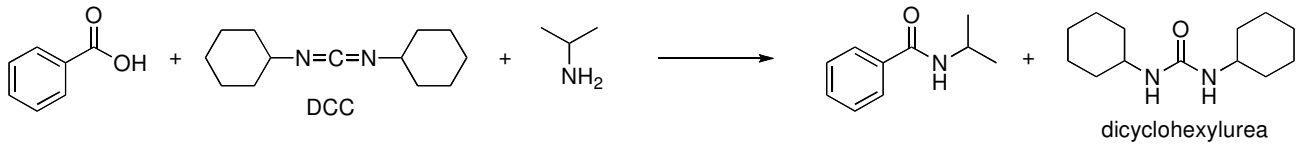
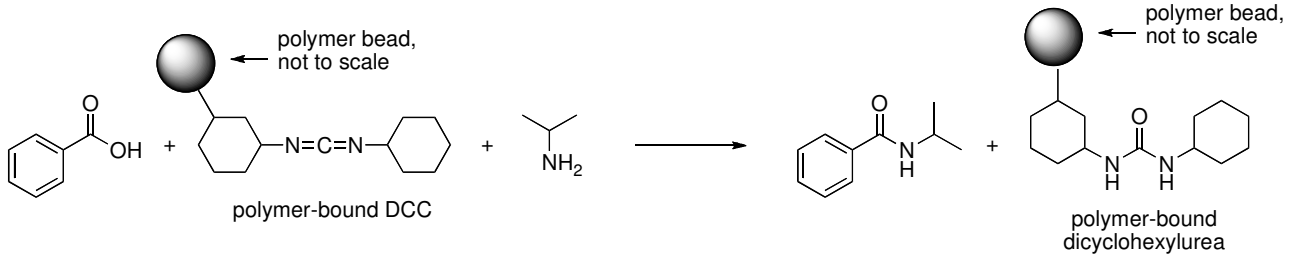
Solid Phase Organic Chemistry: Amide Synthesis
CHEM352L, Spring 2012

In solid phase organic synthesis (SPOC), a reactant or reagent is "immobilized" on a solid support, such as polymeric beads made of polystyrene or silica gel. "Immobilized" simply means that the reactant or reagent is covalently bonded to the support material. *This can greatly simplify purification of the product.* For example, consider the following amide-forming reaction using dicyclohexylcarbodiimide (DCC):

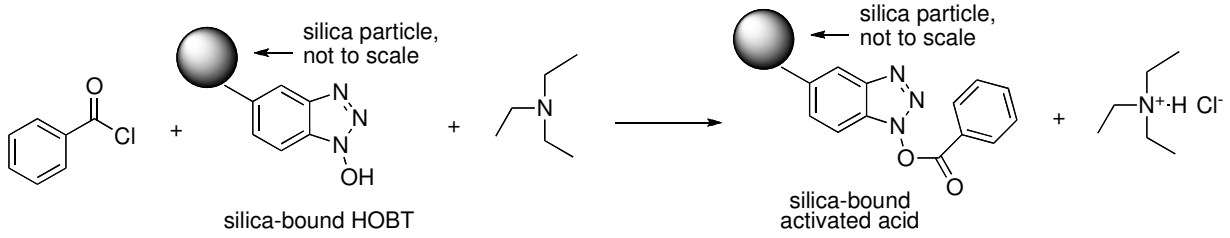


The by-product of the reaction, dicyclohexylurea (DCU), cannot be readily protonated or deprotonated under aqueous conditions. This means that if you were to wash the crude reaction mixture with both aqueous acid and aqueous base in a separatory funnel after completion of the reaction, both the amide product and the DCU would remain in the organic phase; an additional purification step would be required to remove the DCU from the product. This additional step would typically involve column chromatography, which is time-consuming and requires large amounts of solvent relative to an extraction. What if, instead, the DCC was covalently bonded to a solid support such as beads made of polystyrene? The polystyrene beads are quite large, and at the end of the reaction, they can simply be filtered out of the reaction mixture along with the covalently-linked byproduct, DCU:



This represents one important general application of SPOC.

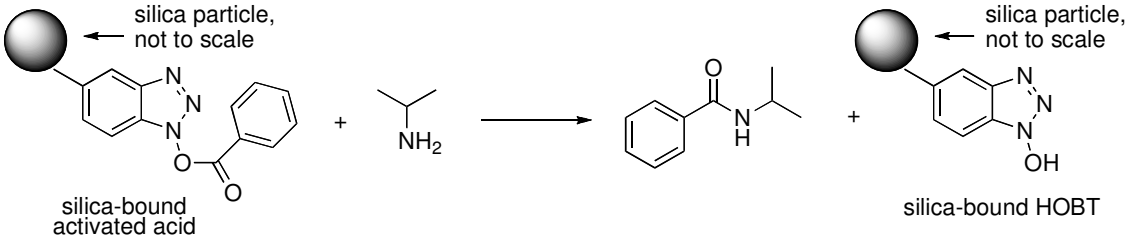
In the experiment you will carry out this week, you will synthesize the same amide as last week, but the leaving group is the conjugate base of the heterocycle hydroxybenztriazole (HOBT), which is covalently bonded to silica gel. You will first "load" an acid chloride on to the solid support:



The silica can then be washed to remove the triethylammonium chloride formed and any excess or unreacted triethyl amine and acid chloride. The silica will be in a small plastic "reaction tube", so

washing can be accomplished by simply passing some pure solvent through the tube, similar to running solvent through a chromatography column.

In a second step, the amine is added to the activated acid on the support. Attack by the amine releases the product amide from the support and the silica-bound HOBT is regenerated:



In this second step, if the moles of amine used is less than the moles of acid chloride loaded onto the silica, elution of the silica with solvent should provide pure product - unreacted triethylamine and acid chloride along with triethylammonium chloride were removed by washing the silica after loading, so no extraction! Thus, the major advantage to the solid-phase approach in an experiment like this is that it *eliminates the need for product purification*. In our experiment, we will actually use excess amine relative to activated acid in the second step; this is OK, because isopropylamine has a low boiling point, and will be removed when the solvent is removed from the product by heating. Excess amine is used to maximize yield, as the theoretical yield for the experiment will be approximately 20 mg (not a lot, but enough to screen for biological activity, for example).

The reaction schemes above are a little misleading in that the polystyrene beads and silica particles involved are MUCH, MUCH larger than molecules like DCC and HOBT, and there are large numbers of DCC or HOBT molecules immobilized on a single bead or particle. The "activity" or "loading capacity" of solid phase reagent or reactant is reported as the number of millimoles per gram of material (mmol/g); for this experiment, you will be using 0.50g of HOBT-silica with an activity of 0.35mmol/g. For your data table, include the mass of the silica, the activity, and the total millimoles of HOBT - no other physical properties are required for the HOBT-silica. Because we are synthesizing such a small quantity of product, you will not be required to get a mass or calculate a percent yield for the product, but do take a melting point. Work in pairs for this one.

Pre-lab questions:

1. What is the structure of HOBT?
2. You will be using a 1.2 molar solution of triethylamine in DCM for the experiment. This will already be prepared for you, but if it was not, how would you make 100mL of such a solution?
3. In step 10 of the procedure below, you will "regenerate" the silica by adding a concentrated solution of isopropylamine. What do we mean by the term "regenerate", and how does this action serve to "regenerate" the column?

Post-lab questions:

1. Provide a mechanism for amide formation between benzoic acid and isopropylamine using DCC.
2. Find another example of a solid-phase reagent that is used in organic synthesis, and give an example of a specific reaction where it has been used. In this case, what advantage does the solid-phase reagent provide over the analogous solution-phase reaction?

Procedure:

1. In a small test tube (13x100mm) combine 0.50 mL of acid chloride stock (1.0 M) with 0.30 mL of 1.2 M triethylamine (TEA) stock solution (both are in dichloromethane (DCM) and are to be dispensed with dedicated 1.0mL graduated pipettes). Mix with a disposable glass Pasteur pipette and then transfer to the column using same pipet. Wash the container with a small amount (about 0.1 mL) of dichloromethane and transfer this to the reaction tube as well.
2. Open stopcock and allow the solution to drain onto the silica until it reaches the bottom, then close the stopcock. DO NOT LET THE SOLUTION PASS THROUGH THE BOTTOM FRIT! Gentle shaking and/or tapping during this step will assist the solution loading. If, after there is no more liquid on top of the upper frit, the solution has not reached the bottom frit, add small amounts DCM with a clean pipette until it does - the silica should be completely wetted.
3. Let this solution sit in the column for 15 minutes while periodically giving the tube a gentle shake/gentle tapping (once every 2-3 minutes tap the tube for about 30 seconds, being sure the cap is on).
4. After 15 minutes, open the stopcock and add approximately 1mL of DCM to the tube. Allow this to drain through the silica, removing unwanted reactants. To obtain a reasonable flow rate, use a syringe to apply GENTLE pressure, but **do not** allow the liquid to go below the top frit. Wash the silica five more times with approximately 1 mL portions of DCM, again being careful not to force air onto the silica. These combined washings should be saved in a labeled flask until you have obtained your product, at which time they can be disposed of in the proper waste container.
5. Add 0.7 mL of 0.5 M isopropylamine in DCM to the reaction tube and allow it to drain by gravity until the liquid level is just at the top of the top frit. If the drip rate is very slow, you can apply a very small amount of pressure via syringe to expedite the process. DO NOT LET THE TOP OF THE SILICA GET DRY!
6. Once the isopropylamine solution is loaded, allow the tube to rest for 15 minutes. During this time you should gently tap the tube for 30 seconds every 2 – 3 minutes.
7. Open the stopcock and add approximately 1mL of DCM to the tube. Allow this to drain through the silica, eluting your product. To obtain a reasonable flow rate, use a syringe to apply GENTLE pressure, but **do not** allow the liquid to go below the top frit. Elute the silica three more times with approximately 1 mL portions of DCM, again being careful not to force air onto the silica.
8. Add a boiling stick to the Erlenmyer flask, and gently warm on the hotplate, reducing the volume to approximately 2 mL. Tilt the flask at an angle to collect the liquid on one side and allow it to cool; crystals should begin to form. If no crystals appear, evaporate half the remaining solvent and allow the solution to cool again – repeat this until crystals appear. CAUTION: Sometimes the crystals will form on the bottom of the flask in such a thin layer

that it is not visible until scratched, if the volume is very low and you do not see crystals, attempt to scratch the bottom of the flask with a spatula to see if this thin layer has formed.

9. Determine the melting point for your product.
10. To regenerate the silica, place a waste flask beneath the tube and fill with 10% (v/v) isopropylamine in DCM. Allow this to drain through the silica, applying GENTLE pressure with a syringe, but **do not** allow the liquid to go below the top frit. Repeat this two more times. Fill the tube with pure DCM, allowing this to drain through the silica, applying GENTLE pressure with a syringe. Then push 3 full syringes of air through the column to dry the silica and leave the column uncapped with the stopcock open. Remove the stopcock and rinse it with acetone.