COMMUNICATION

Use of polymer supported reagents for clean *multi-step* organic synthesis: preparation of amines and amine derivatives from alcohols for use in compound library generation

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The automated sequential application of polymer supported perruthenate (PSP) and polymer supported cyanoborohydride (PSCBH) in an oxidation–reductive amination procedure allowed the efficient transformation of simple alcohols into more complex amines which can be further derivatised by the use of polymer bound amino sulfonylpyridinium chlorides.

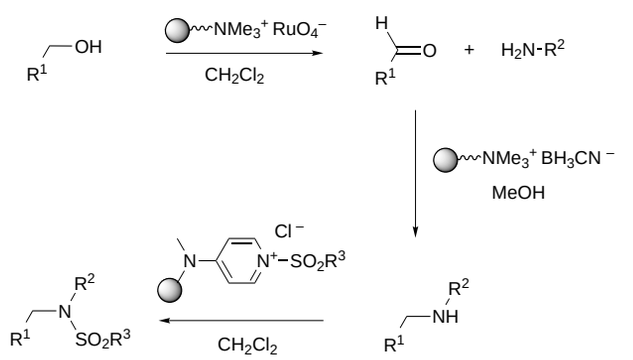
The methods of organic synthesis are changing. We are seeing dramatic developments in the need for compound library preparation and methods for cleaner organic synthesis of complex molecules. It is becoming popular to assemble molecules on polymer supports and these methods are set to revolutionise the pharmaceutical and agrochemical industries. We are also seeing innovative ideas to solve many of the problems associated with solution phase organic synthesis on a *multi-parallel* fashion. For example using fluorous solvents,[1] polymer supported reagents,[2] solid phase extraction and capture techniques,[3] and polymer supported quenching and sequestration methods[4] considerable improvement over conventional methods are being realised.

In addition it is highly desirable to devise chemistry which leads to the clean and rapid production of a greater range of starting material building blocks than those currently available from chemical supply houses. For these many reasons we have been developing polymer supported reagents, which in combination with other known polymer supported systems, allow *multi-step* operations to be performed leading to novel compounds or a much greater variety in available starting materials for combinatorial chemistry.

Here we show that the combination of polymer supported perruthenate (PSP)[5] and polymer supported cyanoborohydride (PSCBH)[6] makes use of readily available alcohols as a primary feedstock which after oxidation and further coupling by reductive amination affords a wide range of amines.[7] Some of these may be further sulfonylated using a third polymer system to give a more complex array of products (Scheme 1).

While the individual use of these polymer systems was known previously, it is their specific combination that enhances the opportunities for *multi-parallel* synthesis.

Details for the preparation of the polymer reagents PSP[5a] and PSCBH[6] have been reported, however we obtained PSCBH by filtering a solution of $NaBH_3CN$ through an ion exchange resin (Amberlyst A-26) containing quaternary ammonium groups. The resin was then washed with water, methanol and finally briefly with acetone to remove excess $NaBH_3CN$. It was then dried *in vacuo*. The loading of the resin was estimated to approximately 2 mmol BH_3CN^- ion per gram of resin.



Scheme 1

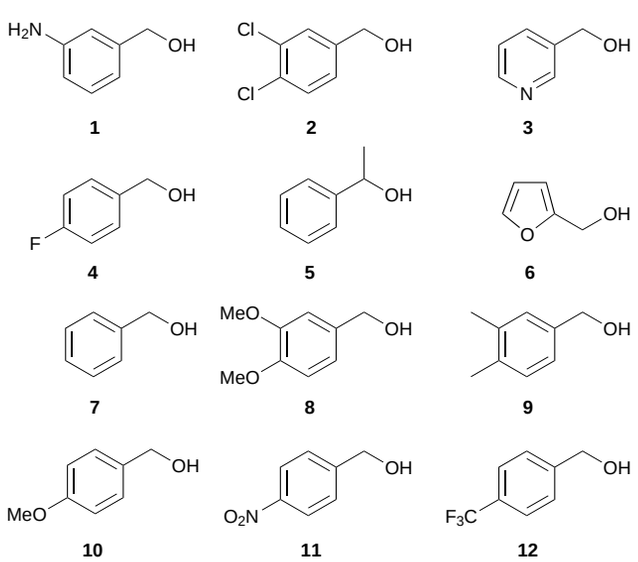


Fig. 1 Alcohol set oxidised by PSP in a *multi-parallel* fashion to the corresponding aldehydes

Many examples of using the PSP[5] oxidant and the PSCBH[6] individually are known, however this chemistry was conceived to run in parallel using robotic synthesis methods to achieve overall oxidation and reductive amination. Consequently we prepared an 8 × 12 array of secondary and tertiary amines using an ACT 496 Multiple Organic Synthesizer. Twelve alcohols **1**–**12** (Fig. 1), were firstly oxidised using PSP and were subsequently reacted with eight amines **A**–**H** (Fig. 2), and reduced with PSCBH according to Scheme 1.

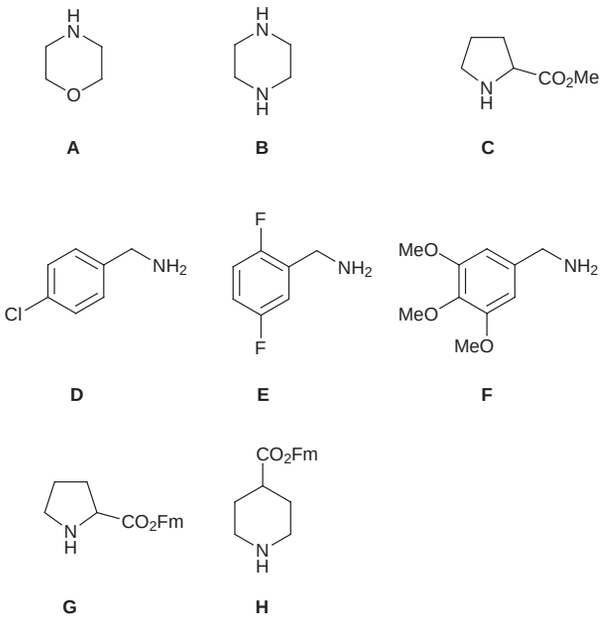


Fig. 2 Amine set used in the PSCBH effected reductive amination

Table 1 Summarised product purities of the automated sequential application of PSP and PSCBH

Alcohol	Amine							
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								

<30% 30–60% <60%

The products are characterised by LC-MS which indicated that 88 out of 96 two step syntheses had been successful with product purities in the range of 35–92%. These results are illustrated in Table 1.

The electron rich amine **F** gave a significant proportion of bis-alkylated product. However reaction of the piperazine **B** afforded only a small amount of the doubly-alkylated product. The procedures for these syntheses involved each alcohol (0.26 mmol) being dissolved in toluene (5 ml) and PSP (1.3 mmol g^{-1}, 200 mg, 0.26 mmol) added. The mixtures were stirred at 80 °C for two hours and then the resin was filtered off and washed with toluene (3 ml). The filtrate and washings were combined to afford the aldehyde solutions which were dispensed into 96 wells each containing PSCBH (1.0 mmol g^{-1}, 35 mg, 35 μmol). Each amine was dissolved in methanol (10 ml) and the robot used to dispense these such that each well contained 32 μmol of amine. The resulting mixtures were shaken at room temperature for 72 hours. The resin was removed by filtration and washed with methanol (1 ml). The filtrate and washings were collected and evaporated in a vacuum centrifuge (Genevac) to afford the product amines.

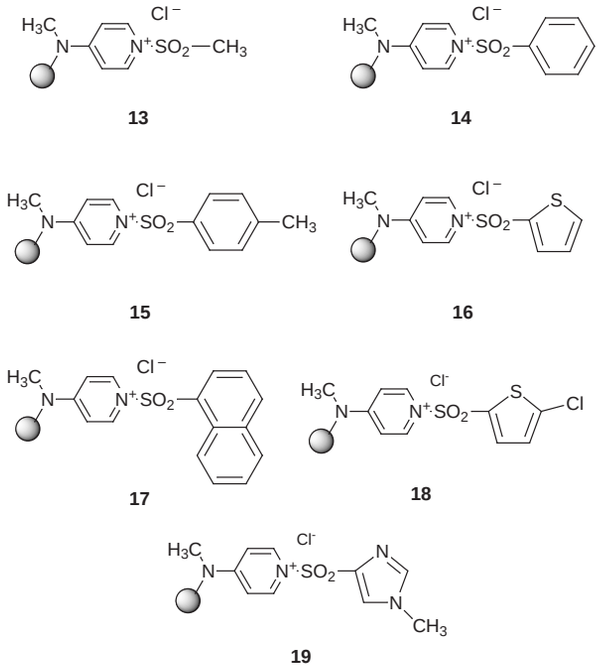


Fig. 3 Polymer bound amino sulfonylpyridinium chlorides

This two step automated polymer bound reagent synthesis was unoptimised yet the success rate observed is considered to be very acceptable for combinatorial chemistry.

In order to extend this process further we chose just one combination of benzyl alcohol with benzylamine to afford dibenzylamine after the sequential reactions with PSP and PSCBH. The yield at this stage was estimated to be 91%. Next this amine was dissolved in CH_2Cl_2, partitioned and reacted with seven different polymer bound amino sulfonylpyridinium chlorides **13**–**19** (Fig. 3). These all reacted well (*i.e.* >90%) to give the corresponding sulfonated products showing that a further level of diversity is possible using additional polymer bound reagent systems.

The sulfonylated amino pyridine polymers **13**–**19** were prepared by adding 0.22 g of carefully dried commercial dimethylaminopyridine[8] on polystyrene to 0.4 mmol of the sulfonylpyridinium chloride. The mixture was suspended in dry CH_2Cl_2 (4 ml). After stirring for half an hour 0.25 mmol of dibenzylamine was added. The reaction mixture was stirred at room temperature for 0.5–6 hours and the progress of the reaction was monitored by TLC. Eventually, the resin was removed by filtration and washed with further CH_2Cl_2 (4 ml). The filtrate and washings were combined and evaporated. GLC and ^1H NMR analysis revealed that the crude products were all of high purity (>90%). These promising results encouraged us to perform this third step on the Multiple Organic Synthesizer as well in order to generate an array of sulfonamides.

In summary we have demonstrated the opportunity of using polymer supported reagents in tandem for the clean and efficient preparation of amines and amine derivatives for potential use in combinatorial chemistry programmes. We can envisage many other schemes which could harness these concepts for compound production. Indeed the process could be extremely powerful if used in combination with the developing methods of polymer quenching and sequestration.

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