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On the nucleophilic *tele*-substitution of dichloropyrazines by metallated dithianes

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Abstract—The reaction of dichloropyrazines with a dithiane anion gave isomers of the expected formylated chloropyrazines after deprotection with methyl iodide. A *tele*-substitution mechanism accounts for these observations and is supported by deuterium labelling studies.

1. Introduction

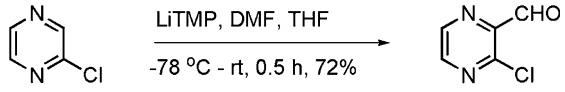
Aromatic heterocycles are commonly observed motifs in a wide variety of drugs, due in part to their involvement in binding and physicochemical properties.[1] In addition, the development of contemporary synthetic methodology for the preparation of substituted heteroaromatic compounds continues to be an important and productive area of research.[2,3] Among the diazines, the pyrazine ring system is important, and substituted pyrazine motifs are often to be found in compounds with applications as anti-cancer agents, including currently marketed drugs[4] and those recently reported.[5]

In the context of a medicinal chemistry project, we required synthetic access to a set of pyrazine templates bearing formyl and halogen substituents. The metallation and quenching of halopyrazines seemed an attractive approach.[6] We report here some of our initial observations in this area, which resulted in the development of an alternative method for the preparation of this type of compound, and which subsequently uncovered some interesting examples of a nucleophilic *tele*-substitution mechanism.[7]

2. Results and discussion

We first attempted to prepare the formylated chloropyrazine **2** by metallation and quenching of **1**,[6] as shown in Scheme 1. After one successful outcome (72% yield), in our hands the reaction could not be reliably repeated, despite brief attempts to optimise the reaction conditions and the formyl source.[8]

One indirect alternative to this approach would involve nucleophilic substitution of dichloropyrazines with a dithiane-based anion,[9] followed by conversion to the corresponding aldehyde.[10] To the best of our knowledge, pyrazines bearing a formyl substituent have not previously been prepared by such a method.[11] Surprisingly, on treatment of commercially available **3** with 2-lithio-1,3-dithiane, only the 2,3-disubstituted product **4** was obtained in 69% yield after column chromatography (Scheme 2).[9,12,13] This unexpected structure was suggested by the appearance of two doublets in the aromatic region, each with a coupling constant of 2.4 Hz



1 **2**

Scheme 1.

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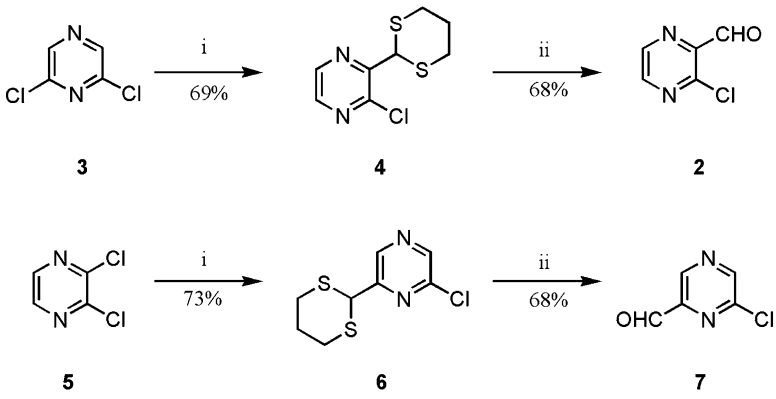


Scheme 2. Reagents and conditions: (i) ^{n}BuLi, 1,3-dithiane, THF, −70 °C, 1 h; (ii) MeI, $CaCO_3$, MeCN, H_2O, 60 °C, 24 h.

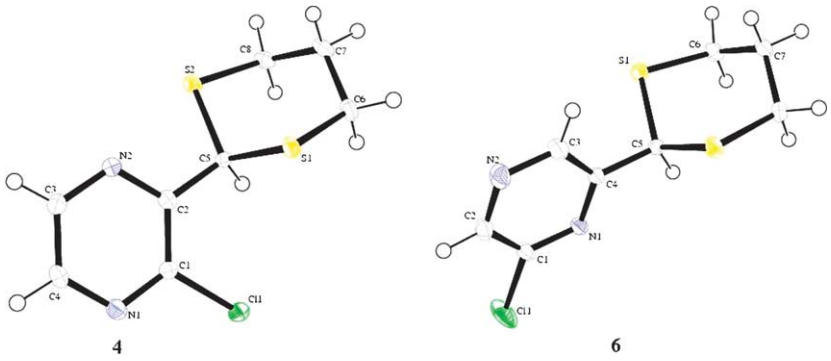


Figure 1. ORTEP drawings of compounds **4** and **6**.

(representing H-5 and H-6) in the ^{1}H NMR spectrum, and subsequently confirmed by X-ray crystallography (see Fig. 1).[14] Treatment of **4** with iodomethane and aqueous calcium carbonate in acetonitrile[15] gave a 68% yield of aldehyde **2**, whose spectroscopic data matched those previously reported.[6]

Similarly, reaction of 2,3-dichloropyrazine **5** under the same conditions provided the corresponding 2,6-product **6** in good yield—none of the expected 2,3-compound was observed in the crude reaction mixture. The identity of **6** was again established by ^{1}H NMR spectroscopy (the two pyrazine protons showed no discernible coupling) and by X-ray crystallography. Pyrazine **6** could be converted to aldehyde **7** using the procedure described above. The substitution products **4** and **6** can be prepared in large quantities and are stable under ambient conditions; both can be conveniently transformed into the (potentially unstable) aldehydes[6] as required.

We probed these findings further by undertaking reactions with D_2O as the quenching electrophile. These experiments afforded deuterated products **8** and **9**, respectively (Fig. 2, from reaction of **3** and **5**). Analysis by NMR spectroscopy revealed that the level of deuterium incorporation in **8** and **9** was 90% and 73%, respectively. When the same procedure was carried out using deuterated THF as solvent and H_2O as the quenching agent, no deuterium incorporation was observed.[16]

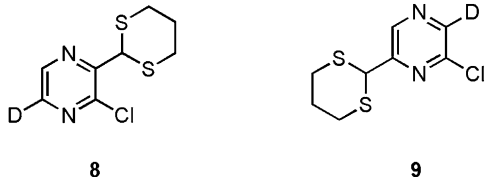
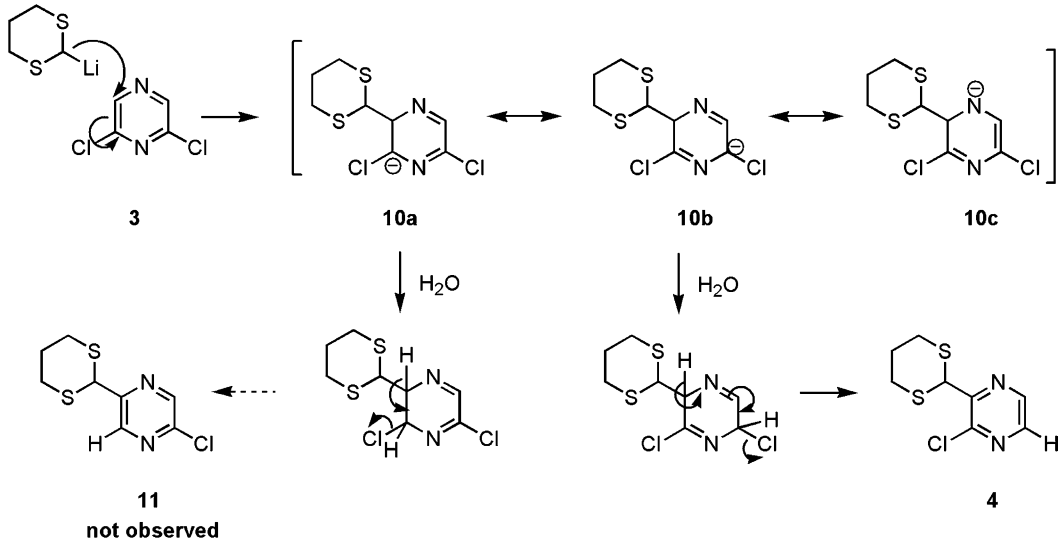


Figure 2. Products of D_2O quench.

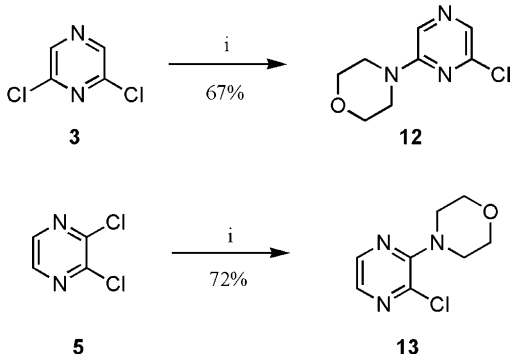
This indicates that the deuterium atoms in **8** and **9** originate from the quenching agent and not from the solvent.

A plausible mechanistic explanation for these observations is shown in Scheme 3, for the case of 2,6-dichloropyrazine **3**.[17] Nucleophilic addition of the lithiated dithiane on **3** must lead to intermediate **10**, which cannot aromatise directly prior to quenching. Protonation of **10** is followed by 1,4-elimination of HCl to give **4**. None of isomer **11**, the product of 1,2-elimination is formed. A similar mechanism explains the formation of **6** as the only product from dichloropyrazine **5**.

Conversely, the reactions of **3** and **5** with morpholine as the nucleophile under non-anionic conditions afforded the previously reported products **12**[18] and **13**[19] respectively (Scheme 4). Structural assignment by ^{1}H NMR spectroscopy was unambiguous, showing that these products were formed by straightforward nucleophilic aromatic substitution.



Scheme 3.



Scheme 4. Reagents and conditions: (i) 6 equiv morpholine, CH_2Cl_2, 50 °C, 3 h.

In summary, we have explored a novel route to formylated chloropyrazines utilising dithiane-derived nucleophiles and, in so doing, uncovered an interesting *tele*-substitution mechanism. This work represents a useful and practical alternative to currently existing methodology for the preparation of compounds of this type.

Acknowledgements

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13. *Preparation of* **4**: ^{n}BuLi (9.00 ml, 2.5 M in hexanes, 22.50 mmol) was added dropwise to a cooled (−78 °C), nitrogen flushed, solution of 1,3-dithiane (2.65 g, 22.04 mmol, 1.1 equiv) in anhydrous THF (10 ml) and left for 30 min. 2,6-Dichloropyrazine (3.01 g, 20.20 mmol, 1 equiv) in THF (2 ml) was added. TLC indicated the complete consumption of the starting material after 10 min. The reaction mixture was poured into water (10 ml) and the organic components were extracted (ethyl acetate), rinsed (brine) and dried (sodium sulfate) and the solvent evaporated in vacuo to give an orange solid (4.49 g). Purification by flash chromatography (silica, 20 g, hexane–ethyl acetate 20:1) gave the title compound (3.33 g, 69%) as a white solid; mp 120–122 °C; R_f 0.36 (hexane–ethyl acetate, 5:1); δ_H ($CDCl_3$, 250 MHz) 8.52

(1H, d, $J = 2.4$, H^5), 8.32 (1H, d, $J = 2.4$, H^6), 5.55 (1H, s, CH), 3.07 (4H, m, $2 \times$ SCH_2), 2.14 (2H, m, CH_2); δ_C ($CDCl_3$, 70 MHz) 153.1 (C^3), 147.0 (C^2), 142.9 (C^6), 142.2 (C^5), 46.7 (CH), 29.9 (SCH_2), 25.3 (CH_2); GC–MS (+ve CI) t_R 4.20 min, m/z 233 ($^{35}M^+$), 235 (42%, $^{37}M^+$).

14. For further details see crystallographic data (excluding structure factors) for compounds **4** and **6** that have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 280191 and CCDC 280192. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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