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Synthesis of 2-Cyanopyrimidines

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Abstract: 4,6-Dichloro-2-(methylthio)pyrimidine (**7**) was converted to 4-chloro-6-methoxy-2-(methylthio)pyrimidine (**15**) and 4,6-dimethoxy-2-(methylthio)pyrimidine (**14**). Chlorination of the latter with *N*-chlorosuccinimide (NCS) affords 5-chloro-4,6-dimethoxy-2-(methylthio)pyrimidine (**16**) in 56% yield. Both methylthiopyrimidines **15** and **14** were converted in two steps to 4-chloro-6-methoxypyrimidine-2-carbonitrile (**13**) and 4,6-dimethoxypyrimidine-2-carbonitrile (**12**), respectively, after oxidation to sulfones and displacement of the sulfinate group with KCN. 4,6-Dimethoxypyrimidine-2-carbonitrile (**12**) was chlorinated with NCS to give 5-chloro-4,6-dimethoxypyrimidine-2-carbonitrile (**10**) in 53% yield. All new compounds were fully characterized.

Keywords: heterocycle; pyrimidine; nucleophilic displacement; chlorination

1. Introduction

Pyrimidines are important aromatic N-heterocycles that are found in nature, for example, as components of pyrimidine nucleotides and vitamin B1 (thiamine). Not surprisingly, the chemistry of pyrimidines has been investigated for over a century and numerous reviews have appeared [1]. Pyrimidines are also present in many drugs such as the CNS depressant phenobarbital, the anti-HIV agent zidovudine and the hyperthyroidism drug propylthiouracil (Figure 1). Additional pharmaceutical applications include uses as diuretics [2], anti-inflammatory [3], anti-malarial [4], and anti-tumor [5] agents.

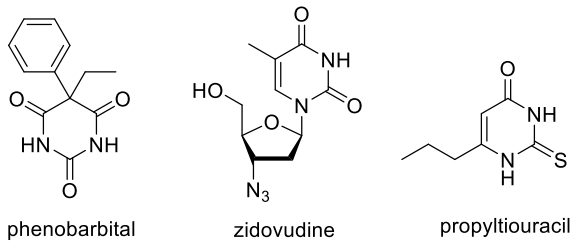
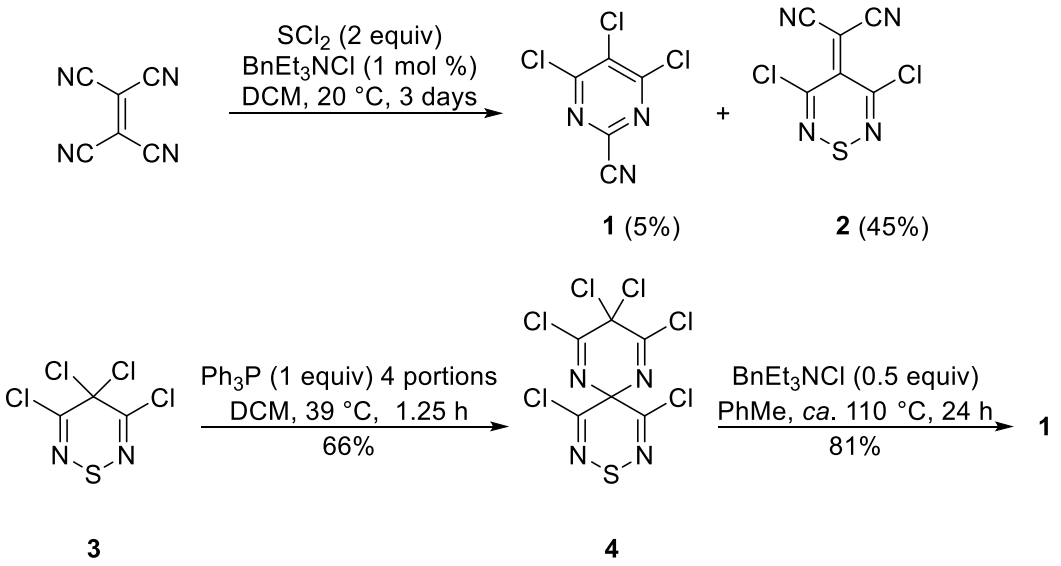


Figure 1. Pyrimidine containing drugs.

Our interest in pyrimidines began with 4,5,6-trichloropyrimidine-2-carbonitrile (**1**), which was isolated as an unexpected minor product (1–5%) 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**) [6] (Scheme 1). To obtain access to larger quantities of trichloropyrimidine **1**, so that its chemistry could be investigated, we pursued various independent syntheses.

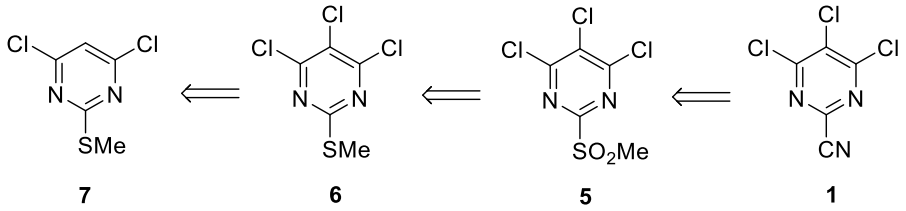


Scheme 1. Preparation of trichloropyrimidine **1** from TCNE and from tetrachlorothiadiazine **3** [6,7].

To date, our most efficient synthesis of pyrimidine **1** starts from the highly reactive tetrachlorothiadiazine **3** via perchloro-9-thia-1,5,8,10-tetraazaspiro[5.5]undeca-1,4,7,10-tetraene (**4**) in a 53% overall yield [7] (Scheme 1).

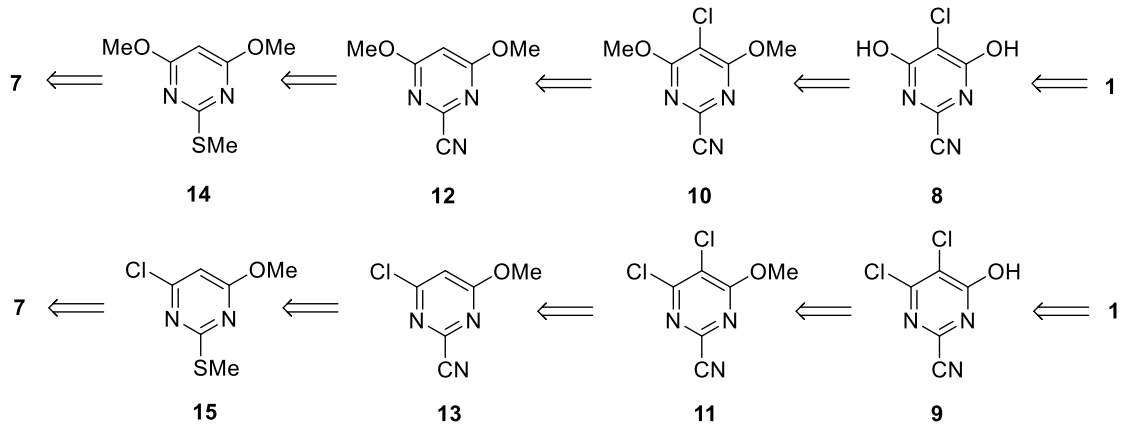
Below we report an alternative effort to prepare pyrimidine **1** that failed but did lead to the preparation of several new poly-substituted pyrimidines.

A retrosynthetic analysis of trichloropyrimidine **1** revealed that the cyano-group could be introduced by a nucleophilic displacement of a suitable leaving group in the C2 position by cyanide. Such a group could be sulfinate **5** that can be prepared by oxidation of thioether **6**. The latter could be formed by C5 chlorination of the readily available starting pyrimidine **7** (Scheme 2).



Scheme 2. Retrosynthetic analysis of trichloropyrimidine **1**.

In two alternative retrosynthetic strategies, pyrimidine **1** could be formed by 4,6-dihydroxypyrimidine **8** or 4-hydroxypyrimidine **9** (Scheme 3). These compounds could be formed by deprotection of the respective ethers **10** and **11**. The presence of alkoxy groups in the C5 and C6 positions would enable the easier chlorination of the C5 in precursors **12** and **13** due to the electron-donating character of these groups. The cyano groups could be introduced in a similar manner to that described above from thioethers **14** and **15**, which could be formed from chloride displacement of dichloropyrimidine **7**.

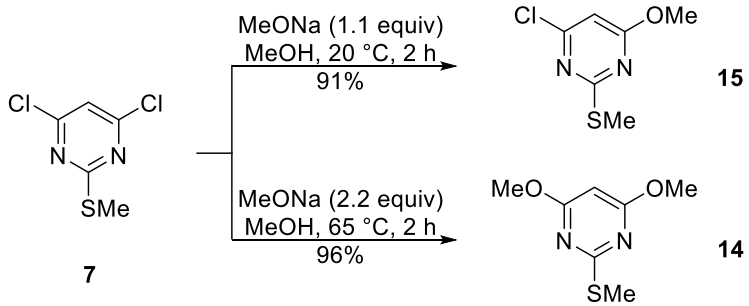


Scheme 3. Alternative retrosynthetic analysis via methoxypyrimidines **14** and **15**.

2. Results and Discussion

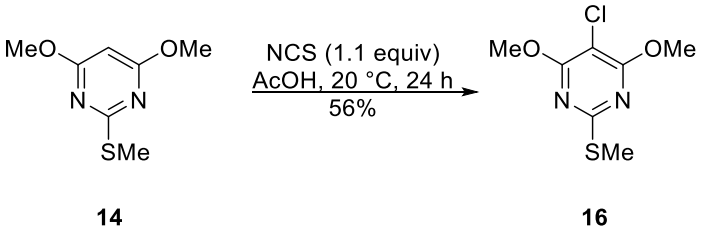
As described above, our independent synthesis began from the known 4,6-dichloro-2-(methylthio) pyrimidine (**7**) that was prepared in two steps and 92% overall yield from thiobarbituric acid [8]. This starting material was selected because of the availability of the starting thiobarbituric acid and the high yield of its transformation to dichloropyrimidine **7**. The latter has a versatile thioether group at C2 that can be displaced by cyanide and chlorides at the C4,6 positions. Early efforts to chlorinate the C5 position of dichloropyrimidine **7** with either NCS in AcOH, at ca. 117 °C, refluxing $PCl_5/POCl_3$ or neat PCl_5 in a sealed tube at ca. 130 °C failed, giving only recovered starting material. Tentatively, this was attributed to the electron-deficient nature of the ring in the presence of the C4/6 electronegative chlorine atoms.

As such, we 'activated' the pyrimidine C5 position towards electrophilic chlorination by displacing one or both chlorides by the strong electron-releasing alkoxides. The substitution reaction is known [9,10], but by slightly modifying the reaction procedure to involve a more concentrated reaction mixture we reduced the literature reaction time from 18 h to 2 h and obtained a high yield of methoxypyrimidine **15** (Scheme 4). Similarly, for the preparation of dimethoxy-pyrimidine **14**, elevating the reaction temperature to ca. 65 °C from 20 °C also led to shorter reaction time (2 h vs. 18 h) and a high yield of **14** (Scheme 4).



Scheme 4. Preparation of methoxypyrimidines **14** and **15**.

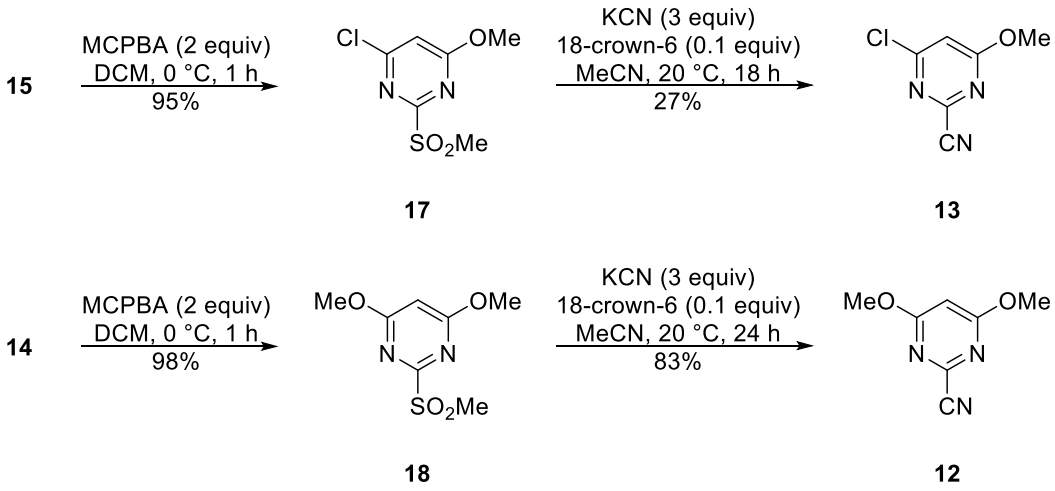
Attempted C5 chlorination of the methoxypyrimidine **15** using either NCS or PCl_5 as chlorinating agents failed to give a complex mixture of products, but fortunately, dimethoxy-pyrimidine **14** reacted smoothly with NCS in AcOH to give the new 5-chloropyrimidine **16** in a moderate 56% yield (Scheme 5, see the supplementary materials for NMR spectra).



14 **16**

Scheme 5. Preparation of 5-chloro-4,6-dimethoxy-2-(methylthio)pyrimidine (**16**).

Encouraged by this result, we then proceeded to functionalize the C2 ring position. Oxidation of the thioether moiety in both pyrimidines **15** and **14** was performed by MCPBA (2 equiv), in DCM, at ca. 0 °C, to give sulfones **17** and **18**, respectively in excellent yields (Scheme 6). For comparison, the literature procedure for the preparation of methoxypyrimidine **17** used the oxidant oxone and obtained 78% yield of product **17** [11], whereas for dimethoxypyrimidine **18**, MCPBA was used at a temperature of ca. 30 °C giving a 67% yield of product **18** [12]. Subsequent displacement of the sulfinate with KCN in MeCN yielded the new 2-cyanopyrimidines **13** and **12** in 27 and 83% yields, respectively (Scheme 6, see the supplementary materials for NMR spectra).



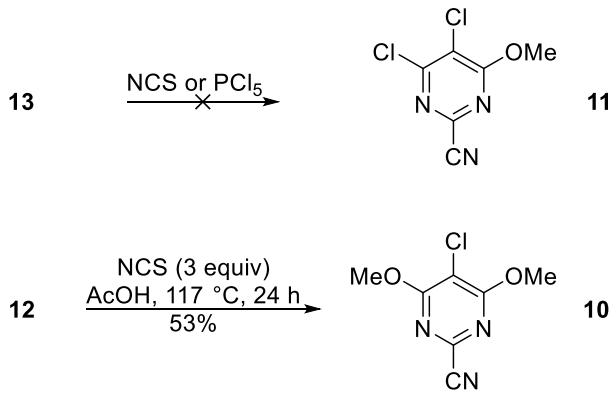
17 **13**

18 **12**

Scheme 6. Preparation of 4-chloro-6-methoxypyrimidine-2-carbonitrile (**13**) and 4,6-dimethoxypyrimidine-2-carbonitrile (**12**).

Unfortunately, attempts to chlorinate cyanopyrimidine **13** failed but the chlorination of dimethoxypyrimidine **12** was successful and gave the new 5-chloropyrimidine **10** a potential precursor to trichloropyrimidine **1** (Scheme 7, see SI for NMR spectra). Disappointingly, the subsequent step of demethylation required to reach the target compound failed. In more detail, the reaction of chloropyrimidine **10** with BBr_3 (5 equiv) in DCM at ca. 20 °C gave a complex mixture of products, while the use of TMSI in MeCN at ca. 82 °C led to degradation of the starting material to give tentatively acyclic side-products.

Although this study has not yielded the desired trichloropyrimidine **1**, it has given access to four new polyfunctionalized pyrimidines that could be of use for the further investigation of the chemistry and properties of pyrimidines.



Scheme 7. Preparation of 5-chloro-4,6-dimethoxypyrimidine-2-carbonitrile (**10**).

3. Materials and Methods

The reaction mixture was monitored by TLC using commercial glass-backed thin-layer chromatography (TLC) plates (Merck Kieselgel 60 F_{254}). The plates were observed under UV light at 254 and 365 nm. Dichloromethane (DCM) and acetonitrile (MeCN) were distilled over CaH_2 before use. The 1 M and 3 M solutions of sodium methoxide (MeONa) in methanol (MeOH) were freshly prepared by the reaction of sodium metal with MeOH. The melting point was determined using a PolyTherm-A, Wagner & Munz, Kofler Hotstage 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), 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}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 spectrometer [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. Attached proton test (APT) NMR studies were used for the assignment of the ^{13}C peaks as CH_3, CH_2, CH, 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. 4,6-dichloro-2-(methylthio)pyrimidine (**7**) was prepared according to the literature procedure [8].

4-Chloro-6-methoxy-2-(methylthio)pyrimidine (**15**)

To a stirred mixture of 4,6-dichloro-2-(methylthio)pyrimidine (**7**) (585 mg, 3.00 mmol) in MeOH (15 mL) at ca. 20 °C was added in one portion a solution of MeONa 1 M in MeOH (3.30 mL, 3.30 mmol). The mixture was protected with a $CaCl_2$ drying tube and stirred at this temperature until complete consumption of the starting material (TLC, 2 h). Et_2O (20 mL) and $NaHCO_3$ sat. (10 mL) were then added, the two layers separated, and the aqueous layer extracted with a further 10 mL of Et_2O. The combined organic phases were then dried over Na_2SO_4, filtered, and evaporated in vacuo to give the title compound **15** (518 mg, 91%) as a colorless oil; R_f 0.31 (*n*-hexane/DCM, 70:30), δ_H(500 MHz; $CDCl_3$) 6.41 (1H, s, C*H*), 3.96 (3H, s, OCH_3), 2.55 (3H, s, SCH_3), identical to the one reported [11].

4,6-Dimethoxy-2-(methylthio)pyrimidine (**14**)

To a stirred mixture of 4,6-dichloro-2-(methylthio)pyrimidine (**7**) (780 mg, 4.00 mmol) in MeOH (15 mL) at ca. 20 °C was added in one portion a solution of MeONa 3 M in MeOH (2.93 mL, 8.80 mmol). The mixture was protected with a $CaCl_2$ drying tube and heated to ca. 65 °C until complete consumption of the starting material (TLC, 2 h). DCM (10 mL) was then added, the mixture adsorbed onto silica, and chromatography (*n*-hexane/DCM 70:30) gave the title compound **14** (717 mg, 96%) as yellow plates,

mp 53–54 °C (from *n*-hexane/−40 °C, lit. 53–54 °C [13]); R_f 0.18 (*n*-hexane/DCM, 70:30); δ_H(500 MHz; $CDCl_3$) 5.71 (1H, s, C*H*), 3.92 (6H, s, OCH_3), 2.54 (6H, s, SCH_3), identical to the one reported [14].

5-Chloro-4,6-dimethoxy-2-(methylthio)pyrimidine (**16**)

To a stirred mixture of 4,6-dimethoxy-2-(methylthio)pyrimidine (**14**) (93.1 mg, 0.500 mmol) in AcOH (1 mL) at ca. 20 °C was added in one portion *N*-chlorosuccinimide (73.4 mg, 0.55 mmol). The mixture was protected with a $CaCl_2$ drying tube and stirred at this temperature until complete consumption of the starting material (TLC, 24 h). DCM (10 mL) was then added, the mixture adsorbed onto silica, and chromatography (*n*-hexane/DCM 70:30) gave the *title compound* **16** (61.6 mg, 56%) as colorless needles, mp 128–129 °C (from *n*-hexane/−40 °C); R_f 0.46 (*n*-hexane/DCM, 70:30); (found: C, 37.94; H, 4.12; N, 12.53. $C_7H_9ClN_2O_2S$ requires C, 38.10; H, 4.11; N, 12.69%); λ_{max}(DCM)/nm 258 inf (log ε 4.11), 267 (4.16); υ_{max}/cm^{-1} 2963w and 2930w (C-H), 1560m, 1555s, 1493m, 1458w, 1389m, 1358s, 1335w, 1319m, 1290m, 1269m, 1186m, 1182m, 1126s, 1070m, 926m, 770m; δ_H(500 MHz; $CDCl_3$) 4.03 (6H, s, OCH_3), 2.53 (3H, s, SCH_3); δ_C(125 MHz; $CDCl_3$) 167.5 (*C*q), 165.1 (*C*q), 95.2 (*C*q), 55.0 (*C*H_3), 14.4 (*C*H_3); *m/z* (MALDI-TOF) 221 (M^+-H + 2, 33%), 220 (M^+, 75), 219 (M^+ − H, 100), 206 (12).

4-Chloro-6-methoxy-2-(methylsulfonyl)pyrimidine (**17**)

To a stirred mixture of 4-chloro-6-methoxy-2-(methylthio)pyrimidine (**15**) (572 mg, 3.00 mmol) in DCM (10 mL) cooled in an ice-bath to ca. 0 °C was added in one portion m-chloroperbenzoic acid of 77% purity (1.344 g, 6.000 mmol). The mixture was protected with a $CaCl_2$ drying tube and stirred at this temperature until complete consumption of the starting material (TLC, 1 h). Et_2O (20 mL) and Na_2CO_3 sat. (10 mL) were then added, the two layers separated, and the aqueous layer extracted with a further 10 mL of Et_2O. The combined organic phases were then dried over Na_2SO_4, filtered, and evaporated in vacuo to give the title compound **17** (634 mg, 95%) as colorless needles, mp 85–86 °C (from *n*-hexane/−40 °C, lit. 87–88 °C [11]); R_f 0.22 (*n*-hexane/DCM, 20:80); δ_H(500 MHz; $CDCl_3$) 6.92 (1H, s, C*H*), 4.10 (3H, s, OCH_3), 3.33 (3H, s, $SO_2C$$H_3$); identical to the one reported [11].

4,6-Dimethoxy-2-(methylsulfonyl)pyrimidine (**18**)

To a stirred mixture of 4,6-dimethoxy-2-(methylthio)pyrimidine (**14**) (186 mg, 1.00 mmol) in DCM (5 mL) cooled in an ice-bath to ca. 0 °C was added in one portion m-chloroperbenzoic acid of 77% purity (448 g, 3.000 mmol). The mixture was protected with a $CaCl_2$ drying tube and stirred at this temperature until complete consumption of the starting material (TLC, 1 h). Et_2O (20 mL) and Na_2CO_3 sat. (10 mL) were then added, the two layers separated, and the aqueous layer extracted with a further 10 mL of Et_2O. The combined organic phases were then dried over Na_2SO_4, filtered and evaporated in vacuo to give the title compound **18** (124 mg, 98%) as colorless plates, mp 125–126 °C (from EtOH, lit. 126–128 °C [13]); R_f 0.74 (DCM); δ_H(500 MHz; $CDCl_3$) 6.18 (1H, s, C*H*), 4.03 (6H, s, OCH_3), 3.32 (3H, s, $SO_2C$$H_3$); identical to the one reported [13].

4-Chloro-6-methoxypyrimidine-2-carbonitrile (**13**)

To a stirred mixture of 4-chloro-6-methoxy-2-(methylsulfonyl)pyrimidine (**17**) (223 mg, 1.00 mmol) in MeCN (5 mL) at ca. 20 °C was added in one portion 18-crown-6 (26 mg, 0.10 mmol) followed by KCN (195 mg, 3.00 mmol). The mixture was protected with a $CaCl_2$ drying tube and stirred at this temperature until complete consumption of the starting material (TLC, 18 h). Et_2O (20 mL) and H_2O (10 mL) were then added, the two layers separated, and the aqueous layer extracted with a further 10 mL of Et_2O. The combined organic phases were then dried over Na_2SO_4, filtered, and the mixture adsorbed onto silica and chromatography (*n*-hexane/DCM 20:80) gave the *title compound* **13** (48 mg, 27%) as colorless needles, mp 69–70 °C (from *n*-hexane/−40 °C); R_f 0.67 (*n*-hexane/DCM 20:80); (found: C, 42.65; H, 2.40; N, 24.63. $C_6H_4ClN_3O$ requires C, 42.50; H, 2.38; N, 24.78%); λ_{max}(DCM)/nm 241 (log ε 3.59), 262 (3.41); υ_{max}/cm^{-1} 3084w (C-H), 1562s, 1533m, 1518m, 1470m, 1396m, 1360s, 1341m, 1244w, 1190m, 1130s, 1038s, 978s, 945m, 880m, 862m, 770w; δ_H(500 MHz; $CDCl_3$) 6.95 (1H, s, C*H*), 4.06 (3H, s,

OCH_3); δ_C(125 MHz; $CDCl_3$) 170.8 (*C*q), 161.3 (*C*q), 143.5 (*C*q), 114.6 (*C*q), 111.1 (*C*H), 55.7 (CH_3); *m/z* (MALDI-TOF) 170 (M^+-H + 2, 20%), 169 (M^+, 40), 168 (M^+ − H, 100), 132 (36).

4,6-Dimethoxypyrimidine-2-carbonitrile (**12**)

To a stirred mixture of 4,6-dimethoxy-2-(methylsulfonyl)pyrimidine (**18**) (218 mg, 1.00 mmol) in MeCN (5 mL) at ca. 20 °C was added in one portion 18-crown-6 (26 mg, 0.10 mmol) followed by KCN (195 mg, 3.00 mmol). The mixture was protected with a $CaCl_2$ drying tube and stirred at this temperature until complete consumption of the starting material (TLC, 24 h). Et_2O (20 mL) and H_2O (10 mL) were then added, the two layers separated, and the aqueous layer extracted with a further 10 mL of Et_2O. The combined organic phases were then dried over Na_2SO_4, filtered, and the mixture adsorbed onto silica and chromatography (*n*-hexane/DCM 60:40) gave the *title compound* **12** (138 mg, 83%) as colorless needles, mp 113–114 °C (from *n*-hexane/−40 °C); R_f 0.31 (*n*-hexane/DCM, 60:40); (found: C, 50.77; H, 4.35; N, 25.26. $C_7H_7N_3O_2$ requires C, 50.91; H, 4.27; N, 25.44%); λ_{max}(DCM)/nm 259 (log ε 3.69); υ_{max}/cm^{-1} 3094w, 3003w, 2926w and 2849w (C-H), 1591s, 1566m, 1530m, 1468m, 1387m, 1352m, 1202s, 1173m, 1059s, 984m, 964m, 864m, 772m; δ_H(500 MHz; $CDCl_3$) 6.20 (1H, s, C*H*), 3.98 (6H, s, OCH_3); δ_C(125 MHz; $CDCl_3$) 171.2 (*C*q), 142.6 (*C*q), 115.5 (*C*q), 94.1 (*C*H), 54.9 (CH_3); *m/z* (MALDI-TOF) 166 (MH^+, 100%), 165 (M^+, 25), 164 (M^+ − H, 51), 162 (55).

5-Chloro-4,6-dimethoxypyrimidine-2-carbonitrile (**10**)

To a stirred mixture of 4,6-dimethoxypyrimidine-2-carbonitrile (**12**) (50.0 mg, 0.303 mmol) in AcOH (2 mL) at ca. 20 °C was added in one portion *N*-chlorosuccinimide (121 mg, 0.908 mmol). The mixture was protected with a $CaCl_2$ drying tube and stirred at ca. 117 °C until complete consumption of the starting material (TLC, 24 h). Et_2O (20 mL) and H_2O (10 mL) were then added, the two layers separated, and the aqueous layer extracted with a further 10 mL of Et_2O. The combined organic phases were then dried over Na_2SO_4, filtered, and the mixture adsorbed onto silica and chromatography (*n*-hexane/DCM 60:40) gave the *title compound* **10** (31.8 mg, 53%) as colorless needles, mp 145–147 °C (from *n*-hexane/−40 °C); R_f 0.48 (*n*-hexane/DCM, 60:40); (found: C, 41.96; H, 2.89; N, 20.96. $C_7H_6ClN_3O_2$ requires C, 42.12; H, 3.03; N, 21.05%); λ_{max}(DCM)/nm 278 (log ε 3.66), 290 (3.45); υ_{max}/cm^{-1} 3003w, 2980w and 2918w (C-H), 1572s, 1566s, 1545w, 1524w, 1493w, 1462m, 1443w, 1385m, 1373s, 1362m, 1294m, 1182m, 1126s, 1088w, 1076w, 1013w, 968m, 914m, 781s, 741w, 712m; δ_H(500 MHz; $CDCl_3$) 4.09 (6H, s, OCH_3); δ_C(125 MHz; $CDCl_3$) 166.0 (*C*q), 138.5 (*C*q), 115.1 (*C*q), 104.4 (*C*q), 56.1 (CH_3); *m/z* (MALDI-TOF) 202 (MH^+ + 2, 34%), 201 (M^+ + 2,29), 200 (M^+,38), 199 (M^+, 100), 192 (41), 156 (10).

Supplementary Materials: The following are available online, ^1H and ^{13}C NMR spectra.

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.

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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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