Wiley ChemPlanner™
Synthesis Solved

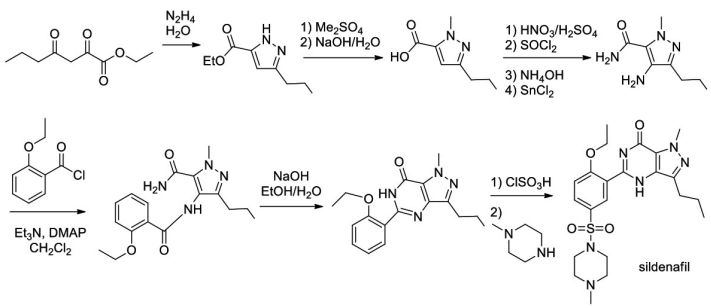
Synthesis of Sildenafil Citrate (Viagra®)

Sildenafil citrate is one of the most well-known drugs on the market today. Famously, it was initially developed by Pfizer in the late 1990's as a potential treatment for high blood pressure, until some "interesting" side-effects were noted in clinical trials. Thus, the first treatment for male erectile dysfunction, better known as Viagra®, was born. Although numerous routes to sildenafil have been published over the years, we'll take a look at the routes used in the development and production of sildenafil, as it's in the development process that Wiley ChemPlanner can have a big impact.

Pfizer's initial medicinal chemistry route to sildenafil is shown in scheme 1[1].

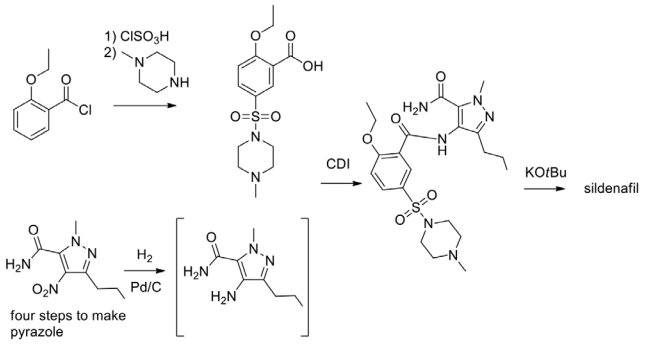
There were several sub-optimal features in this synthesis. As the process chemists who worked on the route later used to produce sildenafil commercially noted[2]:

- "The route is linear (nine linear steps).
- Potentially toxic materials […] 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."



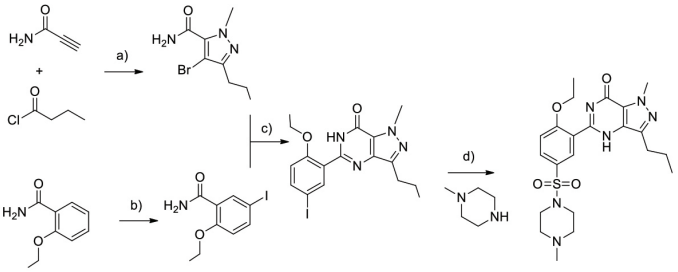
Scheme 1 Medicinal chemistry route to sildenafil

The process chemistry route to sildenafil shown in scheme 2 solved some of these problems by moving the chlorosulfonation to earlier in the synthesis and optimizing the route to the pyrazole intermediate so that the process was more convergent. The nitration remained as part of the synthesis of the pyrazole component.



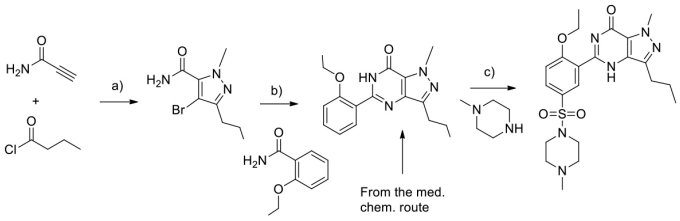
Scheme 2 Commercial route to sildenafil[2]

ChemPlanner predicts that the pyrazole ring could be made in one step, avoiding the undesirable nitration and several other steps completely, as shown in scheme 3. This is one of 46 predicted routes to sildenafil generated by ChemPlanner.



Scheme 3 ChemPlanner's four-step synthesis of Pfizer's sildenafil. As well as predicting possible reactions based on examples in the literature, ChemPlanner also highlights reactions that are known in the literature to provide chemists extra confidence in their synthetic design. Steps a)-c) are predicted reactions and step d) is known in the literature. A possible reaction sequence could be: a) 1) NEt_3, $PdCl_2(PPh_3)_2$, CuI; 2) AcOH, $MeNHNH_2$; 3) NBS[3]; b) NIS, $[Au(PPh_3)]NTf_2$[4]; c) basic alumina, MW[5]; d) 1) Et_4NBr, $K_2S_2O_5$, HCOONa, $Pd(OAc)_2$/PPh_3/phen; 2) NBS[6].

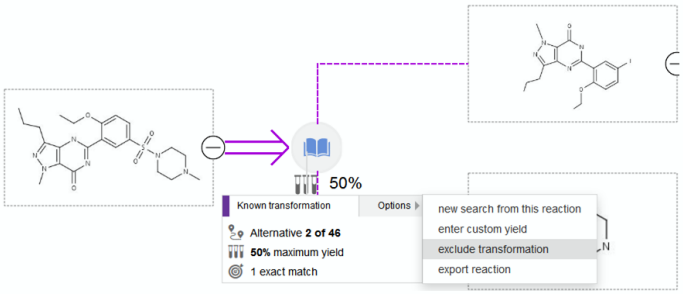
The last chlorosulfonation step is very similar in the ChemPlanner and medicinal chemistry routes, but the conditions in the ChemPlanner route are different. This suggests that it may even be possible to shorten the ChemPlanner route to three steps, as shown in scheme 4, if the chlorosulfonylation step from the medicinal chemistry route is reintroduced.



Scheme 4 Combining ChemPlanner's proposed route and the medicinal chemistry route to sildenafil, it may be possible to reduce the synthesis to only three steps. A possible reaction sequence could be: a) 1) NEt_3, $PdCl_2(PPh_3)_2$, CuI; 2) AcOH; 3) NBS[3]; b) basic alumina, MW[5]; c) $ClSO_3H$[1].

In a real development process the economic and practical implications will all be taken into consideration in route design. In this case, do the advantages of a three-step synthesis outweigh the disadvantages of the medicinal chemistry method for chlorosulfonation as the last step? Does adding another step involving a palladium catalyst mean that the potentially toxic byproduct from the chlorosulfonation won't be produced and recrystallization can be avoided, or should chlorosulfonation be avoided altogether?

In such a situation, ChemPlanner offers a development team the flexibility of excluding any given reaction or reagent, as shown in scheme 5 with the chlorosulfonation, to help answer such questions.



Scheme 5 Reactions or reagents can easily be excluded to create new routes, avoid hazards, or select preferred pathways.

This means that the 45 other alternative routes to the desired product can be explored almost instantly without a long slog back through the retrosynthesis and the literature.

[1] Bioorg. Med. Chem. Lett. 1996, 6, 1819, DOI: 10.1016/0960-894X(96)00323-X
[2] Org. Proc. Res. Dev. 2000, 4, 17, DOI: 10.1021/op9900683
[3] Org. Lett. 2011, 13, 2082, DOI: 10.1021/ol2004947
[4] Synlett 2014, 25, 399, DOI: 10.1055/s-0033-1340321
[5] J. Heterocycl. Chem. 2005, 42, 1085, DOI: 10.1002/jhet.5570420608
[6] Org. Lett. 2013, 15, 6226, DOI: 10.1021/ol403072r