

EDAC - Water soluble Carbodiimide

EDAC is commonly known as water-soluble carbodiimide (WSC) and is used as a versatile coupling agent to form amide, ester or thioester bond and thus to cross-link proteins, nucleic acids or to bind molecules to surfaces in aqueous or organic media. There are also examples in which WSC is used as water scavenger or as a reagent for heterocyclic ring formation....

other names: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

CASRN [25952-53-8]; EDAC.HCl; EDC.HCl;EDCI.HClStructure of EDC.HClWater-soluble carbodiimide exists in different

forms as the free base or its hydrochloride salt. The HCl salt is the most convenient form due to its long term storage stability, non-hygroscopicity and is only slightly sensitive to hydrolysis. EDC displays ring-chain tautomeric forms. The IR absorption spectrum in chloroform solution displays a band at 2130 cm^{-1} ($-\text{N}=\text{C}=\text{N}-$) which is indicative of the open chain form. However, KBr disc or Nujol dispersion of the solid has ν_{max} values at 3250 and 1700 cm^{-1} that are characteristic of N-H and C=N bonds respectively which are derived from the cyclic tautomers in the crystal form of EDC. EDC.HCl is superior to DCC with regards to its high solubility in water (>200 g/L) and organics like CH_2Cl_2 , THF, DMF and its ease of use. Although WSC hydrolyses slowly and should be stored dry, it also can be applied as coupling agent in aqueous solution. WSC is less sensitizing than DCC but should be handled with care to prevent skin or eye exposure. Mechanism of reaction of carboxylic acid with EDC.xHCl Carboxyl group activation with EDC.xHCl proceeds similarly to other carbodiimide couplings. An O-acylisourea intermediate is formed by the reaction of a carboxylic acid and the carbodiimide. The O-acylisourea is a highly reactive species that readily reacts with amines, peptide coupling additives or reducing agents. EDC.HCl is transformed to the corresponding urea during coupling reactions, which has the advantage over DCU that it can be removed from the reaction mixture by extraction or be washed out from solid phase synthesis applications. However, the O-acylisourea can rearrange irreversibly to an N-acylurea and also racemise the α -carbon of the amino acid via formation of an oxazol-4(5H)-one [azlactone]. N-Acyurea formation and racemisation may be reduced by using intermediate nucleophiles, which convert the O-acylurea to an activated ester containing the nucleophile. Commonly used additives are 1-hydroxy-1,2,3-benzotriazole (HOBt), HOBt/ CuCl_2 , 7-aza-1-hydroxy-1,2,3-benzotriazole (HOAt), 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazole (HOObt), N-hydroxysuccinimide (NHS), 3-sulfo-1-hydroxysuccinimide (S-NHS). The use of CuCl_2 as co-additive to HOBt further reduces the levels of racemisation (<0.1%). The Lewis acid interaction of CuCl_2 with the oxazol-5(4H)-one suppresses racemisation while the acidity of the CuCl_2 also lowers the basicity of the medium and HOBt. The mechanism of amide bond formation applies both to EDC and EDC.HCl. Differences are that the free base can be applied as a bifunctional reagent: a coupling agent (carbodiimide) and a base (dimethylamino) while the HCl salt can form a O-acylisourea cyclic intermediate. The coupling of amine salt forms (HCl, tosylate etc.) requires liberation with bases like TEA, EDIPA or N-methylmorpholine before coupling with a carboxyl group. In some examples the dimethylamino tail of EDC acts as a tertiary base to liberate the reacting amino group from its salt in situ. Effect of additives Reducing the amount of additives used leads to the rapid completion of the reaction, regardless of the amino acids, carbodiimides, or solvents employed. It is generally accepted that the carbodiimide-N-hydroxy compound-mediated coupling proceeds predominantly via two steps: formation of an active ester with the N-hydroxy compound followed by aminolysis of the ester to liberate the additive. The rate of aminolysis of OBt-active esters with primary or secondary amines decreases with addition of further additive. The use of 0.1 eq. additive decreases the rate of active ester formation but also favours increased racemisation. Investigations suggested that using more than 0.1 eq. of additive decreases the levels of racemisation and decrease the rate due to the acidity of the additive thereby reducing the electron density of the nitrogen atoms of the amine. Using greater than 1 eq. of additive further decreases the coupling rate which is explained by the extent of hindrance caused by abundant additives. Non-stoichiometric interactions of amines and additives have also been reported and explains the lower rates by hindrance, caused by the excess additives surrounding the additive-amine salt. Coupling rates of amino acids with EDC.HCl in polar solvents (DMF, water, alcohols) are slower than in apolar media (CHCl_3 , CH_2Cl_2). Selected Applications of EDC DMAP catalysed esterification The esterification of amino acids with EDC/DMAP results in optically pure products (except Ser and Cys) but the bulkier the alcohol the greater racemisation ($\text{MeOH} < \text{EtOH} < \text{BzIOH} < \text{tBuOH}$). Lower levels of racemisation is achieved by reducing amount of DMAP used and utilising shorter reaction times. Synthesis of cyanoguanidines The use of EDC.HCl in the synthesis of cyanoguanidines significantly improved the yields over previous procedures. It was shown that both the amine and WSC should be applied in the same time. Other carbodiimides such as DCC gave low yields but DCC along with pyridinium tosylate increased yields. This suggested the participation of the dimethylammonium tail in the reaction whereby thiourea formation is achieved easily by room temperature decomposition of the S-acylisourea (Fig 10). The corresponding S-acylisourea that is formed from using DCC is more stable and requires acidic cleavage. Heterocyclic ring formation EDC plays an important role in heterocyclic chemistry via activation of carbonyl compounds into suitable cyclisation precursors Synthesis of oxadiazoles The synthesis of oxadiazoles consists usually of two steps that can be carried out in a one pot procedure. The first is an acylation and the second is a thermal condensation. The acylation can be performed by acid chloride, anhydride or by using carboxylic acid-coupling with carbodiimides. The latter has the advantage over the acid chloride method that is compatible with a variety of functional groups such as alcohols. Application of 0.5-2 eq. EDC.HCl gives the oxadiazoles in 30-63% overall yield. Other heterocycles The modified amino acid salts were coupled using EDC.HCl and HOBt. The amino group was freed by N-methyl-morpholine.