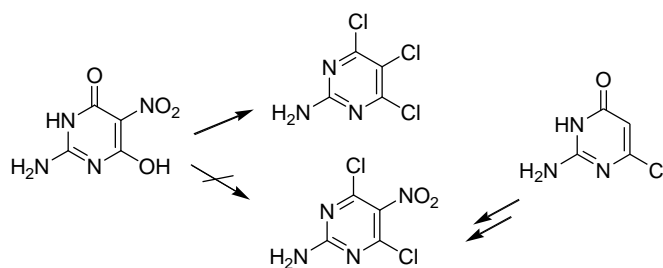


## Graphical Abstract

### Syntheses of 2-amino-4,6-dichloro-5-nitropyrimidine and 2-amino-4,5,6-trichloropyrimidine: an unusual aromatic substitution

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R. Stanley McElhinney,<sup>†</sup> T. Brian H. McMurry,\*  
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LETTERS

## Syntheses of 2-amino-4,6-dichloro-5-nitropyrimidine and 2-amino-4,5,6-trichloropyrimidine: an unusual aromatic substitution

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**Abstract**—2-Amino-4,6-dichloro-5-nitropyrimidine is an intermediate required for the preparation of nitropyrimidines as inactivators of the DNA repairing protein MGMT. When attempting its synthesis 2-amino-4,5,6-trichloropyrimidine is obtained instead, via unusual aromatic substitution of the nitro group in the 2-amino-4-hydroxy-5-nitropyrimidin-6-one by chloride. The synthesis, the reactivity of 4,5,6-trichloropyrimidine and the efficient preparation of 2-amino-4,6-dichloro-5-nitropyrimidine are presented © 2013 Elsevier Science. All rights reserved

Based on our interest in the synthesis of 2-amino-4,6-disubstituted pyrimidines for the preparation of new inactivators of the DNA repairing protein methylguanine methyl transferase (MGMT),<sup>1-4</sup> 2-amino-4,6-dichloro-5-nitropyrimidine **1** (Scheme 1) appeared to be a potentially valuable intermediate. Compound **1** had previously been mentioned in a patent,<sup>5</sup> which gave no preparative details but records that it was difficult to make. Additionally, derivative **1** had been reported as a minor impurity in some reactions, again without providing any experimental details.<sup>6</sup>

The preparation of nitropyrimidines as analogues of *O*<sup>6</sup>-benzylguanine was reported previously by displacement of a chlorine from 2-amino-4-chloro-5-nitropyrimidine by an alkoxide involving very harsh experimental conditions.<sup>7,8</sup> Therefore, an alternative method for the preparation of these nitropyrimidine adducts needs to be devised. Considering that compound **1** is such a versatile molecule, we have explored several synthetic strategies, and in this paper, we report our efforts to prepare this compound, and on the chemistry of some of the other pyrimidines synthesised.

In our hands, and not surprisingly, direct nitration of the known 2-amino-4,6-dichloropyrimidine was unsuccessful.<sup>9</sup> The 5-position is hindered and also deactivated by the two neighbouring chlorine substituents. Thus, we decided to introduce the nitro group initially into 2-amino-4-

hydroxypyrimidin-6-one (**2**). This nitration has been well documented and under carefully controlled conditions (potassium nitrate in sulfuric acid),<sup>10</sup> the required 5-nitro compound **3** can be obtained in high yield (Scheme 1).

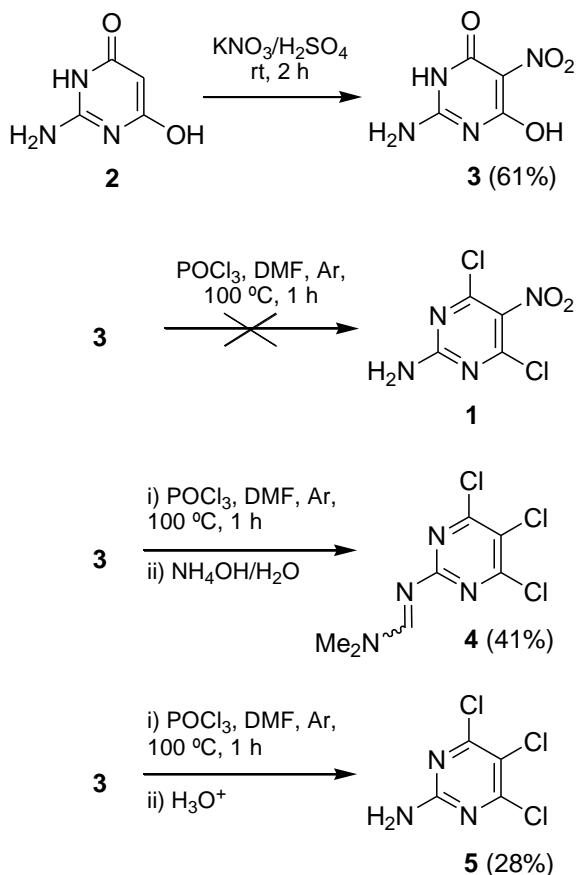
The next step involved replacement of the two oxygen substituents by chloride. Direct reaction with phosphorus oxychloride gave a mixture of products, and thus, we turned our attention to the Vilsmeier-Haack reagent, chloromethylenedimethylammonium chloride, which is prepared from phosphorus oxychloride in the presence of DMF. In addition to its role as a formylating reagent,<sup>11,12</sup> it has been used to replace hydroxy groups with chloride.<sup>13</sup> Reaction of compound **3** with this reagent, and allowing the reaction mixture to stand after pouring it onto aqueous ammonia, gave a product which was not the expected dichloronitro compound **1** but rather the trichloro compound **4** in which the 2-amino group is protected with a methylenedimethylamino group.<sup>12</sup> When the reaction mixture was poured into water and allowed to stand, the 2-protecting group was removed and 2-amino-4,5,6-trichloropyrimidine (**5**) was obtained. In addition, when intermediate **4** was stirred in acid, compound **5** was formed in a reasonable yield.

Subsequent experimentation suggested that, for the optimal conditions for nitro group displacement by chloride, the best ratio of **3** to the reagents, POCl<sub>3</sub>/DMF, was 1:8:4.4, rather than that suggested earlier for a similar reaction with other pyrimidines.<sup>14</sup> These experiments

<sup>†</sup> In memoriam

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confirmed that replacement of the nitro group occurred during the reaction with the Vilsmeier-Haack reagent rather than in the subsequent hydrolysis step. Even though this type of aromatic nucleophilic substitution had been reported previously in the diazotization of several benzene derivatives,<sup>15</sup> to our knowledge, it has never been described for the halogenation of pyrimidines. Based on the review of Bunnett *et al.*,<sup>15</sup> it seems feasible that, initially the 4,6-(keto)hydroxy groups in compound **3** are substituted by chlorine, as expected, and then these two chlorine atoms could facilitate subsequent substitution of the 5-nitro group.

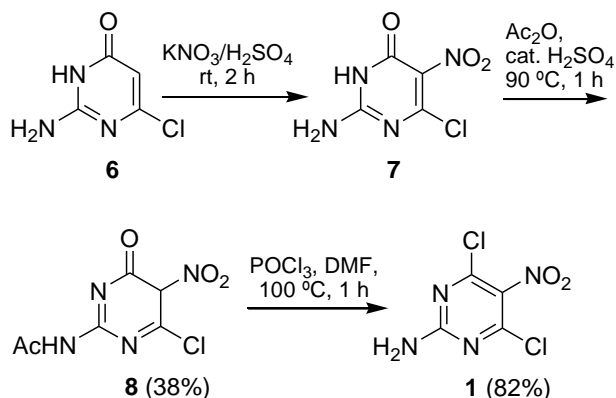


Scheme 1. 2-Amino-4,5,6-trichloropyrimidine syntheses

Having failed to prepare **1** from compound **3**, we turned our attention back to the work of Temple *et al.*<sup>6</sup> These authors reported compound **1** as a minor impurity without giving experimental details. Therefore, we were able to optimise the conditions for the nitration of **6** to give **7**, though the product always contained ca. 10% of the starting material. It was impossible to separate the two compounds as they were both insoluble in suitable organic solvents. However, acetylation of the mixture gave the

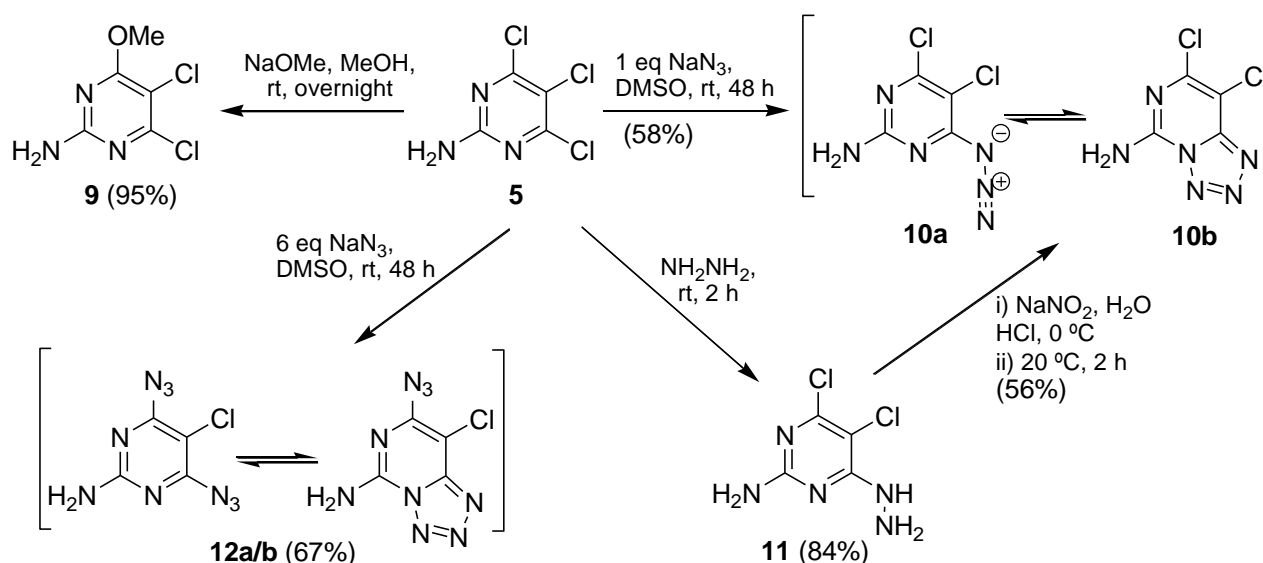
corresponding acetylamino compound **8** and the 2-acetyl derivative of **7**, from which **8** could be isolated in 38% overall yield on crystallisation. The Vilsmeier-Haack reagent was used to convert **8** into the required dichloronitropyrimidine **1** in very good yield, and even though compound **5** was still present, they could be separated easily by flash chromatography (Scheme 2).

Considering these results a question arises: why the nitro group is displaced in the Vilsmeier-Haack reaction in compound **3** but not in **8**. In heteroaromatic systems, the substitution of the nitro group by chlorine is an unusual chemical reaction and, therefore, very little information regarding this particular type of substitution, and its mechanism could be obtained from the literature; however, two alternative explanations can be given. The displacement of the nitro group in compound **3** will be promoted by an electron withdrawing group at the 2-position. This can arise from either protonation of the 2-amino group, or, if the 2-aminomethylenedimethylamino group had been introduced first, by reaction of this with a proton or other electrophilic species derived from the reagent. A 2-acetylamino group, as that in **8**, would not be so basic, and it would not protonate or promote the replacement reaction at the 4-position.



Scheme 2. Synthesis of 2-amino-4,6-dichloro-5-nitropyrimidine

Having obtained trichloro compound **5**, and considering the versatility of this derivative we studied its reactivity and report some of the results obtained. Reaction of **5** with sodium methoxide in methanol at room temperature gave 2-amino-4,5-dichloro-6-methoxypyrimidine (**9**) (Scheme 3), the structure of which was confirmed by X-ray analysis (Figure 1). This structure corroborated the unusual displacement of the nitro group by chlorine in compound **5**. After introduction of the methoxy group, we were unable to replace the second chlorine in **9**. Neither 2-amino-5-chloro-4,6-dimethoxypyrimidine, nor 4-azido-5-chloro-6-methoxy analogues were obtained under quite forcing conditions.

Scheme 3. Reactivity of 2-amino-4,5-dichloropyrimidine **5**

Pfleiderer<sup>9</sup> managed to prepare 4-alkylamino-2-amino-6-alkoxy-pyrimidines in two steps from 2-amino-4,6-dichloropyrimidine though the introduction of the alkoxy group in the second stage required more vigorous conditions than those we tried. Interestingly, we were able to react **5** with one equivalent of azide (Scheme 3) to give a product, the IR spectrum of which (Nujol) demonstrated a peak at 2142 cm<sup>-1</sup> which suggests that it exists as the azido compound **10a** in the solid state.

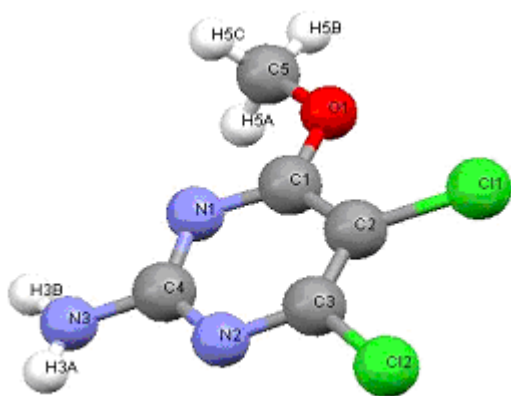


Figure 1. Crystal structure of 2-amino-4,5-dichloro-6-methoxypyrimidine (**9**), CCDC code: pwe1m.

In solution (*d*<sub>6</sub>-DMSO) the <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra suggest that the bicyclic tetrazolo[1,5-*c*]pyrimidine **10b** is the main component in a 8:1 mixture with **10a**. The latter spectrum, in particular, is quite different from the other substituted pyrimidines synthesised, and can be assigned by analogy.<sup>16,17</sup>

The mono azido compound **10a/b** was also prepared by the action of nitrous acid on the dichloro hydrazide **11**

prepared by us. We were unable to introduce a methoxy group when **10** was reacted with methoxide in methanol.

Excess azide converts **5** into the '5-chloro-4,6-diazido' compound **12a/b**. In the solid state there are peaks at 2162 and 2127 cm<sup>-1</sup> in the IR spectrum showing the presence of azido groups. The <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra in *d*<sub>6</sub>-DMSO again suggest that the main component of the mixture is the bicyclic tetrazolo[1,5-*c*]pyrimidine **12b** (ratio 10:1) in solution. This equilibrium behaviour shown by **10a/b** and **12a/b** has been widely explored by Montgomery.<sup>18-20</sup>

When attempting the synthesis of 2-amino-4,6-dichloro-5-nitropyrimidine, 2-amino-4,5,6-trichloropyrimidine is obtained instead via unusual aromatic substitution of the nitro group in 2-amino-4-hydroxy-5-nitropyrimidin-6-one by chloride. The reactivity of this 4,5,6-trichloropyrimidine has been studied and the efficient preparation of 2-amino-4,6-dichloro-5-nitropyrimidine achieved.

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### Supplementary Material

Supplementary material is available. Synthesis and spectroscopic data of all compounds prepared, combustion analyses of target compounds and X-ray data of compound **9** are included.