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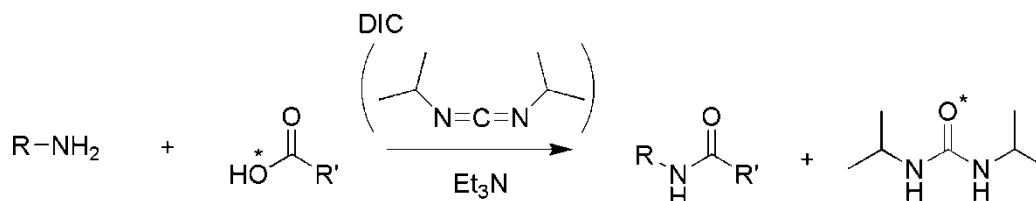
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**PS #3 - Amide Bond Formation Using DIC, and a Complex Synthesis Requiring Protecting Groups**

**Part A)** Amides can be made by mixing an acid chloride with an amine, but the conditions for producing acid chlorides are harshly acidic. A milder coupling method for amines and carboxylic acids is treatment with a reagent such as DIC, pictured below. Propose a detailed mechanism for this transformation.

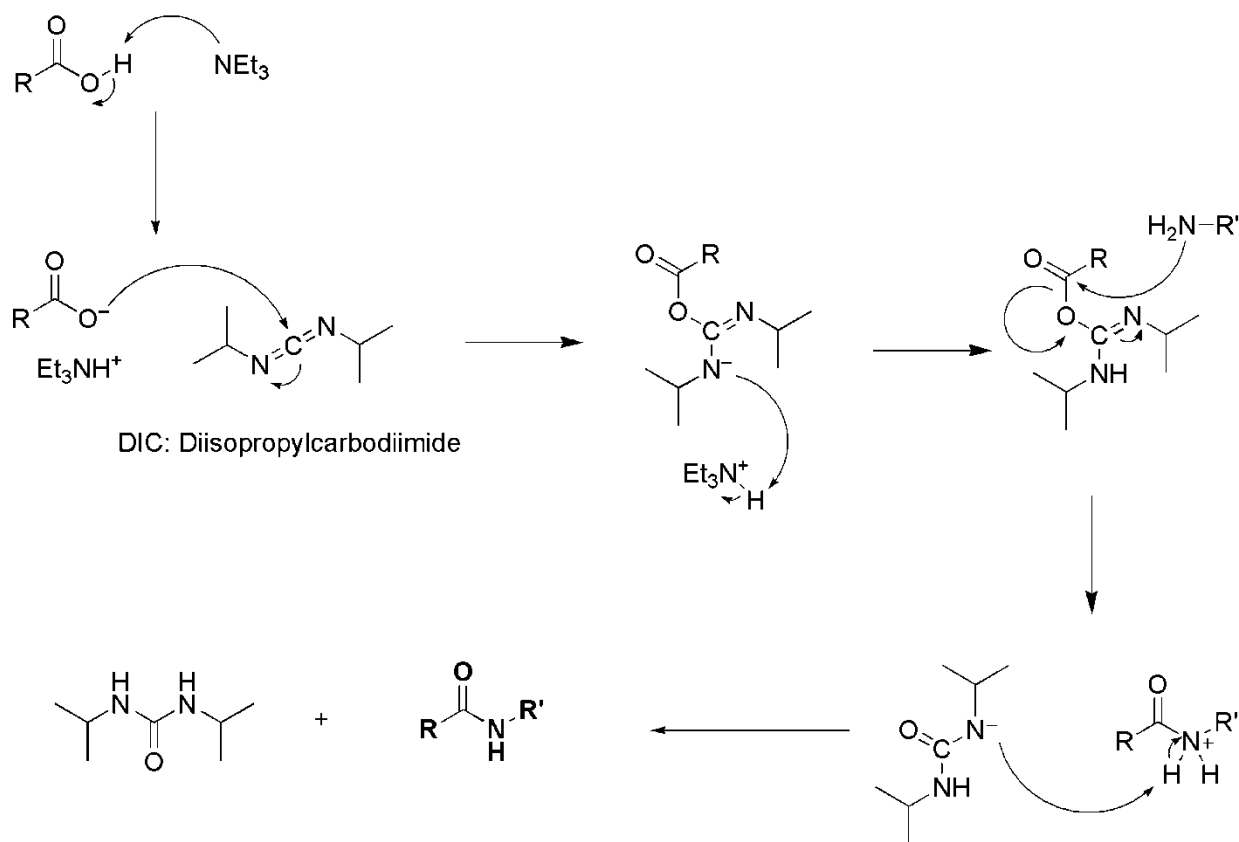
Hints: One equivalent of DIC is consumed and converted to the diisopropylurea shown at right. The oxygen atom indicated with an asterisk is transferred to the diisopropyl urea as shown. The attack of that oxygen atom onto the carbodiimide is a very early step in the mechanism.



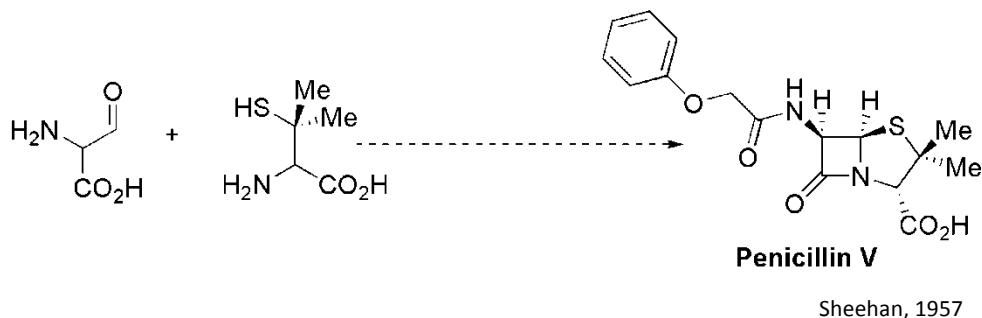
*The carboxylic acid is utterly non-electrophilic in its starting form. Attacking it with the primary amine is a terrible first step.*

*Et<sub>3</sub>N is a base with pK<sub>a</sub> ~ 10. Which proton is acidic enough to be pulled off?*

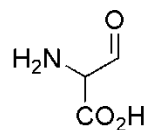
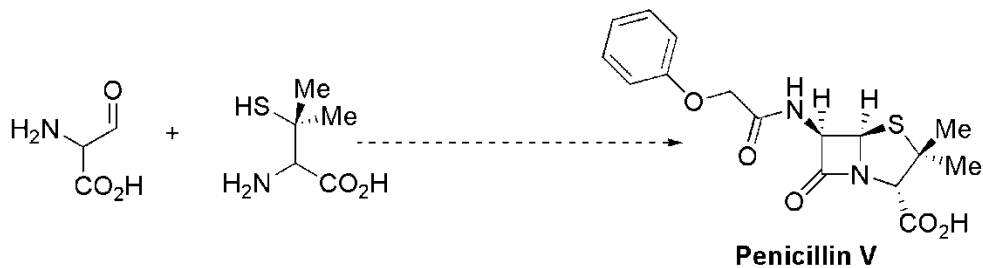
*A carbodiimide reacts essentially as a double imine - the carbon atom is very electrophilic.*



**Part B)** Penicillin is a group of  $\beta$ -lactam antibiotics produced naturally from the mold *Penicillium notatum* and is commonly used in the treatment of bacterial infections. The term penicillin usually refers to the entire family of  $\beta$ -lactam antibiotics which differ only in the acyl group attached to the nitrogen that is  $\alpha$  to the lactam carbonyl (got that?). The specific penicillin molecule examined here is penicillin V. It took Prof J. Sheehan and his group at MIT ten years to synthesize penicillin V; the synthesis was finally completed in 1957. As a group propose a reasonable synthetic scheme for the synthesis of penicillin V from oxidized serine and the dimethylated cysteine derivative shown below.

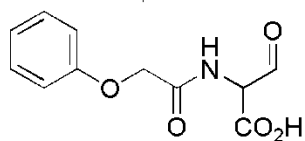


*Identify the transformations that are needed and the bonds that must be formed. Identify which part of the molecule is the cysteine part and which part was originally serine. Now consider which functional groups must be protected in order to direct the amino acid condensation so that the desired reaction occurs.*



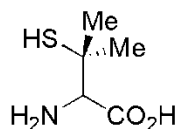
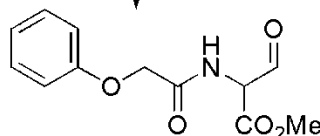
Both the acid and the amine will need to be protected prior to the condensation to form the thiazolidine ring. The amine should be protected with a phenoxyacetyl group because this group appears in the final product.

**PhOCH<sub>2</sub>COCl, Et<sub>3</sub>N**



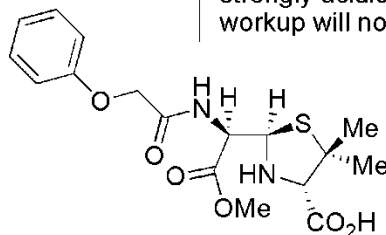
Next protect the carboxylic acid (Fischer esterification).

**MeOH, cat. H<sub>2</sub>SO<sub>4</sub>**



**NaOH, EtOH**

Now the residue is set up to condense with the cysteine derivative. The reaction is a base catalyzed condensation between an aldehyde and cysteine, which contains two nucleophiles. It may help you understand the condensation if you work through the mechanism.



+ diastereomer

**1 eq. KOH, DIC**

DIC can be used as a mild reagent to form the final amide bond between the carboxylic acid and the secondary amine and close the ring.

**1. NaOH, H<sub>2</sub>O  
2. mild HCl**

Remove the methyl group that is protecting the carboxylic acid so that the final amide bond (and therefore the 4 membered lactam ring) can be formed. A base catalyzed ester hydrolysis was chosen as acetyl groups are also cleaved under strongly acidic conditions. A mild HCl workup will not cleave the acetyl group.

Aside: In practice the diastereomer is selectively isolated from the reaction mixture. The desired isomer crystallizes upon cooling and is isolated selectively by filtration.