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Two-step conversion of 3,4,4,5-tetrachloro-4*H*-1,2,6-thiadiazine into 4,5,6-trichloropyrimidine-2-carbonitrile

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ABSTRACT

Tin reduction of 3,4,4,5-tetrachloro-4*H*-1,2,6-thiadiazine afforded perchloro-9-thia-1,5,8,10-tetraaza-spiro[5.5]undeca-1,4,7,10-tetraene (10%) and 3,5-dichloro-4*H*-1,2,6-thiadiazine-4-thione (27%), the structures of which were supported by single crystal X-ray crystallography. Treating the tetrachlorothiadiazine with Ph_3P (1 equiv.) afforded the corresponding spirocycle in a useful 66% yield, the degradation of which with $BnEt_3NCl$ (0.5 equiv.) afforded densely functionalized 4,5,6-trichloropyrimidine-2-carbonitrile in 81% yield. Rational mechanisms for the formation of products are proposed.

Introduction

Pyrimidines (Fig. 1), known for over 100 years, are abundant in nature (*e.g.* in DNA and in thiamine),[1] and there are many pyrimidine-based marketed drugs such as Uramustine (antineoplastic), Trimethoprim (antibacterial), Flucytosine (antifungal), and Broxuridine (antiviral).[2] Numerous pyrimidine syntheses exist, including many ring transformations.[3] Interestingly, 4*H*-1,2,6-thiadiazines are structurally closely related to pyrimidines in that both heterocycles share five common atoms with the same carbon-nitrogen connectivity in their ring structure (Fig. 1). Considering this, it is somewhat surprising that there is only one report regarding the transformation of 1,2,6-thiadiazines into pyrimidines.[4]

During ongoing studies on non-S-oxidized 4*H*-1,2,6-thiadiazines such as 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one (**1**)[5a] and 3,4,4,5-tetrachloro-4*H*-1,2,6-thiadiazine (**2**),[5b] we isolated 4,5,6-trichloropyrimidine-2-carbonitrile (**3**) as the major product (21%) during the preparation of ylidenemalononitrile **4** from the reaction of tetrachlorothiadiazine **2** with dimethylsulfonium dicyanomethylide (Scheme 1).[4]

Interestingly, trichloropyrimidine **3** was also isolated in low yield (5%) during an early synthesis of ylidenemalononitrile **4** that involved the reaction of tetracyanoethylene (TCNE) with SCl_2.[6] Since we never observed the formation of trichloropyrimidine **3** from pure ylidenemalononitrile **4**, we tentatively considered that it originated from tetrachlorothiadiazine **2**. It is noteworthy that ring transformations of non-S-oxidized 4*H*-1,2,6-thiadiazines into other heterocycles are rare and only one example, the ring contraction to 1,2,5-thiadiazoles, has been reported.[7]

4,5,6-Trichloropyrimidine-2-carbonitrile (**3**) is polyfunctional and potentially offers rich chemistry *via* transition metal-catalyzed coupling reactions or nucleophilic substitutions on the chloride-substituted C4-6 carbons, as well as *via* modification of the C2 nitrile group. Nevertheless, owing to the low yielding synthesis of trichloropyrimidine **3**, its chemistry has remained unexplored. In contrast, isomeric 2,4,6-trichloropyrimidine-5-carbonitrile (**5**), which is readily prepared,[8a] has been extensively used as a building block to prepare pyrimidine-based dyes,[8a] compounds for antithrombotics,[8b] metobotropic glutamate (mGluR 1) antagonists for treating chronic neurological disorders,[8c] herbicides,[8d] and as a precursor for highly fluorinated pyrimidines.[8e] More recently, trichloropyrimidine **5** has been used to prepare a series of mono-, di- or tri-aminopyrimidines **6** that act as selective inhibitors of phosphoinositide 3-kinases (PI3Ks)[8f] (Scheme 2).

Herein, we describe a two-step synthesis of 4,5,6-trichloropyrimidine-2-carbonitrile (**3**) in a practically useful 53% yield from tetrachlorothiadiazine **2**. The reaction sequence was based on the hypothesis that the initial step of such a transformation involved removal of the tetrachlorothiadiazine **2** ring sulfur *via* a thiophile-mediated reductive cleavage.

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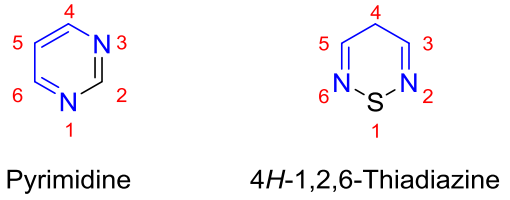
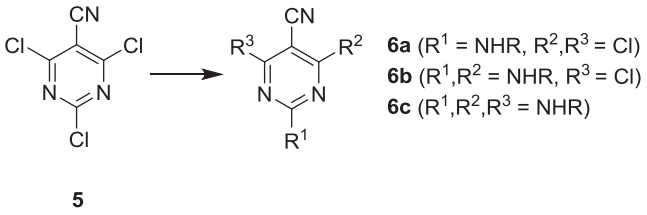
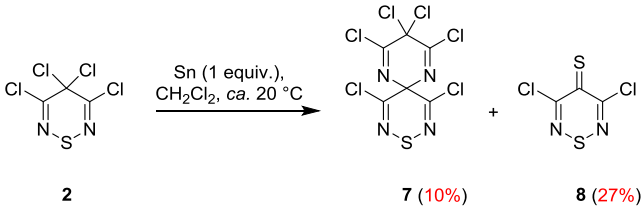


Fig. 1. Structures of pyrimidine and 4*H*-1,2,6-thiadiazine with IUPAC numbering in red and common bonds and atoms highlighted in blue.



Scheme 2. Reactions of 2,4,6-trichloropyrimidine-5-carbonitrile (**5**).



Scheme 3. Reaction of 3,4,4,5-tetrachloro-4*H*-1,2,6-thiadiazine (**2**) with Sn powder.

Results and discussion

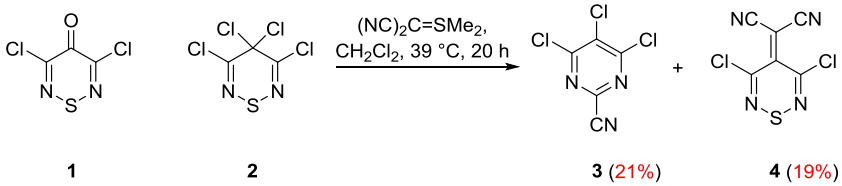
The C-Cl, C=N and N-S bonds of 3,4,4,5-tetrachloro-4*H*-1,2,6-thiadiazine (**2**) are all susceptible to reductive cleavage. For our strategy to succeed, we needed to identify reaction conditions to selectively cleave the N-S bonds. Early investigations involving silane, $H_3B{\cdot}SMe_2$, NaH and reducing metal powders (Zn, Mg and Ni) gave only polar intractable baseline material (TLC) and a notable smell of H_2S. Reaction with Fe and Cu powders gave complex reaction mixtures of colored and colorless products (TLC). Fortunately, the use of the milder reductants Sn and In, led to reaction mixtures from which two low melting non-polar products **7** [colorless, R_f 0.54, *n*-hexane; mp 79–81 °C (MeCN)] and **8** [yellow-green, R_f 0.35, *n*-hexane; mp 72–74 °C (*n*-pentane)] were isolated by chromatography. Initial efforts to optimize the yields of both products *via* the use of a metal reductant included adjusting the metal reductant equivalents (0.33–2 equiv.), the reaction solvent (CH_2Cl_2, THF, MeCN, PhH), the reaction temperature (0 °C to reflux), and time (0.5–3 h). Unfortunately, the best yields required the use of Sn powder (1 equiv.) in CH_2Cl_2 at *ca.* 20 °C for 1 h, affording compounds **7** and **8** in only 10% and 27%, respectively (Scheme 3).

While detailed spectroscopic data was collected on both compounds (ESI), we were initially unable to confirm their structure. Fortunately, single crystals of compounds **7** and **8** could be grown *via* sublimation under static vacuum (13 mTorr) and single crystal X-ray crystallography identified them as perchloro-9-thia-1,5,8,10-tetraazaspiro[5.5]undeca-1,4,7,10-tetraene (**7**) and 3,5-dichloro-4*H*-1,2,6-thiadiazine-4-thione (**8**) (Fig. 2).

Spirocycle **7** looked to be a promising intermediate for the desired trichloropyrimidine **3** since it contained the complete carbon–nitrogen scaffold together with the desired chloride substituents. Presumably, its formation was due to reductive cleavage of the N-S bonds to release a synthon equivalent to 2,2-dichloromalonimidoyl dichloride (**9**), which then was trapped by unreacted tetrachlorothiadiazine **2** *via* its highly reactive C4 germinal dichloride. Similarly, a released nucleophilic source of sulfur, S^{2-}, could have reacted with additional tetrachlorothiadiazine **2**, again at the germinal C4 position, to give thione **8** (Scheme 4). Interestingly, multiple efforts to treat the tetrachlorothiadiazine **2** with H_2S (g) failed to generate thione **8**, affording only intractable polar materials (TLC), tentatively suggesting that H_2S (g) was not responsible for its formation.

Further attempts to improve the yield of spirocycle **7** involved treatment of thiadiazine **2** with alternative thiophiles such as halides and phosphines; the use of these thiophiles would avoid the *in situ* formation of nucleophilic sulfur which could compete for unreacted tetrachlorothiadiazine **2** to give thione **8**. While the reaction of tetrachlorothiadiazine **2** with halides led to complex reaction mixtures, which are currently under study, the use of Ph_3P (1 equiv.) in CH_2Cl_2 at *ca.* 20 °C, led to rapid consumption of the thiadiazine (TLC, 5 min) and gave spirocycle **7** in a more favorable 27% yield. Efforts were then made to optimize this reaction, however, the use of alternative solvents (MeCN, THF, PhH), increased equivalents of Ph_3P (up to 1.5 equiv.), higher or lower concentrations (0.2, 0.4 or 1 *vs* 0.5 M of tetrachlorothiadiazine **2**), lower reaction temperatures (0–5 °C), and the use of milder phosphine sources such as polymer bound Ph_3P or $(PhO)_3P$ (1 equiv.), led to slower reactions (24 h) and lower yields. Fortunately, performing the reaction in CH_2Cl_2 at *ca.* 39 °C gave an improved yield of 38%. Ultimately, at these elevated temperatures the portionwise addition of Ph_3P (1 equiv. in 4 portions over 1 h) led to the best yield of spirocycle **7** (66%) (Scheme 5).

Next, we investigated the conversion of spirocycle **7** to the desired 4,5,6-trichloropyrimidine-2-carbonitrile (**3**). Thermal stability studies of spirocycle **7** gave a decomposition onset at 227.3 °C (peak max: 233.5 °C) but analysis of the thermolysis residue did not identify any notable product (TLC). A preliminary investigation of its reactivity also indicated that spirocycle **7** was significantly more stable than tetrachlorothiadiazine **2**. Pure recrystallized spirocycle **7** failed to react with Sn (1 equiv.), in CH_2Cl_2 at *ca.* 20 °C after 48 h, and was also stable to glacial formic acid and 2 M HCl (rt-reflux, 24 h), which are known to transform tetrachlorothiadiazine **2** into thiadiazinone **1**.[4,5] Furthermore, spirocycle **7** did not react with either catechol or other primary alcohols to form chloride substitution products such as ketals.[9] This lack of reactivity indicated that the geminal dichloride of spirocycle **7** was less reactive than that of the tetrachlorothiadiazine **2**, which was expected as the geminal dichloride of the latter is strongly



Scheme 1. Reaction of tetrachlorothiadiazine **2** with dimethylsulfonium dicyanomethylide.