

Selective Stille Coupling Reactions of 3-Chloro-5-halo(pseudohalo)-4*H*-1,2,6-thiadiazin-4-ones

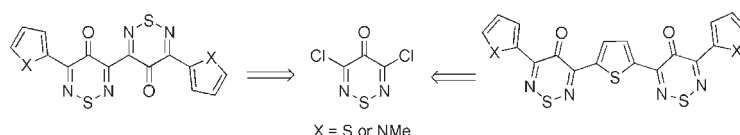
Heraklidia A. Ioannidou, Christos Kizas, and Panayiotis A. Koutentis*

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

koutenti@ucy.ac.cy

Received September 17, 2011

ABSTRACT



A series of 3-chloro-5-halo(pseudohalo)-4*H*-1,2,6-thiadiazin-4-ones (halo/pseudohalo = Br, I, OTf) are prepared from 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one (**3**) in good yields. Of these the triflate reacts with tributyltin arenes (Stille couplings) chemoselectively to give only the 5-aryl-3-chloro-4*H*-1,2,6-thiadiazin-4-ones in high yields. This allowed the preparation of a series of unsymmetrical biaryl thiadiazines and ultimately a series of oligomers. Furthermore, treatment of 3-chloro-5-iodo-4*H*-1,2,6-thiadiazin-4-one (**10**) with Bu_3SnH and $\text{Pd}(\text{OAc})_2$ gave the bithiadiazinone which can also be further arylated *via* the Stille reaction to give bithien-2-yl and bis(*N*-methylpyrrol-2-yl) analogs.

A recent note about R. B. Woodward's "unfinished symphony" identified 1,2,6-thiadiazine polymers such as **1** as potential stable alternatives to the superconductor poly(sulfur nitride) $(\text{SN})_x$.¹ Similarly, C. W. Rees proposed polymer **2**² (Figure 1). In both proposals, the readily prepared 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one (**3**)³ was featured as a key building block. Despite the above, the chemistry of this useful heterocycle has not been extensively explored.^{2–4}

Recently, the synthesis of symmetrical 3,5-biaryl-4*H*-1,2,6-thiadiazin-4-ones *via* Stille and Suzuki–Miyaura reactions on the dichlorothiadiazinone **3** was described.^{4d} Included was the synthesis of the thien-2-yl substituted analogs **4** ($n = 0$) and **5** ($n = 1$) that potentially could find

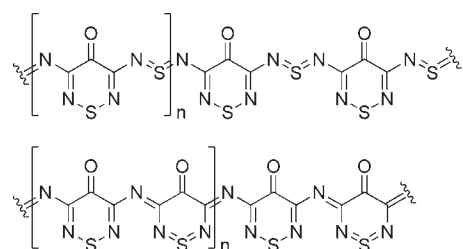


Figure 1. 1,2,6-Thiadiazinone polymers proposed by Woodward (polymer **1**) and Rees (polymer **2**) that could act as alternatives to poly(sulfur nitride) $(\text{SN})_x$.

use as monomer feedstocks for π -conjugated polymers such as **6** (Figure 2).^{4d}

In a continuation of our studies on 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one (**3**) we have now synthesized unsymmetrical 3,5-bis-heteroarylated thiadiazinones and related oligomers using the Stille reaction.

(5) (a) Bailey, J. M.; Bit, R. A.; Demont, E. H.; Harrison, L. A.; Jones, K. L.; Smethurst, C. A. P.; Witherington, J. WO Pat. 146105, 2010. (b) Fuss, R. W.; Manero, J.; Schlosser, H.; Winger, R. US Pat. 5,847,149, 1998.

(1) Cava, M. P.; Lakshmikantham, M. V.; Hoffmann, R.; Williams, R. M. *Tetrahedron* **2011**, *67*, 6771.

(2) (a) Koutentis, P. A.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2601. (b) Koutentis, P. A.; Rees, C. W.; White, A. J. P.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **2000**, 303. (c) Koutentis, P. A.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1089.

(3) Geever, J.; Trompen, W. P. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 270.

(4) (a) Koutentis, P. A.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2601. (b) Koutentis, P. A.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1081. (c) Kalogirou, A. S.; Koutentis, P. A. *Tetrahedron* **2009**, *65*, 9967. (d) Ioannidou, H. A.; Kizas, C.; Koutentis, P. A. *Org. Lett.* **2011**, *13*, 3466.

The selective replacement of only one halogen by carbon groups using Suzuki–Miyaura, Stille, or Sonogashira chemistry can be efficient with symmetrical dihaloheteroarenes that are electron poor (e.g., 1,3,4-thiadiazoles,⁵ pyridines,⁶ and pyrimidines⁷). In some cases (e.g., 2,6-dihalopyridine) the selective displacement of only one halogen using the Stille protocol required the presence of a large excess of the substrate to prevent the formation of the bis-coupled product,⁸ while the Sonogashira reaction of 3,5-dibromopyridine gave mixtures of mono- and bis-ethynylated derivatives.⁹

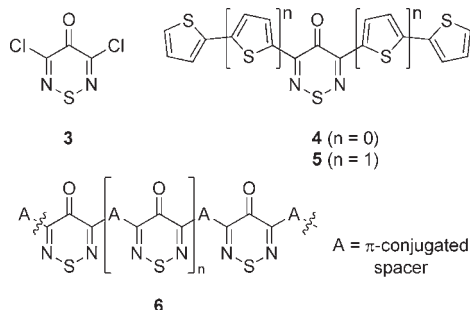


Figure 2. Structures of 3,5-dichloro- and 3,5-di(thien-2-yl)-substituted 4*H*-1,2,6-thiadiazin-4-ones **3**, **4**, and **5** and the proposed π -conjugated polythiadiazinone **6**.

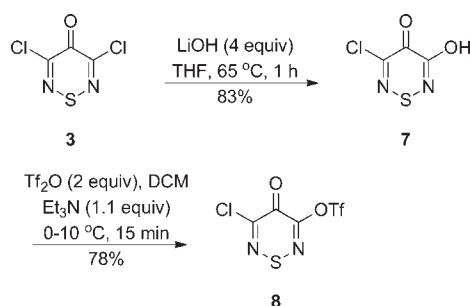
Attempts to synthesize 3-aryl-5-chlorothiadiazinone starting from dichlorothiadiazinone **3** using our typical Suzuki–Miyaura or Stille conditions^{4d} with only 1 equiv. of arylboronic acid or aryltin reagent, gave only mixtures of mono- and bis-arylated systems, despite varying the reaction solvent, temperature and catalysts. As such, an alternative pathway was proposed that required access to nonsymmetrical 3,5-dihalo or 3-halo-5-(pseudohalo)-thiadiazinones, which could favor chemoselective Pd catalyzed C–C coupling reactions. Pd catalyzed C–C coupling reactions of “non-symmetrical” mixed dihalo systems 2-bromo-

6-chloropyridine¹⁰ and 2-bromo-5-chlorothiophene¹¹ occur chemoselectively at the more reactive bromine.

Initial attempts to exchange selectively one halide with KBr or KI in acetone (Finkelstein reaction)¹² failed and only the starting dichlorothiadiazinone **3** was recovered. Nevertheless, thiadiazinone **3** could be converted into 3-chloro-5-trifluoromethanesulfonyloxy-4*H*-1,2,6-thiadiazin-4-one (**8**) in two steps (Scheme 1) and this in turn could be readily converted into the 3-bromo-5-chloro- and the 3-chloro-5-iodothiadiazinones **9** and **10**, respectively (Scheme 2).

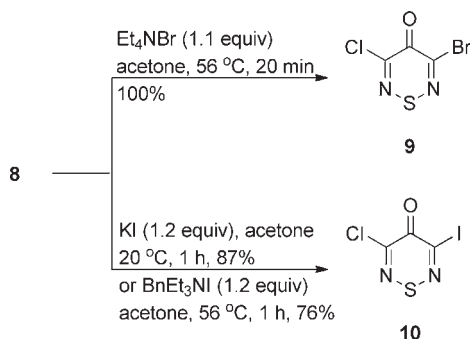
As such, 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one (**3**) treated with LiOH (4 equiv) in dry THF heated at ca. 65 °C for 1 h gave 3-chloro-5-hydroxy-4*H*-1,2,6-thiadiazin-4-one (**7**) directly in 83% yield. The reaction of the alcohol **7** with trifluoromethanesulfonic anhydride (Tf₂O) (2 equiv) in the presence of Et₃N (1.1 equiv) in DCM at ca. 0–10 °C for 15 min gave the 3-chloro-5-triflate-1,2,6-thiadiazin-4-one **8** in 78% yield (Scheme 1).

Scheme 1. Preparation of 3-Chloro-5-hydroxy-4*H*-1,2,6-thiadiazin-4-one (**7**) and 3-Chloro-5-trifluoromethanesulfonyloxy-4*H*-1,2,6-thiadiazin-4-one (**8**)



By treating the triflate **8** with Et₄NBr (1.1 equiv) in acetone at ca. 56 °C for 20 min, 3-bromo-5-chloro-4*H*-1,2,6-thiadiazin-4-one (**9**) was obtained in 100% yield, while treatment with either KI (1.2 equiv) in acetone at rt for 1 h or BnEt₃NI (1.2 equiv) in acetone at ca. 56 °C for 1 h gave 3-chloro-5-iodo-4*H*-1,2,6-thiadiazin-4-one (**10**) in 87% and 76% yields, respectively (Scheme 2).

Scheme 2. Preparation of 3-Bromo-5-chloro-4*H*-1,2,6-thiadiazin-4-one (**9**) and 3-Chloro-5-iodo-4*H*-1,2,6-thiadiazin-4-one (**10**)



(6) (a) Heuberger, B. D.; Shin, D.; Switzer, C. *Org. Lett.* **2008**, *10*, 1091. (b) Crowley, J. D.; Leigh, D. A.; Lusby, P. J.; McBurney, R. T.; Perret-Aebi, L.-E.; Petzold, C.; Slawin, A. M. Z.; Symes, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 15085. (c) Yamaguchi, Y.; Kobayashi, S.; Wakamiya, T.; Matsubara, Y.; Yoshida, Z.-i. *Angew. Chem., Int. Ed.* **2005**, *44*, 7040. (d) Woods, C. R.; Benaglia, M.; Toyota, S.; Hardcastle, K.; Siegel, J. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 749. (e) Orlandi, S.; Annunziata, R.; Benaglia, M.; Cozzi, F.; Manzoni, L. *Tetrahedron* **2005**, *61*, 10048. (f) Gaviña, P.; Tatay, S. *Tetrahedron Lett.* **2006**, *47*, 3471.

(7) (a) Hartung, C. G.; Backes, A. C.; Felber, B.; Missio, A.; Philipp, A. *Tetrahedron* **2005**, *62*, 10055. (b) Schauerte, H.; Allgeier, H.; Pleiss, M. A.; Augustin, M.; Peraus, G.; Stumm, G.; Wabnitz, P. US Pat. 2010/184780, 2010.

(8) Bouet, A.; Heller, B.; Papamicaël, C.; Dupas, G.; Oudeyer, S.; Marsais, F.; Levacher, V. *Org. Biomol. Chem.* **2007**, *5*, 1397.

(9) Rajadurai, C.; Ivanova, A.; Enkelmann, V.; Baumgarten, M. *J. Org. Chem.* **2003**, *68*, 9907.

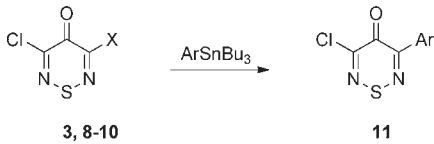
(10) Choppin, S.; Gros, P.; Fort, Y. *Org. Lett.* **2000**, *2*, 803.

(11) (a) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358. (b) Bolliger, J. L.; Frech, C. M. *Chem.—Eur. J.* **2010**, *16*, 4075. (c) Dupuis, C.; Adiey, K.; Charruault, L.; Michelet, V.; Savignac, M.; Genêt, J.-P. *Tetrahedron Lett.* **2001**, *42*, 6523. (d) Li, G.; Wang, E.; Chen, H.; Li, H.; Liu, Y.; Wang, P. G. *Tetrahedron* **2008**, *64*, 9033. (e) Kim, S.-H.; Rieke, R. D. *Tetrahedron* **2010**, *66*, 3135.

A preliminary screen of Stille reaction conditions for the monoarylation of the dihalo- and pseudohalothiadiazinones **8–10** using 2-(tributyltin)thiophene (1 equiv) and Pd(Ph₃P)₂Cl₂ (5 mol %) at rt included varying the solvents (*e.g.*, THF, PhH, PhMe, and MeCN). 2-(Tributyltin)thiophene was used instead of the tributylphenyltin, because the dihalo-, 3-chloro-5-phenyl- and 3,5-diphenylthiadiazinones corun on TLC. From the solvents screened, PhH gave the fastest reactions and cleanest mixtures, while in MeCN the starting thiadiazinones were insoluble at rt and required heating to *ca.* 50 °C to solubilize, but this led to mixtures of mono- and bisthienylated thiadiazinones. The use of THF led to a very fast but complex reaction mixture (by TLC) while in the case of the PhMe a small amount (4%) of the bis-thienylated product was also isolated.

Of the four thiadiazinones screened, the dichlorothiadiazinone **3** gave mixtures of mono- and bis-thienylated products, while the chloriodothiadiazinone **10** gave a complex reaction mixture from which no desired product was detectable (by TLC). Fortunately, the chlorotriflate thiadiazinone **8** and the bromochlorothiadiazinone **9** reacted chemoselectively with 2-(tributyltin)thiophene to give 3-chloro-5-thien-2-yl-4*H*-1,2,6-thiadiazin-4-one (**11a**) in 85% and 83% yields, respectively.

Table 1. Reaction of the 3-Chloro-5-halo(pseudohalo)-1,2,6-thiadiazinones **3, 8–10** (0.22 mmol) with ArSnBu₃ (1 equiv), Pd(Ph₃P)₂Cl₂ (5 mol %), in PhH (2 mL) at rt



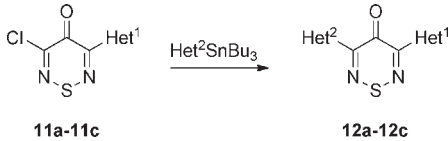
X	Ar	time (h)	yield 11 (%)
Cl	Thien-2-yl	48	^a
Br	Thien-2-yl	44	11a (83)
I	Thien-2-yl	0.5	^b
OTf	Thien-2-yl	2	11a (85)
OTf	Fur-2-yl	0.8	11b (76)
OTf	<i>N</i> -Me-pyrrol-2-yl	0.08	11c (94)
OTf	Ph	4	^a

^a Mixture of mono and biarylated thiadiazinones. ^b Complex reaction mixture.

The Stille reaction of the 2-(tributyltin)thiophene with the triflate thiadiazinone **8** was significantly faster than that of the bromochlorothiadiazinone **9** (2 h vs 2 d). In light of this we subsequently chose the triflate thiadiazinone **8** as the starting material for the synthesis of a series of monoaryl chloro thiadiazinones (Table 1) that could later be modified into a series of mixed biaryl thiadiazinones (Table 2).

Disappointingly, attempts to perform a one-pot Stille mediated two-step mixed arylation failed. Nevertheless, unsymmetrical biheteroaryl thiadiazinones were prepared in high yields by reacting the isolated 3-chloro-5-heteroaryl

Table 2. Reaction of the 3-Chloro-5-heteroarylthiadiazin-4-ones **11** (0.22 mmol) with ArSnBu₃ (1.2 equiv), Pd(Ph₃P)₂Cl₂ (5 mol %), in MeCN (2 mL) at *ca.* 82 °C

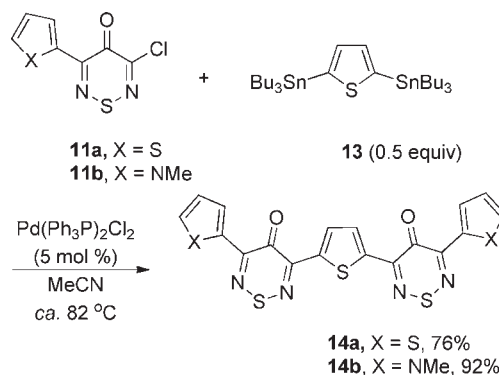


Het ¹	Het ²	time (min)	yield 12 (%)
Thien-2-yl	Fur-2-yl	20	12a (88)
Thien-2-yl	<i>N</i> -Me-pyrrol-2-yl	45	12b (88)
Fur-2-yl	Thien-2-yl	20	12a (78)
Fur-2-yl	<i>N</i> -Me-pyrrol-2-yl	20	12c (100)
<i>N</i> -Me-pyrrol-2-yl	Thien-2-yl	45	12b (100)
<i>N</i> -Me-pyrrol-2-yl	Fur-2-yl	15	12c (94)

thiadiazinones **11a–c** with heteroaryltin and Pd(Ph₃P)₂Cl₂ (5 mol %) in MeCN at *ca.* 82 °C (Table 2).

Furthermore, by reacting either the 3-chloro-5-(thien-2-yl)- or the 3-chloro-5-(*N*-methylpyrrol-2-yl)thiadiazin-4-ones **11a** or **11c** with 2,5-bis(tributyltin)thiophene **13** the potentially useful **14a** and **14b** were synthesized in 76 and 92% yields, respectively (Scheme 3).

Scheme 3. Preparation of Pentamers **14a** and **14b**



An alternative synthesis of compounds **14a** and **14b** was also targeted by building first 5,5'-(thiophene-2,5-diyl)bis-(3-chloro-4*H*-1,2,6-thiadiazin-4-one) (**15**). Nevertheless the synthesis of **15** from 2,5-bis(tributyltin)thiophene and the 3-chloro-5-triflate thiadiazinone **8** was low yielding (40%) and the route was abandoned (Scheme 4).

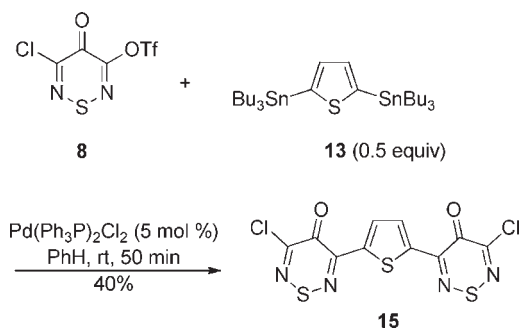
We also tried to make 5,5'-dichloro-4*H*,4'*H*-[3,3'-bi-(1,2,6-thiadiazine)]-4,4'-dione (**16**) from the dihalothiadiazinones **3, 9**, and **10** *via* the Ullmann reaction, but the use of copper powder¹³ led to complex reaction mixtures (by TLC) and the use of Pd(OAc)₂¹⁴ gave only decomposition. Nevertheless,

(13) Goshav, M.; Otroshchenko, O. S.; Sdaykov, A. S. *Russ. Chem. Rev.* **1972**, *41*, 1046.

(14) Christoforou, I. C.; Koutentis, P. A. *Org. Biomol. Chem.* **2006**, *4*, 3681.

(12) Finkelstein, H. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1528.

Scheme 4. Preparation of 5,5'-Dichloro-4*H*,4'*H*-[3,3'-bi-(1,2,6-thiadiazine)]-4,4'-dione **15**



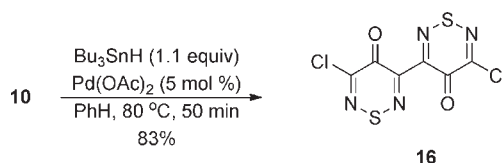
Bu_3SnH in the presence of a Pd catalyst and KOAc was known to react with iodoarenes to give the tributyltinarenes, but in the absence of base these reactions often gave some biaryls.¹⁵ In light of this, chloroiodothiadiazinone **10** was treated with Bu_3SnH (1.1 equiv) and $\text{Pd}(\text{OAc})_2$ (5 mol %) in PhH heated at reflux, and after 50 min the desired 5,5'-dichloro-4*H*,4'*H*-[3,3'-bi-(1,2,6-thiadiazine)]-4,4'-dione (**16**) was isolated in 83% yield (Scheme 5). Similar treatment of the dichloro- and bromochlorothiadiazinones **3** and **9** gave only recovered starting materials.

The dimer **16** reacted readily with either 2-(tributyltin) thiophene or 1-methyl-2-(tributyltin)pyrrole (2.2 equiv) and $\text{Pd}(\text{Ph}_3\text{P})_2\text{Cl}_2$ (5 mol %) in MeCN heated to reflux to give 5,5'-di(thien-2-yl)-4*H*,4'*H*-[3,3'-bi-(1,2,6-thiadiazine)]-4,4'-dione (**17a**) and 5,5'-di(*N*-methylpyrrol-2-yl)-4*H*,4'*H*-[3,3'-bi-(1,2,6-thiadiazine)]-4,4'-dione (**17b**) in 67% and 70% yields, respectively (Scheme 6).

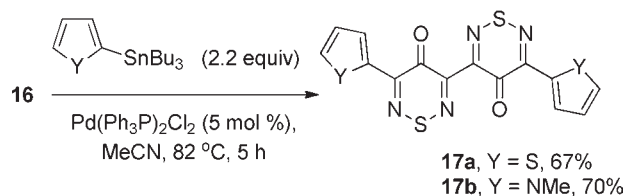
In conclusion, desymmetrization of dichlorothiadiazinone **3** via modified Finkelstein reaction conditions gave triflate-, bromo-, and iodo-substituted chlorothiadiazinones **8–10**, respectively. Both the triflate and the bromochloro-

(15) (a) Murata, M.; Watanabe, S.; Masuda, Y. *Synlett* **2000**, 1043. (b) Choudary, B. M.; Madhi, S.; Chowdari, N. S.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2002**, *124*, 14127.

Scheme 5. Preparation of 5,5'-Dichloro-4*H*,4'*H*-[3,3'-bi(1,2,6-thiadiazine)]-4,4'-dione **16**



Scheme 6. Preparation of 5,5'-Di(heteroaryl)-4*H*,4'*H*-[3,3'-bi(1,2,6-thiadiazine)]-4,4'-diones **17a** and **17b**



thiadiazinones suffered chemoselective Stille couplings to give 3-chloro-5-heteroaryl thiadiazinones **12**, while treatment of the chloroiodothiadiazinone **10** with Bu_3SnH and $\text{Pd}(\text{OAc})_2$ gave the dimer dichlorobithiadiazinone **16**. Manipulation of the above gave the π -extended oligomers **14**, **15**, and **17** that could find use in optoelectronic applications. Their physical properties are now under study.

Acknowledgment. The authors thank the Cyprus Research Promotion Foundation (Grant Nos. ENIΣX/0504/08 and NEKYII/0308/02).

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