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Regioselective Synthesis of Dihydrothiophenes and Thiophenes via the Rhodium-Catalyzed Transannulation of 1,2,3-Thiadiazoles with Alkenes

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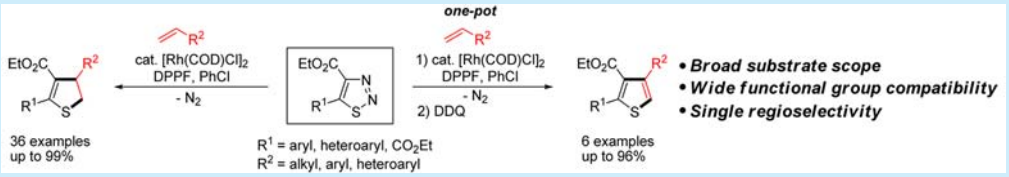
Supporting Information

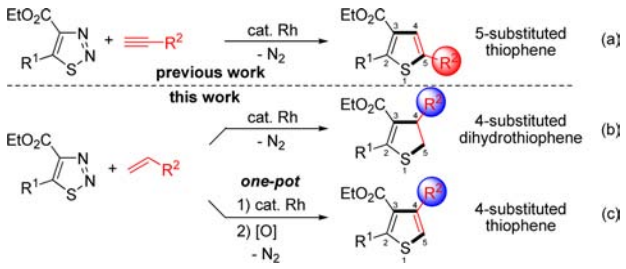


ABSTRACT: A method for the regioselective synthesis of a wide range of dihydrothiophenes was developed from the rhodium-catalyzed transannulation of 1,2,3-thiadiazoles with aliphatic, aromatic, and heteroaromatic alkenes. Tandem rhodium-catalyzed transannulation of 1,2,3-thiadiazoles with alkenes followed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation was also demonstrated for the one-pot regioselective synthesis of various thiophenes. Advantages of the present method include a broad substrate scope, wide functional group compatibility, and high regioselectivity.

Sulfur-containing five-membered heterocyclic compounds such as dihydrothiophenes and thiophenes represent key structural motifs due to their biological activities in natural products and pharmaceuticals.[1] In addition, thiophene derivatives are very attractive compounds in the field of material science due to their peculiar structural rigidity and useful electronic properties.[2] Thus, the development of synthetic methods for these core scaffolds has received considerable attention in contemporary chemistry. The regioselective introduction of a wide range of substituents onto dihydrothiophene and thiophene rings from readily available starting materials is required.[3]

Recently, denitrogenative transannulations have been recognized as an efficient method for the synthesis of a myriad of heterocyclic compounds.[4] For example, *N*-sulfonyl-1,2,3-triazoles have received a substantial amount of attention as the precursors of α-imino Rh carbenoid complexes.[5] Because these complexes have a nucleophilic imino nitrogen and an electrophilic carbene carbon in the molecule, they could serve as the 1,3-dipoles in the transannulations with dipolarophiles, affording a diverse array of nitrogen heterocycles. More recently, Rh-catalyzed transannulations of 1,2,3-thiadiazoles with alkynes were reported to regioselectively produce thiophenes via the Rh thiavinyl carbene intermediate (Scheme 1a).[6] In this case, when terminal alkynes were used, aryl and alkyl groups present on terminal alkyne moieties were regioselectively introduced onto the 5-position of the thiophene ring. Based on these results, we expected the formation of dihydrothiophenes with the introduction of various substituents onto the 5-position of the ring from the transition metal-catalyzed transannulation of 1,2,3-thiadiazoles with alkenes. However, in contrast to alkynes, we found serendipitous results in which a variety of substituents were regioselectively introduced onto the 4-position of dihydrothiophene rings from this reaction. In our continuing efforts to develop heterocyclic compounds, we report the regioselective Rh-catalyzed transannulation of 1,2,3-thiadiazoles with aliphatic, aromatic, and heteroaromatic alkenes, producing dihydrothiophenes with the introduction of a wide range of substituents onto the 4-position of the rings (Scheme 1b). In addition, tandem Rh-catalyzed transannulations of 1,2,3-thiadiazoles with alkenes followed by oxidation were demonstrated for the one-pot regioselective synthesis of thiophenes (Scheme 1c). These methods enabled modular synthesis of new functionalized dihydrothiophenes and thiophenes via Rh thiavinyl carbenes from 1,2,3-thiadiazoles.

Scheme 1. Regioselective Synthesis of Dihydrothiophenes and Thiophenes



We began our investigation by optimizing the transannulation of ethyl 5-phenyl-1,2,3-thiadiazole-4-carboxylate (**1a**) with styrene (**2a**) in the presence of $[Rh(COD)Cl]_2$ (2 mol %) and

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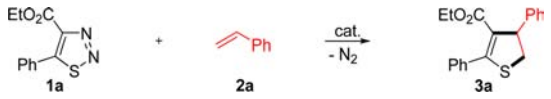
DPPF (5 mol %) (Table 1). Chloroform, dichloroethane (DCE), and toluene as solvents were ineffective for the transannulation

Table 1. Reaction Optimization[a]



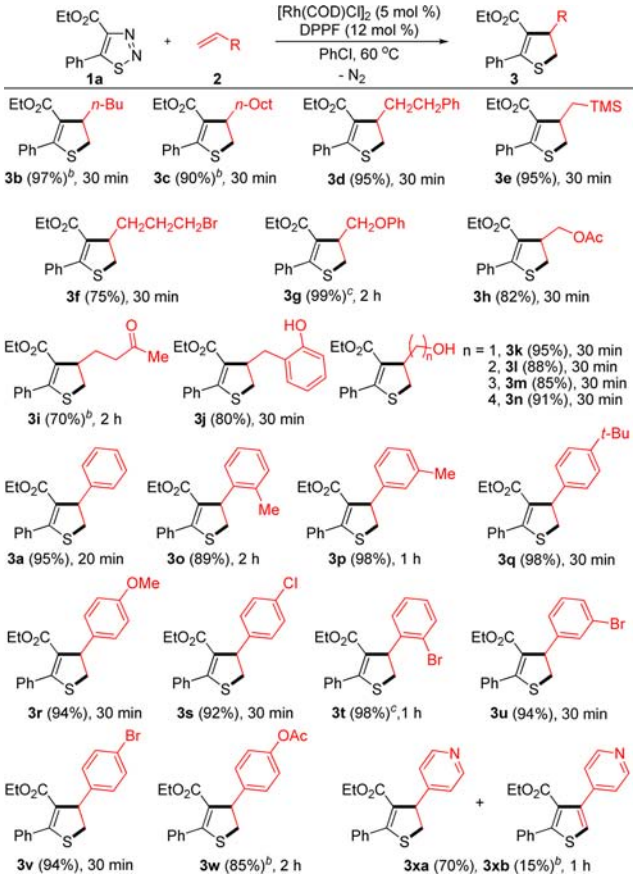
entry	cat. (mol %)	ligand (mol %)	solvent	temp. (°C)	time (h)	yield (%)[b]
1	$[Rh(COD)Cl]_2$ (2)	DPPF (5)	$CHCl_3$	60	12	0
2	$[Rh(COD)Cl]_2$ (2)	DPPF (5)	DCE	80	12	0
3	$[Rh(COD)Cl]_2$ (2)	DPPF (5)	toluene	110	12	0
4	$[Rh(COD)Cl]_2$ (2)	DPPF (5)	dioxane	100	12	32
5	$[Rh(COD)Cl]_2$ (2)	DPPF (5)	DCM	40	12	58
6	$[Rh(COD)Cl]_2$ (2)	DPPF (5)	PhCl	60	12	84
7	$[Rh(COD)Cl]_2$ (5)	DPPF (12)	PhCl	60	0.33	99(95)[c]
8	$[Rh(COD)Cl]_2$ (5)	DPPF (12)	PhCl	25	12	30
9	$Rh_2(oct)_4$ (5)	-	PhCl	60	1	0
10	$RhCl_3 \cdot H_2O$ (5)	DPPF (12)	PhCl	60	1	0
11	$Rh(PPh_3)_3Cl$ (5)	DPPF (12)	PhCl	60	1	0
12	$[Ir(COD)Cl]_2$ (5)	DPPF (12)	PhCl	60	1	0

[a]Reaction conditions: **1a** (0.2 mmol, 1 equiv), **2a** (2 equiv), $[Rh(COD)Cl]_2$, and DPPF in solvent (1.0 mL) were used under N_2. [b]NMR yields using dibromomethane as an internal standard. [c]Isolated yield.

(entries 1−3). However, dioxane and dichloromethane (DCM) gratifyingly gave the desired dihydrothiophene **3a** in 32% and 58% yields, respectively, via the transannulation (entries 4 and 5). Among the solvents examined, chlorobenzene provided the dihydrothiophene **3a** in 84% yield at 60 °C for 12 h (entry 6). An increased amount of $[Rh(COD)Cl]_2$ (5 mol %) and DPPF (12 mol %) afforded **3a** in 30% yield in chlorobenzene at 25 °C for 12 h (entry 8). When the reaction mixture was heated in chlorobenzene at 60 °C for 20 min, the desired dihydrothiophene **3a** was obtained in quantitative yield (95% isolated yield) (entry 7). Isomeric 5-phenyl-substituted dihydrothiophene was not formed. Among the catalysts studied, $Rh_2(oct)_4$, $RhCl_3 \cdot H_2O$, $Rh(PPh)_3Cl$, and $[Ir(cod)Cl]_2$ were not effective for the transannulation (entries 9−12). Control experiments demonstrated that both $[Rh(COD)Cl]_2$ and DPPF were crucial for the transannulation reaction (see the Supporting Information).

With these optimized conditions in hand, we then investigated the scope and limitations of a wide range of alkenes in the transannulation with ethyl 5-phenyl-1,2,3-thiadiazole-4-carboxylate (**1a**) (Scheme 2). When aliphatic alkenes such as 1-hexene and 1-decene were treated with **1a** in chlorobenzene, the desired dihydrothiophene products (**3b** and **3c**) were regioselectively produced in excellent yields. 4-Phenyl-1-butene was smoothly transannulated to afford dihydrothiophene **3d** in 95% yield under the optimized conditions. Substituents such as trimethylsilyl, ether, and acetoxy groups on the alkyl group of aliphatic alkenes **2** did not influence the efficiency of the transannulation, leading to the formation of a wide range of new functionalized

Scheme 2. Substrate Scope of Alkenes[a]



[a]Reaction conditions: **1a** (0.2 mmol, 1 equiv) was reacted with **2** (2 equiv) in the presence of $[Rh(COD)Cl]_2$ (5 mol %) and DPPF (12 mol %) in PhCl (1.0 mL) under N_2 at 60 °C. [b]80 °C. [c]**2** (4 equiv) at 100 °C.

dihydrothiophenes (**3e**, **3g**, and **3h**) in good to excellent yields ranging from 82% to 99%. However, bromo and carbonyl groups slightly influenced the transannulation, and the desired dihydrothiophenes (**3f** and **3i**) were obtained in 75% and 70% yields, respectively. In particular, note that an unprotected hydroxyl group was compatible with the present method. In addition, the directing effect was not induced upon increasing the chain length between the hydroxyl group and the double bond. For example, 2-allylphenol and various ω-hydroxy-1-alkenes were smoothly cyclized to afford the desired dihydrothiophenes (**3j**−**3n**) in good to excellent yields ranging from 80% to 95%. No isomeric 5-substituted dihydrothiophenes were formed in any reactions.

Next, a wide range of aromatic alkenes were examined to further explore the generality of the present transannulation under the optimized conditions. Electronic variation of the substituents on the aryl group of aromatic alkenes and steric congestion did not affect the reaction efficiency. For example, the styrene derivatives bearing electron-donating groups (Me, *t*-Bu, OAc, and MeO) on the aryl moiety did not influence the efficiency of the transannulation. In addition, electron-withdrawing groups (Cl and Br) on the aryl moiety were highly compatible under the reaction conditions and furnished the corresponding functionalized dihydrothiophenes **3s**−**3v** in excellent yields ranging from 92% to 98%. When 4-vinylpyridine was treated with thiadiazole **1a**, the desired pyridin-4-yl-substituted dihydrothiophene **3xa**

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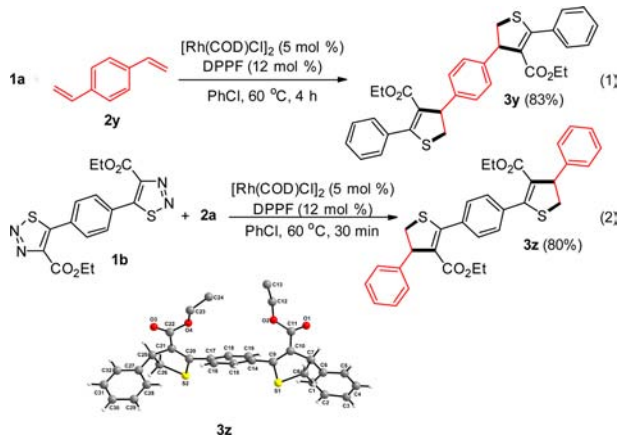
was obtained in 70% yield along with thiophene **3xb** (15%). However, internal and 1,1-disubstituted alkenes such as *trans*-β-methylstyrene and α-methylstyrene and ethyl acrylate were not effective for this transannulation.

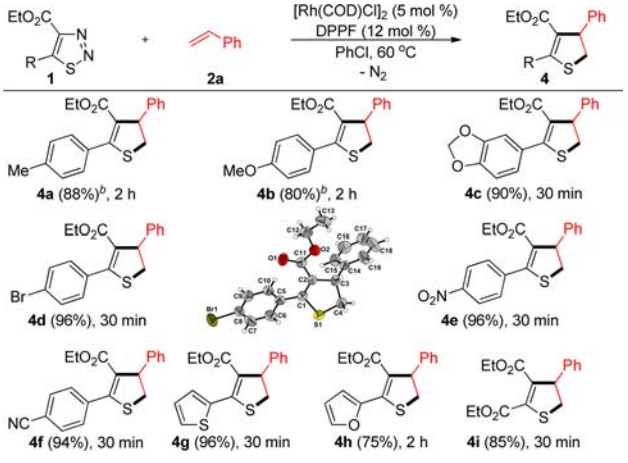
Encouraged by these results, the synthesis of oligomeric compounds consisting of benzene and dihydrothiophene rings was attempted using the developed reaction. When thiadiazole (**1a**) (2.5 equiv) was treated with 1,4-divinylbenzene (**2y**, 1 equiv) under the optimized conditions, twofold transannulations smoothly occurred, leading to the formation of pentameric compounds consisting of benzene and dihydrothiophene rings (**3y**) in 83% yield (eq 1). A pentaoligomer with a different



connectivity of the sulfur and carbon bond in two dihydrothiophene rings was also prepared. When 1,4-di(thiadiazolyl)benzene **1b** (1 equiv) was reacted with styrene (**2a**, 4 equiv), the desired pentameric compound **3z** consisting of three benzene and two dihydrothiophene rings was produced in 80% yield (eq 2).

Stimulated by these results, we studied the scope of a number of thiadiazoles (**1**) in the transannulation with styrene (**2a**) (Scheme 3). Ethyl 5-aryl-1,2,3-thiadiazole-4-carboxylates (**1**) bearing an electron-donating methyl, methoxy, and methylenedioxy group on the aryl ring were efficiently subjected to the transannulation with **2a**, regioselectively affording the desired dihydrothiophenes **4a**, **4b**, and **4c**, respectively, in good to excellent yields (80−90%)

Scheme 3. Substrate Scope of Thiadiazoles[a]

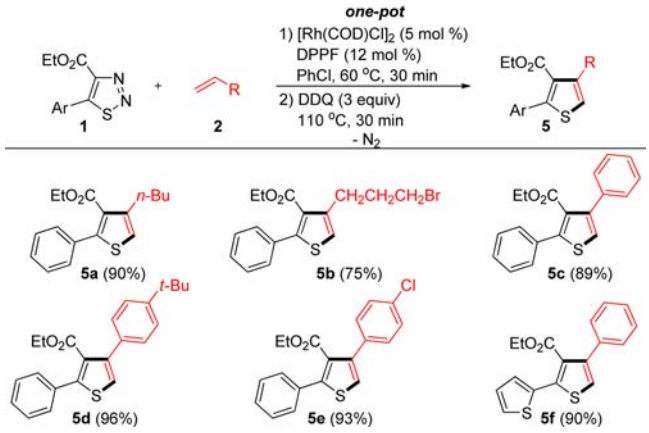


[a]Reaction conditions: **1** (0.2 mmol, 1 equiv) was reacted with **2a** (2 equiv) in the presence of $[Rh(COD)Cl]_2$ (5 mol %) and DPPF(12 mol %) in PhCl (1.0 mL) under N_2 at 60 °C. [b]80 °C.

under the optimized conditions. Electron-withdrawing bromo, nitro, and cyano groups on the aryl ring of thiadiazoles did not affect the transannulation efficiency and afforded a variety of new functionalized dihydrothiophenes (**4d**, **4e**, and **4f**) in excellent yields ranging from 94% to 96%. Heteroaryl-substituted thiadiazoles were easily converted to the corresponding dihydrothiophenes. For example, thiadiazoles with thiophen-2-yl and furan-2-yl groups at the 5-position are applicable to the present transformation, providing the corresponding dihydrothiophenes (**4g** and **4h**) in 96% and 75% yields, respectively. When diethyl 1,2,3-thiadiazole-4,5-dicarboxylate was employed, the desired dihydrothiophene **4i** was obtained in 85% yield.

As an extension of this work, we attempted the synthesis of thiophenes directly from the Rh-catalyzed transannulation of thiadiazoles with alkenes followed by oxidation in one pot (Scheme 4). Rh-catalyzed transannulation of **1a** with 1-hexene

Scheme 4. Synthesis of Thiophenes from Thiadiazoles and Alkenes *via* the One-Pot Rh-Catalyzed Transannulation and Subsequent Oxidation[a]



[a]Reaction conditions: **1** (0.2 mmol, 1 equiv) was reacted with **2** (2 equiv) in the presence of $[Rh(COD)Cl]_2$ (5 mol %) and DPPF (12 mol %) in PhCl (1.0 mL) under N_2 at 60 °C for 30 min, followed by the addition of DDQ (3 equiv).

and 5-bromo-1-pentene and sequential oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) provided the corresponding thiophenes **5a** and **5b** in 90% and 75% yields, respectively. To our delight, the catalytic transannulation followed by oxidation using styrene as well as styrene derivatives bearing the 4-*tert*-butyl and 4-chloro groups on the aryl ring smoothly occurred to give the desired thiophenes (**5c**, **5d**, and **5e**) in good to excellent yields ranging from 89% to 96%. Thiadiazole containing the thiophen-2-yl group was found to transannulate with styrene (**2a**) to afford the corresponding thiophene **5f** in 90% yield.

After thiadiazole (**1a**) was treated with allyl alcohol under the optimized conditions, heating of the reaction mixture to 130 °C for 12 h produced tandem products **6a** (30%) via Rh-catalyzed transannulation followed by lactonization and **6b** (30%) via Rh-catalyzed transannulation, lactonization, and then oxidation in one pot (eq 3). After **1a** was subjected to 3-buten-1-ol in the presence of the Rh-catalyst, thermal lactonization followed by DDQ oxidation in one pot provided **6c** in 55% yield (eq 4).

A plausible reaction mechanism is proposed in Scheme 5. The α-thiavinyl Rh-carbenoid **II** is provided from the denitrogenation of the α-diazo thiocarbonyl **I** derived from a reversible ring-chain

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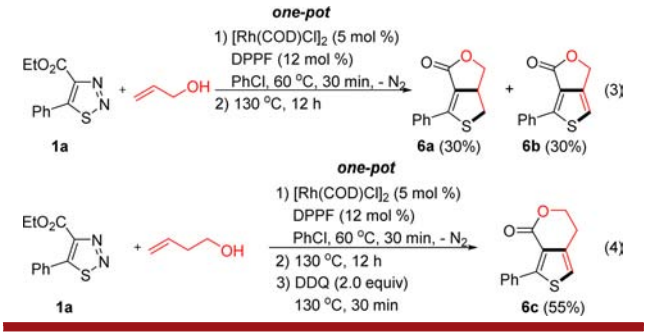
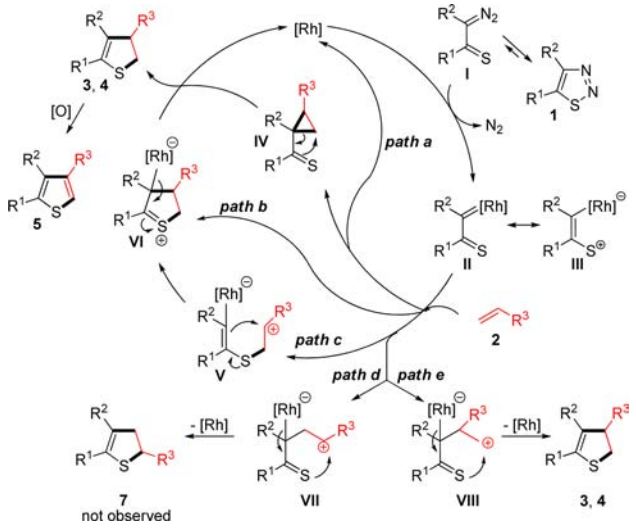


Scheme 5. A Proposed Mechanism



tautomerization of thiadiazole **1** with the Rh catalyst.[6] The [2 + 1] cycloaddition of **II** with alkene **2** affords the cyclopropyl thioketone **IV**, which then cycloisomerizes to dihydrothiophene **3** and **4** (path a). In addition, the sulfenium intermediate **III** reacts with alkene **2** (path c) to provide the zwitterionic intermediate **V**, which then cyclizes to the intermediate **VI**. Alternatively, the intermediate **VI** can be generated via the [3 + 2] cycloaddition of the Rh-carbenoid **II** with alkene **2** (path b). Eventually, **VI** releases the Rh catalyst and produces dihydrothiophenes **3** and **4**. Based on the selective formation of 4-substituted dihydrothiophene, the intermediate **VII** is ruled out in the catalytic cycle (path d). Path e is also ruled out due to the instability of the intermediate **VIII**. The elucidation of the detailed mechanism of the transannulation must wait for further study.

In summary, a method for the regioselective synthesis of a wide range of dihydrothiophenes was developed from the Rh-catalyzed transannulation of 1,2,3-thiadiazoles with aliphatic, aromatic, and heteroaromatic alkenes. Rh-catalyzed transannulation of thiadiazoles with alkenes and sequential oxidation with DDQ were also demonstrated for the one-pot regioselective synthesis of thiophenes. This method was employed to efficiently synthesize pentaoligomeric compounds consisting of three benzene and two dihydrothiophene rings. Advantages of the present method include a broad substrate scope, wide functional group compatibility, and high regioselectivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02805.

Experimental procedures, characterization data, X-ray crystallography data (**3e**, **3z**, and **4d**), and copies of NMR spectra for all products (PDF)
Crystallography data for **3e** (CIF)
Crystallography data for **3z** (CIF)
Crystallography data for **4d** (CIF)

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Notes

The authors declare no competing financial interest.

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