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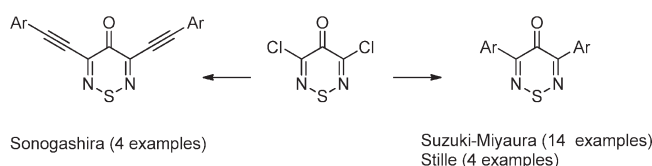
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ABSTRACT

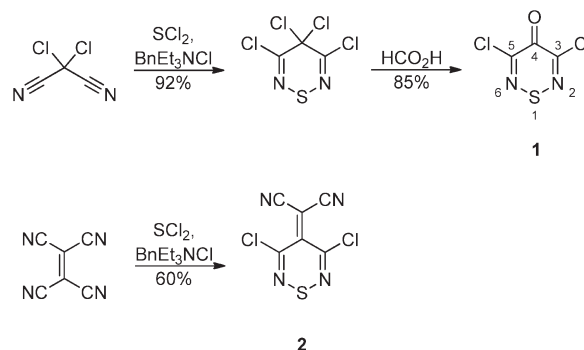


Palladium catalyzed Suzuki–Miyaura, Stille, and Sonogashira coupling reactions are reported for the electron-deficient heterocyclic scaffold 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one (**1**). Furthermore, 3,5-di(thien-2-yl)-4*H*-1,2,6-thiadiazin-4-one (**7m**) is further elaborated to afford the tetrathienyl 3,5-bis[(2,2'-bithien)-5-yl]-4*H*-1,2,6-thiadiazin-4-one (**9**). All compounds are fully characterized.

Various oxidized 1,2,6-thiadiazines such as the sulfoxides and, more importantly, the sulfones have received considerable attention in various areas of applied chemistry including the pharmaceutical,¹ agrochemical,² and materials³ sectors. Commercially, an important 1,2,6-thiadiazine is bentazone [3-isopropyl-1*H*-2,1,3-benzothiadiazin-4(3*H*)-one 2,2-dioxide], which is a selective herbicide of long-standing.⁴

Surprisingly little, however, has appeared in the literature on nonoxidized 4*H*-1,2,6-thiadiazines. Monocyclic 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one (**1**)⁵ and its 4-dicyanomethylene analogue 2-(3,5-dichloro-4*H*-1,2,6-thiadiazin-4-ylidene)malononitrile (**2**)⁶ have been prepared, the former in two steps starting from dichloromalononitrile and the latter in one step from tetracyanoethylene (TCNE) (Scheme 1). Both are useful precursors to several polycyclic 1,2,6-thiadiazine systems.⁷

Scheme 1. Synthesis of 4*H*-1,2,6-Thiadiazines **1** and **2**



Many monochloro derivatives of thiadiazinones have high fungicidal activity,⁸ while fused 4*H*-1,2,6-thiadiazines such as acenaphtho[5,6-*cd*][1,2,6]thiadiazine (**3**)⁹ and naphtho[1,8-*cd*:4,5-*c'd'*]bis[1,2,6]thiadiazine (**4**)¹⁰ (Figure 1) have been studied as examples of “extreme quinoids” that have ambiguous aromatic character.

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More recently, Torroba et al. prepared cyclopenta[1,2,6]-thiadiazines **5** and **6** starting from cyclic enaminonitriles,¹¹ some of which displayed unusual liquid crystalline properties or behaved as near-infrared dyes. The synthesis and chemistry of 1,2,6-thiadiazines have been reviewed.¹²

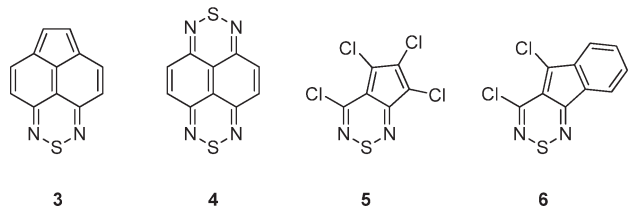


Figure 1. Selected fused 4H-1,2,6-thiadiazines.

The known chemistry of dichlorothiadiazines **1** and **2** includes nucleophilic substitution of the C-3 and/or C-5 chlorine atoms by nitrogen, oxygen, and sulfur nucleophiles.^{7,8} X-ray diffraction shows the thiadiazine ring of thiadiazine **1** to be almost planar¹³ while that of the ylidene malononitrile **2** to be a shallow boat.^{6a} Bird's aromaticity index (I_A), based upon the statistical evaluation of deviations in peripheral bond orders derived from experimental bond lengths,¹⁴ gives I_A 54¹⁴ and 60^{6a} for thiadiazines **1** and **2**, respectively, that indicated modest aromaticity (cf. I_A = 53 for furan and 100 for benzene). Owing to these properties, we were interested in incorporating the 4H-1,2,6-thiadiazine motif into π -conjugated polymers (Figure 2). As such, we needed to develop efficient conditions for C-functionalization of the C-3 and C-5 positions.

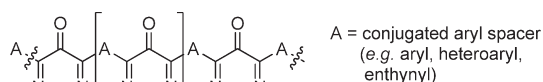


Figure 2. Proposed 4H-1,2,6-thiadiazine polymers.

Herein, we describe several Suzuki–Miyaura, Stille, and Sonogashira palladium-catalyzed C–C coupling reactions of dichlorothiadiazine **1** to give symmetrical 3,5-bis-arylated, heteroarylated, and alkynylated thiadiazines.

Palladium-catalyzed C–C coupling reactions have widely been used for the synthesis of alkylated and/or arylated arenes and heteroarenes.¹⁵ Interestingly, while there are many electron-rich symmetrical dihalo heterocyclic systems that participate in palladium-catalyzed C–C coupling reactions to give in one-pot bis-arylated/alkylated systems there are relatively few examples of electron-poor symmetrical dihaloheteroarenes, e.g., 1,2,5-thiadiazoles,¹⁶ 1,3,4-thiadiazoles,¹⁷ pyridines,¹⁸ and pyrimidines.¹⁹

Owing to the facile displacement of chloride by a wide variety of nucleophiles, the initial attempts at Suzuki–Miyaura coupling of the dichlorothiadiazine **1** focused on protocols that were nonaqueous with the hope of limiting base-catalyzed hydrolysis of the heterocycle. Similar anhydrous protocols worked well for the C-5 selective Suzuki–Miyaura reactions of highly reactive 3,5-dichloroisothiazole-4-carbonitrile.²⁰ Nevertheless, when the dichlorothiadiazine **1** was reacted with phenylboronic acid (2.2 equiv) and Pd(OAc)₂ (5 mol %) in organic solvents (PhH, PhMe, DCM, MeCN, 1,4-dioxane, THF) and inorganic bases [M₂CO₃ (M = Li, Na, K, Cs), KHCO₃, KF, KOH, K₃PO₄] or organic (Et₃N, *i*-Pr₂NEt, pyridine) together with phase-transfer agents (18-C-6, Adogen 464, Aliquat 336, BnEt₃NI, BnEt₃NCl) only mixtures of unreacted dichlorothiadiazine **1** and mono- and bisphenylated thiadiazines were isolated after 24 h. In light of this, we switched to biphasic systems, and fortunately, this led to complete consumption of the dichlorothiadiazine **1**. We screened a range of solvents (PhH, PhMe, DCM, 1,4-dioxane, DME, MeCN, THF, DMA, DMF), bases [KOH, M₂CO₃, MHCO₃, MF (M = Na, K, Cs)], and catalysts [(Pd(Ph₃P)₄, Pd(OAc)₂, (Ph₃P)₂PdCl₂, (PhCN)₂-PdCl₂, (MeCN)₂PdCl₂, (dba)₃Pd₂, [1,1'-(Ph₂P)ferrocene]-PdCl₂.DCM]. The best conditions required the use of PhB(OH)₂ (2.2–3 equiv), Pd(Ph₃P)₄ (5 mol %), and Na₂CO₃ (2 equiv) in either 1,4-dioxane/H₂O (5:3) or benzene/H₂O (5:3) at 20–100 °C. The concentration of the reaction mixture proved to be important: high concentrations (e.g., 0.8 mL for 0.27 mmol of **1**) led to faster and cleaner reaction. Using the best conditions, 12 analogues were synthesized that tested both steric and electronic limits (Table 1).

In most cases, 2-substituted phenylboronic acids reacted as well as the 3- and 4-substituted analogues, indicating that there was little steric effect; however, when the more sterically demanding 2,6-dimethylphenylboronic acid was used no product was obtained (Table 1, entry 5). In the case of 3-nitrophenyl analogue, the yield was low and could not

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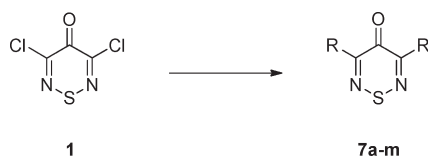
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Table 1. Reaction of Dichlorothiadiazinone **1** (0.273 mmol) with RB(OH)_2 (2.2 equiv), $\text{Pd(Ph}_3\text{P)}_4$ (5 mol %), and Na_2CO_3 (2 equiv) in Dioxane/ H_2O (0.5:0.3 mL) at 20–100 °C



entry	RB(OH)_2 (equiv)	time (min)	yield (%)
1	PhB(OH)_2 (2.2)	20	7a (91)
2	2-TolB(OH)_2 (2.2)	30	7b (94)
3	3-TolB(OH)_2 (2.2)	30	7c (91)
4	4-TolB(OH)_2 (2.2)	15	7d (99)
5	$2,6\text{-Me}_2\text{C}_6\text{H}_3\text{B(OH)}_2$ (2.2)	40	^a
6	$2\text{-MeOC}_6\text{H}_4\text{B(OH)}_2$ (2.2)	15	7e (87)
7	$3\text{-MeOC}_6\text{H}_4\text{B(OH)}_2$ (2.2)	15	7f (88)
8	$4\text{-MeOC}_6\text{H}_4\text{B(OH)}_2$ (2.2)	15	7g (86)
9	$2\text{-ClC}_6\text{H}_4\text{B(OH)}_2$ (2.2)	40	7h (80)
10	$3\text{-ClC}_6\text{H}_4\text{B(OH)}_2$ (2.2)	40	7i (81)
11	$4\text{-ClC}_6\text{H}_4\text{B(OH)}_2$ (2.2)	40	7j (89)
12	$3\text{-O}_2\text{NC}_6\text{H}_4\text{B(OH)}_2$ (2.2)	30	7k (54)
13	$3\text{-O}_2\text{NC}_6\text{H}_4\text{B(OH)}_2$ (3)	30	7k (64)
14	$3\text{-O}_2\text{NC}_6\text{H}_4\text{B(OH)}_2$ (4)	30	7k (66)
15	thien-3-ylB(OH) ₂ (2.2)	15	7l (98)
16	thien-2-ylB(OH) ₂ (2.2)	75	7m (42)
17	thien-2-ylB(OH) ₂ (3)	60	7m (90)
18	pyrid-3-ylB(OH) ₂ (2.2)	60	^a
19	pyrid-4-ylB(OH) ₂ (2.2)	60	^a
20	MeB(OH)_2 (2.2)	30	^a

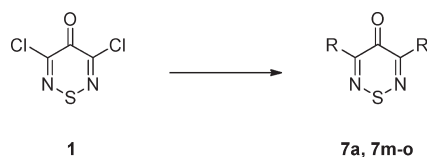
^a Consumption of the starting material, no product.

be significantly improved by increasing the quantity of the boronic acid from 2.2 to 4 equiv (entries 12–14). The other electron-poor 3- and 4-pyridylboronic acids gave only intractable polar products (baseline on TLC) (entries 18 and 19). The reaction with methylboronic acid was also unsuccessful (entry 20). Fortunately, both the 2- and 3-thienylboronic acids reacted to give the expected bithienyl-substituted thiadiazinones **7m** and **7l**, although the former required additional equivalents to give high yields (entry 17). This was not surprising considering the ease with which thien-2-ylboronic acid suffers protodeboronation.²¹

The Stille coupling of dichlorothiadiazinone **1** with phenyl, fur-2-yl, thien-2-yl, and *N*-methylpyrrol-2-yltributylstannanes in the presence of $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ (5 mol %) in MeCN gave the expected products in very high yields. Other stannyl reagents such as thiazol-2-yl, vinyl, propynyl, and tributylstannyl led to either decomposition or no reaction (Table 2).

Having access to a high-yielding synthesis of 3,5-di-(thien-2-yl)-4*H*-1,2,6-thiadiazin-4-one (**7m**) and in light

Table 2. Reaction of Dichlorothiadiazinone **1** (0.273 mmol) with R_3SnBu_3 , $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ (5 mol %) in MeCN (1 mL) at 20–82 °C

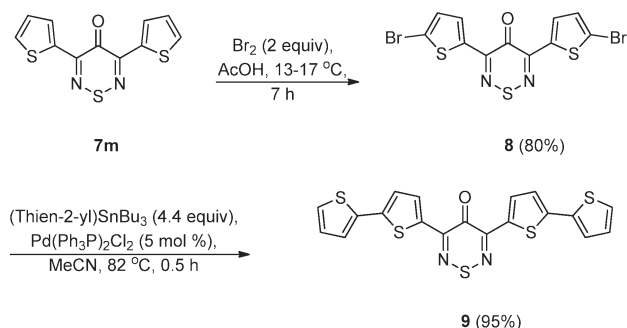


entry	R	R_3SnBu_3 (equiv)	time (h)	yield (%)
1	Ph	2.2	2.5	7a (95)
2	fur-2-yl	2.2	0.75	7n (92)
3	thien-2-yl	2.2	1	7m (92)
4	<i>N</i> -Me-pyrrol-2-yl	2.2	1	7o (93)
5	thiazol-2-yl	2.2	20	^a
6	vinyl	2.2	4	^a
7	propynyl	3	4	^b
8	Bu_3Sn	3	24	^b

^a Consumption of the starting material, no product. ^b Recovered starting material.

of our ongoing goal for the incorporation of thiadiazine into conjugated polymers, we proceeded to synthesize oligothiophene 1,2,6-thiadiazin-4-one **9** (Scheme 2). Oligo- and polythiophenes are shown to be important as advanced electronic and photonic materials, such as organic TFT's, liquid crystals, photovoltaic cells, etc.²²

Scheme 2. Synthesis of Tetrathienyl-1,2,6-thiadiazine **9**

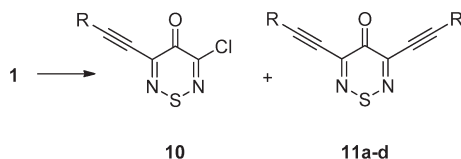


Bromination of bis(thien-2-yl) 1,2,6-thiadiazin-4-one **7m** using 2 equiv of either Br_2 or NBS in AcOH at low temperature (13–15 °C) gave the 3,5-di(5-bromothiophen-2-yl)-4*H*-1,2,6-thiadiazin-4-one (**8**) in 80% yield. The latter underwent the Stille conditions developed previously using 2-tributylstannylthiophene in refluxing MeCN to afford the tetrathiophene **9** in very high yield (95%).

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Table 3. Reaction of Dichlorothiadiazinone **1** (0.273 mmol) with Acetylene (2.2 equiv), Et₃N (4 equiv), CuI (10 mol %), and (Ph₃P)₂PdCl₂ (5 mol %) in MeCN



entry	R	time (min)	yield (%)
1	Ph	10	11a (73)
2	thien-3-yl	30	11b (69)
3	pyrid-2-yl	30	^a
4	pyrid-3-yl	45	11c (68)
5	ferrocenyl	180	10 (10), 11d (17)
6	TMS	60	^b

^a Complex reaction mixture. ^b Decomposition.

The photophysical properties of the bis- and tetrathio-phenes **7m** and **9** are now under investigation.

Attempts to carry out the Sonogashira reaction between the dichlorothiadiazinone **1** and phenylacetylene included the examination of the solvent (PhH, PhMe, 1,4-dioxane, THF, DMF, DCM, MeCN) and organic base (Et₃N, Hünig's, lutidine, pyridine) using 5 mol % of a palladium source [Pd(Ph₃P)₄, (dba)₃Pd₂, Pd(OAc)₂, (PhCN)₂PdCl₂, (MeCN)₂PdCl₂, (Ph₃P)₂PdCl₂, and [1,1'-(Ph₂P)ferrocene]—PdCl₂·DCM] and CuI (10 mol %) at rt. The best yield of bisacetylene **11a** (73%) was obtained using MeCN, Et₃N

(4 equiv), (Ph₃P)₂PdCl₂ (5 mol %), and CuI (10 mol %) at rt (Table 3, entry 1). Using these conditions, the 3,5-bis(thien-3-ylacetylene) derivative **11b** was synthesized in 69% yield at 20–80 °C. While 3-pyridinylacetylene gave the 3,5-bis(pyrid-3-ylacetylene) **11c** in 68% yield, the 2-pyridinyl acetylene led to a very complex reaction mixture even at higher temperature (80 °C). Use of the ferrocenyl acetylene (3 equiv) gave mixtures of the mono- and disubstituted thiadiazin-4-ones **10** and **11d** in 10 and 17% yields, respectively, while use of TMS-acetylene led to decomposition of the starting material (Table 3).

In conclusion, the dichlorothiadiazinone **1** undergoes Pd-catalyzed Suzuki–Miyaura, Stille, and Sonogashira C–C coupling reactions to afford symmetrical bis-arylated, heteroarylated, and alkynylated systems, respectively. 3,5-Di(thien-2-yl)-4*H*-1,2,6-thiadiazin-4-one (**7m**) was further modified to afford 3,5-bis[(2,2'-bithien)-5-yl]-4*H*-1,2,6-thiadiazin-4-one (**9**).

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Supporting Information Available. Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.