

Short Note

# 4-Chloro-6-ethoxy-2-(methylthio)pyrimidine

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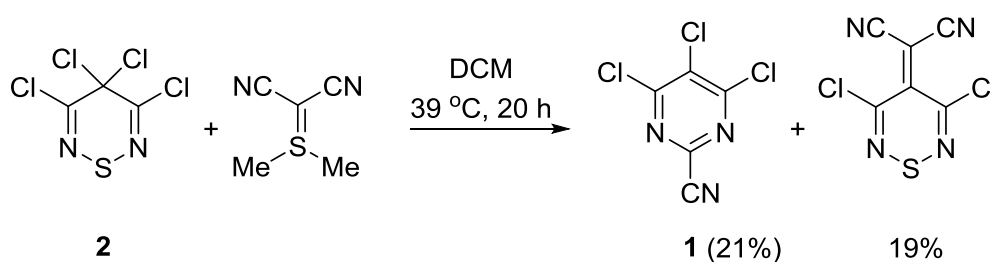
**Abstract:** 4,6-Dichloro-2-(methylthio)pyrimidine (**3**) reacts with EtONa in EtOH, at ca. 20 °C, for 2 h, to give exclusively 4-chloro-6-ethoxy-2-(methylthio)pyrimidine (**5**) in 89% yield. The latter is presented as a useful multifunctionalised pyrimidine scaffold.

**Keywords:** heterocycle; pyrimidine; multifunctionalised

## 1. Introduction

Pyrimidines are well known owing to their presence in biological systems as components of the nucleic acid bases cytosine, thymine, and uracil, as well as the vitamin thiamine, which illustrates their importance. The presence of pyrimidines has been reported for over a century and their chemistry has been reviewed [1]. Pyrimidines also find a plethora of uses as pharmaceuticals, as anti-inflammatory [2], anti-microbial [3], anti-HIV [4], anti-malarial [5] and anti-tumour [6] agents.

As part of our ongoing work in the chemistry of 1,2,6-thiadiazines [7–10] we identified 4,5,6-trichloropyrimidine-2-carbonitrile (**1**) as a product of the degradation of 3,4,4,5-tetrachloro-4*H*-1,2,6-thiadiazine (**2**) (Scheme 1) [8]. The former was also previously identified as a minor side product from the reaction of tetracyanoethene (TCNE) with SCl<sub>2</sub> [11].

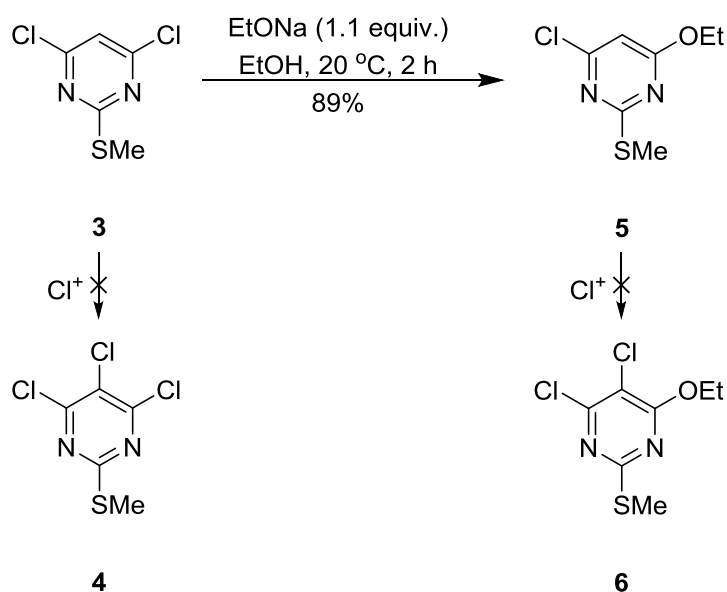


**Scheme 1.** Isolation of trichloropyrimidine **1** from 3,4,4,5-tetrachloro-4*H*-1,2,6-thiadiazine (**2**) [11].

Polyhalogenated pyrimidines are useful scaffolds as they can be modified either by nucleophilic aromatic substitution or by palladium coupling reactions. However, these reactions often suffer from regioselectivity issues. For example, the Suzuki-Miyaura coupling of 2,3,4,5-tetrachloropyrimidine with arylboronic acids gives either the 2- [12] or the 4-arylpyrimidine [13]. Moreover, on the same scaffold, while nucleophilic substitution by alkoxide occurs at C2 [14], hydroxide attacks the C4 position [15]. On the other hand, nucleophilic substitution by amine nucleophiles often gives mixtures of products [16,17]. The complexity of the chemistry of pyrimidines means that it is often difficult to access specific pyrimidine targets from a simple and symmetrical pyrimidine scaffold, indicating the necessity for asymmetrical and sometimes multi-functionalized scaffolds.

## 2. Results and Discussion

In our efforts to develop an independent synthesis for the trichloropyrimidine **1** we prepared the known 4,6-dichloro-2-(methylthio)pyrimidine (**3**) as an early and readily available [18] intermediate towards the preparation of 3,4,5-trichloro-2-(methylthio)pyrimidine (**4**). Nevertheless, attempts to chlorinate the C5 position, using either NCS or  $\text{PCl}_5$  to obtain 3,4,5-trichloro-2-(methylthio)pyrimidine (**4**) all failed. As such, we attempted to increase the electron density at C5 to facilitate the desired chlorination. To do this, we introduced an ethoxy group via simple nucleophilic aromatic substitution of chlorine. Interestingly, treating the dichloropyrimidine **3** with EtONa (1.1 equiv.) in EtOH proceeded smoothly at ca. 20 °C to give exclusively the mono-displaced 4-chloro-6-ethoxy-2-(methylthio)pyrimidine (**5**), but this disappointingly also failed to undergo C5 chlorination to give the expected 5,6-dichloro-4-ethoxy-2-methylthiopyrimidine (**6**) (Scheme 2).



**Scheme 2.** Synthesis of 4-chloro-6-ethoxy-2-(methylthio)pyrimidine (**5**) and attempted synthesis of 5-chlorinated pyrimidines **4** and **6**.

Despite this setback, we note that ethoxypyrimidine **5** is potentially a useful pyrimidine scaffold. Pyrimidine **5** has been previously prepared by treatment of dichloropyrimidine **3** with NaOEt in dry dimethylformamide, at 70 °C overnight [19], however, the synthesis described herein uses a non-toxic solvent (EtOH) and milder conditions (20 °C) that are more suitable for a regioselective reaction. A very similar analogue 4-chloro-6-methoxy-2-(methylthio)pyrimidine [20] is a versatile scaffold and can undergo Suzuki-Miyaura coupling to afford 4-aryl-6-methoxy-2-(methylthio)pyrimidines [21], as well as, amine [20] or alcohol displacement of the chloride [22], oxidation to sulfone [23], and condensation reactions to give polycyclic systems [24,25].

## 3. Materials and Methods

The reaction mixture was monitored by chromatography (TLC) using commercial glass backed TLC plates (Merck Kieselgel 60 F<sub>254</sub>, Darmstadt, Germany). The plates were observed under UV light at 254 and 365 nm. The melting point was determined using a PolyTherm-A, Wagner and Munz, Kofler hot-stage microscope apparatus (Wagner and 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) and inflections are identified by the abbreviation “inf”. The IR spectrum was recorded on a Shimadzu FTIR-NIR Prestige-21 spectrometer (Shimadzu, Kyoto, Japan) with Pike Miracle Ge ATR accessory

(Pike Miracle, Madison, WI, USA) and strong, medium, and weak peaks are represented by s, m, and w, respectively.  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectra were recorded on a Bruker Avance 500 machine (at 500 and 125 MHz, respectively (Bruker, Billerica, MA, USA)). Deuterated solvents were used for homonuclear lock and the signals are referenced to the deuterated solvent peaks. APT (Advance Proton Test) NMR studies identified carbon multiplicities, which are indicated by (s), (d), (t) and (q) notations. The MALDI-TOF (Matrix Assisted Laser Desorption/Ionization-Time of Flight) 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. 4,6-Dichloro-2-(methylthio)pyrimidine (**3**) was prepared according to the literature procedure [18].

#### 4-Chloro-6-ethoxy-2-(methylthio)pyrimidine (**5**)

To a stirred mixture of 4,6-dichloro-2-(methylthio)pyrimidine (**3**) (50 mg, 0.256 mmol) in EtOH (1 mL) at ca. 20 °C was added dropwise to a freshly prepared solution of EtONa (0.28 mL, 0.28 mmol, 1 M in EtOH). The mixture was protected with a  $\text{CaCl}_2$  drying tube and stirred at this temperature until complete consumption of the starting material (TLC, 2 h). DCM (10 mL) was then added, followed by a saturated aqueous solution of  $\text{NaHCO}_3$  (10 mL) and the mixture extracted. The aqueous phase was then extracted with a further 10 mL of DCM. The combined organic phases were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and evaporated under vacuum to yield 4-Chloro-6-ethoxy-2-(methylthio)pyrimidine **5** (46.6 mg, 89%) as colourless needles, m.p. 59–60 °C (from *n*-pentane, –60 °C);  $R_f$  0.16 (*n*-hexane/DCM, 90:10); (found: C, 41.13; H, 4.36; N, 13.60.  $\text{C}_7\text{H}_9\text{ClN}_2\text{OS}$  requires C, 41.08; H, 4.43; N, 13.69%);  $\lambda_{\text{max}}$  (DCM)/nm 276 inf (log  $\epsilon$  3.78), 255 (4.06);  $\nu_{\text{max}}/\text{cm}^{-1}$  3007w (aryl C-H), 2982w, 2934w, 2888w and 2849w (alkyl C-H), 1562s, 1557m, 1541s, 1537s, 1429m, 1420w, 1379m, 1352m, 1333m, 1323m, 1317m, 1273s, 1221w, 1038s, 989w, 833w, 870m, 814s;  $\delta_{\text{H}}$  (500 MHz;  $\text{CDCl}_3$ ) 6.37 (1H, s, Ar H), 4.41 (2H, q,  $J$  7.1,  $\text{OCH}_2$ ), 2.52 (3H, s,  $\text{SCH}_3$ ), 1.37 (3H, t,  $J$  7.1,  $\text{CH}_2\text{CH}_3$ );  $\delta_{\text{C}}$  (125 MHz;  $\text{CDCl}_3$ ) 172.7 (s), 169.4 (s), 160.2 (s), 102.4 (d), 63.3 (t), 14.2 (q), 14.1 (q);  $m/z$  (MALDI-TOF) 206 ( $\text{M}^+ + 2$ , 53%), 204 ( $\text{M}^+$ , 100), 176 (52), 160 (59).

**Supplementary Materials:** The following are available online at [www.mdpi.com/1422-8599/2017/1/M923](http://www.mdpi.com/1422-8599/2017/1/M923).

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**Author Contributions:** P.A. Koutentis conceived the experiments; A.S. Kalogirou designed and performed the experiments, analyzed the data and wrote the paper.

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

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