

Efficient Access to 1,4-Benzothiazine: Palladium-Catalyzed Double C—S Bond Formation Using $\text{Na}_2\text{S}_2\text{O}_3$ as Sulfurating Reagent^{||}

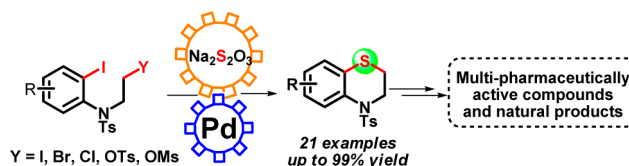
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ABSTRACT



A novel Pd-catalyzed double C—S bond formation coupling reaction has been developed. This protocol, in which $\text{Na}_2\text{S}_2\text{O}_3$ was used as sulfurating reagent in metal-catalyzed reactions, provides an efficient method for the synthesis of substituted 1,4-benzothiazine derivatives, 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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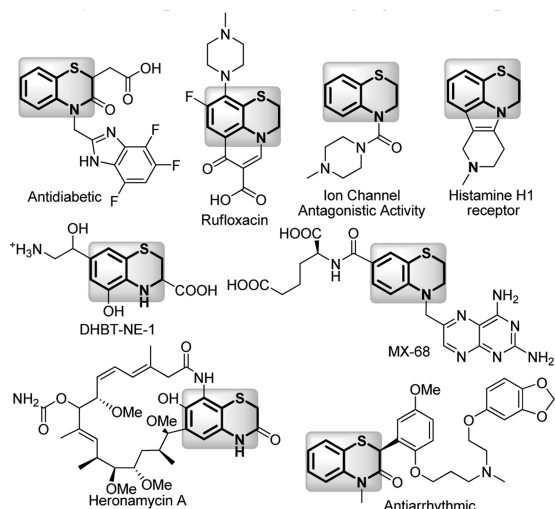
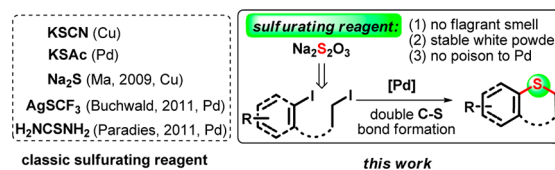


Figure 1. Bioactive 1,4-benzothiazine scaffolds.

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 Rh¹⁵ 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 Na₂S as sulfuration reagent.^{16a} In 2011, a general method for the Pd-catalyzed Ar–SCF₃ bond-forming reaction using AgSCF₃ 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 thiuration of 1,2-allenyl sulfones by using Na₂S₂O₃ as sulfur source.¹⁸ However, to the best of our knowledge, Na₂S₂O₃ 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 Na₂S₂O₃ 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-methylbenzenesulfonamide) catalyzed by PdCl₂(dppf) in the presence of Na₂S₂O₃·5H₂O. 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 Cs₂CO₃ as base in MeCN (Table 1, entry 1). The structure of **2a** was confirmed by X-ray analysis.¹⁹ To enhance the solubility of Na₂S₂O₃·5H₂O, H₂O 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 Na₂S₂O₃·5H₂O were used, but too much Na₂S₂O₃·5H₂O 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**): C₁₅H₁₅NO₂S₂, MW = 305.40, monoclinic, space group P2(1)/n, final *R* indices [*I* > 2σ(*I*)], *R*₁ = 0.0393, *wR*₂ = 0.1131, *R* indices (all data), *R*₁ = 0.0461, *wR*₂ = 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) Å³, *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.

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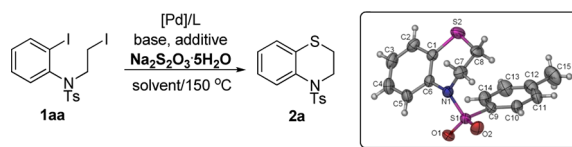
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Table 1. Optimization of Pd-Catalyzed Double C–S Bond Formation^a

entry	[Pd]	ligand (mol %)	base	solvent	additive	yield ^b (%)
1	PdCl ₂ (dppf)		Cs ₂ CO ₃	MeCN		10 ^c
2	PdCl ₂ (dppf)		Cs ₂ CO ₃	MeCN/H ₂ O (10:1)		15 ^c
3	PdCl ₂ (dppf)		Cs ₂ CO ₃	MeCN/H ₂ O (10:1)		20
4	PdCl ₂ (dppf)		Cs ₂ CO ₃	MeCN/H ₂ O (10:1)		19 ^d
5	PdCl ₂ (dppf)		Cs ₂ CO ₃	MeCN/H ₂ O (10:1)	TBAC	10
6	PdCl ₂ (dppf)		Cs ₂ CO ₃	MeCN/H ₂ O (10:1)	TBAB	39
7	PdCl ₂ (dppf)		Cs ₂ CO ₃	MeCN/H ₂ O (10:1)	TBAI	8
8	PdCl ₂ (dppf)	dppf (2)	Cs ₂ CO ₃	MeCN/H ₂ O (10:1)	TBAB	70
9	PdCl ₂ (dppf)	dppf (5)	Cs ₂ CO ₃	MeCN/H ₂ O (10:1)	TBAB	78
10	PdCl ₂ (dppf)	dppf (10)	Cs ₂ CO ₃	MeCN/H ₂ O (10:1)	TBAB	79
11	Pd(OAc) ₂	dppf (5)	Cs ₂ CO ₃	MeCN/H ₂ O (10:1)	TBAB	55
12	Pd(dba) ₂	dppf (5)	Cs ₂ CO ₃	MeCN/H ₂ O (10:1)	TBAB	63
13	Pd(PPh ₃) ₂ Cl ₂	dppf (5)	Cs ₂ CO ₃	MeCN/H ₂ O (10:1)	TBAB	50
14	PdCl ₂ (dppf)	TFP (10) ^e	Cs ₂ CO ₃	MeCN/H ₂ O (10:1)	TBAB	25
15	PdCl ₂ (dppf)	Sphos (10) ^f	Cs ₂ CO ₃	MeCN/H ₂ O (10:1)	TBAB	21
16	PdCl ₂ (dppf)	PCy ₃ (10) ^g	Cs ₂ CO ₃	MeCN/H ₂ O (10:1)	TBAB	trace
17	PdCl ₂ (dppf)	dppf (5)	Na ₂ CO ₃	MeCN/H ₂ O (10:1)	TBAB	28
18	PdCl ₂ (dppf)	dppf (5)	K ₂ CO ₃	MeCN/H ₂ O (10:1)	TBAB	30
19	PdCl ₂ (dppf)	dppf (5)	Ag ₂ CO ₃	MeCN/H ₂ O (10:1)	TBAB	42
20	PdCl ₂ (dppf)	dppf (5)	Cs ₂ CO ₃	MeCN/H ₂ O (5:1)	TBAB	57
21	PdCl₂(dppf)	dppf (5)	Cs₂CO₃	MeCN/H₂O (20:1)	TBAB	96
22	PdCl ₂ (dppf)	dppf (5)	Cs ₂ CO ₃	MeCN/H ₂ O (20:1)	TBAB	complicated ^h
23	PdCl ₂ (dppf)	dppf (5)	Cs ₂ CO ₃	MeCN/H ₂ O (20:1)	TBAB	complicated ⁱ

^a Reaction conditions: **1aa** (0.1 mmol), [Pd] (0.01 mmol), base (0.3 mmol), Na₂S₂O₃·5H₂O (0.5 mmol), additive (0.03 mmol), solvent (2.0 mL), 150 °C, 6 h. ^b Isolated yield. ^c Na₂S₂O₃·5H₂O (0.2 mmol, 2.0 equiv). ^d Na₂S₂O₃·5H₂O (1.0 mmol, 10.0 equiv). ^e TFP = tri(2-furyl)phosphine. ^f Sphos = 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl. ^g PCy₃ = tricyclohexylphosphine. ^h Replace Na₂S₂O₃ with S₈. ⁱ Replace Na₂S₂O₃ with Na₂S.

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 Cs₂CO₃ (Table 1, entries 14–19). Significantly, when MeCN:H₂O (20:1) was used, the highest yield (96%) was achieved (Table 1, entry 21). Neither S₈ nor Na₂S could take the integrant place of Na₂S₂O₃ (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 C_{sp}³-I, Br, Cl, OM, 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 derivatives 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-2H-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-2H-benzo[*b*][1,4]-thiazine **2a** could be converted to sulfoxide by NaIO₄, which was an analogue of rifloxacin. When compound **2a** was subjected to

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Scheme 2. Synthetic Transformation

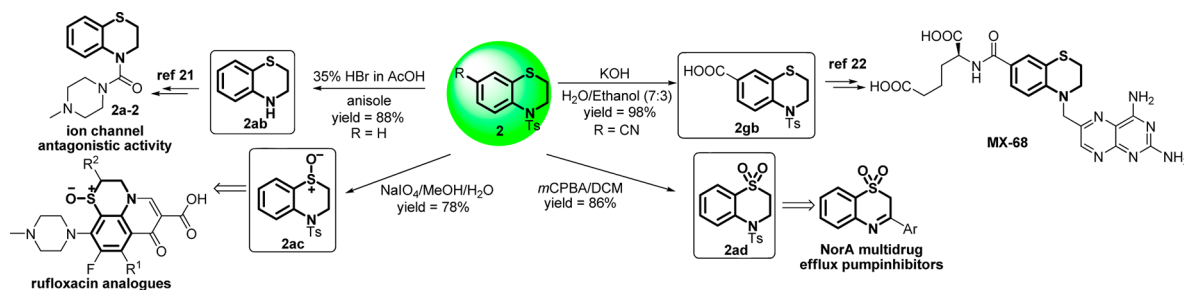
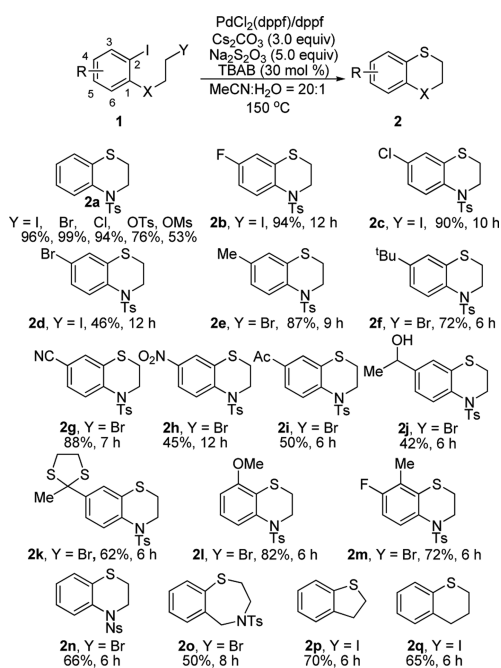


Table 2. Pd-Catalyzed Double C–S Bond Formation^a

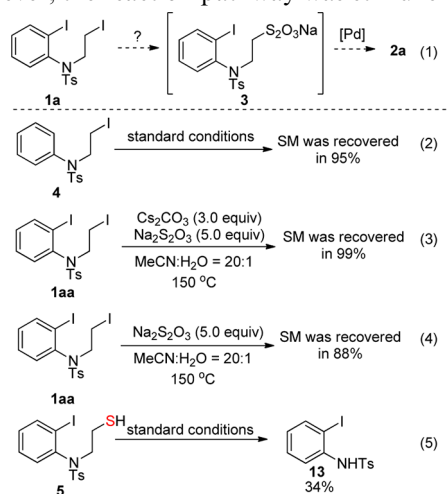


^a Reaction conditions: **1** (0.1 mmol), PdCl₂(dppf) (0.01 mmol, 10 mol %), dppf (0.005 mmol, 5 mol %), Cs₂CO₃ (0.3 mmol), Na₂S₂O₃·5H₂O (0.5 mmol), TBAB (0.03 mmol, 30 mol %), MeCN:H₂O (2.0 mL, 20:1), 8 h. ^b Isolated yield.

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

To investigate that how the Na₂S₂O₃ was introduced to this system, some control experiments were tentatively examined. Straightforward alkylated thiosulfate intermediate **3** via S_N2 replacement²³ were proposed (eq 1). However, no reaction was detected and compound **4** was almost fully recovered (eq 2). When **1aa** was tested without PdCl₂(dppf)/dppf (eq 3) or Cs₂CO₃ (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 standard 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 Csp³. However, the reaction pathway was still unsharp.



In conclusion, we have developed a novel method for the synthesis of substituted 1,4-benzothiazine derivatives which relies on a Pd-catalyzed coupling reaction. The important feature of this method is using stable Na₂S₂O₃ salt as sulfurating reagent which makes it free from foul-smelling thiols. The successful application of Na₂S₂O₃ 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. Na₂S₂O₃ 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.