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Polymer-Supported Reagents for Multi-Step Organic Synthesis: Application to the Synthesis of Sildenafil

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Abstract—Sildenafil **1** (Viagra™), a well known and commercially important pharmaceutical drug, has been prepared using polymer-supported reagents in a multi-step, convergent process resulting in a clean and efficient preparation without the need for conventional purification methods.

Introduction

The unprecedented opportunities for medicinal chemistry arising from high-throughput screening and genomics programmes is driving the need for new drug candidates at phenomenal rates.[1] In order to satisfy these extended biological evaluation protocols, large numbers of structurally and functionally diverse compounds are required. Currently these compounds are prepared in a combinatorial fashion either in solution or by assembly on a solid support. The greater versatility of the solution phase approach is far outweighed by the requirement for individual purification of all members of the compound library. As a consequence, polymer-supported reagents[2] have been developed which combine the advantages of substrate supported chemistry with the flexibility of solution phase preparation. In this approach the reagent is the immobilised species and the reactant remains free in solution. This gives tremendous advantages in terms of the easy monitoring of reaction progress and increased user safety if the reagent on support is toxic or hazardous. It also avoids the need for conventional work-up allowing isolation of the pure product through simple filtration and solvent removal. We have demonstrated the power of this methodology by using polymer-supported reagents in multi-step organic syntheses leading to a variety of different heterocyclic systems[3] and more complex natural products.[4]

Sildenafil (Viagra™) **1** (Scheme 1), Pfizer's world renowned treatment for male erectile dysfunction has rapidly become one of the largest selling globally marketed prescription drugs.[5] It is an orally administrated pharmacotherapy whose mode of action as a potent and selective inhibitor of the enzyme phophodiesterase type 5 (PDE-5); responsible for the degradation of cyclic guanosine monophosphate; has been well documented.[6] As an example of the utility of polymer-supported reagents in the fast and efficient preparation of drug substances, we report here a convergent synthesis of sildenafil **1**.

Synthesis

Following a precedented[5] route to sildenafil **1** we envisaged convergent coupling of amino-pyrazole **3** with benzoic acid derivative **2** followed by dehydrative ring closure to give **1** (Scheme 1). The construction of the substituted pyrazole **3** began from butyraldehyde, with the two step conversion from **4** to **6** being achieved in a one-pot procedure involving only filtrations as work-up (Scheme 2). Treatment of the readily available aldehyde **4** with methyl hydrazine at ambient temperature in the presence of magnesium sulfate or molecular sieves gave essentially quantitative conversion to the hydrazone **5**. *N*-Alkylation of **5** with a slight excess of ethyl bromoacetate (1.25 equiv) mediated by the polymer-supported base BEMP (PS-BEMP)[7] proceeded in excellent yield, with any unreacted α-bromoester being scavenged with aminomethyl polystyrene. Alternatively, polymer-supported trisamine could be used for the sequestering with no effect on the attainable yields or purity.[8] It was then possible to convert **6** to **7** using an ion exchange cyanide resin[9] in a modified Strecker reaction. The optimum conditions required two equivalents of the resin at reflux

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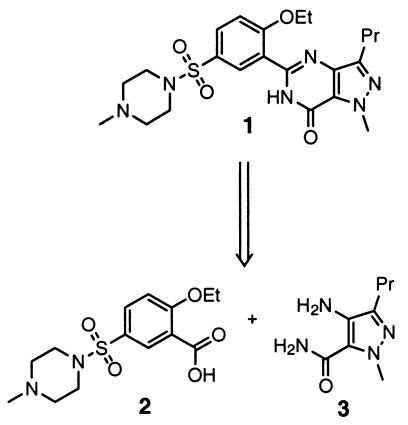


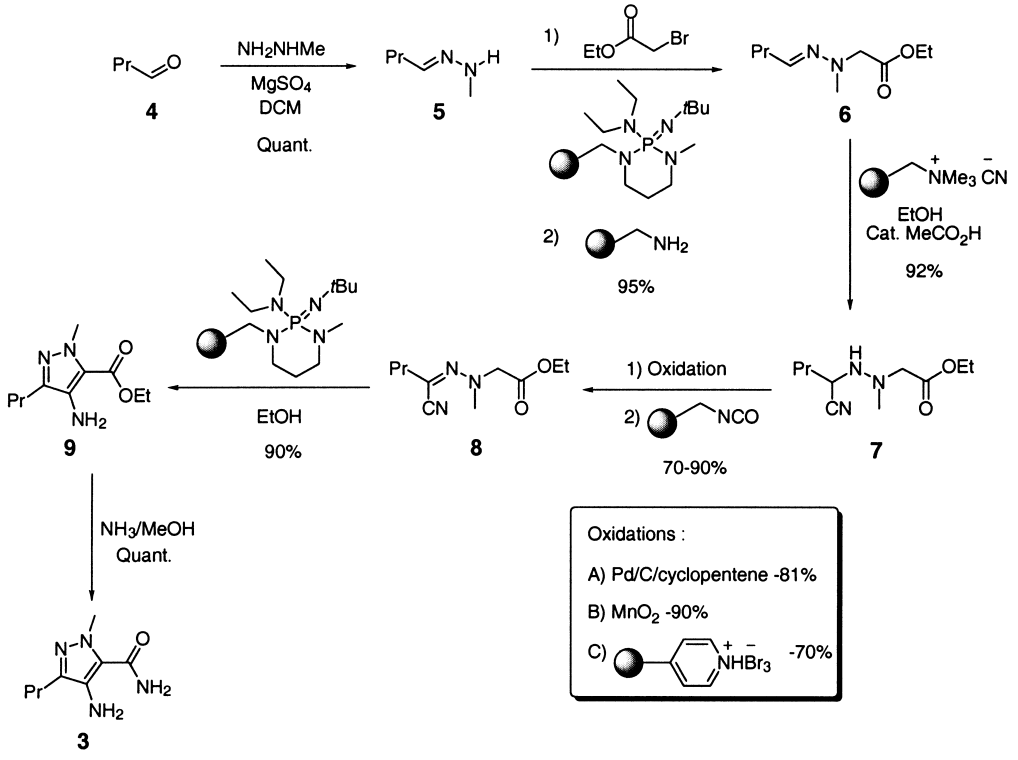
Scheme 1. Retrosynthesis of the drug sildenafil **1** (Viagra™).

in ethanol containing a catalytic amount of acetic acid. This reaction proved to be remarkably efficient yielding only the desired hydrazine product nitrile **7** with no unreacted starting material **6** being detected by either LC-MS or ^{1}H NMR. A number of procedures were investigated for the oxidation of compound **7** to the corresponding hydrazone **8**. The polymer-supported pyridinium bromide perbromide,[10] although yielding predominately the desired product, also produced a number of unidentified by-products that could not be removed using conventional sequestering techniques. The use of the alternative 'clean' oxidation systems Pd/C/cyclopentene[11] or manganese dioxide[12] proved far superior giving solely the oxidation product albeit not with complete conversion. Treatment of the mixture with a polymer-supported isocyanate resin[13] however facilitated the removal of the unreacted starting material **7** (in addition to any residual traces of **5**) to yield a pure solution of **8**. The phosphazene base PS-BEMP was found to be suitable for the rapid deprotonation and concomitant cyclisation of **8** to the tetra-substituted pyrazole **9**.[14] The subsequent conversion of the ester **9** to the required amide **3** was achieved by simply dissolving **9** in a saturated solution of ammonia in methanol. Initially two products could be detected which were identified as the amide **3** and the methyl ester resulting from transesterification of **9**. This compound was transformed in turn through to the amide **3**.[15]

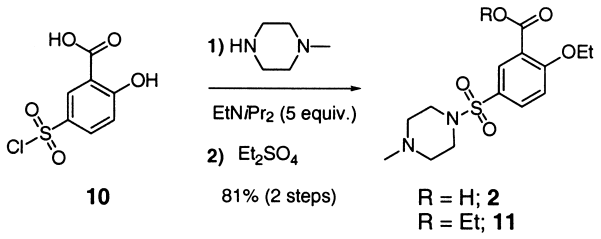
The benzoic acid unit **2** was prepared from the commercial sulfonyl chloride **10**[16] in a one-pot procedure (Scheme 3) and used as a crude solution in the following coupling step. The addition of *N*-methyl piperazine to a solution of **10** with 5 equiv of Hünig's base in DMF promoted complete conversion to the sulfonamide. This was transformed in situ to the ether **2** by addition of diethylsulfonate (1.2 equiv) with heating at 60 °C.

The resulting material was found to be contaminated with a small amount (~10%) of the bis-ethylated material **11**, resulting from esterification of the carboxylic acid.

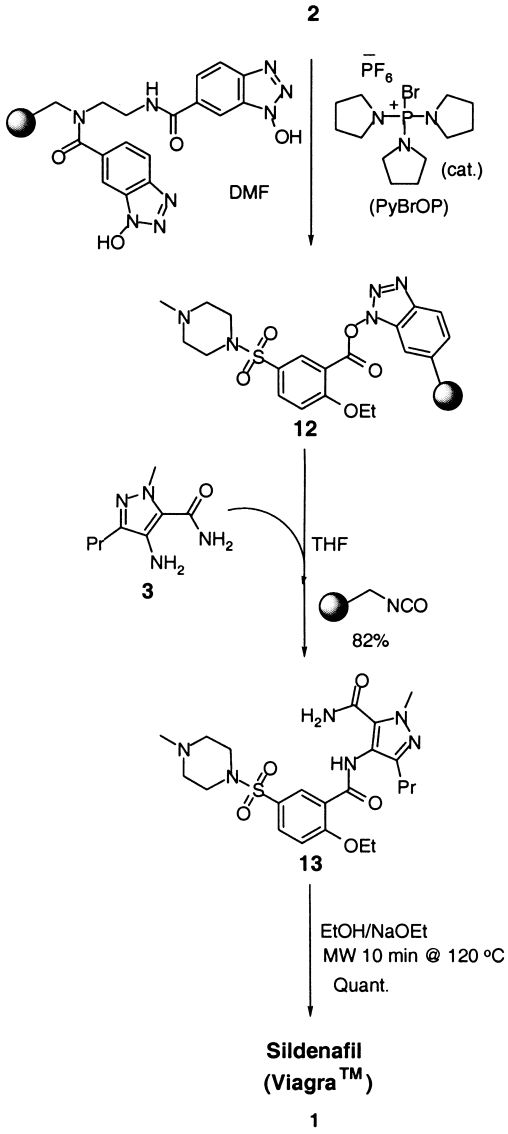
The coupling strategy (Scheme 4) was designed to additionally act as a purification step for the acid component **2**. Formation of the resin bound activated ester **12** with a polymer-supported HOBt variant[17] and coupling catalyst bromo-tris-pyrrolidinophosphonium (PyBrOP) allowed direct filtration of the DMF solution and removal of the contaminating impurities (compound **11**, EtN^iPr_2, unreacted diethylsulfate and its degradation products) produced in the formation of **2**. The exact



Scheme 2. The sequential multi-step synthesis of heterocycle **3**, using polymer-supported reagents.



Scheme 3. Synthesis of the acid coupling component **2**.



Scheme 4. Coupling strategy and dehydration step involved in the formation of sildenafil **1**.

loading of the resin **12** was not determined but was assumed to be 100% based on the original HOBt resin (a two-fold excess of the DMF solution of acid **2** was used in its preparation). Immersion of the resin **12** in a THF solution of the amino-pyrazole **3** gave, after removal of the unreacted pyrazole **3** with an isocyanate resin, the coupled material in a reasonable yield and as a clean product. The final cyclisation and dehydration step was achieved by microwave irradiation (MW)[18] of an ethanolic solution of **13** containing a catalytic amount of sodium ethoxide (10 mol%). Simple removal of the water formed during the cyclisation step (magnesium sulfate) and evaporation of the solvent gave a quantitative yield of sildenafil **1** as a white analytically pure powder.

Conclusions

Our synthesis of this commercially important molecule demonstrates the principles of using supported reagents in both a sequential and convergent fashion. We believe this route also indicates how these reagents could be easily adapted to the synthesis of other drug-like molecules either as target directed syntheses, or in a multi-parallel mode. Clearly these methods would also allow for the preparation of analogues of **1**.[5c]

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