

SYNLETT Spotlight 211

Dicyclohexylcarbodiimide (DCC)

Compiled by Miroslav Kvasnica



This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

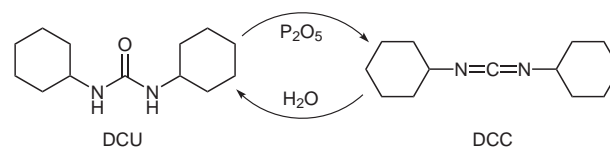
M. Kvasnica completed his M.Sc. in organic chemistry at the Faculty of Science, Charles University in Prague, Czech Republic, in 2003. He is currently finishing his Ph.D. under the supervision of Dr. Jan Šarek (Charles University) and Dr. Hana Chodounská (Academy of Science, CZE) at the Faculty of Sciences, Charles University in Prague. His research interests include chemistry of natural compounds, especially the synthesis and isolation of triterpenes with potential use as antitumor agents. Recently he has also been working at the Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic.

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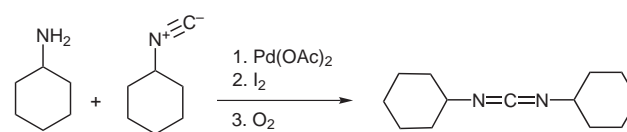
Introduction

1,3-Dicyclohexylcarbodiimide (DCC) is a versatile organic reagent. It is a powerful dehydrating agent commonly used for the preparation of amides,^{1,2} esters,³ and anhydrides.⁴ It can also be used with dimethylsulfoxide for mild oxidation of alcohols to ketones and aldehydes (Moffatt oxidation), dehydration of hydroxy compounds, and many other reactions. Under standard conditions, DCC exists in the form of white crystals with a heavy, sweet odor. The low melting point (34 °C) of this material allows it to be melted for easy handling. DCC is highly soluble in many organic solvents (e.g., dichloromethane, tetrahydrofuran, acetonitrile, or *N,N'*-dimethylformamide). The main drawback of its use is the formation of *N,N'*-dicyclohexylurea (DCU), which partially remains in solution with the product. The low solubility of DCU in most organic solvents complicates purifications, especially in the peptide synthesis.

DCC can be prepared from DCU by treatment with phosphorus pentoxide⁵ (Scheme 1). Another method starts from cyclohexylamine and cyclohexylisocyanide that react with palladium acetate, iodine, and oxygen (Scheme 2).⁶



Scheme 1

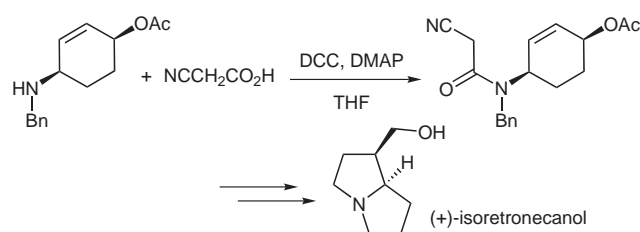


Scheme 2

Abstracts

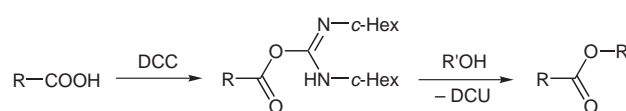
(A) Synthesis of amides, lactams and peptides:

The primary use of DCC is in coupling of amino acids during peptide synthesis and in other amide-bond-forming reactions. Typically, DCC is added to a solution of the carboxylic acid and the amine. Sometimes, the reaction rate is increased by the use of a catalyst, for example DMAP. Lemaire and co-workers used DCC in the synthesis of alkaloid (+)-isoretrotraneanol.¹ DCC was also used in polypeptide synthesis.²



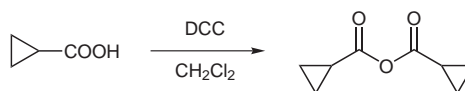
(B) Synthesis of esters, lactones, and thioesters:

In some cases it is necessary to carry out the esterification in two steps. The first step includes the reaction of carboxylic acid with DCC to create an active intermediate, *O*-acylurea, and in the second step an alcohol is added to the reaction mixture to create an ester.³

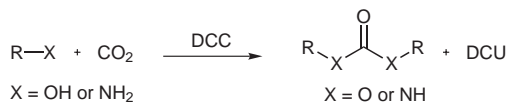


(C) *Synthesis of anhydrides:*

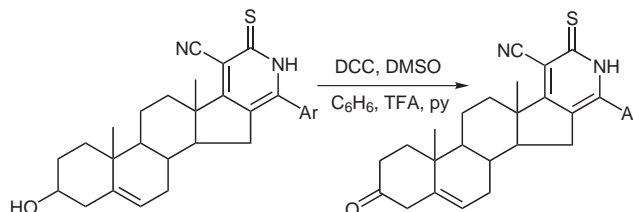
DCC is one of the mildest and most effective reagents for preparation of symmetrical anhydrides. Clarke and co-workers used this procedure for the synthesis of cyclopropanecarboxylic anhydride.⁴

(D) *Synthesis of carbonates, lactames, and isothiocyanates:*

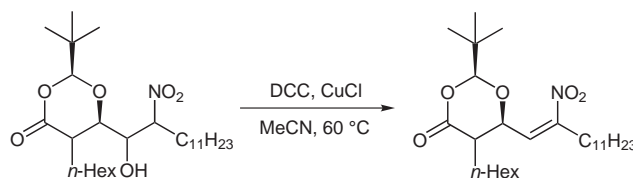
Aresta and co-workers used DCC as a reagent for facile synthesis of organic carbonates from aliphatic alcohols and carbon dioxide with quantitative yield.⁷ Replacement of alcohols by primary amines provides ureas.⁸ Reaction of DCC with primary amines and carbon disulfide affords isothiocyanates.⁹

(E) *Oxidation of alcohols to ketones and aldehydes:*

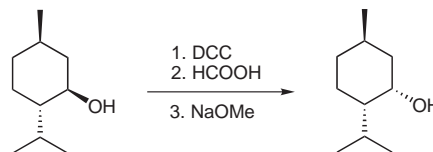
Oxidation of primary and secondary alcohols to ketones or aldehydes can be carried out by reaction with DCC and DMSO. This reaction, the Moffatt oxidation,¹⁰ is carried out under very mild conditions and is often used for the oxidation of hydroxy compounds with other sensitive functional groups. Amr and co-workers¹¹ reported oxidation of a steroidal alcohol to a ketone without any isomerization of 5(6)-double bond, as is often observed during oxidation with other stronger oxidizing agents.

(F) *Dehydration:*

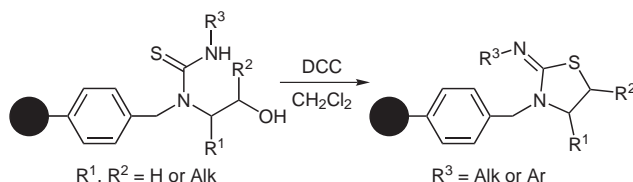
Hydroxy ketones or β -hydroxy esters can be dehydrated to α,β -unsaturated ketones or esters using DCC. Ghosh and co-workers used DCC with CuCl for the dehydration of the alcohol in one step in the course of the synthesis of tetrahydropipstatin.¹²

(G) *Isomerization of alcohol:*

Kaulen reported the isomerization of a secondary hydroxy group in several compounds.¹³ The hydroxy group is stereochemically inverted by reaction with DCC to create an isourea adduct, then the adduct is treated with formic acid to provide formate and DCU. Finally, the formyl group is removed by saponification with sodium methoxide with 99% de.

(H) *Heterocyclization reactions:*

DCC is widely used as a reagent (or reactant) in the synthesis of heterocycles. Jeon and co-workers published the solid-phase synthesis of 2-amino-2-thiazolines using the DCC-mediated cyclization of *N*-(2-hydroxyethyl)thioureas.¹⁴



References

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