Reactions of Tetrachloropyridazine with Aliphatic Nitrogen Nucleophiles

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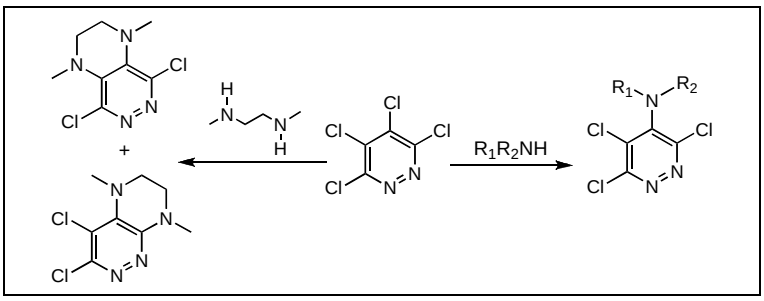

Nucleophilic aromatic substitution reactions of tetrachloropyridazine with a series of aliphatic primary and secondary amines led selectively to products arising from replacement of chlorine at the 4-position in all cases. The structures of the products were unambiguously confirmed by X-ray crystallography. Substitution occurs at the most activated site *para* to ring nitrogen, despite the possible steric hindrance to substitution by adjacent chlorine atoms, reflecting the activating influence of ring nitrogen *meta* to the site of attack. *N*,*N*'-Dimethylethylene diamine gave a mixture of [6,6] ring fused products following initial substitution at the 4-position.

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INTRODUCTION

Although pyridazines are a structurally simple class of heterocycles, many derivatives possess very useful biological activity and the life science industries have employed various polysubstituted pyridazine systems for applications ranging from herbicides to anthelmintic agents [1]. In general, pyridazine systems are synthesized from reaction of hydrazine with an appropriate acyclic dicarbonyl derivative [1-3] which, although very successful, can limit the range of functionalities present on the pyridazine ring.

There is great interest in developing efficient and selective methodology for the synthesis of low molecular weight poly-functional heterocyclic systems for use in drug discovery programmes [4-6]. The application of polyfunctional 'core scaffolds' [7,8], that is, a heterocycle bearing several functional groups, to the synthesis of many analogues of a particular biologically active heterocyclic molecule using Rapid Analogue Synthesis (RAS) techniques [7,8], is an established part of the 'hit-to-lead' medicinal chemistry process. Furthermore, the concept that small heterocycles are 'privileged structures' [9,10] and generally fall within the Lipinski parameters [11], has provided further stimulus for the development of methodology for the synthesis of multisubstituted small-ring heterocycles.

In this context, perchlorinated heterocycles [12], such as tetrachloropyridazine, could, in principle, act as excellent scaffolds for the synthesis of many pyridazine derivatives. For example, all four chlorine atoms attached to the pyridazine ring could, potentially, be displaced by a sequence of, for instance, nucleophilic substitution, dechlorolithiation, and palladium catalysed coupling processes. However, the utility of tetrachloropyridazine, and, indeed, all other perchlorinated heteroaromatic systems, as a scaffold has been hampered by the almost total lack of chemistry reported for this system. At first sight this is perhaps surprising for such a simple and potentially valuable molecule, but the chemistry of perchlorinated derivatives has, in general, not been developed to any great extent because of a previous lack of effective, definitive structural probes. However, the advent of rapid X-ray crystallography should now allow the field to make significant progress.

Tetrachloropyridazine should react efficiently with nucleophiles because of the presence of the four chlorine atoms that decrease electron density in the ring. In this paper, we aim to unambiguously establish the outcome of reactions between tetrachloropyridazine and a representative sample of aliphatic nitrogen centred nucleophiles with varying steric demands to make an initial assessment of the potential utility of tetrachloropyridazine as a scaffold for wider synthetic application and to establish fundamental principles of nucleophilic substitution reactions of perchloro-heteroaromatic systems.

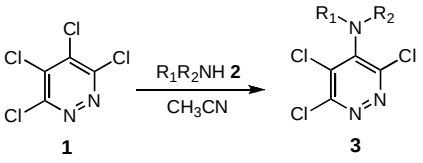
RESULTS AND DISCUSSION

Reaction between tetrachloropyridazine **1** and a range of aliphatic nitrogen centred nucleophiles **2a-f** (2 equivalents) was carried out in acetonitrile and the results are collated in Table 1.

In all cases, GC/MS and NMR analysis of the crude product mixture showed that only one product **3a-f** was formed although only good yields of isolated products were obtained due to the sometimes difficult separation by column chromatography. X-ray analysis of products **3b** and **3d** (Figure 1), arising from displacement of chlorine by a primary and secondary amine respectively, confirmed that in all cases substitution occurs selectively at the 4-position.

The geometrical parameters of molecules **3b** and **3d** are close to expected values. (Figure 1) The aromatic rings in molecule **3b** are almost perpendicular to each other, the dihedral angle between their planes being 99.2º. The molecules **3b** in the crystal are linked together by N-H…N hydrogen bonds (N…N 2.922(1)Å) into unusual tubular chains (Figure 2) along the *c*-axis and the π…π interactions between the phenyl rings connect the adjacent chains. The packing of the molecules **3d** is more typical with their aromatic rings arranged in anti-parallel stacks with alternating interplanar distances of 3.27 and 3.87Å.

Table 1



1 **3**

R_1R_2NH	Product (yield%)
CH_3NH_2 **2a**	**3a** 43%
2b	**3b** 54%
2c	**3c** 45%
2d	**3d** 49%
2e	**3e** 25%
2f	**3f** 47%

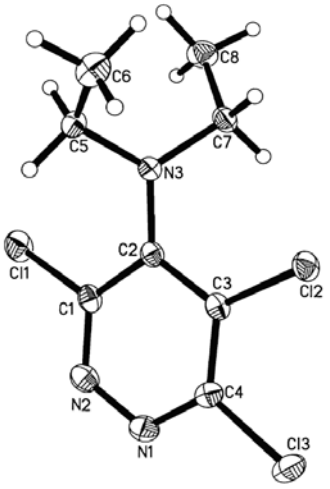


Figure 1. X ray structures of **3b** and **3d**.

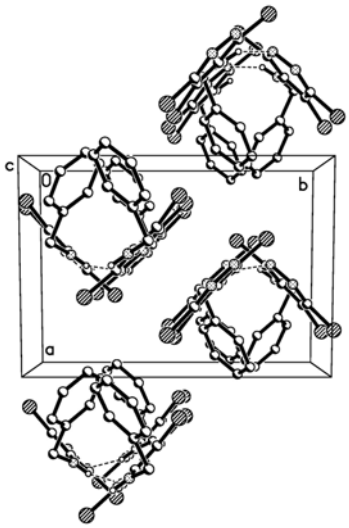
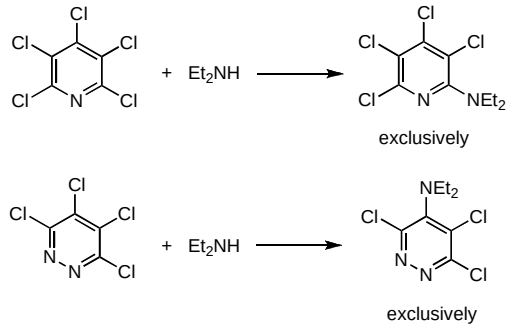


Figure 2. Packing of the molecules **3b** in a crystal.

It is well established that nitrogen *para* to the site of nucleophilic attack is very activating in perhalogenated heteroaromatic systems and, consequently we would

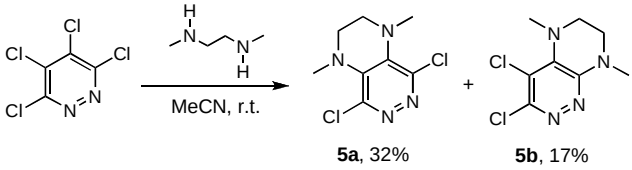
expect substitution to occur predominantly at the 4-position in the case of tetrachloropyridazine. However, the regiospecificity is surprising because, in related processes involving substitution reactions of pentachloropyridine, substitution at the less sterically hindered 2-position competes significantly and, in the case of diethylamine, substitution occurs almost exclusively at the 2-position rather than the electronically most favoured 4-position (Scheme 1) [12,13]. Consequently, in the tetrachloropyridazine case, ring nitrogen *meta* to the site of nucleophilic attack is far more activating than chlorine substituents at the same position and activation of the 4-position outweighs any steric factors.

Scheme 1



Reaction of tetrachloropyridazine with a difunctional nitrogen nucleophile, *N*,*N*'-dimethylethylene diamine **4**, gave a mixture of [6,6] ring fused products **5a** and **5b** in an 8:3 ratio arising from initial substitution at the 4-position followed by cyclisation onto the 5- and 3- sites respectively (Scheme 2).

Scheme 2



The product distribution reflects the slightly higher activity of the 5-position which is also *para* to activating ring nitrogen and, again, X-ray crystallography confirmed the structure of the major product (Figure 3).

Molecules in the crystal of **5a** are located at a special position on a 2-fold axis. The conformation of the piperazine ring is a half-chair with a pyramidal bond configuration at both nitrogen atoms. The anti-parallel π…π stacking of the heterocycles in a crystal of **5a** is typical for similar compounds and the mean interplanar distance between adjacent molecules in the stacks is 3.67Å, the shortest inter-atomic distance being 3.571Å (Cl…C).

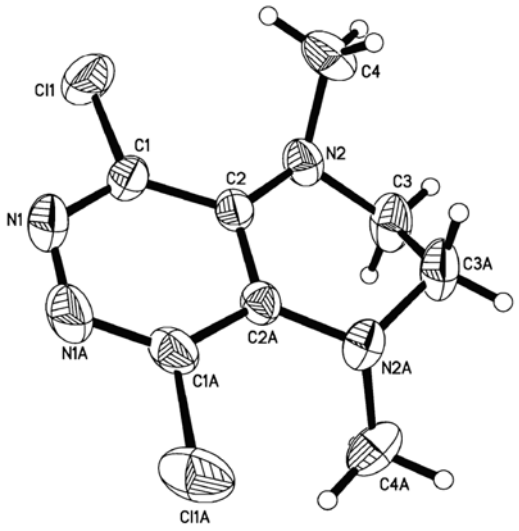


Figure 3. X ray structure of **5a**.

Molecules in the crystal of **5a** are located at a special position on a 2-fold axis. The conformation of the piperazine ring is a half-chair with a pyramidal bond configuration at both nitrogen atoms. The anti-parallel π…π stacking of the heterocycles in a crystal of **5a** is typical for similar compounds and the mean interplanar distance between adjacent molecules in the stacks is 3.67Å, the shortest inter-atomic distance being 3.571Å (Cl…C).

In summary, reactions of primary and secondary nitrogen nucleophiles with tetrachloropyridazine proceed very efficiently and regiospecifically to give products arising from substitution of the most activated 4-position. The surprising regiospecificity of the reactions makes the use of tetrachloropyridazine as a scaffold for library synthesis possible.

EXPERIMENTAL

General. All starting materials were obtained commercially (Aldrich, Lancaster or Fluorochem) All solvents were dried using literature procedures. NMR spectra were recorded in deuteriochloroform, unless otherwise stated, on a Varian VXR 400S NMR spectrometer operating at 400 MHz (^{1}H n.m.r.) and 100 MHz (^{13}C n.m.r.) with tetramethylsilane as internal standards. Mass spectra were recorded on a Fisons VG-Trio 1000 Spectrometer coupled with a Hewlett Packard 5890 series II gas chromatograph using a 25m HP1 (methyl-silicone) column. Elemental analyses were obtained on a Exeter Analytical CE-440 elemental analyser. Melting points and boiling points were recorded at atmospheric pressure unless otherwise stated and are uncorrected. Column chromatography was carried out on silica gel (Merck no. 109385, particle size 0.040-0.063mm) and TLC analysis was performed on silica gel TLC plates (Merck).

X-ray crystallography. The single crystal X-ray data were collected on a Bruker SMART CCD 6K (3b and 5a) and Bruker Proteum M CCD (3d) at 120 (3b and 3d) and 200K using graphite monochromated Mo-K radiation (λ = 0.71073 Å). All structures were solved by direct methods and refined by full-matrix least squares analysis on F^2 for all data using SHELXL software. All non-hydrogen atoms were refined with anisotropic displacement parameters, H-atoms were found in the difference Fourier maps and refined isotropically. CCDC 641086 and 641088 contains the supplementary crystallographic data for this paper. These data can be viewed free of charge via http://www.ccdc.cam.ac.uk/cont/retrieving.html or from the CCDC, 12 Union Road, Cambridge, CB2 1EZ; fax: +44-1223-336033. E-mail: deposit@ccdc.cam.ac.uk.

General Procedure for the reaction of Tetrachloropyridazine with Nitrogen Nucleophiles. Tetrachloropyridazine 1 was dissolved in acetonitrile (25ml) under argon with stirring. The amine 2 was added and the mixture stirred at rt or heated at reflux until TLC indicated complete conversion to products. After this period water (20ml) was added and the solution acidified with 10% HCl, followed by extraction with ethyl acetate (3 x 20ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under vacuum to yield a crude product which was purified by recrystallisation.

3,5,6-Trichloro-N-methylpyridazin-4-amine (3a). 1 (1.00g, 4.59mmol) and methylamine (**2a**) (4.6ml, 9.18mmol, 2.0M in EtOH) in acetonitrile (25ml) gave a crude yellow product (0.62g) which after recrystallisation gave 3a (0.42g, 43%) as a pale yellow solid; mp 113 – 114 °C (from hexane/ethyl acetate, 2:3); ^{1}H nmr: δ 3.41 (d, 3H, CH_3, $^3J_{HH}$ = 5.5 Hz), 5.26 (br s, 1H, NH); ^{13}C nmr: δ 33.2 (s, Me), 115.8 (s), 142.1 (s), 143.6 (s), 154.8 (s); ms (70eV, electron impact m/z 215 (4%, $[M]^+$), 213 (15, $[M]^+$), 211 (18, $[M]^+$), 187 (4, $[M\text{-}NHMe]^+$), 185 (15, $[M\text{-}NHMe]^+$), 183 (16, $[M\text{-}NHMe]^+$); *Anal.* Calcd. for $C_5H_4Cl_3N_3$: C, 28.6; H, 1.9; N, 19.5. Found: C, 28.3; H, 1.9; N, 19.8.

N-Benzyl-3,5,6-trichloropyridazin-4-amine (3b). 1 (1.00g, 4.59mmol) and benzylamine (**2b**) (1.0ml, 9.18mmol) in acetonitrile (25ml) gave a crude yellow product (0.86g) which after recrystallisation gave **3b** (0.71g, 54%) as yellow crystals; mp 75 – 77 °C from hexane/ethyl acetate (2:1); ^{1}H nmr: δ 4.95 (d, 2H, NH*CH*$_2$Ph, $^3J_{HH}$ = 5.9 Hz), 5.42 (br s, 1H, *NH*CH_2Ph), 7.29 – 7.40 (m, 5H, ArH); ^{13}C nmr: δ 49.6 (s, NH*CH*$_2$Ph), 116.8 (s), 127.3 (s, Ph), 128.2 (s, Ph), 129.1 (s, Ph), 137.2 (s), 141.4 (s), 144.1 (s, NHPh), 154.8 (s); ms (70eV, electron impact m/z 291 (3%, $[M]^+$), 289 (12, $[M]^+$), 287 (11, $[M]^+$), 91 (100, $[CH_2Ph]^+$), 77 (11), 65 (63); *Anal.* Calcd. for $C_{11}H_8N_3Cl_3$: C, 46.0; H, 2.9; N, 14.5. Found: C, 45.8; H, 2.8; N, 14.6. Crystals suitable for X-ray diffraction were obtained from slow evaporation of ethyl acetate. *Crystal data for* **3b**: $C_{11}H_8Cl_3N_3$, M = 288.55, monoclinic, space group P 2_1/c, a = 8.9251(3), b = 12.4466(5), c = 10.8975(4) Å, β = 100.70(1)°, U = 1189.52(8)Å^3, F(000) = 584, Z = 4, D_c = 1.611 mg m^{-3}, μ = 0.748 mm^{-1}. 18653 reflections (2.32 ≤ θ ≤ 29.50°) were collected yielding 3314 unique data (R_{merg} = 0.0269). Final $wR_2(F^2)$ = 0.0852 for all data (186 refined parameters), conventional R (F) = 0.0296 for 2973 reflections with I ≥ 2σ, GOF = 1.030.

***N*-*tert*-Butyl-3,5,6-trichloropyridazin-4-amine (3c). 1** (1.00g, 4.59mmol) and *tert*-butylamine 2c (0.96ml, 9.18mmol) in acetonitrile (25ml) gave a crude yellow product (0.67g) which after recrystallisation gave **3c** (0.52g, 45%) as a yellow-orange solid; mp 64 – 66 °C from hexane/ethyl acetate (2:3); ^{1}H nmr: δ 1.49 (s, 9H, CH_3), 4.82 (br s, 1H, NH); ^{13}C nmr: δ 31.4 (s, CH_3), 57.2 (s, *C*CH_3), 121.7 (s), 142.9 (s), 148.4 (s), 155.0 (s); ms (70eV, electron impact m/z 255 (2%, $[M]^+$), 253 (2, $[M]^+$), 242 (4, $[M\text{-}CH_3]^+$), 240 (9, $[M - CH_3]^+$), 238 (9, $[M - CH_3]^+$), 201 (5, $[M - {}^tBu]^+$), 199 (13, $[M - {}^tBu]^+$), 197 (15, $[M - {}^tBu]^+$), 57 (100, $[{}^tBu]^+$); *Anal.* Calcd. for $C_8H_{10}Cl_3N_3$: C, 37.9; H, 3.8; N, 16.3. Found: C, 37.8; H, 4.0; N, 16.5.

3,5,6-Trichloro-N,N-diethylpyridazin-4-amine (3d). 1 (1.00g, 4.59mmol) and diethylamine 2d (0.95ml, 9.18mmol) in acetonitrile (25ml) gave a crude red-brown product (1.04g) which after recrystallisation gave 3d (0.57g, 49%) as a yellow solid; mp 52 – 54 °C from hexane; ^{1}H nmr: δ 1.09 (t, 6H, CH_3, $^3J_{HH}$ = 7.2 Hz), 3.37 (q, 4H, CH_2 , $^3J_{HH}$ = 7.0 Hz); ^{13}C nmr: δ 13.9 (s, CH_2), 45.9 (s, CH_3), 133.2 (s), 146.4 (s), 155.1 (s), 155.4 (s); ms (70eV, electron impact m/z 257 (3%, $[M]^+$), 255 (9, $[M]^+$), 253 (12, $[M]^+$), 242 (22, $[M\text{-}CH_3]^+$), 240 (63, $[M\text{-}CH_3]^+$), 238 (60, $[M\text{-}CH_3]^+$), 214 (15, $[M\text{-}CH_2CH_3]^+$), 212 (45, $[M\text{-}CH_2CH_3]^+$), 210 (48, $[M\text{-}CH_2CH_3]^+$), 29 (100, $[CH_2CH_3]^+$); *Anal.* Calcd. for $C_8H_{10}N_3Cl_3$: C, 37.7; H, 4.0; N, 16.4. Found: C, 37.8; H, 4.0; N, 16.5. Crystals suitable for X-ray diffraction were obtained by recrystallisation from hexane. *Crystal data for* **3d**: $C_8H_{10}Cl_3N_3$, M = 254.54, monoclinic, space group P 2_1/c, a = 9.8565(3), b = 7.2922(3), c = 15.0344(5) Å, β = 94.56(1)°, U = 1077.18(7)Å^3, F(000) = 520, Z = 4, D_c = 1.570 mg m^{-3}, μ = 0.814 mm^{-1}. 11707 reflections (2.72 ≤ θ ≤ 29.50°) were collected yielding 2978 unique data (R_{merg} = 0.0397). Final $wR_2(F^2)$ = 0.0787 for all data (167 refined parameters), conventional R (F) = 0.0274 for 2622 reflections with I ≥ 2σ, GOF = 1.097.

3,4,6-Trichloro-5-piperidine-1-yl-pyridazine (3e). 1 (2.00g, 9.17mmol) and piperidine 2e (1.8ml, 18.31mmol) in acetonitrile (50ml) gave a crude yellow solid (1.48 g) which after recrystallisation gave **3e** (0.60g, 25%) as a yellow solid; mp 76.3 - 78.3 °C from ethyl acetate; ^{1}H nmr: δ 1.73 (m, 6H, CH_2), 3.33 (t, 4H, NCH_2, $^3J_{HH}$ = 5.27 Hz); ^{13}C nmr: δ 23.7 (s, C-4'), 26.2 (s, C-3'), 51.9 (s, C-2') 129.7 (s), 146.8 (s), 152.8 (s) 155.5 (s); ms (70eV, electron impact m/z 271 (3%, $[M]^+$), 270 (5%, $[M\text{-}H]^+$), 269 (18%, $[M]^+$), 268 (48%, $[M\text{-}H]^+$) 267 (53%, $[M]^+$), 266 (100%, $[M\text{-}H]^+$), 265 (53%, $[M]^+$), 264 (100%, $[M\text{-}H]^+$), 55 (35%, $[C_4H_7]^+$); *Anal.* Calcd. for $C_9H_{10}Cl_3N_3$: C, 40.6; H, 3.8; N, 15.6. Found: C, 40.6; H, 3.8; N, 15.8.

4-(3,5,6-Trichloro-pyridazine-4-yl)-morpholine (3f). 1 (2.00g, 9.17mmol) and morpholine 2f (1.60ml, 18.34mmol) in acetonitrile (50ml) gave a crude yellow product which after recrystallisation gave **3f** (1.15g, 47%) as yellow crystals; mp 100.8-102.8 °C (from hexane / ethyl acetate, 1:1); ^{1}H nmr: δ 3.43 (t, 4H, H_a, $^3J_{HH}$ = 4.4 Hz), 3.86 (t, 4H, H_b, $^3J_{HH}$ = 4.6 Hz); ^{13}C nmr: δ 50.6 (s, C-2'), 67.1 (s, C-3'), 103.3 (s), 145.5 (s), 152.7 (s), 155.7 (s); ms (70eV, electron impact m/z 273 (2%, $[M]^+$), 272 (2%, $[M\text{-}H]^+$), 271 (15%, $[M]^+$), 270 (7%, $[M\text{-}H]^+$), 269 (43%, $[M]^+$), 268 (10%, $[M\text{-}H]^+$), 267 (46%, $[M]^+$), 266 (6%, $[M\text{-}H]^+$), 234 (30, $[M\text{-}Cl]^+$), 232 (69, $[M\text{-}Cl]^+$), 211 (95, $[M\text{-}C_3H_6O]^+$), 209 (100, $[M\text{-}C_3H_6O]^+$), 148 (36, $[M\text{-}C_4H_8NOCl]^+$), 146 (54, $[M\text{-}C_4H_8NOCl]^+$), 117.9 (32), 85 (23, $[C_4H_8NO]^+$), 77 (34); *Anal.* Calcd. for $C_8H_8N_3OCl_3$: C, 35.9; H, 3.0; N, 15.4. Found: C, 35.8; H, 3.0; N, 15.7.

Reaction with *N*,*N*'-Dimethylethylene diamine (4). 1 (1.00g, 4.59mmol) and *N*,*N*'-dimethylethylene diamine (**4**) (0.54ml, 5.05mmol) in acetonitrile (100ml) gave a crude red-brown product (0.98g). Purification by flash column chromatography using hexane:ethyl acetate as eluant, 5,8-dichloro-1,2,3,4-tetrahydro-1,4-dimethylpyrazino[2,3-*d*]pyridazine (**5a**)

(0.34g, 32%) as a cream solid; mp 143.5 – 146 °C; ^{1}H nmr: δ 3.05 (s, 6H, CH_3), 3.07 (s, 4H, CH_2CH_2); ^{13}C nmr: δ 42.7 (s, CH_2CH_2), 46.1 (s, CH_3), 135.7 (s), 146.0 (s); ms (70eV, electron impact m/z 233 (0.4%, $[M]^+$), 231 (1.6, $[M]^+$), 91 (100); *Anal*. Calcd. for $C_8H_{10}N_4Cl_2$: C, 41.2; H, 4.3; N, 23.8. Found: C, 41.2; H, 4.3; N, 24.0. Crystals suitable for X-ray diffraction were obtained from slow evaporation of ethyl acetate; *Crystal data for* **5a**: $C_8H_{10}Cl_2N_4$, M = 233.10, monoclinic, space group C 2/c, a = 8.8096(4), b = 14.0969(7), c = 7.9734(4) Å, β = 93.02(2)°, U = 988.82(8)Å^3, F(000) = 480, Z = 4, D_c = 1.566 mg m^{-3}, μ = 0.620 mm^{-1}. 5535 reflections (2.73 ≤ θ ≤ 29.49°) were collected yielding 1371 unique data (R_{merg} = 0.0204). Final $wR_2(F^2)$ = 0.1091 for all data (85 refined parameters), conventional R(F) = 0.0378 for 1249 reflections with I ≥ 2σ, GOF = 1.004; and, 3,4-dichloro-5,6,7,8-tetrahydro-5,8-dimethylpyrazino[2,3-c]pyridazine (5b) (0.18g, 17%) as a cream solid; mp 121 – 123 °C; ^{1}H nmr: δ 3.40 (m, 2H, CH_2), 3.35 (m, 2H, CH_2), 3.20 (s, 3H, CH_3), 3.16 (s, 3H, CH_3); ^{13}C nmr: δ 36.9 (s, CH_2), 41.8 (s, CH_2), 45.4 (s, CH_3), 50.1 (s, CH_3), 134.4 (s), 136.9 (s), 145.5 (s), 150.5 (s), 153.9 (s); ms (70eV, electron impact m/z 217 ($[M\text{-}Me]^+$, 1%), 106 (28), 85 ($[C_5H_9N_2]^+$, 29), 71 ($[C_3H_7N_2]^+$, 34), 49 (32), 47 (100), 35 (72); *Anal*. Calcd. for $C_8H_{10}N_4Cl_2$: C, 42.5; H, 4.7; N, 22.7. Found: C, 41.2; H, 4.3; N, 24.0.

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