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A one-pot sulfide to sulfone oxidation with *m*-chloroperoxybenzoic acid and sodium permanganate

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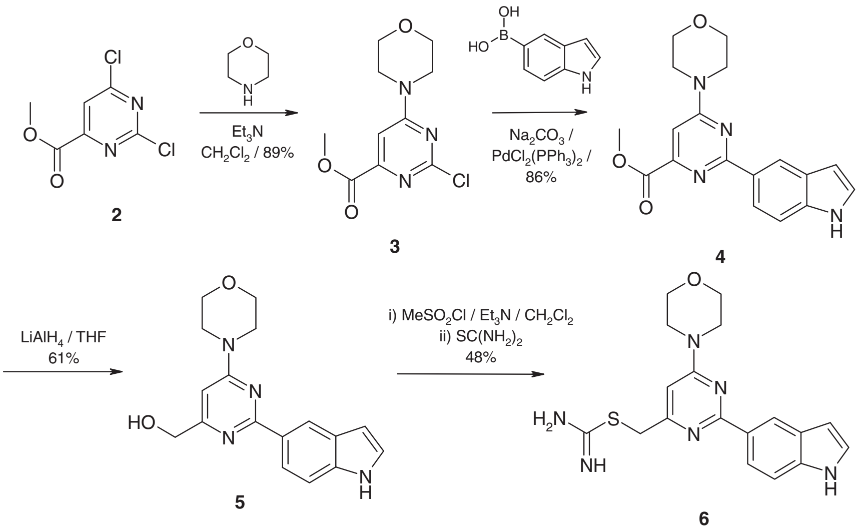
A synthetic strategy towards [2-(1*H*-indol-5-yl)-6-morpholin-4-ylpyrimidin-4-yl]methylsulfones is described, utilising *m*-chloroperoxybenzoic acid and sodium permanganate in a one-pot sulfide-sulfone oxidation.

As part of our ongoing studies, we sought to explore the structure–activity relationships around the sulfone moiety in a series of morpholinopyridines exemplified by structure **1**.[1] These compounds can be prepared from methyl 2,4-dichloro-6-pyrimidinylcarboxylate via reaction with morpholine and subsequent Suzuki reaction with 5-indolylboronic acid. The methyl ester can be reduced to the alcohol, converted into the thiol, alkylated and finally oxidised to the sulfone. We wished to assemble a small library of



Scheme 1. Preparation of the functionalised pyrimidine.

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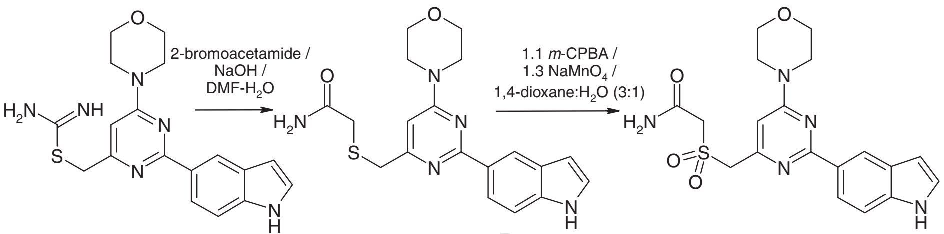
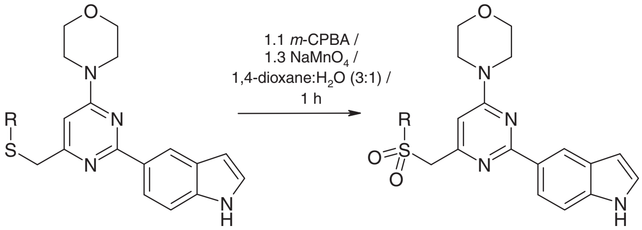


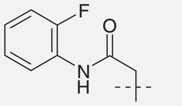
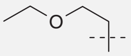
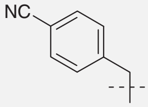
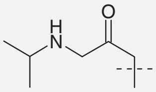
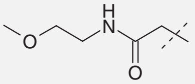
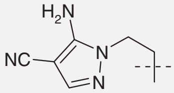
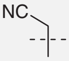
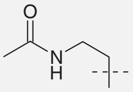
6 7 8

Scheme 2. Preparation and oxidation of the sulfide.

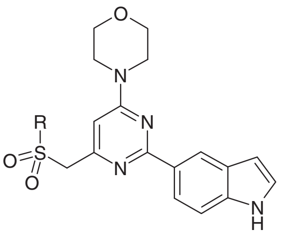
Table 1
One-pot oxidation of sulfides **7a**–**h** to sulfones **8a**–**h**



7a-h 8a-h

Sulfide **7**	R=	Yield (%)
7a		46
7b		76
7c		43
7d		34
7e		66
7f		52
7g		56
7h		68

sulfones and since the diversification would be introduced in the penultimate sulfide-forming step, a reliable method for the oxidation of a sulfide group to the sulfone, subsequent to the diversification step, was required.[2]



1

The dichloropyrimidine[3] **2** was treated with morpholine and triethylamine in dichloromethane to give the mono-chloropyrimidine **3** in 89% yield. This chloride was coupled with 5-indolylboronic acid under Suzuki conditions using dichlorobis(triphenylphosphine)palladium(II) and sodium carbonate in 18% *N*,*N*-dimethylformamide, in 7:3:2 dimethoxyethane/water/ethanol at 120 °C for 30 min in a microwave reactor to afford the ester **4** in 86% yield. Reduction of ester **4** was achieved with lithium aluminium hydride to give alcohol **5** in 61% yield. Conversion of alcohol **5** into the mesylate (methanesulfonyl chloride/triethylamine/dichloromethane) and then reaction with thiourea gave thioimidate **6** in 48% yield after SCX purification (Isolute SCX-2, the desired product was eluted with 0.35 M ammonia/methanol) (Scheme 1).

The masked thiolate was revealed and then alkylated in a one-pot procedure with sodium hydroxide and the appropriate alkyl bromide in *N*,*N*-dimethylformamide and water to give the sulfide.[4] Thus, reaction of the masked thiolate **6** with 2-bromoacetamide gave thiolate **7**. Initial attempts were made to oxidise sulfide **7** to sulfone **8** with *m*-chloroperoxybenzoic acid and Oxone. However, despite apparent facile oxidation to the sulfoxide as was evident from LC–MS analysis, further oxidation to sulfone **8** was plagued with over-oxidation problems, presumably linked to N-oxidation of the pyrimidine ring.

It is known that sodium permanganate is a mild and selective oxidant for sulfoxides to sulfones.[5] We reasoned that the one-pot combination of the oxidants *m*-chloroperoxybenzoic acid and sodium permanganate would provide, selectively, the required sulfones from the sulfides. Gratifyingly when sulfide **7** was treated with *m*-chloroperoxybenzoic acid and sodium permanganate in 1,4-dioxane/water (3:1) for 5 h sulfone **8** was obtained in 56% yield after purification by SCX chromatography (Scheme 2). We next sought to determine whether this one-pot procedure was widely applicable. A range of sulfides **7a**–**h** was prepared and oxidised under the standard conditions (Table 1).[6]

In total, over 100 sulfones were prepared in a library fashion using this procedure although the yields were not optimised. The crude reaction mixtures were subjected to SCX purification and then reverse-phase HPLC to provide pure isolated material in good to moderate yields. A range of functional groups are tolerated including nitriles, amines and nitrogen-containing heterocycles. In conclusion, we have found a one-pot reagent combination allowing the selective conversion of sulfides into sulfones in the presence of other oxidisable functions within the same molecule.

References and notes

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6. *Typical procedure*: The sulfide (0.3 mmol) was dissolved in 1,4-dioxane/H_2O (3 ml:0.5 ml) and treated with *m*-CPBA (75%, 1.1 equiv) followed immediately by sodium permanganate (1.3 equiv). The mixture was stirred at 21 °C for 1 h. The mixture was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 0.35 M NH_3/MeOH and pure fractions were evaporated to dryness to afford the crude product. This was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of H_2O (containing 0.1% NH_3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the pure product.