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Synthesis of *N*-Aryl-3,5-dichloro-4*H*-1,2,6-thiadiazin-4-imines from 3,4,4,5-Tetrachloro-4*H*-1,2,6-thiadiazine

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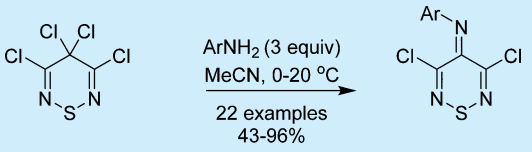
Supporting Information

ABSTRACT: Condensation of 3,4,4,5-tetrachloro-4*H*-1,2,6-thiadiazine with a range of anilines gave 22 *N*-aryl-3,5-dichloro-4*H*-1,2,6-thiadiazin-4-imines in 43−96% yields. The scope and limitations of this condensation are briefly investigated. Furthermore, mono- and bis-substitution of the C-3 and C-5 chlorines of 3,5-dichloro-*N*-phenyl-4*H*-1,2,6-thiadiazin-4-imine by amine and alkoxide nucleophiles is explored. Finally, Stille coupling chemistry is used to prepare several *N*-phenyl-3,5-diaryl-4*H*-1,2,6-thiadiazin-4-imines.



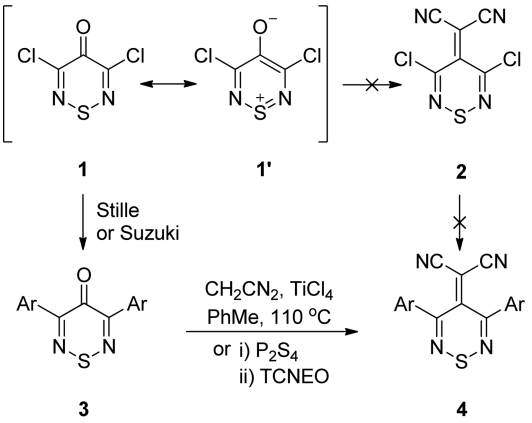
The majority of research on 1,2,6-thiadiazines has focused on the S-oxidized analogues. Nonoxidized 4*H*-1,2,6-thiadiazines are less well studied. Despite this, several analogues display interesting biological and physical properties: 5-substituted 3-chloro-4*H*-1,2,6-thiadiazin-4-ones act as fungicides,[1] while some fused 4*H*-1,2,6-thiadiazines behave as "extreme quinoids",[2] as atypical liquid crystals, or as near-infrared dyes.[3] More recently, non-S-oxidized 4*H*-1,2,6-thiadiazines were proposed as precursors to molecule-based radical anions,[4] as monomers of conjugated polymers,[5,6] and as acceptor components in small molecule donor−acceptor−donor containing solution-processed bulk heterojunction solar cells.[7−9]

To date, the most used non-S-oxidized 4*H*-1,2,6-thiadiazine scaffold is 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one (**1**). The C-3/5 chlorine atoms readily undergo nucleophilic substitution by N-, O-, and S-nucleophiles[10] and can participate in palladium catalyzed Stille, Suzuki−Miyaura, and Sonogashira couplings.[11] Furthermore, reactions with vicinal bisnucleophiles afford highly colored polycyclic systems.[6c]

While the C-3 and C-5 positions of thiadiazinone **1** can be easily manipulated, it has, to date, been difficult to develop reactions to modify the C-4 position which bears an attractive carbonyl moiety. Simple condensation reactions fail because of three competing reactions: (1) direct nucleophilic displacement of the C-3/5 chlorine atoms; (2) thiophilic attack that leads to ring cleavage owing to the relatively weak S−N bond and the good nucleofugality of the C-3/5 chlorine atoms; and (3) halophilic attack that also leads to cleavage of the ring system via the weak N−S bond and concomitant formation of a thermodynamically stable nitrile. Moreover, the charge separated resonance form **1′** (Scheme 1) also reduces the electrophilicity of the C-4 position.

Transformation of the C-4 carbonyl to afford an ylidene-malononitrile can only be achieved when both the 3- and 5-halogens are replaced first by poor nucleofuges such as aryl groups and then via a base-free $TiCl_4$-mediated condensation with malononitrile[12] or via a two-step protocol involving thionation followed by reaction with tetracyanoethylene oxide (TCNEO)[11] (Scheme 1).

Scheme 1. Synthesis of 3,5-Diaryl-1,2,6-thiadiazin-4-ones 3 and Dicyanoylidines 4



Even though some 4*H*-1,2,6-thiadiazin-4-ylidenes have been prepared,[6c,11a] to our knowledge nonoxidized 4*H*-1,2,6-thiadiazin-4-imines are unknown. As such, in an effort to expand the available chemistry of this ring system and to access new chemical structures, we decided to investigate the synthesis of this new category of 4*H*-1,2,6-thiadiazines.

Having in mind our previous success with the $TiCl_4$ mediated condensation of 3,5-diaryl-1,2,6-thiadiazin-4-ones **3** with malononitrile,[12] we investigated the analogous condensation with amines. Gratifyingly, reacting 3,5-diphenyl-4*H*-1,2,6-thiadiazin-4-one (**3a**) with aniline (3 equiv) and $TiCl_4$ (3 equiv) in PhMe at 110 °C gave *N*,3,5-triphenyl-4*H*-1,2,6-thiadiazin-4-imine (**5**) in 91% yield (Scheme 2).

Despite the successful synthesis of the triphenylimine **5**, this route is limited:[12] owing to the relative harshness of $TiCl_4$ this

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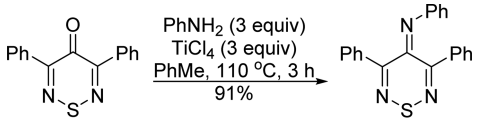
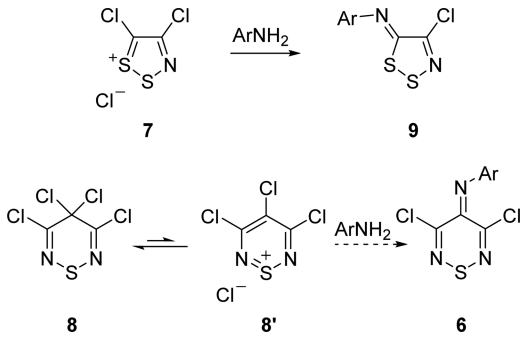
Scheme 2. Synthesis of *N*,3,5-Triphenyl-4*H*-1,2,6-thiadiazin-4-imine (5)



route cannot readily be applied to thiadiazines substituted at C-3/5 with electron-rich hetaryls such as the more desirable thien-2-yl, fur-2-yl, and pyrrol-2-yl systems. A more versatile synthesis was therefore required to access the thiadiazinimines **6** that can subsequently be functionalized at the C-3/5 positions.

The direct synthesis of dichlorothiadiazinimines **6** from dichlorothiadiazinone **1** was not possible as the 3,5-chlorines can be easily displaced by amine nucleophiles.[10] By recognizing the structural similarities of the ionic 4,5-dichloro-1,2,3-dithiazolium chloride (**7**)[13] and the covalent 3,4,4,5-tetrachloro-4*H*-1,2,6-thiadiazine (**8**) and the potential contribution of the ionic form **8′** (Scheme 3), we were able to solve this

Scheme 3. Reactions of Dithiazolium 7 and Tetrachlorothiadiazine 8 with Anilines

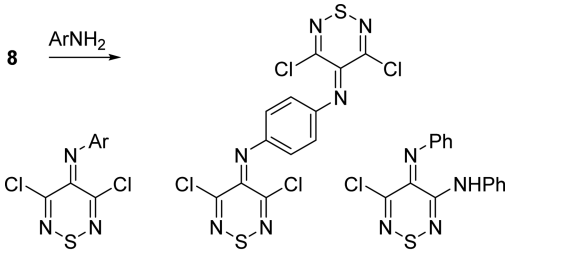


problem. 4,5-Dichloro-1,2,3-dithiazolium chloride (**7**) readily condenses with anilines to give the corresponding *N*-arylimines **9**,[13] and in a similar manner, we considered that the tetrachlorothiadiazine **8**, which could be in equilibrium with its ionic form **8′**, should also react with anilines to give the desired thiadiazinimines **6** (Scheme 3).

3,4,4,5-Tetrachloro-4*H*-1,2,6-thiadiazine (**8**) is readily prepared by the reaction of dichloromalononitrile and SCl_2[11] and can be isolated by vacuum distillation (bp 90 °C at 30 mbar) and stored for several months at −40 °C in the absence of air and moisture. While the compound has been known for over 40 years, its chemistry to date was limited to the reaction with 98% formic acid to give the thiadiazinone **1**[10] and to its degradation in moist air to give 2-chloromalonamide.[14] Presumably, while both thiadiazines **1** and **8** are highly electrophilic and have multiple sites of reactivity toward nucleophiles, halophiles, and thiophiles, it is the nonaromatic nature of the latter which contains an sp^3 hybridized carbon at C-4, which makes the ring more labile to hydrolytic fragmentation. Potentially, this has deterred researchers from further investigating this compound as a scaffold in the synthesis of thiadiazines or other heterocycles. Herein, we identify facile conditions for the regioselective reactions of thiadiazine **8** with anilines and demonstrate the subsequent modification of the remaining C-3/5 positions via direct nucleophilic substitution and Stille coupling chemistry.

Initially, we reacted the tetrachlorothiadiazine **8** with aniline (1 equiv) in DCM with the addition of Hünig's base (2 equiv) and obtained the desired 3,5-dichloro-*N*-phenyl-4*H*-1,2,6-thiadiazin-4-imine (**6a**) in a modest 33% yield. A brief optimization identified MeCN as a better solvent for these reactions and that using excess aniline (3 equiv) to act as both a nucleophile and base improved the yield of the imine **6a** to 86% (Table 1, entry 1). The only minor side product isolated from

Table 1. Preparation of *N*-Aryl-3,5-dichloro-4*H*-1,2,6-thiadiazin-4-imines 6 from Tetrachlorothiadiazine 8 (0.42 mmol) with Arylamines (3 equiv) in MeCN at 0−20 °C



entry	Ar	time (h)	yields of **6** (%)
1	Ph	0.50	**6a** (86)[a]
2	2-Tol	3	**6b** (84)
3	3-Tol	1	**6c** (84)
4	4-Tol	0.75	**6d** (81)
5	$2\text{-NCC}_6\text{H}_4$	2	**6e** (76)
6	$4\text{-NCC}_6\text{H}_4$	2	**6f** (96)
7	$2\text{-O}_2\text{NC}_6\text{H}_4$	8	**6g** (61)
8	$4\text{-O}_2\text{NC}_6\text{H}_4$	2	**6h** (95)
9	$2\text{-MeOC}_6\text{H}_4$	1	**6i** (88)
10	$3\text{-MeOC}_6\text{H}_4$	0.67	**6j** (93)
11	$4\text{-MeOC}_6\text{H}_4$	1	**6k** (74)
12	$4\text{-FC}_6\text{H}_4$	1	**6l** (92)
13	$2\text{-ClC}_6\text{H}_4$	3	**6m** (74)
14	$3\text{-ClC}_6\text{H}_4$	0.67	**6n** (84)
15	$4\text{-ClC}_6\text{H}_4$	1	**6o** (87)
16	$2,6\text{-Cl}_2\text{C}_6\text{H}_3$	24	**6p** (89)
17	$2\text{-BrC}_6\text{H}_4$	3	**6q** (83)
18	$3\text{-BrC}_6\text{H}_4$	0.67	**6r** (90)
19	$4\text{-BrC}_6\text{H}_4$	1	**6s** (84)
20	$2\text{-IC}_6\text{H}_4$	1.5	**6t** (91)
21	$4\text{-IC}_6\text{H}_4$	0.67	**6u** (73)
22	$4\text{-H}_2\text{NC}_6\text{H}_4$	2.5	**6v** (43)

[a]Bis-adduct **10** also isolated 3%.

the reaction was 3-anilino-5-chloro-*N*-phenyl-4*H*-1,2,6-thiadiazin-4-imine (**10**), in a low 3% yield. While the use of excess aniline was not atom economic, it could be recovered as its hydrochloride salt in near-quantitative yields. By using these optimized reaction conditions, a range of analogues were prepared in good to excellent yields (Table 1).

In general, the reaction worked well with a variety of primary anilines but failed for primary alkylamines. Interestingly, both steric and electronic effects were observed: the reactions of anilines bearing *ortho* substituents were slower but with little or no effect on the product yield. The presence of the bulky *ortho* nitro group [Table 1, entry 7, $A(NO_2)$ = 1.05 kcal/mol][15] gave a suppressed yield of only 61%, while the hindered 2,6-dichloroaniline gave the longest reaction time (24 h) but a good yield of imine **6p** (89%, Table 1, entry 16). Anilines

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bearing electron-withdrawing substituents such as cyano, nitro, and fluoro in the *para* position gave excellent yields of imine (Table 1, entries 6, 8, 12, respectively), while electron-donating substituents such as *para*-MeO gave slightly reduced yields. This can be attributed to the higher nucleophilicity of electron-rich anilines that can lead to side reactions that degrade the starting tetrachlorothiadiazine **8**, e.g., thiophilic attack. Interestingly, reaction of tetrachlorothiadiazine **8** with 1,4-diaminobenzene (3 equiv) using identical conditions yielded the bisthiadiazine **6v** in 43% yield (Table 1, entry 22).

Unfortunately, reactions with hetarylamines, such as pyridyl-, pyrimidyl-, and pyrazinylamines, degraded the starting material. This was tentatively attributed to the basicity of these amines since during our optimization studies tetrachlorothiadiazine **8** was unstable to the presence of nonhindered pyridine bases.

To assess the reactivity of these imines, their stability and functionalization at the C-3/5 positions was investigated. 3,5-Dichloro-*N*-phenyl-4*H*-1,2,6-thiadiazin-4-imine (**6a**) was shown by single crystal X-ray crystallography to adopt a shallow boat conformation (Figure 1) and to be weakly aromatic (I_A = 49; *cf.* I_A = 53 for furan and 100 for benzene).[16]

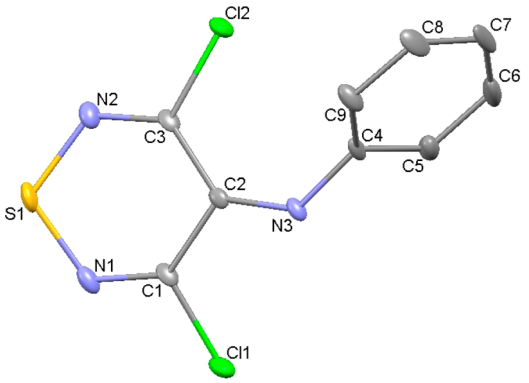
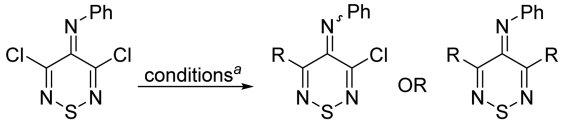


Figure 1. Geometry of 3,5-dichloro-*N*-phenyl-4*H*-1,2,6-thiadiazin-4-imine (**6a**) (CCDC-1407948) in the crystal and the crystallographic atom numbering. Thermal ellipsoids are shown at 50% probability. Hydrogens are omitted for clarity.

The imine **6a** was stable in the solid phase up to 196 °C (DSC mp: onset 71.2 °C, peak max 71.8 °C, decomp. onset 197.0 °C, peak max 199.0 °C), while in solution it was stable in EtOH or PhMe heated at reflux for 24 h and also in biphenyl heated at 200 °C for 24 h. The imine **6a** was also stable in a dilute solution of trialkylamines (Et_3N 2 equiv in MeCN at ca. 20 °C), while in the presence of 2 M HCl, in THF/H_2O at ca. 20 °C, the imine hydrolyzed to give the thiadiazinone **1** in 93% yield.

Reaction of the imine **6a** with NaOMe in MeOH at ca. 0 °C led to a fast displacement of the C-3 chlorine to give 3-chloro-5-methoxy-*N*-phenyl-4*H*-1,2,6-thiadiazin-4-imine (**11**) (as a mixture of *E* and *Z* isomers) in 83% yield, while using 2 equiv of methoxide yielded the dimethoxythiadiazine **12** in good yield (Table 2, entries 1 and 2, respectively). Reaction of the imine **6a** with morpholine (2 equiv) in MeCN at ca. 20 °C led to a fast displacement of the C-3 chlorine giving the 3-morpholinothiadiazine **13** in 76% yield (Table 2, entry 3). Not surprisingly, owing to electron release from the first morpholine, the displacement of the second chlorine was more difficult and was achieved by treating the imine **6a** with neat morpholine (8 equiv) at ca. 20 °C for 3 days, to afford the desired product **14** in 89% yield (Table 2, entry 4).

Table 2. Reactions of the Thiadiazinimine 6a with Nucleophiles



6a **11, 13** **5, 12, 14, 15**

entry	conds.[a]	R	time (h)	product (%)
1	a	MeO	0.5	**11** (83)
2	b	MeO	1	**12** (90)
3	c	morpholin-4-yl	2	**13** (76)
4	d	morpholin-4-yl	72	**14** (89)
5	e	Ph	0.5	**5** (92)
6	f	thien-2-yl	1	**15** (93)

[a]Conditions: (a) NaOMe (1 equiv), MeOH, 0 °C; (b) NaOMe (2 equiv), MeOH, 0–20 °C; (c) morpholine (2 equiv), MeCN, 20 °C; (d) morpholine (8 equiv), neat, 20 °C; (e) $PhSnBu_3$ (2.2 equiv), $Pd(Ph_3P)_2Cl_2$ (5 mol %), PhMe, Ar, 110 °C; (f) (Thien-2-yl)$SnBu_3$ (2.2 equiv), $Pd(Ph_3P)_2Cl_2$ (5 mol %), PhMe, Ar, 110 °C.

Furthermore, Stille and Suzuki couplings of 3,5-dichloro-*N*-phenyl-4*H*-1,2,6-thiadiazin-4-imine (**6a**) were investigated. Stille coupling with $PhSnBu_3$ (2.2 equiv) using catalytic $Pd(Ph_3P)_2Cl_2$ (5 mol %) was successful, and the best results were obtained when the reaction was performed in dry PhMe at ca. 110 °C giving the product *N*,3,5-triphenyl-4*H*-1,2,6-thiadiazin-4-imine (**5**) in 92% yield while coupling with (thieny-2-yl)$SnBu_3$ under similar conditions gave the 3,5-di(thien-2-yl)thiadiazine **15** in excellent yield (Table 2, entries 5 and 6, respectively). Unfortunately, Suzuki couplings with $PhB(OH)_2$ in both aqueous[11b] and anhydrous[17] conditions led to degradation of the starting material.

In conclusion, 3,4,4,5-tetrachloro-4*H*-1,2,6-thiadiazine (**8**) readily condenses with anilines at the C-4 position to afford the thiadiazinimines **6a–v** in 43–96% yields. Furthermore, the C-3 and C-5 chlorines of 3,5-dichloro-*N*-phenyl-4*H*-1,2,6-thiadiazin-4-imine (**6a**) were displaced by morpholine and methoxide to give mono- and/or bis-displacement products. Finally, the Stille coupling reactions of thiadiazinimine **6a** with $PhSnBu_3$ and (thieny-2-yl)$SnBu_3$ gave the corresponding 3,5-diarylated imines **5** and **15** in 92% and 93% yields, respectively. This paper describes the first use of the tetrachlorothiadiazine **8** for preparing thiadiazinimines and highlights the potential of this unexplored reagent.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02237.

Experimental Section, X-ray data for imine **6a**, and NMR spectra (PDF)

CIF for imine **6a** (CIF)

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Notes

The authors declare no competing financial interest.

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