*molbank*

MDPI

*Communication*

# Reactions of Polychlorinated Pyrimidines with DABCO

**Andreas S. Kalogirou [1,*] and Panayiotis A. Koutentis [2]**

[1] Department of Life Sciences, School of Sciences, European University Cyprus, 6 Diogenis Str., Engomi, P. O. Box 22006, 1516 Nicosia, Cyprus

[2] Department of Chemistry, University of Cyprus, P. O. Box 20537, 1678 Nicosia, Cyprus; koutenti@ucy.ac.cy

* Correspondence: A.Kalogirou@euc.ac.cy; Tel.: +357-22892804

Received: 27 September 2019; Accepted: 12 October 2019; Published: 14 October 2019


**Abstract:** The reaction of 2,4,5,6-tetrachloropyrimidine (**4**) and 4,5,6-trichloropyrimidine-2-carbonitrile (**1**) with DABCO (1 equiv.), in MeCN, at ca. 20 °C gives 2,4,5-trichloro-6-[4-(2-chloroethyl) piperazin-1-yl]pyrimidine (**5**) and 4,5-dichloro-6-[4-(2-chloroethyl)piperazin-1-yl]pyrimidine-2-carbonitrile (**6**) in 42% and 52% yields, respectively. The new compounds were fully characterized.

**Keywords:** heterocycle; piperazine; pyrimidine; DABCO

## 1. Introduction

Piperazines and pyrimidines are useful nitrogen heterocycles owing to their use in pharmaceuticals. Among nitrogen heterocycles, these two rank as third and tenth in the most frequently used in U.S. FDA approved drugs [1]. Examples of piperazine-containing drugs include the antihypertensive prazosin and the antibiotic ciprofloxacin, while examples of pyrimidine drugs are fluorouracil (anticancer) and trimethoprim (antibacterial) (Figure 1).

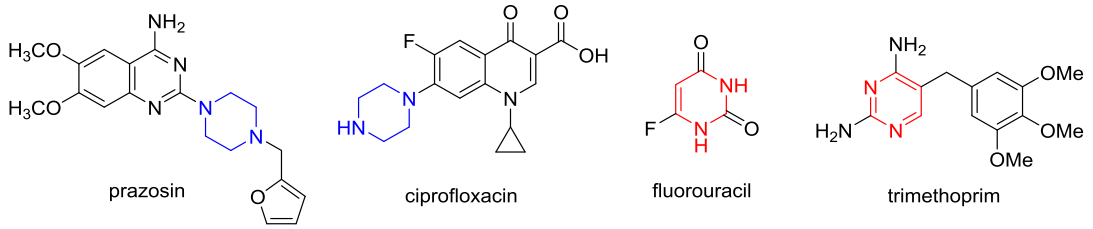
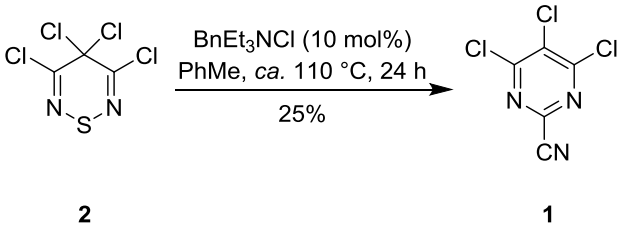



**Figure 1.** Piperazine- and pyrimidine-containing drugs.

Piperazines are often used as linkers in medicinal chemistry as well as to improve physicochemical properties of drug molecules such as water solubility and pharmacokinetic properties [2]. Unsymmetrical N-substituted piperazines and, in particular, those containing the *N*-ethylpiperazine moiety are useful pharmacophores but are often tricky to prepare [1–3]. One strategy to access these compounds is starting from the familiar tertiary amine 1,4-diazabicyclo[2.2.2]octane (DABCO). DABCO acts as a nucleophile in a variety of displacement reactions and often leads to the formation of quaternary ammonium salts that, in the presence of other nucleophiles, can ring open forming substituted *N*-ethylpiperazines [2–5].

Of particular interest are *N*-(2-chloroethyl)piperazines as these can be further functionalized via the 2-chloroethyl group. Surprisingly few reports of such compounds are found in the literature [6–11], and often the chloroethyl moiety was not isolated but converted in situ to other derivatives by nucleophilic displacement of the chloride [2–5].

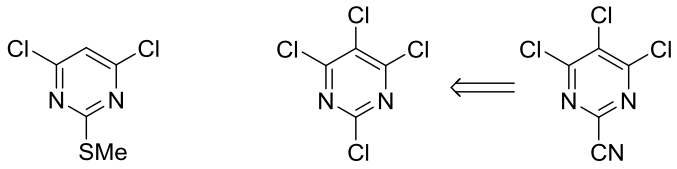
As part of our ongoing work in the chemistry of 1,2,6-thiadiazines [12,13], we identified 4,5,6-trichloropyrimidine-2-carbonitrile (**1**) as a product of the chloride-induced thermal degradation of 3,4,4,5-tetrachloro-4*H*-1,2,6-thiadiazine (**2**) (Scheme 1) [12], while the same product has reappeared in previous work with 1,2,6-thiadiazines [13–15].




**2** **1**

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

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. Previous efforts to access pyrimidine **1** involve the use of the starting material 4,6-dichloro-2-(methylthio)-pyrimidine (**3**) [16,17]. Another potentially useful scaffold for accessing pyrimidine **1** is the readily available 2,4,5,6-tetrachloropyrimidine (**4**), prepared by the treatment of barbituric acid with a refluxing mixture of $PCl_5$ and $POCl_3$ in 67% yield [18]. Retrosynthetically, the C2 cyano group of pyrimidine **1** could be introduced via a nucleophilic displacement of the C2 chloride of tetrachloropyrimidine **4** (Scheme 2).



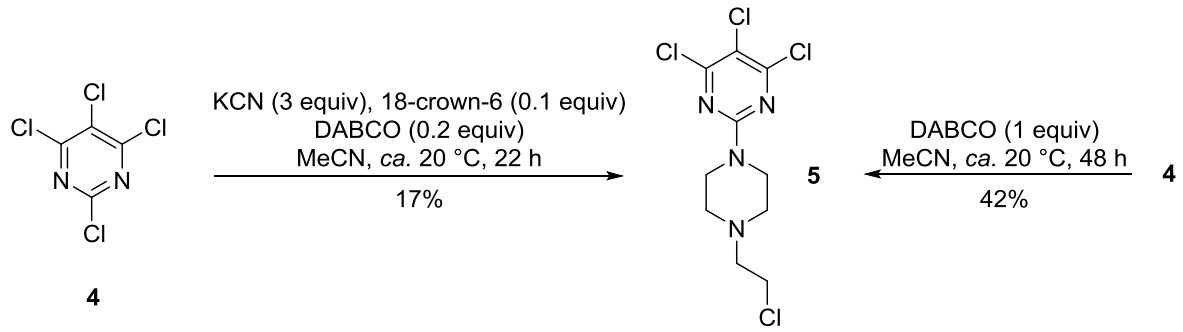

**3** **4** **1**

**Scheme 2.** Structure of 4,6-dichloro-2-(methylthio)pyrimidine (**3**) and retrosynthetic analysis of trichloropyrimidine **1**.

## 2. Results and Discussion

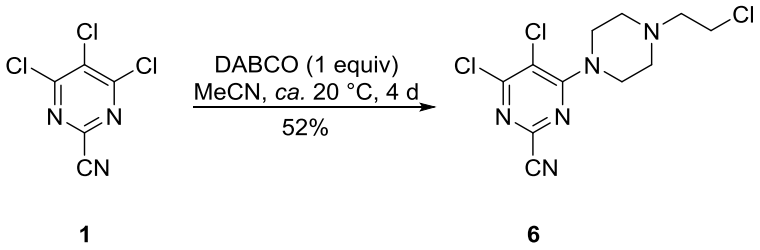
We subjected tetrachloropyrimidine **4** to a variety of displacement conditions involving the use of KCN with 18-crown-6 (0.1 equiv.), in the solvents MeCN, dioxane, DCM, or $H_2O$ and temperature ranging between 20 and 100 °C, which led to either no reaction or degradation of the starting material. In light of this, we turned to using *n*-$Bu_4NCN$ as the cyanide source that has been reported to afford the cyanide substitution of 4-chloropyrimidine derivatives [19]. We therefore screened this reagent in the presence of DABCO, which was used as a catalyst for the reported transformation [19]. Reaction with *n*-$Bu_4NCN$ (2 equiv.) in the solvents MeCN, DMSO, acetone, PhH, MeOH, or even neat led to the degradation of the starting material. Similarly, biphasic systems such as DCM/$H_2O$ or Pd-catalyzed conditions ($Pd(OAc)_2$ with the ligand dppb) [20] also led to degradation of the starting materials.

Interestingly, among our efforts to displace the C2 chloride in the presence of DABCO, we observed the formation of a colorless side-product, identified as 2,4,5-trichloro-6-[4-(2-chloroethyl) piperazin-1-yl]pyrimidine (**5**), which was isolated in 17% yield along with 60% recovered starting material (Scheme 3). Reaction of tetrachloropyrimidine **4** with 1 equiv. of DABCO in MeCN, at ca. 20 °C, gave a 42% yield of piperazine **5** as the only product (Scheme 3, see the Supplementary Materials for NMR spectra).




**Scheme 3.** Synthesis of 2,4,5-trichloro-6-[4-(2-chloroethyl)piperazin-1-yl]pyrimidine (**5**).

Intrigued by this result, we then subjected 4,5,6-trichloropyrimidine-2-carbonitrile (**1**) to the same reaction conditions that led to a slow consumption of the starting material, giving 4,5-dichloro-6-[4-(2-chloroethyl)piperazin-1-yl]pyrimidine-2-carbonitrile (**6**) as the only product in 52% yield (Scheme 4, see the Supplementary Materials for NMR spectra). The formation of the two products **5** and **6** reveals that the most reactive chloride of tetrachloropyrimidine **4**, towards DABCO, is at the C2 position, while the most reactive site in trichloropyrimidine **1** is the C4 position. This result shows that the chemistry of trichloropyrimidine **1** is complementary to other pyrimidine scaffolds and supports its potential as a synthetic scaffold.




**Scheme 4.** Synthesis of 4,5-dichloro-6-[4-(2-chloroethyl)piperazin-1-yl]pyrimidine-2-carbonitrile (**6**).

## 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. Acetonitrile (MeCN) was distilled over $CaH_2$ before use. 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 the 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 machine (at 500 and 125 MHz, respectively, (Bruker, Billerica, MA, USA)). Deuterated solvents were used for homonuclear lock, and the signals were 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 Cq (quarternary). 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**) and 2,4,5,6-tetrachloropyrimidine (**4**) were prepared according to the literature procedures [12,18].

*4,5,6-Trichloro-2-[4-(2-chloroethyl)piperazin-1-yl]pyrimidine* (**5**)

One portion 1,4-diazabicyclo[2.2.2]octane (DABCO, 56.0 mg, 0.500 mmol) was added to a stirred mixture of 2,4,5,6-tetrachloropyrimidine (**4**) (109 mg, 0.500 mmol) in MeCN (5 mL) at ca. 20 °C. The mixture was protected with a $CaCl_2$ drying tube and stirred at this temperature until complete consumption of the starting material (TLC, 48 h). DCM (10 mL) was then added, the mixture adsorbed onto silica, and chromatography (DCM) gave the *title compound* **5** (63.3 mg, 42%) as colorless plates, mp 84–85 °C (from MeCN); $R_f$ 0.21 (DCM); (found: C, 36.47; H, 3.76; N, 16.86. $C_{10}H_{12}Cl_4N_4$ requires C, 36.39; H, 3.67; N, 16.98%); $\lambda_{max}$(DCM)/nm 262 (log $\varepsilon$ 4.76), 332 (3.77); $\upsilon_{max}/cm^{-1}$ 2955 w, 2857 w and 2810 w (C-H), 1566 s, 1520 w, 1483 m, 1450 w, 1366 w, 1302 m, 1283 m, 1196 m, 1179 w, 1144 w, 1076 w, 1001 m, 986 m, 812 m, 762 m; $\delta_H$(500 MHz; $CDCl_3$) 3.81 (4H, *t*, *J* 5.0, pip. NC$H_2$), 3.61 (2H, *t*, *J* 6.8, C$H_2$Cl), 2.77 (2H, *t*, *J* 6.8, NC$H_2$), 2.56 (4H, *t*, *J* 4.8, pip. NC$H_2$); $\delta_C$(125 MHz; $CDCl_3$) 159.2 (Cq), 157.2 (Cq), 113.1 (Cq), 59.6 ($CH_3$), 52.7 ($CH_3$), 44.0 ($CH_3$), 40.8 ($CH_3$); *m/z* (MALDI-TOF) 331 ($MH^+$ + 2, 80%), 329 ($MH^+$, 100), 266 (36).

*4,5-Dichloro-6-[4-(2-chloroethyl)piperazin-1-yl]pyrimidine-2-carbonitrile* (**6**)

One portion 1,4-diazabicyclo[2.2.2]octane (DABCO, 56.0 mg, 0.500 mmol) was added to a stirred mixture of 4,5,6-trichloropyrimidine-2-carbonitrile (**1**) (104 mg, 0.500 mmol) in MeCN (5 mL) at ca. 20 °C. The mixture was protected with a $CaCl_2$ drying tube and stirred at this temperature until complete consumption of the starting material (TLC, 4 days). DCM (10 mL) was then added, the mixture adsorbed onto silica, and chromatography (DCM/$Et_2O$, 95:5) gave the *title compound* **6** (83.4 mg, 52%) as colorless needles, mp 47–48 °C (from MeOH/−60 °C); $R_f$ 0.73 (DCM/$Et_2O$, 95:5); (found: C, 41.27; H, 3.83; N, 21.65. $C_{11}H_{12}Cl_3N_5$ requires C, 41.21; H, 3.77; N, 21.84%); $\lambda_{max}$(DCM)/nm 237 (log $\varepsilon$4.27), 285 (4.20); $\upsilon_{max}/cm^{-1}$ 2924 w and 2853 w (C-H), 1647 s, 1468 m, 1450 m, 1445 m, 1371 m, 1302 m, 1269 m, 1234 w, 1209 w, 1161 w, 1144 m, 1128 m, 1096 m, 1040 m, 997 s, 897 m, 800 w, 766 w; $\delta_H$(500 MHz; $CDCl_3$) 3.86 (4H, *t*, *J* 4.9, pip. NC$H_2$), 3.61 (2H, *t*, *J* 6.7, C$H_2$Cl), 2.79 (2H, *t*, *J* 6.7, NC$H_2$), 2.65 (4H, *t*, *J* 4.9, pip. NC$H_2$); $\delta_C$(125 MHz; $CDCl_3$) 160.6 (Cq), 159.7 (Cq), 139.5 (Cq), 116.3 (Cq), 114.6 (Cq), 59.3 ($CH_3$), 52.7 ($CH_3$), 47.9 ($CH_3$), 40.7 ($CH_3$); *m/z* (MALDI-TOF) 324 ($MH^+$ + 4, 35%), 322 ($MH^+$ + 2, 72), 320 ($MH^+$, 100), 217 (11).

**Supplementary Materials:** The following are available online: molfile, $^1H$ 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.

**Funding:** This research was funded by the Cyprus Research Promotion Foundation (Grants: ΣΤΡΑΤΗΙΙ/0308/06, ΝΕΚΥΡ/0308/02 ΥΓΕΙΑ/0506/19 and ΕΝΙΣΧ/0308/83).

**Acknowledgments:** The authors thank the following organizations and companies in Cyprus for generous donations of chemicals and glassware: the State General Laboratory, the Agricultural Research Institute, the Ministry of Agriculture, MedoChemie Ltd., Medisell Ltd. and Biotronics Ltd. Furthermore, we thank the A. G. Leventis Foundation for helping to establish the NMR facility at the University of Cyprus.

**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.

## References

1. Vitaku, E.; Smith, D.T.; Njardarson, J.T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257–10274. [CrossRef] [PubMed]
2. Gettys, K.E.; Ye, Z.; Dai, M. Recent Advances in Piperazine Synthesis. *Synthesis* **2017**, *49*, 2589–2604. [CrossRef]
3. Bugaenko, D.I. 1,4-Diazabicyclo[2.2.2]octane in the synthesis of piperazine derivatives. *Chem. Heterocycl. Com.* **2017**, *53*, 1277–1279. [CrossRef]
4. Yavari, I.; Bayat, M.J.; Ghazanfarpour-Darjani, M. Synthesis of N-alkyl-N′-aryl-piperazines via copper-catalyzed C–N bond formation. *Tetrahedron Lett.* **2014**, *55*, 5595–5596. [CrossRef]

5. Dong, H.-R.; Chen, Z.-B.; Li, R.-S.; Dong, H.-S.; Xie, Z.-X. Convenient and efficient synthesis of disubstituted piperazine derivatives by catalyst-free, atom-economical and tricomponent domino reactions. *RSC Adv.* **2015**, *5*, 10768–10772. [CrossRef]
6. Wang, H.-J.; Earley, W.G.; Lewis, R.M.; Srivastava, R.R.; Zych, A.J.; Jenkins, D.M.; Fairfax, D.J. An efficient one-pot, two-step synthesis of 4-substituted 1-heteroarylpiperazines under microwave irradiation conditions. *Tetrahedron Lett.* **2007**, *48*, 3043–3046. [CrossRef]
7. Wu, H.-Q.; Yang, K.l.; Chen, X.-Y.; Arulkumar, M.; Wang, N.; Chena, S.-H.; Wang, Z.-Y. A 3,4-dihalo-2(5*H*)-furanone initiated ringopening reaction of DABCO in the absence of a metal catalyst and additive and its application in a one-pot two-step reaction. *Green Chem.* **2019**, *21*, 3782–3788. [CrossRef]
8. Wang, H.-J.; Wang, Y.; Csakai, A.J.; Earley, W.G.; Herr, R.J. Efficient N-Arylation/Dealkylation of Electron Deficient Heteroaryl Chlorides and Bicyclic Tertiary Amines under Microwave Irradiation. *J. Comb. Chem.* **2009**, *11*, 355–363. [CrossRef] [PubMed]
9. Fu, Y.; Xu, Q.-S.; Li, Q.-Z.; Li, M.-P.; Shi, C.-Z.; Du, Z. Sulfonylation of 1,4-Diazabicyclo[2.2.2]octane: Charge-Transfer Complex Triggered C–N Bond Cleavage. *ChemistryOpen* **2019**, *8*, 127–131. [CrossRef] [PubMed]
10. Kolesinska, B.; Barszcz, K.; Kaminski, Z.J.; Drozdowska, D.; Wietrzyk, J.; Switalska, M. Synthesis and cytotoxicity studies of bifunctional hybrids of nitrogen mustards with potential enzymes inhibitors based on melamine framework. *J. Enzyme Inhib. Med.* **2011**, *27*, 619–627. [CrossRef] [PubMed]
11. Koyioni, M.; Manoli, M.; Koutentis, P.A. The Reaction of DABCO with 4-Chloro-5*H*-1,2,3-dithiazoles: Synthesis and Chemistry of 4-[*N*-(2-Chloroethyl)piperazin-1-yl]-5*H*-1,2,3-dithiazoles. *J. Org. Chem.* **2016**, *81*, 615–631. [CrossRef] [PubMed]
12. Kalogirou, A.S.; Manoli, M.; Koutentis, P.A. Reaction of 3,4,4,5-tetrachloro-4*H*-1,2,6-thiadiazine with benzyltriethylammonium chloride. *Tetrahedron Lett.* **2018**, *59*, 3589–3593. [CrossRef]
13. Kalogirou, A.S.; Koutentis, P.A. A qualitative comparison of the reactivities of 3,4,4,5-tetrachloro-4*H*-1,2,6-thiadiazine and 4,5-dichloro-1,2,3-dithiazolium chloride. *Molecules* **2015**, *20*, 14576–14594. [CrossRef] [PubMed]
14. Koutentis, P.A.; Rees, C.W.; White, A.J.P.; Williams, D.J. Reaction of tetracyanoethylene with $SCl_2$; new molecular rearrangements. *Chem. Commun.* **2000**, 303–304. [CrossRef]
15. Koutentis, P.A.; Rees, C.W. Reaction of tetracyanoethylene with $SCl_2$; new molecular rearrangements. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1089–1094. [CrossRef]
16. Kalogirou, A.S.; Koutentis, P.K. 4-Chloro-6-ethoxy-2-(methylthio)pyrimidine. *Molbank* **2017**, *2017*, M923. [CrossRef]
17. Kalogirou, A.S.; Koutentis, P.K. Synthesis of 2-cyanopyrimidines. *Molbank* **2019**. submitted.
18. Childress, S.J.; McKee, R.L. Chloroaminopyrimidines. *J. Am. Chem. Soc.* **1950**, *729*, 4271–4272. [CrossRef]
19. Griffith, D.A. Purine Compounds and Uses Thereof as Cannabinoid Receptor Ligands. WO2004/37823, 6 May 2004.
20. Schareina, T.; Zapf, A.; Cotté, A.; Müller, N.; Beller, M. A Bio-inspired Copper Catalyst System for Practical Catalytic Cyanation of Aryl Bromides. *Synthesis* **2008**, *20*, 3351–3355. [CrossRef]