The Chemical Development of the Commercial Route to Sildenafil: A Case History

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Abstract:
This paper is a case history of the chemical development of sildenafil which covers various aspects of work in chemical development namely: route selection, scale-up issues, the development of an efficient synthesis with high throughput, process safety, and environmental issues. Interesting chemical points include improved methods of preparing pyrazolo[4,3-d]-pyrimidines and the unusual isolation of an intermediate as its double salt (10). The potential dangers of nitrating pyrazole-5-carboxylic acids which are activated to a decarboxylation reaction are discussed.

Introduction
Sildenafil is a selective inhibitor of phosphodiesterase 5 (PDE5) and is the first agent with this mode of action for the treatment of male erectile dysfunction (a disease more commonly known as male impotence). This new drug was approved for prescription use within the United States and the European Union during 1998 and has become one of the fastest-selling drugs of all time. Male erectile dysfunction is a widespread condition which effects an estimated 30 million men and their partners in the United States.1

The Medicinal Chemistry Route
The medicinal chemistry route3 is outlined in Scheme 1. This route was used for the synthesis of early toxicity and clinical batches and with the normal development modifications was perfectly serviceable for the synthesis of development quantities. However, this route was suboptimal as a commercial manufacturing route for the following reasons:

- The route is linear (nine linear steps).
- Potentially toxic materials [such as the sulphonyl chloride (7)] are in the final bond-forming reaction. Multiple recrystallisations of the final material were required to get the usual high-quality material required by the pharmaceutical industry and to get these potentially toxic impurities to appropriately low levels.
- The difficulties of scaling up chlorosulphonation reactions are well-known in chemical development due to competing hydrolysis during the increased quench times on scale-up (and this was also noted for this project). Having the chlorosulphonation late in the synthesis meant that these yield losses occurred from a more expensive intermediate.
- Chlorosulphonating a late-stage, relatively high molecular weight intermediate, leads to larger quench volumes and hence increases both aqueous waste streams and the environmental burden.

A key finding during the development of the medicinal chemistry route, which impacted on the programme as a whole, was the optimisation of the cyclisation reaction to make the pyrimidinone (6). The medicinal chemistry method was to cyclise compound 4 with an aqueous alcoholic solution of sodium hydroxide and hydrogen peroxide. A literature review of alternative cyclisation methods revealed that such reactions had previously only been performed in moderate yield (30–70%). The main side product from the medicinal chemistry reaction, in the presence or absence of hydrogen peroxide, was the hydrolysis of the carboxamide to give the acid (5). By conducting the cyclisation under anhydrous conditions, KOtBu/tBuOH, the hydrolysis side product was avoided, and the reaction proceeded in 100% isolated yield with no impurities detected. This exceptionally clean reaction led us to consider reordering the steps so that the clean cyclisation was the final bond-forming reaction.

Strategic Commercial Route Selection

A summary of the two routes is outlined in Scheme 2 below. The flow diagrams in Scheme 2 clearly show that the strategic advantages of the commercial route were as follows:

- Greater convergency.
- The clean cyclisation reaction is now at the end of the synthesis in the final bond-forming step. The potentially toxic materials now occur near the start of the synthesis.
- The scale-up and environmental issues associated with the chlorosulphonation reaction are placed earlier in the synthesis and are associated with a cheaper, lower molecular weight material, hence minimising the problems.

Commercial Route Development

(a) Preparation of the Sulphonamide (8). The chlorosulphonation of 2-ethoxybenzoic acid was reasonably straightforward although it was essential to add thionyl chloride to ensure the intermediate sulphonic acid was converted to the sulphonyl chloride (9) (see Figure 1). The sulphonamide was originally prepared and isolated as an unusual double salt (10). This had two main disadvantages. First, it was found that to get the double salt to crystallise, the in-going sulphonyl chloride needed to be dry. The problems of drying sulphonyl chlorides on a pilot plant scale are well-known, and as expected, we obtained a lot of acidic, corrosive fumes in our pilot plant ovens. The second problem was that the double salt was very insoluble and was difficult to process onwards using scaleable methods. Both problems were solved when on treatment with water, the double salt spontaneously dissociated to give a new crystalline form of the free amino acid (8). This procedure had been run many times before without crystallisation and shows the importance of having a seed in crystallisation. In our experience a seed is particularly important with zwitter-ionic compounds such as (8).

The process was quickly redesigned to take advantage of this new finding. The water-wet sulphonyl chloride could...
be used directly in the sulphonamide reaction which was now performed in water. On completion of the reaction, the product was isolated by pH adjustment to the isoelectric point and collection of the precipitated sulphonamide by filtration.

(b) Hydrogenation and Coupling Reaction. The stannous chloride/hydrochloric acid reduction of (3) as used by medicinal chemistry was replaced by a palladium-catalysed hydrogenation reaction to give the amine (12) (see Figure 2). Activation of the carboxylic acid for the coupling reaction was initially examined using either thionyl chloride or oxalyl chloride to make the acid chloride. Eventually we decided to use a slightly more expensive coupling agent, N,N’-carbonyldiimidazole (CDI), which had the following advantages and in our view outweighed the small additional cost:

- The nitro reduction, acid activation, and acylation reactions could all be performed in ethyl acetate as solvent. All three reactions could thus be telescoped into a single step.
- The process step had a very low environmental impact. There was no aqueous waste stream, and the use of ethyl acetate as a single solvent allowed for easy solvent recovery.

- The process was very simple, just mixing ethyl acetate solutions of the imidazolide (11) and the amine (12) gave the desired amide (13) which crystallised directly from the reaction. The main by-product, imidazole, was very soluble in ethyl acetate and remained in the mother liquors.
- The process was very robust. Ethyl acetate solutions/suspensions of the amine, imidazolide or the acylation mixture could be refluxed for several days without any detriment to the quality of the isolated product.

On scale-up into the full manufacturing plant some problems were observed charging CDI (a sticky hygroscopic reagent) through charging chutes. Additional in-process controls had to be put in place to ensure a robust and reproducible manufacturing process.

(c) Cyclisation Reaction. The final bond forming reaction was performed by heating the amide (13) with 1.2 equiv of potassium tert-butoxide at reflux for several hours (Figure 3). A simple high throughput isolation was devised, in which the reaction was diluted with water and acidified with 4 M hydrochloric acid to the isoelectric point (pH 7.5). Clinical quality sildenafil was obtained directly from the reaction by filtration, and hence our strategy of using the clean reaction at the final step had been reduced to successful practice.

Process Safety

All reactions were evaluated in detail for exothermic reactions and decompositions, and in our view, the nitration reaction to give the pyrazole (2) posed the most significant hazard and is worthy of further discussion. Initial differential scanning calorimetry (DSC) screening showed no cause for concern with the intermediate (1); however the nitropyrazole (2) showed two exotherms. The first exotherm was detected at 130 °C by DSC and evolved 16.2 kJ/mol and was attributed to the decarboxylation reaction of the acid (2). This is a well-known reaction which provides synthetic access to 3-nitropyrazoles which are unsubstituted in the 4-position.6 The second much larger exothermic event was detected at 295 °C by DSC and evolved 294 kJ/mol. It was calculated that at normal chemical reaction concentrations (approx 6 L/kg) the energy in the first exothermic event was not sufficient to raise the reaction temperature to a point which could trigger the second decomposition under adiabatic conditions. The nitropyrazole (2) was then examined further using a Setaram C80 calorimeter and a Phi-Tec adiabatic calorimeter, and these tests detected the two exotherms at 115 °C and 220 °C. The first exotherm was accompanied by gas evolution and a corresponding pressure rise, and the

Figure 1.

Figure 2.

Figure 3.

(5) DSC performed at a scanning rate of 10 °C/min.
second exotherm rapidly became self-sustaining and violent, causing large self-heats and pressure increases.

It was also discovered that in highly acidic media (i.e., the reaction mixture) the onset temperature for the start of exothermic decarboxylation was reduced to around 100 °C, and hence a process needed to be devised in which there was no possibility of this reaction temperature being reached.

Hence, our major concerns in scaling up this reaction were the following:

1. That if the decarboxylation reaction temperature was reached, the large volume of carbon dioxide produced could lead to excessive frothing or an unacceptable pressure increase.

2. That uncontrolled reaction could lead to a catastrophic runaway conditions.

The medicinal chemistry procedure involved adding solid pyrazole (1) to a mixture of fuming nitric acid and oleum at 50 °C. This procedure involved the liberation of 249 kJ/mol of heat, and it was calculated that under adiabatic conditions this reaction (with a dilution of 6 L/kg) had the potential to raise the temperature from 50 to 127 °C, well above the decomposition reaction temperature.

It was decided to break the procedure down into three parts in order to minimise the available energy. First, the pyrazole (1) was dissolved in concentrated sulphuric acid, eliminating 67 kJ/mol of energy from the reaction. Next, the fuming nitric and concentrated sulphuric acids were mixed, eliminating 44 kJ/mol from the reaction. We wanted to run the reaction at around 6 L/kg so as to keep throughput high and minimise the aqueous environmental waste in the quench reaction. However, under these conditions the potential adiabatic temperature rise was still 50–92 °C, which we felt was still unacceptably close to the decomposition start point. Reducing the reaction temperature would lower this potential rise but would increase the level of accumulated reactants and in our opinion did not add to the safety margin.

To introduce a greater margin of safety in traditional pilot plant equipment and to avoid any consequences of a valve jamming open, the decision was taken to only charge one-third of the nitrating mixture to the header at any one time. A HPLC analysis was then performed to ensure that the appropriate degree of reaction completion had occurred before charging the next portion of the nitrating acid mixture to the header. Under these conditions the maximum adiabatic temperature rise was calculated to be 21 °C. Obviously more sophisticated engineering solutions would provide an even greater margin of safety.

Environmental Assessment

The volume and the number and nature of solvents required by the medicinal chemistry route and by the commercial route to produce 1000 kg of drug substance are compared strikingly in the pie-charts in Figure 4. In addition the total aqueous volume was reduced by a factor of 5 by switching to the commercial route.

A further advantage of the commercial route is that the solvents are used as single organic solvents, which simplifies solvent recovery.
Conclusion

The commercial route described in this paper contains all of the desired attributes required in chemical development, namely:

- a safe, robust route
- a convergent synthesis
- a high yielding process [75.8% overall from pyrazole (2) compared with the medicinal chemistry yield of 7.5%–]
- a high throughput in production plant
- an exceptionally low environmental impact.

Experimental Section

Proton NMR data were recorded on a Varian Unity 300 spectrometer operating at 300 MHz. Microanalytical data were performed by Exeter Analytical UK Ltd. Melting points were determined on a Buchi melting point apparatus. The experimental procedures below represent the reactions when first discovered and may not be the final procedures selected for scale-up into pilot plant trials.

1-Methyl-4-nitro-3-propyl-1H-pyrazole-5-carboxylic Acid (2). 1-Methyl-3-propyl-1H-pyrazole-5-carboxylic acid (1) (1.59 kg, 9.45 mol) dissolved in concentrated sulphuric acid (6.36L) was heated to 50 °C and treated with a mixture of fuming nitric acid (90%, 0.55 L) dissolved in concentrated sulphuric acid (1.35 L). The addition was made over at least 2 h keeping the reaction temperature between 50 and 55 °C. On completion of the addition the reaction was stirred for 8 h at 50 °C, cooled to room temperature, and then carefully added to cold water (34 L, 4 °C) over 1 h, keeping the temperature below 25 °C. The precipitated title compound was granulated for 2 h, collected by filtration, and then dried in vacuo to give a white solid (1.93 kg, 96%): mp 125–127 °C (lit.3 124–127 °C). 1H NMR (CDCl3) δ = 1.05 (3H, t), 1.74 (2H, hexet), 2.91(2H, t), 4.20 (3H, s), 9.35 [1H, s(br)].

1-Methyl-4-nitro-3-propyl-1H-pyrazole-5-carboxamide (3). The carboxylic acid (2) (1 kg, 4.69mol) was slurried in toluene (5 L) and a catalytic quantity of dimethylformamide (37 mL) was added. The mixture was heated to 50 °C and thionyl chloride (0.544 L, 7.5 mol) added over 10 min. On completion of the addition the reaction was stirred and heated for 55–60 °C for 6 h. The mixture was distilled under vacuum (vessel temperature 55 to 65 °C) until 0.5 L of solvent had been removed. The mixture was cooled to 20 °C and cold (5 °C) concentrated ammonia solution (6 L) added over 100 min. The precipitated product was granulated, collected by filtration, washed with water (2 × 2 L), and dried at 50 °C to give an off white solid (0.92 kg, 92.3%): mp 140–42 °C (lit.3 141–143 °C). 1H NMR (CDCl3) δ 1.02 (3H, t), 1.74 (2H, hexet), 2.90 (2H, t), 4.07 (3H, s), 6.13 [1H, s (br)], 7.52 [1H, s(br)].

5-Chlorosulphon-2-ethoxybenzoic Acid (9). Molten 2-ethoxybenzoic acid (25 g) was added to a mixture of thionyl chloride (11 mL) and chlorosulphonic acid (41.3 mL) whilst keeping the temperature below 25 °C. The resulting mixture was stirred overnight at room temperature before being quenched into a mixture of ice (270 g) and water (60 mL). An off-white precipitate formed which was stirred for 60 min, collected by filtration and washed with water and dried in vacuo to give the title product (36.08 g, 90.6%). A small reference sample of the purified product was obtained by crystallisation from hexane/toluene: mp 115–116 °C. Found C, 41.02; H, 3.27. C14H12ClO2S requires C, 40.84; H, 3.43%. 1H NMR (CDCl3) δ = 1.64 (3H, t), 4.45 (2H, q), 7.26 (1H, d), 8.20 (1H, dd), 8.80 (1H, d).

2-Ethoxy-5-(4-methyl-1-piperazinesulphonyl)benzoic Acid (Double Salt) (10). A solution of 5-chlorosulphonyl-2-ethoxybenzoic acid (9) (50 g) in acetone (150 mL) was added dropwise to a solution of triethylamine (28.9 mL) and N-methylpiperazine (20.8 g) whilst keeping the temperature below 20 °C. A white crystalline product formed during the addition. After the mixture stirred for 1.5 h, the white solid was collected by filtration, washed with acetone, and dried in vacuo (78.97 g, 89.7%): mp 166–169 °C. Found C, 51.33; H, 8.14; N, 9.06; Cl, 8.02. C14H20N2O5S.C6H15N.HCl requires C, 51.54; H, 7.79; N, 9.02; Cl, 7.61%. 1H NMR [(CD3)2SO] δ = 1.17 (9H, t), 1.32 (3H, t), 2.15 (3H, s), 2.47 [6H, s (br)], 2.86 [2H, s(br)], 3.02 (6H, q), 4.18 (2H, q), 7.32 (1H, d), 7.78 (1H, dd), 7.85 (1H, d).

2-Ethoxy-5-(4-methyl-1-piperazinesulphonyl)benzoic Acid (8). Method 1. The double salt (10) (30 g) was stirred in water (120 mL) to give an almost clear solution. Rapid crystallisation occurred, and after 2 h the solid was collected by filtration, washed with water, and dried in vacuo to give a white solid (14.61 g, 69.1%). 1H NMR [(CD3)2SO] δ = 1.31 (3H, t), 2.12 (3H, s), 2.34 [4H, s (br)], 2.47 [6H, s (br)], 4.20 (2H, q), 7.32(1H, d), 7.80 (1H, dd), 7.86(1H, s).

A small reference sample was obtained by recrystallisation from aqueous alcohol, mp 201 °C. Found C, 51.09; H, 6.16; N, 8.43. C14H20N2O5S requires C, 51.21; H, 6.14; N, 8.53%.

2-Ethoxy-5-(4-methyl-1-piperazinesulphonyl)benzoic Acid (8). Method 2. The sulphonyl chloride (9) (34.4 g) (dried or used directly as a wet cake) was added to 124 mL of water and the resulting suspension cooled to 10 °C. N-methylpiperazine (33.6 mL) was added, keeping the temperature below 20 °C. The resulting solution was cooled to 10 °C. After 5 min the title compound started to crystallise. The solid was collected after 2 h and washed with ice water, and the resulting solid was dried in vacuo (36.7 g, 86%). Part of this material (15 g) was purified by heating in refluxing acetone for 1 h. The suspension was cooled to room temperature, and the crystalline solid was collected by filtration and dried in vacuo to give a white solid (11.7 g): mp 198–199 °C. 1H NMR [(CD3)2SO] in agreement with that reported above.

4-Amino-1-methyl-3-propyl-1H-pyrazole-5-carboxamide (12). The nitropyrazole (3) (237.7 g, 1.12 mol) was suspended in ethyl acetate (2.02 L), and 47.5 g of 5% palladium on carbon added. The resulting mixture was hydrogenated at 50 °C and 50 psi for 4 h when the uptake of hydrogen was complete. The reaction was cooled, and the catalyst was filtered off and washed with ethyl acetate to give an ethyl acetate solution of the title compound which was used directly in the next step.

4-[2-Ethoxy-5-(4-methyl-1-piperazinylsulphonyl)benzamido]-1-methyl-3-propyl-1H-pyrazole-5-carboxamide (13). The benzoic acid (8) (408.6 g, 1.24 mol) was suspended...
in ethyl acetate (1.5 L). \(N,N'\)-Carbonyldiimidazole (210.8 g, 1.30 mol) was added and was washed into the vessel with further ethyl acetate (1.36 L). The mixture was heated to 55 °C for 30 min and then for 2 h at reflux before being allowed to cool to 27 °C. A solution of aminopyrazole (12) in ethyl acetate (as prepared above, total solution weight 2.185 kg, 1.12 mol based upon an assumed 100% yield in the hydrogenation) was added and the reaction stirred for 70 h at room temperature. The title compound crystallised and was collected by filtration and dried in a vacuum (425 g): mp. 204–205.5 °C. The filtrates were concentrated to a low volume, and a second crop of pure title compound (70 g) was collected by filtration and dried in vacuo: yield as two crops = 90%. A small reference sample was obtained by recrystallisation from methanol/water mp 206–208 °C. Found C, 53.65; H, 6.54; N, 17.07. \(C_{22}H_{32}N_{6}O_{5}\) requires C, 53.64; H, 6.55; N, 17.06%. \(^1\)H NMR (CDCl\(_3\)) \(\delta = 0.96\) (3H, t), 1.58 (3H, t), 1.66 (2H, m), 2.27 (3H, s), 2.43 (2H, t), 3.05 [4H, s (br)], 4.05 (3H, s), 4.40 (2H, q), 5.61 [1H, s (br)], 7.61 (1H, d), 7.65 [1H, s (br)], 7.90 (1H, dd), 8.62 (1H, d), 9.25 [1H, s (br)].

1-[4-Ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo][4,3-d]pyrimidin-5-ylphenylsulphonyl]-4-methylpiperazine (Sildenafil). The pyrazolecarboxamidine (13) (12.32 g, 0.025 mol) was slurried in tert-butyl alcohol (61 mL) and potassium tert-butoxide (3.37 g) added. The resulting mixture was heated at reflux for 8 h. On the mixture being cooled 62.5 mL of water was added and the resulting solution filtered into a speck-free flask. A speck-free solution of concentrated HCl (2.3 mL) in water (60 mL) was prepared and added dropwise to the mixture over 2 h. The precipitated product was granulated at pH 7 and 10 °C for a further hour. The title compound was collected by filtration, washed with water, and dried in vacuo to give a white solid, (10.70 g, 90.2%): mp 189–190 °C (lit.\(^3\) 187–189 °C). Analysis of the material by HPLC and quantitative TLC indicated that clinical quality material had been obtained directly from the reaction. Found C, 55.55; H, 6.34; N, 17.69. \(C_{22}H_{30}N_{6}O_{4}\)S requires C, 55.68; H, 6.37; N, 17.71%. \(^1\)H NMR [(CD\(_3\))\(_2\)-SO] \(\delta = 0.94\) (3H, t), 1.32 (3H, t), 1.73 (2H, hextet), 2.15 (3H, s), 2.35 [4H, s (br)], 2.76 (2H, t), 2.88 [4H, s (br)], 4.14 (3H, s), 4.18 (2H, q), 7.36 (1H, d), 7.80 (2H, m) 12.16 [1H, s (br)].

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