

Dicyclohexylcarbodiimide is a dehydrating agent, which is exactly what is needed to carry out the acylation reaction between a carboxylic acid and an amine. Dicyclohexylcarbodiimide requires no other reagents to work, so it meets the criterion of experimental convenience, and it's functional under neutral conditions. The yields can be extraordinarily high, and a single byproduct is the reaction outcome between dicyclohexylcarbodiimide (DCC) and water, dicyclohexylurea (DCU).

The reaction mechanism occurs in two stages.

In the first stage, DCC reacts with the carboxylic acid of the N-protected amino acid to produce a reactive acylating agent in a two-step mechanism:

- (1) one of the nitrogen atoms in DCC deprotonates the carboxylic acid
- (2) the resulting carboxylate adds to the protonated carbon-nitrogen double bond

The resulting functional group is reminiscent of an anhydride, which is also one of the better acylating agents. The transformation of this carboxylic acid of an amino acid is not unique. DCC can be used to transform any carboxylic acid into a good acylating agent, comparable to the way thionyl chloride ( $\text{SOCl}_2$ ) transforms acids into acid halides for their subsequent reactions with nucleophiles.

In the second stage, the DCC-derivatized acid undergoes a typical acylation reaction with the nucleophilic amine of the C-protected amino acid to give BocAla-GlnOBb.

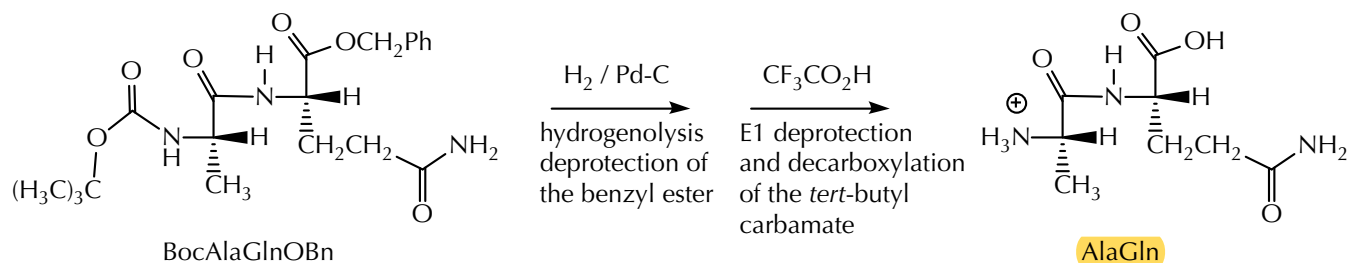
The DCU byproduct is highly insoluble.

The overall acylation process is often called the DCC peptide coupling reaction. In general, the carbodiimide functional group is well suited to forming these amide bonds, and many different reagents with the  $\text{R-N=C=N-R}$  structure have been used. The most significant difference in their properties is whether they are water soluble or not, which relates to experiment convenience in being able to easily separate the reaction byproduct.

Once the amide (peptide) bond has been formed, removing the protecting groups completes the synthesis (Figure 1733).

**Figure 1733**

**Removing the protecting groups from the dipeptide completes the synthesis of Ala-Gln.**



The deprotection methods are prescribed, and because there are no other steps needed in the synthesis, the order of the deprotection steps does not matter. The benzyl ester is removed by hydrogenolysis, restoring the carboxylic acid, and the Boc group is removed using trifluoroacetic acid.

In an acidic medium, the amine group of the dipeptide would be protonated. A pH adjustment would be needed to give the neutral zwitterion. There is no fixed convention about what to draw, although if there is a neutral form it is perhaps used most often. For the purposes of the text (or an exam), you should expect to see instructions about the pH and/or whether pH adjustments need to be included as steps or assumed. Usually, the pH adjustment step is indicated by simply writing "adjust pH."