The use of polymer supported isoureas for the *O*-alkylation of carboxylic acids – Bruno Linclau (bruno.linclau@soton.ac.uk)

The breakthrough of combinatorial chemistry was made possible by the development of solid supported reactions. By immobilising the substrate onto an insoluble polystyrene support, the reaction workup could be drastically simplified as a simple filtration could be employed to remove excess reagents, byproducts etc. However, this method also had significant disadvantages, such as difficult reaction monitoring and the fact that unreacted substrate or side-products could not be separated from the product as all were linked to the insoluble support.

In polymer-assisted-solution-phase (PASP) chemistry, the *reagents* are immobilised onto an insoluble support, while the substrate and products remain in the solution phase. Equally, reaction workup consists of a simple filtration, with the desired product now located in the filtrate. Obviously, for optimal efficiency, the system has to be designed such that all reagent byproducts remain linked to the support. This methodology combines the main advantages of traditional solution phase chemistry (eg reaction monitoring) with those of solid-supported chemistry (filtration as reaction workup), allowing for significant gains in time-efficiency. Another advantage is that there are no restrictions any more for the substrates used in terms of a necessary functional groups for linking to an insoluble support. Because the product is not immobilised, should the need arise, a purification can still be performed in case unreacted starting material remains, or side products are formed. This purification could be effected by polymer supported scavengers, or by traditional chromatography. PASP is currently a much used method in the pharmaceutical industry for the synthesis of small libraries of compounds. The use of PASP chemistry in multisptep synthesis has also been established. Hence, the development of new solid supported reagents suitable for PASP methodology is very important.

The synthesis of esters from carboxylic acids is a very common transformation in organic synthesis, yet, efficient PASP methodology was not available until a few years ago. We have successfully investigated the use of solid-supported isoureas for the *O*-alkylation of carboxylic acids. Initially we studied the protection of carboxylic acids using simple alcohols. The required solid-supported isoureas could easily be synthesised from solid-supported carbodiimide by reaction with an excess of alcohol and a copper (II) catalyst. Solid-supported carbodiimides are commercially available, but we also have developed an improved synthesis for immobilised carbodiimides from aminomethyl polystyrene resin. It was found that simply heating an acetonitrile solution of the carboxylic acid with the immobilised isourea, followed by filtration/resin washing and evaporation of the solvent, afforded the ester products in good yield with excellent purity. When microwave irradiation was employed, the actual reaction time was as short as 3-5 minutes! For the synthesis of methyl esters, our methodology clearly is a better approach than the use of diazomethane.

The ester formation using more complex alcohols using a catch/release method is also being investigated. Catch/release is a 2-step process where the desired substrate switches phase twice, allowing for an extra purification step. Hence, the alcohol (1equiv) was attached to the resin as the corresponding isourea, which could be purified by filtration to remove unreacted alcohol and Cu(II) catalyst. Residual carbodiimide groups were inactivated by reaction with water. The purified isourea was then reacted with a carboxylic acid, "releasing" the alcohol moiety to the solution phase again, as the ester. Excess or unreacted carboxylic acid was removed by adding an immobilised basic scavenger immediately to the reaction mixture. Finally, a filtration removed all resin material, leaving pure ester in solution.

Polymer-assisted-solution-phase chemistry is a very active research field, and the use of reaction databases has proved to be an excellent tool to find necessary information. In particular, the 'Solid-Phase Synthesis' database contained in ISIS/Base, maintained by CDS, was found to be of excellent value to search for reactions on solid support. In addition, the ACD finder database also was very useful to quickly obtain information about available starting materials and substrates. The way the use of these databases has advanced our research is an illustration of the excellent value of the CDS service for the UK chemical community.