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Efficient Access to 1,4-Benzothiazine: Palladium-Catalyzed Double C–S Bond Formation Using $Na_2S_2O_3$ as Sulfurating Reagent[‖]

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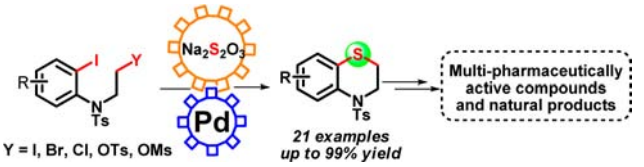
ABSTRACT



A novel Pd-catalyzed double C–S bond formation coupling reaction has been developed. This protocol, in which $Na_2S_2O_3$ was used as sulfurating reagent in metal-catalyzed reactions, provides an efficient method for the synthesis of substituted 1,4-benzothiazine derivates, which are structural elements of numerous bioactivity molecules rendering this protocol attractive to both synthetic and medicinal chemistry.

Organosulfur heterocycles, standing for an important class of biological organic compounds, have been widely used as pharmaceuticals, functional materials, and synthetic intermediates.[1] 1,4-Benzothiazine derivatives are well-known to display diverse biological activities *in vivo* and *in vitro*, such as antibacterial,[2] antidiabetic,[3] antiarrhythmic,[4] antitumor,[5] and neurodegenerative diseases (Parkinson's disease and Alzheimer's disease).[6] On the basis of a broad spectrum of important pharmaceutically active compounds and natural products (Figure 1), 1,4-benzothiazine derivatives have triggered sustainably increasing attention in the synthetic and medicinal chemistry communities.

Due to the significance of organosulfur compounds, the development of new and efficient methods for the incorporation of sulfur into organic frameworks is today an important and challenging task. Compared to the construction of C–N and C–O bonds by transmetal-catalyzed cross-coupling, C–S bond formation has been less studied due to deactivation of the metal catalysts by the strong coordinating properties of sulfur compounds (Scheme 1).[7] In 1980, Migita and co-workers first reported

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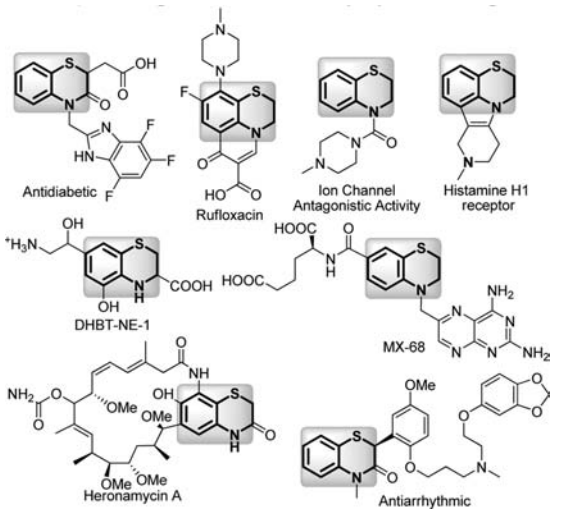
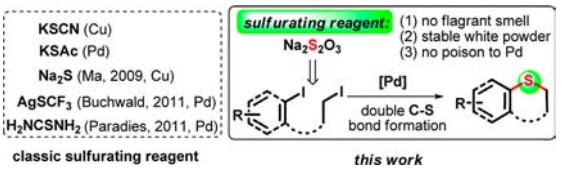


Figure 1. Bioactive 1,4-benzothiazine scaffolds.

the coupling of thiols and aryl halides catalyzed by Pd-$(PPh_3)_4$.[8] A wide range of transition metals, such as Pd,[9] Ni,[10] Co,[11] In,[12] Cu,[13] Fe,[14] and Rh[15] have been developed to achieve C−S bond formation. However, in most cases, the thiols as the sulfur source are indispensable partners, which generally suffer from preparation difficulties due to the apt oxidation and unpleasant smell during the whole process. Therefore, the search for new sulfurating reagents to apply to the construction of S-containing heterocycles is an urgent need. Some elegant metal sulfides have been developed recently for constructing organosulfur molecules.[16] In 2009, Ma and co-workers reported the first example for the use of Na_2S as sulfuration reagent.[16a] In 2011, a general method for the Pd-catalyzed Ar-SCF_3 bond-forming reaction using $AgSCF_3$ was developed by the Buchwald group.[16b] Thiourea as a thiol surrogate has also been applied in the synthesis of sulfur-containing molecules.[17] Ma *et al.* developed a novel thiiranation of 1,2-allenyl sulfones by using $Na_2S_2O_3$ as sulfur source.[18] However, to the best of our knowledge, $Na_2S_2O_3$ as a sulfurating reagent, which is readily available as stable salt without any smell, is untouched in metal-catalyzed coupling. Herein, we report a novel one-pot Pd-catalyzed double C−S bond formation reaction using $Na_2S_2O_3$ as the sulfurating reagent.

Scheme 1. Metal-Catalyzed C−S Bond Construction



Our study commenced with the reaction of **1aa** (*N*-(2-iodoethyl)-*N*-(2-iodophenyl)-4-methylbenzenesulfon-amide) catalyzed by $PdCl_2$(dppf) in the presence of $Na_2S_2O_3 \cdot 5H_2O$. Gratifyingly, the desired 4-tosyl-3,4-dihydro-2*H*-benzo[b]-[1,4]thiazine **2a** was isolated in 10% yield with 66% **1aa** recovered by using Cs_2CO_3 as base in MeCN (Table 1, entry 1). The structure of **2a** was confirmed by X-ray analysis.[19] To enhance the solubility of $Na_2S_2O_3 \cdot 5H_2O$, H_2O was added as cosolvent which made a slight improvement to the yield (Table 1, entry 2). It afforded a 20% yield when 5.0 equiv of $Na_2S_2O_3 \cdot 5H_2O$ were used, but too much $Na_2S_2O_3 \cdot 5H_2O$ did not favor this transformation (Table 1, entries 3 and 4). Then phase-transfer catalysts were tested and TBAB was proved to be a better choice affording 39% yield (Table 1, entry 6). A great

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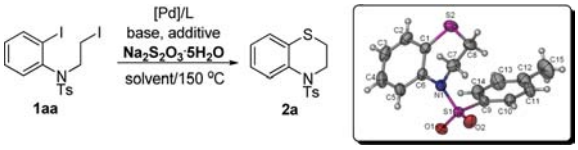
(19) CCDC-917799 (**2a**): $C_{15}H_{15}NO_2S_2$, MW = 305.40, monoclinic, space group $P2(1)/n$, final R indices [$I > 2\sigma(I)$], R1 = 0.0393, wR2 = 0.1131, R indices (all data), R1 = 0.0461, wR2 = 0.1187, a = 8.3042(5) Å, b = 8.0453(5) Å, c = 22.1419(14) Å, α = 90°, β = 98.853(2)°, γ = 90°, V = 1461.67(16) Å^3, T = 296(2) K, Z = 4, reflections collected/unique: 119430/3560 (R(int) = 0.0239). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 1. Optimization of Pd-Catalyzed Double C−S Bond Formation[a]



entry	[Pd]	ligand (mol %)	base	solvent	additive	yield[b] (%)
1	$PdCl_2$(dppf)		Cs_2CO_3	MeCN		10[c]
2	$PdCl_2$(dppf)		Cs_2CO_3	MeCN/H_2O (10:1)		15[c]
3	$PdCl_2$(dppf)		Cs_2CO_3	MeCN/H_2O (10:1)		20
4	$PdCl_2$(dppf)		Cs_2CO_3	MeCN/H_2O (10:1)		19[d]
5	$PdCl_2$(dppf)		Cs_2CO_3	MeCN/H_2O (10:1)	TBAC	10
6	$PdCl_2$(dppf)		Cs_2CO_3	MeCN/H_2O (10:1)	TBAB	39
7	$PdCl_2$(dppf)		Cs_2CO_3	MeCN/H_2O (10:1)	TBAI	8
8	$PdCl_2$(dppf)	dppf (2)	Cs_2CO_3	MeCN/H_2O (10:1)	TBAB	70
9	$PdCl_2$(dppf)	dppf (5)	Cs_2CO_3	MeCN/H_2O (10:1)	TBAB	78
10	$PdCl_2$(dppf)	dppf (10)	Cs_2CO_3	MeCN/H_2O (10:1)	TBAB	79
11	$Pd(OAc)_2$	dppf (5)	Cs_2CO_3	MeCN/H_2O (10:1)	TBAB	55
12	$Pd(dba)_2$	dppf (5)	Cs_2CO_3	MeCN/H_2O (10:1)	TBAB	63
13	$Pd(PPh_3)_2Cl_2$	dppf (5)	Cs_2CO_3	MeCN/H_2O (10:1)	TBAB	50
14	$PdCl_2$(dppf)	TFP (10)[e]	Cs_2CO_3	MeCN/H_2O (10:1)	TBAB	25
15	$PdCl_2$(dppf)	Sphos (10)[f]	Cs_2CO_3	MeCN/H_2O (10:1)	TBAB	21
16	$PdCl_2$(dppf)	PCy_3 (10)[g]	Cs_2CO_3	MeCN/H_2O (10:1)	TBAB	trace
17	$PdCl_2$(dppf)	dppf (5)	Na_2CO_3	MeCN/H_2O (10:1)	TBAB	28
18	$PdCl_2$(dppf)	dppf (5)	K_2CO_3	MeCN/H_2O (10:1)	TBAB	30
19	$PdCl_2$(dppf)	dppf (5)	Ag_2CO_3	MeCN/H_2O (10:1)	TBAB	42
20	$PdCl_2$(dppf)	dppf (5)	Cs_2CO_3	MeCN/H_2O (5:1)	TBAB	57
21	**$PdCl_2$(dppf)**	**dppf (5)**	**Cs_2CO_3**	**MeCN/H_2O (20:1)**	**TBAB**	**96**
22	$PdCl_2$(dppf)	dppf (5)	Cs_2CO_3	MeCN/H_2O (20:1)	TBAB	complicated[h]
23	$PdCl_2$(dppf)	dppf (5)	Cs_2CO_3	MeCN/H_2O (20:1)	TBAB	complicated[i]

[a] Reaction conditions: **1aa** (0.1 mmol), [Pd] (0.01 mmol), base (0.3 mmol), $Na_2S_2O_3·5H_2O$ (0.5 mmol), additive (0.03 mmol), solvent (2.0 mL), 150 °C, 6 h. [b] Isolated yield. [c] $Na_2S_2O_3·5H_2O$ (0.2 mmol, 2.0 equiv). [d] $Na_2S_2O_3·5H_2O$ (1.0 mmol, 10.0 equiv). [e] TFP = tri(2-furyl)phosphine. [f] Sphos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl. [g] PCy_3 = tricyclohexylphosphine. [h] Replace $Na_2S_2O_3$ with S_8. [i] Replace $Na_2S_2O_3$ with Na_2S.

improvement was achieved by using additional 5 mol % of dppf, which is thought to be stabilized the Pd intermediate,[20] and the yield was elevated to 78% (Table 1, entries 8−10). Other Pd catalysts were tested, which gave low efficiency, respectively (Table 1, entries 11−13). Different ligands and bases were also screened, which, however, did not exhibit any superior performance than dppf and Cs_2CO_3 (Table 1, entries 14−19). Significantly, when MeCN:H_2O (20:1) was used, the highest yield (96%) was achieved (Table 1, entry 21). Neither S_8 nor Na_2S could take the integrant place of $Na_2S_2O_3$ (Table 1, entries 22 and 23).

Under the optimized reaction conditions, we examined a series of substrates to establish the scope of this methodology shown in Table 1. Substrates bearing Csp^3-I, Br, Cl, OMs, and OTs on the saturated carbon could afford good to excellent yields (Table 2, **2a**). Fluoro and chloro atoms are well-tolerated under the standard conditions with 90−94% yields (Table 2, **2b** and **2c**). The yield was reduced to 46% with a bromo substitution at C4, which is sensitive under these conditions (Table 2, **2d**). Both electron-withdrawing and electron-donating substitutions on the aromatic ring gave the corresponding products in good yields (Table 2, **2e**−**l**). It is worth noting that **2j** with free alcohol proceeds smoothly in 42% yield. **2k** containing other sulfur atom did not prevent the coupling reaction (Table 2, **2k**). Multisubstituted iodobenzene could also afford the desired product in good yield (Table 2, **2m**). Ns (4-Nitrobenzenesulfonyl) on nitrogen did not change the reactivity (Table 2, **2n**). And not only the six-membered ring but also the seven- and five-membered rings **2o** and **2p** could be obtained in moderate yields. Carbon-tethered substrates could also afford the desired products in good yields (Table 2, **2p** and **2q**).

As mentioned above, 1,4-benzothiazine derivates are versatile intermediates and building blocks in organic synthesis. When the Ts group was removed with 35% HBr in HOAc in the presence of anisole,[21] **2ab** could be efficiently transformed to **2a-2**, which is the ion channel antagonistic activity molecule (Scheme 2, **2a-2**). Another practical application was achieved through the hydrolysis of **2g** to the 4-tosyl-3,4-dihydro-2*H*-benzo[*b*][1,4]-thiazine-7-carboxylic acid **2gb**, which is the key intermediate for the synthesis of antirheumatic agent MX-68.[22] 4-Tosyl-3,4-dihydro-2*H*-benzo[*b*][1,4]-thiazine **2a** could be converted to sulfoxide by $NaIO_4$, which was an analogue of rufloxacin. When compound **2a** was subjected to

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Scheme 2. Synthetic Transformation

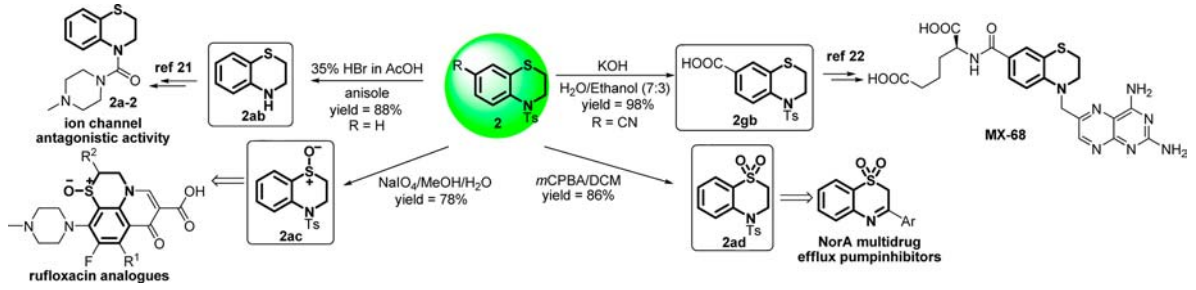
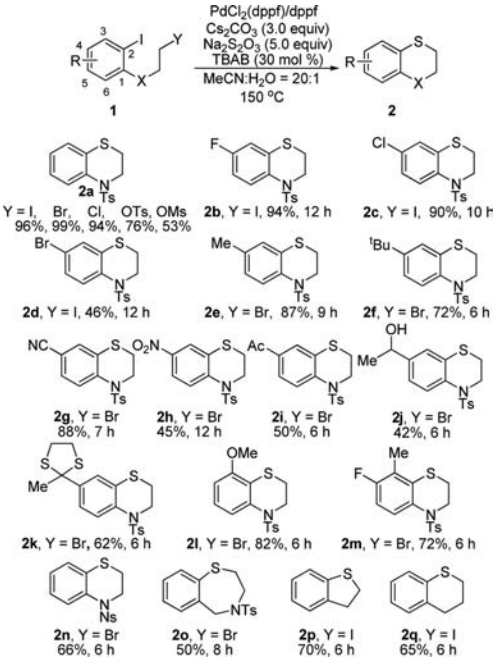


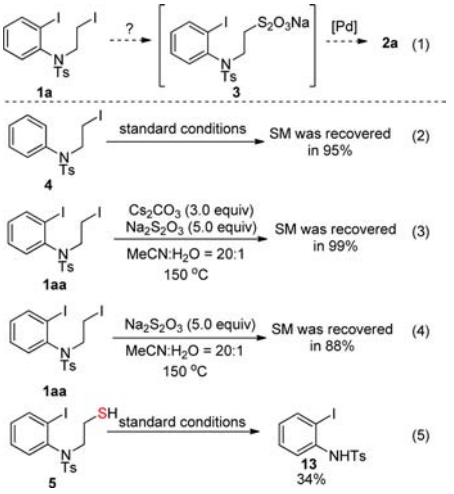
Table 2. Pd-Catalyzed Double C−S Bond Formation[a]



[a] Reaction conditions: **1** (0.1 mmol), $PdCl_2$(dppf) (0.01 mmol, 10 mol %), dppf (0.005 mmol, 5 mol %), Cs_2CO_3 (0.3 mmol), $Na_2S_2O_3 \cdot 5H_2O$ (0.5 mmol), TBAB (0.03 mmol, 30 mol %), MeCN:H_2O (2.0 mL, 20:1), 8 h. [b] Isolated yield.

m-CPBA, sulfone **2ad** was obtained efficiently, which is the analogue of NorA multidrug efflux pump inhibitors.

To investigate that how the $Na_2S_2O_3$ was introduced to this system, some control experiments were tentatively examined. Straightforward alkylated thiolsulfate intermediate **3** *via* S_N2 replacement[23] were proposed (eq 1). However, no reaction was detected and coumpound **4** was almost fully recovered (eq 2). When **1aa** was tested without $PdCl_2$(dppf)/dppf (eq 3) or Cs_2CO_3 (eq 4), no intermediate **3** was formed. Another possible transformation was that **3** was hydrolyzed to thiol **5** which might be converted to **2a** *via* Pd-catalyzed cross coupling. However, when compound **5** was subjected to stardard conditions, no product **2a** was detected but the C−N bond cleavage product **6** was found in 34% yield (eq 5). These evidence indicated that sulfuration should not start from C*sp*^{3}. However, the reaction pathway was still unsharp.



In conclusion, we have developed a novel method for the synthesis of substituted 1,4-benzothiazine derivates which relies on a Pd-catalyzed coupling reaction. The important feature of this method is using stable $Na_2S_2O_3$ salt as sulfurating reagent which makes it free from foul-smelling thiols. The successful application of $Na_2S_2O_3$ as sulfur source will stimulate studies on metal catalyzed C−S bond formation by employing those inexpensive readily available reagents. The significance of the 1,4-benzothiazine scaffold as a structural element should render this protocol attractive for both synthetic and medicinal chemistry. $Na_2S_2O_3$ as sulfurating reagent in other useful natural product syntheses is undergoing in our laboratory.

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Supporting Information Available. Experimental procedures and spectra for all previously unreported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.