

SYNLETT Spotlight 389

Diisopropylcarbodiimide

Compiled by Amit Verma



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

Amit Verma was born in Lucknow, Uttar Pradesh, India. He graduated in Pharmacy (2004) from the UP Technical University, Lucknow and completed his M. Pharm. (2006) from UPTU, Lucknow, India. He got trained in CDRI, Lucknow for one year during his Master program. He then joined as a lecturer in NIE College, Lucknow, India. Before starting his PhD studies at The M.S. University, he was working with Jubilant Chemsys Ltd. as a research associate. Currently he is working with Prof. Rajani Giridhar and Prof. M. R. Yadav as NDF-AICTE research scholar. His studies are focused on the synthesis of novel heterocycles as potent CNS agents for neurological disorders.

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Introduction

N,N'-Diisopropylcarbodiimide (DIC) is a liquid carbodiimide used in peptide synthesis and contains the functional group $\text{RN}=\text{C}=\text{NR}$. Carbodiimides hydrolyze to form ureas, which makes them uncommon in nature. Between the different sources of carbodiimide coupling reagents in peptide synthesis, the use of DIC as a liquid carbodiimide is more convenient. By using DIC one can avoid the tedious removal of dicyclohexylurea (DCU) formed during the use of dicyclohexylcarbodiimide (DCC),¹ as diisopropylurea (DIU) is comparatively easy to remove at the time of purification, which is formed after the generation of peptide bond. Besides being a less expensive and commercially available reagent, DIC is a good coupling agent

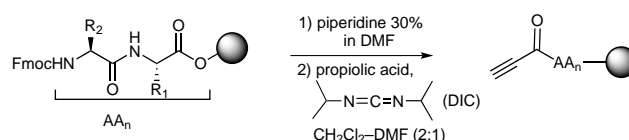
and widely used in solid-phase peptide synthesis. As a liquid, it is easier to handle than the commonly used DCC.

Carbodiimides are formed by dehydration of ureas or from thioureas. They are also formed by treating organic isocyanates with suitable catalysts (generally based on phosphine oxides); in this process, carbon dioxide evolves from the isocyanate.²

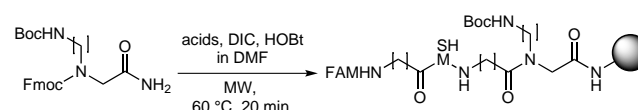
In synthetic organic chemistry, compounds containing the carbodiimide functionality are dehydrating agents and are often used to activate carboxylic acids towards amide or ester formation.³ Additives, such as *N*-hydroxybenzotriazole or *N*-hydroxysuccinimide, are often added to increase yields and decrease side reactions. Carbodiimides can also react with amines to form guanidines.

Abstracts

(A) Mata and co-workers have described a methodology for the preparation of triazolyl aminoacyl (peptidyl) penicillins utilising acylation of immobilized amino acid with propiolic acid and DIC.⁴



(B) Bradley and co-workers have reported microwave-mediated secondary amine couplings and the labelling of peptides with a variety of fluorophores and quenchers in presence of HOBt/DIC.⁵



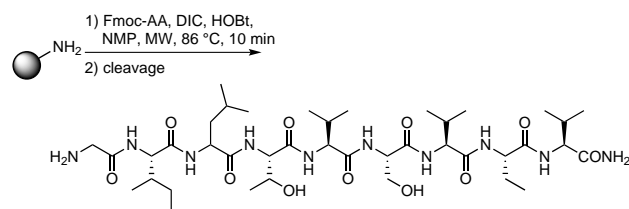
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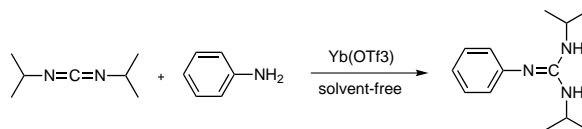
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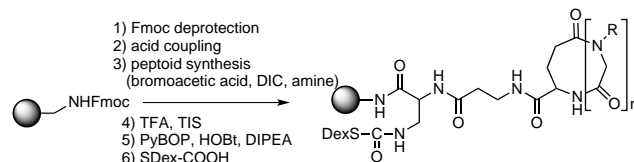
(C) Kappe and colleagues have reported the Fmoc/*t*-Bu solid-phase synthesis of three difficult peptide sequences (a 9-mer, 15-mer, and 24-mer) using DIC/HOBt as coupling reagent on polystyrene, Tentagel, and ChemMatrix resins.⁶



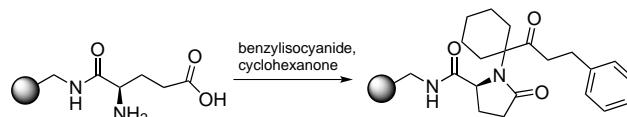
(D) Shen and co-workers have found ytterbium triflate as an efficient catalyst for the addition of amines to carbodiimides to *N,N',N''*-trisubstituted guanidines with a wide scope of amines under solvent-free conditions.⁷



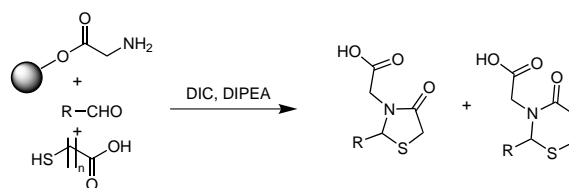
(E) Kwon and colleagues have reported the solid-phase synthesis of a series of cyclic and linear peptoid-dexamethasone conjugates for systematic cell permeability studies using reporter gene-based assays.⁸



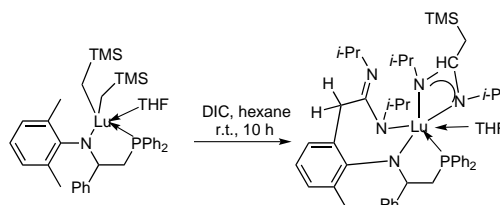
(F) Nefzi and co-workers have described an efficient synthesis of *N*-substituted pyrrolidinones, using the Ugi four-component reaction. The same methodology was employed to produce *N*-substituted pyrrolidinone tethered *N*-substituted piperidines.⁹



(G) Saraf and colleagues have reported an efficient method for DIC-mediated small library synthesis of thiazolidine-4-one and 1,3-thiazinan-4-one derivatives using one-pot, three-component condensations of amino acids, aldehydes and mercapto carboxylic acids on a polymer support. The study have shown significantly higher yields of the thiazolidine-4-ones, thereby indicating a lower dependence on the nature of the amino acids and aldehyde components.¹⁰



(H) Cui and co-workers have reported the preparation of a lutetium bis(alkyl) complex stabilized by a flexible amino-phosphine ligand $LLu(CH_2TMS)_2(THF)$ [$L = (2,6-C_6H_3Me_2)NCH(C_6H_5)CH_2P(C_6H_5)_2$], which upon insertion of *N,N'*-diisopropylcarbodiimide led to C–H activation via metalation of the ligand aryl methyl followed by reduction of the C=N double bond.¹¹



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