# THE CHEMISTRY OF NON-S-OXIDISED 4*H*-1,2,6-THIADIAZINES

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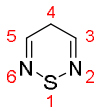
***Abstract.*** *Non-S-oxidised 4H-1,2,6-thiadiazines are a rare category of heterocycles. This review covers the physical properties, synthesis, reactivity and applications of mono- and polycyclic non-S-oxidised 4H-1,2,6-thiadiazines. Emphasis is made on the three main synthetic scaffolds, 2-(3,5-dichloro-4H-1,2,6-thiadiazin-4-ylidene)malononitrile **4**, 3,5-dichloro-4H-1,2,6-thiadiazin-4-one **5** and 3,4,4,5-tetrachloro-4H-1,2,6-thiadiazine **18**.*

**Contents**

## 1. Introduction

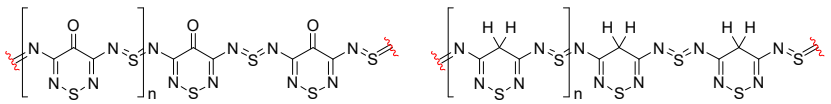
The sulfones and sulfoxides of 1,2,6-thiadiazines have numerous applications in the pharmaceutical[1,2] and agrochemical[3] sectors. In contrast, non-S-oxidised 4*H*-1,2,6-thiadiazines **1** (Figure 1) have received much less attention. Only five publications on non-S-oxidised 4*H*-1,2,6-thiadiazines appeared in the literature before 2000. To date, there are thirty six publications. The chemistry of non-S-oxidised 4*H*-1,2,6-thiadiazines has been partially reviewed along with oxidised derivatives and 1,2,6-oxadiazines in *Comprehensive Heterocyclic Chemistry I*,[4] *II*[5] and *III*.[6] This review covers all the reported properties, syntheses, reactions and applications of non-S-oxidised 4*H*-1,2,6-thiadiazines to date.




**1**

**Figure 1.** The numbering system of mononuclear non-S-oxidised 4*H*-1,2,6-thiadiazine **1**.

Woodward[7] recognised the potential applications of non-S-oxidised 4*H*-1,2,6-thiadiazines by proposing polymers containing 4*H*-1,2,6-thiadiazines (*e.g.* polymers I and II, Figure 2) as stable alternatives to the superconducting polymer poly(sulfur nitride) $(SN)_x$. At the time, however, the chemistry of non-S-oxidised 4*H*-1,2,6-thiadiazines was not well understood and no such polymers have yet to be reported.



**I** **II**

**Figure 2.** Non-S-oxidised 4*H*-1,2,6-thiadiazine polymers I and II proposed by Woodward as stable alternatives to poly(sulfur nitride) $(SN)_x$.

## 2. Theoretical methods

Hückel molecular orbital (HMO) wave functions were used to calculate spin densities and ring currents of naphtho[1,8-*cd*:4,5-*c'd'*]bis[1,2,6]thiadiazine **2** (Figure 3).[8]

The geometrical structures of ylidenemethylene **3**, ylidenemalononitrile **4** and dichlorothiadiazinone **5** (Figure 3) were fully optimised in their ground state using Møller-Plesset perturbation theory (MP2) at the 6-311G(d) level of theory and the results compared to the experimental X-ray crystallography data.[9] Frequency calculations using the same method were used to predict the infrared (IR) absorptions while energy calculations using the time-dependent density functional theory (TD-DFT) at the B3LYP/6-311+G(2d) level of theory on MP2/6-311G(d) optimised structures were used to predict the ultraviolet/visible (UV/vis) absorptions.[9]

DFT calculations at the RB3LYP/6-311G(d) level of theory were used to compare 3,5-di(thien-2-yl)-4*H*-1,2,6-thiadiazin-4-one **6** and *N*-(perfluorophenyl)-3,5-di(thien-2-yl)-4*H*-1,2,6-thiadiazin-4-imine **7** (Figure 3), showing that the two have similar frontier molecular orbitals (FMOs), energy levels and bandgaps, *i.e.* they were suitable for use in organic photovoltaics (OPVs).[10]

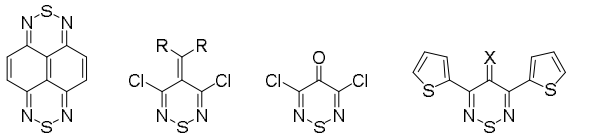


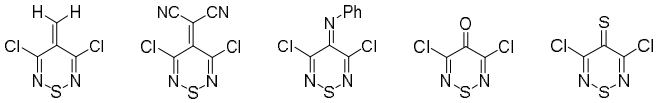

**Figure 3.** Structures of 4*H*-1,2,6-thiadiazines studied computationally.

## 3. Experimental structural methods

### 3.1. X-Ray diffraction

Single crystal X-ray structures have appeared for monocyclic and fused non-S-oxidised 4*H*-1,2,6-thiadiazines. Comparison of the X-ray structures of 3,5-dichloro-4*H*-1,2,6-thiadiazines **3-5**,[9,11-12] that vary only at the $sp^2$ C4 position, revealed the influence of the C4 substitution on the thiadiazine bond lengths and angles (Table 1). While the respective bond lengths within the thiadiazine were similar, strongly electron withdrawing groups at C4 (*e.g.* the ylidenemalononitrile **4** and dichlorothiadiazinone **5)** shorten the S-N bond lengths which has been attributed to electron release from the ring sulfur to the exocyclic C4 moiety. Furthermore, while the dichlorothiadiazinone **5**, thiadiazinethione **8** and ylidenemethylene **3** were planar, the *N*-phenylthiadiazinimine **9a** and ylidenemalononitrile **4** had shallow boat conformations, presumably owing to steric interactions.

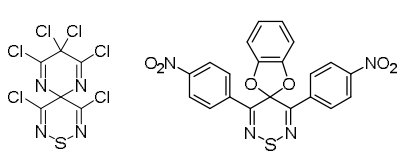
**Table 1.** Selected bond lengths (pm) of 3,5-dichloro-4*H*-1,2,6-thiadiazines **3-5**, **8** and **9a**.



| | **3** | **4** | **9a** | **5** | **8** |
|---|---|---|---|---|---|
| **S-N** | 166.1/165.7 | 160.0/161.3 | 163.6/163.6 | 161.5/161.8 | 163.1/163.4 |
| **N-C3** | 126.6/127.3 | 127.1/128.1 | 127.4/128.1 | 127.2/127.6 | 129.0/129.6 |
| **C3-C4** | 143.7/147.0 | 146.9/147.1 | 148.7/148.9 | 147.4/147.7 | 146.9/146.9 |
| **C4=X** | 134.1 | 136.1 | 127.8 | 120.9 | 164.9 |

X-Ray structures of 4*H*-1,2,6-thiadiazines **10**, **11a**, **12a** and **12b** that have an $sp^3$ C4 carbon show that the respective endocyclic bond lengths are similar (Table 2), but while the thiadiazine moieties of the spirocycle **10** and ketal **11a** are planar, those of both dihydroindeno[2,1-*c*][1,2,6]thiadiazines **12a** and **12b** have a boat structure.[12-14]

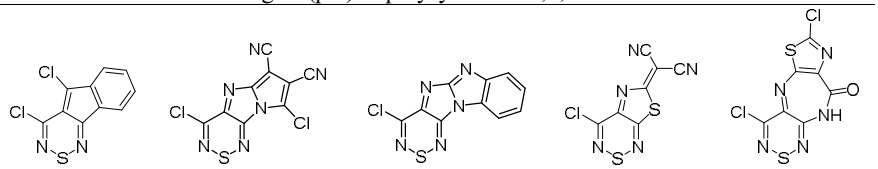
**Table 2.** Bond lengths (pm) of selected 4*H*-1,2,6-thiadiazines.



| | **10** | **11a** | **12a** | **12b** |
|---|---|---|---|---|
| **S-N** | 165.6/165.7 | 163.4/164.8 | 164.4/166.1 | 164.4/166.0 |
| **N-C3** | 125.0/126.2 | 128.7/128.8 | 127.4/127.5 | 127.1/127.9 |
| **C3-C4** | 153.0/153.2 | 151.7/152.0 | 152.1/152.2 | 151.1/151.6 |

The X-ray structures of several polycyclic 4*H*-1,2,6-thiadiazines were also reported.[15-19] The 5-chloro-3,4-fused systems **13-17** (Table 3) all have planar structures indicating a large degree of conjugation. Interestingly, pyrrolothiadiazine **14**[17] and imidazolothiadiazine **15**[18] exhibited polymorphism.

**Table 3.** Selected bond lengths (pm) of polycyclic 4*H*-1,2,6-thiadiazines **13-17**.



| | **13** | **14** | **15** | **16** | **17** |
|---|---|---|---|---|---|
| **S-N** | 164.0/164.1 | 161.4/162.9 | 162.3/163.0 | 161.2/161.7 | 161.9/162.0 |
| **N-C3** | 129.8/132.2 | 128.8/129.2 | 129.1/129.9 | 130.6/131.2 | 128.0/129.4 |
| **C3-C4** | 144.8/149.2 | 141.8/145.9 | 142.3/146.8 | 140.6/148.9 | 146.0/148.3 |
| **C4=X** | 134.9 | 132.4 | 137.0 | 137.0 | 128.8 |

### 3.2. NMR spectroscopy

$^{13}$C NMR spectroscopic data exist for a plethora of non-S-oxidised 4*H*-1,2,6-thiadiazines enabling a comparative analysis of the thiadiazine carbon resonances. The $^{13}$C NMR resonances of the C3/5 carbons vary ($\delta_{C3/5}$ 138.5-159.5) when the C4 substitution was modified with the thiadiazinethione **8** having the most downfield resonance at $\delta_{C3/5}$ 159.5 (Figure 4).[11,12,20,21] The C3/5 resonances of 4*H*-1,2,6-thiadiazin-4-imines **9**, however, do not appear in the spectra, presumably due to *E/Z* isomerisation of the exocyclic imine.[11] The C4 resonance is most upfield in the analogues **18** and **19a** owing to $sp^3$ hybridisation ($\delta_{C4}$ 72.1 in **18** and $\delta_{C4}$ 92.2 in **19a**) and is most downfield in thiadiazinethione **8** ($\delta_{C4}$ 179.4).[12]

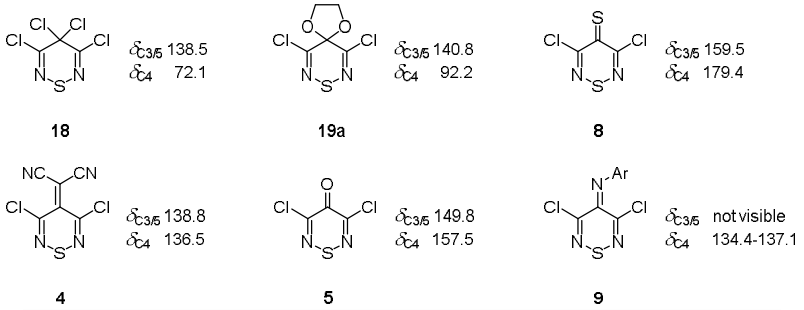
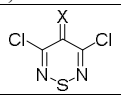



**Figure 4.** $^{13}$C NMR resonances of selected 3,5-dichloro-4*H*-1,2,6-thiadiazines.

### 3.3. UV/vis spectroscopy

The UV/vis absorption spectra of three 3,5-dichloro-4*H*-1,2,6-thiadiazines, differing in the electron withdrawing nature of their C4 substituent: (a) ylidenemethylene **3**, (b) ylidenemalononitrile **4** and (c) dichlorothiadiazinone **5** were studied.[9] While the methylene **3** (X=$CH_2$) showed a lowest energy absorption ($\lambda_{max}$) at 309 nm, the dichlorothiadiazinone **5** (X=O) showed a broad absorption with a $\lambda_{max}$ at 324 nm (Table 4), with the peak showing the largest wavelength attributed in both cases to a HOMO→LUMO transition. Thiadiazinethione **8** showed a more red-shifted absorption attributed to the low energy n→$\pi^*$ transition of the thiocarbonyl.[12] The absorption spectrum of the ylidenemalononitrile **4** [X=$C(CN)_2$] was red-shifted, with $\lambda_{max}$ at 403 nm (HOMO→LUMO transition), consistent with increased electron delocalisation. Also red-shifted was the absorption spectrum of *N*-phenylthiadiazinimine **9a** (X=NPh), with a $\lambda_{max}$ at 426 nm.[11]

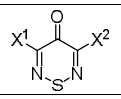
**Table 4.** UV/vis absorptions of 3,5-dichloro-4*H*-1,2,6-thiadiazines **3-5**, **8**, **9a**.



| **4*H*-1,2,6-Thiadiazine** (X) | $\lambda_{max}$ (nm) | log $\varepsilon$ |
|---|---|---|
| **3** ($CH_2$) | 309 | 3.72 |
| **4** ($C(CN)_2$) | 403 | 4.38 |
| **9a** (NPh) | 426 | 3.55 |
| **5** (O) | 324 | 4.10 |
| **8** (S) | 389 | 4.42 |

Regarding the C3/5 substituents, substitution of one chloride in dichlorothiadiazinone **5** with an electron donating group or a group that extends the conjugation leads to a red-shifted $\lambda_{max}$ (Table 5), with the substitution of the remaining chloride leading to a further but less significant red-shift.

**Table 5.** UV/vis absorptions of 3-chloro-5-substituted-4*H*-1,2,6-thiadiazines **5**, **20-27**.



| 4*H*-1,2,6-Thiadiazine | $X^1$ | $X^2$ | $\lambda_{max}$ (nm) |
|---|---|---|---|
| **5** | Cl | Cl | 324 |
| **20a** | Ph | Cl | 335 |
| **20b** | 2-furyl | Cl | 371 |
| **20c** | 2-thienyl | Cl | 380 |
| **21a** | NH$^n$Pr | Cl | 398 |
| **22a** | OMe | Cl | 344 |
| **23a** | SMe | Cl | 366 |
| **24a** | Ph | Ph | 348 |
| **24b** | fur-2-yl | fur-2-yl | 415 |
| **6** | thien-2-yl | thien-2-yl | 430 |
| **25a** | NH$^n$Pr | NH$^n$Pr | 401 |
| **26a** | OMe | OMe | 355 |
| **27a** | SMe | SMe | 394 |

A similar trend was observed with ylidenemalononitriles derived from the yellow coloured ylidenemalononitrile **4**: displacement of the first chloride by alkyl or arylamines led to deep red products, *e.g.* 5-pyrrolidino **28a** ($\lambda_{max}$ 520 nm), and the subsequent displacement of the second chloride gave purple-blue diamino products, *e.g.* 3,5-dipyrrolidino **29a** ($\lambda_{max}$ 591 nm) (Figure 5).[22]

The lowest energy absorptions of many fully unsaturated polycyclic 4*H*-1,2,6-thiadiazines, *e.g.*, the tricyclic systems **30a-c**, are typically highly structured, owing to increased rigidity, and more red-shifted due to the higher conjugation of the system. The most red-shifted is thiadiazinoquinoxaline **30a** ($\lambda_{max}$ 595 nm),

while thiadiazinobenzothiazine **30b** and thiadiazinobenzoxazine **30c** show $\lambda_{max}$ of 463 and 446 nm, respectively (Figure 6).[23]

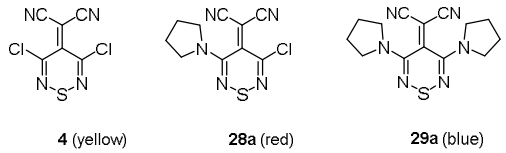



**Figure 5.** Colours of selected (4*H*-1,2,6-thiadiazin-4-ylidene)malononitriles **4**, **28a** and **29a**.

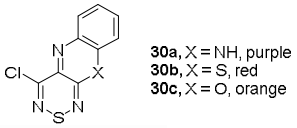



**Figure 6.** Colours of polycyclic 4*H*-1,2,6-thiadiazines **30a-c**.

As expected, 4*H* analogues that have an $sp^3$ carbon at C4 are colourless ($\lambda_{max}$ 279-344 nm) due to the disruption of conjugation in the thiadiazine ring.[24]

### 3.4. Infrared and Raman spectroscopy

The infrared (IR) and Raman spectra of selected 4*H*-1,2,6-thiadiazines were studied.[9] The most intense bands observed in the Raman spectrum of dichlorothiadiazinone **5** after excitation at 282.4 nm were the symmetric and asymmetric C=N stretches at 1478 and 1504 $cm^{-1}$, respectively, while in the IR spectrum only the asymmetric stretch was observed at 1503 $cm^{-1}$. Other major Raman absorptions were the C=O stretch at 1678 $cm^{-1}$ (IR at 1657 $cm^{-1}$), the C-C-C symmetric stretch at 1063 $cm^{-1}$ (IR at 1063 $cm^{-1}$), the N-S-N symmetric stretch at 849 $cm^{-1}$ (IR at 854 $cm^{-1}$) and the N-S-N bend at 486 $cm^{-1}$ (not seen in the IR).

### 3.5. Mass spectrometry

The mass spectra of non-S-oxidised 4*H*-1,2,6-thiadiazines have been obtained using various techniques such as electron ionisation (EI), electrospray ionisation (ESI), matrix assisted laser desorption ionisation-time of flight (MALDI-TOF) and atmospheric pressure chemical ionisation (APCI). Common fragments observed in the EI mass spectra of 3-chloro-4*H*-1,2,6-thiadiazines are: Cl, $Cl_2$, NS, ClS, CClN, CClNS and $CCl_2N$.[20-23] MALDI and ESI mass spectra showed significantly less fragmentation than EI spectra.

## 4. Thermodynamic aspects

### 4.1. Physical properties

The two most studied non-S-oxidised 4*H*-1,2,6-thiadiazines are tetrachlorothiadiazine **18** and dichlorothiadiazinone **5**. The former is a pale yellow liquid that distils at 90 °C (30 mbar) and crystallises on cooling to -20 °C [mp (DSC) onset: 10.3 °C, peak max: 12.8 °C], while the latter crystallises as pale yellow needles with a mp of 81-82 °C (from *c*-hexane).[20] The stability of various 4*H*-1,2,6-thiadiazines was assessed by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). Non S-oxidised 4*H*-1,2,6-thiadiazine-containing polymers were found to be thermally stable up to 270 °C (by TGA).[10]

### 4.2. Aromaticity

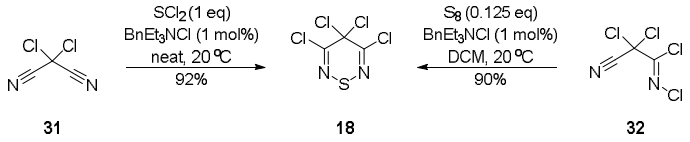
Bird aromaticity indices of 3,5-dichloro-4*H*-1,2,6-thiadiazines **3**, **4** and **5** were calculated based on statistical evaluation of deviations in peripheral bond orders derived from crystallography determined bond lengths within the ring.[25,26] Ylidenemethylene **3** has a low Bird's aromaticity index $I_A$=45, dichlorothiadiazinone **5** has an $I_A$=54 and ylidenemalononitrile **4** an $I_A$=60,[9] indicating that the three thiadiazines are weakly aromatic systems [*cf.* $I_A$(furan)=53[26] and $I_A$(benzene)=100[25]].

**5. 1,2,6-Thiadiazine ring synthesis**

The synthetic methods for the generation of the 1,2,6-thiadiazine ring can be divided to the synthesis of monocyclic and that of polycyclic 4*H*-1,2,6-thiadiazines. While only two monocyclic scaffolds were directly prepared, tetrachlorothiadiazine **18** and ylidenemalononitrile **4**, a number of synthetic routes to polycyclic 4*H*-1,2,6-thiadiazines were reported distinguished by whether the thiadiazine ring was built or whether it pre-existed and fusion occurred onto it.

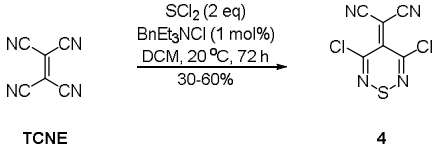
**5.1. Synthesis of monocyclic 4*H*-1,2,6-thiadiazines**

The primary non-S-oxidised 1,2,6-thiadiazine used to prepare other derivatives is tetrachlorothiadiazine **18**, which was first prepared by Kristinsson in 1973 by reacting dichloromalononitrile (**31**) with $SCl_2$.[27] In 1974, Geevers and Trompen developed a modified route to tetrachlorothiadiazine **18** by reacting *N*-2,2-trichloro-2-cyanoacetimidoyl chloride **32** with elemental sulfur (Scheme 1).[28] Both methods give ~90% yields of product that was isolated by distillation under reduced pressure as a yellow oil. The two reports gave conflicting distillation data for the product (100 °C, 8 mbar[27] *vs* 90 °C, 4 mbar[28]); in our hands thiadiazine **18** distils at 90 °C, 30 mbar as a pale yellow oil that crystallised on cooling to -20 °C and can be stored for several months at -40 °C.[20]




**Scheme 1.** Syntheses of tetrachlorothiadiazine **18**.

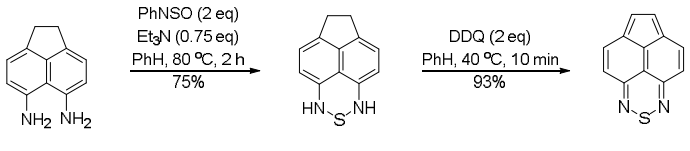
Reacting tetracyanoethene (TCNE) with $SCl_2$ in the presence of benzyltriethylammonium chloride (1 mol%) gives the monocyclic ylidenemalononitrile **4** in variable yields (30-60%, Scheme 2).[17,21] The reaction is complex and chromatography is needed to separate ylidenemalononitrile **4** from various minor side products.




**Scheme 2.** Preparation of the ylidenemalononitrile **4** from TCNE and $SCl_2$.

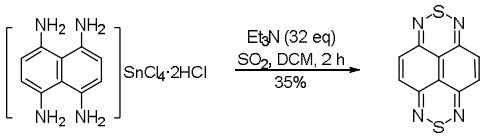
**5.2.1. Synthesis of polycyclic 4*H*-1,2,6-thiadiazines by building of the thiadiazine ring**

The first polycyclic 4*H*-1,2,6-thiadiazine was reported in 1970 by Perkins *et al.* who prepared acenaphtho[5,6-*cd*][1,2,6]thiadiazine **33** from the 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)-mediated oxidation of 6,7-dihydroacenaphtho[5,6-*cd*][1,2,6]thiadiazine **34**.[29,30] The latter was prepared from 1,2-dihydroacenaphthylene-5,6-diamine **35** and *N*-thionylaniline (Scheme 3).[31]




**Scheme 3.** Preparation of acenaphtho[5,6-*cd*][1,2,6]thiadiazine **33**.

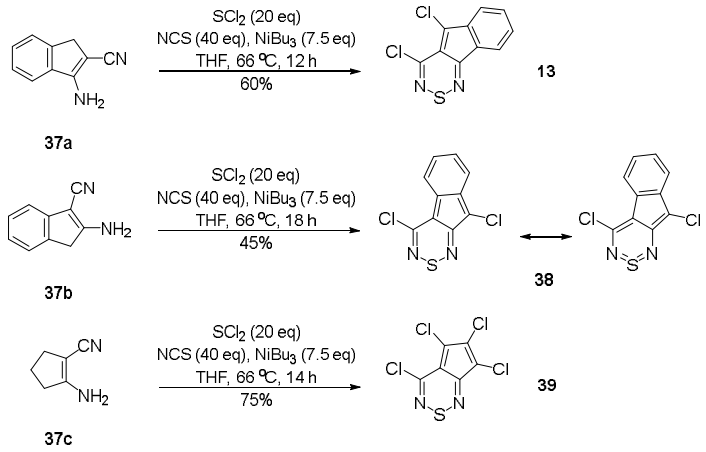
1,4,5,8-Tetraaminonaphthalene **36** reacts with $SO_2$ to give naphtho[1,8-*cd*:4,5-*c'd'*]bis[1,2,6]thiadiazine **2** in 35% yield (Scheme 4).[8] The latter was studied as a compound with ambiguous aromatic character: its chemical stability indicated an aromatic structure, but its electronic spectrum, electrochemistry and $^1$H NMR chemical shifts were typical of antiaromatic structures.




**36** **2**

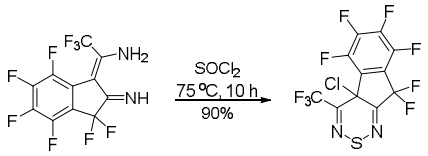
**Scheme 4.** Preparation of naphtho[1,8-*cd*:4,5-*c'd'*]bis[1,2,6]thiadiazine **2**.

Cyclic enaminonitriles **37a-c** react with $SCl_2$, *N*-chlorosuccinimide (NCS) and triisobutylamine to give cyclopenta[1,2,6]thiadiazines **13**, **38** and **39** in 45-75% yields (Scheme 5).[15,16]




**Scheme 5.** Synthesis of cyclopenta[1,2,6]thiadiazines **13**, **38** and **39**.

Hexafluoroiminoindan **40** reacts with $SOCl_2$ at 70-75 °C for 10 h to give 4-(trifluoromethyl)-4*a*,9-dihydroindeno[2,1-*c*][1,2,6]thiadiazine **12c** in 90% yield (Scheme 6).[14]

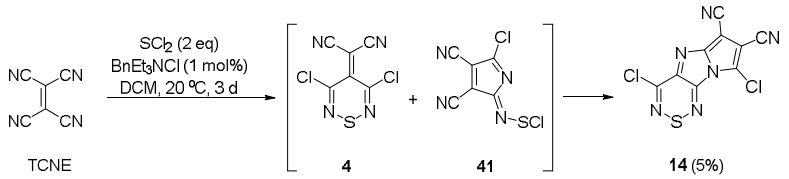



**40** **12c**

**Scheme 6.** Synthesis of 4-(trifluoromethyl)-4*a*,9-dihydroindeno[2,1-*c*][1,2,6]thiadiazine **12c**.

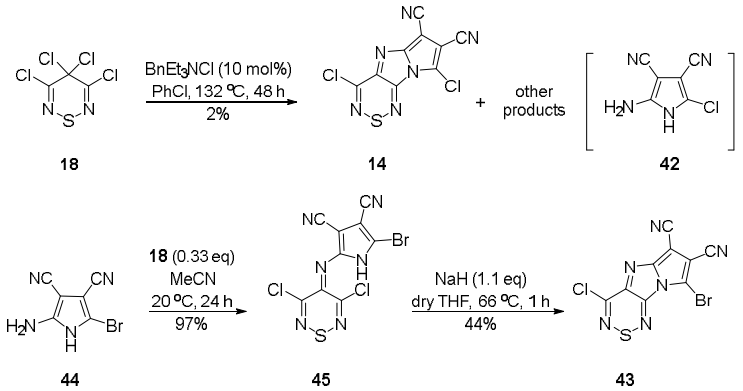
### 5.2.2. Synthesis of polycyclic 4*H*-1,2,6-thiadiazines by fusion onto the thiadiazine ring

The chloride-catalysed reaction of TCNE with $SCl_2$ to afford ylidenemalononitrile **4** (Sect. 5.1) was accompanied by several side products, one of which was pyrrolothiadiazine **14**. The latter was proposed to form *via* the reaction of ylidenemalononitrile **4** with pyrrole intermediate **41** (Scheme 7), a tentative product of the chloride induced reaction of TCNE in the presence of $SCl_2$.[17]



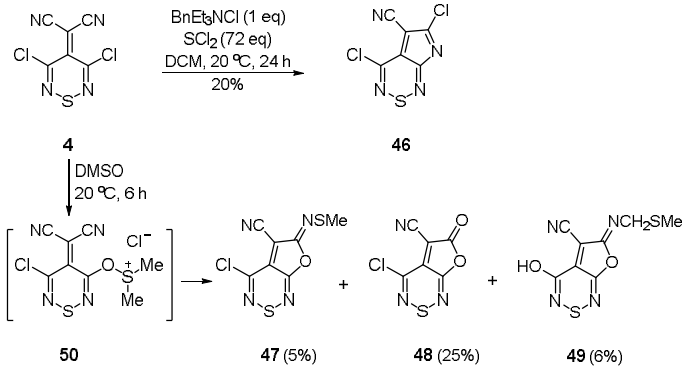

**Scheme 7.** Synthesis of pyrrolothiadiazine **14**.

Pyrrolothiadiazine **14** was also isolated as a minor side product in 2% yield from the chloride-mediated degradation of tetrachlorothiadiazine **18**.[19] The intermediate to pyrrolothiadiazine **14** was presumed to be chloropyrrole **42**. The independent synthesis of bromo analogue **43** from bromopyrrole **44** and tetrachlorothiadiazine **18** was also reported in a two-step synthesis with a 43% overall yield (Scheme 8).[19]




**Scheme 8.** Synthesis of pyrrolothiadiazines **14** and **43**.

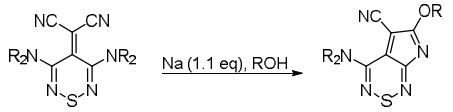
Ylidenemalononitrile **4** is a useful scaffold for the construction of other bicyclic systems. Treatment of ylidenemalononitrile **4** with excess of $SCl_2$ led to pyrrolothiadiazine **46** in 20% yield (Scheme 9).[21] The high reactivity of ylidenemalononitrile **4** led to reactivity with DMSO at 20 °C to give a mixture of 6*H*-furo[2,3-*c*][1,2,6]thiadiazines **47**-**49**.[22] The reaction mechanism involves the nucleophilic substitution of chloride by the oxygen atom of DMSO to give intermediate **50** that then converts to the three products **47**-**49**.




**Scheme 9.** Reaction of ylidenemalononitrile **4** with $SCl_2$ and with DMSO.

3,5-Dialkylamino-substituted ylidenemalononitriles **29** can be converted to pyrrolothiadiazines **51** by treatment with alkoxides.[32] The dialkylamino substituents include pyrrolidino, piperidino and morpholino groups and give variable yields (25-92%) of pyrrolothiadiazines **51** (Table 6). Two tentative reaction mechanisms are proposed: i) addition of alkoxide to the nitrile followed by cyclisation onto the thiadiazine C3 position and elimination of the C3 substituent, and ii) an Addition of the Nucleophile, Ring Opening, and Ring Closure (ANRORC) style ring opening of the thiadiazine by thiophilic attack of the alkoxide followed by alkoxide addition to the nitrile and reforming of the thiadiazine ring.

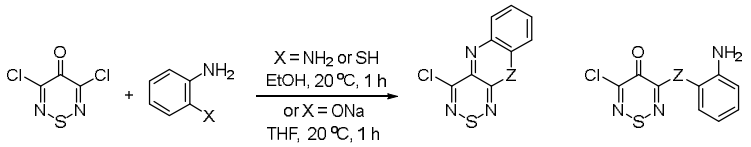
**Table 6.** Reaction of 3,5-dialkylamino-substituted ylidenemalononitriles **29** with alkoxides.




**29a-c** **51a-f**

| **29a-c** ($R_2N$) | ROH | Temp. (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|
| **29a** (pyrrolidin-1-yl) | EtOH | 80 | 2 | **51e** (37) |
| **29a** (pyrrolidin-1-yl) | MeOH | 65 | 24 | **51f** (25) |
| **29b** (piperidin-1-yl) | EtOH | 80 | 24 | **51c** (73) |
| **29b** (piperidin-1-yl) | MeOH | 65 | 72 | **51d** (26) |
| **29c** (morpholin-4-yl) | EtOH | 80 | 4 | **51a** (90) |
| **29c** (morpholin-4-yl) | MeOH | 65 | 24 | **51b** (92) |

Fused 1,2,6-thiadiazines can also be prepared by reacting dichlorothiadiazinone **5** with benzene-1,2-diamine, 2-aminothiophenol and sodium 2-aminophenoxide to give, respectively, thiadiazinoquinoxaline **30a**, thiadiazinobenzothiazine **30b** and thiadiazinobenzoxazine **30c** in good yields (Scheme 10).[23] Similar reactions of dichlorothiadiazinone **5** with *N*-methylbenzene-1,2-diamine or methylation of thiadiazinoquinoxaline **30a** with MeI in DMSO give 4-chloro-10-methyl-10*H*-[1,2,6]thiadiazino[3,4-*b*]quinoxaline **30d** in 70 and 95% yields, respectively. Mechanistically, an initial displacement of the C3 chloride gives intermediate **52**, that subsequently cyclises by formation of an endocyclic imine.

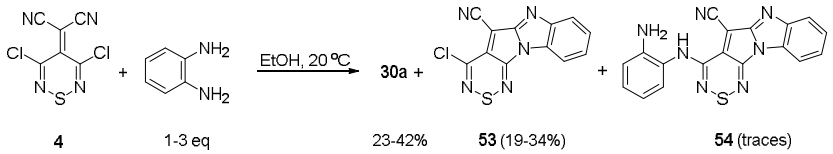



**5** **30a-d** (95-99%) Z = NMe, NH, S or O **52**

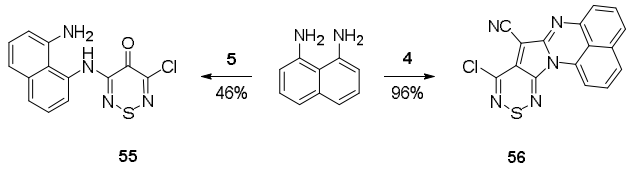
**Scheme 10.** Reaction of dichlorothiadiazinone **5** with bis-nucleophiles.

The analogous chemistry of the ylidenemalononitrile **4** with 2-aminothiophenol gives thiadiazino-benzothiazine **30b** in 87% yield, but reaction with benzene-1,2-diamine gives thiadiazinoquinoxaline **30a** (23-42%) along with two other products **53** and **54** (Scheme 11). The benzo[4',5']imidazo[1',2':1,5]pyrrolo[2,3-*c*][1,2,6]thiadiazines **53** and **54** arise from an initial displacement of the C3 chloride followed by the intramolecular 5-exo-dig cyclisation of the secondary amino group onto the neighbouring nitrile and subsequent second cyclisation with loss of ammonia.

The reaction of dichlorothiadiazinone **5** with 1,8-diaminonaphthalene only affords the chloride displacement product **55** (Scheme 12), which does not cyclodehydrate, while reaction with ylidenemalono-nitrile **4** gives 9-chloro-[1,2,6]thiadiazino[4',3':4,5]pyrrolo[1,2-*a*]perimidine-8-carbonitrile **56** in 96% yield due to the favourable 5-exo-dig cyclisation on the nitrile.

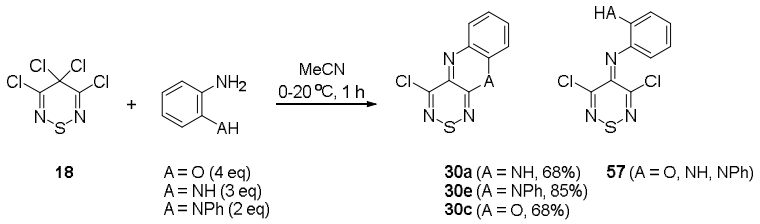



**Scheme 11.** Reaction of ylidenemalononitrile **4** with benzene-1,2-diamine.




**Scheme 12.** Reaction of 1,8-diaminonapthalene with thiadiazines **4** and **5**.

Similar cyclisations onto 1,2,6-thiadiazine start from tetrachlorothiadiazine **18**.[20] Treatment of tetra-chlorothiadiazine **18** with 2-aminophenol and benzene-1,2-diamine gives fused 4*H*-1,2,6-thiadiazines in 68-85% yields (Scheme 13). Mechanistically, the first displacement occurs at the highly electrophilic geminal dichloride (C4 position) to afford intermediate imine **57**, followed by cyclisation onto the C3 position. This is in contrast to the respective chemistry of dichlorothiadiazinone **5** where the nucleophilic displacement first occurs at the C3 position and is followed by cyclodehydration at C4.




**Scheme 13.** Reaction of tetrachlorothiadiazine **18** with bis-nucleophiles.

## 6. Chemistry of 1,2,6-thiadiazines

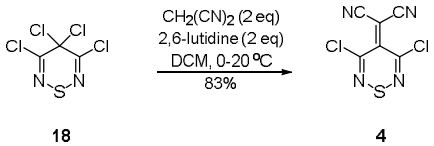
The chemistry of 1,2,6-thiadiazines can be divided into the functional group interconversions at the C4 position, the displacement of C3/5 chlorides by nucleophiles of monocyclic or polycyclic 4*H*-1,2,6-thiadiazines, as well as the Pd-catalysed C-C and C-N couplings of chloro-4*H*-1,2,6-thiadiazines. Only one report of S-oxidation has appeared.

### 6.1. Functional group interconversions at the C4 position of monocyclic 4*H*-1,2,6-thiadiazines

#### 6.1.1. Interconversions of 3,4,4,5-tetrachloro-4*H*-1,2,6-thiadiazine 18

##### 6.1.1.1. Conversion to 2-(3,5-dichloro-4*H*-1,2,6-thiadiazin-4-ylidene)malononitrile 4

Condensation of tetrachlorothiadiazine **18** with malononitrile in the presence of 2,6-lutidine gives the ylidenemalononitrile **4** in 83% yield (Scheme 14).[20] A chromatography free work up on a 4 mmol reaction scale led to a slightly lower 64% yield.[20] This route to prepare ylidenemalononitrile **5** is superior to its direct preparation from TCNE and $SCl_2$ (Sect. 5.1).

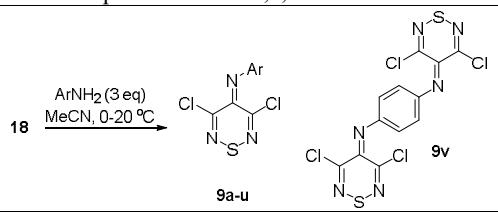



**Scheme 14.** Transformation of the tetrachlorothiadiazine **18** into to the ylidenemalononitrile **4**.

### 6.1.1.2. Conversion to 4*H*-1,2,6-thiadiazin-4-imines

Tetrachlorothiadiazine **18** reacts with electron rich and poor anilines to give 4*H*-1,2,6-thiadiazin-4-imines **9** (Table 7).[11] The reaction also works with benzene-1,4-diamine to give bisthiadiazine **9v** in 43% yield but fails with primary alkylamines and hetarylamines, such as pyridyl-, pyrimidyl- and pyrazinylamines.

**Table 7.** Preparation of 4*H*-1,2,6-thiadiazin-4-imines **9**.




| Ar | Time (h) | Yield (%) | Ar | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| Ph | 0.50 | **9a** (86) | 4-$FC_6H_4$ | 1 | **9l** (92) |
| 2-Tol | 3 | **9b** (84) | 2-$ClC_6H_4$ | 3 | **9m** (74) |
| 3-Tol | 1 | **9c** (84) | 3-$ClC_6H_4$ | 0.67 | **9n** (84) |
| 4-Tol | 0.75 | **9d** (81) | 4-$ClC_6H_4$ | 1 | **9o** (87) |
| 2-$NCC_6H_4$ | 2 | **9e** (76) | 2,6-$Cl_2C_6H_3$ | 24 | **9p** (89) |
| 4-$NCC_6H_4$ | 2 | **9f** (96) | 2-$BrC_6H_4$ | 3 | **9q** (83) |
| 2-$O_2NC_6H_4$ | 8 | **9g** (61) | 3-$BrC_6H_4$ | 0.67 | **9r** (90) |
| 4-$O_2NC_6H_4$ | 2 | **9h** (95) | 4-$BrC_6H_4$ | 1 | **9s** (84) |
| 2-$MeOC_6H_4$ | 1 | **9i** (88) | 2-$IC_6H_4$ | 1.5 | **9t** (91) |
| 3-$MeOC_6H_4$ | 0.67 | **9j** (93) | 4-$IC_6H_4$ | 0.67 | **9u** (73) |
| 4-$MeOC_6H_4$ | 1 | **9k** (74) | 4-$H_2NC_6H_4$ | 2.5 | **9v** (43) |

### 6.1.1.3. Conversion to 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one 5

Geevers and Trompen reported that tetrachlorothiadiazine **18** reacts with glacial formic acid to afford, after a quench with water, dichlorothiadiazinone **5** in 85% yield.[33] Recently, the use of glacial formic acid (96-98%) was shown to be critical as in the presence of formic acid with a higher water content the starting material degrades to 2-chloromalonamide (Table 7).[20] Other reagents, such as glacial acetic acid, nitrates, sulfates or DMSO can act as alternative sources of nucleophilic oxygen to afford dichlorothiadiazinone **5** (Table 8).

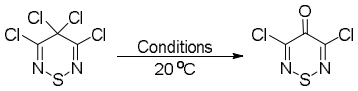
### 6.1.1.4. Conversion to ketals and thioketals

The labile C4 chlorides of tetrachlorothiadiazine **18** can be readily displaced by weak nucleophiles such as alcohols, phenols and thiols to afford ketals and thioketals (Table 9).[24] Tetrachlorothiadiazine **18** reacts with alkanols like ethylene glycol and methanol to give ketals **19a** and **19b** in good yields. Phenol was less reactive giving low yields of diphenoxy ketal **19c**, but catechol worked well to give ketal **19d** in 87% yield. Thiols and thioacetic acid quickly react at room temperature to give good yields of thioketals **58a-d** with the exception of benzene-1,2-dithiol that gave the product **58c** in low 31% yield, presumably due to ring degradation.

### 6.1.1.5. Other conversions

Tin reduction of tetrachlorothiadiazine **18** affords spirocycle **10** and thiadiazinethione **8** in 10 and 27% yields, respectively (Scheme 15).[12] The formation of spirocycle **10** was attributed to reductive cleavage of the N-S bonds of tetrachlorothiadiazine **18** to release a synthon equivalent of 2,2-dichloromalonimidoyl dichloride **59**, which then condensed with unreacted tetrachlorothiadiazine **18** *via* its highly reactive C4 geminal dichloride. The origins of thiadiazinethione **8** was attributed to a nucleophilic source of sulfur, possibly $H_2S$, which reacted with additional tetrachlorothiadiazine **18** at the geminal C4 position.

**Table 8.** Hydrolysis of tetrachlorothiadiazine **18** to dichlorothiadiazinone **5**.

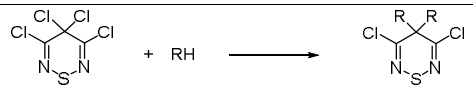



**18** **5**

| Conditions | Time (h) | Yield (%) |
|---|---|---|
| $HCO_2H$ (98%) neat | 24 | 75 |
| $HCO_2H$ (85%)[a] neat | 18 | 0[b] |
| AcOH neat | 48 | 74 |
| $NaNO_3$ (1 eq), DCM | 18 | nr[c] |
| $NaNO_3$ (1 eq), MeCN | 1.5 | 71 |
| $AgNO_3$ (1 eq), MeCN | 0.5 | 85 |
| $Ag_2SO_4$ (0.5 eq), MeCN | 4 | 77 |
| $H_2O$ (1 eq), DMSO (1 mol%), MeCN | 20 | 0[b] |
| DMSO (1 eq), MeCN | 20 | 31 |
| DMSO neat | 1 | 45 |

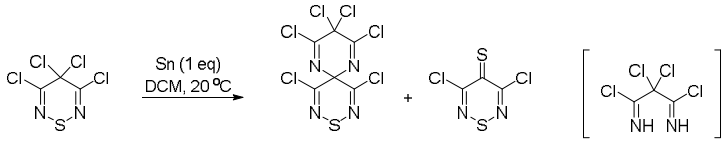
[a]Technical grade formic acid, contains 15% $H_2O$. [b]Degradation to chloromalonamide. [c]nr=no reaction.

**Table 9.** Transformation of tetrachlorothiadiazine **18** to ketals **19a-d** and thioketals **58a-d**.




**18** **19a-d** or **58a-d**

| Reagent (eq) | Solvent (Temp. °C) | Time (h) | R | Yield, % |
|---|---|---|---|---|
| $(CH_2OH)_2$ (1) | MeCN (82) | 1 | $(CH_2O)_2$ | **19a** (81) |
| MeOH (neat) | MeOH (20) | 0.2 | MeO | **19b** (89) |
| PhOH (2) | DCE (83) | 2 | PhO | **19c** (44) |
| catechol (1) | DCM (39) | 0.5 | 1,2-$C_6H_4O_2$ | **19d** (87) |
| BnSH (2.5) | THF (20) | 0.5 | BnS | **58a** (80) |
| PhSH (2.5) | THF (20) | 0.2 | PhS | **58b** (97) |
| 1,2-$(HS)_2.C_6H_4$ (1) | DCM (20) | 0.4 | 1,2-$C_6H_4S_2$ | **58c** (31) |
| AcSH (2.5) | DCM (20) | 0.2 | AcS | **58d** (87) |




**18** **10** (10%) **8** (27%) **59**

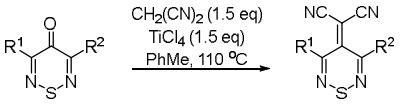
**Scheme 15.** Reaction of tetrachlorothiadiazine **18** with tin.

### 6.1.2. Interconversions of 4*H*-1,2,6-thiadiazin-4-ones

Condensation of 3,5-substituted-4*H*-1,2,6-thiadiazin-4-ones **24a-t** and **6** with malononitrile, in the presence of $TiCl_4$, affords the ylidenemalononitriles **60a-t** in good yields.[34] The reaction works well with 3,5-diaryl-, diphenoxy-, dimethoxy- and diphenylthio-substituted thiadiazinones, as well as with 3-halo-5-phenyl and 3-chloro-5-methoxy-substituted thiadiazinones, but was ineffective with 3,5-diamino- and some electron-rich hetaryl-substituted thiadiazinones. The 2-methoxyphenyl analogue **60f** gives as a product the mono-protodemethylated 2-[3-(2-hydroxyphenyl)-5-(2-methoxyphenyl)-4*H*-1,2,6-thiadiazin-4-ylidene]-malononitrile **60f** in good yield (87%), while the 3-methoxyphenyl analogue **60g** gives surprisingly a low yield of ylidenemalononitrile **60g**. The reaction works well with 3-halo-5-phenyl-thiadiazinones **60q-s**,

but with bromo and iodo analogues the products are contaminated with *ca.* 10% of the 3-chloro ylidenemalononitrile **60q** owing to halogen scrambling. The condensation does not work with the dichlorothiadiazinone **5** (Table 10).

**Table 10.** Reaction of thiadiazinones **24a-t** and **6** with malononitrile.

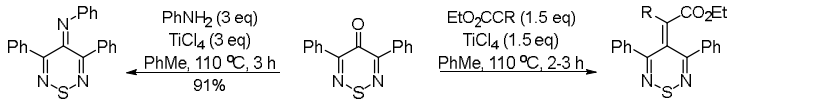



24a-t, 6 → 60a-t

| $R^1 = R^2$ | Time (h) | Yield (%) | $R^1$ | $R^2$ | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|
| Ph | 5.5 | **60a** (88) | 4-$ClC_6H_4$ | | 5.5 | **60k** (96) |
| 2-Tol | 2.5 | **60b** (96) | fur-2-yl | | 4 | **60l** (84) |
| 3-Tol | 4.5 | **60c** (93) | thien-2-yl | | 8 | **60m** (18)[a,c] |
| 4-Tol | 5.5 | **60d** (86) | MeO | | 0.25 | **60n** (86) |
| 3-$O_2NC_6H_4$ | 24 | **60e** (43)[a] | PhO | | 0.25 | **60o** (74) |
| 2-$MeOC_6H_4$ | 5 | **60f** (87)[b] | PhS | | 3 | **60p** (69) |
| 3-$MeOC_6H_4$ | 5 | **60g** (12) | Ph | Cl | 3 | **60q** (93) |
| 4-$MeOC_6H_4$ | 7 | **60h** (94) | Ph | Br | 9 | **60r** (82)[d] |
| 2-$ClC_6H_4$ | 4.5 | **60i** (98) | Ph | I | 6 | **60s** (82)[d] |
| 3-$ClC_6H_4$ | 6 | **60j** (97) | MeO | Cl | 0.16 | **60t** (84) |

[a]5 eq of $TiCl_4$ and $CH_2(CN)_2$ used. [b]2-[3-(2-Hydroxyphenyl)-5-(2-methoxyphenyl)-4*H*-1,2,6-thiadiazin-4-ylidene]malononitrile **60f**. [c]Recovered starting material (46%). [d]Contains *ca.* 10% of 2-(3-chloro-5-phenyl-4*H*-1,2,6-thiadiazin-4-ylidene)malononitrile **60q**.

In the presence of $TiCl_4$, diphenylthiadiazinone **24a** can be condensed with other active methylenes such as ethyl cyanoacetate and diethyl malonate (1.5 eq) to give ylidenecyanoacetate **61a** and ylidenemalonate **61b** in 77 and 90% yields, respectively.[11] Disappointingly, condensation with Meldrum's acid, dimidone or nitromethane failed. Similarly, in the presence of $TiCl_4$, diphenylthiadiazinone **24a** reacts with aniline to give *N*,3,5-triphenyl-4*H*-1,2,6-thiadiazin-4-imine **62a** in 91% yield (Scheme 16).[11]



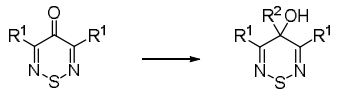

**62a** ← **24a** → **61a** (R = CN, 77%); **61b** (R = $CO_2Et$, 90%)

**Scheme 16.** Synthesis of ylidenes **61a** and **61b** and *N*,3,5-triphenyl-4*H*-1,2,6-thiadiazin-4-imine (**62a**).

3,5-Diaryl-4*H*-1,2,6-thiadiazin-4-ones **24a** and **6** can be reduced by $NaBH_4$ in methanol to give alcohols **63a** and **63b**, respectively, in high yields,[35] while addition of MeLi affords alcohols **64a** and **64b**, respectively, in high yields (Table 11).

By heating toluene solutions of the alcohols **64a** and **64b** in the presence of catalytic *p*-toluenesulfonic acid (*p*TSA) dehydration occurs to give the ylidenemethylenes **65a** and **65b** in 90 and 96% yields, respectively. The 3,5-diphenyl-substituted ylidenemethylene **65a** can subsequently be brominated with *N*-bromosuccinimide (NBS) to give 4-(bromomethylene)-3,5-diphenyl-4*H*-1,2,6-thiadiazine **66** in 80% yield. Dihalo(thiadiazin-4-ylidene)methylenes **67** can be produced *via* an alternative route, by treating 3,5-diphenyl-thiadiazinone **24a** with $Ph_3P$ in $CCl_4$ or $CBr_4$ at 140 °C, under microwave irradiation. The protocol gave the dichloro- and dibromomethylene **67a** and **67b** in 95 and 70% yields, respectively (Scheme 17).[35] Treating 3,5-diarylthiadiazinones **24a** (R=Ph) and **6** (R=thien-2-yl) with $P_2S_5$ (0.5 eq) in xylene heated at reflux for 5 h gave the analogous thiadiazine-4-thiones **68a** and **68b** in 68 and 45% yields, respectively (Scheme 18).[35]

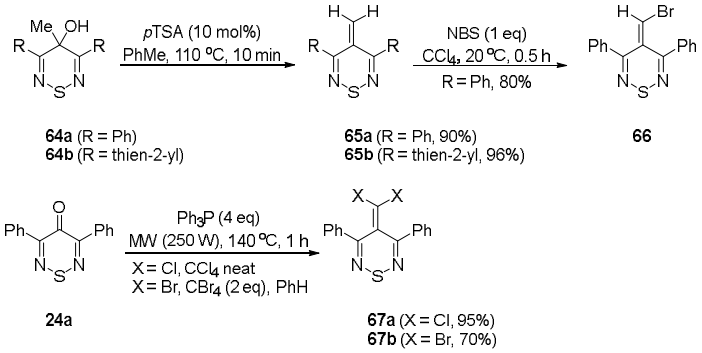
**Table 11.** Addition reactions to 3,5-diaryl-4*H*-1,2,6-thiadiazin-4-ones **6** and **24a**.



**6** ($R^1$ = thien-2-yl)
**24a** ($R^1$ = Ph)

**63a,b, 64a,b**

| $R^1$ | Conditions | Time (min) | $R^2$ | Yield, % |
|---|---|---|---|---|
| Ph | $NaBH_4$ (2 eq), MeOH, 50 °C | 5 | H | **63a** (97) |
| thien-2-yl | $NaBH_4$ (2 eq), MeOH/DCM (1:1), 50 °C | 15 | H | **63b** (98) |
| Ph | MeLi (4 eq), THF, 0-10 °C | 60 | Me | **64a** (90) |
| thien-2-yl | MeLi (4 eq), THF, 0-10 °C | 60 | Me | **64b** (79) |




**64a** (R = Ph)
**64b** (R = thien-2-yl)

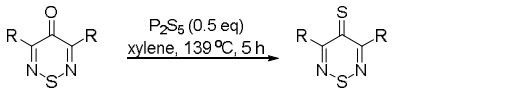
**65a** (R = Ph, 90%)
**65b** (R = thien-2-yl, 96%)

**66**

**24a**

**67a** (X = Cl, 95%)
**67b** (X = Br, 70%)

**Scheme 17.** Synthesis of 4-(bromomethylene)-3,5-diphenyl-4*H*-1,2,6-thiadiazine **66** and dihalo(thiadiazin-4-ylidene)methylenes **67a** and **67b**.



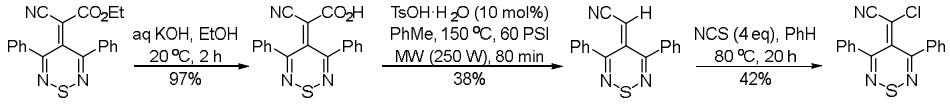

**24a** (R = Ph)
**6** (R = thien-2-yl)

**68a** (R = Ph, 68%)
**68b** (R = thien-2-yl, 45%)

**Scheme 18.** Synthesis of thiadiazine-4-thiones **68a** and **68b**.

### 6.1.3. Interconversions of 2-(4*H*-1,2,6-thiadiazin-4-ylidene)malononitriles 61a and 69a

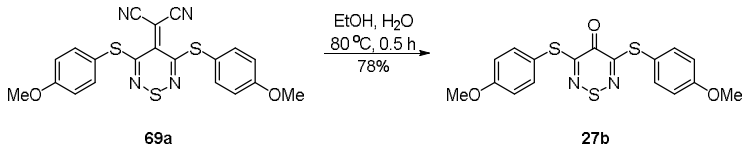
Ylidenecyanoacetate **61a** can be transformed in three steps to ylidenechlorocyanomethylene **61c** (Scheme 19).[34] This involves ester hydrolysis with KOH to afford carboxylic acid **61d**, acid catalysed decarboxylation to ylideneacetonitrile **61e** and chlorination with NCS.




**61a** **61d** **61e** **61c**

**Scheme 19.** Conversion of ylidenecyanoacetate **61a** to ylidenechlorocyanomethylene **61c**.

Heating a solution of 2-{3,5-bis[(4-methoxylphenyl)thio]-4*H*-1,2,6-thiadiazin-4-ylidene}malononitrile **69a** in aqueous ethanol affords 3,5-bismethoxyphenylthiothiadiazinone **27b** in 78% yield (Scheme 20).[22]

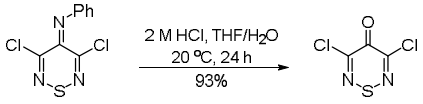



**69a** **27b**

**Scheme 20.** Hydrolysis of 2-{3,5-bis[(4-methoxyphenyl)thio]-4*H*-1,2,6-thiadiazin-4-ylidene}malononitrile **69a**.

### 6.1.4. Interconversions of 4*H*-1,2,6-thiadiazin-4-imines

Treating *N*-phenylthiadiazinimine **9a** with 2M HCl in THF at 20 °C for 24 h gives dichlorothiadiazinone **5** in 93% yield (Scheme 21).[11]

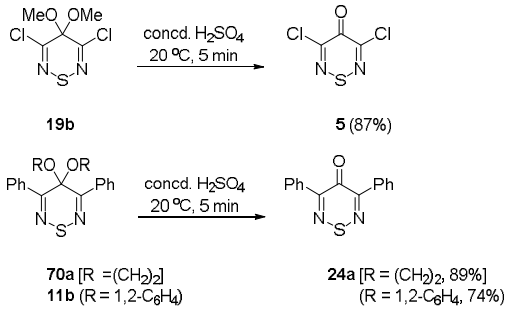



**9a** **5**

**Scheme 21.** Acid hydrolysis of *N*-phenylthiadiazinimine **9a**.

### 6.1.5. Interconversions of 1,2,6-thiadiazine-4-ketals

1,2,6-Thiadiazine-4-ketals were studied as protected versions of thiadiazin-4-ones, as such their hydrolysis to the latter was investigated. While most 3,5-dichloro-4,4-dioxo- and dithioketals **19a-d** and **58a-d** resisted hydrolysis, the dimethoxy analogue **19b** hydrolysed on treatment with concd. $H_2SO_4$ at 20 °C to give dichlorothiadiazinone **5** in 87% yield.[13] The 3,5-diphenylthiadiazine 4,4-ethylene glycol and catechol ketals **70a** and **11b** can also be hydrolysed under the same reaction conditions to give diphenylthiadiazinone **24a** in 89 and 74% yields, respectively (Scheme 22).




**19b** **5** (87%)

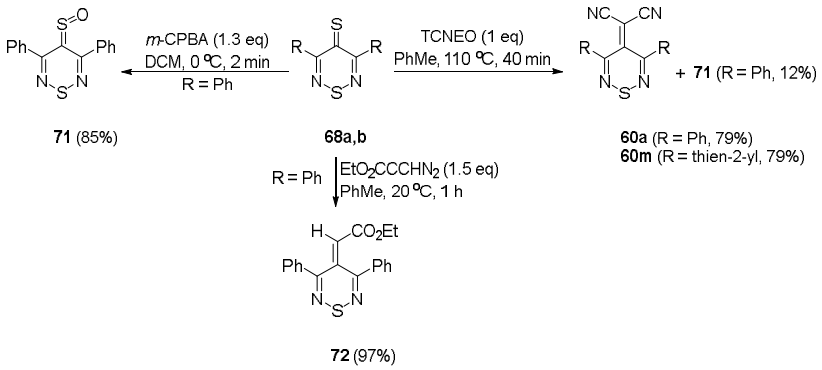
**70a** [R =$(CH_2)_2$] **24a** [R = $(CH_2)_2$, 89%]
**11b** (R = 1,2-$C_6H_4$) (R = 1,2-$C_6H_4$, 74%)

**Scheme 22.** Acid hydrolysis of 1,2,6-thiadiazine-4-ketals.

### 6.1.6. Interconversions of 4*H*-1,2,6-thiadiazin-4-thiones

Diarylthiadiazine-4-thiones **68a** (R=Ph) and **68b** (R=thien-2-yl) react with tetracyanoethylene oxide (TCNEO) (1.2 eq) in PhMe at 110 °C for 40 min to give ylidenemalononitriles **60a** and **60m** in 72 and 79% yields, respectively (Scheme 23).[35] The reaction of diphenylthiadiazine-4-thione **68a** with TCNEO also gave 3,5-diphenyl-4*H*-1,2,6-thiadiazine-4-thione oxide (**71**) as a side product indicating that TCNEO can transfer oxygen to sulfur and release TCNE as a by-product. Sulfine **71** was produced in high yield by treatment of thione **68a** with 3-chloroperbenzoic acid (*m*-CPBA) (1.3 eq), but the same conditions with dithienyl thione **68b** led to decomposition of the starting material. Mechanistically, the reaction of thiones **68a** and **68b** with TCNEO, tentatively, involves a [2+3]-cycloaddition followed by a fragmentation *via* retro-cycloaddition to give carbonyl cyanide and elemental sulfur. Diphenylthiadiazine-4-thione **68a** reacts with ethyl diazoacetate (1.5 eq) *via* a [2+3]-cycloaddition reaction to give ylideneacetate **72** in 97% yield (Scheme 23).[35]

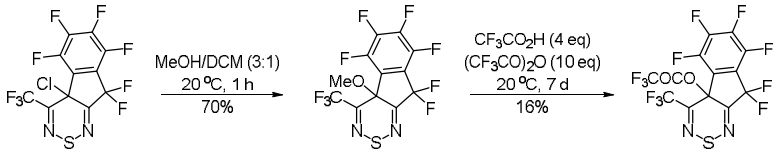
Dithienylthiadiazine-4-thione **68b** under the same reaction conditions gave a complex mixture which was tentatively attributed to competing reactions of the thiophenes with ethyl diazoacetate.




**Scheme 23.** Synthesis of ylidenemalononitriles **60a** and **60m**, ylideneacetate **72** and 3,5-diphenyl-4*H*-1,2,6-thiadiazine-4-thione oxide (**71**).

### 6.2. Functional group interconversions at the C4 position of polycyclic 4*H*-1,2,6-thiadiazines

Simply stirring a solution of 4-(trifluoromethyl)-4*a*,9-dihydroindeno[2,1-*c*][1,2,6]thiadiazine **12c** in MeOH/DCM (3:1) at 20 °C for 1 h gives the 4-methoxythiadiazine **12d** in 70% yield (Scheme 24).[14] The latter can then be converted to 4-trifluoroacetate **12e** albeit in a low 16% yield. The C4 displacement is analogous to the displacement of the C4 chlorides of tetrachlorothiadiazine **18** (see Sect. 6.1.1).

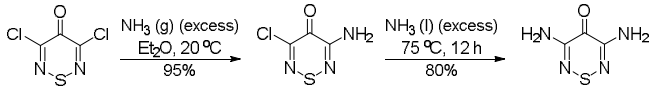



**Scheme 24.** Chemistry of 4-(trifluoromethyl)-4*a*,9-dihydroindeno[2,1-*c*][1,2,6]thiadiazine **12c**.

### 6.3. Displacement of C3/5 chlorides by nucleophiles on monocyclic 4*H*-1,2,6-thiadiazines

#### 6.3.1. Chloride displacements of 4*H*-1,2,6-thiadiazin-4-ones

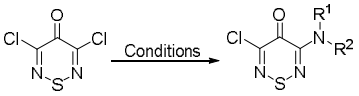
Geevers and Trompen first described the nucleophilic displacement of chloride from dichloro-thiadiazinone **5** by amines, alkoxides and thiolates.[33] Typically, the first chloride is easily displaced by nucleophiles while the displacement of the second chloride requires more forcing conditions. This is attributed to electron donation by the first substituent (from N, O or S) that reduces the electrophilicity of the thiadiazine and thus the susceptibility to a second nucleophilic displacement. For example, displacing the first chloride of dichlorothiadiazinone **5** to give 3-aminothiadiazinone **73** can be achieved by saturating an ether solution with ammonia gas at 20 °C, while the second displacement to yield diaminothiadiazinone **74** requires the use of liquid ammonia in a Carius tube heated to 75 °C overnight (Scheme 25).




**Scheme 25.** Reaction of dichlorothiadiazinone **5** with ammonia.

The displacement of the first chloride by the primary and secondary alkylamines, *e.g.* *n*-propylamine[33] and morpholine,[36] can be carried out in a solution of dichlorothiadiazinone **5** in EtOH at 20 °C, with 2 eq of amine to give the monoamino products **21a** and **21b**, respectively, in excellent yields (Table 12). The reaction of anilines at the same conditions also gives excellent yields of 5-arylamino-3-chlorothiadiazinones **21c-i**. Alternative protocols can also be used that require only 1 eq of aniline and 1 eq of pyridine[23] or 2,6-lutidine[37] as base. These protocols are useful when the required aniline is expensive or too reactive to be used in excess.

**Table 12.** Mono-displacement of dichlorothiadiazinone **5** with amines.



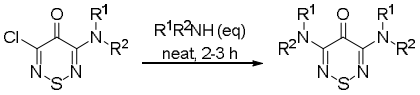

**5** **21a-i**

| Amine (eq) | Solvent (temp.) | Base (eq) | Time (h) | Yield (%) |
|---|---|---|---|---|
| *n*-$PrNH_2$ (2) | EtOH (20 °C) | - | 3 | **21a** (95) |
| morpholine (2) | EtOH (20 °C) | - | 2 | **21b** (96) |
| $PhNH_2$ (2) | EtOH (20 °C) | - | 3 | **21c** (95) |
| PhNHMe (2) | EtOH (20 °C) | - | 2 | **21d** (95) |
| 2-(NHBoc)$C_6H_4NH_2$ (2) | EtOH (20 °C) | - | 3 | **21e** (76) |
| 1,4-$(H_2N)_2C_6H_4$ (1) | EtOH (20 °C) | pyridine (1) | 6 | **21f** (20) |
| 4-(NHBoc)$C_6H_4NH_2$ (1) | DCM (20 °C) | pyridine (1) | 3 | **21e** (38) |
| 3-HO-4-Tol$NH_2$ (1) | EtOH (20 °C) | 2,6-lutidine (1) | 1 | **21g** (77) |
| 2-(CONHMe)aniline (1) | EtOH (20 °C) | 2,6-lutidine (1) | 48 | **21h** (77) |
| 4-(1*H*-imidazol-2-yl)aniline (1)[a] | EtOH (20 °C) | 2,6-lutidine (3) | 2 | **21i** (42) |

[a]Dihydrochloride salt used.

Treating 5-amino-3-chlorothiadiazinones **21a,c,d** with excess neat amine at 150-180 °C gives 3,5-diaminothiadiazines **25a-c** in 65-88% yields (Table 13).[33] The need for forcing reaction conditions further demonstrates the difficulty of displacing the thiadiazine chloride when strongly electron releasing groups are at C3/5. An alternative way to access 3,5-diaminothiadiazines **25** is *via* a Buchwald-Hartwig C-N coupling (see Sect. 6.6).

**Table 13.** Synthesis of 3,5-diaminothiadiazines **25a-c**.




**21a,c,d** **25a-c**

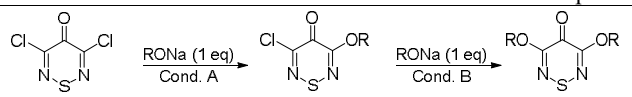
| $R^1/R^2$ | $R^1R^2NH$ (eq) | Temp. (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|
| *n*-propyl/H | 5 | 150 | 3 | **25a** (80) |
| Ph/H | 8 | 180 | 3 | **25b** (88) |
| Ph/Me | 4 | 150 | 2 | **25c** (65) |

The displacement of the first chloride by MeONa can be carried out in a solution of dichloro-thiadiazinone **5** in MeOH, at 0 °C, using alkoxide (1 eq) to give 5-methoxythiazinone **22a** in 95% yield.[33] Similar displacement by BnONa (1.5 eq) in THF at 20 °C gives the 5-benzyloxythiadiazinone **22b** in 88% yield,[38] while reaction with PhONa was run in an aqueous solution and gave the product **22c** in 95% yield. The subsequent displacements of the second chloride for 5-methoxy and 5-phenoxy analogues **22a** and **22c** run smoothly at 20 °C and give good yields of products **26a** and **26b** (Table 14).

Reaction of dichlorothiadiazinone **5** with methanethiol (1 eq) or benzenethiol (1 eq) and $Et_3N$ (1 eq) in $Et_2O$ at 0 °C gives the 5-methylthio- and 5-phenylthiothiadiazinones **23a** and **23b** in 84 and 93% yields,

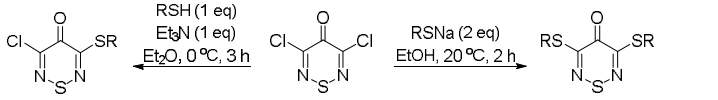
respectively (Scheme 26).[33] The displacement of both chlorides of dichlorothiadiazinone **5** requires the use of the respective sodium thiolates in EtOH at 20 °C and gives products **27a** and **27c** in 92 and 87% yields, respectively.

**Table 14.** Reaction of dichlorothiadiazinone **5** with alkoxides or phenoxide.




**5** **22a-c** **26a,b**

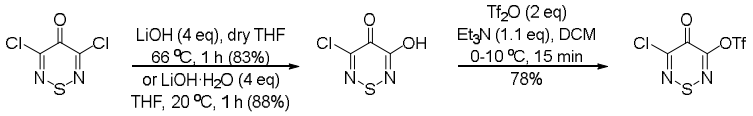
| R | Cond. A | **22** (%) | Cond. B | **26** (%) |
|---|---|---|---|---|
| Me | MeOH, 0 °C, 15 min | **22a** (95) | MeOH, 20 °C, 4 h | **26a** (85) |
| Bn | BnOH (1.5 eq), NaH (2 eq), THF, 20 °C, 8 h | **22b** (88) | - | - |
| Ph | $H_2O$, 20 °C, 1 h | **22c** (95) | DME, 20 °C, 12 h | **26b** (90) |




**23a**, R = Me, 84%
**23b**, R = Ph, 93%
**5**
**27a**, R = Me, 92%
**27c**, R = Ph, 87%

**Scheme 26.** Reaction of dichlorothiadiazinone **5** with thiolates.

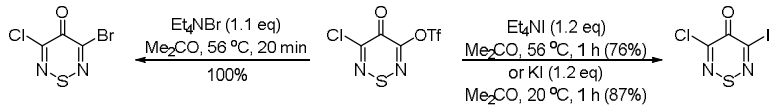
Dichlorothiadiazinone **5** was reported to react with LiOH (4 eq) in dry THF at 66 °C to afford hydroxythiadiazinone **75** in 83% yield,[39] but, more recently, in our hands the hydroxylation worked better using LiOH·$H_2O$ (4 eq) in wet THF at 20 °C to afford hydroxythiadiazinone **75** in 88% yield (Scheme 27). Subsequent treatment with trifluoromethanesulfonic anhydride (2 eq) and $Et_3N$ (1.1 eq) in DCM at 0-10 °C gives the 3-chloro-5-triflatethiadiazinone **76** in 78% yield.




**5** **75** **76**

**Scheme 27.** Synthesis of hydroxythiadiazinone **75** and 3-chloro-5-triflatethiadiazinone **76**.

Treating 3-chloro-5-triflatethiadiazinone **76** with $Et_3NBr$ in acetone at 56 °C or with either $Et_3NI$ or KI in acetone affords 3-bromo-5-chlorothiadiazinone **77** and 3-chloro-5-iodothiadiazinone **78**, respectively (Scheme 28).[39]

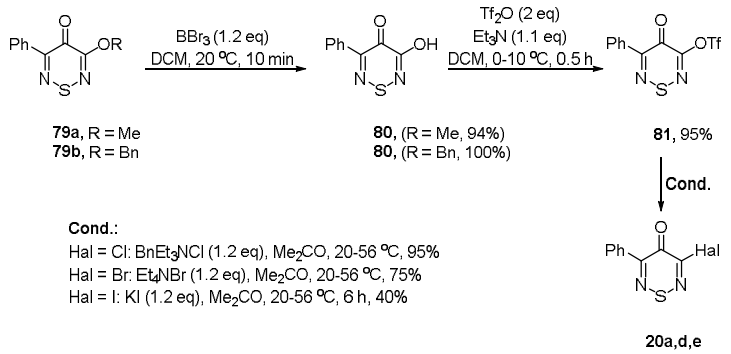



**77** **76** **78**

**Scheme 28.** Synthesis of 3-bromo-5-chlorothiadiazinone **77** and 3-chloro-5-iodothiadiazinone **78**.

Reacting 3-alkoxy-5-phenylthiadiazinones **79a** (R=Me) and **79b** (R=Bn) (see Sect. 6.5.1.2) with $BBr_3$ in DCM gives the 3-hydroxy-5-phenylthiadiazinone **80** in 94 and 100% yields, respectively (Scheme 29).[38] Subsequent treatment of the latter with trifluoromethanesulfonic anhydride (2 eq) and $Et_3N$ (1.1 eq) in DCM at 0-10 °C gives the 3-phenyl-5-triflate thiadiazinone **81** in 95% yield. Reaction with tetralkylammonium

halides or KI gives the 3-halo-5-phenylthiadiazinones **20a** (Hal=Cl), **20d** (Hal=Br) and **20e** (Hal=I) in 40-95% yields.

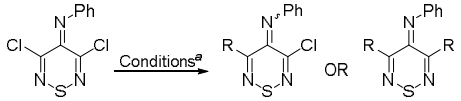



**Scheme 29.** Synthesis of 3-halo-5-phenylthiadiazinones **20a,d,e**.

### 6.3.2. Chloride displacements of 4*H*-1,2,6-thiadiazin-4-imines

One or both chlorides of *N*-phenylthiadiazinimine **9a** can be displaced by alkoxide or amine nucleophiles.[11] In particular, use of 1 eq of methoxide leads to a fast displacement of the C3 chlorine forming a mixture of *E* and *Z* isomers of 3-chloro-5-methoxy-*N*-phenylthiadiazinimine **82**, while 2 eq of the nucleophile gives dimethoxythiadiazinimine **83** in good yield (Table 15). Similarly, reaction with 2 eq of morpholine led to a fast displacement of the C3 chlorine to give the 3-morpholinothiadiazine **84** in 76% yield. The displacement of the second chlorine by morpholine requires more forcing conditions (neat) due to the electron release from the first morpholine but gives the desired product **85** in 89% yield.

**Table 15.** Chloride displacement reactions of *N*-phenylthiadiazinimine **9a**.



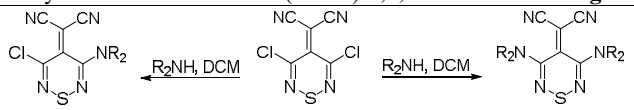

| Nucleophile (eq) | Conditions | Time (h) | Yield (%) |
|---|---|---|---|
| MeONa (1) | MeOH, 0 °C | 0.5 | **82** (83) |
| MeONa (2) | MeOH, 0-20 °C | 1 | **83** (90) |
| morpholine (2) | MeCN, 20 °C | 2 | **84** (76) |
| morpholine (8) | neat, 20 °C | 72 | **85** (89) |

### 6.3.3. Chloride displacements of 2-(4*H*-1,2,6-thiadiazin-4-ylidene)malononitriles

Both chlorides of ylidenemalononitrile **4** can be displaced by amine or thiol nucleophiles. A selective substitution of the first and then the second chloride was reported for dialkylamines. Slow addition of 2 eq of the amine at -5 °C displaces the first chloride, while the second chloride requires 4 (or more) eq of amine and heating (up to 45 °C). The reactions worked with five secondary amines, but with sterically bulky alkyl groups the reaction times increased and yields decreased (Table 16).[22] The limit of reactivity was reached with diisopropylamine which gives only the mono-amino derivative **28g** in a low 30% yield. The reaction of **4** with ammonia or primary amines was complex, tentatively, due to cyclisations onto the cyano groups.

Thiophenols can also selectively displace both chlorides from ylidenemalononitrile **4**. The use of thiol (1.1 eq) and Hünig's base (1.1 eq) at -78 °C achieves the first displacement, while subsequent treatment of the mono-displaced product with the same quantities of reagents at 20 °C leads to a second displacement (Table 17).[22] The reactions work well with thiophenols bearing electron donating and withdrawing substituents.

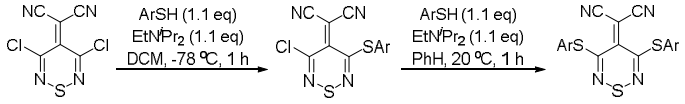
**Table 16.** Synthesis of mono and bis(amino)-1,2,6-thiadiazines **28a-g** and **29a-f**.




**28a-g** **4** **29a-f**

| Nucleophile (eq) | Temp. (°C) | Time (h) | Yield (%) |
|---|---|---|---|
| pyrrolidine (2) | -5 to 20 | 1 | **28a** (77) |
| pyrrolidine (4) | -5 to 45 | 12 | **29a** (84) |
| piperidine (2) | 20 to 45 | 12 | **28b** (81) |
| piperidine (5) | 20 to 45 | 24 | **29b** (78) |
| morpholine (2) | -5 to 45 | 12 | **28c** (83) |
| morpholine (5) | 20 to 45 | 24 | **29c** (76) |
| $Bn_2NH$ (2) | -5 to 45 | 12 | **28d** (74) |
| $Bn_2NH$ (5) | 20 to 45 | 24 | **29d** (81) |
| PhNHMe (2) | -5 to 45 | 12 | **28e** (85) |
| PhNHMe (12) | 20 to 45 | 24 | **29e** (87) |
| $^{n}Pr_2NH$ (2) | -5 to 20 | 1 | **28f** (74) |
| $^{n}Pr_2NH$ (4) | -5 to 45 | 12 | **29f** (82) |
| $^{i}Pr_2NH$ (6) | 45 | 3 | **28g** (30) |

**Table 17.** Reaction of ylidenemalononitrile **4** with thiophenols.




**4** **86a-e** **69a-d**

| Compound | Ar | Yield (%) |
|---|---|---|
| **86a** | Ph | 76 |
| **69b** | Ph | 92 |
| **86b** | 4-Tol | 69 |
| **69c** | 4-Tol | 93 |
| **86c** | 4-$ClC_6H_4$ | 96 |
| **69d** | 4-$ClC_6H_4$ | 85 |
| **86e** | 4-$MeOC_6H_4$ | 74 |
| **69a** | 4-$MeOC_6H_4$ | 98 |

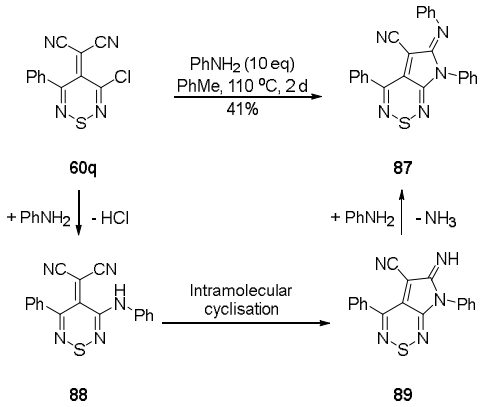
The 3-chloride of 3-chloro-5-phenylthiadiazinylidenemalononitrile **60q** can be readily displaced by aniline, followed by an intramolecular cyclisation onto the nitrile and transamination to give the pyrrolo[2,3-*c*][1,2,6]thiadiazine **87** (Scheme 30).[34]

### 6.3.4. Chloride displacements of thiadiazine-4-ketals

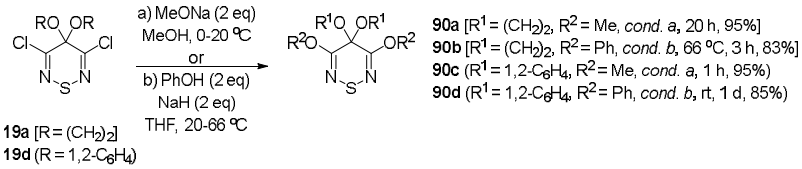
The chlorides of 4,4-dioxoketals **19a-d** can be displaced by the oxygen nucleophiles methoxide and phenoxide. Two cyclic ketals, the ethylene glycol ketal **19a** and the catechol ketal **19d** react smoothly with 2 eq of MeONa and PhONa giving the 3,5-dimethoxy and 3,5-diphenoxy thiadiazines **90a-d** (Scheme 31).[13] Non-cyclic ketals **19b,c** and dithioketals **58a-d** were unsuitable under these reaction conditions giving degradation of the starting material.

Reaction of the two ketals **19a** and **19d** with pyrrolidine (2 eq) in EtOH at 20 °C leads to the 3-chloro-5-pyrrolidinothiadiazines **91a** and **91b** in 98 and 91% yield, respectively (Scheme 32). Attempts to displace the second chloride under more forceful conditions lead to degradation. The reaction with aniline

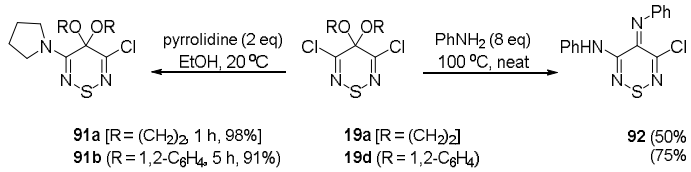
was more intriguing as the two ketals were fairly unreactive with aniline (EtOH at 78 °C or 100 °C in a sealed tube) and when more forcing conditions were used (neat aniline, 100 °C), only the *N*-phenyl-(3-anilinothiadiazinimine) **92** was isolated as the product, indicating that the ketal protecting group was displaced by aniline under these conditions.[13]




**Scheme 30.** Synthesis of pyrrolo[2,3-*c*][1,2,6]thiadiazine **87**.




**Scheme 31.** Nucleophilic substitution reactions on ketals **19a** and **19d** by oxygen nucleophiles.




**Scheme 32.** Nucleophilic substitution reactions on ketals **19a** and **19d** by amines.

### 6.4. Displacement of C3/5 chlorides by nucleophiles on polycyclic 4*H*-1,2,6-thiadiazines

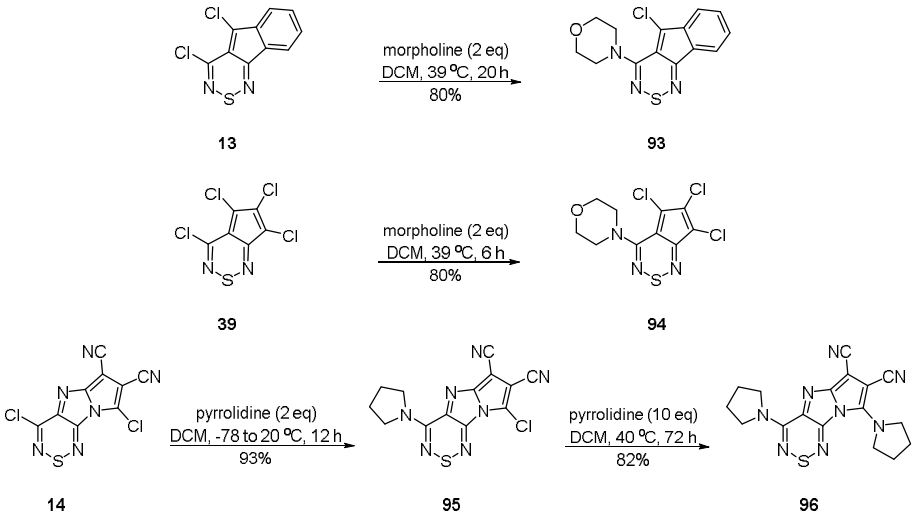
The thiadiazine chlorides of the polychlorinated tricyclic systems **13**, **39** and **14** can be regioselectively displaced by cyclic secondary amines to give 3-amino derivatives **93**, **94** and **95** in 80, 80 and 93% yields, respectively.[15,16] The remaining C8 chloride of imidazo[4,5-*c*][1,2,6]thiadiazine **95** can be subsequently displayed under more forcing conditions to yield the dipyrrolidino product **96** (Scheme 33).[21]

During attempts to methylate thiadiazinoquinoxaline **30a** with MeI and NaOH in ethanol, the displacement of the chloride was observed due to the generation of sodium ethoxide in the reaction conditions.[23] The chloride on similar systems such as thiadiazinobenzothiazine **30b** can also be displaced by amine nucleophiles like piperidine to give the 4-piperidino derivative **97** in 99% yield (Scheme 34).[23]

### 6.5. Pd C-C coupling of chloro-4*H*-1,2,6-thiadiazines

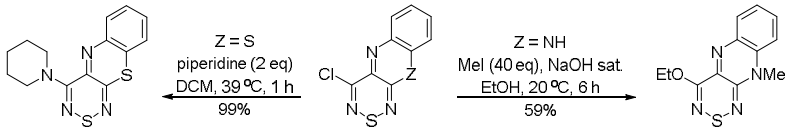
Palladium-catalysed Suzuki-Miyaura, Stille and Sonogashira reactions of dichlorothiadiazinone **5** were first reported in 2011.[40] Acting as an activated halogenoarene, the C3/5 chlorides of dichlorothiadiazinone **5** can be displaced in Pd-catalysed C-C couplings to yield a plethora of mainly 3,5-(het)aryl-substituted

thiadiazines, which greatly increases the use of this synthetic scaffold. The Pd-catalysed Suzuki-Miyaura and Stille reactions of ketal protected thiadiazines and 4*H*-1,2,6-thiadiazin-4-imines were also investigated.




13 93 39 94 14 95 96

**Scheme 33.** Regioselective displacement of chloride from polychlorinated tricyclic systems **13**, **39** and **14**.




97 30a,b 98

**Scheme 34.** Synthesis of 4-ethoxy-10-methyl-10*H*-[1,2,6]thiadiazino[3,4-*b*]quinoxaline **98** and 4-(piperidin-1-yl)benzo[5,6][1,4]thiazino[2,3-*c*][1,2,6]thiadiazine **97**.

### 6.5.1. Couplings of 4*H*-1,2,6-thiadiazin-4-ones

#### 6.5.1.1. Suzuki-Miyaura couplings (symmetrical)

Suitable Suzuki-Miyaura coupling conditions [$RB(OH)_2$ (2.2 eq), $Pd(Ph_3P)_4$ (5 mol%), and $Na_2CO_3$ (2 eq) in 1,4-dioxane/$H_2O$ (5:3) at 100 °C] for the reaction of dichlorothiadiazinone **5** with arylboronic acids were developed following extensive optimisation efforts.[40] Thirteen analogues **24a-m** and **6** were prepared that tested the limitations of the reaction to steric and electronic effects (Table 18). Steric effects were less significant than electronic effects: 3-nitrophenylboronic acid gave lower yields (66%) and/or required more equivalents of boronic acid to fully consume the starting dichlorothiadiazinone **5**. Pyridylboronic and methylboronic acids were unreactive to the coupling conditions.

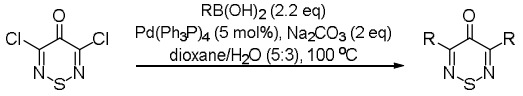
#### 6.5.1.2. Suzuki-Miyaura couplings (unsymmetrical)

5-Alkoxy-3-chlorothiadiazinones **22a** (R=Me) and **22b** (R=Bn) (see Sect. 6.3.1) undergo Suzuki-Miyaura reactions with phenylboronic acid (1.1 eq) to give 3-alkoxy-5-phenylthiadiazinones **79a** and **79b** in 90 and 88% yields, respectively (Scheme 35).[38]

3-Chloro- and 3-bromo-5-phenylthiadiazinones **20a** and **20d** (see Sect. 6.3.1) subjected to the above Suzuki-Miyaura couplings conditions,[40] with arylboronic acids (1 eq) gave unsymmetrical diarylthiadiazin-ones **24n-q** (Table 19),[38] The reaction tolerated arylboronic acids with electron donating or withdrawing substituents. The attempted Suzuki-Miyaura reaction of 3-phenyl-5-triflate thiadiazinone **81**

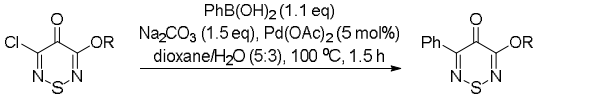
with phenyl-boronic acid failed due to hydrolysis of the starting material to 3-hydroxy-5-phenylthiadiazinone **80**.

**Table 18.** Suzuki-Miyaura reactions of dichlorothiadiazinone **5**.




**5** **24, 6**

| $RB(OH)_2$ (eq) | Time (min) | Yield (%) |
|---|---|---|
| $PhB(OH)_2$ (2.2) | 20 | **24a** (91) |
| 2-Tol$B(OH)_2$ (2.2) | 30 | **24c** (94) |
| 3-Tol$B(OH)_2$ (2.2) | 30 | **24d** (91) |
| 4-Tol$B(OH)_2$ (2.2) | 15 | **24e** (99) |
| 2-$MeOC_6H_4B(OH)_2$ (2.2) | 15 | **24f** (87) |
| 3-$MeOC_6H_4B(OH)_2$ (2.2) | 15 | **24g** (88) |
| 4-$MeOC_6H_4B(OH)_2$ (2.2) | 15 | **24h** (86) |
| 2-$ClC_6H_4B(OH)_2$ (2.2) | 40 | **24i** (80) |
| 3-$ClC_6H_4B(OH)_2$ (2.2) | 40 | **24j** (81) |
| 4-$ClC_6H_4B(OH)_2$ (2.2) | 40 | **24k** (89) |
| 3-$O_2NC_6H_4B(OH)_2$ (4) | 30 | **24l** (66) |
| thien-3-yl$B(OH)_2$ (2.2) | 15 | **24m** (98) |
| thien-2-yl$B(OH)_2$ (3) | 60 | **6** (90) |

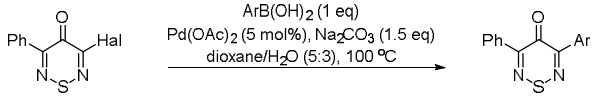



**22a**, R = Me
**22b**, R = Bn

**79a**, R = Me, 90%
**79b**, R = Bn, 88%

**Scheme 35.** Suzuki-Miyaura couplings of 5-alkoxy-3-chlorothiadiazinones **22a** and **22b**.

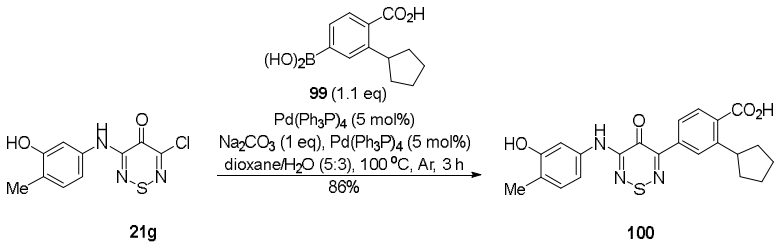
**Table 19.** Suzuki-Miyaura reaction of 3-halo-5-phenylthiadiazinones **20a** (Hal=Cl) and **20d** (Hal=Br).




**20a** or **20d** **24n-q**

| Hal | Ar | Time (h) | Yield (%) |
|---|---|---|---|
| Cl | 2-$MeOC_6H_4$ | 6.0 | **24n** (78) |
| Br | 2-$MeOC_6H_4$ | 5.0 | **24n** (79) |
| Cl | 4-$MeOC_6H_4$ | 6.3 | **24o** (81) |
| Br | 4-$MeOC_6H_4$ | 5.5 | **24o** (91) |
| Cl | 3-$O_2NC_6H_4$ | 3.6 | **24p** (83) |
| Br | 3-$O_2NC_6H_4$ | 3.5 | **24p** (81) |
| Cl | 4-$ClC_6H_4$ | 4.0 | **24q** (80) |
| Br | 4-$ClC_6H_4$ | 3.5 | **24q** (77) |

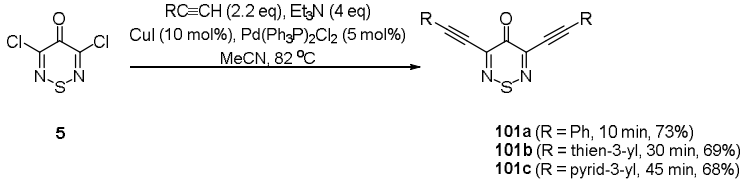
Suzuki-Miyaura coupling of 5-(arylamino)-3-chlorothiadiazinone **21g** with 4-borono-2-cyclopentyl-benzoic acid **99** gave 3-aryl-5-(arylamino)thiadiazinone **100** in 86% yield (Scheme 36).[37] Product **100** was investigated as a calcium/calmodulin-dependent protein kinase kinase 2 (CaMKK2) inhibitor (see Sect. 9.1).




**Scheme 36.** Suzuki-Miyaura coupling of 5-(arylamino)-3-chloro-4*H*-1,2,6-thiadiazin-4-one **21g**.

**6.5.1.3. Sonogashira couplings**

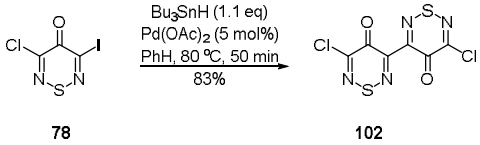
Sonogashira couplings of dichlorothiadiazinone **5** with arylacetylenes can be achieved using $Et_3N$ (4 eq), CuI (10 mol%), and $Pd(Ph_3P)_2Cl_2$ (5 mol%) in MeCN, at 82 °C. These conditions were identified from a brief optimisation of solvent, base and catalyst. Three bisacetylenes **101a-c** were prepared in 68-73% yields (Scheme 37).[40]




**Scheme 37.** Sonogashira coupling reactions of dichlorothiadiazinone **5**.

**6.5.1.4. Homocoupling**

Attempted Ullmann couplings using copper powder or $Pd(OAc)_2$ failed. Nevertheless, treating 3-chloro-5-iodothiadiazinone **78** with $Bu_3SnH$ (1.1 eq) and $Pd(OAc)_2$ (5 mol%), in PhH, at 80 °C led to the homo-coupled 3,3'-bithiadiazine **102** in 83% yield (Scheme 38).[39]




**Scheme 38.** Synthesis of 3,3'-bithiadiazine **102**.

**6.5.1.5. Stille couplings (symmetrical)**

Stille reactions of dichlorothiadiazinone **5** with (het)aryltributylstannanes (2.2 eq) in acetonitrile at 82 °C were effective using $Pd(Ph_3P)_2Cl_2$ as the catalyst, leading to the formation of 3,5-di(het)arylthiadiazinones **24a,b**,**r** and **5** in 92-95% yields (Table 20). The coupling with thiazol-2-yl, vinyl and propynyl tributyl-stannanes, however, failed.[40]

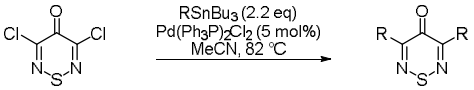
The Stille coupling was used to extend the $\pi$ conjugation of 3,5-di(thien-2-yl)-4*H*-1,2,6-thiadiazin-4-one (**6**) to afford 3,5-di(2,2'-bithien-5-yl)-4*H*-1,2,6-thiadiazin-4-one (**103**) *via* a two-step synthesis (Scheme 39).[40] Thienyl-substituted thiadiazines are of interest for their optoelectronic properties (see Sect. 9.3).

The synthesis above was used to prepare small molecule donors bearing the 1,2,6-thiadiazinone motif for application in OPVs. Stille couplings with aryltributylstannanes afforded oligomers **105a-g** containing a carbazyl-thienyl-thiadiazine motif with 0-3 thienyl units, while long alkyl chains on the carbazole nitrogen or thiophene were incorporated to improve the solubility of the products (Scheme 40).[41]

Similarly, the Stille reaction was used in the preparation of thiadiazine copolymers: 3,5-dichloro- and 3,5-bis(5-bromothien-2-yl)-substituted 4*H*-1,2,6-thiadiazinones **5** and **102** were coupled with the bis-stannyl

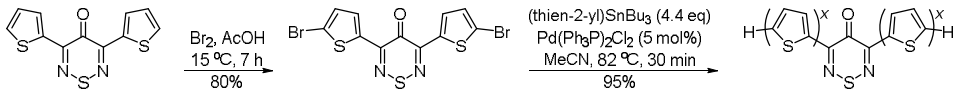
reagents bis(trimethylstannyl)tetra(*n*-hexyl)-substituted phenyl- indacenodithiophene (IDT) and thien-2-yl-IDT **106a** and **106b** using [$Pd_2(dba)_3$] (2 mol%), P(*o*-tol)$_3$ (4 mol%) in PhMe at 110 °C for 48 h to give polymers **107a-d** in 35-96%yields (Scheme 41).[10]

**Table 20.** Reaction of dichlorothiadiazinone **5** with (het)aryl tributylstannanes.



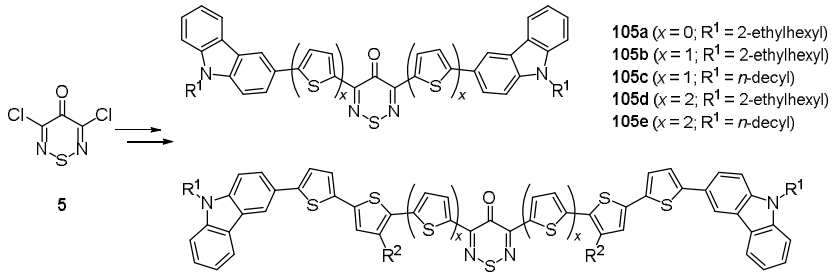

5 → 24a,b,r, 6

| R | Time (h) | Yield (%) |
|---|---|---|
| Ph | 2.5 | **24a** (95) |
| fur-2-yl | 0.75 | **24b** (92) |
| thien-2-yl | 1 | **6** (92) |
| *N*-Me-pyrrol-2-yl | 1 | **24r** (93) |




**6** **104** **103** (*x* = 2)

**Scheme 39.** Synthesis of 3,5-di(2,2'-bithien-5-yl)-4*H*-1,2,6-thiadiazin-4-one **103**.

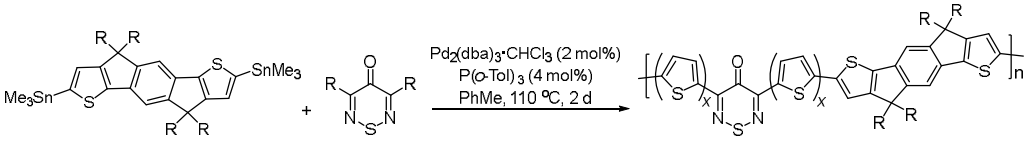


**105a** (*x* = 0; $R^1$ = 2-ethylhexyl)
**105b** (*x* = 1; $R^1$ = 2-ethylhexyl)
**105c** (*x* = 1; $R^1$ = *n*-decyl)
**105d** (*x* = 2; $R^1$ = 2-ethylhexyl)
**105e** (*x* = 2; $R^1$ = *n*-decyl)

**5**

**105f** (*x* = 0; $R^1$ = *n*-decyl; $R^2$ = *n*-hexyl)
**105g** (*x* = 1; $R^1$ = *n*-decyl; $R^2$ = *n*-hexyl)

**Scheme 40.** Structures of 4*H*-1,2,6-thiadiazin-4-one oligomers.



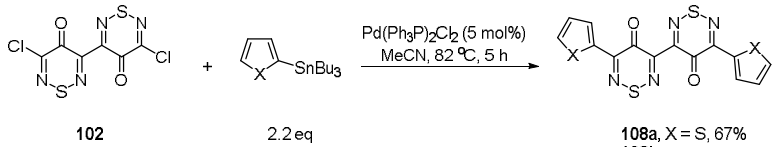

**106a** (R = 4-*n*-hexyl-$C_6H_4$)
**106b** (R = 5-*n*-hexylthien-2-yl)

**5** (R = Cl)
**104** (R = 5-Br-thien-2-yl)

**107a** (*x* = 0, R = 4-*n*-hexyl-$C_6H_4$, 96%)
**107b** (*x* = 0, R = 5-*n*-hexylthien-2-yl, 54%)
**107c** (*x* = 1, R = 4-*n*-hexyl-$C_6H_4$, 86%)
**107d** (*x* = 1, R = 5-*n*-hexylthien-2-yl, 35%)

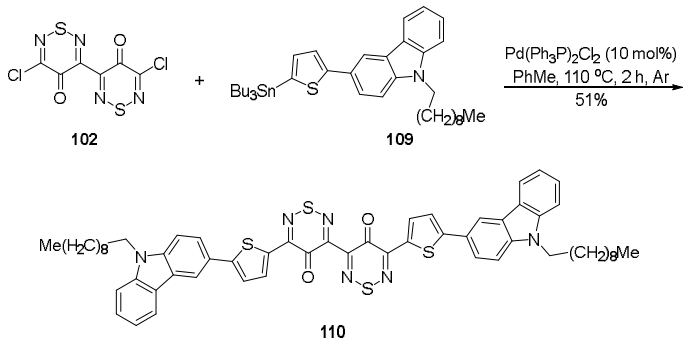
**Scheme 41.** Synthesis of 4*H*-1,2,6-thiadiazin-4-one copolymers **107a-d**.

Bithiadiazine **102** was also Stille coupled to 2-tributylstannylthiophene and *N*-methyl-2-(tributyl-stannyl)-1*H*-pyrrole to give 5,5'-dihetaryl-4*H*,4'*H*-[3,3'-bi(1,2,6-thiadiazine)]-4,4'-diones **108a** and **108b** in 67 and 70% yields, respectively (Scheme 42).[40]




**Scheme 42.** Stille coupling reactions of bithiadiazine **102**.

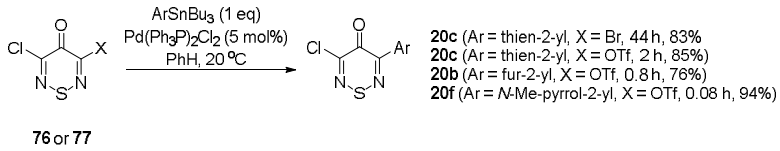
Stille coupling of bithiadiazine **102** with 9-decyl-3-[5-(tributylstannyl)thien-2-yl]-9*H*-carbazole **109** in PhMe at 110 °C gave 5,5'-bis[5-(9-decyl-9*H*-carbazol-3-yl)thien-2-yl]-4*H*,4'*H*-[3,3'-bi(1,2,6-thiadiazine)]-4,4'-dione **110** in 51% yield (Scheme 43).[42] Oligomer **110** was investigated for its potential use in OPVs.




**Scheme 43.** Synthesis of 5,5'-bis[5-(9-decyl-9*H*-carbazol-3-yl)thien-2-yl]-4*H*,4'*H*-[3,3'-bi(1,2,6-thiadiazine)]-4,4'-dione **110**.

**6.5.1.6. Stille couplings (unsymmetrical)**

Unsymmetrically substituted diaryls cannot easily be prepared from dichlorothiadiazinone **6** as the monoarylation using aryltributylstannanes (1 eq) even at mild conditions gave mixtures of starting material with mono and bis-arylated products. One solution to this problem was the preparation of thiadiazines with different C3/5 leaving groups that would enable fast and selective mono-displacement, allowing the preparation of monoarylthiadiazines. Three such thiadiazines were used bearing C3/5 Cl/OTf, Cl/Br and Cl/I groups (see Sect. 6.3.1). Stille reactions of both the 3-chloro-5-triflate thiadiazinone **76** and the 3-bromo-5-chlorothiadiazinone **77** with 2-(tributylstannyl)thiophene were chemoselective to give 3-chloro-5-thien-2-yl-4*H*-1,2,6-thiadiazin-4-one **20c** in 85 and 83% yields, respectively (Scheme 44).[39] 3-Chloro-5-triflate thiadiazinone **76** gave a faster reaction time, and was chosen as the starting material for the preparation of two other mono-hetarylthiadiazines, furyl- and *N*-Me-pyrrolylthiadiazinones **20c** and **20f**. Nevertheless, with tributylphenylstannane this Stille protocol gave mixtures of mono and biarylthiadiazines.



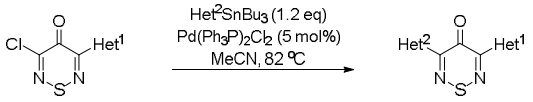

**Scheme 44.** Synthesis of 5-aryl-3-chloro-4*H*-1,2,6-thiadiazin-4-ones **20b,c,f**.

Subsequent displacement of the remaining chloride using the previously developed reaction conditions gave unsymmetrical biheteroayl thiadiazinones **24s-x**,[40] in good yields (Table 21).[39]

3-Chloro-5-(thien-2-yl)- or 3-chloro-5-(*N*-methylpyrrol-2-yl)thiadiazin-4-ones **20c** and **20f** react with 2,5-bis(tributylstannyl)thiophene under Stille coupling conditions to give thiophenes **111** and **112** in **76** and

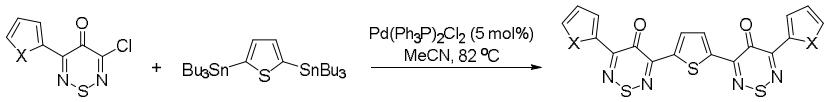
92% yields, respectively (Scheme 45). This synthetic strategy can be used to prepare oligomers with alternating donor-acceptor units for use in OPVs.[41]

**Table 21.** Reaction of 3-chloro-5-hetarylthiadiazin-4-ones **20b,c,f** with hetaryl tributylstannanes.




**20b,c,f** **24s-x**

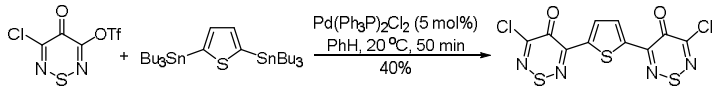
| $Het^1$ | $Het^2$ | Time (min) | Yield (%) |
|---|---|---|---|
| thien-2-yl | fur-2-yl | 20 | **24s** (88) |
| thien-2-yl | *N*-Me-pyrrol-2-yl | 45 | **24t** (88) |
| fur-2-yl | thien-2-yl | 20 | **24u** (78) |
| fur-2-yl | *N*-Me-pyrrol-2-yl | 20 | **24v** (100) |
| *N*-Me-pyrrol-2-yl | thien-2-yl | 45 | **24w** (100) |
| *N*-Me-pyrrol-2-yl | fur-2-yl | 15 | **24x** (94) |




**20c**, X = S
**20f**, X = NMe
0.5 eq
**111**, X = S, 76%
**112**, X = NMe, 92%

**Scheme 45.** Synthesis of pentamers **111** and **112**.

An alternative route to thiophenes **111** and **112** was also investigated *via* 5,5'-(thiophene-2,5-diyl)bis-(3-chloro-4*H*-1,2,6-thiadiazin-4-one) **113**. Thiophene **113** was prepared from 3-chloro-5-triflate thiadiazinone **76** and 2,5-bis(tributylstannyl)thiophene in 40% yield (Scheme 46).




**76** 0.5 eq **113**

**Scheme 46.** Synthesis of 5,5'-(thien-2,5-diyl)bis(3-chloro-4*H*-1,2,6-thiadiazin-4-one) **113**.

3-Chloro-, 3-bromo-, 3-iodo- and 3-triflate-5-phenylthiadiazinones **20a,d,e** and **81** (see Sect. 6.3.1) were subjected to Stille couplings with hetaryltributylstannanes to give unsymmetrical diarylthiadiazinones (Table 22).[38] The reaction used the previously developed Stille coupling conditions,[40] with the exception of using only 1 eq of aryltributylstannane and the analogues prepared showed that the reaction tolerates both electron rich and electron deficient hetaryltributylstannanes. The most reactive substrate was the triflate **81** that gave the fastest reaction times.

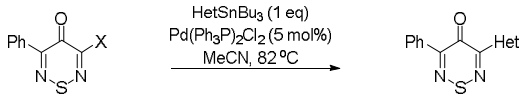
### 6.5.2. Couplings of 4*H*-1,2,6-thiadiazin-4-imines

The Stille coupling of *N*-phenylthiadiazinimine **9a** and $PhSnBu_3$ or (thien-2-yl)$SnBu_3$ (2.2 eq) with $Pd(Ph_3P)_2Cl_2$ (5 mol%), in dry PhMe at 110 °C gave 3,5-diphenyl- and 3,5-di(thien-2-yl)thiadiazinimines **62a** and **62b** in 92 and 93% yields, respectively (Scheme 47).[11] Unfortunately, Suzuki-Miyaura couplings between the *N*-phenylthiadiazinimine **9a** and $PhB(OH)_2$ led to degradation of the starting material.

Similar Stille reaction conditions [$Pd_2(dba)_3$ (2 mol%), P(*o*-tol)$_3$ (4 mol%) in PhMe at 110 °C for 48 h] were used to polymerise a combination of either 3,5-dichloro-*N*-(perfluorophenyl)-4*H*-1,2,6-thiadiazin-4-imine **9w** or 3,5-bis(5-bromothien-2-yl)-substituted *N*-(perfluorophenyl)-4*H*-1,2,6-thiadiazin-4-imine **114**

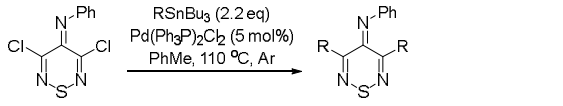
with bis(trimethylstannyl)tetra(*n*-hexyl)-substituted phenyl-IDT or thien-2-yl-IDT **106a** and **106b** to give polymers **115a-d** in yields of 78-91% (Scheme 48).[10]

**Table 22.** Stille reaction of 3-halo- and 3-triflate-5-phenyl-4*H*-1,2,6-thiadiazin-4-ones **20a,d,e** and **81** with hetaryltributylstannanes.




**20a,d,e, 81** **24y-aa**

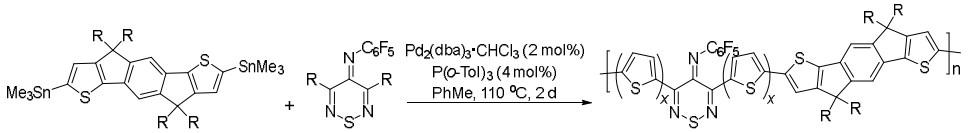
| Starting thiadiazine, (X) | Het | Time (h) | Yield (%) |
|---|---|---|---|
| **20a** (X = Cl) | *N*-Me-pyrrol-2-yl | 3.5 | **24y** (77) |
| **20d** (X = Br) | *N*-Me-pyrrol-2-yl | 3.0 | **24y** (86) |
| **81** (X = OTf) | *N*-Me-pyrrol-2-yl | 0.8 | **24y** (88) |
| **20a** (X = Cl) | fur-2-yl | 3.8 | **24z** (100) |
| **20d** (X = Br) | fur-2-yl | 3.6 | **24z** (88) |
| **81** (X = OTf) | fur-2-yl | 0.7 | **24z** (94) |
| **20a** (X = Cl) | thien-2-yl | 4.0 | **24aa** (99) |
| **20d** (X = Br) | thien-2-yl | 3.5 | **24aa** (89) |
| **20e** (X = I) | thien-2-yl | 1.5 | **24aa** (80) |
| **81** (X = OTf) | thien-2-yl | 0.5 | **24aa** (92) |




**9a**

**62a** (R = Ph, 30 min, 92%)
**62b** (R = thien-2-yl, 1 h, 93%)

**Scheme 47.** Stille coupling reactions of *N*-phenylthiadiazinimine **9a**.




**106a** (R = 4-*n*-hexyl-$C_6H_4$)
**106b** (R = 5-*n*-hexylthien-2-yl)

**9w** (R = Cl)
**114** (R = 5-Br-thien-2-yl)

**115a** (*x* = 0, R = 4-*n*-hexyl-$C_6H_4$, 91%)
**115b** (*x* = 0, R = 5-*n*-hexylthien-2-yl, 88%)
**115c** (*x* = 1, R = 4-*n*-hexyl-$C_6H_4$, 89%)
**115d** (*x* = 1, R = 5-*n*-hexylthien-2-yl, 78%)

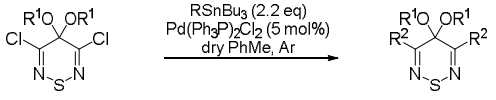
**Scheme 48.** Synthesis of *N*-(perfluorophenyl)-4*H*-1,2,6-thiadiazin-4-imine copolymers **115a-d**.

### 6.5.3. Couplings of 4*H*-thiadiazine-4-ketals

Stille couplings of both spirocyclic ketals **19a** and **19d** with tributylphenylstannane gave the respective 3,5-diphenylthiadiazines **70a** and **11b** in 92 and 97% yields, respectively (Table 23), while 4,4-dimethoxy- or the 4,4-diphenoxythiadiazine acyclic ketals **19b** and **19c** led to partial degradation of the starting materials.[13] The Stille couplings of spirocyclic ketals **19a** and **19d** tolerated aryltributylstannanes bearing electron withdrawing (F) and donating groups (Me), as well as tributyl(phenylethynyl)stannane to give thiadiazines **70a-d** and **11b-e** in good yields. While heating a toluene solution to 110 °C was sufficient for the Stille coupling of ethylene glycol ketal **19a**, slightly milder conditions (80 °C) were required for catechol ketal **19d** which gave complex reaction mixtures at higher temperatures owing to unexpected ring contractions to 1,2,5-thiadiazoles (see Sect. 7.2). 3,5-Dichlorothiadiazine-4-thioketals did not react with

aryltributylstannanes, presumably due to catalyst poisoning by traces of thiols, and no ketal or thioketal gave a successful Suzuki-Miyaura couplings; degradation of the starting materials was observed.

**Table 23.** Reaction of 3,5-dichlorothiadiazine ketals **19a-d** with aryl and phenylethynyl tributylstannanes.

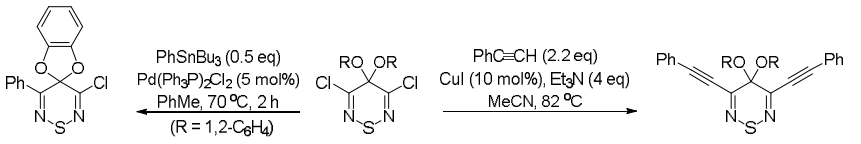



**19a-d** → **70a-d**, **11b-e**

| Starting ketal **19** | $R^1$ | $R^2$ | Temp.(°C) | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| **19b** | Me | Ph | 110 | 24[a] | 0 |
| **19c** | Ph | Ph | 110 | 24[b] | 0 |
| **19a** | -$(CH_2)_2$- | Ph | 110 | 1.5 | **70a** (92) |
| **19a** | -$(CH_2)_2$- | 4-Tol | 110 | 1 | **70b** (98) |
| **19a** | -$(CH_2)_2$- | 4-$FC_6H_4$ | 110 | 1 | **70c** (89) |
| **19a** | -$(CH_2)_2$- | PhC≡C | 110 | 1 | **70d** (91) |
| **19d** | 1,2-$C_6H_4$ | Ph | 80 | 2 | **11b** (97) |
| **19d** | 1,2-$C_6H_4$ | 4-Tol | 80 | 1 | **11c** (86) |
| **19d** | 1,2-$C_6H_4$ | 4-$FC_6H_4$ | 80 | 1 | **11d** (92) |
| **19d** | 1,2-$C_6H_4$ | PhC≡C | 80 | 1.5 | **11e** (90) |

[a]Recovered starting material **19b** (58%). [b]Recovered starting material **19c** (26%).

The two spirocyclic ketals **19a** and **19d** reacted smoothly in a Sonogashira coupling with phenyl-acetylene to give the 3,5-bis(phenylethynyl)thiadiazines **116** and **117** in 75 and 76% yields, respectively. Monoarylation of catechol ketal **19d** was also possible by a Stille coupling with an excess of dichlorothiadiazine **19d** (2 eq) (Scheme 49).[13]




**118** (83%, based on 60% recovered **19d**) → **19a** [R = $(CH_2)_2$] / **19d** (R = 1,2-$C_6H_4$) → **116** [R = $(CH_2)_2$, 1.5 h, 76%] / **117** (R = 1,2-$C_6H_4$, 0.5 h, 75%)

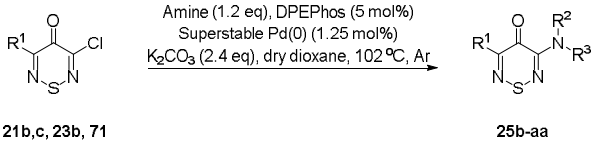
**Scheme 49.** Synthesis of 3,5-bis(phenylethynyl)thiadiazines **116** and **117** and 3-chloro-5-phenylthiadiazine **118**.

### 6.6. Pd-Catalysed C-N coupling of chloro-4*H*-1,2,6-thiadiazines

A Pd-catalysed Buchwald-Hartwig C-N coupling was developed for the conversion of 5-substituted 3-chlorothiadiazinones **21b**, **21c**, **22c**, **23b** and **71** to 5-substituted 3-arylaminothiadiazinones **25b-aa**. This route avoids the use of elevated temperatures and excess amine (see Sect. 6.3.1) and can be used to prepare 3,5-diaminothiadiazines containing sensitive or expensive arylamines. A brief optimisation identified the best catalyst to be Pd{[3,5-$(F_3C)_2C_6H_3$]$_3$P}$_3$ (1.25 mol%) [aka Superstable Pd(0)] in combination with the ligand bis[(2-diphenylphosphino)phenyl] ether (DPEPhos) (5 mol%), base $K_2CO_3$ (2.4 eq), in 1,4-dioxane, at 102 °C.[36] Twenty new 5-substituted 3-arylaminothiadiazinones **25b-aa** were prepared in 56-99% yields, while the scope of the reaction involves primary anilines bearing steric, electron donating or withdrawing substituents, as well as electron rich or poor hetarylamines (Table 24). 2-Iodoaniline or secondary arylamines such as diphenylamine, carbazole or *N*-methylaniline, however, were not tolerated.

The above C-N coupling was used to prepare fourteen 3,5-dianilino-1,2,6-4*H*-thiadiazin-4-ones **119a-e** that were studied as CaMKK2 inhibitors (Scheme 50).[37]

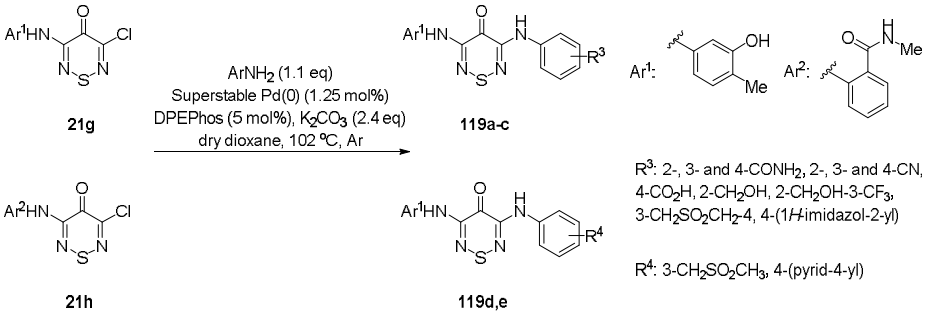
**Table 24.** Reaction of 5-subsituted 3-chlorothiadiazinones with (het)arylamines.




**21b,c, 23b, 71** **25b-aa**

| Starting thiadiazinone | $R^1$ | $R^2$ | $R^3$ | Time (h) | Yield (%)[a] |
|---|---|---|---|---|---|
| **21c** | PhNH | Ph | H | 0.5 | **25b** (99) |
| **21c** | PhNH | 2-Tol | H | 2 | **25d** (61) |
| **21c** | PhNH | 2-$AcC_6H_4$ | H | 8 | **25e** (85)[b] |
| **21c** | PhNH | 2-$NCC_6H_4$ | H | 1 | **25f** (81) |
| **21c** | PhNH | 2-$HO_2CC_6H_4$ | H | 1 | **25g** (90) |
| **21c** | PhNH | 2-$F_3CC_6H_4$ | H | 4 | **25h** (68) |
| **21c** | PhNH | 2-$MeOC_6H_4$ | H | 2 | **25i** (89) |
| **21c** | PhNH | 2-$HOC_6H_4$ | H | 4 | **25j** (83) |
| **21c** | PhNH | 2-$O_2NC_6H_4$ | H | 1 | **25k** (86)[b] |
| **21c** | PhNH | 2-$ClC_6H_4$ | H | 3 | **25l** (82) |
| **21c** | PhNH | 2-$BrC_6H_4$ | H | 2 | **25m** (91)[b] |
| **21c** | PhNH | 4-$BrC_6H_4$ | H | 1.5 | **25n** (92) |
| **21c** | PhNH | 2-$IC_6H_4$ | H | 18 | **25o** (-)[c] |
| **21c** | PhNH | pyrid-2-yl | H | 1 | **25p** (70)[b] |
| **21c** | PhNH | pyrid-4-yl | H | 1 | **25q** (72) |
| **21c** | PhNH | pyrimid-2-yl | H | 0.5 | **25r** (78) |
| **21c** | PhNH | 1,2,4-triazin-3-yl | H | 0.5 | **25s** (85) |
| **21c** | PhNH | thiaz-2-yl | H | 0.5 | **25t** (91) |
| **21c** | PhNH | Ph | Me | 24 | **25u** (-)[d] |
| **21c** | PhNH | Ph | Ph | 18 | **25v** (-)[d] |
| **21c** | PhNH | carbazol-1-yl | - | 18 | **25w** (-)[d] |
| **21b** | morpholino | Ph | H | 2 | **25x** (56) |
| **73** | $NH_2$ | Ph | H | 2 | **25y** (-)[e] |
| **23b** | PhS | Ph | H | 1 | **25z** (96) |
| **22c** | PhO | Ph | H | 1 | **25aa** (93) |

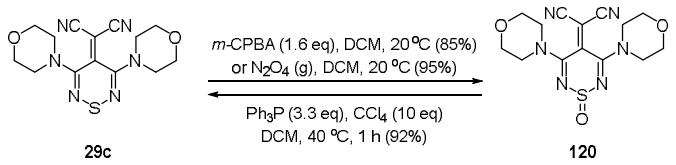
[a]Isolated yields. [b]Product was unstable to chromatography, chromatography free isolation applied. [c]Complex reaction mixture (by TLC). [d] No reaction. [e] Intractable baseline (by TLC).




**Scheme 50.** Synthesis of 3,5-dianilino-1,2,6-4*H*-thiadiazin-4-ones **119a-e** active as CaMKK2 inhibitors.

### 6.7. Oxidation of the 4*H*-1,2,6-thiadiazine sulfur atom

Reaction of the purple-coloured 2-(3,5-dimorpholino-4*H*-1,2,6-thiadiazin-4-ylidene)malononitrile **29c** with *m*-CPBA (1.6 eq) or with $N_2O_4$ (g) in DCM at 20 °C gave the orange-coloured sulfoxide **120** in 85 and 95% yields, respectively (Scheme 51).[22] Treating the sulfoxide **120** with $Ph_3P$ (3.3 eq) and $CCl_4$ (10 eq) gave back the thiadiazine **29c** in 95% yield.



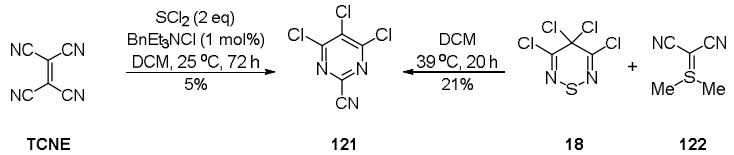

**Scheme 51.** Oxidation of 2-(3,5-dimorpholino-4*H*-1,2,6-thiadiazin-4-ylidene)malononitrile **29c**.

### 7. Transformations of 1,2,6-thiadiazine to other ring systems

Only few transformations of non-S-oxidised 1,2,6-thiadiazines to other ring systems are known including the transformation to 4,5,6-trichloropyrimidine-2-carbonitrile **121**, to 1,2,5-thiadiazoles and to fused ring systems, *e.g.* pyrrolothiadiazine **14** and diazepine **17**.

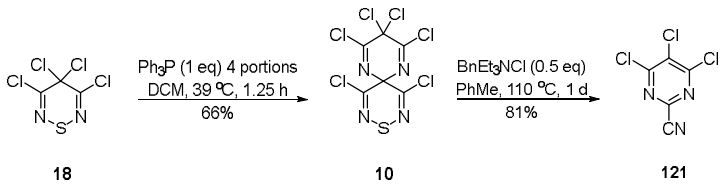
### 7.1. Transformations to 4,5,6-trichloropyrimidine-2-carbonitrile 121

4,5,6-Trichloropyrimidine-2-carbonitrile **121**, which first appeared as a minor side product (5%) during the preparation the ylidenemalononitrile **4** from TCNE and $SCl_2$,[17,21] was recently isolated as a side product in 21% yield during the preparation of the ylidenemalononitrile **4** from tetrachlorothiadiazine **18** and dimethylsulfonium dicyanomethylide **122** (Scheme 52).[20]




**Scheme 52.** Formation of trichloropyrimidine **121** from tetrachlorothiadiazine **18** and from TCNE and $SCl_2$.

Subsequently, the formation of spirocycle **10** allowed for the development of a more efficient two step synthesis of trichloropyrimidine **121** from tetrachlorothiadiazine **18**. Treatment of tetrachlorothiadiazine **18** with $Ph_3P$ (1 eq) gave the spirocycle **10** in 66% yield and subsequent degradation with $BnEt_3NCl$ (0.5 eq) afforded trichloropyrimidine **121** in 81% yield (Scheme 53).[12]



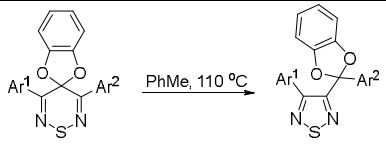

**Scheme 53.** Two step synthesis of trichloropyrimidine **121** from tetrachlorothiadiazine **18**.

### 7.2. Transformations to 1,2,5-thiadiazoles 123

The most unexpected transformation of 4*H*-1,2,6-thiadiazines is that to 1,2,5-thiadiazoles. 3',5'-Diaryl-spiro[benzo[*d*][1,3]dioxole-2,4'-[1,2,6]thiadiazines] **11a-l** (see Sect. 6.5.3) under thermal and Brønsted or Lewis acid catalysed conditions ring contract to give 3-aryl-4-(2-arylbenzo[*d*][1,3]dioxol-2-yl)-1,2,5-thia-diazoles **123** in high yields. Eleven analogues were reported to undergo this transformation and the reaction scope involves both electron rich and electron poor

aryls as well as heteroaryl groups (Table 25).[43] In unsymmetrical diarylthiadiazines **11**, the more electron rich aryl group preferentially migrated, supporting a double Wagner-Meerwein rearrangement mechanism. 6,10-Diaryl-1,4-dioxa-8-thia-7,9-diazaspiro[4.5]deca-6,9-dienes **70** failed to undergo this rearrangement.

**Table 25**. Thermolysis of 1,2,6-thiadiazines **11a-l** to give 1,2,5-thiadiazoles **123**.



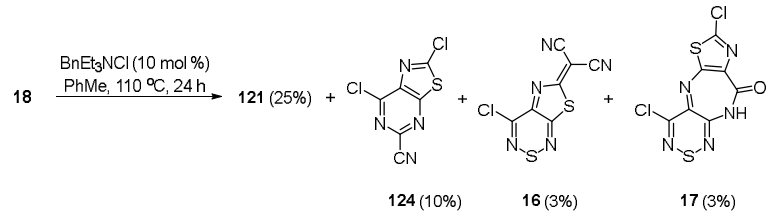

**11a-l** **123a-n**

| Starting ketal | $Ar^1$ | $Ar^2$ | Time (h) | Yield (%) |
|---|---|---|---|---|
| **11b** | Ph | | 3 | **123a** (94) |
| **11c** | 4-Tol | | 1 | **123b** (98) |
| **11f** | 4-$MeOC_6H_4$ | | 0.5 | **123c** (99) |
| **11g** | 4-$BnOC_6H_4$ | | 1 | **123d** (98) |
| **11d** | 4-$FC_6H_4$ | | 4.5 | **123e** (98) |
| **11a** | 4-$O_2NC_6H_4$ | | 24 | **123f** (9)[a] |
| **11a** | 4-$O_2NC_6H_4$ | | 0.3 | **123f** (86)[b] |
| **11h** | Ph | 4-$MeOC_6H_4$ | 1 | **123g/123h** (98)[c] |
| **11i** | 4-$O_2NC_6H_4$ | Ph | 3.5 | **123i/123j** (98)[d] |
| **11j** | 4-$O_2NC_6H_4$ | 4-$MeOC_6H_4$ | 1 | **123k** (95) |
| **11k** | fur-2-yl | | 24 | **123m** (84) |
| **11l** | thien-2-yl | | 6 | **123n** (99) |

[a]Recovered starting material 88%. [b]Reaction run in biphenyl at 190 °C. [c]Inseparable mixture of **123g** and **123h** (**123g**/**123h**, 82:18). [d]Inseparable mixture of **123i** and **123j** (**123i**/**123j** 83:17).

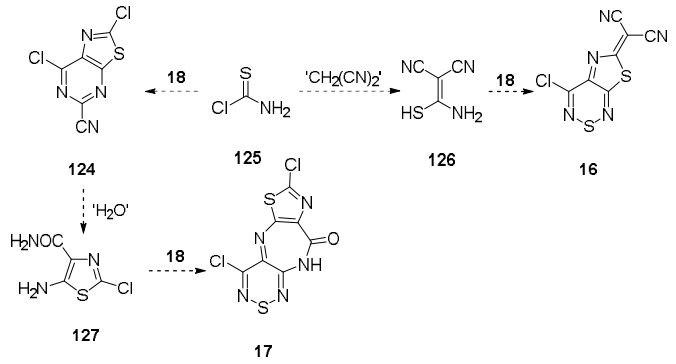
### 7.3. Transformations to other ring systems

Thiazoles **124** and **16** and diazepine **17** (Scheme 54) were isolated from the chloride-mediated thermal degradation of tetrachlorothiadiazine **18** in addition to trichloropyrimidine **121** (see Sect. 7.1) and pyrrolothiadiazine **14** (see Sect. 5.2.2).[19]




**Scheme 54.** Synthesis of thiazoles **124** and **16** and diazepine **17** from tetrachlorothiadiazine **18**.

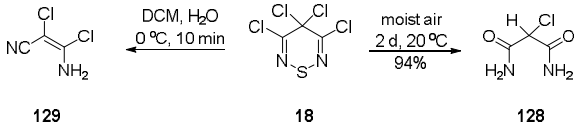
Tentatively, thiazolo[5,4-*d*]pyrimidine **124** is a product of trichloropyrimidine **121** and thiocarbomyl chloride **125** that could form during the degradation of tetrachlorothiadiazine **18** (Scheme 55). Reaction of thiocarbomyl chloride **125** with any free malononitrile or an equivalent combination could give [amino-(mercapto)methylene]malononitrile **126**, which can then react with tetrachlorothiadiazine **18** to give thiazole **16**. In situ hydrolysis of thiazolo[5,4-*d*]pyrimidine **124** was proposed to release 5-amino-2-chlorothiazole-4-carboxamide **127** that was trapped by unreacted tetrachlorothiadiazine **18** to give diazepine **17**.



**Scheme 55.** Origins of thiazoles **124** and **16** and diazepine **17**.

**8. Degradation of the 1,2,6-thiadiazine ring**

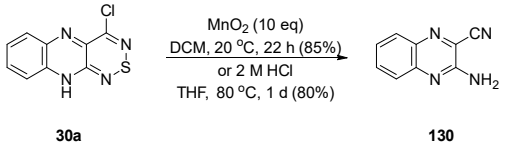
Tetrachlorothiadiazine **18** degrades in moist air over 2 days to give 2-chloromalonamide **128** in 94% yield.[20,28] This reactivity is not surprising as the presence of four electronegative chlorine atoms makes thiadiazine **18** highly reactive even towards weak nucleophiles like water. Interestingly, treatment of a solution of **18** in DCM with water at 0 °C gives initially 3-amino-2,3-dichloroacrylonitrile **129** that subsequently converts to 2-chloromalonamide **128** (Scheme 56).[28]



**Scheme 56.** The degradation of tetrachlorothiadiazine **18** in moist air.

Pale yellow crystals of ylidenemethylene **3** stored at 20 °C gradually become red and give off an odour of sulfur chlorides with thin layer chromatography (TLC) showing only traces of the ylidenemethylene together with several new unidentified products.[9]

Thiadiazinoquinoxaline **30a** is stable in mildly basic conditions (neat $Et_3N$, 48 h), but is unstable in acid, oxidative and reductive conditions. Heating a solution of **30a** in glacial AcOH at reflux for 15 min led to consumption of the starting material and isolation of 3-aminoquinoxaline-2-carbonitrile **130** in 38% yield. By heating a solution of the thiadiazinoquinoxaline **30a** in aqueous HCl/THF at 80 °C or by reacting it with $MnO_2$ (10 eq) in DCM at 20 °C the 3-aminoquinoxaline-2-carbonitrile **130** was isolated in 80 and 85% yields, respectively (Scheme 57).[20] Reduction of thiadiazinoquinoxaline **30a** with Zn powder (4 eq) in AcOH led to degradation and isolation of 3-aminoquinoxaline-2-carbonitrile **130** in only 6% yield.



**Scheme 57.** The degradation of thiadiazinoquinoxaline **30a**.

4*H*-Thiadiazines bearing 3,5-chlorines are susceptible to thiophiles that can cleave open the thiadiazine. For example, $Ph_3P$ reacts with tetrachlorothiadiazine **18** to afford spirocycle **10** (see Sect. 7.1),[12] while halides like $BnEt_3NCl$ and $BnEt_3NI$ react either with spirocycle **10**[12] or with tetrachlorothiadiazine **18** to give a plethora of degradation products.[19]

A recent stability study of 3,5-dianilinothiadiazin-4-one **25b** showed that this compound was stable to neutral, acidic, slightly basic, oxidising and reducing conditions as well as in the presence of amine or thiol nucleophiles,[37] indicating that the substitution of the 3,5-chlorides by amines has reduced the susceptibility of the ring sulfur atom to attack by thiophiles.

## 9. Important compounds and applications

### 9.1. Medicinal applications

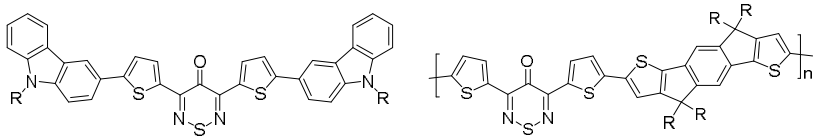
3,5-Dianilino-1,2,6-4*H*-thiadiazin-4-ones **119a-e** were investigated as calcium/calmodulin-dependent protein kinase kinase 2 (CaMKK2) inhibitors (Scheme 50).[37] Out of the fifteen analogues prepared, several showed micromolar activity through targeted displacement of bound water molecules in the active site. The studied thiadiazines were less active than their 2,4-dianilinopyrimidine counter parts; the study is a starting point for the development of highly selective thiadiazine kinase inhibitors.

### 9.2. Agrochemical applications

5-Substituted 3-chloro-4*H*-1,2,6-thiadiazin-4-ones are plant antifungals. Peake *et al.* described the antifungal activity of sixty one 5-aryloxy derivatives against thirteen fungi species[44] and this study was then expanded to 5-thio[45,46] and 5-hetaryloxy[47] thiadiazines. Later, Portnoy described the antifungal activity of selected 5-alkoxy, 5-aryloxy and 5-thio thiadiazines against the diseases scab of apple, late blight of tomato and downy mildew of grapes.[48]

### 9.3. Electronic applications

Non-S-oxidised 4*H*-1,2,6-thiadiazines behave as acceptor components of small molecular[41] or polymeric[10] donors in BHJ OPVs with [6,6]-phenyl-C71-butyric acid methyl ester (PC71BM) as the fullerene acceptor. The first publication studied the optical, electrochemical, morphological and transport properties of a series of thiadiazinone and (thienyl)carbazole containing $\pi$-extended donor-acceptor-donors (D-A-D), exploring the effect of the number of the thienyl units as well as the choice of branched or straight alkyl side chains in the optoelectronic behaviour of the molecules (see Sect. 6.5.1.5). The study revealed that the best performing small molecule with a power conversion efficiency (PCE) of 2.7% was thiadiazinone **105b** (Figure 7).[41] Later, the respective properties of D-A type polymer donors containing 1,2,6-thiadiazin-4(*H*)-one or *N*-(perfluorophenyl)-1,2,6-thiadiazin-4(*H*)-imine and (het)aryl-substituted indacenodithiophenes were reported, with the former having the best performance (up to 3.83%, compound **107a**.[10]



**105b** (R = 2-ethylhexyl) **107a** (R = 4-*n*-hexyl-$C_6H_4$)

**Figure 7.** Best performing OPV donor 1,2,6-thiadiazine small molecule and polymer.

### 9.4. Other applications

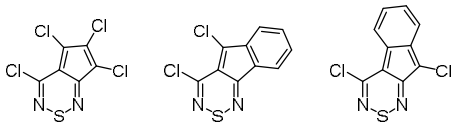
Cyclopenta[1,2,6]thiadiazines **13**, **38** and **39** have interesting properties: compound **39** has liquid crystalline behaviour while compounds **13** and **38** behave as near infrared dyes (Figure 8).[15,16]

Both Woodward[7] (see Sect. 1) and Rees[17,21,23] (Figure 9) proposed polymers containing 4*H*-1,2,6-thiadiazines as potentially stable alternatives to the superconducting polymer poly(sulfur nitride) $(SN)_x$. The polymer proposed by Rees, is based on the mildly aromatic thiadiazin-4-one with thiadiazine units alternating between the S(II) and S(IV) oxidation states.

## 10. Conclusions

The chemistry of non-S-oxidised 4*H*-1,2,6-thiadiazines has rapidly developed over the last twenty years leading to several interesting new applications in both the materials and biological sciences. In light of

these recent advances, we anticipate further investigations of this ring system in the applied sciences that can include examples of Woodward's and Rees's polymeric analogues of poly(sulfur nitride) as well as additional examples of the ring system in biologically active small molecules.



39 13 38

**Figure 8.** Structures of cyclopenta[1,2,6]thiadiazines **13**, **38** and **39**.

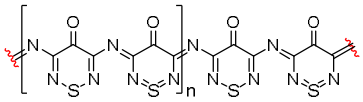


**Figure 9**. 1,2,6-Thiadiazine polymer proposed by Rees that could act as alternatives to poly(sulfur nitride) $(SN)_x$.

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