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# RECENT DEVELOPMENTS IN THE CARBODIIMIDE CHEMISTRY†

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## INTRODUCTION AND SCOPE

As a consequence of their ready accessibility coupled with their versatile chemical properties, carbodiimides rank as one of the most important classes of compounds in organic chemistry. Of particular significance is their use as condensing agents in the preparation of nucleotides and peptides. The chemistry of carbodiimides, the beginning of which may be considered to be the first correct formulation and characterisation of N,N'-disubstituted carbodiimides by Weith[1] in 1873, has been

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†Dedicated to Professor J. Michalski on the occasion of his 60th birthday.

discussed in many excellent reviews.[2-7] The first was provided by Khorana[2] in 1953. The recent one is by Kurzer and Douraghi-Zadeh[7] which covers the literature to the end of 1964.

The purpose of this article is to present recent achievements in the carbodiimide chemistry for the period 1965–79. The literature was covered through *Chemical Abstracts* to the end of 1979. Earlier works on carbodiimides are discussed only in those cases, where it was necessary to give the background to the subject discussed.

In order to limit the scope of the present overview, the industrial applications of carbodiimides, the formation and structure of the complexes of carbodiimides with inorganic salts as well as the utilisation of carbodiimides in some biological studies are not discussed. Beyond the limits of the present article are also those carbodiimides which contain the silyl, germyl and stannyl groups connected with nitrogen since their reactivity is completely different from that of the carbodiimides containing organic substituents.

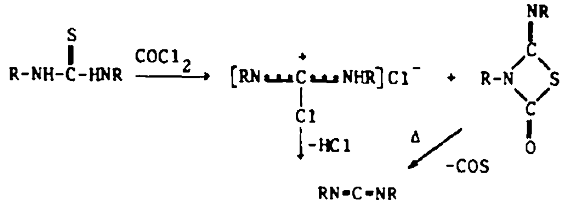
Finally, it should be noted that the syntheses of carbodiimides are presented in a cursory manner. Only new reactions and procedures leading to carbodiimides are included. A comprehensive treatment of this subject may be found in the review by Kurzer and Douraghi-Zadeh[7] and in a chapter of the book "*Methodicum Chimicum*".[8]

## (A) PREPARATION OF CARBODIIMIDES

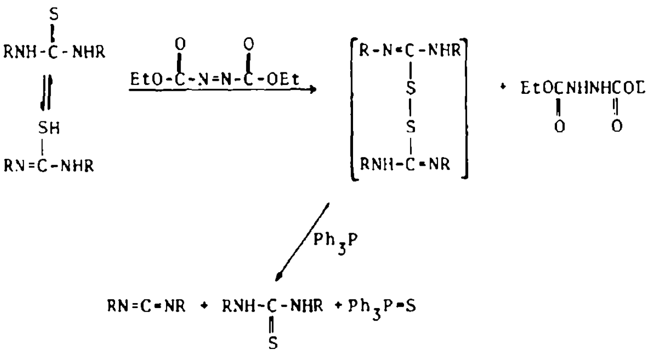
### 1. *From thioureas*

Elimination of hydrogen sulphide fom N,N′-disubstituted thioureas is a classical and most common method of synthesis of carbodiimides.[7-9] In the recent years a range of new reagents have been used for that purpose. Thus carbodiimides were obtained by heating thioureas with sodium amide in boiling toluene;[10] by treating thioureas with dichlorodicyano-benzoquinone and subsequent heating the resulting equimolar adducts with NaOH;[11] by treating thioureas with $SO_2$,[12] $SOCl_2$, $SO_2Cl_2$, $SCl_2$ or $S_2Cl_2$,[13] 2-chlorobenzothiazole,[14] 2-chloro-1-methylpyridinium iodide in the presence of triethylamine[15] or cyanuric chloride.[16]

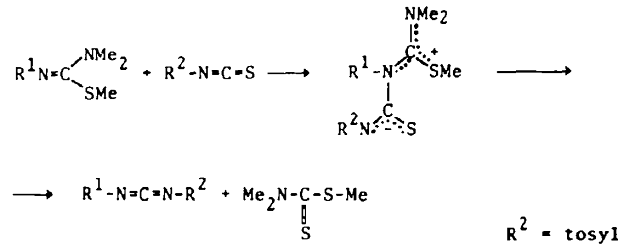
Carbodiimides are also obtained in the reaction of thioureas with phosgene:[9,17]



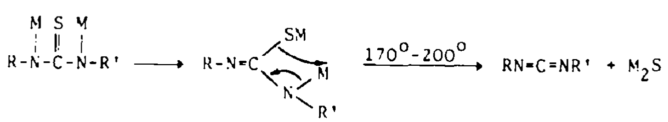
as well as with diethylazodicarboxylate[18] or azodibenzoyl[19] in the presence of triphenylphosphine:



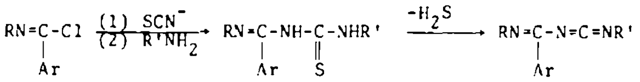
Reaction of isothioureas and tosylisothiocyanates forms the 1,4-dipoles, which in the case of bulky substituents on the nitrogen atom in isothiourea undergo [2 + 2]-cycloreversion reaction to give carbodiimides and dithiocarbamates:[20]



Carbodiimides are also obtained by pyrolysis of dimetallated thiourea derivatives[21] which are obtained by treating thioureas with alkyllithium or Grignard reagents:



Recently a new class of carbodiimides, *vis* imidoylcarbodiimides, has been obtained via desulphuration of thioureas:[22,23]



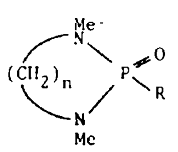
$$\mathrm{RN{=}\underset{\substack{|\\Ar}}{C}{-}Cl} \xrightarrow[(2)\ R'NH_2]{(1)\ SCN^-} \mathrm{RN{=}\underset{\substack{|\\Ar}}{C}{-}NH{-}\underset{\substack{\|\\S}}{C}{-}NHR'} \xrightarrow{-H_2S} \mathrm{RN{=}\underset{\substack{|\\Ar}}{C}{-}N{=}C{=}NR'}$$

2. *From isocyanates*[7]

The synthesis of carbodiimides from isocyanates consists in the condensation of two isocyanate molecules in the presence of a catalyst with evolution of $CO_2$:

$$2RN{=}C{=}O \xrightarrow[\text{catalyst}]{\Delta} RN{=}C{=}NR + CO_2$$

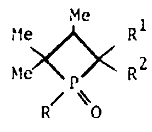
Various organic derivatives of phosphorus, e.g. isopropylmethylphosphonofluoridate,[24] 1,3-dimethyl-1,3,2-diazaphospholidine or phosphorine oxides (**1**),[25,26] and phosphetane oxides (**2**)[27] were used as catalysts.



a, n = 2

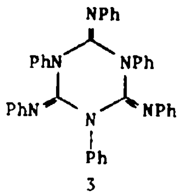
b, n = 3

1



2

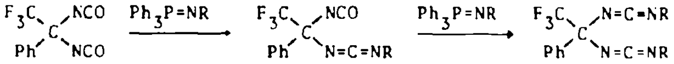
Also compounds of urea and amide type[28] as well as organometallic compounds such as $(i\text{-}PrO)_4Ti$, $(C_8H_{17}O)_4Zr$, $(EtO)_5Nb$,[29] wolfram and vanadium oxides or chlorides[30] were used as catalysts. By heating phenylisocyanate with N-methylhexamethyldisalazane a diphenylcarbodiimide trimer (**3**) was obtained:[31]



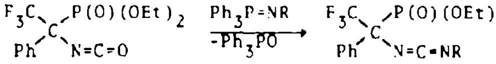
3

The reaction of isocyanates with tributyltincarbamates gives carbodiimides in low yields.[32]

Gem-bis-carbodiimides and gem-isocyanatocarbodiimides have been obtained in the reaction of gem-bis-isocyanates with triphenylphosphinimide:[33]

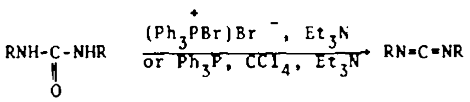


α-Phosphorylated carbodiimides were obtained in a similar manner:[34]

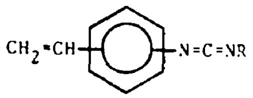


3. *From ureas*

Dehydration of N,N'-disubstituted ureas with $P_2O_5$ gives carbodiimides in a good yield.[35] Similar yields are obtained in the reactions of ureas with metal carbonyls such as $Fe(CO)_5$, $Fe(CO)_9$, $Fe(CO)_4CNPh$, $W(CO)_6$ and $Mo(CO)_6$.[36] Carbodiimides were also obtained by treating ureas with triphenylphosphine dibromide in the presence of triethylamine[37] or with triphenylphosphine in carbon tetrachloride in the presence of triethylamine.[38]



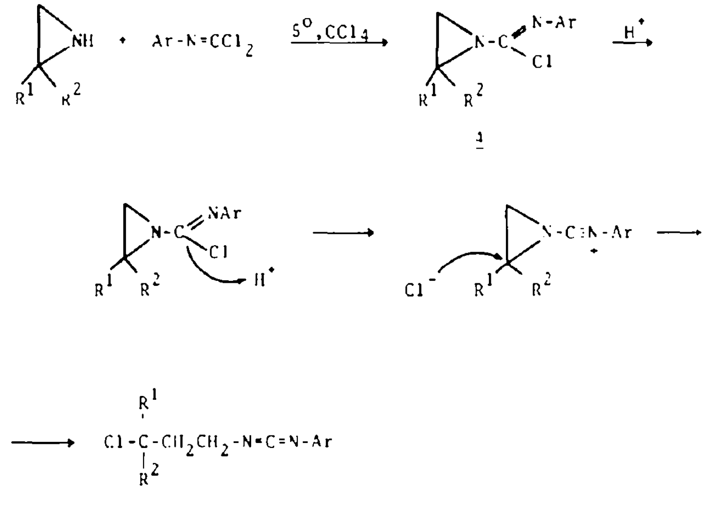
N-(*p*-or-*m*-vinylphenyl)-N'-isopropyl- and cyclohexylcarbodiimides were prepared from the corresponding ureas using *p*-toluenesulfonyl chloride in pyridine as dehydrating agent.



The monomers polymerise smoothly to afford vinyl polymers bearing the corresponding carbodiimide units as pendant groups in more or less crosslinked forms.[39]

4. *Other reactions leading to carbodiimides*

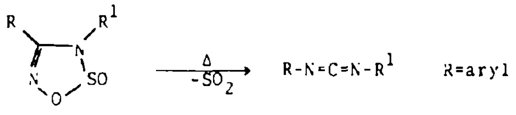
N-aryl-1-aziridinecarboxyimidoyl chlorides (**4**), prepared from aziridines and aryl cyanide dichlorides, undergo facile rearrangement to carbodiimides. The rearrangement is catalysed by strong Bronsted acids.[40]



N,N'-Dicyclohexylformamidine reacts with N-bromosuccinimide in the presence of pyridine or with $Br_2$ followed by treatment with 10 % NaOH to give DCC with a 61 or 78 % yield, respectively.[41] Cyanamides react with alkyl halides to give carbodiimides or disubstituted cyanamides.[42]

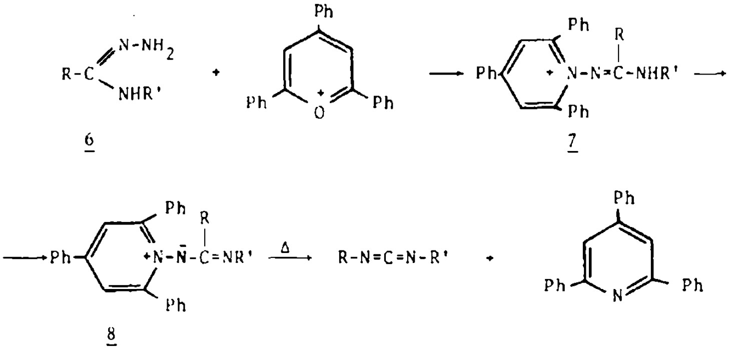
$$R'\text{-}NH\text{-}C{\equiv}N \xrightarrow[-HX]{R''X} R'\text{-}N{=}C{=}NR'' + R'R''N\text{-}C{\equiv}N$$

3,4-Disubstituted 1,2,3,5-oxathiadiazole-2-oxides (5) prepared by cyclisation of amidoximes $R^1NHC(R) = NOH$ with $SOCl_2$ in the presence of triethylamine, undergo decomposition to $SO_2$ and carbodiimides under mild thermolysis conditions.[43]

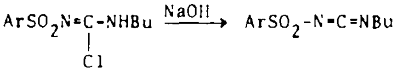


5

Amidrazones (6) form in the reaction with the triphenylpyrylium cation the salts (7) which are easily converted by mild bases into substituted pyridine-N-imides (8). Pyrolysis of the latter gives carbodiimides.[44]

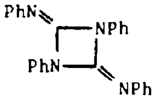


N-Substituted phenylsulphonyl-N'-alkylcarbodiimides were obtained in the reaction of suitable chloroformamidines with NaOH.[45]

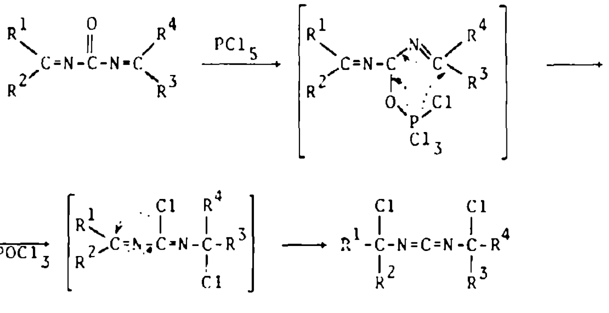


$$ArSO_2N{=}\underset{\displaystyle Cl}{\underset{|}{C}}\text{-}NHBu \xrightarrow{NaOH} ArSO_2\text{-}N{=}C{=}NBu$$

In the reaction of N-phenyldichloroformimide with aniline the diphenylcarbodiimide dimer was obtained.[46]



N,N'-Bis(1-chloroalkyl)carbodiimides were prepared from N,N'-bis(alkylidene)ureas by treatment with phosphorus pentachloride:[47]



## (B) PHYSICAL PROPERTIES AND STRUCTURE OF CARBODIIMIDES

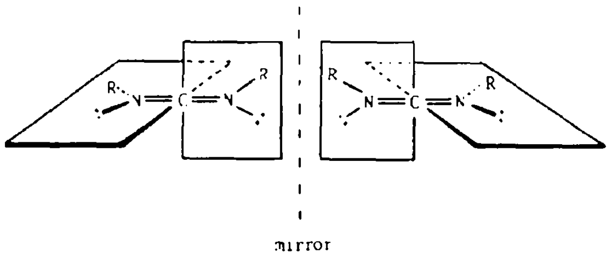
At room temperature carbodiimides are liquids or low melting solids. Their stability depends on substituents in the molecule. The stability of aliphatic carbodiimides increases with the branching of the carbon skeleton in the substituents. Among aromatic carbodiimides, those containing electron-acceptor groups in the aryl rings reveal lowest stability.[7]

In UV spectra the absorption band of the N=C=N group lies below 2000 Å, and in IR spectra the characteristic absorption bands of the N=C=N group lie at 1460 $\mathrm{cm}^{-1}$ [48] and 2150 2100 $\mathrm{cm}^{-1}$. Recently Mogul *et al.*[49] investigated spectral properties of several carbodiimides. They assigned absorption bands in IR spectra, measured UV spectra and determined dipole moments.

In $^{13}$C NMR spectra the chemical shifts of the sp-hybridised carbon in carbodiimides appear at *ca* 140 ppm.[50] It is interesting to note that the chemical shift for the sp-hybridised carbon in allenes is *ca* 210 ppm. The $^{14}$N NMR spectra allow to distinguish easily the carbodiimide structure from the cyanamide one.[51]

Very recently, the first paper appeared on the structural determination of N,N′-disubstituted carbodiimides by means of X-ray diffraction. Irngartinger and Jager[52] have found on the basis of X-ray analysis of bis(diphenylmethyl)carbodiimide and bis(*p*-methoxyphenyl)carbodiimide that the azacumulene systems deviate from a linear arrangement by 9.8 and 11.0 respectively. The cumulenic Π-bond systems have a nearly perpendicular orientation (89.7 and 87.9 , respectively).

Therefore, carbodiimides have a chiral structure, which is analogous to that of allenes, and can exist in optically active forms.

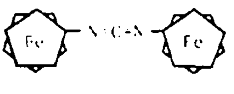


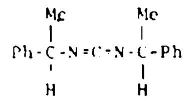
On the basis of INDO calculations it was shown that the configurational stability of carbodiimides is low (comparable to that of ammonia), the isomerisation being a combination of rotation and inversion processes.[53] The calculated value of the inversion barrier around nitrogen in carbodiimide is 8.4 kcal/mole.[54,56]

Some substituents can, however, stabilise the nonlinear structure of carbodiimides and allow their separation into enantiomers.[53,55] Schlögl and Mechtler[57] were the first who succeeded in partial optical separation of N,N′-diferrocenyl carbodiimide into enantiomers by chromatography on acetylated cellulose. This carbodiimide was also obtained in optically active state by kinetic resolution in the reaction with optically active (−)-S-6,6′-dinitrodiphenic acid.[57]

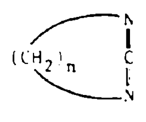
Červinka *et al.*[58] isolated very recently both enantiomers of (R,S)-N,N′-bis (α-phenylethyl) carbodiimide obtained from meso-N,N′-bis(α-phenylethyl)thiourea. They managed to determine the absolute configuration of the enantiomers and found that they undergo racemisation at room temperature.[58]

Similarly, cyclic heptamethylenecarbodiimide was chromatographed on a column of partially acetylated cellulose and the (−) enantiomer was obtained. Attempts to resolve undecamethylenecarbodiimide into enantiomers by the same method failed since the 14-membered ring, owing to its enhanced mobility, obviously enables the carbodiimide grouping to racemise rapidly.[59]





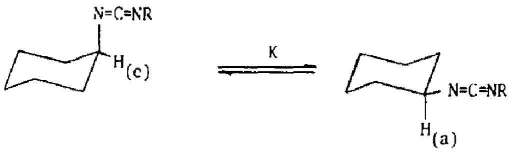
$\mathrm{Ph{-}\underset{H}{\overset{Me}{C}}{-}N{=}C{=}N{-}\underset{H}{\overset{Me}{C}}{-}Ph}$



n=7, 11

Several theoretical works were concerned with calculations of hybridization of the free electron pair at nitrogen,[60] explanation of the carbodiimide protonation and isomerisation mechanism,[61] and the expected $^{14}N$-nuclear quadrupole coupling constants.[62]

Bushweller *et al.* have studied the N,N'-dicyclohexylcarbodiimide (DCC) conformation.[63] They found on the basis of the low-temperature $^1H$-NMR that the carbodiimide group exerts a significant preference for the equatorial position. The K and A values determined at $-80^\circ$ for the conformational equilibrium given below are 12 and 1 kcal/mole, respectively.



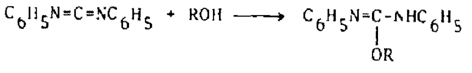
$$A = -\Delta G = \frac{RT\ln K}{1000}$$

### (C) CHEMICAL PROPERTIES OF CARBODIIMIDES

This section provides a general overview of the most important reactions of carbodiimides. Special emphasis is placed on the recent results and mechanistic aspects of the reactions investigated. In the first part of this section the reactions of carbodiimides with various compounds containing functional groups like OH, SH, NH, acidic CH are reviewed. In order to limit repetitions, the previously discussed reactions of carbodiimides with water, hydrogen sulphide, hydrogen selenide, hydrogen cyanide and phosphine are not included. The next part of the present section deals with the reactions of carbodiimides with organic acids. It does not include, however, the application of these reagents in the synthesis of peptides and nucleotides. This subject has been discussed in previous reviews especially by Khorana[2] as well as by Kurzer and Douraghi-Zadeh.[7] Moreover, the formation of the peptide or nucleotide bond using carbodiimides as dehydration reagents has now become the routine procedure and there is no reason to list exhaustively reactions of this type. The final part of the present section includes a discussion on the cycloaddition reactions of carbodiimides and their miscellaneous transformations.

### 1. *Reactions of carbodiimides with alcohols and diols*

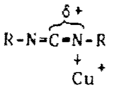
In the absence of catalysts the reaction of carbodiimides with alcohols proceeds under very drastic conditions i.e. under pressure and at high temperature. On this way Lengfeld and Stieglitz obtained for the first time the series of O-alkyl-N,N'-diphenylisoureas (9).[64] Somewhat later Stieglitz found that in the presence of sodium ethoxide alcohols react with carbodiimides exothermically giving the corresponding O-alkylisoureas in quantitative yields.[65]



$$C_6H_5N{=}C{=}NC_6H_5 + ROH \longrightarrow C_6H_5N{=}\underset{OR}{\underset{|}{C}}{-}NHC_6H_5$$

9

The formation of the adducts between alcohols and carbodiimides was utilized by Khorana in his synthesis of mixed phosphoric esters. He found, however, that alcohols do not react with dicyclohexylcarbodiimides (DCC) and with other aliphatic carbodiimides.[66] Synthesis of O-alkylisoureas from aliphatic carbodiimides was accomplished by applying copper or zinc salts as catalysts.[67–70] The catalytic action of metal ions consists probably in the formation of a coordinative complex on the N atom which contributes to a significant increase of the electrophilicity of the central C atom in carbodiimide.



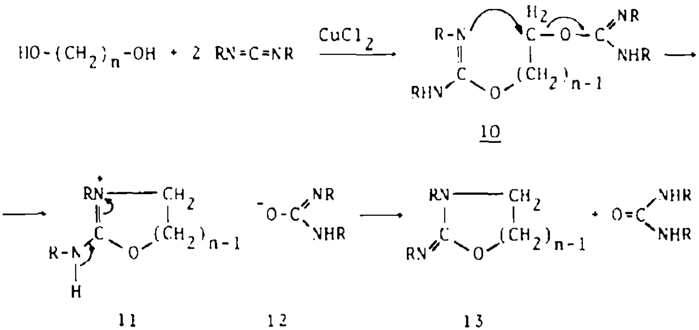
$$R{-}N{=}\overset{\delta+}{\overbrace{C{=}N}}{-}R \qquad \underset{Cu^+}{\uparrow}$$

Moffatt and Khorana have shown that acids are the best catalysts for this reaction[71] since the protonation of the nitrogen atom in carbodiimide increases considerably the electrophilicity of the central carbodiimide C atom.

Hartke and Radau obtained recently O-alkylisoureas in the reaction of alcohols with sterically hindered and therefore poorly reactive, di-t-butylcarbodiimide in the presence of equimolar amounts of fluoroboric acid ($HBF_4$) dissolved in ether.[72] This method failed, however, in the case of aliphatic carbodiimides since $HBF_4$ caused their dimerisation or polymerisation.[73]

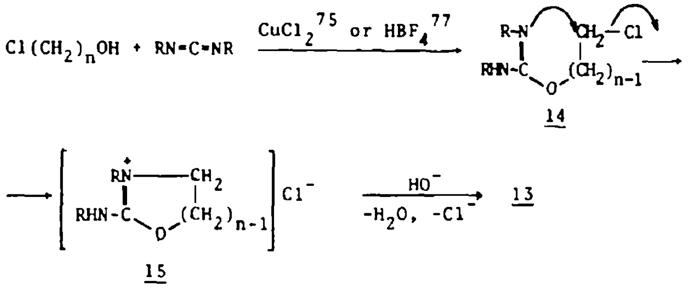
$$RN=C=NR \overset{H^+}{\rightleftharpoons} [R-N=C=\overset{+}{N}H-R \leftrightarrow RN=\overset{+}{C}-NHR]$$

The above mentioned Cu catalysts have also been used in the reactions of carbodiimides with diols. The presence of two active OH groups in the diol molecule makes the reaction somewhat more complicated. According to Schmidt *et al.* the reaction proceeds as shown below:[74,75]

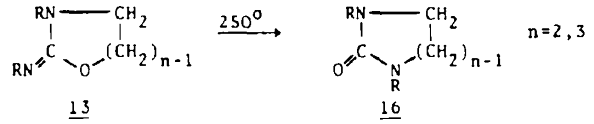


In the first step the corresponding O,O′-alkylenebisisoureas (**10**) are formed. They are the final products of the reaction when the number of the methylene groups in diol is greater than 3. The adducts of ethylene and propylene glycols with carbodiimides undergo spontaneous cyclisation due to the intramolecular nucleophilic attack of the imine N atom on the terminal methylene group in **10**. Then, the proton transfer from the cyclic isouronium ion (**11**) to the strongly basic isourea anion (**12**) leads to final products of the structure of 1,3-oxazolidines (**13**, n = 2) or 1,3-oxazolines (**13**, n = 3).

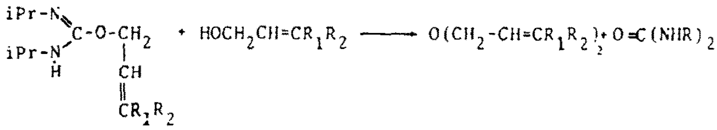
In the case of cyclohexanediol the formation of the corresponding oxazolidines was observed only with the *trans*-isomer.[76] Cyclic compounds of type **13** can also be obtained in the reaction of carbodiimides with ω-halogenoalcohols.[75,77] The hydrochloride **15** formed as a result of intramolecular nucleophilic substitution of the Cl atom by the imino N atom in imino ether **14** yields the corresponding cyclic derivatives **13** after elimination of hydrogen chloride under basic conditions.



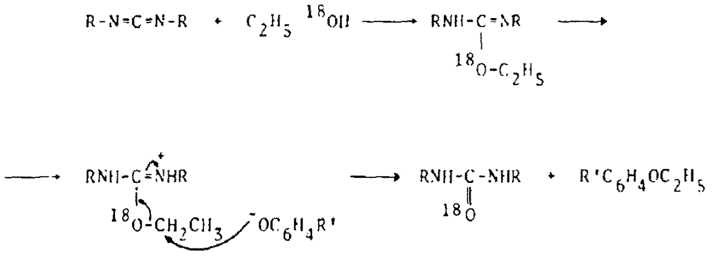
Isoureas **13** rearrange upon heating at 250° affording the corresponding derivatives of the ureas (**16**):[78]



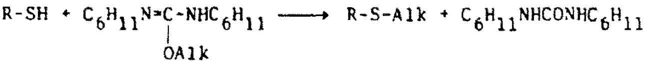
O-Alkylisoureas **9**, **13** are very reactive and form with alochols and phenols the corresponding ethers and ureas[75,79,80] for example:



Using in the reaction $^{18}O$ labelled ethanol, Bach has demonstrated that ethers are formed *via* the attack of alkoxy or phenoxy anions on the alkyl group in O-alkylisourea:[81]



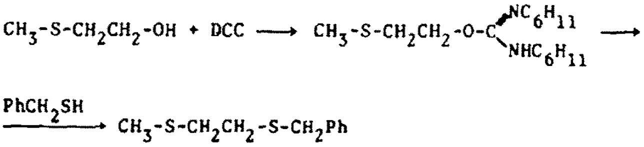
O-Alkylisoureas react with mercaptans and thiophenols to give the corresponding thioethers in high yields:[82,83]



$$R\text{-}SH + C_6H_{11}N{=}\underset{\displaystyle OAlk}{C}\text{-}NHC_6H_{11} \longrightarrow R\text{-}S\text{-}Alk + C_6H_{11}NHCONHC_6H_{11}$$

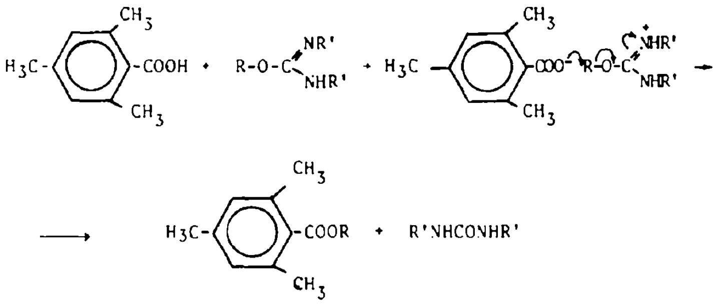
It is interesting to note that in the reaction of O-alkylisoureas with mercaptoalcohols only the thiol group being more nucleophilic was alkylated.

Vowinkel and Wolff took advantage of this property to develop a convenient method of synthesis of asymmetrically alkylated dithiols[82].

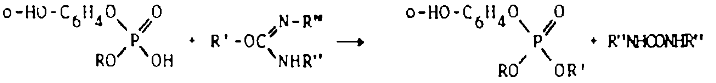


O-Alkylisoureas are also convenient reagents for alkylation of amines. Markiw and Canellakis ave found that alkylation of thymine, thymidine and uridine with alochols in the presence of DCC esulted in the formation of N-alkylation products only. No traces of isomeric O-alkylation products vere detected.[84,85]

Reaction of O-alkylisoureas with carboxylic acids leads to the formation of esters in high ields.[86,87] In the first step of that reaction protonation of O-alkylisourea takes place followed by an ttack of the acid anion on the alkyl group as shown below. Since this stage does not require the ormation of a tetrahedral transition intermediate at the carbonyl carbon atom, it is possible to use his method for esterification of the sterically hindered acids.



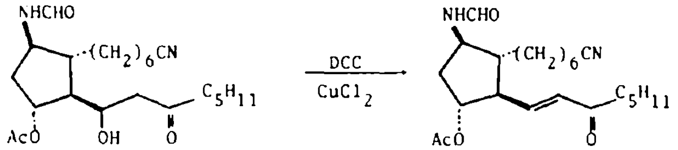
Similar reaction takes place between dialkyl phosphates and O-alkylisoureas.[88]



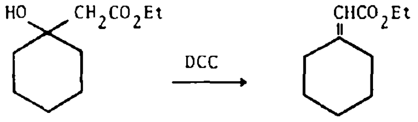
Adducts of carbodiimides and suitably protected sugars have been used for glycosidation of a variety of organic compounds.[89]

O-Alkyl and O-arylisoureas are easily reduced with hydrogen on a Pd catalyst to the corresponding alkanes and arenes.[90,91] This reaction can be utilised as a general method for reducing alcohols to hydrocarbons.

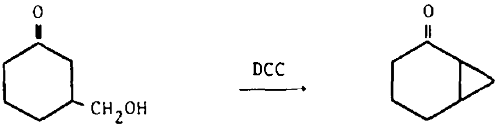
β-Hydroxyketones when heated with DCC undergo intramolecular dehydration to α,β-unsaturated ketones.[92,93] Corey *et al.* used this method in their PGE$_1$ synthesis to introduce under mild conditions the double bond in the position 13.[92]

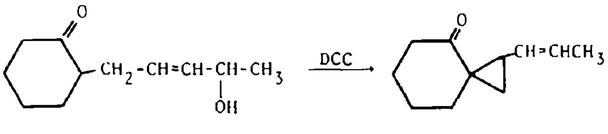


Dehydration of β-hydroxyesters leads likewise to α,β-unsaturated esters.[94]



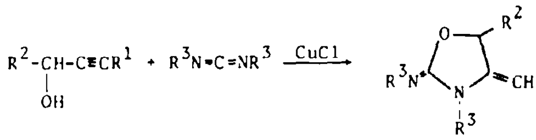
γ-Hydroxyketones[93] and ε-hydroxyketones[95] form under these conditions cyclic products, e.g.





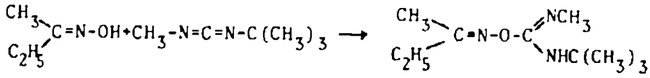
Dehydration of 4-hydroxyclohexanone using chiral carbodiimides exhibited no asymmetric induction whatever, giving only racemic bicyclo [3.1.0] hexan-2-one[96]

The reaction of hydroxyalkynes with carbodiimides yields the corresponding oxazolidines:[97]



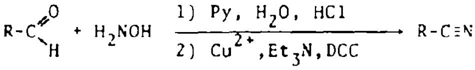
2. *Reaction of carbodiimides with* N-*hydroxy compounds*

Ketoximes and aldoximes like alcohols undergo addition to carbodiimides in the presence of catalysts such as powdered sodium hydroxide,[68] hydrofluoric acid[98] or Cu salts,[99] yielding corresponding adducts.

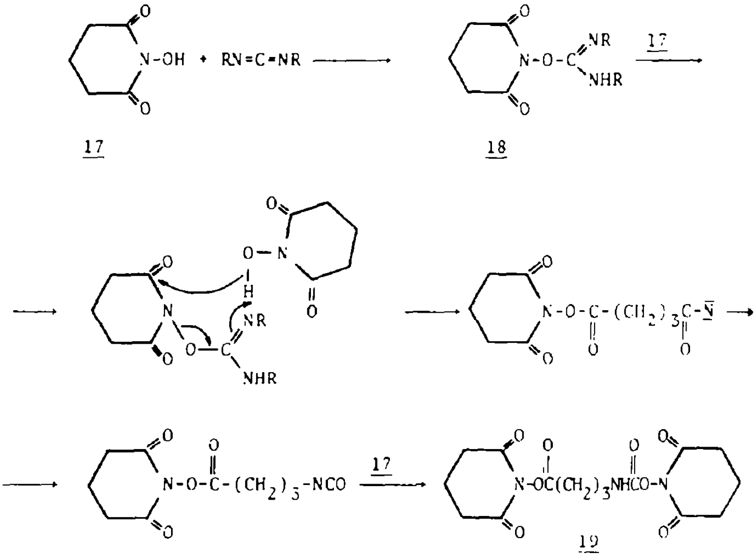


However, the adducts of aldoximes and carbodiimides are unstable and decompose to the corresponding nitriles and ureas.[94]

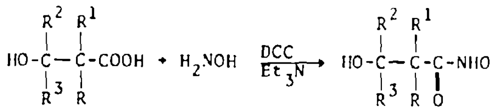
This fact has been utilised to synthesise nitriles from aldoximes.[100,101] Vowinkel has developed a one-step method of obtaining nitriles from aldehydes and hydroxylamine in the presence of DCC.[99,102]



Carbodiimides react with cyclic hydroxyimides of aliphatic dicarboxylic acids (**17**) affording in the first step the adducts having the structure of isourea ethers (**18**). However, these compounds are not the final products of the reaction and react further with two hydroxyimide molecules to yield derivatives of the corresponding amino acid (**19**).[103,104]

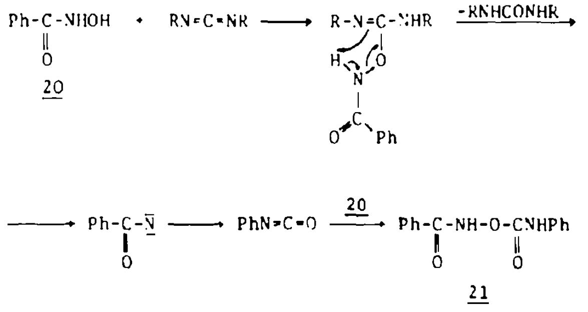


Hydroxamic acids can be obtained in the reaction of carboxylic acids with hydroxylamine or its hydrochloride in the presence of carbodiimides.[105-107]



$$HO-C(R^2)(R^3)-C(R^1)(R)-COOH + H_2NOH \xrightarrow[Et_3N]{DCC} HO-C(R^2)(R^3)-C(R^1)(R)-C(=O)-NHOH$$

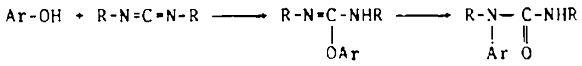
It was found that hydroxamic acids react also with carbodiimides[108] as illustrated below:



The adduct formed in the first step of the reaction undergoes the Lossen rearrangement to give urea and phenylisocyanate. The latter reacts with the next hydroxamic acid (**20**) molecule giving N-(N'-phenylcarbaminoxy)-benzamide (**21**) as final product. Hoare *et al.* succeeded in stopping that reaction at the isocyanate stage by using an excess of water-soluble 1-benzyl-3-dimethylaminepropyl-carbodiimide for the reaction with hydroxamic acids. This allowed them to obtain after hydrolysis the corresponding amines in high yields.[109]

### 3. *Reaction of carbodiimides with phenols*

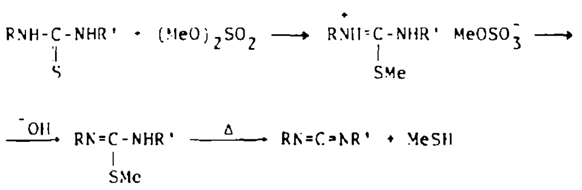
The reaction of carbodiimides with phenols depends both on the acidity of the phenol and on the type of carbodiimide. Weakly acidic phenols and diphenylcarbodiimide yield at high temperatures O-aryl-N,N'-diphenylisoureas, whereas strongly acidic phenols afford under the same conditions N-aryl-N,N'-diphenylureas.[110] DCC behaves likewise with respect to phenols.[111,112] It is obvious that the N-aryl urea derivatives are formed from the primary O-arylisoureas as a result of migration of the aryl group from the oxygen to the N atom.



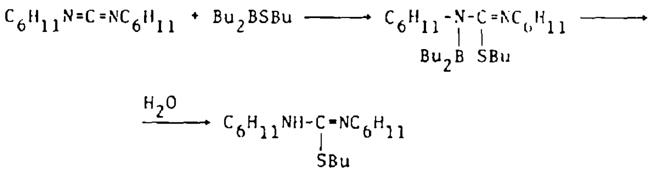
Comparison of the data from the literature strongly suggests that O-arylisoureas are the final products when weakly acidic phenols react with weakly basic carbodiimides, whereas N-arylureas are the final products when strongly acidic phenols react with strongly basic carbodiimides. Of course, this is a rather general rule and some exceptions are reported in the literature. As long as picric acid, which is a strongly acidic phenol, yields the respective N-picrylureas with every carbodiimide [113,114] (for different result see[115]), 2-carboethoxy-4,6-dinitrophenol still gives with DCC N-aryl-substituted urea but with di-*p*-tolylcarbodiimide already O-arylisourea, while 2,6-dichloro-4-nitrophenol yields O-arylisourea even with DCC.[116] It deserves noting that *m*-and *p*-dihydroxybenzenes do not react with DCC at all.[113]

### 4. *Reaction of carbodiimides with mercaptans and thiophenols*

Mercaptans react with carbodiimides to give S-alkylisothioureas.[110] Addition of mercaptans to aliphatic carbodiimides is a reversible reaction, what has been utilised in the synthesis of carbodiimides by pyrolysis of the S-alkylisothioureas obtained in another way.[117]



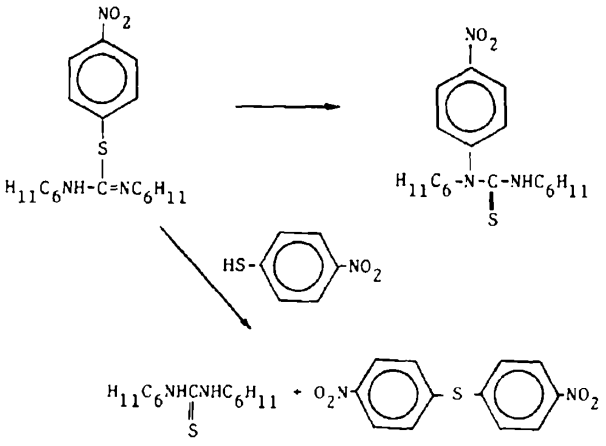
S-alkylisothioureas are also obtained as a result of hydrolysis of the adducts formed in the reaction of thioboronites with carbodiimides.[118]



$$C_6H_{11}N{=}C{=}NC_6H_{11} + Bu_2BSBu \longrightarrow C_6H_{11}\text{-}\underset{Bu_2B}{N}\text{-}\underset{SBu}{C}{=}NC_6H_{11} \xrightarrow{H_2O} C_6H_{11}NH\text{-}\underset{SBu}{C}{=}NC_6H_{11}$$

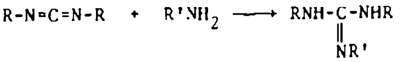
In contrast to O-alkylisoureas S-alkylisothioureas do not react with alcohols or mercaptans.[98] However, S-alkylisothioureas have been applied for synthesis of heterocyclic compounds in the reaction with isatoic anhydride.[119]

Thiophenols react with DCC in a somewhat different manner.[120] At O all thiophenols form with DCC S-arylisothioureas, whereas at 80–100° further reactions proceed whose character depends on the acidity of the thiophenols used. In the case of *p*-thiocresol, S-*p*-tolyl-N,N'-dicyclohexylisothiourea formed in the first step yields in the presence of excess *p*-thiocresol a complicated mixture of products. The main products of the reaction of *p*-nitrothiophenol with DCC are: bis-*p*-nitrophenyl sulphide, N,N'-dicyclohexylthiourea and the accompanying them N-*p*-nitrophenyl-N,N'-dicyclohexylthiourea produced as a result of the S → N migration of the aryl group.

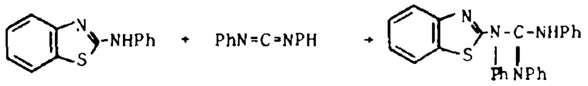


### 5. *Reactions of carbodiimides with compounds containing amino group*

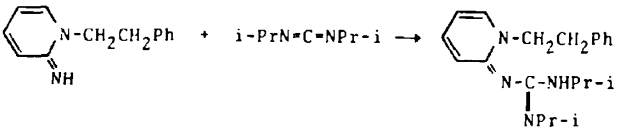
Ammonia and primary as well as secondary amines undergo addition to carbodiimides yielding di-, tri- and tetra-substituted guanidines[121–126]



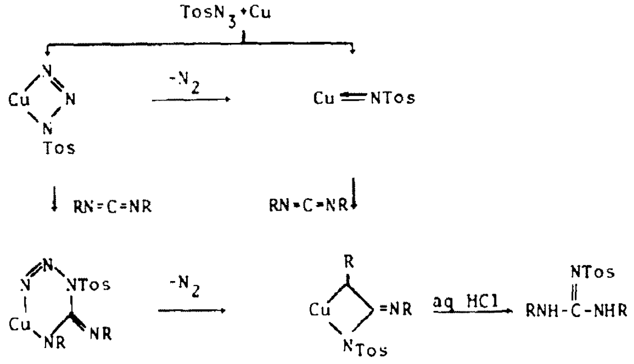
$$R\text{-}N{=}C{=}N\text{-}R + R'NH_2 \longrightarrow RNH\text{-}\underset{NR'}{\underset{\|}{C}}\text{-}NHR$$



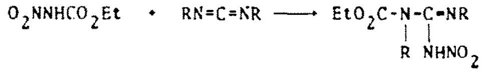
Imines react with carbodiimides in a similar manner[127]



N-Sulphonylguanidines have been obtained in the reaction of carbodiimides with tosyl azide in the presence of copper as catalyst. Copper plays here a significant role forming in the first step a complex with tosyl azide[128]

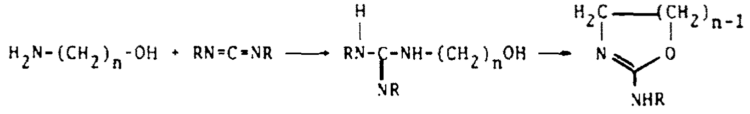


Addition of N-nitrourethane and carbodiimides leads to the formation of the corresponding N-nitro-N′-carboalkoxyguanidines[129]



$$O_2NNHCO_2Et + RN{=}C{=}NR \longrightarrow EtO_2C\text{-}\underset{R}{N}\text{-}\underset{NHNO_2}{C}{=}NR$$

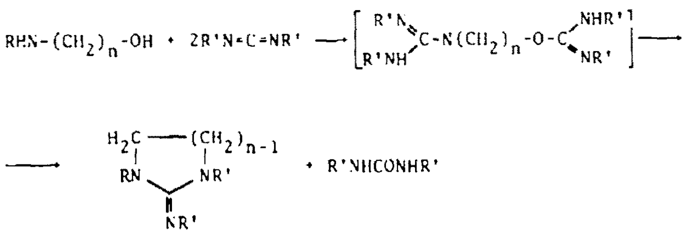
The reaction of carbodiimides with aminoalcohols or aminomercaptans is interesting for two reasons. Firstly, it allows the comparison of the reactivity of each of the functional groups, and secondly, it should be accompanied by the successive cyclisation reactions leading to heterocyclic compounds. Aminoalcohols containing the primary amino groups react with carbodiimides as follows:[117,130]



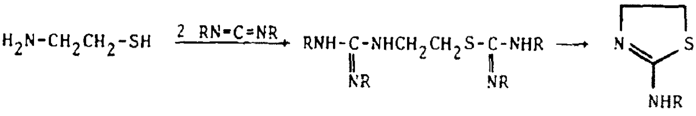
n=2,3

In the first step, the amino group adds to the double bond of carbodiimide to form the respective guanidine. Subsequently, as a result of the intramolecular attack of the O atom on the imino C atom and splitting off the amino group the corresponding 1,3-oxazaheterocycles are formed. Salts of aminoalcohols react in a similar manner.[131]

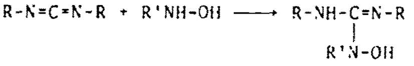
When carbodiimide is used in a molar ratio 2:1 with respect to aminoalcohol, the addition takes place at both functional groups.[illegible] The resulting compound undergoes cyclisation to yield 1,3-diazoheterocyclic compounds. In this case, the cyclisation occurs in a different way to that described above since urea functions here as a leaving group.



Analogous compounds are formed in the reaction of 2-mercaptoethylamine with diarylcarbodiimides. At low temperatures the double addition products are formed whereas at about 100° cyclisation occurs with the formation of 2-arylamino-1,3-thiazoline:[7]



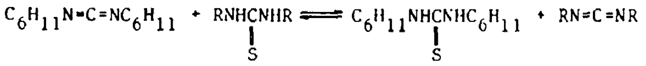
In the case of hydroxylamine and its derivatives the amino group shows greater reactivity towards carbodiimides what in consequence always leads to the formation of the respective guanidines and not isourea ethers.[132-135]



$$R-N=C=N-R + R'NH-OH \longrightarrow \underset{\displaystyle R'N-OH}{R-NH-\underset{|}{C}=N-R}$$

Among compounds containing the amino group, enamines,[136] hydrazines,[137,138] carbohydrazides[139] and thiocarbohydrazides[140] were studied as regards their reactions with carbodiimides. In the first step, the formation of the corresponding guanidines (products of mono- and bi-addition) was always observed. In the successive reactions these guanidines yielded heterocyclic compounds.

Quite interesting is the reaction of DCC with thioureas.[141] It turned out that the reaction of DCC with N,N'-disubstituted thioureas is a typical reversible reaction in which DCC and the starting thiourea on the one hand, and N,N'-dicyclohexylthiourea and the N,N'-disubstituted carbodiimide formed on the other hand are in equilibrium.



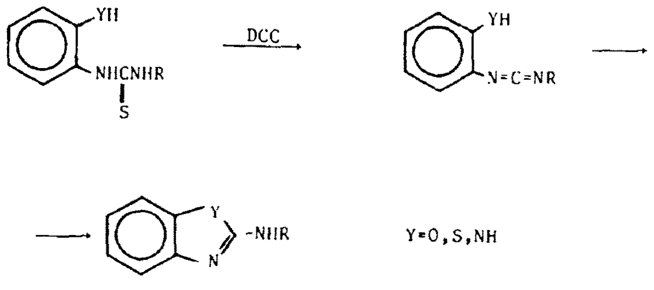
$$C_6H_{11}N=C=NC_6H_{11} + RNH\underset{\displaystyle S}{\underset{|}{C}}NHR \rightleftharpoons C_6H_{11}NH\underset{\displaystyle S}{\underset{|}{C}}NHC_6H_{11} + RN=C=NR$$

However, in the case of unsubstituted thiourea, monosubstituted thioureas or asymmetrically disubstituted ones the reaction is irreversible, and N,N'-dicyclohexylthiourea and the respective cyanamides are obtained as products:

(a) R=R'=H
(b) R=H, R'=alkyl or aryl
(c) R,R'=alkyl or aryl

This confirms the results of earlier studies indicating that both the unsubstituted carbodiimide and monosubstituted carbodiimides occur solely in the tautomeric form of cyanamides.

The occurrence of equilibrium between DCC and thiourea has found application in the cyclisation reaction of *ortho*-substituted phenylthioureas yielding the respective heterocyclic systems.[142]

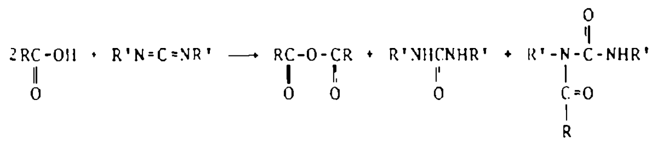


Y=O,S,NH

It has recently been reported that the reaction of amines with carbon dioxide in the presence of riethylamine and DCC leads to ureas.[143]

### 6. *Reaction of carbodiimides with carboxylic acids*

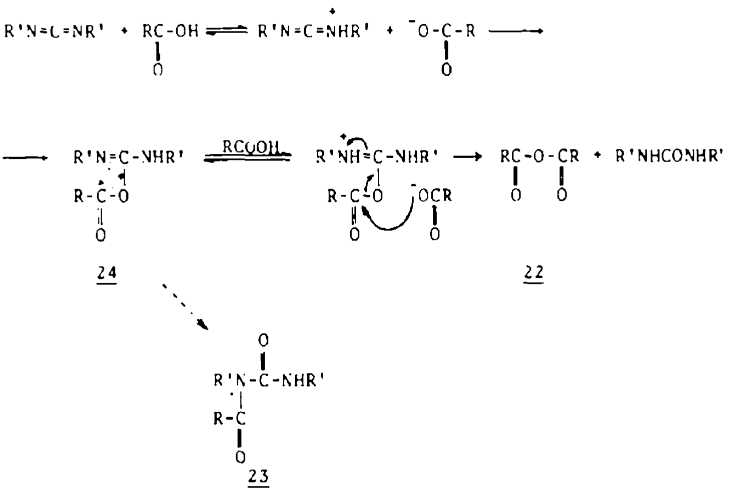
6.1. *Reaction with monocarboxylic acids.* Carboxylic acids react with carbodiimides to form acid anhydrides (**22**) and the appropriate N,N′-disubstituted ureas and/or N-acyl-N,N′-disubstituted ureas (**23**).



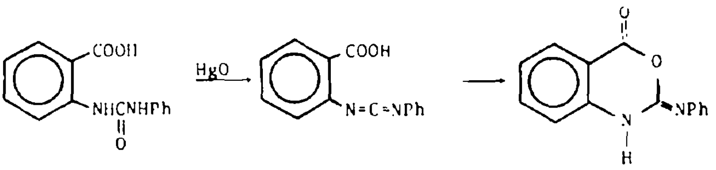
$$2RC(=O)OH + R'N{=}C{=}NR' \longrightarrow RC(=O)\text{-}O\text{-}C(=O)R + R'NHC(=O)NHR' + R'\text{-}N(C(=O)R)\text{-}C(=O)\text{-}NHR'$$

22 23

The mechanism of this reaction suggested by Khorana[2,144,145] to explain its bidirectional course is as follows:

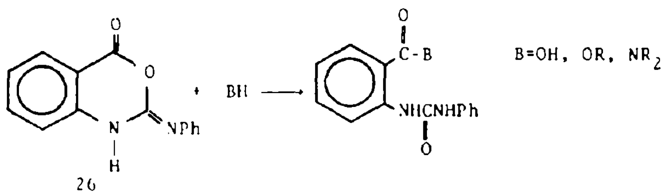


In the first step carbodiimide is protonated and then the acid anion attacks the C atom of the cation formed leading to the formation of the very active O-acylisourea (**24**). The latter, in turn, can react further in two ways. On the one hand, intramolecular migration of the acyl group from the O atom to N yields N-acylurea (**23**). On the other hand, after initial protonation of O-acylisourea (**24**) by the next acid molecule the anion of that acid may attack the carbonyl C atom and yield the acid anhydride and urea. A very convincing argument speaking in favour of that mechanism has been given by Doleschall and Lempert[146] who isolated the cyclic intermediate with O-acylisourea structure (**26**) formed as a result of intramolecular reaction of the carbodiimide moiety and the carboxyl group in N-*o*-carboxyphenyl-N′-phenylcarbodiimide (**25**):



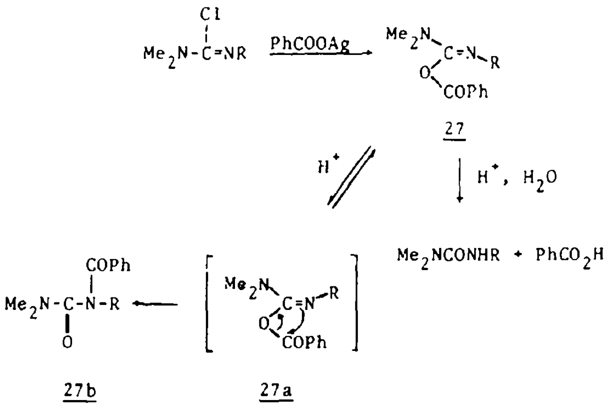
25 26

This compound reacts in the presence of hydrogen chloride with water, alcohols or amines to yield acid, esters or amides, respectively[147]



26

Hegarty *et al.* have obtained acyclic O-acylisourea (**27**) in an independent way and studied its reaction with water as well as the intramolecular rearrangement to N-acylurea.[148] The O-acylisourea (**27**) obtained was stable in the absence of light, acids and bases. When dissolved in water/dioxane it underwent competing acid catalysed intermolecular transfer of the acyl group to $H_2O$ to give benzoic acid and urea, and intramolecular transfer to N-acylurea (**27b**).



It was found that at pH > 3 N-acylation occurred perferentially, but that intermolecular transfer is then progressively favoured as the pH is reduced. These observations can be rationalised as follows. Rearrangement of **27** to **27b** cannot take place unless preceded by N inversion or rotation about the C=N bond. Acid catalysis (protonation of the imine nitrogen) reduced the C=N double bond character in **27** facilitating isomerisation to **27a** and ultimately to **27b**. The reduction in the rate conversion of **27** to **27b** at pH < 2 occurs since the free bases **27** and **27a** are now present largely as their conjugate acids; the N-protonated form of **27a** does not undergo O → N-acyl transfer to **27b**. The conclusion is that the O → N-acyl migration, which is acid catalysed, can be suppressed by the use of excess acid. This is especially important in peptide synthesis, where the N-acylureas are undesired by-products.

Arendt and Kolodziejczyk succeeded in tracing the intermediate O-acylurea by radiochemical tlc/lsc methods in the reaction of N-blocked phenylalanine with O-methylleucine in the presence of DCC. The authors concluded from the O-acylisourea and N-acylurea concentration curves that in this case both compounds are formed in parallel reactions, and that N-acylurea is not produced as a result of intramolecular transfer of the acyl group from the oxygen to N- atom in O-acylisourea. So far the quoted authors have not advanced any other mechanism of formation of N-acylureas.[149]

The rate of the reaction of carbodiimides with carboxylic acids and the ratio of the products obtained are affected by a whole range of factors. Among them the most important are:

(i) the type of carbodiimide used,
(ii) strength of the acid and the nucleophilicity of its anion,
(iii) kind of solvent,
(iv) presence in the reaction medium of other active compounds.

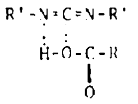
*ad(i).* Under comparable conditions aromatic carbodiimides yield N-acylureas as main reaction products whereas aliphatic carbodiimides form chiefly anhydrides and N,N'-disubstituted ureas.[145,150-155] In general, the migration of the acyl group from the O to N atom is the more preferred the less basic is the N atom.

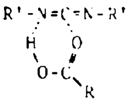
*ad(ii).* The reaction rate is the greater the greater is the strength of the acid used[156,157] and the nucleophilicity of its anion.[144] The results of kinetic studies of the reaction of DCC with various acids in tetrahydrofurane[158] given below illustrate this effect.

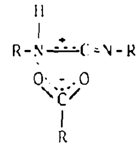
| | $CH_3COOH$ < | $ClCH_2CH_2CO_2H$ < | $HCOOH$ < | $ClCH_2CO_2H$ < | $N{\equiv}CCH_2CO_2H$ |
|---|---|---|---|---|---|
| $pK_a$ | 4.75 | 4.08 | 3.75 | 2.86 | 2.47 |
| $K_k\ \frac{l}{mol \cdot min}$ | 0.07 | 0.21 | 0.27 | 1.5 | 3.3 |

The strength of the acid has also a significant effect on the ratio of the resulting products. The general relationship is such: the higher the strength of the acid the higher is the yield of anhydride and N,N′-disubstituted urea, and the lower that of N-acylurea. For instance, in the reaction of DCC with acetic acid in THF one obtains 40 % of N-acylurea, whereas in the reaction with chloroacetic acid the sole products are anhydride and N,N′-dicyclohexylurea.

The reaction exhibits first-order kinetics both in the acid and in the carbodiimide, and the rate-determining step is addition of the acid molecule to one of two C=N double bonds in carbodiimide resulting in the formation of O-acylisourea.[a, 156] Its formation is considered to occur in three different ways:

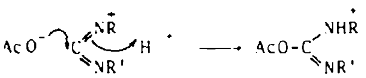






According to DeTar and Silverstein most probable is the path via an intermediary ion pair. Moreover, they consider the fully ionic mechanism suggested by Khorana as a less probable, since the addition of triethylammonium acetate to the reaction not only does not accelerate the reaction (what should occur if free ions were present), but on the contrary it has an inhibiting effect.[156]

Very recently Ibrahim and Williams, investigating the reaction of a water soluble carbodiimide ($EtN{=}C{=}NCH_2CH_2CH_2\overset{+}{N}Me_3$) with acetate buffer, have excluded a stepwise mechanism for O-acylisourea formation by the observation of general acid catalysis. According to these authors O-acylisourea is formed in the reaction in which acetate ion attack on carbodiimide is concerted with proton transfer.

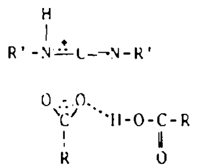


However, they do not comment, whether this mechanism is general for all kinds of carbodiimides.[159]

*ad(iii)*. Solvents exert a fairly surprising effect on the reaction rate of carbodiimides with acids. It was found that the reaction rate is highest in carbon tetrachloride and lowest in THF, as it is illustrated by the relative reaction rates[157] of DCC with acetic acid placed under the formulae of the solvents:

$$\begin{array}{ccccccc} CCl_4 & > & C_6H_5NO_2 & > & CH_3CN & > & THF \\ 34 & & 18 & & 6 & & 1 \end{array}$$

The solvents have also a distinct effect on the ratios of the reaction products.[156,157,160,161] The proportion of N-acylurea is greatest from the reaction in THF and smallest from that in $CCl_4$. In the reaction of DCC with acetic acid in THF the yield of N-acetylurea is 40 %, in $CH_3CN$ is 6 %, and in nitrobenzene and $CCl_4$ it reduced to O. According to DeTar and Silverstein these results can be explained as follows. Primarily one should note that the carboxylic acids show a strong tendency to form dimers the amount of which depends strongly on the solvent used.[156,160] For instance, in $CCl_4$ acetic acid exists almost exclusively in dimeric form, whereas in $CH_3CN$ or THF it is monomeric. The quoted authors claim that the presence of acetic acid dimer is responsible for the higher reaction rate in $CCl_4$, since it shows higher reactivity towards DCC. That higher activity is supposedly due to the strong tendency of carboxylic acids to form complexes involving hydrogen bonds and the ensuing possibility of stabilisation of the initially produced ion pair.



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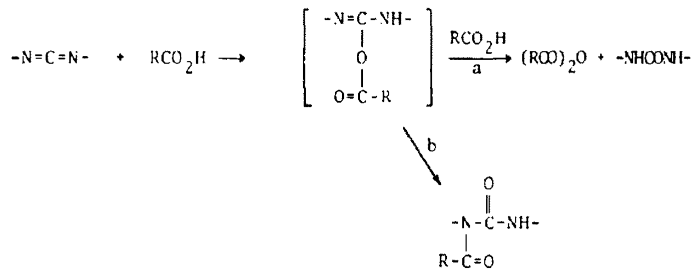
[a] It should be pointed out, however, that the reaction is strongly dependent on the kind of the acid used, since it was possible to isolate some stable O-acylisoureas (cf. ref. 146 and 149).

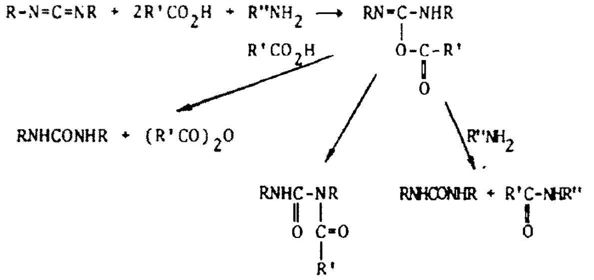
Of course, this effect should be more pronounced in $CCl_4$, which itself does not give effective hydrogen bonds, than in $CH_3CN$ which forms them very easily. The presence of two acid molecules and one carbodiimide molecule in the same solvent cage, which takes place when the acid exists largely in the form of dimer, may account for the predominant formation of anhydride. However, Mironova *et al* definitely discard this explanation and are of opinion that the concentration of the dimer in solution has no effect at all on the reaction rate and the ratio of products obtained.[157] In fact, in the reaction of DCC with chloroacetic acid in THF, where the content of the dimer is close to zero, chloroacetic anhydride and N,N′-dicyclohexylurea are solely formed.[162] Moreover, Mironova *et al* provided some evidence that the reactivities of the monomer and dimer of a given acid are similar and vary with the solvent used (e.g. in THF the dimer is more active, whereas in $CCl_4$ the monomer).[157] The quoted authors ascribe the variation of reaction rate with kind of solvent to a specific solvation effect. The reaction rate increases with the lowering of the solvation properties of the solvents (from THF to $CCl_4$), whereas the polarizabilities of the solvents increase in the order from THF to *p*-nitrobenzene and rapidly decrease on passing to $CCl_4$. If one takes into account that the activation energy of the reaction is 16 times lower in $CCl_4$ as compared with THF, the conclusion can be drawn that the preliminary polarisation of the O–H bond in the acid is not decisive for the formation of the intermediary compound. Of greater importance must be energy losses connected with desolvation of the acid. Thus in THF the less solvated dimer is more active, whereas in $CCl_4$ the weakly solvated monomer shows higher activity.[157] The varying ratio of the yields of the particular reaction products with solvent used and other reaction parameters (e.g. temperature) are explained by Mironova and Dvorko by the change of the relative reaction rates at steps a and b:[157,162]



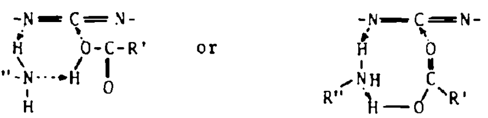
However, the effect of solvent on the mechanism of the reaction between acids and carbodiimides is very complicated and further studies would be very desirable.

*ad*(*iv*). Amines, depending on their order and basicity, affect the reaction of carbodiimides with acids in a different manner. The strongly basic tertiary amines (e.g. $Et_3N$) decrease significantly the reaction rate.[160,163] They also decrease the yield of anhydride and increase that of N-acylurea in both $CCl_4$ and $CH_3CN$ solutions. This can only be due to the "trapping" of the acid by the amine (salt formation), or the amine may catalyse the O-acylisourea to N-acylurea rearrangement. A different effect is exerted by pyridine. It lowers, indeed, the reaction rate,[163] but leads to an increased yield of the anhydride at the expense of N-acylurea.[160] The latter effect can be explained by the possibility of O-acylisourea being stabilised due to the formation of an acylpyridinium complex.

Primary amines (benzylamine,[160,162] aniline, *p*-toluidine[164]) should exert an analogous effect as triethylamine. On the other hand, however, being nucleophilic compounds, they give with acids in the presence of carbodiimides the respective amides:



Usually it is difficult to observe the anhydride formed in this reaction, since it reacts immediately with amine to yield amide. In order to eliminate the formation of anhydride Mironova *et al.* reacted equimolecular quantities of acid, carbodiimide and amine.[164] They found that primary amines, in contrast to tertiary ones, increase the reaction rate. According to those authors this is due to the formation of a cyclic complex which facilitates the transfer of the proton to carbodiimide and the formation of O-acylisourea:

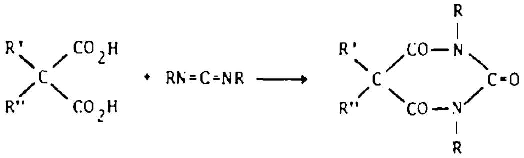


Addition of a primary amine so as of a tertiary one leads to an increased yield of N-acylurea. This proves that the amide is formed in a secondary reaction of the amine with the preliminarily synthesized O-acylisourea.

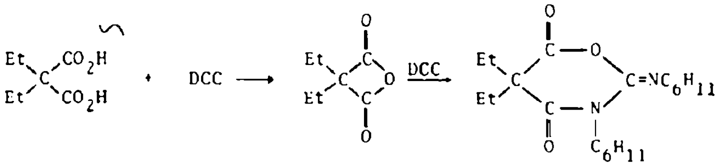
Among the works concerned with the mechanism of the reaction of carboxylic acids with carbodiimides those of Knorre *et al.*,[165-168] devoted to the kinetics of reaction of carboxylic acids with water-soluble carbodiimides, e.g. N-cyclohexyl-N'(4-methylmorpholine-*β*-yl)-carbodiimide *p*-toluenesulphonate, deserve special attention. Similarly, the work of Muramatsu *et al.*[169] deserves mentioning, since the authors reacted DCC with formic acid to obtain formic anhydride. As a matter of fact, they did not isolate that anhydride on account of its instability, however, they proved its presence in the solution in an indirect manner.[169] Recently, Olah *et al.* have repeated this experiment and established the structure of the anhydride by means of spectroscopic methods.[170]

6.2 *Reactions with dicarboxylic acids.* Reaction of carbodiimides with dicarboxylic acids affords different products depending on the structure of the acid. Oxalic acid yields quantitatively under any conditions the corresponding urea and mixture of carbon mono- and dioxides. This reaction has been applied by Zetzsche *et al.* for the quantitative determination of carbodiimides.[171]

According to Mironova and Dvorko[172] malonic acid yields with DCC a polyanhydride. Other authors claim that malonic acid and its homologues react with aliphatic carbodiimides to yield the substituted barbiturates:[173]

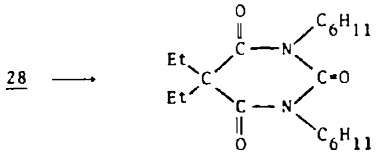


An ultimate explanation has been provided by Resofszki *et al.* who showed that in the reaction of diethylmalonic acid with DCC a cyclic anhydride is first produced which undergoes further reaction with DCC to yield substituted 1,3-oxazinedione-4,6 (**28**).[174,175]



28

The latter compound undergoes slowly rearrangement in the solution to yield the corresponding barbiturate (**29**).



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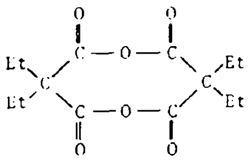
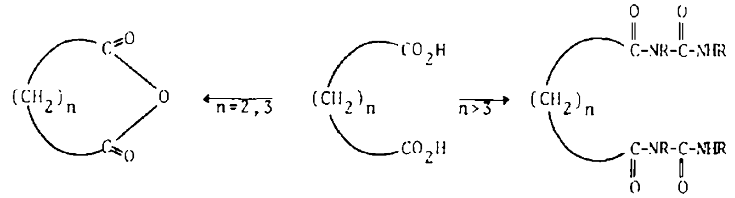
Furthermore, the quoted authors isolated in this reaction the compound **30** which is a dimer of diethylmalonic anhydride.

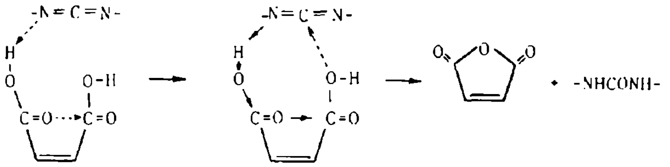


30

Dicarboxylic acids containing two or three methylene groups yield in the reaction with carbodiimides cyclic anhydrides whereas acids containing four or more C atoms in the methylene chain give bis-adducts.[172,176]



Mironova and Dvorko studied the kinetics of the reaction between a number of dicarboxylic acids and DCC giving cyclic anhydrides.[158,172] They found that, although the reaction rate increases with growing acid strength, the activation energy of anhydride formation depends only very slightly on the kind of acid involved (11.3–12.3 kcal/mole in THF). The change of the reaction rate with the change of acid depends primarily on the variation of activation entropy. Therefore, the reaction rate increases with the probability of the anhydride ring formation. Mironova and Dvorko believe that O-acylisourea does not have to be an intermediate and that the formation of the cyclic anhydride is the rate determining step of the reaction proceeding as shown below:



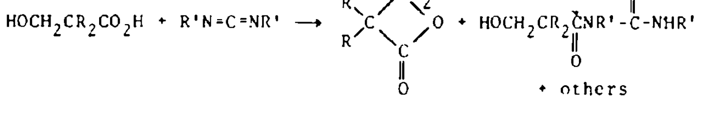
The reaction rate decreases with the solvent used in the following order:

$$CH_3CN > MeOH > acetone > THF > pyridine$$

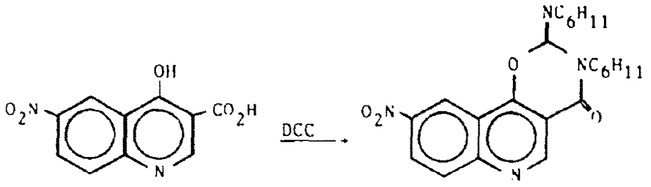
Tertiary amines markedly lower the reaction rate.

Bis-carboxylic acids react with bis- or polycarbodiimides to produce substituted polyureides.[177]

6.3 *Reactions with acids containing an additional functional group.* The structure of the products formed from hydroxycarboxylic acids and carbodiimides depends on the relative positions of the hydroxy and carboxy groups. Cyclic lactones are obtained when conditions exist for easy cyclisation.[178,179] The respective N-acylureas are sometimes formed as by-products.[180]



In other cases cyclic products are also formed which contain, however, fragments of carbodiimides in the molecule, e.g. in the reaction of 4-hydroxy-6-nitroquinoline-3-carboxylic acid with DCC the respective oxazine (**31**) is formed:[181]



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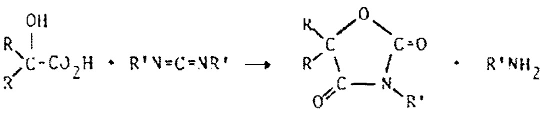
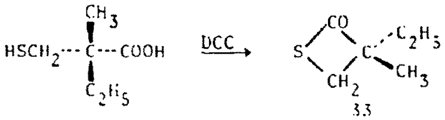
Robba and Maume found that in the reaction of α-hydroxycarboxylic acids with carbodiimides oxazolidinediones (**32**) are formed:[182]



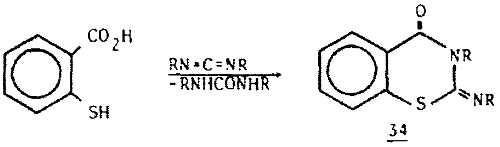
32

When optically active R-(+)-2-methyl-2-ethyl-3-mercaptopropionic acid was reacted with DCC, optically active thiololactone (**33**) was obtained:[183]



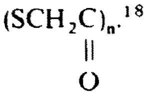
33

Thiosalicylic acid reacts with carbodiimides to yield the corresponding 2-imine-1,3-benzothiazinones-4 (**34**):[184]



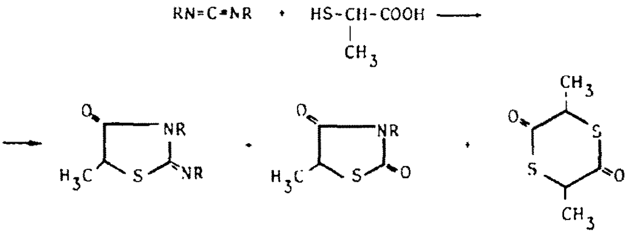
34

Similar compounds are obtained from mercaptoacetic acid and aryl carbodiimides. The same reaction with aliphatic carbodiimides leads, however, to the polythioglycolate

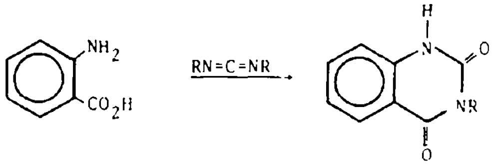


$(SCH_2\overset{\overset{\displaystyle O}{\|}}{C})_n$.[185]

Reaction of carbodiimides with 2-mercaptopropionic acid affords a mixture of thiazolidinones, diazolidinediones and dithiolactide:[186]

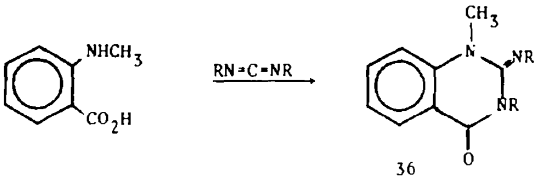


The structure of products of the reaction between carbodiimides and carboxylic acids containing an amino group in the molecule depends on the kind of acid, and especially on the substituent at the N atom. Anthranilic acid when reacted with aromatic carbodiimides yields the respective benzodiazinediones (**35**):



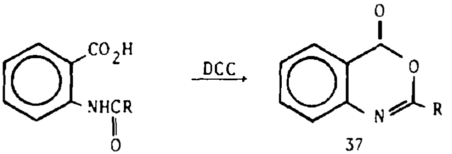
35

N-Methylanthranilic acid when reacted with carbodiimides yields iminobenzodiazinones (**36**):[187]



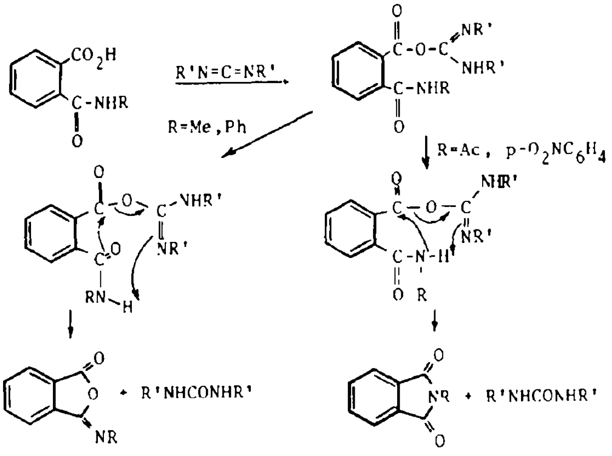
36

In distinction, N-acylanthranilic acids yield with DCC benzoxazines (**37**):[188]



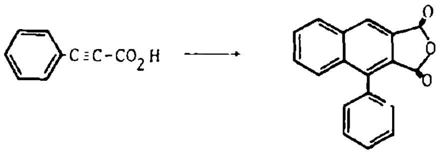
37

Phthalamic acids substituted at the N atom react with DCC giving either imides (**38a**), when the substituents are electron-attracting groups ($p$-$NO_2C_6H_4$, acyl), or isoimides (**38b**), when the substituents are aryls or alkyls. The mechanism of the formation of these compounds is as follows:[189]

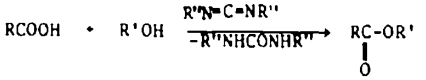


38b 38a

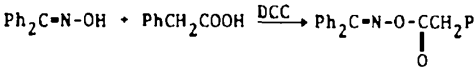
The reaction of phenylpropiolic acid with DCC is more complicated and yields substituted 1-phenylnaphthalene-2,3-dicarboxylic anhydrides as a result of additional condensation:[190]



6.4 *Ester and amide formation reactions.* Equimolar mixtures of acids and alcohols undergo in the presence of carbodiimides condensation giving esters in high yields.[191-197] Under similar conditions oximes are acylated by carboxylic acids:[198]



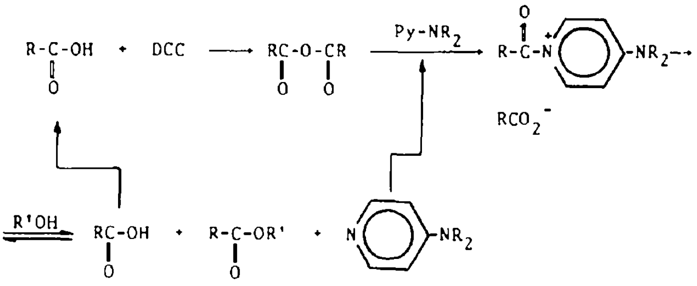
$$\mathrm{RCOOH} + \mathrm{R'OH} \xrightarrow[-\mathrm{R''NHCONHR''}]{\mathrm{R''N{=}C{=}NR''}} \mathrm{R}\underset{\substack{| \\ \mathrm{O}}}{\mathrm{C}}\mathrm{{-}OR'}$$



$$\mathrm{Ph_2C{=}N{-}OH} + \mathrm{PhCH_2COOH} \xrightarrow{\mathrm{DCC}} \mathrm{Ph_2C{=}N{-}O{-}}\underset{\substack{| \\ \mathrm{O}}}{\mathrm{C}}\mathrm{CH_2Ph}$$

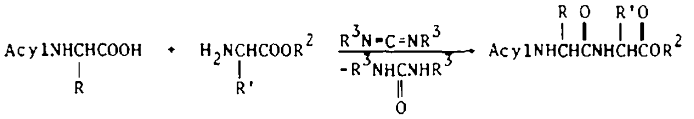
However, in some cases this procedure failed. For instance, attempts to esterify fatty acids with alcohols in the presence of DCC have led as a rule to the formation of N-acylureas.[199]

It is generally accepted that the mechanism of formation of esters in this reaction is analogous to that of obtaining anhydrides (Section 6.1), i.e. O-acylisourea is the active acylating agent. A modification of the esterification procedure has been introduced, which consists in the addition of catalytic amount of 4-dialkylaminopyridine to a mixture of acid, alcohol and carbodiimide. Carboxylic anhydride, which is formed first, serves in this case as an acylating agent.[200-202] The yields of esters obtained by this procedure (also from fatty acids[202]) are 65-96%.



Reactions conducted in the presence of carbodiimides containing chiral substituents, e.g. esterification of racemic carboxylic acids with achiral alcohols and acylation of achiral amines with racemic carboxylic acids, did not give a measureable enantioselective effect.[203] Acylation of racemic amines with achiral carboxylic acids carried out under the same conditions was found by Rebek *et al.*[204] to be highly enantioselective. However, Krawczyk and Bełżecki claim that this reaction, just as the above-mentioned ones, exhibits a very low enantioselectivity.[203]

The reaction of amines with carboxylic acids in the presence of carbodiimides leads to the corresponding amides (*cf* Section 6.1.d).[160-164,205-208] This reaction has found very wide use in the chemistry of peptides. As early as in 1955 Sheehan and Hess[209] as well as Khorana[210] found that suitably protected amino acids can be condensed in the presence of carbodiimides to form amide bonds:



$$\mathrm{Acyl\,NHCHCOOH} + \mathrm{H_2NCHCOOR^2} \xrightarrow[-\mathrm{R^3NHCNHR^3}]{\mathrm{R^3N{=}C{=}NR^3}} \mathrm{AcylNHCHCNHCHCOR^2}$$

The mechanism is here analogous as for amide formation.[211,212,213] A role of an acylating agent plays O-acylisourea,[b] although under the conditions of solid phase peptide synthesis the DCC reaction mechanism follows the alternate path and the active acylating agent is the symmetrical anhydride.[212] Sometimes products being the result of the O → N migration of the acyl group

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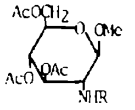
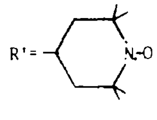
[b] It should be pointed out that the exact nature of the acylating agent in the peptide synthesis by means of DCC is still controversial. According to D. S. Kemp and J. H. Jones as well as to A. Arendt the structure of the acylation agent formed from amino acid and DCC may be different from that of O-acylisourea (A. Arendt, Technical University, Gdansk, private communication concerning the discussion at the 15-th European Peptide Symposium, Gdansk 1978).

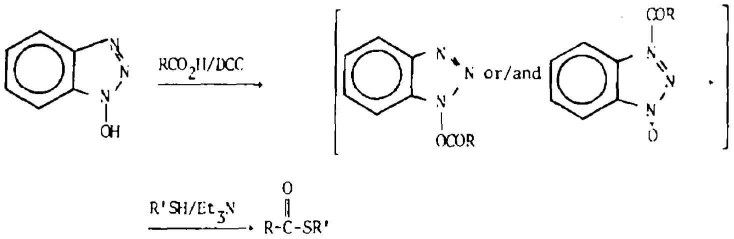
predominate.[214,215] The contribution of this direction can be limited by using carbodiimides with suitably chosen substituents, e.g. $PhCH_2N{=}C{=}NEt$.[215] The use of carbodiimides in the synthesis of peptides has found exhaustive treatment in the 15th volume of the Houben-Weyl "*Methoden der organischen Chemie*",[217] and in a review of Rich and Singh.[218] Recently DCC has also been used in the synthesis of phosphonic dipeptide analogues.[219]

DCC, glucopyranoside (R = H) and piperydynoxyl $R^1CO_2H$ give the corresponding spin labelled sugars (R = $R'\underset{\underset{O}{\|}}{C}$).[220]





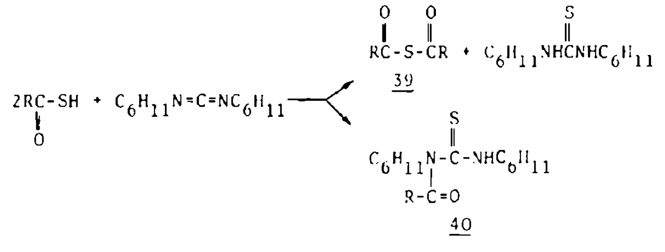
The direct reaction of mercaptans with carboxylic acids in the presence of DCC gives thiolesters in moderate yields.[221,222] Addition of a catalytic amount of 4-dialkylaminopyridine increases considerably the yield of thiolesters[200] (*cf* esterification). Another improvement has been described by Horiki who esterified in the first step carboxylic acids with 1-hydroxybenzotriazole in the presence of DCC and subsequently reacted the resulting compound with mercaptans. This procedure makes it possible to synthesize thiolesters in yields exceeding 90%.[223]



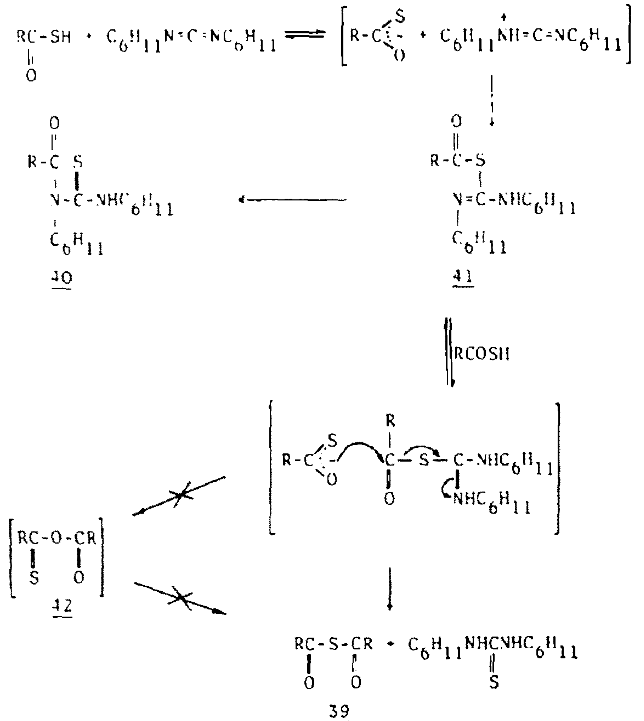
The reaction of carboxylic acids with diazoalkanes gave in the presence of DCC diazoketones in yields not exceeding 50% because of the competitive ester formation process.[224,225]

## 7. *Reactions of carbodiimides with thio analogues of carboxylic acids*

7.1 *Reaction with monothiocarboxylic acids.*[226,227] Monothiocarboxylic acids react with DCC in two ways yielding symmetrical diacyl sulphides (**39**) and N,N'-dicyclohexylthiourea and/or N-acyl-N,N'-dicyclohexylthioureas (**40**).

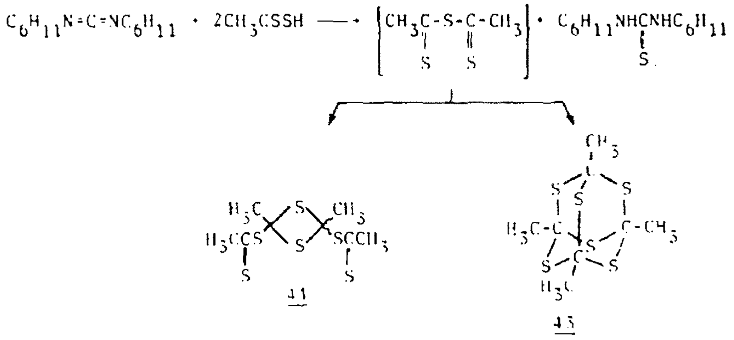


The latter compounds are the main product of the reaction between DCC and thioacids containing n their molecules strong electron-acceptor groups (for example $p$-$NO_2C_6H_4$-, $ClCH_2$-). It is assumed hat the mechanism of this reaction is similar to that of DCC with carboxylic acids. In the first step the mbident monothio acid anion attacks the protonated carbodiimide molecule with S yielding S-cylisothiourea (**41**). The resulting adduct can react further in two ways. Intramolecular migration of ne acyl group from S to N leads to the formation of N-acylthiourea (**40**). On the other hand, S-acylisothiourea (**41**) can react, after preliminary protonation, with the next thioacid anion to give diacyl sulphide (**39**) and dicyclohexylthiourea:



From the two possible paths of this step one has been excluded, i.e. the one proceeding via asymmetric monothioanhydride (**42**). Therefore, symmetric diacyl sulphides are directly formed in this reaction.

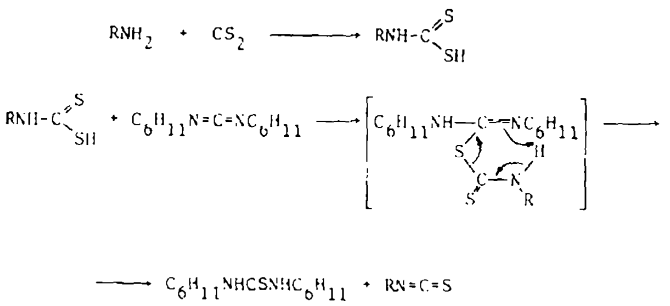
7.2 *Reaction with dithiocarboxylic acids.* It was found that the reaction of dithioacetic acid with DCC gives in the first step dithioacetyl sulphide which owing to its instability undergoes dimerisation yielding a mixture of 1,3,5,7-tetramethyl-3,4,6,8,9,10-hexathiaadamantane (**43**) and *cis*- and *trans*-2,4-dimethyl-2,4-bis-thioacetylthio-1,3-dithietane (**44**).[226,228]



In the reaction of DCC with dithiopropionic acid only the mixture of *cis*- and *trans*- dithietanes is formed.[229]

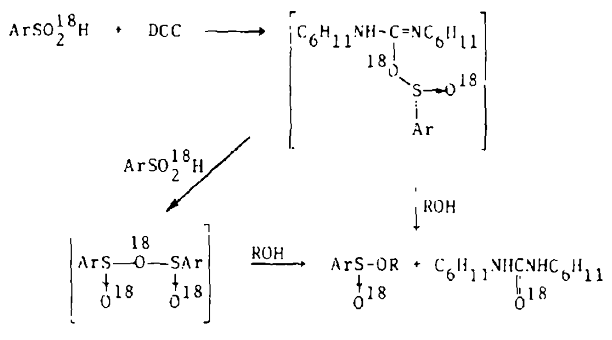
In the case of the reaction of DCC with substituted dithiobenzoic acids as well as dithioisobutyric acid dithioacyl sulphides formed proved to be sufficiently stable to allow their isolation.[230,231]

7.3 *Reaction with dithiocarbamic acids.* When dithiocarbamic acids are reacted with DCC, instead of the formation of the respective anhydrides, an intramolecular elimination of hydrogen sulphide takes place leading to the formation of isothiocyanates. This behaviour was utilized by Jochims and Seeliger[232,233] to develop a simple method of synthesizing isothiocyanates from amines and carbon disulphide in the presence of DCC. Dithiocarbamic acid formed in the first step reacts with DCC via the intermediary S-acylisothiourea and yields thiourea and the respective isothiocyanate:



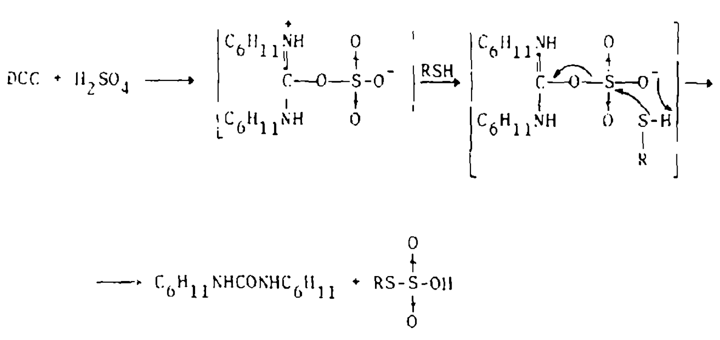
### 8. *Reactions of carbodiimides with sulphinic and sulphonic acids*

Sulphinic and sulphonic acids react readily with carbodiimides yielding the respective anhydrides.[234-236] The synthesis of esters proceeds analogously as in the case of carboxylic acids. Japanese authors obtained, upon treating sulphinic acids with alcohols in the presence of DCC, the corresponding sulphinates.[237] Using $^{18}O$ labelled sulphinic acid they showed that the esters can be formed on two paths:



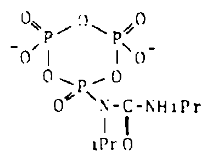
Sulphinamides are obtained in the similar reaction of sulphinic acids with amines in the presence of DCC which acts here as dehydrating agent.[238]

In the reaction of sulphuric acid with alcohols, mercaptans and amines in the presence of DCC the respective sulphates, thiosulphates and sulphuric acid amides are obtained, e.g.:[239-242]



### . *Reactions of carbodiimides with phosphorus acids*

9.1 *Reaction with* $H_3PO_4$. The carbodiimide induced condensation of $H_3PO_4$ in the presence of trong tertiary amines leads, as evidenced by the $^{31}P$ NMR spectra, to condensation only slightly eyond the metaphosphate components. However, in the absence of amine the condensation roceeds into the ultraphosphate region about halfway between the metaphosphate and phosphoric nhydride components. When amine is used, the principal product consists of the cyclic trimetaphosphate anion, with one of the nonbridging O-atoms substituted by the urea resulting from hydration of the carbodiimide, e.g. **45** for the condensation with diisopropylcarbodimide:



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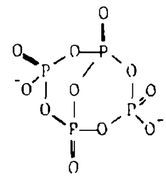

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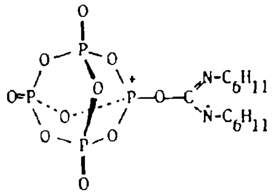
The major product of the reaction obtained without amine is the 1,5-μ-oxotetrametaphosphate anion (**46**).[243,244] Carbodiimide mediated phosphorylations carried out with ortho-, pyro-, trimeta-, tetrameta- and long-chain polyphosphoric acids dissolved in various alcohols consist of complicated reaction sequences involving various phosphoric acids, then esters and complexes formed by carbodiimide and these acids or esters. In the case of condensation of orthophosphoric acid, the process of stepwise esterification competes with the process of condensation to form condensed phosphoric acids and their esters. In general, esterification as opposed to condensation is promoted by increased acidity, smaller size and increased concentration of alcohol as well as by increased concentration of dissociable protons in the solution.[245]

By $^{31}P$ NMR the existence in the solution of phosphoric anhydride $P_4O_{10}$ of bird-cage structure has been proved for the first time. It was obtained in the form of adduct with DCC (**48**):[246]



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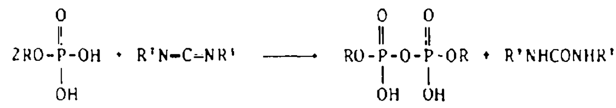
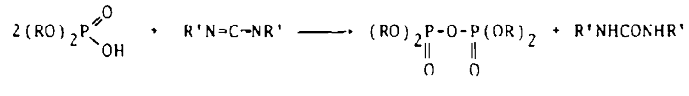
9.2 *Reactions with organic phosphorus acids.* In 1953 Khorana and Todd observed that mono- and di-substituted phosphoric acids react with DCC to give pyrophosphates:[2,247]

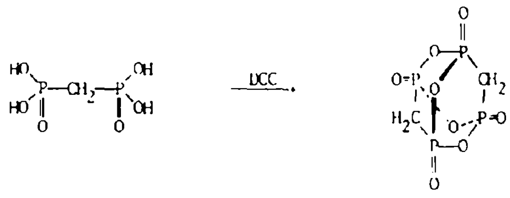


$$2RO-\underset{OH}{\overset{O}{\overset{\|}{P}}}-OH + R'N=C=NR' \longrightarrow RO-\underset{OH}{\overset{O}{\overset{\|}{P}}}-O-\underset{OH}{\overset{O}{\overset{\|}{P}}}-OR + R'NHCONHR'$$



$$2(RO)_2P(=O)OH + R'N=C=NR' \longrightarrow (RO)_2\underset{O}{\underset{\|}{P}}-O-\underset{O}{\underset{\|}{P}}(OR)_2 + R'NHCONHR'$$

The formation of pyrophosphate systems was also observed in the case of phosphinic acids.[236,248] Methylenediphosphonic acid yields the anhydride (**49**) having a bird-cage structure when treated with DCC.[249]



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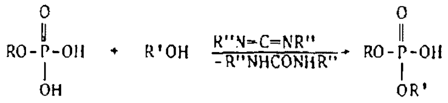
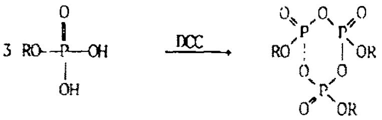
Monoesters of phosphoric acid react in the presence of carbodiimides with alcohols and phenols giving the corresponding phosphoric acid diesters quantitatively.[250-255]



$$RO{-}\overset{\overset{O}{\|}}{\underset{\underset{OH}{|}}{P}}{-}OH + R'OH \xrightarrow[-R''NHCONHR'']{R''N{=}C{=}NR''} RO{-}\overset{\overset{O}{\|}}{\underset{\underset{OR'}{|}}{P}}{-}OH$$

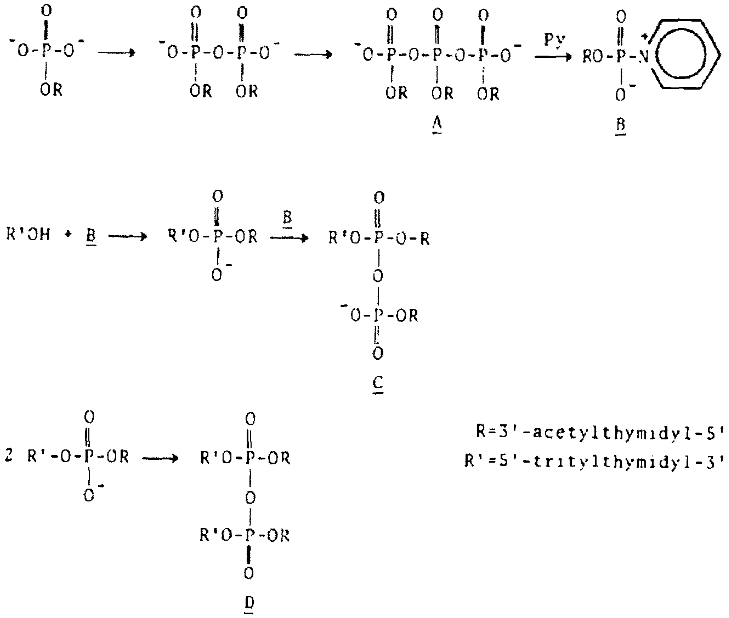
This reaction has found wide application in nucleic acid chemistry.[7,256] Carbodiimides have been used as condensing agents in the synthesis of nucleoside phosphates, cyclic phosphates and polynucleotides.

According to Weimann and Khorana,[257] in the reaction of phosphoric acid monoesters with alcohols in the presence of DCC first the cyclic metaphosphate trimer (**50**) is formed, which then serves as an active phosphorylating agent:



50

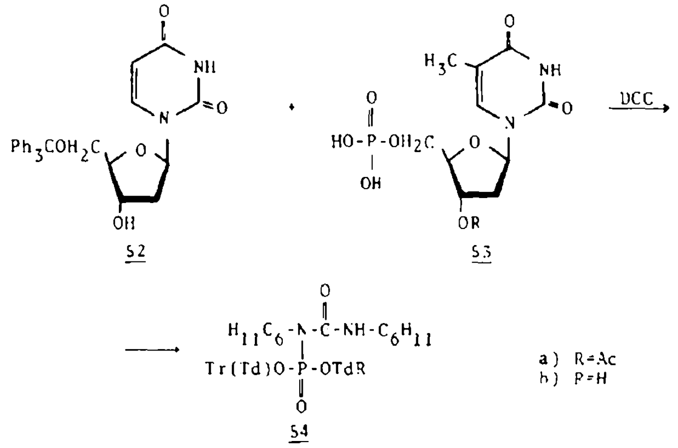
Recently, Knorre *et al.* have established the structure of three main types of intermediates (**B**, **C** and **D**) being active phosphorylating agents both in the case of using DCC or triisopropylbenzenesulphonyl chloride (TPS) as condensing reagents. **B**-type derivatives, formed only in pyridine solutions, are designed as complexes of metaphosphates with pyridine.[258,259] C-type derivatives formed both in pyridine and DMF solutions possess phosphomonoester and phosphodiester residues, combined to trisubstituted pyrophosphate.[258,260] **D**-type derivatives contain two phosphodiester groups combined to tetrasubstituted pyrophosphate. The pathways established with the most simple representatives of mononucleotides and dinucleoside phosphates may be represented by the following scheme:



R=3'-acetylthymidyl-5'
R'=5'-tritylthymidyl-3'

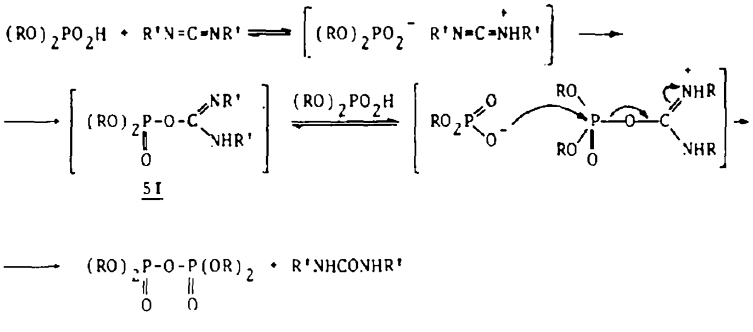
Among the recent works concerning the application of DCC in nucleic acids chemistry a series of publications of Russian authors should be mentioned.[261-264] An interesting result has been obtained by Zarytova *et al.*[261] who have found that N-(P-5'-O-tritylthymidyl-P-3'-O-acetylthymidylphosphoryl)-N,N'-dicyclohexylurea (**54**) is formed as one of the reaction products on treatment nucleotide

(**52**) with nucleoside (**53**) in the presence of DCC. It is of interest to point out that the product (**54**) has the structure of N-phosphorylurea and this is the first synthesis of equimolar adducts of carbodiimides and disubstituted phosphoric acids reported in the literature.



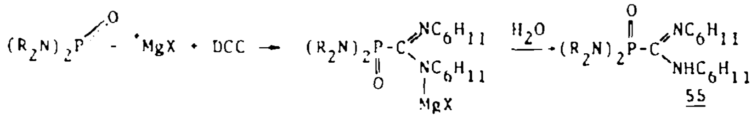
The compound described is stable under nucleotide synthesis conditions. It does not react with amines or electrophilic reagents, but undergoes rapid, quantitative hydrolysis in aqueous pyridine. Zarytova *et al.*, took advantage of the possibility of easy removing the dicyclohexylurea moiety and applied (**54b**) as the protected nucleoside component in the synthesis of oligonucleotides.[264] The same reaction course was observed for other carbodiimides, e.g. N-cyclohexyl-N′-β-ethylmorpholyl-carbodiimide.[263]

In the case of disubstituted phosphoric acids and phosphinic acids the mechanism of their reaction with carbodiimides proposed by Khorana and Todd is analogous as for carboxylic acids:[2,247]

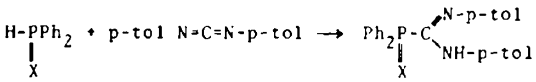


O-Phosphorylated isourea (**51**) formed in the first reaction step reacts with another acid molecule which leads to the respective pyrophosphate and urea.

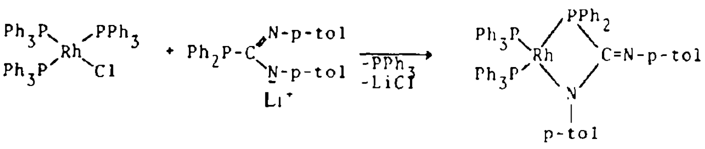
When halogenomagnesium salts of tetraalkylamidophosphorous acid are reacted with DCC, equimolecular adducts with C-phosphorylated formamidine structure (**55**) are obtained.[265]



The reactions of secondary phosphines, phosphinites and thiophosphinites with di-*p*-tolylcarbodiimide also yield C-phosphorylformamidines. The latter have found application as transition metal complexing agents (see for example the synthesis of **55-A**):$^{266}$

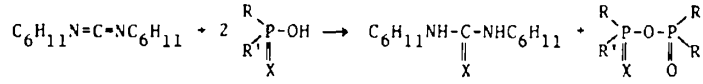


X=electron lone pair, S,O



55-A

9.3 *Reactions with organic phosphorus thio- and seleno-acids.* The course of the reaction of carbodiimides with phosphorus thio- and seleno-acids is dependent on both reactants. Phosphonothioic and phosphinothioic acids,$^{267}$ as well as phosphonoselenoic$^{268,269}$ and phosphinoselenoic$^{268}$ acids react with DCC analogously as phosphorus oxy-acids giving rise in a rapid exothermic reaction to N,N'-dicyclohexylthiourea (or selenourea) and the corresponding unsymmetrical monothiopyrophosphate (selenopyrophosphate) systems:

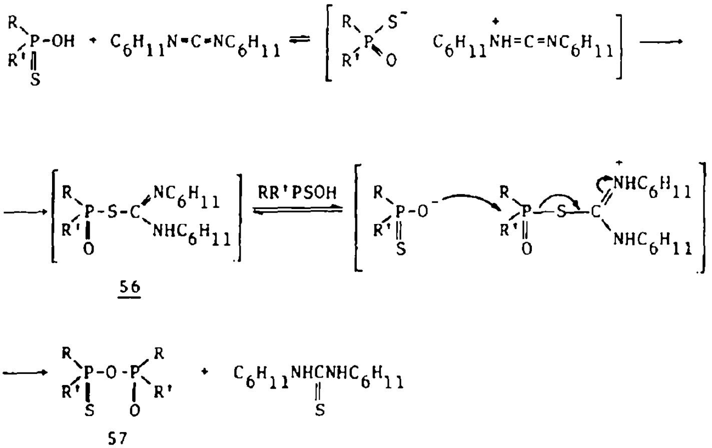


57

(a) R=Et, R'=OEt, X=S (c) R=Et, R'=OEt, X=Se

(b) R=R'=Et, X=S (d) R=R'=Et, X=Se

The proposed mechanism of this reaction is shown below:



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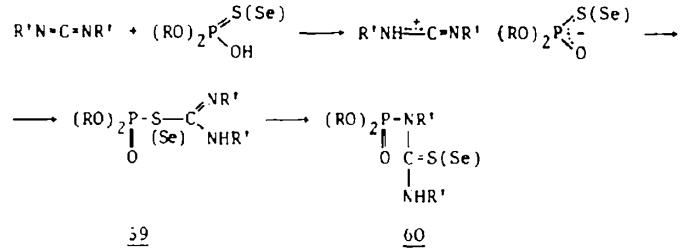
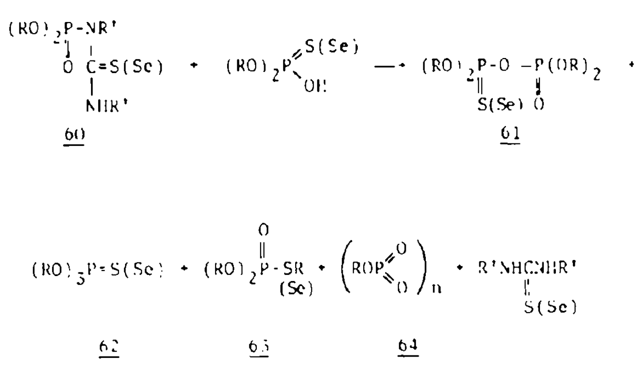
57

In the first step the thioacid anion adds to the protonated carbodiimide molecule by means of its nucleophilic centre at the sulphur atom. As a result S-phosphorylisothiourea (**56**) is formed as intermediary product. In the next step a second thioacid anion attacks the P atom in the adduct by means of its O atom which leads directly to the formation of an unsymmetrical monothiopyrophosphate system and thiourea. Stereochemical studies with the use of optically active O-ethyl ethylphosphonothioic acid speak in favour of this mechanism.[267] The formation of the optically active thiopyrophosphonate (**57a**) with opposite configurations at the thiophosphoryl and phosphoryl centres provided a proof that the second step proceeds with inversion of the configuration at the P atom in the adduct (**56**).

In the reaction of carbodiimides with phosphorothioic, phosphorodithioic and phosphoroselenoic acids stable equimolar adducts of N-phosphorylthio(seleno)urea structure (**60**) are initially produced[c].[270,271] It has been proved by low-temperature $^{31}$P-NMR investigations that these adducts are formed as a result of migration of the phosphoryl group from the S (Se) atom to N in very unstable S(Se)-phosphorylisothio(seleno)ureas (**59**). The latter are produced in the first step of the reaction as a result of addition of the acid anion to the protonated carbodiimide:



N-Phosphorylthio(seleno)ureas are the final reaction products in the case of R′ = benzyl, *p*-nitrophenyl or *p*-chlorophenyl. However, when R = cyclohexyl or isopropyl, the adducts react slowly with the next acid molecule yielding thio(seleno)-pyrophosphates (**61**), phosphorothion(selenon)ates (**62**) phosphorothiol(selenol)ates (**63**) and metaphosphate polymers (**64**)



By means of cross-over experiments and using $^{35}$S labelled sulphur it was demonstrated that in this case the rearrangement of S(Se)-phosphorylisothio(seleno)ureas (**59**) to N-phosphorylthio(seleno)ureas (**60**) is a reversible reaction. Thus, N-phosphorylthio(seleno)ureas (**60**) are in equilibrium with S(Se)-phosphorylisothio(seleno)ureas (**59**), the latter being active phosphorylating agents responsible for the formation of all the reaction products. In summary the mechanism of the reaction under discussion consists of the following principal steps:[268]

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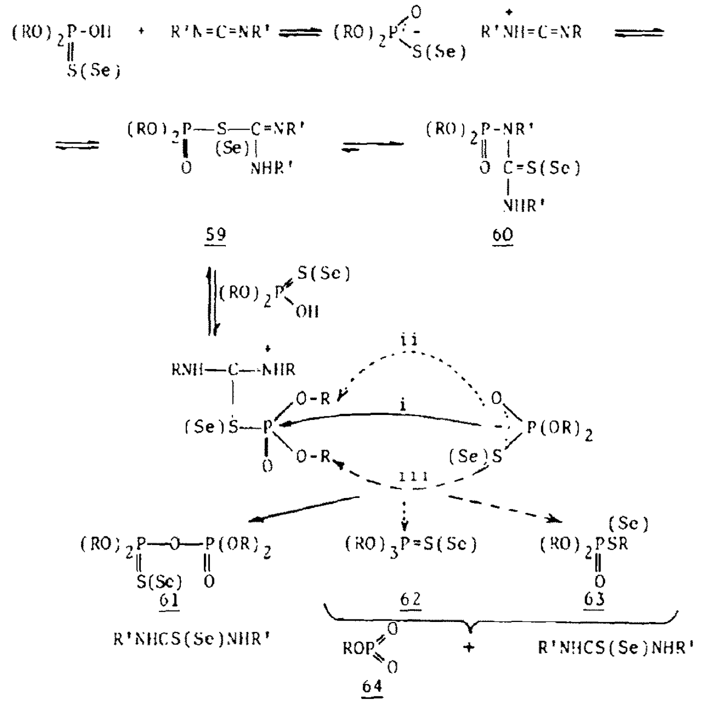
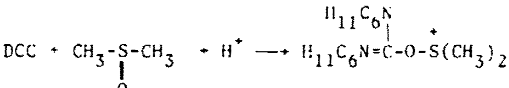
[c] Equimolar adducts of carbodiimides with phosphorothioic and -dithioic acids were already known in the patent literature but their structure was not determined unequivocally.[272]

In the first step the acid and carbodiimide form a salt; then, the acid anion attacks the protonated carbodiimide molecule producing an adduct (**59**) which is in equilibrium with the stable, isolable adduct (**60**); in the next reaction step another acid anion may react with the protonated adduct (**59**) in two ways: it either attacks the phosphorus atom (i) which leads to the formation of thio(seleno)pyrophosphate (**61**) and thio(seleno)urea, or attacks the C atom in the alkoxy group. The attack by means of the O atom (ii) leads to the formation of phosphorothion(selenon)ate (**62**) and by means of the S(Se) atom (iii) results in phosphorothiol(selenol)ate (**63**). Both directions (ii) and (iii) produce also thio(seleno)urea and very reactive metaphosphate (**64**), which under the reaction conditions undergoes polymerisation.



10. *Reactions of nucleophiles with dimethyl sulphoxide (DMSO) in the presence of DCC*

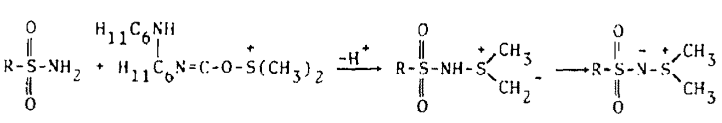
The reaction of DCC with DMSO in the presence of acids affords the oxysulphonium intermediate (**65**):



$$\mathrm{DCC} + CH_3-\underset{\substack{|\\ O}}{S}-CH_3 + H^+ \longrightarrow H_{11}C_6N=\overset{\substack{H_{11}C_6N\\ |}}{C}-O-\overset{+}{S}(CH_3)_2$$

65

This intermediate can be attacked by various nucleophiles. For instance, the reaction of **65** with sulphonamides gives S,S-dimethyl-N-sulphonylsulphilimines (**66**) in high yields:[273]

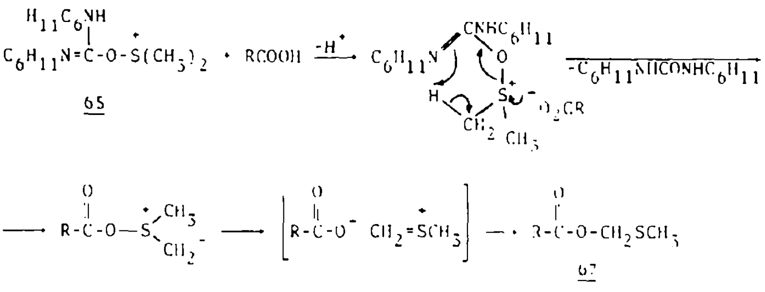


$$R-\underset{\substack{\|\\ O}}{\overset{\substack{O\\ \|}}{S}}-NH_2 + H_{11}C_6N=\overset{\substack{H_{11}C_6NH\\ |}}{C}-O-\overset{+}{S}(CH_3)_2 \xrightarrow{-H^+} R-\underset{\substack{\|\\ O}}{\overset{\substack{O\\ \|}}{S}}-NH-\overset{+}{S}\begin{matrix}CH_3\\ CH_2^-\end{matrix} \longrightarrow R-\underset{\substack{\|\\ O}}{\overset{\substack{O\\ \|}}{S}}-\overset{-}{N}-\overset{+}{S}\begin{matrix}CH_3\\ CH_3\end{matrix}$$

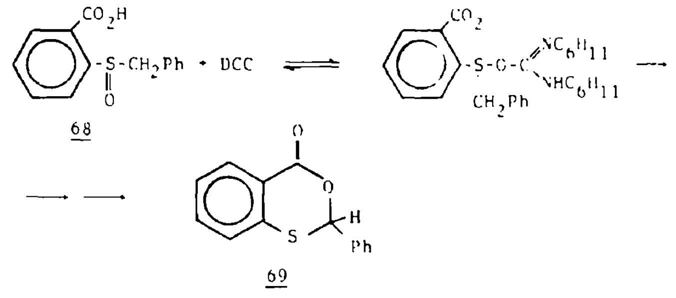
65 66

Under similar conditions amines and carboxylic acids amides give S,S-dimethylsulphilimes and N-acyl-S,S-dimethylsulphilimines, respectively.[274]

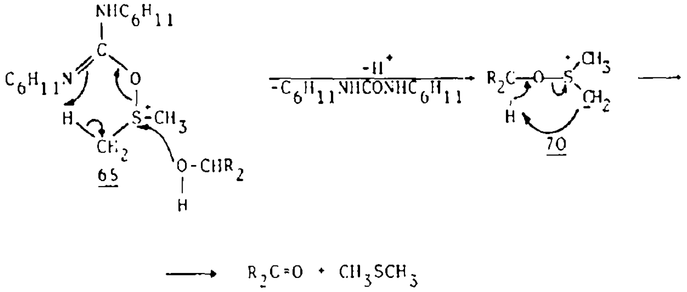
When carboxylic acids are treated with DMSO in the presence of DCC methylthiomethyl esters (**67**) are obtained:[275]



Starting from the optically active sulphoxide (**68**) the DCC reaction gave optically active **69** (5–29% optical purity):[276]

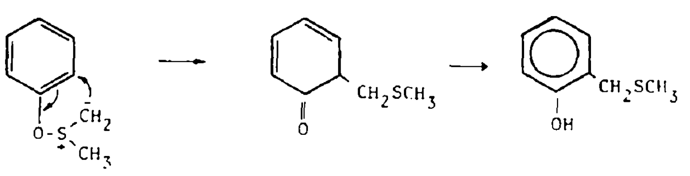


Particularly well known is the reaction of oxidation of alcohols by means of DMSO in the presence of DCC leading to the formation of the corresponding carbonyl compounds.[277,278] Instead of DCC other carbodiimides were also used.[279] The oxidation proceeds here under very mild conditions and can be applied to very sensitive and unstable compounds.[280–282] Of great importance is the selectivity of the method towards primary alcohols, which are oxidised solely to aldehydes without traces of acids being formed. The reaction mechanism is as follows:[283,284]



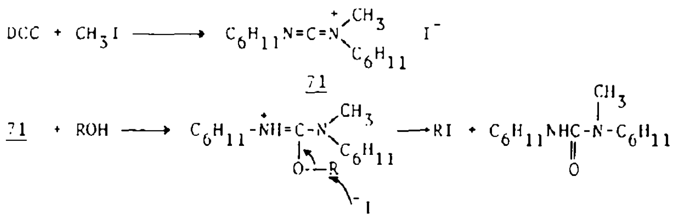
The nucleophilic attack of the alcohol molecule at sulphur of the oxysulphonium intermediate (**65**) leads to the formation of the sulphonium ylide (**70**) which decomposes yielding the carbonyl compound and dimethyl sulphide.

In the reaction of phenols with DMSO and DCC *o*- and *p*-methylthiomethyl derivatives are formed according to the scheme:[285–288]

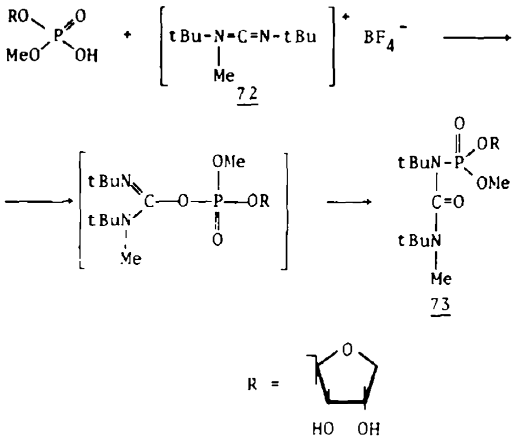


### 11. N-*Alkylated carbodiimides derivatives*

Heating DCC with methyl iodide yields N-methyl-N,N'-dicyclohexylcarbodiimide iodide (**71**).[289] This compound has been used for obtaining alkyl iodides from alcohols. It deserves mentioning that even highly sterically hindered alkyl iodides can be prepared by this method:

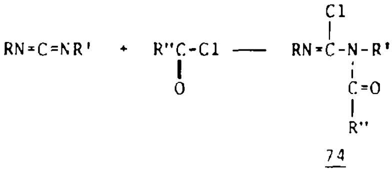


Schnur and van Tamelen[290] have described the use of N-methyl-N,N'-di-t-butylcarbodiimide tetrafluoroborate (**72**) as condensing agent in the synthesis of ethers and esters. They obtained, for instance N-phosphorylurea (**73**) by condensing dialkylphosphoric acid with **72**:

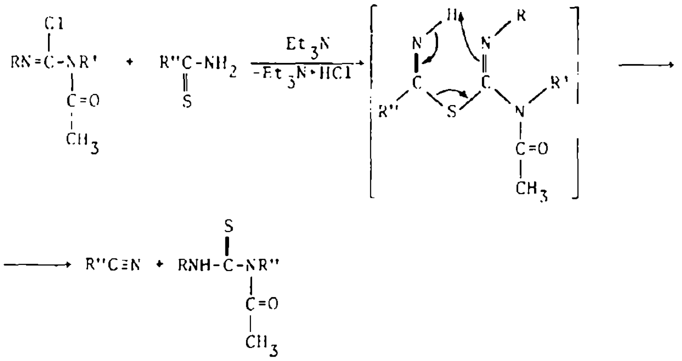


### 12. *Adducts of carbodiimides and acyl chlorides*

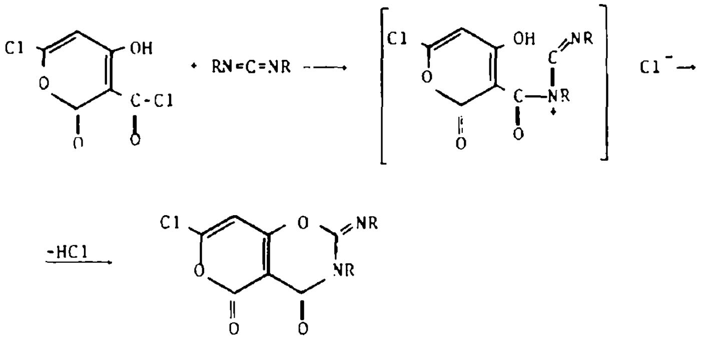
Acyl chlorides and carbodiimides yield the corresponding chloroformamidines[291,292]



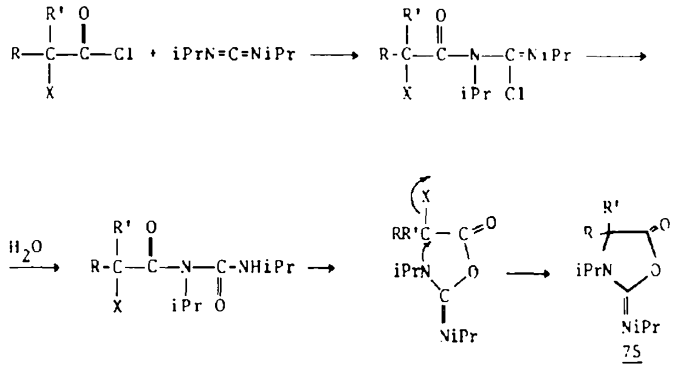
Hartke[293] applied these compounds for elimination of hydrogen sulphide from primary thioamides converting them into the corresponding nitriles in high yields:



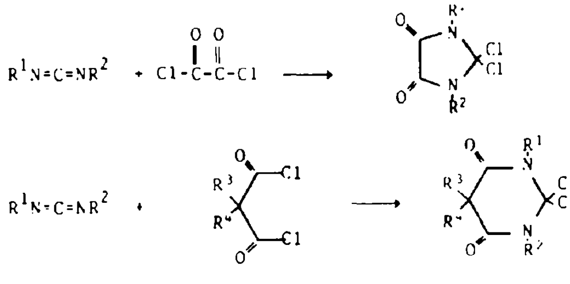
β-Hydroxycarboxylic acids chlorides yield in the reaction with carbodiimides corresponding substituted oxazines[294]



The reaction of α-halo acids chlorides with diisopropylcarbodiimide yields the corresponding acylchloroformamidines. Their hydrolysis gives N-acylureas which, upon heating, undergo ring closure (*via* O-acylisoureas) to the 5-oxazolidines (**75**):[295]



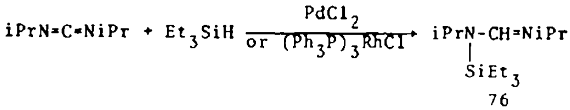
Dicarboxylic acids chlorides and carbodiimides give the corresponding cyclic products which can serve as substrates for the synthesis of a range of heterocyclic compounds:[296,297]



N-Acylcarbodiimides, $R-\underset{\underset{O}{\|}}{C}-N{=}C{=}NR'$, show different chemical properties in comparison with simple aliphatic or aromatic carbodiimides. For instance, when the carboxylic and amine groups are simultaneously present in the molecule subjected to reaction with N-acylcarbodiimide, the amine reacts first which makes it impossible to use these carbodiimides in the synthesis of the peptide bond. With carboxylic acids acylcarbodiimides give imides and isocyanates.[19]

## 13. *Reactions of carbodiimides with organosilicon compounds*

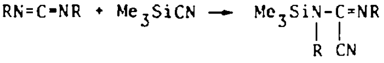
Hydrosilanes react with carbodiimides giving N-silylformamidines (**76**):[298-300]



$$\text{iPrN=C=NiPr} + \text{Et}_3\text{SiH} \xrightarrow[\text{or } (\text{Ph}_3\text{P})_3\text{RhCl}]{\text{PdCl}_2} \text{iPr}\underset{\substack{|\\ \text{SiEt}_3}}{\text{N}}\text{-CH=NiPr}$$

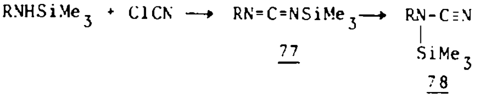
76

Trimethylcyanosilane undergoes addition to carbodiimides in a similar manner:[301,302]



$$\text{RN=C=NR} + \text{Me}_3\text{SiCN} \longrightarrow \text{Me}_3\text{Si}\underset{\substack{|\\ \text{R}}}{\text{N}}\text{-}\underset{\substack{|\\ \text{CN}}}{\text{C}}\text{=NR}$$

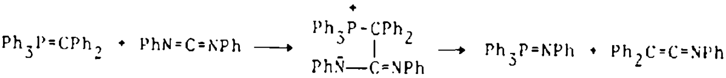
N-Trimethylsilylcarbodiimides (**77**) obtained in the reaction of N-trimethylsilylamine with chlorocyan are unstable and after migration of the trimethylsilyl group give N-trimethylsilylcyanamides (**78**):[303]



$$\text{RNHSiMe}_3 + \text{ClCN} \longrightarrow \underset{77}{\text{RN=C=NSiMe}_3} \longrightarrow \text{R}\underset{\substack{|\\ \text{SiMe}_3 \\ 78}}{\text{N}}\text{-C}\equiv\text{N}$$

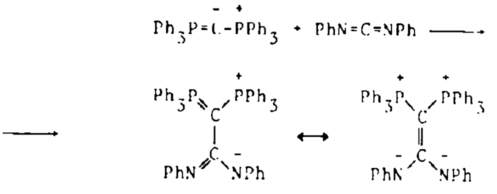
## 14. *Reaction of carbodiimides with ylides*

The reaction of phosphoric ylides with diphenylcarbodiimide gives betaines which are, however, unstable and products of their decomposition are usually isolated:[304]



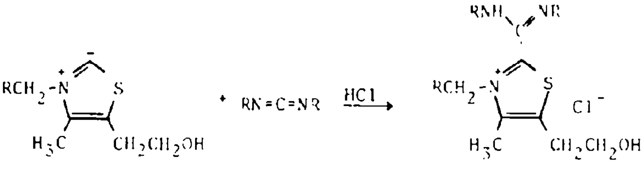
$$\text{Ph}_3\text{P=CPh}_2 + \text{PhN=C=NPh} \longrightarrow \begin{array}{c}\overset{+}{\text{Ph}_3\text{P}}\text{-CPh}_2\\ |\quad\ \ |\\ \text{Ph}\overset{-}{\text{N}}\text{—C=NPh}\end{array} \longrightarrow \text{Ph}_3\text{P=NPh} + \text{Ph}_2\text{C=C=NPh}$$

Ramirez *et al.* obtained in the reaction of hexaphenylcarbodiphosphorane with diphenylcarbodiimide adducts with ethylene-1,1-bis(triphenylphosphonium)-2,2-bis(phenylamide) structure (**79**):[305]

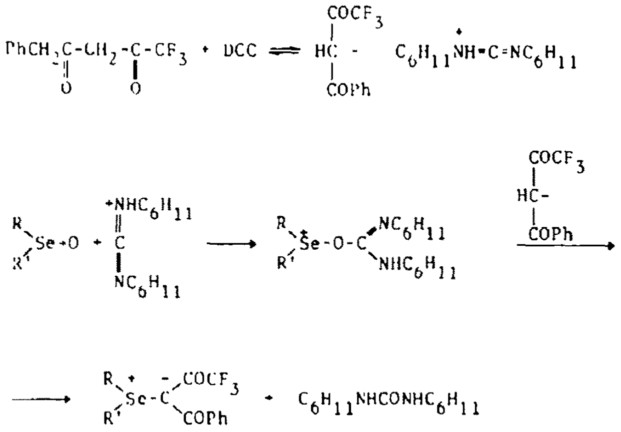


79

Thiazole ylides add to carbodiimides in a similar manner:[306]



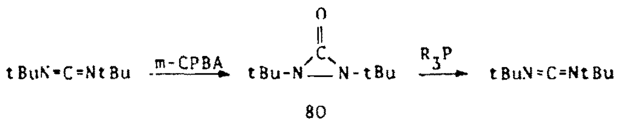
Carbodiimides have also been used in the synthesis of ylides. For example, selenonium ylides were obtained when selenoxides were reacted with benzoylfluoroacetone in the presence of DCC[307,308]



## 15. *Oxidation of carbodiimides*

Ozonisation of carbodiimides gives mainly ketones, isocyanates, cyanamides and oxygen, together with minor amounts of nitro compounds, $CO_2$ and ureas.[309]

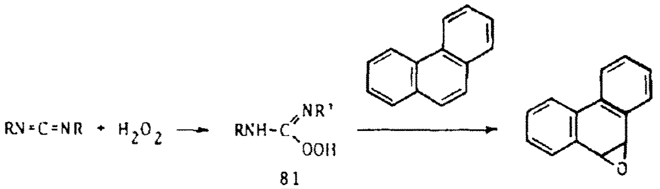
Oxidation of di-t-butylcarbodiimide with m-chloroperbenzoic acid (*m*-CPBA) leads to di-t-butylaziridinone (**80**) which under the action of trivalent P compounds can be transformed back to the initial carbodiimide:[310]



80

Attempts to obtain carbodiimide N-oxides by oxidation of carbodiimides or N-hydroxythioureas with peracids have been unsuccessful.[311]

Reaction of aliphatic carbodiimides with 98% $H_2O_2$ gives peroxycarboximidic acids (**81**) which easily oxidise certain arenes to arene oxides:[312]

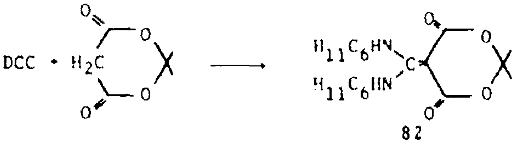


81

The action of diverse dehydrating agents, among them N-benzoyl-N′-t-butylcarbodiimide, on anhydrous hydrogen peroxide generates intermediates which are effective epoxidising agents for olefins. In the absence of olefins the dehydrating agents react with $H_2O_2$ to produce singlet molecular oxygen (in the case of the carbodiimide mentioned above in a yield of *ca* 10%).[313]

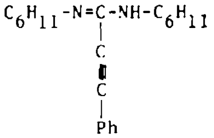
## 16. *Reactions of carbodiimides with* CH-*acids*

DCC reacts with compounds containing strongly acidic protons giving adducts (**82**):[314]



82

The reaction of phenylacetylene with DCC in the presence of sodium leads likewise to the corresponding adduct (**83**):[315]



$$C_6H_{11}{-}N{=}\underset{\substack{| \\ C \\ \| \\ C \\ | \\ Ph}}{C}{-}NH{-}C_6H_{11}$$

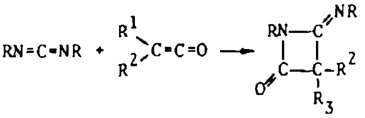
**83**

A variety of active methylene compounds were carboxylated using the DCC-tetraalkylammonium hydroxide-$CO_2$ reagent system in DMSO at room temperature.[316]

## 17. *Cycloadditions of carbodiimides*

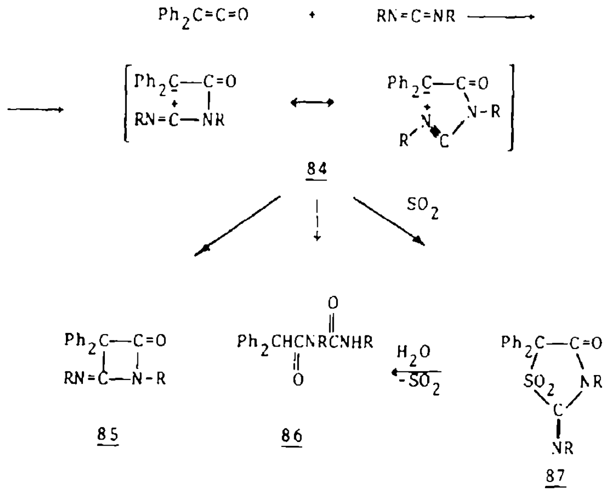
Carbodiimides undergo cycloaddition with a number of compounds having double bonds. The mechanism of cycloaddition varies with the type of compound involved. In some cases the cycloaddition reaction proceeds via non-cyclic dipolar intermediate, in other cases there are evidence supporting the concerted reaction mechanism.

17.1 *Cycloaddition of carbodiimides to ketenes.* Cycloaddition of carbodiimides to ketenes proceeds exclusively at the ketene olefinic bond and leads to the formation of the corresponding 4-imino-2-azetidinones (*β*-lactams) in high yields:[317-324]



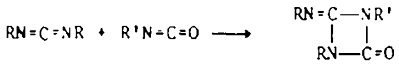
Aliphatic carbodiimides show higher reactivity in comparison with the aromatic analogues. In mixed aliphatic-aromatic carbodiimides the aliphatic substituted C=N bond reacts preferentially.[317]

It has been proved that cycloaddition of ketenes to carbodiimides is not a concerted process, but it proceeds in two steps via the 1,4-dipolar intermediate (**84**). The latter intermediate was detected in two ways. The reaction was interrupted by adding water, when alongside the iminoazetidinone (**85**) product also N-acylurea (**86**) was obtained. On the other hand, cycloaddition carried out in liquid $SO_2$ yielded the adduct (**87**):[323-325]



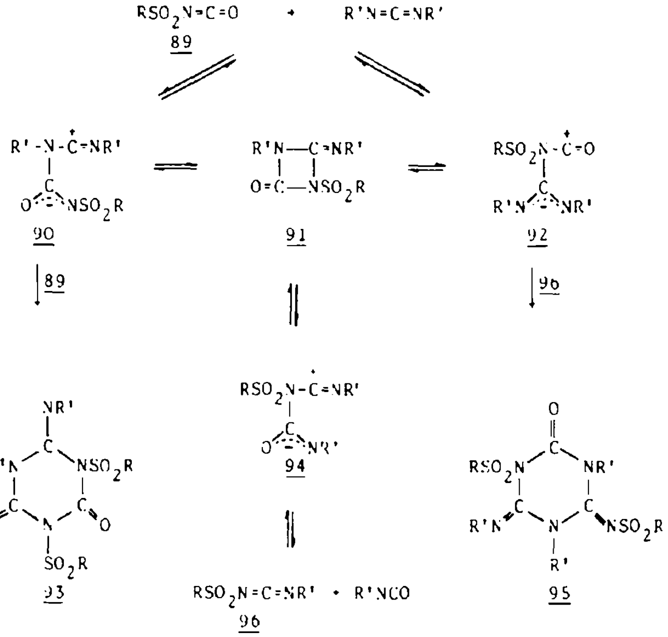
The [2 + 2]-cycloaddition reaction of carbodiimides with ketenes is one of few reactions of carbodiimides in which a new chiral centre can be created. Bełżecki and Krawczyk have found that applying carbodiimides with chiral substituents at N atoms and prochiral ketenes in such a cycloaddition results in the formation of $\beta$-lactams in a highly diastereoselective manner.[326,327]

17.2 *Cycloaddition of carbodiimides to isocyanates.* Cycloaddition of carbodiimides to alkyl or aryl isocyanates proceeds exclusively at the C=N bond and affords the corresponding iminodiazetidinones (**88**):[328,329,331]



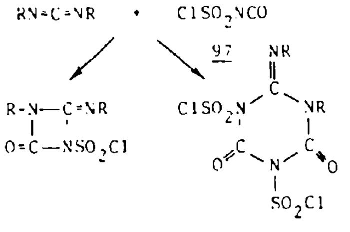
88

The polar cycloaddition reaction of arenesulphonyl isocyanates with carbodiimides gives rise to the formation of 6-membered ring cycloadducts:[330]



The mechanism of their formation is as follows. In the first step acyclic equimolar adducts are formed (**90** and **92**) which can mutually transform into each other *via* the cyclic adduct **91** (all the adducts were observed by NMR). Interception of the adduct **90** by isocyanate (**89**) yields **93**. Opening of cyclic adduct may also lead to the third acyclic adduct **94** which exists in equilibrium with sulphonylcarbodiimide (**96**) and R′N=C=O. Interception of the acyclic adduct **92** by **96** gives **95**.

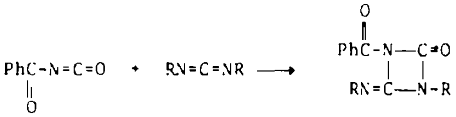
The reaction of carbodiimides with chlorosulphonyl isocyanate also gives two products whose proportions depend on the kind of carbodiimide used and the way the reagents were mixed:[332]



R=cyclohexyl (when **97** was added to DCC)

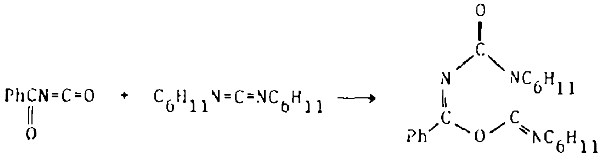
R=Ph
R=cyclohexyl (when DCC was added to **97**)

Three papers have been published so far on the cycloaddition of carbodiimides to benzoylisocyanate, whose authors have assigned three different structures to the reaction products. According to Neidlein the adducts formed have the structure of diazetidinones (**98**). Therefore, isocyanate should undergo cycloaddition across the N=C bond:[333]

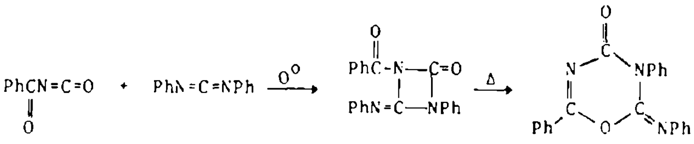


98

Tsuge and Sakai claim, in turn, that cycloaddition of benzoylisocyanate and DCC proceeds according to the [2 + 4] scheme involving the benzoyl C=O group and the N=C bond in isocyanate, which leads to 6-membered adduct of oxadiazine structure **99**. However, cycloaddition and diphenylcarbodiimide proceeds as a [2 + 2]-cycloaddition and the adduct of **98** type produced in the first step undergoes thermal isomerization to give oxidiazine (**100**):[334]

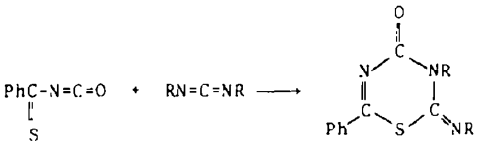


99

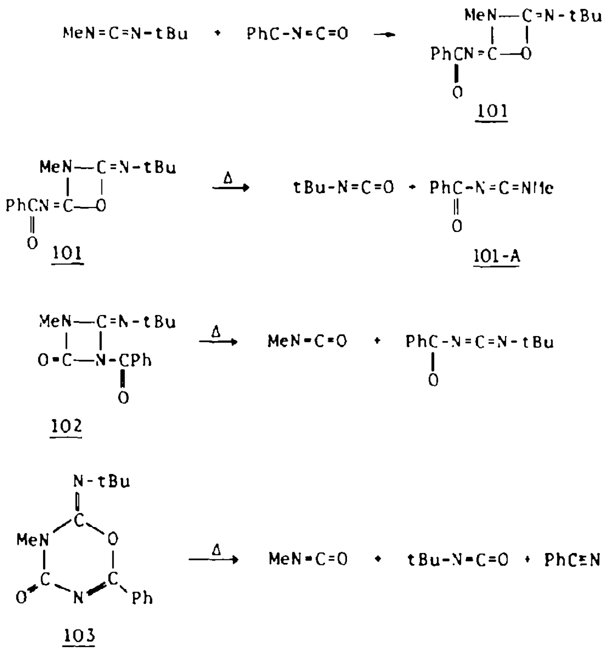


98 100

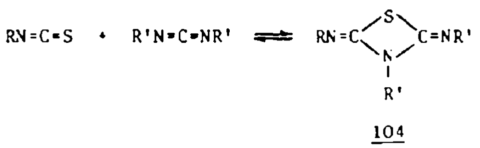
Thiobenzoylisocyanate undergoes cycloaddition of [2 + 4]-type irrespective of the carbodiimide used:[334]



In contrast to the authors quoted above, Ulrich *et al.* determined the structure of the product of ddition of benzoylisocyanate and t-butylmethylcarbodiimide and claim that it is a substituted xazetidine (**101**) produced as result of cycloaddition across the C=O bond in isocyanate. These uthors drew such a conclusion based on the formation of tBuN=C=O and **101-A** upon the pyrolysis f the adduct.[329] If the adduct were of a structure **102** (analogous to that proposed by Neidlein (**98**), he pyrolysis products would have to be MeN=C=O and PhC(O)N=C=N-tBu, whereas in the case of the structure **103** (analogous to that determined by Tsuge and Sakai (**99** and **100**), MeN=C=O, tBuN=C=O and PhCN, respectively:

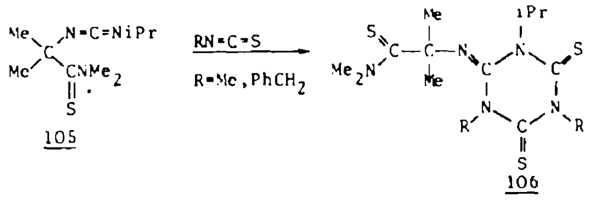


17.3 *Reaction of carbodiimides with isothiocyanates.* Cycloaddition of carbodiimides to isothiocyanates always leads to equimolar adducts of the 1,3-tiazetidine (**104**) structure in whose formation the C=S bond takes part:[335-338]



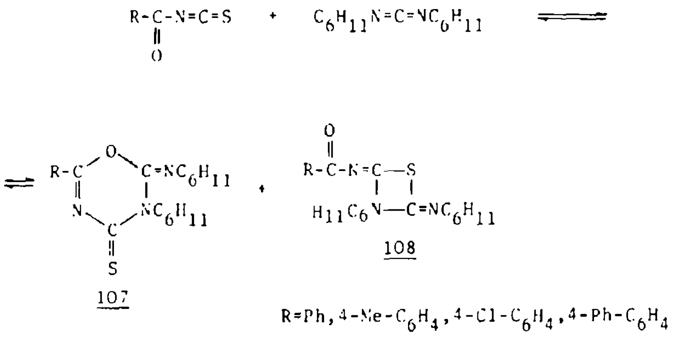
Studies on the reaction mechanism have led to the following conclusion.[337] The reaction rate depends but slightly on the solvent used. The increase of the reaction rate in polar solvents is too small to provide evidence of the formation of a dipolar intermediate. Moreover, trapping experiments did not give evidence of the presence of an open-chain intermediate. If in the reaction one of the substrates is in excess, non-equimolar adducts are not formed. The latter observation speaks against the open-chain intermediate. Finally, cycloaddition proceeds in various solvents with a high negative entropy of activation and a small energy of activation. This is consistent with a tight transition state where redistribution of bonds is mutually assisted. All these data, including the stereoselectivity of cycloaddition, are consistent with a concerted mechanism. However, other mechanisms cannot be unambiguously ruled out.

Walter *et al.* described an example which is inconsistent with the results presented above.[339] They obtained in cycloaddition reaction of carbodiimide (**105**) and MeN=C=S or PhCH$_2$N=C=S, used in excess, the adduct **106** in which two isothiocyanate molecules take part. This is contradictory to the results of Battaglia, Dondoni *et al.*[337,338] and is inconsistent with the pericyclic mechanism proposed.

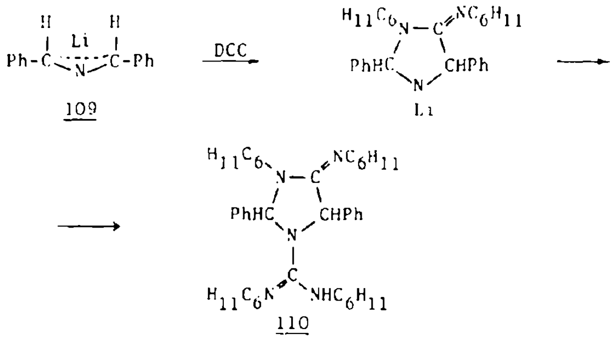


Moreover, cycloaddition proceeds in this case across the N=C bond in isocyanate, and not as always so far observed across the C=S bond.

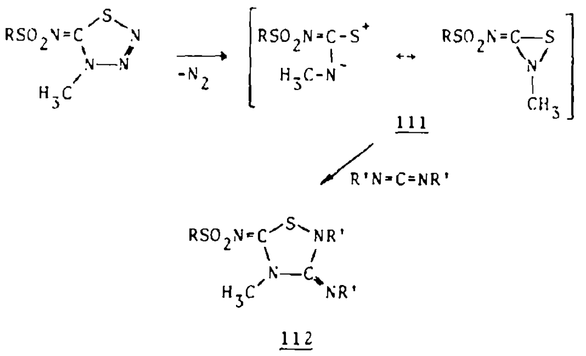
Substituted benzoyl isothiocyanates enter [4 + 2]-cycloaddition reactions with DCC to give 1,3,5-oxadiazine-4-thiones (**107**). In the case of benzoyl isothiocyanate it is possible after a shorter reaction time to isolate also the [2 + 2]-cycloadduct, i.e. 2-benzoyliimino-3-cyclohexyl-4-cyclohexylimino-1,3-thiazetidine (**108**):[340]

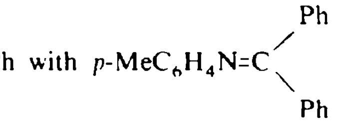

R=Ph, 4-Me-$C_6H_4$, 4-Cl-$C_6H_4$, 4-Ph-$C_6H_4$

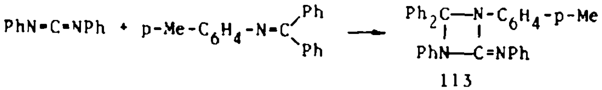
17.4 *Anionic* 1,3-*cycloaddition*. As a result of anionic 1,3-cycloaddition of 1,3-diphenyl-2-azaallyllithium (**109**) and DCC the corresponding final product (**110**) is formed:[341,342]



In a similar cycloaddition reaction of 1,3-dipoles of the type (**111**) and carbodiimides the corresponding thiadiazolidines (**112**) are produced:[343]



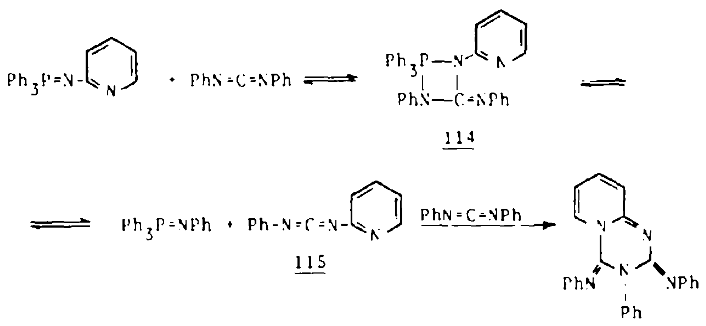
17.5 *Reactions with imines.* In the reaction of PhN=C=NPh with  $p\text{-MeC}_6\text{H}_4\text{N=C}\begin{matrix}\text{Ph}\\ \text{Ph}\end{matrix}$ the formation of the intermediate adduct of 1,3-diazetidine (**113**) structure was observed:[344]



113

Similar products were obtained in the reaction of $[\text{PhCH=N}\bar{\text{A}}\text{lEt}_3]\text{Na}^+$ with RN=C=NR.[345]

N-pyridyl-(2)-triphenylphosphimine reacts with diphenylcarbodiimide to afford the [2 + 2]-cycloaddition product (**114**), which undergoes cycloreversion reaction giving N-phenyltriphenylphosphimine and N-phenyl-N′-2-pyridylcarbodiimide (**115**). Cycloaddition of this carbodiimide with diphenylcarbodiimide proceeds according to the [2 + 4]-scheme and produces the adduct (**116**):[346]

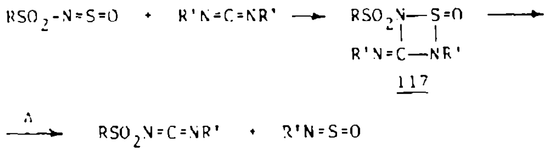


114

115

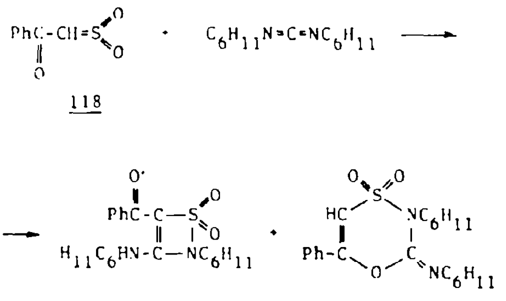
116

N-Sulphinylsulphonamides react with carbodiimides to give the 1,2-cycloadducts namely 3-imino-1,2,4-thiadiazetidin-1-oxides (**117**), which are readily thermolysed to sulphonylcarbodiimides and N-sulphinylimines:[347,329]



117

17.6 *Other cycloaddition reactions of carbodiimides.* DCC reacts with benzoylsulphene (**118**) generated *in situ* to give [2 + 2]- and [2 + 4]-cycloaddition products:[348]



118

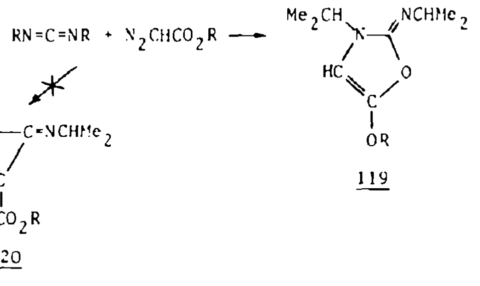
The reaction of carbodiimides with aromatic aldehydes gives the corresponding isocyanates and benzylideneamines probably via the [2 + 2]-cycloaddition reaction:[349]

$$RN{=}C{=}NR + ArCHO \longrightarrow RN{=}C{=}O + RN{=}CHAr$$

$$R{=}C_6H_5,\ c\text{-}C_6H_{11},\ n\text{-}C_4H_9$$

Reaction of carbodiimides with phenylacetylene in the presence of pentacarbonyliron yields adducts having the imidazolidine structure. The probable mechanism assumes the formation of an acetylene-$Fe(CO)_5$ complex in the first step.[350] The reaction of diphenylbutadiyn with carbodiimides proceeds in a similar manner.[351] Cyclotrimerisation of asymmetric acetylenes with PhN=C=NPh gave two 2-imino-1,2-dihydropyridine isomers.[352]

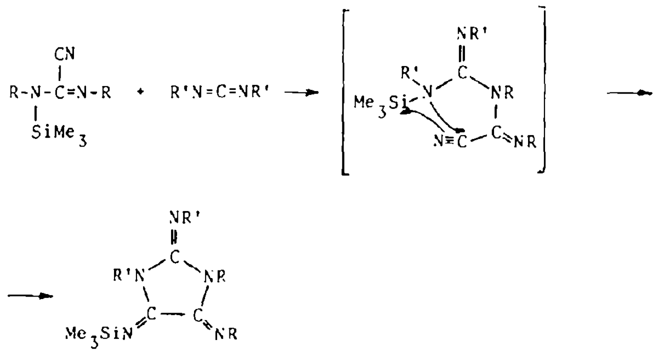
Alkyl diazoacetates react with N,N'-diisopropylcarbodiimide in the presence of transition metal salts to give corresponding oxazolines (**119**)[353] and not aziridines (**120**), as it was stated previously:[354]



119

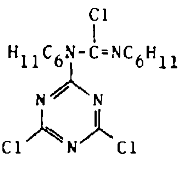
120

Cycloaddition of N-trimethylsilyl-1-cyanoformamidines with carbodiimides leads to substituted imidazolidines. This cycloaddition is not a concerted process, but proceeds via an open-chain intermediate:[302]



## 18. *Other reactions of carbodiimides*

Cyanuric chloride gives with DCC the corresponding adduct (**121**)[355]



121

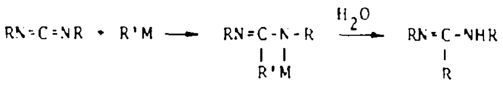
The reaction of DCC with aliphatic primary nitramines $RNH{-}NO_2$ yielded $C_6H_{11}NHCONHC_6H_{11}$ and nitrous oxide together with variable proportions of $RN{=}NO_2R$, $R_2N{-}NO_2$ and the olefin, which might be derived from the alkyl group R.[356]

Carbodiimides when heated or irradiated give cyanamides.

$$RN{=}C{=}NR' \xrightarrow[\text{or } h\nu]{\Delta} RR'N{-}C{\equiv}N$$

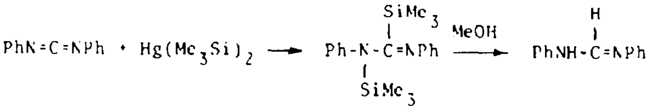
Conceivably cyanamide formation may result from either bond cleavage and radical recombination within the solvent cage or an intramolecular cyclic reorganisation of δ and Π bonds.[357]

Carbodiimides react with Grignard or alkyllithium compounds giving, after hydrolysis, the corresponding formamidines:[358]



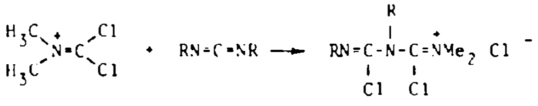
$$RN{=}C{=}NR + R'M \longrightarrow RN{=}\underset{R'}{C}{-}\underset{M}{N}{-}R \xrightarrow{H_2O} RN{=}\underset{R}{C}{-}NHR$$

C,N-Bis-silylformamidines were obtained in the reaction of bis-trimethylsilylmercury with carbodiimides:[359]



$$PhN{=}C{=}NPh + Hg(Me_3Si)_2 \longrightarrow Ph{-}\underset{SiMe_3}{N}{-}\overset{SiMe_3}{C}{=}NPh \xrightarrow{MeOH} PhNH{-}\overset{H}{C}{=}NPh$$

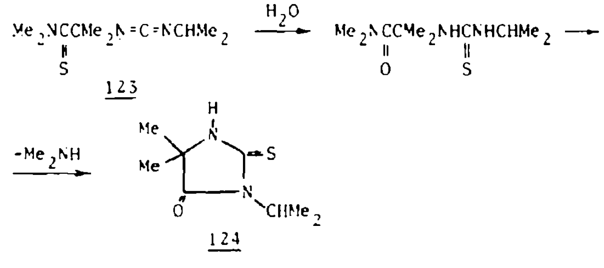
Dichloromethylenedimethylammonium salts react with carbodiimides to give adducts (**122**) which are useful substrates in the synthesis of heterocyclic compounds:[360]



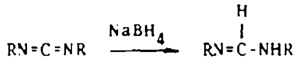
$$(H_3C)_2\overset{+}{N}{=}CCl_2 + RN{=}C{=}NR \longrightarrow RN{=}\underset{Cl}{C}{-}\overset{R}{N}{-}\underset{Cl}{C}{=}\overset{+}{N}Me_2\ Cl^-$$

122

Hydrolysis of thiocarbamoylcarbodiimide (**123**) leads to an unexpected cyclic product (**124**):[361]



Reduction of carbodiimides with $NaBH_4$ leads to the corresponding formamidines:[362]



$$RN{=}C{=}NR \xrightarrow{NaBH_4} RN{=}\overset{H}{C}{-}NHR$$

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