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LETTERS

Regioselective substitution of 2,3-dichloro-6-amino-quinoxaline

Emma Ford,* Andy Brewster, Geraint Jones, John Bailey and Neil Sumner

AstraZeneca, Mereside, Alderley Park, Macclesfield, Cheshire, SK10 4TG, UK

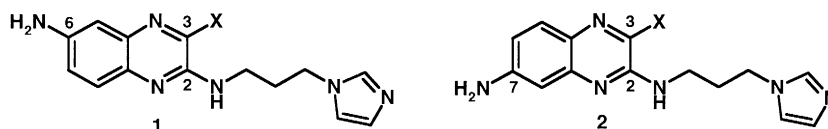
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Abstract

The novel regioselective substitution of 2,3-dichloro-6-amino-quinoxaline is described. A range of nucleophiles were used to provide 2,3-disubstituted-6-aminoquinoxalines with complementary regiochemistry to that obtainable using published methodology. © 2000 Elsevier Science Ltd. All rights reserved.

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As part of a recent study of the biological properties of substituted quinoxalines, we wished to examine a range of 2-amino-3-substituted 6- and 7-aminoquinoxalines **1** and **2**, where the substituent on C-3 would include groups linked through carbon and sulfur.

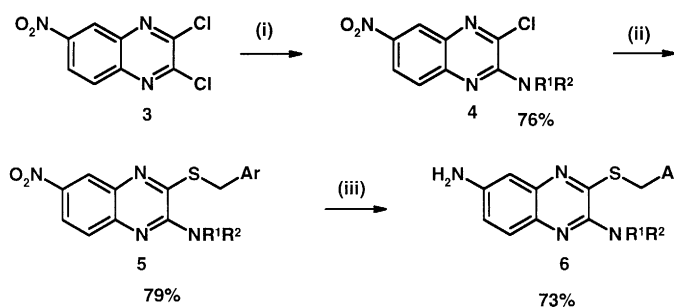


Analogues of compound **1** were readily available via the sequential addition of nucleophiles to 2,3-dichloro-6-nitroquinoxaline **3**^{1,2} as exemplified in Scheme 1. However, compound **2** proved less readily accessible. Attempts to carry out an initial thiol substitution at C-2 of **3** led to a mixture in which the major component was the bis-thioether **7** (Scheme 2). Addition of carbon-based nucleophiles e.g. using the Suzuki reaction on **3** led to incomplete reaction with significant hydrolysis of product and starting material. Non-aqueous conditions were also unsuccessful and so a new approach was thus needed to synthesise the alternative regioisomers of **6**.

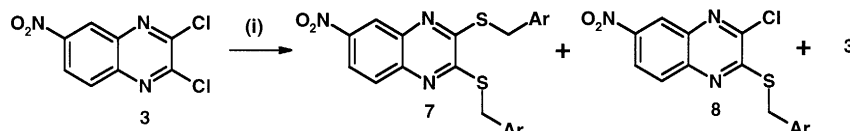
Sarges et al.³ have shown that 2,3-dichloro-6-methoxyquinoxaline reacts with hydrazine to give exclusively the desired regiochemistry, e.g. substitution at C-3. The 6-chloro and 6-fluoro analogues behaved similarly. On the other hand, Katoh et al.² obtained mixtures of regioisomers from the reaction of 2,3,6-trichloroquinoxaline with 2-aminopyridine, although this could be explained by the ambident nucleophilic character of 2-aminopyridine.

We reasoned that 2,3-dichloro-6-aminoquinoxaline should react with nucleophiles to give reverse regioselectivity to that seen with 2,3-dichloro-6-nitroquinoxaline, thereby affording our target com-

* Corresponding author.

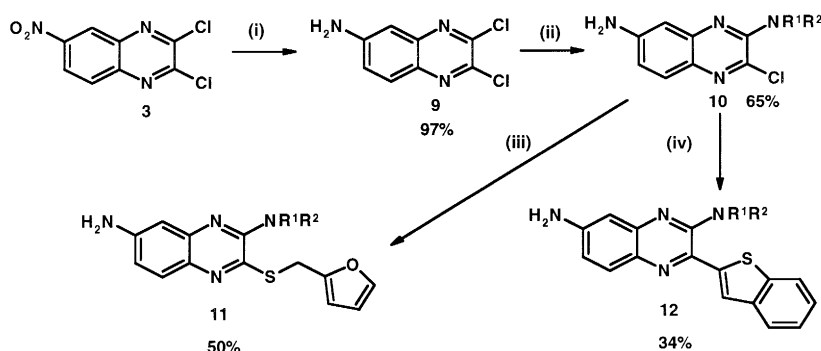


Scheme 1. (i) HNR^1R^2 (2 equiv.), DMA, rt, 1–2 h; (ii) ArCH_2SH , NaH, DMF, rt, 3 h; (iii) $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$, EtOAc, 90°C, 1 h



Scheme 2. (i) ArCH_2SH , K_2CO_3 , acetone, rt, 3 h⁵

pounds **2**. Reduction of **3** to 6-amino-2,3-dichloroquinoxaline, **9**⁴ was readily accomplished using tin(II) chloride dihydrate in ethyl acetate, at reflux for 1 h. As anticipated, addition of amines to **9** occurred regioselectively to give **10**. This was later proved by comparison of NMR data of isomeric final products. Subsequent addition of a second nucleophile then displaced the remaining chlorine atom to give the desired products **11** and **12** (Scheme 3). Interestingly, **9** gave similar regioselectivity in its reaction with other nucleophiles, e.g. thiols.



Scheme 3. (i) $\text{SnCl}_2 \cdot \text{H}_2\text{O}$, EtOAc, 90°C, 1 h; (ii) Amine (xs), 90°C, 30 min; (iii) furfuryl mercaptan (1.1 equiv.), NaH (1.1 equiv.), DMF, rt, 3 h; (iv) benzo-[b]-thiophene-2-boronic acid, satd aq. Na_2CO_3 , $\text{Pd}(\text{PPh}_3)_4$, toluene, 100°C, 4 h

Conclusions. Sequential nucleophilic substitution of 2,3-dichloro-6-aminoquinoxaline gives 2,3-disubstituted-6-aminoquinoxalines with complementary regiochemistry to that obtained when 2,3-dichloro-6-nitroquinoxaline is used.

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5. Isolated yields are given for all reactions except those in Scheme 2 where yields were not optimised or finalised.