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Desymmetrization of Dichloroazaheterocycles

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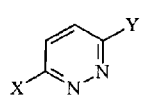
Abstract: 3,6-Dichloropyridizine **1a** was converted in good yield into its mono-iodo derivative **1b** when treated with a mixture of hydriodic acid and sodium iodide. Pure samples of the mono-iodo derivatives **2b**, **3b** and **4b** could not be obtained from their corresponding dichlorinated precursors with these reagents. Compounds **1b** and **4b** underwent palladium catalysed Suzuki, Sonogashira and other coupling reactions.

We have been interested in the synthesis of unsymmetrically substituted aza-heterocycles from readily available symmetrically substituted precursors. A number of symmetrical dichlorinated aza-heterocycles are commercially available including compounds **1a-4a** which have provided the focus for our preliminary studies reported in this paper. In order to achieve our objective we envisaged the possibility of selectively replacing one of the chlorine atoms in compounds **1a-4a** with an iodine atom giving the unsymmetrically halogenated compounds **1b-4b** respectively. This newly introduced iodo-substituent could then be replaced under relatively mild conditions in transition metal catalysed cross-coupling reactions since aryl iodides undergo oxidative addition of transition metals more readily than their corresponding aryl chlorides and hence potential problems with disubstitution at both halogen centres would be avoided. Additionally, temperature sensitive coupling partners could be employed and other reactions which generally fail with aryl chlorides (for example metal-halogen exchange reactions, free radical reactions) might be available to these aryl iodides. The remaining chloro-substituent in compounds **1b-4b** might also be replaced under more forcing conditions at a later stage since transition catalysed reactions of mono-chlorinated aza-heterocycles are well known.[1,2]

In this paper we report (a) the results of our desymmetrization studies on heterocycles **1a-4a** and (b) some reactions of the heterocycle **1b** and **4b**.



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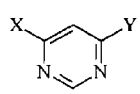

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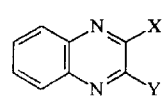

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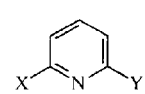

4

a X = Y = Cl; **b** X = Cl, Y = I; **c** X = Y = I

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Desymmetrization studies

We have found that 3,6-dichloropyridazine **1a** could be successfully converted into 3-chloro-6-iodopyridazine **1b** (93 % yield) by treatment with a mixture of 57 % hydriodic acid and sodium iodide at 40 °C for 4 hours. Compound **1b** was essentially free from the diiodinated product **1c** but at higher reaction temperatures and times, the proportion of diiodinated product **1c**[3] increased significantly. The ^{1}H-nmr spectrum of compound **1b** has been reported previously but no details of its preparation were disclosed.[4]

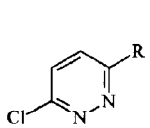
In contrast to heterocycle **1a**, 4,6-dichloropyrimidine **2a** was very reactive towards a mixture of hydriodic acid and sodium iodide and a mixture of products was always obtained as indicated by ^{1}H-nmr spectroscopy. Even at low temperatures, a significant proportion of the diiodinated product **2c** was formed. At 40 °C the diiodo compound **2c** was the major product (> 95 %); at 0 °C for 1 hour the reaction mixture consisted of 83 % of compound **2c** and 17 % of compound **2b** and at 0 °C for 5 minutes there was 56 % of compound **2c**, 37 % of compound **2b** and 7 % of unreacted compound **2a**. At –20 °C for 20 minutes the reaction mixture consisted predominantly of starting material **2a**.

2,3-Dichloroquinoxaline **3a** showed a similar pattern of reactivity to heterocycle **2a** and gave a mixture of unreacted starting material **3a** (17 %), 2-chloro-3-iodoquinoxaline **3b** (39 %) and 2,3-diiodoquinoxaline **3c** (44 %) with these reagents at 0 °C for 1 hour by gc/ms.

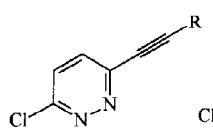
We have also investigated the reaction of 2,6-dichloropyridine **4a** with hydriodic acid and sodium iodide under various reaction conditions and found that a mixture of products was always formed. In a typical reaction at 100 °C for 14 hours the ratio of **4a**:**4b**:**4c** was found to be 1:20:3 by gc/ms.

Reactions of heterocycles 1b and 4b

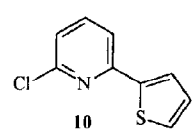
When compound **1b** and either thiophene-2-boronic acid or phenylboronic acid were subjected to a Suzuki reaction in boiling dimethoxyethane, compounds **5**[5] and **6**[6] respectively could be obtained in good yields.[7] Under Sonogashira conditions, compound **1b** reacted with phenylacetylene and 2-methyl-3-butyn-2-ol at room temperature giving the alkynes **8**[8] (26 % yield) and **9** (17 % yield) after chromatography. Interestingly, 3,6-dichloropyridazine **1a** and phenylacetylene have been reacted with these co-reagents at 70 °C yielding compound **8** (37 % yield) together with the di-alkynylated product and other products.[8] Compound **1b** has also been reacted with the trifluoromethyl anion (generated by heating a mixture of $ClCF_2CO_2Me$, CuI and KF in DMF at 115 °C[9]) giving the novel trifluoromethylated heterocycle **7** in 25 % yield after chromatography.



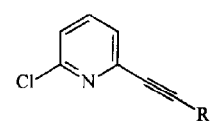
5 R = 2-thienyl
6 R = Ph
7 R = CF_3



8 R = Ph
9 R = $C(Me)_2OH$



10



11 R = Ph
12 R = $C(Me)_2OH$

Although a pure sample of heterocycle **4b** could not be prepared on a synthetically useful scale, a mixture of heterocycles **4a** and **4b** (prepared by treatment of compound **4a** with hydriodic acid and sodium iodide) could be subjected to Suzuki and Sonogashira reactions and the unreacted 2,6-dichloropyridine **4a** removed during purification. Thus, compound **10**[10] (78 %) was obtained from a Suzuki reaction with thiophene-2-boronic acid and the alkynes **11** (46 %) and **12** (47 %) were produced in Sonogashira reactions.

Conclusions

The unsymmetrical heterocycle **1b** can be prepared from its symmetrical dichloro precursor **1a** by treatment with hydriodic acid and sodium iodide. With these reagents, the dichlorinated heterocyles **2a**, **3a** and **4a** always gave a mixture of products.

Experimental

^{1}H-nmr spectra were determined at 270 MHz and high resolution mass spectra refer to the ^{35}Cl isotope. Silica gel was used for column chromatography. In the preparation of compounds **10** - **12** from **4b**, the **4b** is impure (see text) containing amounts of dichloro **4a** material and mass quantities have not been corrected for these impurities.

Reaction of **1a** *with hydriodic acid and sodium iodide*. A mixture of **1a** (10.0g, 67.1 mmol) and sodium iodide (13.5 g, 90 mmol) in hydriodic acid (50 mL) under a nitrogen atmosphere was heated at 40 °C for 24 h. After cooling to room temperature the mixture was then poured into a mixture of ice and concentrated sodium hydroxide solution and stirred for 10 min. The mixture was then extracted with dichloromethane (DCM) and the organic extracts were washed with water, dried (Na_2SO_4) and evaporated giving compound **1b** as a yellow solid (13.7 g, 85 %), m.p. 110-112 °C. [Found: C, 19.7; H, 0.4; N, 11.3; M^+, 239.8940, $C_4H_2ClIN_2$ requires C, 20.0; H, 0.5; N, 11.65%; *M*, 239.8951], δ ($CDCl_3$) 7.82 (1H, d, *J* 8.9 Hz), 7.23 (1H, d, *J* 8.9 Hz).
Reaction of **2a** *with hydriodic acid and sodium iodide*. In a similar manner to that described above, **2a** (0.5 g, 3.35 mmol), sodium iodide (0.68 g, 4.5 mmol) and hydriodic acid (10 mL) gave the mixture of products indicated in the text depending upon the reaction time and temperature. δ($CDCl_3$) **2a** 8.87 (1H, s) and 7.46 (1H, s); **2b** 8.69 (1H, s) and 7.88 (1H, s); **2c** 8.56 (1H, s) and 8.28 (1H, s).
Reaction of **3a** *with hydriodic acid and sodium iodide*. In a similar manner to that described above, compound **3a** (0.5 g, 2.51 mmol), sodium iodide (0.51 g, 3.34 mmol) and hydriodic acid (10 mL) at 0 °C for 1 h gave a mixture of **3a** (17 %), **3b** (39 %) and **3c** (44 %) by gc/ms.
Reaction of **4a** *with hydriodic acid and sodium iodide*. In a similar manner to that described above, **4a** (3.7 g, 25 mmol), sodium iodide (5.0 g, 33 mmol) and hydriodic acid (15 mL) at 100 °C for 14 h gave the mixture of products indicated in the text by gc/ms.
3-Chloro-6-(2'-thienyl)pyridazine **5**. A mixture of **1b** (0.5 g, 2.08 mmol), thiophene-2-boronic acid (0.28 g, 2.18 mmol) and $Pd(PPh_3)_2Cl_2$ (0.06 g) in 2M aqueous Na_2CO_3 solution (2.5 mL), and dimethoxyethane (DME) (12.5 mL) under a nitrogen atmosphere was heated at 100 °C for 12 h. After cooling to room temperature the reaction mixture was extracted with DCM and the organic extracts were washed with water, dried (Na_2SO_4) and evaporated giving the crude product (0.44 g). The crude product was shown to be a mixture of **5** (66 %) and **1b** (34 %) by gc/ms. A small amount was recrystallized from ether giving compound **5** as white solid, m.p. 160-62 °C (lit.[6] m.p. 157-59 °C), δ ($CDCl_3$) 7.71 (2H, m), 7.52 (2H, m) and 7.16 (1H, m).
2-Chloro-6-phenylpyridizine **6**. A mixture of **1b** (0.5 g, 2.08 mmol), phenylboronic acid (0.27 g, 2.18 mmol) and $Pd(PPh_3)_2Cl_2$ (0.2 g) in 2M aqueous Na_2CO_3 solution (2.5 mL) and DME (15 mL) under a N_2 atmosphere was heated at 100 °C for 12 h. After cooling to room temperature the reaction mixture was extracted with DCM and the organic extracts were washed with water, dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography (eluent; petroleum ether b.p. 40-60 °C: ethyl acetate 5:1) giving **6** (0.33 g, 85 %) as a white solid, m.p.158-160 °C (lit.[7] m.p. 159-161 °C), δ ($CDCl_3$) 8.03 (2H, m), 7.84 (1H, d, *J* 8.9 Hz) and 7.57 (m, 4H).
2-Choro-6-trifluoromethylpyridazine **7**. A mixture of **1b** (1.0 g, 4.16 mmol), methyl chlorodifluoroacetate (1.20 g, 8.32 mmol), potassium fluoride (0.48 g, 8.32 mmol) and CuI (1.19 g, 6.24 mmol) in dimethylformamide (75 mL) under a nitrogen atmosphere was heated at 115 °C for 5 h. After cooling to room temperature the solvent was removed under reduced pressure and the residue partitioned between DCM and water. The organic extract was washed with water, dried (Na_2SO_4) and evaporated. The crude product which was purified by column chromatography over silica gel (eluent; petroleum ether b.p. 40-60 °C: ethyl acetate 9:1) giving compound **7** as a pale yellow solid (0.19 g, 25 %), m.p. 50-52 °C. [Found: C, 32.9; H, 0.9; N, 15.0. $C_5H_2ClF_3N_2$ requires C, 32.9; H, 1.1; N, 15.35 %]. δ ($CDCl_3$) 7.82 (1H, d, *J* 9 Hz) and 7.73 (1H, d, *J* 9 Hz).
3-Chloro-6-(2-phenylethynyl)pyridazine **8**. A mixture of **1b** (1.0 g, 4.15 mmol), phenylacetylene (0.43 g, 4.15 mmol), CuI (0.1 g) and $Pd(PPh_3)_2Cl_2$ (0.1 g) in triethylamine (5 mL) and diisopropylamine (5 mL) under a

nitrogen atmosphere was stirred at room temperature for 24 h. The mixture was quenched in DCM and passed through a short plug of silica gel. The organic extracts were washed with water, dried (Na_2SO_4) and evaporated. The crude product which was purified by column chromatography (eluent; petroleum ether b.p. 40-60 °C: ethyl acetate 3:1) giving compound **8** (0.23 g, 26 %) as a white solid, m.p. 102-103 °C (lit.[9] m.p. 107-108 °C), δ ($CDCl_3$) 7.63 (3H, m), 7.51 (1H, d, *J* 8.9 Hz) and 7.40 (3H, m).

3-Chloro-6-(3-methyl-3-hydroxybutynyl)pyridazine **9**. Using 2-methyl-3-butyn-2-ol and a similar method to that described above, compound **9** was obtained as a white solid (17 %), m.p. 114-116 °C. [Found: C, 54.65; H, 4.5; N, 13.95; M^+, 196.0396. $C_9H_9ClN_2O$ requires C, 55.0; H, 4.6; N, 14.25%, *M*, 196.0403], δ ($CDCl_3$) 7.50 (2H, AB system, δ_A 7.51, δ_B 7.48, J_{AB} 9 Hz), 2.81 (1H, s) and 1.67 (6H, s).

2-Chloro-6-(2'-thienylpyridine) **10**. A mixture of **4b** (0.2 g, 0.9 mmol), 2-thiopheneboronic acid (0.13 g, 0.99 mmol) and $Pd(PPh_3)_2Cl_2$ (0.06 g) in 2M aqueous Na_2CO_3 solution (5 mL), DME (9 mL) and water (1 mL) under a nitogen atmosphere was heated at 100 °C for 6 h. After cooling to room temperature the reaction mixture was extracted with ether and the organic extracts were washed with water, dried (Na_2SO_4) and evaporated giving the crude product (0.14 g) which was shown to be an 8:1 mixture of **10** and **4b** by ^{1}H-nmr spectroscopy. A small amount of the crude product was recrystallized from ether to give a white solid, m.p. 38-40 °C (lit. m.p.[11] 39-41 °C), δ ($CDCl_3$) 7.68 (2H, m), 7.50 (2H, m), 7.14 (2H, m).

2-Chloro-6-(2-phenylethynyl)pyridine **11**. A mixture of **4b** (0.92 g, 3.8 mmol), phenylacetylene (0.43 g, 4.18 mmol), CuI (0.1 g) and $Pd(PPh_3)_2Cl_2$ (0.1 g) in triethylamine (5 mL) and diisopropylamine (5 mL) under a nitrogen atmosphere was stirred at room temperature for 24 h. The mixture was quenched in DCM and passed through a short plug of silica gel eluting with DCM. The organic extracts were washed with water, dried (Na_2SO_4) and evaporated giving the crude product as an orange solid. The crude product was purified by column chromatography over silica gel (eluent: petroleum ether, b.p. 40-60 °C, ethyl acetate 3:1) giving compound **11** as a pale yellow solid (0.38 g, 46 %), m.p. 116-118 °C. [Found: M^+ 213.0341. $C_{13}H_8ClN$ requires *M*, 213.0345], δ ($CDCl_3$) 7.68 (1H, t, *J* 7.2 Hz), 7.60 (2H, m), 7.47 (1H, d, *J* 7.2 Hz) and 7.36 (4H, m).

2-Chloro-6-(3-methyl-3-hydroxybutynyl)pyridine **12**. A mixture of **4b** (1.0 g, 4.18 mmol), 2-methyl-3-butyn-2-ol (0.36 g, 4.18 mmol), CuI (0.1 g) and $Pd(PPh_3)_2Cl_2$ (0.1 g) in triethylamine (5 mL) and diisopropylamine (5 mL) under a nitrogen atmosphere was stirred at room temperature for 24 h. The mixture was quenched in DCM and passed through a short plug of silica gel eluting with DCM. The organic extracts were washed with water, dried (Na_2SO_4) and evaporated giving the crude product which was purified by column chromatography over silica gel (eluent: petroleum ether, b.p. 40-60 °C, ethyl acetate 3:1) affording **12** as an orange oil (0.38 g, 47 %). [Found: M^+, 195.0451. $C_{10}H_{10}ClNO$ requires *M*, 195.0451], δ ($CDCl_3$) 7.61 (1H t, *J* 7.6 Hz), 7.28-7.34 (2H, m), 2.77 (1H, s) and 2.05 (6H, s).

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References and notes

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