned to access 2-imino derivatives by using *N*-protected 2-aminoaryl disulfides as precursors (Scheme 5). When reacting *N*-benzoyl starting substrate **29** with copper cyanide and 2,5-difluorobenzoyl chloride, only the *N*,*N*-diacylated disulfide **30** was obtained (Scheme 6). On the other hand, when the *N*-tosylated substrate **31** was used in reaction with CuCN and benzoyl chloride, the domino process led to a mixture of products. Among them, the desired (*N*-tosyl-benzothiazol-ylidene)benzamide **32** was isolated in low yield (25%), as well as a little amount of ditosylated 2-iminobenzothiazole **33** (Scheme 6). It is worth noting that when substrate **31** was placed under standard reaction conditions (CuCN/TMEDA) in the absence of an electrophile, product **33** was

obtained in mixture with 2-amino benzothiazole **34** and isolated in 23% yield. The structures of the obtained compounds **30**, **32** and **33** have been confirmed by X-ray analysis (Scheme 6).

CONCLUSIONS

In conclusion, we developed two methodologies to synthesize *S*-heterocycles and mixed *N,S*-heterocycles *via* metal-mediated domino reactions: one involves a cyclocarbopalladation/ cross-coupling domino process and leads to benzene-fused five- or six-membered sulfur heterocycles (benzothiolanes and isothiochromanes) with a stereodefined tetrasubstituted exocyclic double bond; the other consists in a three-component domino reaction between 2-amino phenyl disulfide, copper cyanide, and an electrophile to access *N*-substituted 2-amino or 2-imino benzothiazoles. Current studies are focused on exploiting these methods to access more complex, highly functionalized sulfur heterocycles, with potential biological properties.

This project was supported by the University of Strasbourg (IDEX grant for T.C.) and the Centre National de la Recherche Scientifique (CNRS). We thank Dr. Lydia Karmazin (analytical department of the University of Strasbourg) for X-ray analyses.

ACKNOWLEDGMENTS

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Supplemental Materials

Crystallographic data for the structural analysis of compounds **23a**, **30**, **32**, and **33** have been deposited at the Cambridge Crystallographic Data Center. Summary of Data **CCDC 1486722**

(product **32**), Formula: $C_{21}H_{16}N_2O_3S_2$, Unit Cell Parameters: a 8.1931(4) b 17.0832(7) c 13.8481(6) P21/c; Summary of Data **CCDC 1486723** (product **30**), Formula: $C_{40}H_{24}F_4N_2O_4S_2$, Unit Cell Parameters: a 10.6893(10) b 11.2057(10) c 15.9469(15) P-1; Summary of Data **CCDC 1486724** (product **23a**), Formula: $C_{11}H_{12}N_2O_1S_1$, Unit Cell Parameters: a 22.535(3) b 8.1096(11) c 24.573(3) Pbca; Summary of Data **CCDC 1486725** (product **33**), Formula: $C_{21}H_{18}N_2O_4S_3$, Unit Cell Parameters: a 7.8455(4) b 8.0210(4) c 33.0465(15) P21/c.

Copies of the information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK (Fax: + 44-1223-336033; email: deposit@ccdc.cam.ac.uk or www.ccdc.can.ac.uk).

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Graphic for Table of Contents Synthesis of Sulfur Heterocycles via Domino Metal-mediated Reactions

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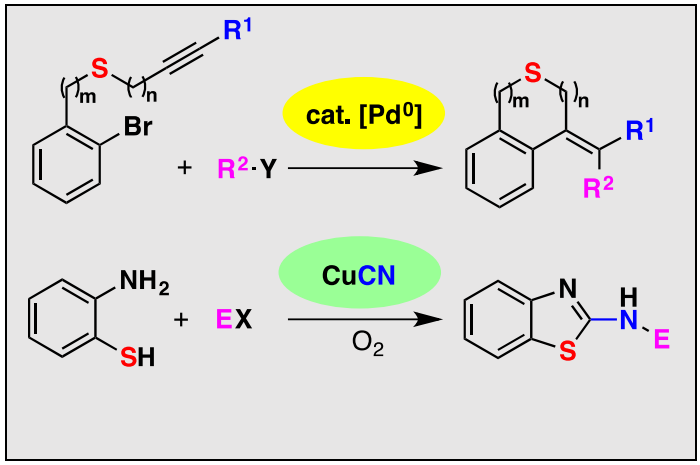


Table 1. Cyclocarbopalladation/cross-coupling domino reactions in sulfides series

Entry	m, n	R^1	Starting sulfide	Coupling partner R^2-Y	Conditions[a]	R^2	Product	Yield (%)
1	m = 0, n = 1	TMS	**1a**	R^2-$SnBu_3$	**A**	2-Furyl	**2a**	65
2	m = 0, n = 1	TMS	**1a**	R^2-$SnBu_3$	**A**	2-Thienyl	**3a**	77
3	m = 0, n = 1	TMS	**1a**	R^2-$SnBu_3$	**A**	Vinyl	**4a**	51
4	m = 0, n = 1	TMS	**1a**	R^2-$SnBu_3$	**A**	Allyl	**5a**	62
5	m = 0, n = 1	Et	**1b**	R^2-$SnBu_3$	**A**	2-Furyl	**2b**	52
6	m = 0, n = 1	Ph	**1c**	R^2-$SnBu_3$	**A**	2-Furyl	**2c**	81
7	m = 1, n = 1	Et	**1d**	R^2-$SnBu_3$	**A**	2-Furyl	**2d**	61
8	m = 1, n = 0	Me	**1e**	R^2-$SnBu_3$	**A**	2-Furyl	**2e**	59
9	m = 0, n = 1	Et	**1b**	R^2-$B(OH)_2$	**B**	Ph	**3b**	66
10	m = 0, n = 1	Ph	**1c**	R^2-$B(OH)_2$	**B**	Ph	**3c**	79
11	m = 1, n = 1	Et	**1d**	R^2-$B(OH)_2$	**B**	Ph	**3d**	91
12	m = 1, n = 0	Me	**1e**	R^2-$B(OH)_2$	**B**	Ph	**3e**	30
13	m = 1, n = 1	Et	**1d**	R^2-$B(OH)_2$	**B**	4-F-C_6H_4	**4d**	83
14	m = 1, n = 1	Et	**1d**	R^2-$B(OH)_2$	**B**	4-CF_3O-C_6H_4	**5d**	86
15	m = 1, n = 1	Et	**1d**	R^2-$B(OH)_2$	**B**	4-CO_2Me-C_6H_4	**6d**	69
16	m = 1, n = 1	Et	**1d**	R^2-$B(OH)_2$	**B**	3-NO_2-C_6H_4	**7d**	86
17	m = 1, n = 1	Et	**1d**	R^2-$B(OH)_2$	**B**	3-CF_3-C_6H_4	**8d**	67
18	m = 1, n = 1	Et	**1d**	R^2-$B(OH)_2$	**B**	2,4-$(MeO)_2C_6H_3$	**9d**	60
19	m = 1, n = 1	Et	**1d**	R^2-BF_3K	**B**	Vinyl	**10d**	64

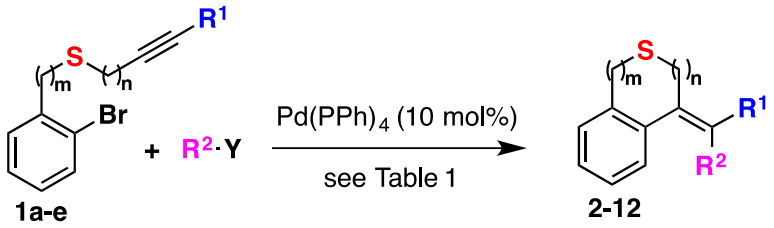
20	m = 1, n = 1	Et	**1d**	R^2-BF_3K	**B**	Allyl	**11d**	73
21	m = 1, n = 1	Et	**1d**	R^2-$B(OH)_2$	**B**	Cyclopropyl	**12d**	55

[a]Conditions **A**: C_6H_6, 115 °C (MW), 3 h; Conditions **B**: MeTHF/H_2O (98/2), K_3PO_4 ,130 °C (MW), 3 h

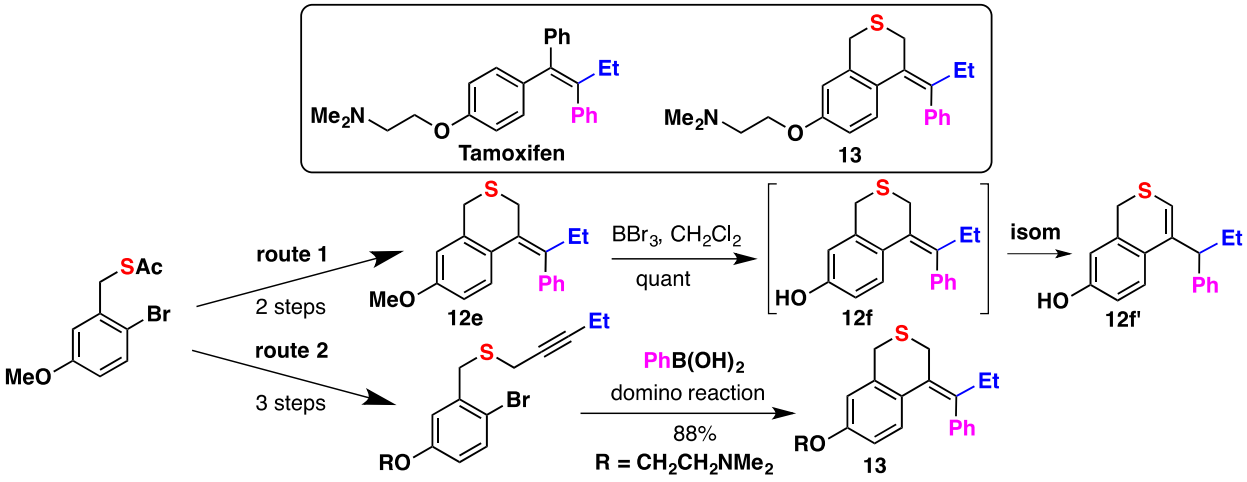
Table 2. Aerobic Cu-mediated domino approach to 2-aminobenzothiazole derivatives

Entry	Starting disulfide	R'	EX	R	Product	Yield (%)
1	**14a**	H	RC(O)Cl	Ph	**15a**	73
2	**14a**	H	RC(O)Cl	4-Me-C_6H_4	**16a**	82
3	**14a**	H	RC(O)Cl	4-MeO-C_6H_4	**17a**	72
4	**14a**	H	RC(O)Cl	4-Br-C_6H_4	**18a**	61
5	**14a**	H	RC(O)Cl	2,5-F_2-C_6H_4	**19a**[a]	80
6	**14a**	H	RC(O)Cl	4-CN-C_6H_4	**20a**	37
7	**14a**	H	RC(O)Cl	2-Thienyl	**21a**	49
8	**14a**	H	RC(O)Cl	Et	**22a**	76
9	**14a**	H	RC(O)Cl	iPr	**23a**[a]	77
10	**14a**	H	RC(O)Cl	Cyclohexyl	**24a**	60
11	**14a**	H	RC(O)Cl	Cyclopropyl	**25a**	61
11	**14b**	Cl	RC(O)Cl	Ph	**15b**	69
12	**14b**	Cl	RC(O)Cl	4-Me-C_6H_4	**16b**	86
13	**14c**	CF_3	RC(O)Cl	Ph	**15c**	93
14	**14a**	H	Boc_2O	OtBu	**26a**	71
15	**14a**	H	ROC(O)Cl	OMenthyl	**27a**	50
16	**14a**	H	PhNCO	NHPh	**28a**	55
17	**14b**	Cl	Boc_2O	OtBu	**26b**	65

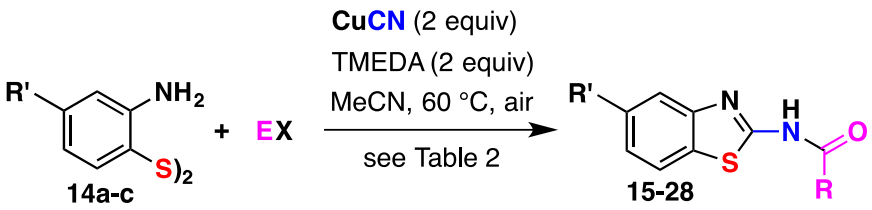
[a]analyzed by X-ray crystallography



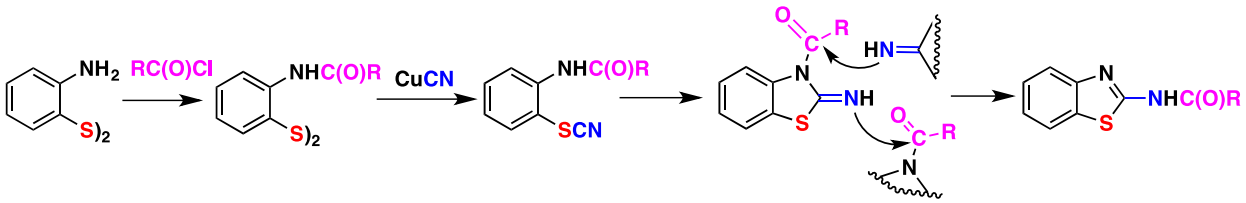
Scheme 1. Synthesis of S-heterocycles by cyclocarbopalladation/cross-coupling domino reactions



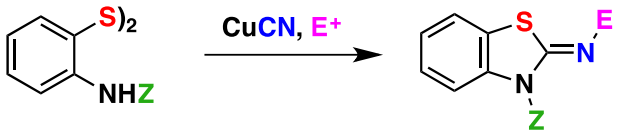
Scheme 2. Synthesis of a potentially bioactive molecule **13**, analogue of Tamoxifen



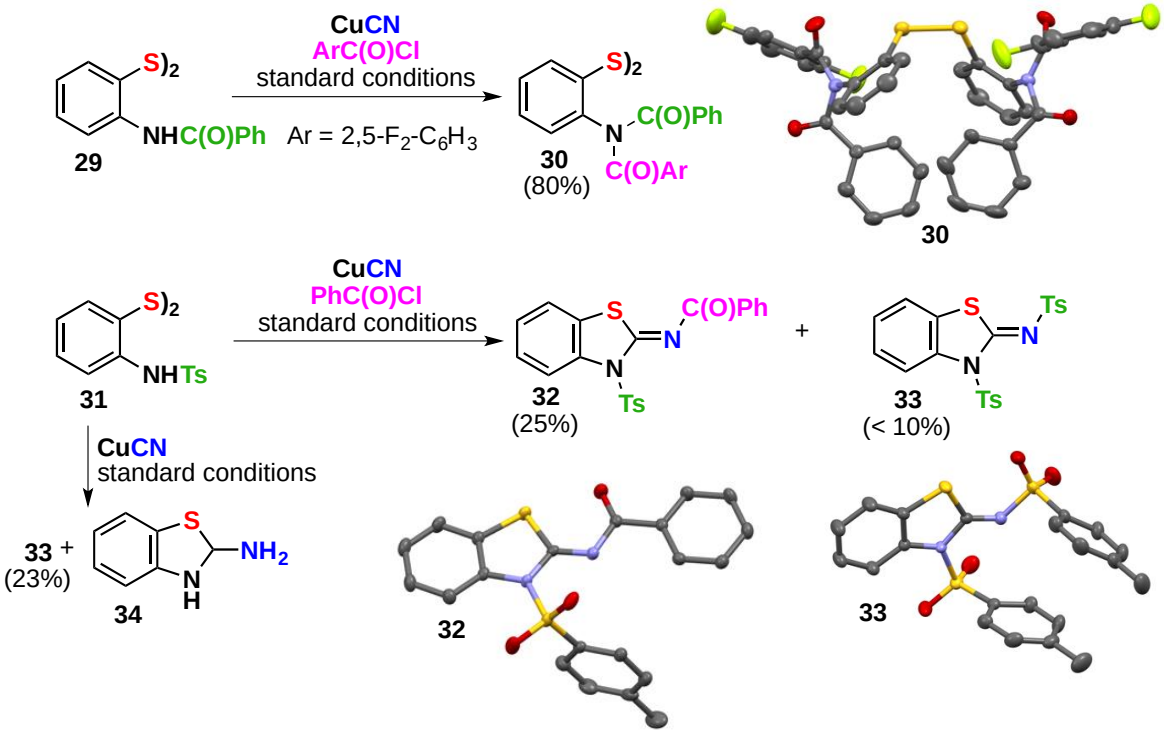
Scheme 3. Synthesis of 2-aminobenzothiazole derivatives by Cu-mediated domino reaction



Scheme 4. Proposed sequence for the overall domino transformation



Scheme 5. Approach to 2-iminobenzothiazole derivatives



Scheme 6. Reactions with *N*-protected 2-aminoaryl disulfides **29** and **31**; X-ray structures of products **30**, **32**, **33**