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Short Note

4,5,6-Trichloropyrimidine-2-carboxamide

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Abstract: Reaction of 4,5,6-trichloropyrimidine-2-carbonitrile (**1**) with concentrated sulfuric acid at ca. 20 °C gave 4,5,6-trichloropyrimidine-2-carboxamide (**5**) in 91% yield. The new compound was fully characterized by IR, MALDI-TOF, NMR and elemental analysis.

Keywords: heterocycle; chloro-substituted; pyrimidine; carboxamide

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1. Introduction

Pyrimidines are important aromatic N-heterocycles that exist in nature; for example, as components of pyrimidine nucleotides (cytosine, thymine and uracil) [1]. Pyrimidines are also frequently used in pharmaceuticals as they rank 10th in the most frequently used nitrogen heterocycles in U.S. FDA approved drugs [2]. Examples of pyrimidine drugs are the CNS depressant phenobarbital, the antibacterial trimethoprim, and the hyperthyroidism drug propylthiouracil (Figure 1). Additional pharmaceutical applications include uses as diuretics [3], anti-inflammatory [4], anti-malarial [5], and anti-tumor [6] agents. The chemistry of pyrimidines has been reviewed [7].

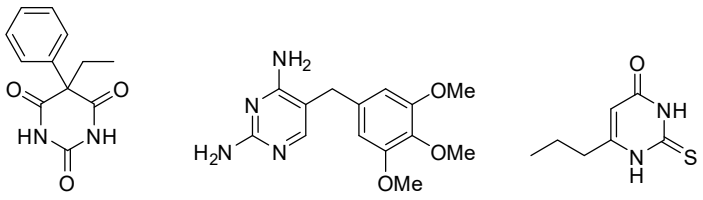
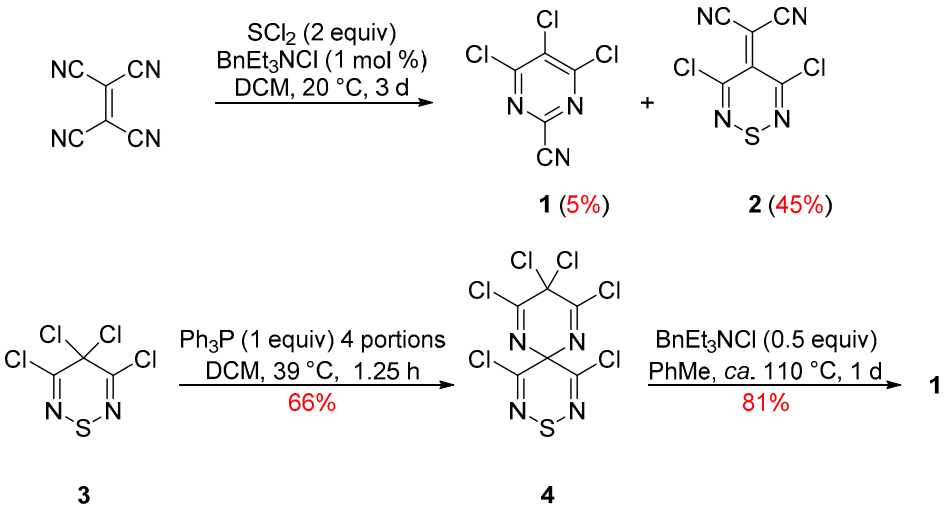


Figure 1. Pyrimidine containing drugs.

2. Results and Discussion

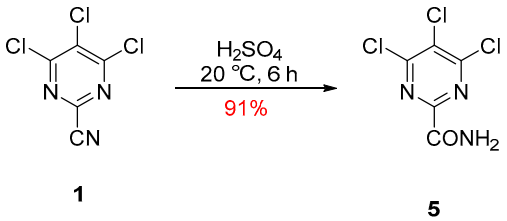
Our interest in pyrimidines began with 4,5,6-trichloropyrimidine-2-carbonitrile (**1**), a compound that was first isolated as an unexpected minor product from the reaction of tetracyanoethene (TCNE) with SCl_2 during the preparation of 2-(3,5-dichloro-4*H*-1,2,6-thiadiazin-4-ylidene)malononitrile (**2**) [8] (Scheme 1). A more efficient synthesis of pyrimidine **1** was subsequently developed, starting from the less readily available but highly reactive tetrachlorothiadiazine **3** via perchloro-9-thia-1,5,8,10-tetraazaspiro[5.5]undeca-1,4,7,10-tetraene (**4**) with a 53% overall yield [9] (Scheme 1). Other efforts to develop an independent synthesis of pyrimidine **1** [10,11] or investigate its chemistry [12] were also reported.



Scheme 1. Preparation of trichloropyrimidine **1** from TCNE and from tetrachlorothiadiazine **3**.

We are interested in studying the use of trichloropyrimidine **1** as a synthetic scaffold as it offers multiple sites of reactivity towards heteroatom nucleophiles or organometallic reagents. To identify any potential side products from the chemistry of pyrimidine **1,** we investigated its hydration to 4,5,6-trichloropyrimidine-2-carboxamide (**5**). Having frequently worked with cyano-substituted heterocycles, we often encountered the hydration products of the nitrile group [13]; therefore, we considered preparing, isolating, and characterizing this carboxamide worthwhile.

The reaction involved stirring a solution of trichloropyrimidine **1** in concentrated sulfuric acid for 6 h that, after workup, gave the desired compound with a 91% yield (Scheme 2). Product **5** was then isolated as colorless plates, melting point (mp) 162–164 °C (from *c*-hexane/DCE), while FTIR spectroscopy showed ν(N-H) stretches at 3402, 3291, 3219 and 3167 cm^{-1}, along with a C=O stretch at 1686 cm^{-1}, indicative of an amide (see Supplementary Material). Two diastereotopic protons in ^{1}H NMR (acetone-d_6) were present as broad singlets, 8.04 and 7.32 ppm, assigned to the amide functionality, while ^{13}C NMR (acetone-d_6) showed the presence of four quaternary carbon resonances at 161.9, 160.6, 155.8, and 131.1 ppm. Compared to the starting material **1**, which had a C≡N resonance at 113.4 ppm, the new product **5** lacked this signal and displayed a new down-field signal at 160.6 ppm, which is typical for an amide C=O resonance supporting the hydration of the nitrile functionality. Finally, a correct elemental analysis (CHN) was obtained for the molecular formula $C_5H_2Cl_3N_3O$.



Scheme 2. Synthesis of 4,5,6-trichloropyrimidine-2-carboxamide (**5**).

Pyrimidine **5** is potentially a useful synthetic scaffold and could be used instead of trichloropyrimidine **1** as it has one less leaving group that could lead to more regioselective substitution chemistry, while its higher melting point (162–164 °C vs. 62–63 °C for cyano **1** [10]) would make it more stable in storage.

3. Materials and Methods

The reaction mixture was monitored by thin layer chromatography (TLC) using commercial glass-backed TLC plates (Merck Kieselgel 60 F_{254}). The plates were observed under UV light at 254 and 365 nm. The melting point was determined using a PolyTherm-A, Wagner & Munz, Kofler hot-stage Microscope apparatus (Wagner & Munz, Munich, Germany). The solvent used for recrystallization is indicated after the melting point. The UV-vis spectrum was obtained using a Perkin–Elmer Lambda-25 UV/Vis spectrophotometer (Perkin–Elmer, Waltham, MA, USA); inflections are identified by the abbreviation "inf". The IR spectrum was recorded on a Shimadzu FTIR-NIR Prestige-21 spectrometer (Shimadzu, Kyoto, Japan) with a Pike Miracle Ge ATR accessory (Pike Miracle, Madison, WI, USA); strong, medium, and weak peaks are represented by s, m, and w, respectively. A Bruker Avance 500 machine (Bruker, Billerica, MA, USA) was used at 500 and 125 MHz to record the ^{1}H and ^{13}C NMR spectra, respectively. Deuterated solvents were used for the homonuclear lock; the signals are referenced to the deuterated solvent peaks. Attached proton test (APT) NMR studies were used for the assignment of the ^{13}C peaks as CH_3, CH_2, *C*H, and *C*q (quaternary). The MALDI-TOF mass spectrum (+ve mode) was recorded on a Bruker Autoflex III Smartbeam instrument (Bruker). The elemental analysis was run by the London Metropolitan University Elemental Analysis Service. 4,5,6-Trichloropyrimidine-2-carbonitrile (**1**) was prepared according to the literature procedure [9].

4,5,6-Trichloropyrimidine-2-carboxamide (**5**)

To stirred concentrated sulfuric acid (2 mL) at ca. 20 °C was added 4,5,6-trichloropyrimidine-2-carbonitrile (**1**) (104 mg, 0.500 mmol), and the mixture was stirred at this temperature until complete consumption of the starting material (TLC, 6 h). The mixture was then poured into crushed ice and the mixture was then extracted with DCM (5 × 10 mL) and dried (Na_2SO_4). The solvent was then evaporated in vacuo to give the *title compound* **5** (103 mg, 91%) as colorless plates, mp 162–164 °C (from *c*-hexane/DCE); R_f 0.21 (DCM); (found: C, 26.47; H, 0.72; N, 18.43. $C_5H_2Cl_3N_3O$ requires C, 26.52; H, 0.89; N, 18.56%); λ_{max}(DCM)/nm 245 (log ε 3.01), 265 inf (2.84); υ_{max}/cm^{-1} 3402w, 3291w, 3219w and 3167w (N-H), 1686s (C=O), 1601m, 1508m, 1497s, 1439w, 1304s, 1234w, 1111w, 1055m, 881w, 822m, 808s, 760m; δ_H(500 MHz; C*D*Cl_3) 7.53 (1H, br s, N*H*$_2$), 6.33 (1H, br s, N*H*$_2$); δ_C(125 MHz; C*D*Cl_3) 161.3 (*C*q), 160.8 (*C*q), 153.5 (*C*q), 131.4 (*C*q); δ_H[500 MHz; (C*D*$_3$)$_2$CO] 8.04 (1H, br s, N*H*$_2$), 7.32 (1H, br s, N*H*$_2$); δ_C[125 MHz; (C*D*$_3$)$_2$CO] 161.9 (*C*q), 160.6 (*C*q), 155.8 (*C*q), 131.1 (*C*q); *m/z* (MALDI-TOF) 229 (M^+ + 4, 34%), 226 (M^+ − H + 2, 100%), 224 (M^+ − H, 91), 207 (M^+ − H_2O, 37).

Supplementary Materials: The following are available online: mol file, IR, mass spectrometry, ^{1}H and ^{13}C NMR spectra in $CDCl_3$ and $(CD_3)_2CO$, UV/Vis spectrum.

Author Contributions: P.A.K. and A.S.K. conceived the experiments; A.S.K. designed and performed the experiments, analyzed the data and wrote the paper. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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