ORGANIC LETTERS
2011
Vol. 13, No. 13
3466–3469

Palladium Catalyzed C−C Coupling Reactions of 3,5-Dichloro-4*H*-1,2,6-thiadiazin-4-one

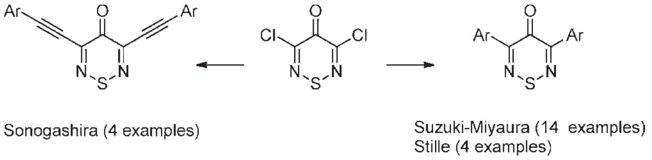
Heraklidia A. Ioannidou, Christos Kizas, and Panayiotis A. Koutentis*

Department of Chemistry, University of Cyprus, P.O. Box 20537, 1678 Nicosia, Cyprus

koutenti@ucy.ac.cy

Received May 6, 2011

ABSTRACT

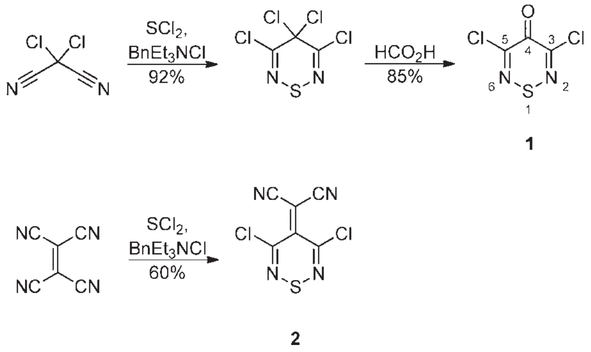


Palladium catalyzed Suzuki−Miyaura, Stille, and Sonogashira coupling reactions are reported for the electron-deficient heterocyclic scaffold 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one (1). Furthermore, 3,5-di(thien-2-yl)-4*H*-1,2,6-thiadiazin-4-one (7m) is further elaborated to afford the tetrathienyl 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 materials[3] sectors. Commercially, an important 1,2,6-thiadiazine is bentazone [3-isopropyl-l*H*-2,l,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.

---

[1] Breining, T.; Cimpoia, A. R.; Mansour, T. S.; Cammack, N.; Hopewell, P.; Ashman, C. *Heterocycles* **1995**, *41*, 87.

[2] McKendry, L. H.; Bland, W. P. U.S. Patent 4,155,746, 1979.

[3] Wigand, R.; Guerra, J. M. *J. Photochem. Photobiol., A: Chem.* **1995**, *88*, 35.

[4] Hamprecht, G.; König, K.-H.; Stubenrauch, G. *Angew. Chem., Int. Ed.* **1981**, *20*, 151.

[5] Geevers, J.; Trompen, W. P. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 270.

[6] (a) Koutentis, P. A.; Rees, C. W.; White, A. J. P.; Williams, D. J. *Chem. Commun.* **2000**, 303. (b) Koutentis, P. A.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1089.

[7] (a) Koutentis, P. A.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2601. (b) Kalogirou, A. S.; Koutentis, P. A.; Rikkou, M. D. *Tetrahedron* **2010**, *66*, 1817.

[8] Peake, C. J.; Harnish W. N.; Davidson, B. L. U.S. Patent 4,097,594, 1978.

[9] (a) Flowerday, P.; Perkins, M. J. *Tetrahedron* **1968**, *9*, 1261. (b) Flowerday, P.; Perkins, M. J.; Arthur, A. R. J. *J. Chem. Soc. C* **1970**, 290.

[10] Haddon, R. C.; Kaplan, M. L.; Marshall, J. H. *J. Am. Chem. Soc.* **1978**, *100*, 1235.

10.1021/ol201212b

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]

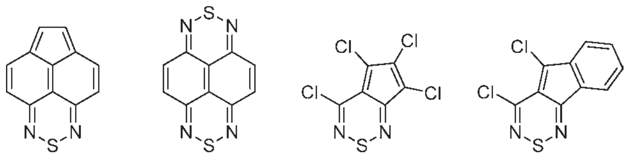


Figure 1. Selected fused 4*H*-1,2,6-thiadiazines.

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 thiadiazinone **1** to be almost planar[13] while that of the ylidenemalononitrile **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 54[14] 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 4*H*-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.

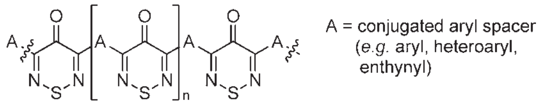


Figure 2. Proposed 4*H*-1,2,6-thiadiazine polymers.

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

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 dichlorothiadiazinone **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 dichlorothiadiazinone **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 [M_2CO_3 (M = Li, Na, K, Cs), $KHCO_3$, KF, KOH, K_3PO_4] or organic (Et_3N, *i*-Pr_2NEt, pyridine) together with phase-transfer agents (18-C-6, Adogen 464, Aliquat 336, $BnEt_3NI$, $BnEt_3NCl$,) only mixtures of unreacted dichlorothiadiazinone **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 dichlorothiadiazinone **1**. We screened a range of solvents (PhH, PhMe, DCM, 1,4-dioxane, DME, MeCN, THF, DMA, DMF,), bases [KOH, M_2CO_3, $MHCO_3$, MF (M = Na, K, Cs)], and catalysts [($Pd(Ph_3P)_4$, $Pd(OAc)_2$, $(Ph_3P)_2PdCl_2$, $(PhCN)_2$-$PdCl_2$, $(MeCN)_2PdCl_2$, $(dba)_3Pd_2$, [1,1′-(Ph_2P)ferrocene]-$PdCl_2$.DCM)]. The best conditions required the use of $PhB(OH)_2$ (2.2–3 equiv), $Pd(Ph_3P)_4$ (5 mol %), and Na_2CO_3 (2 equiv) in either 1,4-dioxane/H_2O (5:3) or benzene/H_2O (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

---

(11) (a) Gómez, T.; Macho, S.; Miguel, D.; Neo, A. G.; Rodríguez, T.; Torroba, T. *Eur. J. Org. Chem.* **2005**, 5055. (b) Macho, S.; Miguel, D.; Neo, A. G.; Rodríguez, T.; Torroba, T. *Chem. Commun.* **2005**, 334.

(12) Weintraub, P. M. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Turnbull, K., Eds.; Elsevier: Oxford, 2008; Vol. 9, Chapter 9.07, p 3355.

(13) Harkema, S. *Acta Crystallogr., Sect. B* **1978**, *34*, 2927.

(14) (a) Bird, C. W. *Tetrahedron* **1986**, *42*, 89. (b) Bird, C. W. *Tetrahedron* **1992**, *48*, 335.

(15) (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2008**, *64*, 3047. (b) Yin, L; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133. (c) Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704.

(16) Merschaert, A.; Gorissen, H. J. *Heterocycles* **2003**, *60*, 29.

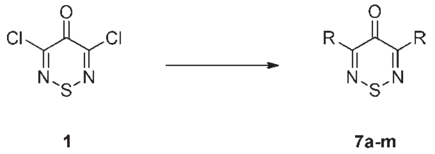
(17) Yasuda, T.; Imase, T.; Nakamura, Y.; Yamamoto, T. *Macromolecules* **2005**, *38*, 4687.

(18) (a) Leblond, J.; Gao, H.; Petitjean, A.; Leroux, J.-C. *J. Am. Chem. Soc.* **2010**, *132*, 8544. (b) Tobe, Y.; Nakanishi, H.; Sonoda, M.; Wakabayashi, T.; Achiba, Y. *Chem. Commun.* **1999**, 1625. (c) Abe, H.; Machiguchi, H.; Matsumoto, S.; Inouye, M. *J. Org. Chem.* **2008**, *73*, 4650. (d) Heller, M; Schubert, U. S. *J. Org. Chem.* **2002**, *67*, 8269.

(19) (a) Moreno-Mañas, M.; Pleixats, R.; Serra-Muns, A. *Synlett* **2006**, 3001. (b) Darabantu, M.; Boully, M.; Turck, A.; Plé, N. *Tetrahedron* **2005**, *61*, 2897.

(20) Christoforou, I. C.; Koutentis, P. A.; Rees, C. W. *Org. Biomol. Chem.* **2003**, *1*, 2900.

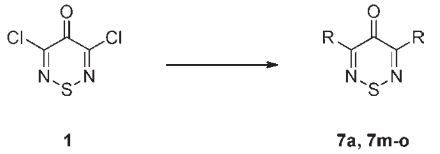
Table 1. Reaction of Dichlorothiadiazinone **1** (0.273 mmol) with $RB(OH)_2$ (2.2 equiv), $Pd(Ph_3P)_4$ (5 mol %), and Na_2CO_3 (2 equiv) in Dioxane/H_2O (0.5:0.3 mL) at 20−100 °C



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-$Me_2C_6H_3B(OH)_2$ (2.2)	40	[a]
6	2-$MeOC_6H_4B(OH)_2$ (2.2)	15	**7e** (87)
7	3-$MeOC_6H_4B(OH)_2$ (2.2)	15	**7f** (88)
8	4-$MeOC_6H_4B(OH)_2$ (2.2)	15	**7g** (86)
9	2-$ClC_6H_4B(OH)_2$ (2.2)	40	**7h** (80)
10	3-$ClC_6H_4B(OH)_2$ (2.2)	40	**7i** (81)
11	4-$ClC_6H_4B(OH)_2$ (2.2)	40	**7j** (89)
12	3-$O_2NC_6H_4B(OH)_2$ (2.2)	30	**7k** (54)
13	3-$O_2NC_6H_4B(OH)_2$ (3)	30	**7k** (64)
14	3-$O_2NC_6H_4B(OH)_2$ (4)	30	**7k** (66)
15	thien-3-yl$B(OH)_2$ (2.2)	15	**7l** (98)
16	thien-2-yl$B(OH)_2$ (2.2)	75	**7m** (42)
17	thien-2-yl$B(OH)_2$ (3)	60	**7m** (90)
18	pyrid-3-yl$B(OH)_2$ (2.2)	60	[a]
19	pyrid-4-yl$B(OH)_2$ (2.2)	60	[a]
20	$MeB(OH)_2$ (2.2)	30	[a]

[a] Consumption of the starting material, no product.

Table 2. Reaction of Dichlorothiadiazinone **1** (0.273 mmol) with $RSnBu_3$, $(Ph_3P)_2PdCl_2$ (5 mol %) in MeCN (1 mL) at 20−82 °C



entry	R	$RSnBu_3$ (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	*N*-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]

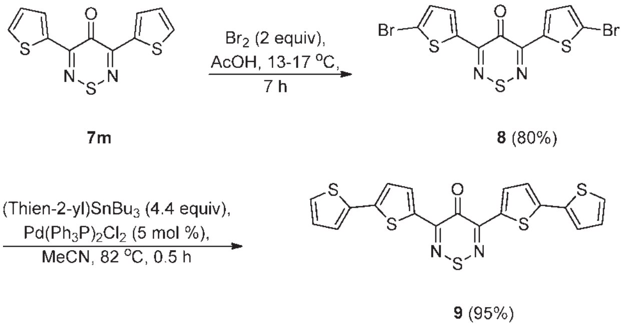
[a] Consumption of the starting material, no product. [b] Recovered starting material.

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 bisthienyl-substituted thiadiazinones **7m** and **7l**, although the former required additional equivalents to give high yields (entry 17). This was not suprising 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 $(Ph_3P)_2PdCl_2$ (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 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**



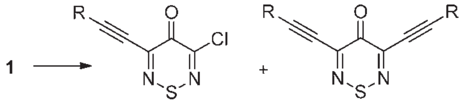
Bromination of bis(thien-2-yl) 1,2,6-thiadiazin-4-one **7m** using 2 equiv of either Br_2 or NBS in AcOH at low temperature (13−15 °C) gave the 3,5-di(5-bromothien-2-yl)-4*H*-1,2,6-thiadiazin-4-one (**8**) in 80% yield. The latter underwent the Stille conditions developed previously using 2-tributylstannylthiophene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

---

(21) (a) Brown, R. D.; Buchanan, A. S.; Humffray, A. A. *Aust. J. Chem.* **1965**, *18*, 1521. (b) Roques, B. P.; Florentin, D.; Callanquin, M. *J. Heterocycl. Chem.* **1975**, *12*, 195. (c) Florentin, D.; Fournié-Zaluski, M. C.; Callanquin, M.; Roques, B. P. *J. Heterocycl. Chem.* **1976** *13*, 1265.

(22) (a) Briehn, C. A.; Schiedel, M.-S.; Bonsen, E. M.; Schuhmann, W.; Baüerle, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 4680. (b) Tour, J. M. *Chem. Rev.* **1996**, *96*, 537. (c) Facchetti, A.; Yoon, M.-H.; Stern, C. L.; Katz, H. E.; Marks, T. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 3900. (d) Izumi, T.; Kobashi, S.; Takimiya, K.; Aso, Y.; Otsubo, T. *J. Am. Chem. Soc.* **2003**, *125*, 5286.

Table 3. Reaction of Dichlorothiadiazinone **1** (0.273 mmol) with Acetylene (2.2 equiv), Et_3N (4 equiv), CuI (10 mol %), and $(Ph_3P)_2PdCl_2$ (5 mol %) in MeCN



10 **11a-d**

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 tetrathiophenes **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 (Et_3N, Hünig's, lutidine, pyridine) using 5 mol % of a palladium source [$Pd(Ph_3P)_4$, $(dba)_3Pd_2$, $Pd(OAc)_2$, $(PhCN)_2PdCl_2$, $(MeCN)_2PdCl_2$, $(Ph_3P)_2PdCl_2$, and [1,1′-(Ph_2P)ferrocene]−$PdCl_2\cdot DCM$)] and CuI (10 mol %) at rt. The best yield of bisacetylene **11a** (73%) was obtained using MeCN, Et_3N (4 equiv), $(Ph_3P)_2PdCl_2$ (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 thadiazin-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**).

Acknowledgment. We thank the Cyprus Research Promotion Foundation (GrantNo. ΠΕΝΕΚ, ΕΝΙΣΧ/0504/08), the State General Laboratory, the Agricultural Research Institute, the Ministry of Agriculture, and Biotronics Ltd. for generous donations of glassware and chemicals. We also thank the A. G. Leventis Foundation for helping to establish the NMR facility at the University of Cyprus.

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.