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Efficient synthesis of the selective COX-2 inhibitor GW406381X

Andrew J. Whitehead,* Richard A. Ward and Martin F. Jones†

Synthetic Chemistry, GlaxoSmithKline Research and Development Limited, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, UK

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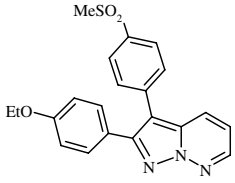
Abstract—An efficient synthesis of the selective COX-2 inhibitor GW406381X is described via a novel intramolecular Mannich-type cyclisation to construct the pyrazolo-[1,5*a*]-pyridazine heterocyclic core.

The potent and highly selective COX-2 inhibitor, GW406381X, **1**, is currently being developed for the treatment of chronic inflammatory pain associated with osteoarthritis, rheumatoid arthritis and chronic lower back pain. An interesting structural feature of this compound is that it contains the rare pyrazolo-[1,5*a*]-pyridazine ring system of which there are few reports within the chemical literature.[1]



GW406381X
1

The discovery route for the synthesis of GW406381X is depicted in Scheme 1.[2]

A number of factors made this approach unsuitable as a long term supply route capable of delivering substantial quantities of **1** for development activities. For example, the highly atom inefficient Corey–Fuchs reaction used in the synthesis of aryl propriolate, and the low yielding [3+2] cycloaddition which requires an excess of **2** and leads to the formation of significant quantities of insoluble residues.

The key step in this original synthesis is the [3+2] cycloaddition of an ylide derived the aminopyridazine salt **2** with aryl propriolate **3** to give pyrazolopyridazine **4**. This step requires several equivalents of aminopyridazine salt **2** to afford a less than the adequate yield of pyrazolopyridazine **4**. All attempts to effect this transformation in acceptable yields failed. The low yield for this reaction was attributed to both the instability of the ylide leading to insoluble by-products, and, to the disproportionation of the initial dihydropyrazolopyridazine adduct **6** of the [3+2] cycloaddition to give the desired product **4** and tetrahydropyridazine **7** (Scheme 2).

Despite concerted attempts to optimise this original route and remove some of the issues it became clear that an alternative synthesis of GW406381X was required.

Initial work concentrated on evaluating alternative routes to the core pyrazolopyridazine based on literature precedent. Such efforts proved unproductive and it quickly became apparent that a novel synthesis of **1** was required.

It was postulated that dihydropyrazolopyridazine **8** could be made by an intramolecular aza-Mannich type reaction as depicted in Scheme 3. In turn the enamine required for this reaction could be made from imine **9** which could be made via the condensation of ketone **11** with *N*-aminopyridazinium salt **10**.

Hence, Friedel–Crafts acylation of phenetole with the commercially available 4-methylsulfonylphenylacetic

* Corresponding author. Tel.: +44 1438 763738; e-mail: andrew.j.whitehead@gsk.com
† Present address: Process Research and Development, AstraZeneca, Silk Road Business Park, Charter Way, Macclesfield, Cheshire SK10 2NA, UK.

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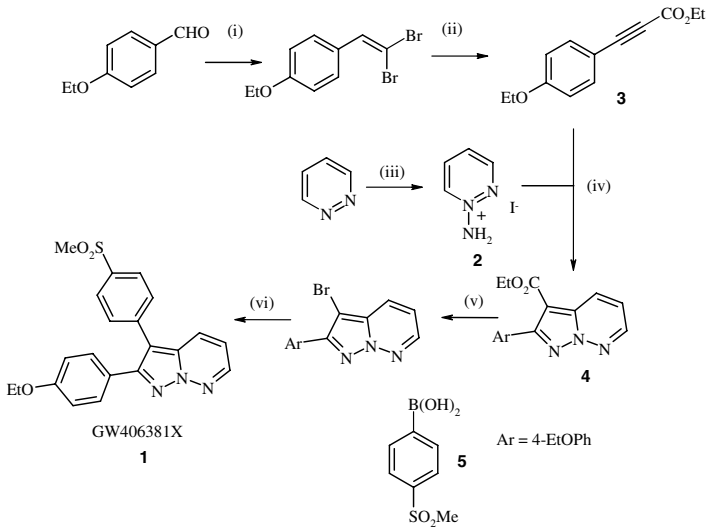
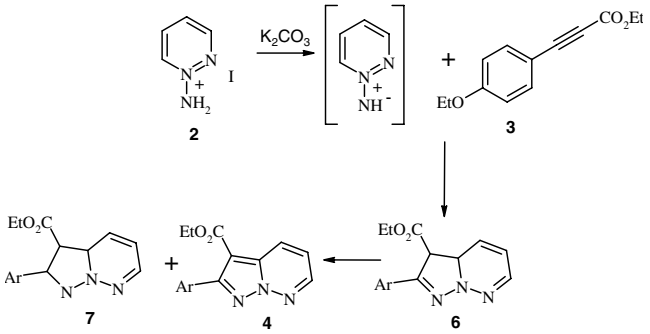
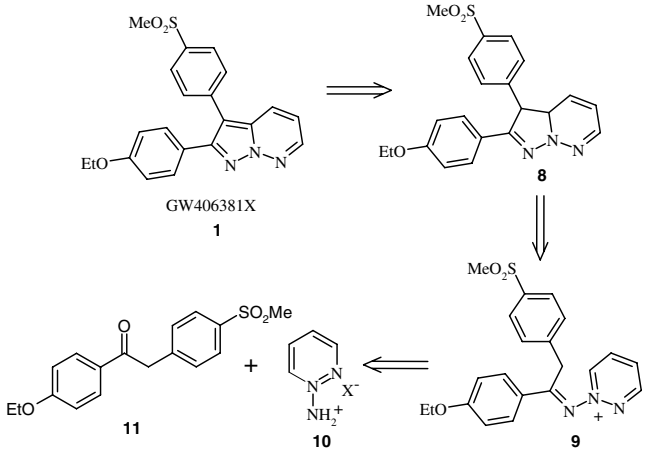


Scheme 1. Reagents and conditions: (i) CBr_4/Ph_3P, CH_2Cl_2, 80%; (ii) *n*-BuLi, Et_2O then MeO_2CCl, 72%; (iii) H_2NOSO_3H, K_2CO_3, H_2O then KI, 40%; (iv) K_2CO_3, DMF, 40%; (v) aq NaOH then NBS/Na_2CO_3, 78%; (vi) (**5**), $Pd(PPh_3)_4$, DMF, Na_2CO_3, 75%.



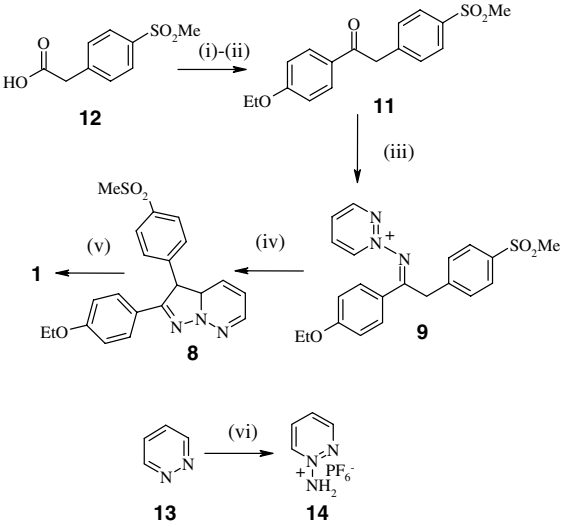
Scheme 2.



Scheme 3.

acid **12** afforded ketone **11** in a 68% isolated yield following crystallisation. Typically a 4:1 ratio of *para*:*ortho* isomers is observed in this reaction and <1% of the *ortho* regioisomer is carried through into the crystallised product **11**. Aminopyridazine salt **10** was prepared by simply aminating an aqueous solution of pyridazine **13** with hydroxylamino-*O*-sulfonic acid (with control of the pH). In the first instance the aminopyridazine was isolated as its iodide salt **2** which required a highly convoluted isolation procedure from the aqueous reaction mixture, involving evaporating water and extracting solid residues with hot methanol. This was circumvented by simply preparing hexafluorophosphate salt **14** by the addition of potassium hexafluorophosphate following amination, and crystallisation direct from the aqueous reaction mixture.

The key step in this new synthesis is the condensation of the aminopyridazine salt **14** with ketone **11** in the presence of titanium tetrachloride (Scheme 4). Attempts to use Brønsted acids such as *para*-toluene sulfonic acid or alternative Lewis acids to effect this condensation were less successful. The initially formed imine **9**, on the addition of a base such as triethylamine or tetra-



Scheme 4. Reagents and conditions: (i) $SOCl_2$, CH_2Cl_2; (ii) phenetole, $AlCl_3$, CH_2Cl_2, 68% yield for both steps; (iii) (**14**), $TiCl_4$, CH_2Cl_2; (iv) Et_3N; (v) 10% Pd/C or I_2, 65% yield for three steps; (vi) NH_2OSO_3H then KPF_6, 80%.

methylethylenediamine, was found to undergo an intramolecular Mannich type reaction to afford dihydropyrazolopyridazine **8** as a mixture of diasteroisomers. This can be either dehydrogenated with catalytic Pd/C or oxidised with iodine to afford GW406381X, **1**, in ca. 85% overall isolated yield for the three chemical transformations.[3] Following an aqueous workup the crude product is isolated as a brown solid which is then recrystallised from aqueous acetone.

In conclusion an efficient synthesis of the selective COX-2 inhibitor, GW406381X, **1** from commercially available starting materials using a novel intramolecular Mannich type cyclisation to access the pyrazolo-[1,5*a*]-pyridazine heterocyclic core is described. The generality of this novel reaction is currently under investigation. This chemistry has been used to prepare significant quantities of GW406381X.

References and notes

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