The Catalyst's Companion: *N*,*N*′-Dicyclohexylcarbodiimide (DCC) in Action

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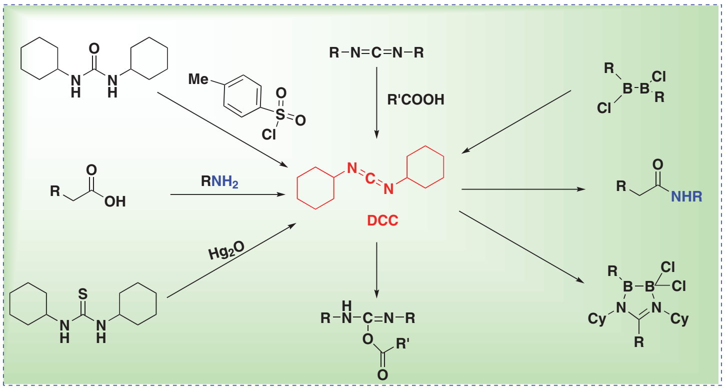

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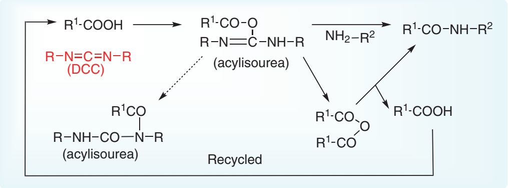
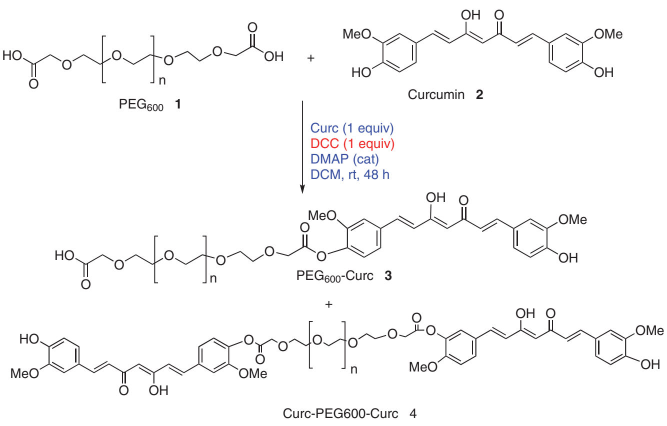
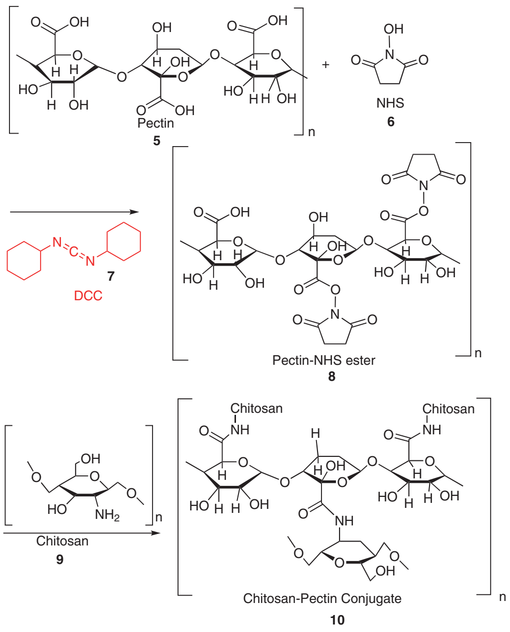
N,*N*′-Dicyclohexylcarbodiimide (DCC) has been widely employed as coupling agent and is used in the synthesis of peptides.[1] The synthesis process utilizing DCC is shown in Scheme 1. Dicyclohexylurea (DCU), a byproduct of the reaction between a protected amino acid and DCC, is formed when an *O*-acylisourea is aminolyzed to produce a peptide. Without an amine component, an *N*-protected amino acid reacts with DCC to form a second active compound known as a symmetrical anhydride which in turn reacts with amine components. Filtration is an easy way to remove the DCU produced in this reaction since nearly all common organic solvents cannot dissolve it.[2] When pyridine derivatives are utilized as catalysts, *N*,*N*′-dicyclohexylcarbodiimide (DCC) has been used as a condensation agent in the esterification of carboxylic acid with alcohols at room temperature.[3] Polyester and telechelic oligoesters can now be produced at room temperature thanks to DCC.[4] This coupling reagent is getting more attention as a condensing agent in ester synthesis.[5] By using this technique, carboxylic acid esters containing primary, secondary, and phenolic alcohols have been produced.[6] Less than 1% racemization occurs during the fragment condensation process using DCC, which is carefully monitored under controlled conditions. This technique was used to create an active peptide from glucagon. Racemization suppresses throughout synthesis; hence a precise racemization test is required to ascertain whether the outcome is completely optically pure. However, when DCC acts as a coupling agent in synthon condensation, acyl urea formation is a problem. It's difficult to get rid of aryl urea.[7] To prevent the formation of acyl urea, racemization-suppressing compounds such as *N*-hydroxy succinimide can be added.[8] One of DCC's key characteristics is its ability to function at mild reaction settings, enabling the synthesis of complex compounds without unfavorable side effects or extreme reaction conditions.

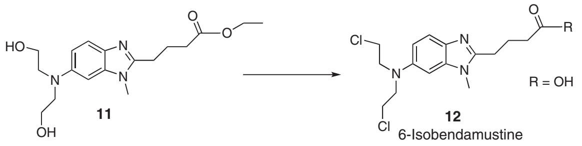
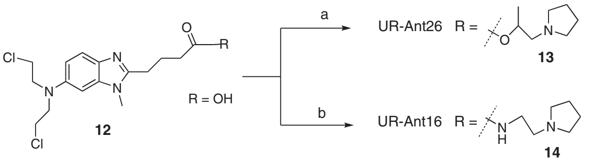
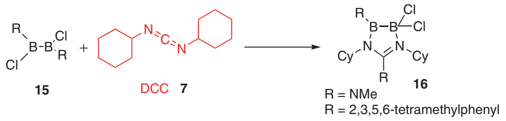
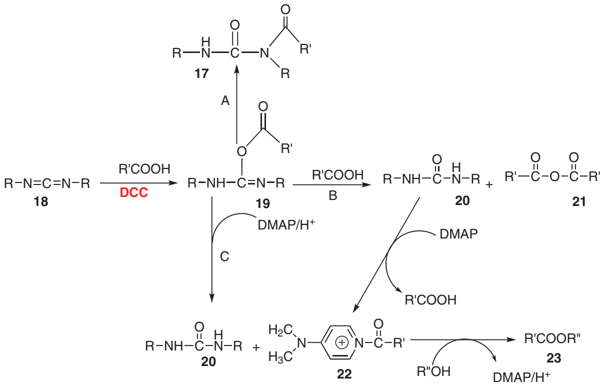


Scheme 1 Reaction mechanism of DCC

DCC also permits the coupling of multiple functional groups and substrates and has a broad range of applications. However, it is important to remember that DCC is a moisture-sensitive substance and needs to be treated carefully. It is usually used in dry or anhydrous environments to stop the creation of undesirable byproducts. Additionally, as with any chemical product, proper safety precautions should be used when working with DCC.

Table 1 Applications of DCC

(A) Guldjan Yakub et al. reported that pegylation of curcumin has been found to be the most efficient way to increase the bioavailability and water solubility of polyphenols for administration at low dosages.[9] Due to its wide range of beneficial medicinal characteristics, curcumin (Curc), popularly known as 'yellow gold', a plant product of polyphenol of significant scientific and clinical interest. Curcumin was directly esterified with a relatively low molecular-weight PEG-diacid (600 g/mol, with a PEG600-diacid/Curc molar ratio of 1:1 in the starting component) in the presence of DCC resulting in a PEG-Curc conjugate with a carefully selected lipophilic/lipophobic balance (curcumin saturation index of about 131,32), which was expected to ensure (1) enhanced Curc water solubility, (2) better stability, and (3) feasible therapeutic index. **Synthesis of PEG600-Curc** To synthesize PEG600-Curc, PEG600 and Curc were air-dried in a reaction flask via azeotropic distillation with anhydrous toluene DMAP, and then newly distilled DCM was added to made the PEG600-Curc conjugate. The resultant yellow suspension was ultimately treated with DCC, followed by DCM. For 48 h, the reaction was mixed at room temperature. After being concentrated to a final volume, the reaction mixture precipitated in cold diethyl ether (DCM/diethyl ether). After separating the precipitate, a small quantity of DCM was added to help it mix and thaw in cold diethyl ether. The precipitate was then filtered, centrifuged to ensure complete isolation, and the product was obtained.[9]	
(B) Lijun Tian et al. remarked that chitosan (CS) and pectin (PEC) polysaccharides are commonly employed in innovative drug delivery methods because they may be used to make novel conjugates and biopolymers.[10] CS is made up of repeated units of the cationic polymer *N*-acetyl-glucosamine and *N*-glucosamine. It includes reactive hydroxy and amino groups and sustains its positive charge in an acidic environment since its RNH$_3$ group has protonated. Pectin is composed of D-galacturonic acid monomer units with repetition that assist in conjugation reactions. It is a charged negative hydrophilic colloid that is sustained by hydration. The goal of this work was to combine PEC and CS to produce a PEC-CS bioconjugate employing the DCC crosslinking technique. **Synthesis of NHS-PEC bioconjugate** The process outlined in the reaction scheme was used to manufacture the *N*-hydroxy succinimide ester of pectin (NHS-PEC). In a nutshell, pectin (PEC) was mixed in a solution of triethylamine (Et$_3$N) and anhydrous dimethyl sulfur oxide (DMSO) by continuous stirring in the dark for a whole night. Dicyclohexylcarbodiimide (DCC) and *N*-hydroxy succinimide (NHS) were added to the PEC solution and agitated in the dark for 24 h in order to activate the carboxyl groups in PEC. Dicyclohexylurea (DCU), a precipitated byproduct, was eliminated using filtration. The NHS-PEC product was filtered followed by three Millipore water washes, and lyophilization.[10]	

(C) According to Antoni and Bernhardt, DCC is used as a coupling reagent for producing bendamustine ester.[11] Since bendamustine is generally given intravenously, there have been a few patent claims for formulations that could be taken orally. Additionally, it has been demonstrated that the esterification process of the carboxylic acid moiety improves the hydrolytic stability of the N-lost moiety (due to many causes), which may increase the likelihood of oral administration. The bendamustine ester, which possesses a simple scaffold, is very cytotoxic anticancer agent from its parent drug, and changing the ester into the liable amide increases stability in the plasma. To get around this, the linear ester moiety is changed to a linked ester, which increases stability, and the ester is changed to an amide. **Synthesis of 6-Isobendamustine and Derivatives** Compound **11** was first treated with the chlorinating agent thionyl chloride and then with hydrochloric acid to hydrolyze the ester bond to synthesize 6-isobendamustine (**12**). The bendamustine ester **13** was made with the use of the coupling reagent *N*,*N′*-dicyclohexylcarbodiimide (DCC), and for the synthesis of the new bendamustine amide **14**, the coupling reagents 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethylammonium tetrafluoroborate (TBTU) and *N*,*N′*-diisopropylethylamine (DIPEA) were consumed.[11]	 **Reagents and conditions**: 1) SOCl$_2$, dichloromethane, reflux, 1 h; 2) HCl aq., 90 °C, 2 h.  **Reagents and conditions:** (a) 1-(pyrrolidin-1-yl) propan-2-ol, ***N,N*-dicyclohexylcarbodiimide**, dimethylformamide (DMF), 0 °C, 15 min, 80 °C (microwave), 30 min; (b) respective alcohol or amine, 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate, *N*,*N*-diisopropylethylamine, DMF, rt, overnight or 60-80 °C (microwave), 45-120 min.
(D) Neutral cyclic sp^2–sp^3 diboranes **16** were synthesized via the reaction of *N*,*N′*-dicyclohexylcarbodiimide with 1,2-dichlorodiboranes **15** at room temperature, as reported by Erkan Firinci et al.[12] Through a rearrangement process, the addition of *N*,*N′*-dicyclohexylcarbodiimide (DCC, **7**) to derivatives of 1,2-dichlorodiborane results in the creation of neutral sp^2–sp^3 diboranes. This rearrangement uses substituent migration to create organoboron compounds. Carbodiimides offer a unique opportunity to investigate the effects of a neutral ligand on the addition reaction between carbodiimides and diboranes due to the presence of two donor nitrogen atoms. In the absence of a transition metal, Hoveyda and colleagues showed that the mono-Lewis base adducts diborane derivatives, sp^2–sp^3 diboranes, can be employed as effective borylation reagents for the borylation of unsaturated organic substrates.[12] The boron atom in sp^2–sp^3 diboranes can operate as the nucleophile in borylation processes and are frequently utilized as the raw material to make sp^2–sp^3 diboranes. In this reaction *N*,*N′*-dicyclohexylcarbodiimide gets introduced into derivatives of 1,2-dichlorodiborane. Through rearrangement and substituent migration, these reactions produce neutral cyclic sp^2–sp^3 diboranes. **Synthesis of sp^2–sp^3 Diboranes** When one equivalent of DCC (**7**) is reacted with B$_2$Cl$_2$R$_2$ **15** (R = dimethylamine, Dur) in toluene at room temperature, the resultant carbodiimide-induced rearrangement products are monocyclic sp^2–sp^3 diboranes **16**.[13]	
(E) To explore the usage of DCC as an activating agent, Vanhaecht et al. synthesized aliphatic polyester. It is thought that a carboxylic acid and a DCC molecule generate an *O*-acylisourea intermediate **19** as part of the mechanism of carbodiimide condensation.[13] From this intermediate, several reactions are possible. The intramolecular migration of an acyl group from an oxygen atom to a nitrogen atom results in the formation of *N*-acyl urea **17** (route A). The chain end is terminated by this inactive *N*-acyl urea, preventing the synthesis of high molecular weight polyesters. A bimolecular reaction between the *O*-acylisourea and a second carboxylic acid (route B) produces urea **20** and acid anhydride **21**. The acid anhydride can be acylated with the aid of DMAP to create an active *N*-acyl pyridinium intermediate **22**. The *N*-acyl pyridinium intermediate is produced by reacting the *O*-acylisourea intermediate with DMAP, which similarly leads to the formation of urea **20** (route C). The *N*-acyl pyridinium intermediate **22** finally regenerates the catalyst that creates the ester bond **23** by reacting with an alcohol.[14]	

The featured article concludes by providing a summary of the importance and adaptability of DCC as a coupling reagent in organic chemistry and a key tool in protein synthesis (Table 1). The core ideas of DCC are examined in order to make polyester and telechelic oligoesters at room temperature. As a condensation agent, *N*,*N′*-dicyclohexylcarbodiimide (DCC) plays a critical role in the esterification of carboxylic acid with alcohols at room temperature, which is another important point made in the study. The broad range of uses for these compounds in the synthesis of proteins and as a condensing agent in the production of ester continue to propel advances in organic chemistry and present chances for creative research and development across several sectors.

Conflict of Interest

The authors declare no conflict of interest.

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