Tetrahedron Letters 50 (2009) 6022–6024

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

Sergio Lopez, Thomas McCabe, R. Stanley McElhinney †, T. Brian H. McMurry *, Isabel Rozas *

School of Chemistry, University of Dublin, Trinity College, Dublin 2, Ireland

ARTICLE INFO

Article history:
Received 10 July 2009
Revised 29 July 2009
Accepted 14 August 2009
Available online 20 August 2009

ABSTRACT

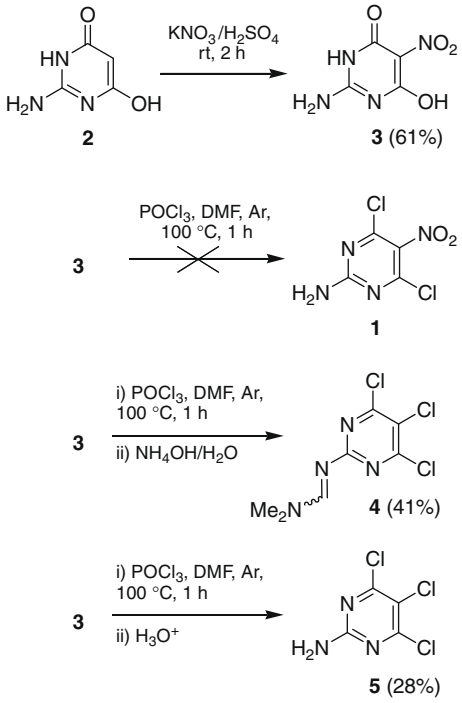
2-Amino-4,6-dichloro-5-nitropyrimidine is an intermediate required for the preparation of nitropyrimidines as inactivators of the DNA repairing protein MGMT. When attempting its synthesis, 2-amino-4,5,6-trichloropyrimidine is obtained instead, via unusual aromatic substitution of the nitro group in 2-amino-4-hydroxy-5-nitropyrimidin-6-one 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.

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),[1–4] 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,[5] which gave no preparative details but reported 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.[6]

The preparation of nitropyrimidines as analogues of O^6-benzylguanine was reported previously by displacement of a chlorine from 2-amino-4-chloro-5-nitropyrimidine by an alkoxide involving very harsh experimental conditions.[7,8] Therefore, an alternative method for the preparation of these nitropyrimidine adducts needs to be devised. Considering the fact that compound **1** is such a versatile molecule, we have explored several synthetic strategies, and in this Letter, 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.[9] 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),[10] the required 5-nitro compound **3** was obtained in good yield (Scheme 1).

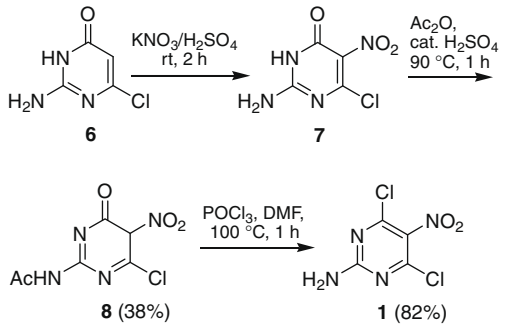
The next step involved replacement of the two oxygen substituents by chloride. Direct reaction with phosphorus oxychloride gave a mixture of products, and thus, we turned our attention to the Vilsmeier–Haack reagent, chloromethylenedimethylammonium chloride, which is prepared from phosphorus oxychloride in the presence of DMF. In addition to its role as a formylating reagent,[11,12] it has been used to replace hydroxy groups with chloride.[13] Reaction of compound **3** with this reagent, and allowing



Scheme 1. Synthesis of 2-amino-4,5,6-trichloropyrimidine.

* Corresponding authors. Tel.: +353 1 896 3731; fax: +353 1 671 2826 (I.R.).
E-mail addresses: tmcmurry@tcd.ie (T. B. H. McMurry), rozasi@tcd.ie (I. Rozas).
† In memoriam.

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.08.029



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

the reaction mixture to stand after pouring 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 was protected with a methylenedimethylamino group.[12] When the reaction mixture was poured into water and allowed to stand, this 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 moderate yield.

Subsequent experimentation suggested that, for the optimal conditions for nitro group displacement by chloride, the best ratio of **3** to the reagents, $POCl_3$/DMF, was 1:8:4.4, rather than that suggested earlier for a similar reaction with other pyrimidines.[14] These experiments confirmed that the 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 diazotisation of several benzene derivatives,[15] to our knowledge, it has never been described for the halogenation of pyrimidines. Based on the review of Bunnett and Zahler,[15] 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.

Having failed to prepare **1** from compound **3**, we turned our attention back to the work of Temple et al.[6] 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 **6**, 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).

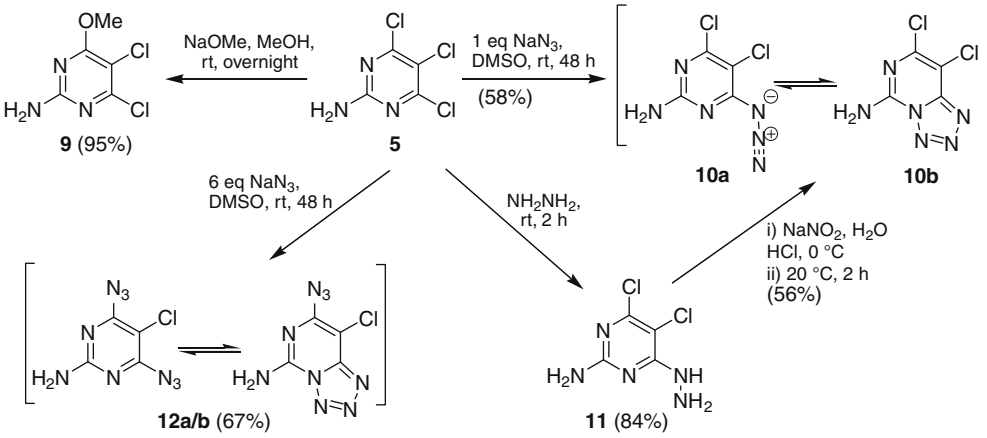
Considering these results, a question arises: why is the nitro group displaced in the Vilsmeier–Haack reaction in compound **3** but not in **8**. In heteroaromatic systems, the substitution of a nitro group by chlorine is an unusual reaction and, therefore, very little information regarding this particular 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 in **8**, would not be as basic, and it would not protonate or promote the replacement reaction at the 4-position.

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.

Pfleiderer[9] managed to prepare 4-alkylamino-2-amino-6-alkoxypyrimidines 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^{-1} which suggests that it exists as the azido compound **10a** in the solid state.

In solution (DMSO-d_6), the ^1H NMR and ^{13}C NMR spectra suggest that bicyclic tetrazolo[1,5-*c*]pyrimidine **10b** is the main component in an 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.[16,17]

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



Scheme 3. Reactivity of 2-amino-4,5,6-trichloropyrimidine **5**.

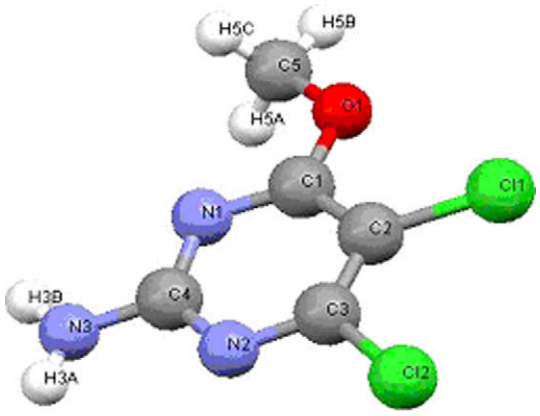


Figure 1. Crystal structure of 2-amino-4,5-dichloro-6-methoxypyrimidine (**9**), CCDC 735089.

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^{-1} in the IR spectrum showing the presence of azido groups. The ^{1}H NMR and ^{13}C NMR spectra in DMSO-d_6 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 and co-workers.[18–20]

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

Acknowledgements

The authors are grateful to the Irish Cancer Society for financial support. They are indebted to Dr. John O'Brien for the NMR studies.

Supplementary data

Supplementary data (synthesis and spectroscopic data of all compounds prepared, combustion analyses of target compounds and X-ray data of compound **9** are included) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.029.

References and notes

1. McElhinney, R. S.; McMurry, T. B. H.; Margison, G. P. *Mini Rev. Med. Chem.* **2003**, *3*, 123.
2. McElhinney, R. S.; Donnelly, D. J.; McCormick, J. E.; Kelly, J.; Watson, A. J.; Rafferty, J. A.; Elder, R. H.; Middleton, M. R.; Willington, M. A. *J. Med. Chem.* **1998**, *41*, 5265.
3. Ranson, M.; Middleton, M. R.; Bridgewater, J.; Lee, S. M.; Dawson, M.; Jowle, D.; Halbert, G.; Waller, S.; McGrath, H.; Gumbril, L.; McElhinney, R. S.; McMurry, T. B. H.; Margison, G. P. *Clin. Cancer Res.* **2006**, *12*, 1577.
4. McMurry, T. B. H. *DNA Repair* **2007**, *6*, 1161.
5. Norbeck, D. W.; Rosen, T. J.; Sham, H. L. US Patent, 1991, US4988703; *Chem. Abstr.* **1991**, *115*, 50218.
6. Temple, C., Jr.; Smith, B. H.; Montgomery, J. A. *J. Org. Chem.* **1975**, *40*, 3141.
7. Chae, M.; Swenn, K.; Kanugula, S.; Dolan, M. E.; Pegg, A. E.; Moschel, R. C. *J. Med. Chem.* **1995**, *38*, 359.
8. Terashima, I.; Kohda, K. *J. Med. Chem.* **1998**, *41*, 503.
9. Pfleiderer, W.; Lohrmann, R. *Chem. Ber.* **1961**, *94*, 2708.
10. Boyle, P. H.; Daly, K. M.; Leurquin, F.; Robinson, J. K.; Scully, D. T. *Tetrahedron Lett.* **2001**, *42*, 1793.
11. Hazebroucq, G. *Ann. Pharm.* **1966**, *24*, 793.
12. Bell, L.; McGuire, H. M.; Freeman, G. A. *J. Heterocycl. Chem.* **1983**, *20*, 41.
13. Hepburn, D. R.; Hudson, H. R. *Chem. Ind.* **1974**, 664.
14. Seela, F.; Steker, H. *Helv. Chim. Acta* **1986**, *69*, 1602.
15. Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273.
16. Denisov, A. Y.; Krivopalov, V. P.; Mamatyuk, V. I.; Mamaev, V. P. *Magn. Reson. Chem.* **1988**, *26*, 42.
17. Riand, J.; Chenon, M. T.; Lumbroso-Bader, N. *Tetrahedron Lett.* **1974**, 2123.
18. Temple, C., Jr.; McKee, R. L.; Montgomery, J. A. *J. Org. Chem.* **1962**, *27*, 1671.
19. Temple, C., Jr.; McKee, R. L.; Montgomery, J. A. *J. Org. Chem.* **1965**, *30*, 829.
20. Temple, C., Jr.; Coburn, W. C., Jr.; Thorpe, M. C.; Montgomery, J. A. *J. Org. Chem.* **1965**, *30*, 2395. and references cited therein.