Carbodiimide Chemistry: Recent Advances

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Contents

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I. Introduction

The heterocumulenes form a large class of unsaturated compounds based on the allene structure (Table I). Some of the members of this class are very well-known whereas others are relatively unstable or have only been detected as transients. Carbodiimides, despite being relatively stable molecules, have only in the past 20 years become other than chemical curiosities. General use of these species was stimulated by Khorana's pioneering investigations[1] of their action in peptide and nucleotide syntheses. Even a decade and a half ago at the time of the second comprehensive review,[2] the only major use of carbodiimides was in peptide and nucleotide coupling reactions. Since that time the discovery of catalysts to convert isocyanate to carbodiimide with the loss of carbon dioxide has allowed the industrial scale production of carbodiimides and their availability for use in many manufacturing processes. The incorporation of carbodiimides into polymeric materials probably takes the bulk of world production. Other growing points in carbodiimide chemistry include the continued use of synthesis of nucleotides and peptides, heterocycle synthesis, oxidation with dimethyl sulfoxide, permease inhibition, biological modification, and cycloaddition reactions.

In this review we shall cover the literature comprehensively from 1965 until mid-1980 and will assume that the reader is cognisant of the material in the two earlier reviews.[1,2] During the period under consideration several large fields have opened up, such as in permease inhibition where carbodiimides have been used extensively and where carbodiimide chemistry is not of primary importance; references not relevant to the chemistry of carbodiimides will therefore only be mentioned in passing.

TABLE I. Some Heterocumulenes

O=N=O	O=C=O	$R_2C=C=O$
O=S=O	S=C=S	$R_2C=C=S$
RN=S=NR	S=C=O	$R_2C=S=O$
RN=S=O	S=C=NR	$R_2C=SO_2$
$RN=SO_2$	O=C=NR	$R_2C=C=NR$
$RN=PO_2$	RN=C=NR	$O=SO_2$
RN=PO | NR_2	O=P=O | O^-	RN=P=NR | NR_2
$R_2C=S=CR_2$	RN=P=S	$R_2C=N\rightarrow O$
$R_2C=N=NR$	|	|
R—N=NR	NR_2	R
↓	$R_2C=N=O$	$N\equiv N\rightarrow O$
O	$R_2C=N\rightarrow NR$	$R-N=\overset{+}{N}=\overset{-}{N}$
R—S—N=O	|	
	NR_2	
	R—N=N—R	
	↓	
	S	

Probably the most important feature of carbodiimides relating to their wide use in their relatively low uncatalyzed reactivity which allows easy storage. The driving force for most of the reactions is the very powerful saturating ability of the C=N bond and in the case of dehydrations the very stable product. The carbodiimide fulfills most of the properties of a perfect reagent: it is unreactive until a catalyst is added but provides a powerful driving force for a reaction to proceed. A drawback to the use of carbodiimides is their powerful action as contact allergens (particularly the lipid-soluble reagents);[3] this need only be obtrusive to the careless worker.

II. Synthesis and Formation of Carbodiimides

A. General

A useful review on carbodiimide synthesis has been published.[4]

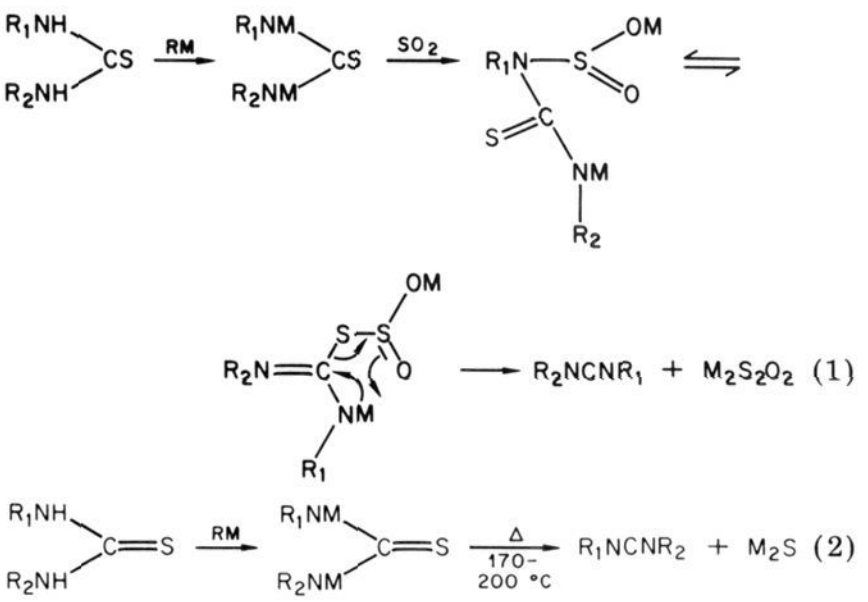
Carbodiimides may be constructed by three major processes, including a preformed N–C–N skeleton, addition of N to C–N, and an N + C + N scheme.

The classical process involves elimination of ligands from the N–C–N skeleton; more recently electrophilic substitution into an existing carbodiimide has been employed. Addition of N to CN is the basis of the modern exchange and catalytic processes. The N + C + N method involves preassociation of C and N followed by further addition of the N grouping.

B. Metal and Metal Oxide Preparations from Thioureas

Lead, silver, and mercury oxides have been used to abstract H_2S from thioureas[5-11] via classical method.[1,2] Active aluminium oxide has also been utilized with thioureas.[12] A novel method has involved the formation of the amide salt from thioureas and Grignard reagent or butyllithium followed by attack of sulfur dioxide (eq 1).[13]

A further interesting method involving metals is the decomposition of the metal salt to yield metal sulfide and carbodiimide in 30–60% yield (eq 2).[14] The reaction with lithium is accelerated by CS_2 probably via a mechanism similar to eq 1. A similar method involves trialkyltin oxide as the "metal salt".[15,16a] *N*-Saccha-



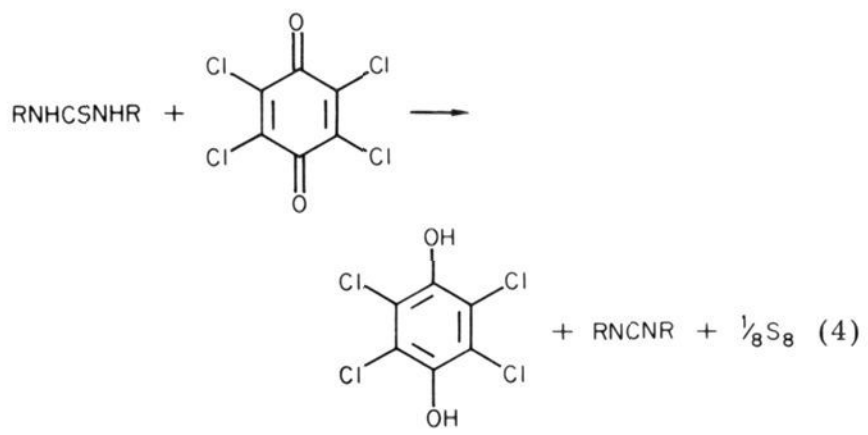
ryl-*N'*-phenylcarbodiimide has been prepared from the urea by heating with lithium carbonate.[16b]

C. Oxidation of Thioureas

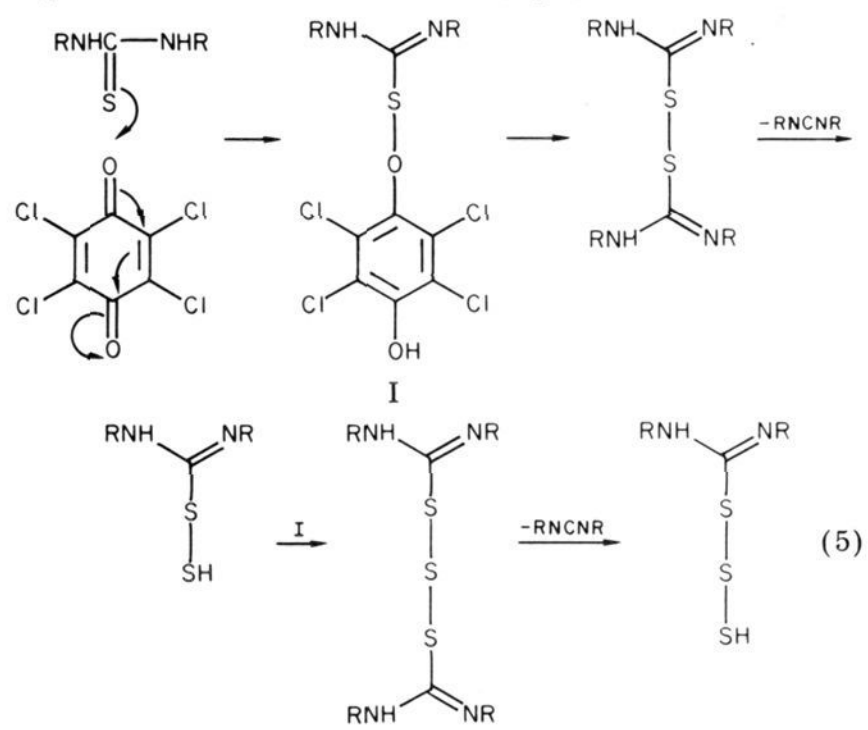
Sodium hypochlorite has continued to be a good oxidizing agent for production of carbodiimides from thioureas (eq 3),[17-21] and *N*-bromosuccinimide has been

$$\mathrm{RNHCSNHR} \xrightarrow{\mathrm{NaClO}} \mathrm{RNCNR} \qquad (3)$$

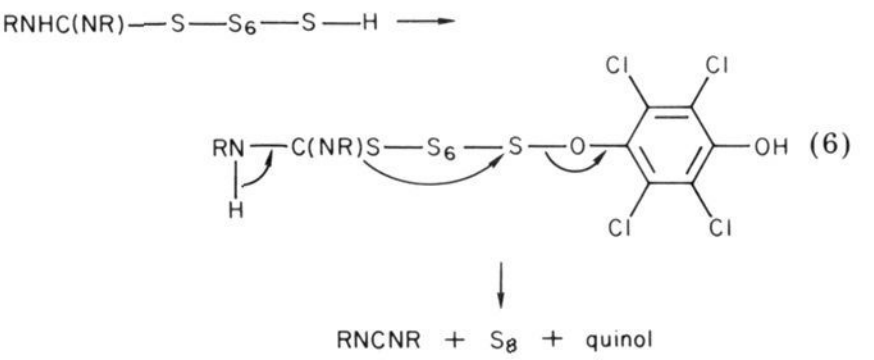
used to good effect.[22] Dehydrosulfuration with a quinone has provided an interesting pathway to carbodiimides[23] with the formation of a quinol and elemental sulfur; the stoichiometric equation (eq 4) masks a



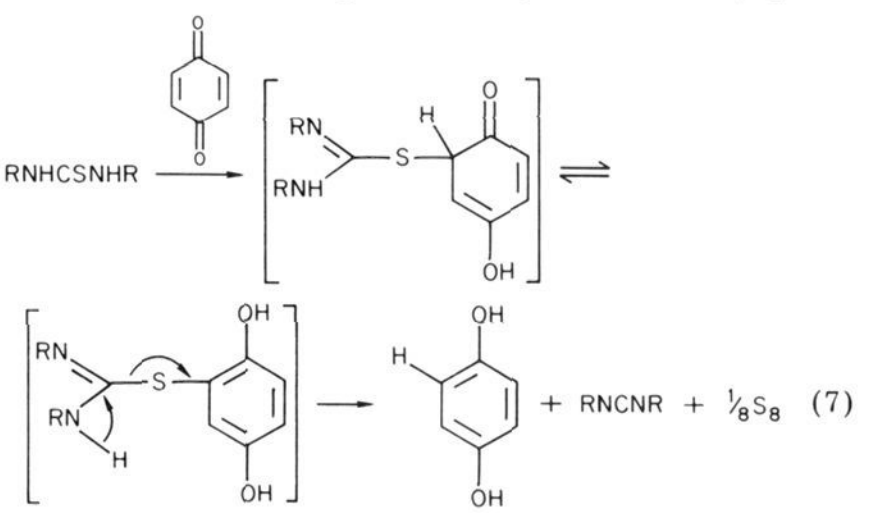
somewhat complicated mechanism. The mechanism involves a 1:1 adduct of thiourea with the quinone, and a possible scheme is outlined (eq 5). The initial reaction of thiourea and quinone yields a sulfenate ester (**I**) which acts as a carrier. The final step in the reaction



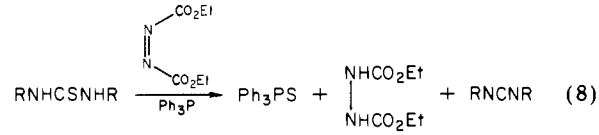
must involve quinone (eq 6) in a cyclization to split out sulfur.



Another method with *p*-quinol involves addition of the thiourea to the ring followed by elimination (eq 7).[23]



Diethyl azodicarboxylate reacts with thiourea in the presence of triphenylphosphine to yield carbodiimide in good yield (eq 8).[24-26] The sulfur is recovered as phosphine sulfide.



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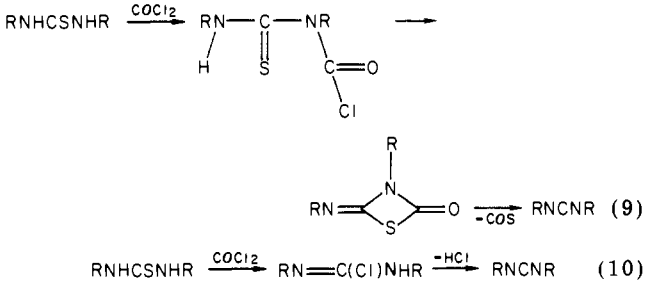
D. Reactions of Thioureas with Acid Halides

a. Phosgene

Reaction of thioureas with phosgene in the presence of base gives very good yields of carbodiimide.[27-34] The mechanism of the reaction is not understood but could involve formation of a four-membered ring followed by expulsion of COS (eq 9) or go through a chloro imide intermediate (eq 10).



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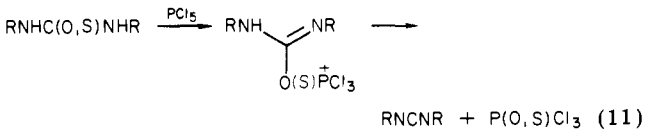
b. Sulfur Acid Halides

Carbodiimides may be obtained by reaction of thioureas with thionyl chloride, sulfenyl chloride, chlorosulfonic acid, SCl_2, and S_2Cl_2 followed by neutralization with base.[35,36]

c. Phosphorus Halides

Ureas and thioureas may be dehydrated or dehydrosulfurated by phosphorus halides, which most likely provide a good leaving function (eq 11).[37-40]



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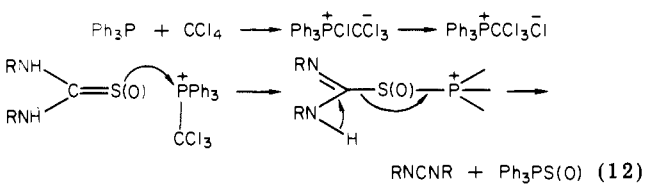
An interesting variation of the above method involves the action of triphenylphosphine, carbon tetrachloride, and tertiary amine on ureas and thioureas (eq 12).[41]



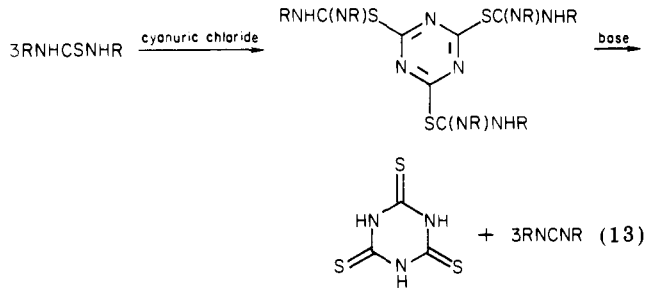
(12)

The stability of the PO and PS bonds provide the driving force for these reactions.

E. Synthesis from Ureas and Thioureas by Elimination

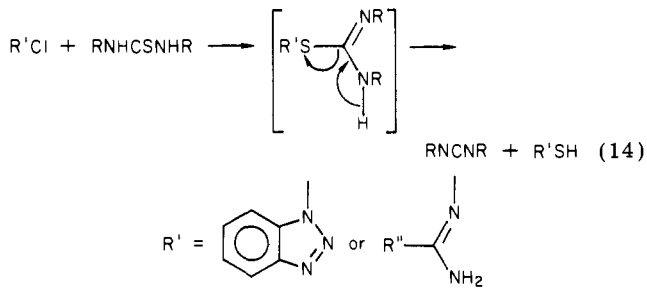
a. Heterocyclic Halides

Cyanuric chloride reacts with thioureas to yield an *S*-heteroarylisothiourea which may be split with base to eliminate a thiol; this procedure is the basis of a synthetic method (eq 13) giving yields of up to 90%[42-46] (eq 13). Similar methods based on chloropyrimidines,[47] *N*-phenylbenzimidoyl chloride,[47] 2-chlorobenzothiazole,[48] and 2-chloropyridinium ion[49] give good yields of carbodiimide. 1-Chlorobenzothiazole[50] and *N*-



(13)

chloroamidines[51] have been used essentially as oxidizing agents; a reasonable mechanism is postulated in eq 14.



(14)

b. Simple Elimination Reactions

Elimination of thiols from *S*-alkyl- or -arylisothioureas has not been used preparatively except where these species are intermediates; carbodiimides are found as intermediates in the decomposition of these species (eq 15).[52]

$$\text{RNHC(SMe)NCN} \xrightarrow{AgNO_3} [\text{RNCNCN}] \xrightarrow{R'NH_2} \text{cyanoguanidine} \quad (15)$$

Direct elimination of HCl from chloroformamidines has been used to form sulfonylcarbodiimides (eq 16)[53,54]

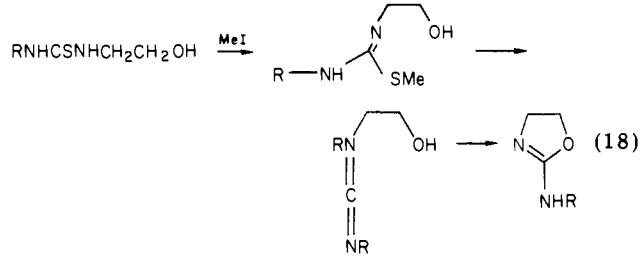
$$ArSO_2N{=}C(Cl)NHR \xrightarrow{base} ArSO_2NCNR \quad (16)$$

The dehydration of ureas with P_4O_{10} and by azeotropic distillation has also been used to prepare carbodiimides.[55,56]

The mechanism of thiol formation from isothiouronium salts in base has been shown to involve cyanamide in the case of the parent thiourea[57] and presumably a carbodiimide in the case of symmetrically disubstituted thioureas (eq 17).

$$R'SC(NHR)_2^+ \xrightarrow{base} R'SH + RNCNR \quad (17)$$

Carbodiimide is probably involved as an intermediate in the cyclization of 2-amino alcohols to give 2-amino-2-oxazolines (eq 18).[58] There is, however, no definitive evidence for this mechanism.

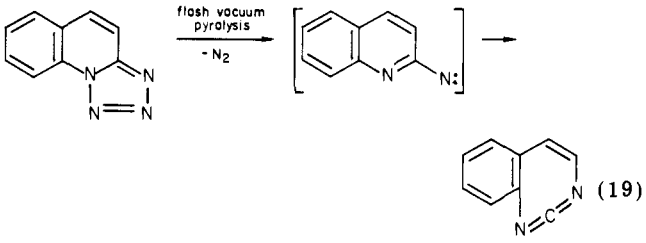


(18)

F. Fragmentation Reactions

a. Five-, Six-, and Seven-Membered Rings

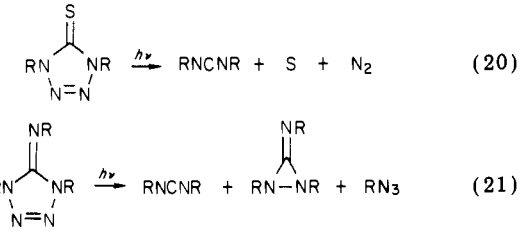
Fragmentations of heterocyclic species to yield carbodiimide and easily removed byproduct have been exploited extensively for synthesis. Tetrazoles have been used to synthesize a novel 7-membered endocyclic carbodiimide (eq 19) through a proposed nitrene.[59] A



(19)

similar reaction involving carbodiimide formation is also thought to involve a nitrene intermediate.[60]

Tetrazole species have also been used in the synthesis of carbodiimides; photolysis of 2-tetrazolines yields carbodiimides in reasonable yield (eq 20 and 21).[61] The



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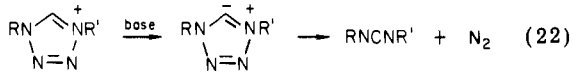
(21)

ylide from a tetrazolium ion also fragments to yield carbodiimide (eq 22).[62]

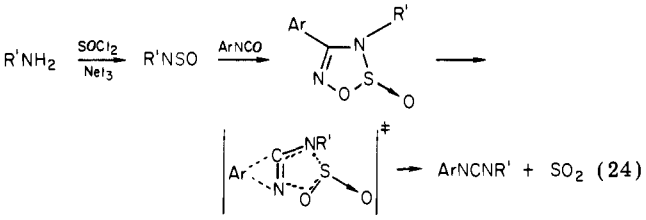


(22)

A limited synthesis related to eq 22 is of an acylcarbodiimide from an oxadiazolium ion (eq 23).[62,63]

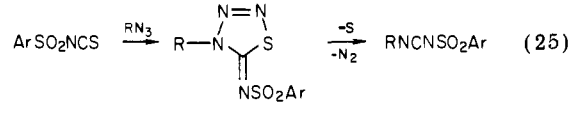
(23)

The extrusion of SO_2 from 1,2,3,5-oxathiadiazole 2-oxides[64-67] involves rearrangement, probably via a multicenter transition state (eq 24).[64]



(24)

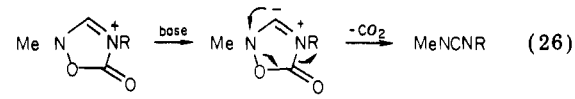
1,2,3,4-Thiatriazolines have been used to prepare carbodiimides where sulfur and nitrogen are fragmented (eq 25).[68]



(25)

Elimination of CO_2 from 1,2,4-oxadiazolin-5-ones and their *N*-alkyl salts yields a carbodiimide in good yield (eq 26).[69]

Triphenylphosphine abstracts sulfur from a thiadiazole (eq 27).[70]



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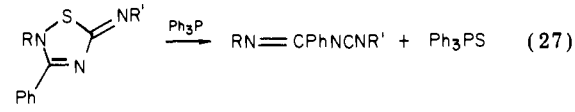
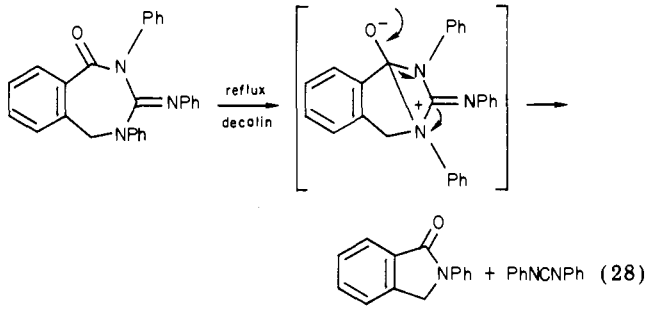


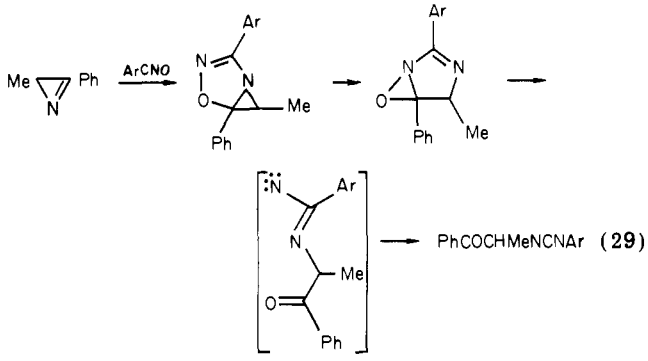
(27)

A novel degradation of a diazepine has been reported where the product is a carbodiimide; the mechanism is believed to involve a bicyclo derivative (eq 28).[71]



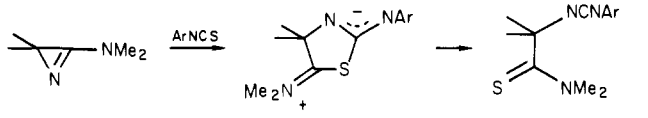
(28)

Cycloaddition of a hindered cyanate with a 2*H*-azirine yields an oxadiazoline which opens probably through a nitrene intermediate to give a carbodiimide (eq 29).[72]



(29)

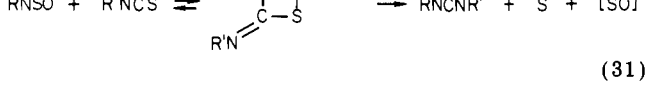
A similar cycloaddition reaction of an azirine with arylisothiocyanate yields a carbodiimide, probably through ring opening of a thiazolium intermediate (eq 30).[73]



(30)

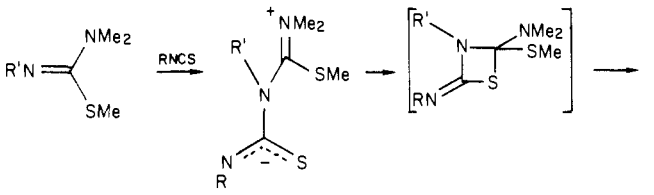
b. Four-Membered-Ring Heterocycles

This fragmentation reaction is essentially the reverse of a [2 + 2] cycloaddition which is considered later in this review. A simple reaction which, however, gives poor yields is the coupling of *N*-sulfinylamines with isothiocyanates to give a four-membered heterocycle which extrudes S and [SO] (eq 31).[74] Dithiocarbamates



(31)

and carbodiimides are the products from the reaction of isothiourea derivatives and isothiocyanates (eq 32).[75]

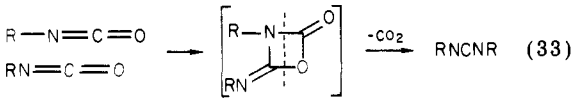


R'NCNR + $Me_2NCSSMe$ (32)

G. Catalytic Methods

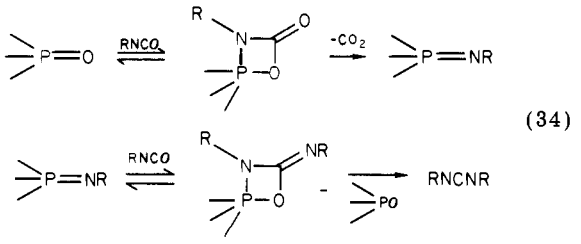
a. Phosphorus Catalysts

The reaction of two molecules of isocyanate to yield one of carbodiimide with the extrusion of CO_2 is essentially a cycloreversion procedure (eq 33),[76,77] and it



(33)

may be catalyzed by compounds with P=X groups. This approach to synthesis has a major disadvantage in that only symmetrical carbodiimides may be prepared. There is now considerable evidence in favor of the original mechanism (eq 34).[78,79] The reaction is



(34)

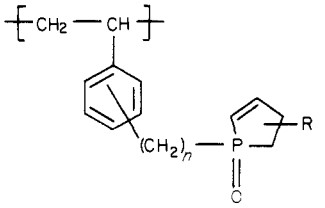
catalyzed by pentavalent phosphorus compounds which may be ring or linear and which may possess different ligands.[80-93] The formation of the ≡P=NR intermediate is confirmed by its synthesis and use with R'NCO as a method for forming mixed carbodiimides (eq 35) in up to 70% yield.[94,95] This method allows the formation of unsymmetrical carbodiimides which are not available from the simpler catalytic procedure and has been reported earlier.[96] The mechanism of eq 34 is consistent with the observation that ^{18}O-enriched phosphine oxide catalysts yield CO_2 with considerable ^{18}O incorporation.[97]

$$ClCH(CCl_3)NCO + Ph_3P{=}NPh \rightarrow ClCH(CCl_3)NCNPh \quad (35)$$

Arsines[98] and vanadium and tungsten oxides[99] have proved to be efficient catalysts of the decarboxylation of isocyanates.

b. Solid-Phase Catalysts Based on Phosphorus

Attachment of the phosphorus catalyst to a solid phase has been attempted, and an example of such a catalyst is given (II)[100,101] in which the phosphorus



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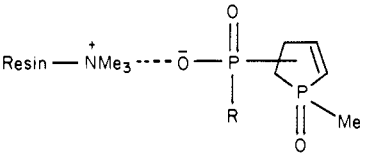
heterocycle is covalently attached to a styrene/divinylbenzene matrix. An alternative solid-phase catalyst involves binding an anionic species to an anion-exchange resin (III).[102,103] Arsine oxides bound cova-



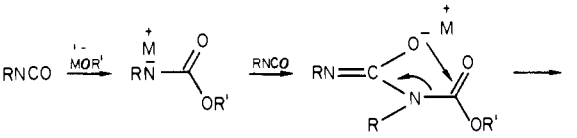
III

lently to polystyrene matrices have also been successfully used as carbodiimide forming catalysts.[104,105]

c. Organometallic Catalysts

Iron pentacarbonyl and other metal carbonyls catalyze the decarboxylation of isocyanates. It is thought that a cycloaddition reaction occurs with the expulsion of carbon dioxide (eq 36).[106,107] Metallic salts of alcohols are also effective catalysts for the decarboxylation of isocyanates, and carbamate esters have been proposed as reactive intermediates (eq 37;[108,109] up to 90% yields have been observed with these catalysts).

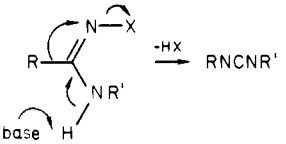
$$MetCO \xrightarrow{RNCO} MetCNR + CO_2$$
$$MetCNR \xrightarrow{RNCO} Met{\cdot}CO + RNCNR \quad (36)$$



RNCNR + CO_2 + MOR' (37)

H. Tiemann Rearrangements

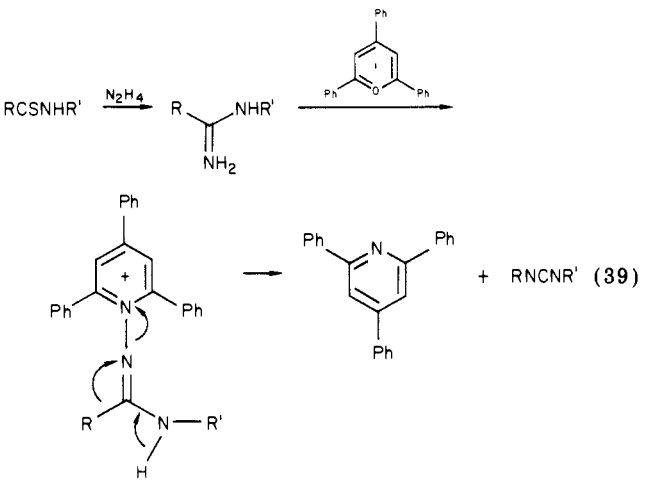
Several useful syntheses of carbodiimides utilize an electron-deficient rearrangement (eq 38). Amidoximes



(38)

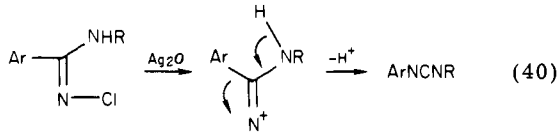
X = $-OPOCl_2$, $-OSO_2Ph$, $-OCOPh$

in the presence of phosphyl halides[110,111] and base give carbodiimides in up to 60% yield. O-Benzoylation of



(39)

an amidoxime followed by base-catalyzed elimination[112] also gives a good yield of carbodiimide. Recently a versatile method of carbodiimide formation from amidrazones has been reported (eq 39);[113,114] triphenylpyrylium ions form the corresponding pyridinium species which then eliminates with rearrangement to carbodiimide. Reaction of *N*-chloroamidines with silver oxide yields carbodiimides, probably through a nitrenium ion (eq 40).[115]



(40)

I. Syntheses through Combination of N + CN

The synthetic method for carbodiimides involving decarboxylation of isocyanates through phosphorus catalysis is strictly an N + CN pathway but is best dealt with separately. The reaction of amines or their derivatives with isocyanides has been exploited as a useful synthesis. Palladium dichloride has been used as a catalyst for the reaction of primary amine with isocyanide in the presence of silver oxide;[116] the reaction yielding up to 90% carbodiimide is thought to involve a complex species (eq 41). Azide and isocyanide in the

$$RNH_2 + R'NC \xrightarrow{PdCl_2}$$

$$PdCl_2(R'NC)[C(NHR')NHR] \xrightarrow{Ag_2O} R'NCNR \quad (41)$$

presence of iron pentacarbonyl catalyst give a 50–60% yield of carbodiimide (eq 42).[117] Carbodiimides are

$$RN_3 + R'NC \xrightarrow[-N_2]{Fe(CO)_5} RNCNR' \quad (42)$$

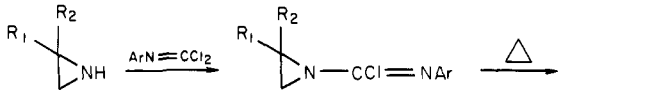
prepared in up to 80% yield by the interaction of amine and –C=N– groups (eq 43);[118] aliphatic amines require

$$ArNH_2 + F_3C{-}N{=}CF_2 \xrightarrow{2HF} F_3C{-}NCNAr$$

$$RNH_2 + F_3C{-}N{=}CF_2 \xrightarrow{-HF}$$

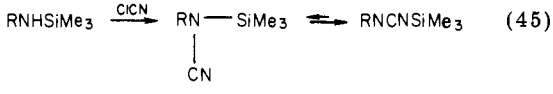
$$F_3CN{=}CF{-}NHR \xrightarrow[\text{distill}]{-HF} F_3C{-}NCNR \quad (43)$$

a distillation step to expel the second HF molecule. Cleavage at a CN bond occurs when the amine is secondary (eq 44).[119] Reaction of aminosilanes with



(44)

cyanogen halides yields silylcyanamide which tautomerizes to the carbodiimide (eq 45).[120,121]



(45)

J. Exchange Reactions

Simple exchange of a carbodiimide with halides have been utilized in preparations with up to 90% yield.[122–125] Equation 46 exemplifies a typical process.[122]

Stannylamines exchange with isothiocyanate to give stannyl sulfides and carbodiimides in up to 90% yield (eq 47).[16,126] A similar exchange process involves iso-

$$R_3SnNCNSnR_3 \xrightarrow{Me_3SiCl} R_3SnNCNSiMe_3 + R_3SnCl \quad (46)$$

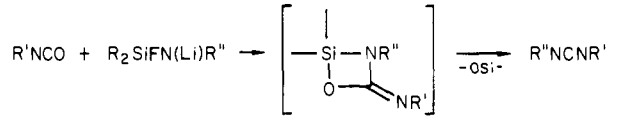
$$(R_3Sn)_2NR + R'NCS \xrightarrow[\text{hexane}]{\Delta} R'NCNR + (R_3Su)_2S \quad (47)$$

cyanate or isothiocyanate and trialkyltincarbamates (eq 48).[127]

$$(R_3Sn)_2O + ArNCO \rightarrow$$

$$R_3SnOCONAr(SnR_3) \xrightarrow[-(R_3Sn)_2S]{+R'NCS,\ -CO_2} R'NCNAr \quad (48)$$

A novel method involves exchange of the nitrogen of a silylamine for oxygen of an isocyanate (eq 49).[128]



(49)

K. Synthesis from Cyanamide and Its Derivatives

The preparation of carbodiimides can be effected through electrophilic substitution on the preformed carbodiimide or cyanamide. Synthesis from metal cyanamides using reactive halides has been exploited (eq 50 and 51)[129,130] for phosphyl (X = S, O) and silyl

$$Ph_2P(X)Cl + Ag_2CN_2 \rightarrow Ph_2P(X)NCNP(X)Ph_2 \quad (50)$$

$$R_3SiCl + KNCNPh \rightarrow Me_3SiNCNPh \quad (51)$$

carbodiimides. Other examples use zinc or lead cyanamide[131,132] and calcium or sodium cyanamide[133] to give moderate to good yields of carbodiimide from reactive halides. Action of halides on N=C=N species in the presence of base has also given good yields of carbodiimide.[15,134–136]

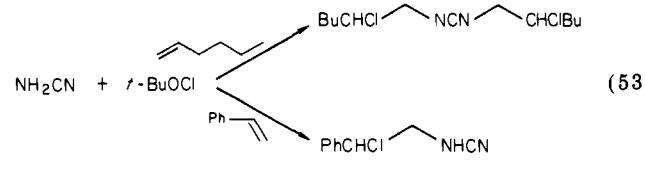
Oxides and amides of group 4 elements can act as electrophilic substitution agents for cyanamides to give carbodiimides in good yield (eq 52).[77,137–140]

$$(R_3M)_2O \xrightarrow{NH_2CN} R_3MNCNMR_3$$

$$(R_3M)_2NR \xrightarrow{NH_2CN} R_3MNCNMR_3 \quad (52)$$

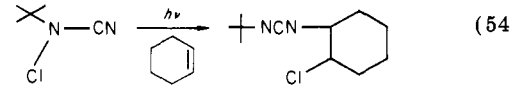
M = Pb, Si, Ge, Sn

Carbodiimides may be prepared from cyanamide and olefins with *tert*-butyl hypochlorite, possibly through a free-radical process (eq 53).[141] A further synthesis



(53)

giving a 22% yield of carbodiimide is also thought to involve free radicals (eq 54).[142]

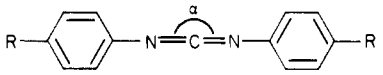


(54)

III. Structure and Physical Properties

A. Structure

The allene-type structure of carbodiimides was well established by the time of the last review.[2] Recent work was aimed at detailed structural analysis. The interesting feature of X-ray crystallographic studies is that the carbodiimide bond itself is nonlinear, with NCN bond angles varying from 166 to about 170° for both aromatic and mixed-aliphatic–aromatic species (IV).[143-146] The dihedral angle between the substituents

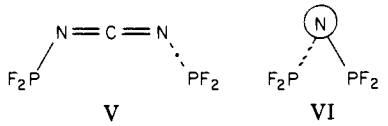


IV, R = MeO; α = 169°
R = NO_2; α = 169.7°
R = H; α = 170.2°
R = Me; α = 170.4°

ranges near 90°, but the CNAr angle is larger than the expected 120°; values range from 123 to 180°. The anomalous NCN angle could be attributed to "packing" factors in the crystals, but the fact that all carbodiimides that have been investigated possess the anomally makes this explanation doubtful.[145] The bending of the NCN bond may be due to steric interactions between the two nitrogen substituents. The X-ray crystallographic structure of allene-1,3-dicarboxylate shows a similar buckling effect occurs in the central allene carbon, and a similar steric explanation is advanced for this.[147] Symmetrically substituted allenes (e.g., 1,1,3,3-tetraphenylpropadiene) have perfectly linear central allene bonds,[147] presumably because steric repulsion from one side is balanced by that on the other. The salt Li_2NCN has of course a linear structure because the NCN^{2-} is a symmetrical dianion.[148a]

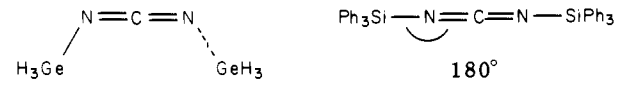
It is interesting to note that other heterocumulenes have also been shown to have a slightly buckled three atom bond. Microwave and electron-diffraction studies of chloroisocyanate (ClNCO)[148b,c] indicate an angle of approximately 171°. This angle has been reproduced by ab initio studies[148d] and CNDO/2[148e] calculations. Microwave studies[148b] also indicate a bent structure (∠NNN ~172°) for chlorine azide (ClN_3). Ab initio calculations[148d] predict trans bent structures for HONCO (∠NCO ~170°), HNCO (∠NCO ≃ 169.7°), MeNCO (∠NCO = 169.6°), H_2BNCO (∠NCO = 171.9°), and NC–NCO, (∠NCO = 168.7°). These data indicate that the buckled carbodiimide group may result from an electronic effect such as steric or lone-pair repulsion rather than from crystal packing.

Electron-diffraction studies on bis(difluorophosphino)carbodiimides indicate a dihedral angle of 55° (V and VI).[149] Both electron diffraction[150] and



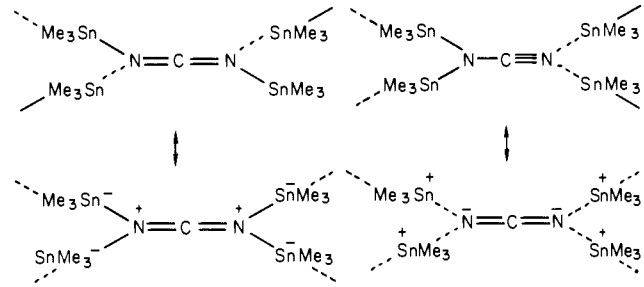
V VI

X-ray crystallographic[151] studies indicate a nonlinear and linear structure respectively for digermyl- (VII) and bis(triphenylsilyl)carbodiimides (VIII); gas-phase electron-diffraction studies also indicate a linear SiNCNSi configuration for disilylcarbodiimide.[152] The crystalline



VII VIII

bis(trimethylstannyl)carbodiimide has been shown by X-ray crystallography to possess a highly aggregated structure with an NCN group intermediate between cyanamide, carbodiimide, and ionic NCN^{2-} (IX).[153]



IX

The structure consists of an infinite helical network of planar trimethyltin groups linked by NCN units; the dihedral angle between the Sn_2NC planes is 68°, and the SnNC angle is 117.6°. The CN bond length is 1.24 Å, close to that in CaN_2C, but the SnN bond is 0.33 Å longer than that in Me_3SnNCS.

B. Electronic Structure

Molecular orbital calculations have been carried out on a number of simple carbodiimides. A geometry search using the INDO method[154] for dimethylcarbodiimide[155] has revealed that the lowest energy singlet state has a dihedral angle of 90° and an angle for CH_3—N=C (CNC) of 90°; the latter value is 120° for difluorocarbodiimide and parent carbodiimide. Energy-optimized geometries were obtained by using the Gaussian 70 program[156] and STO-3G and 6-31G basis sets, and the dihedral angle of carbodiimide was found to be 93° and that of HNC 111.4°.[157] Molecular orbital calculations indicate a negative potential maximum in the region of the nitrogen lone pair;[158] the dihedral angle was assumed to be 90°, and energy minimization of the HNC angle gave a value of 115°.[158] The cyanamide molecule was shown to be more stable than carbodiimide and the equilibrium constant (eq 55) calculated

$$NH_2CN \rightleftharpoons HNCNH \qquad (55)$$

to be 10^{19} at 300 K in the gas phase. The physical parameters: ^{14}N-quadrupole coupling constant, dipole moment, average diamagnetic susceptibility, molecular quadrupole moment, and diamagnetic shielding have been calculated from molecular orbital theory.[159]

Molecular orbital drawings have been published for the parent carbodiimide.[160] The two highest filled orbitals correspond to the n electrons and have vanishingly small coefficients on the central carbon. The lowest vacant orbital (6B) has a large coefficient on the central atom. There is a general similarity between the molecular orbitals of the heterocumulenes CO_2, CH_2CO, CH_2CCH_2, CH_2N_2 and carbodiimide. Table II gives the detailed comparison, and the differences lie in the existence of degeneracy and the type of the highest occupied molecular orbital.

TABLE II. Molecular Orbitals of Species Isoelectronic with Carbodiimide

allene	ketene	diazomethane	CO_2	carbodiimide
	$2B_1-\pi_2$	$2B_1-\pi_2$		5B—n
	$2B_2-\pi_{CO}$	$2B_2-\pi_{N'N}$		6A—n
$2E--\pi_{CC}$	$1B_1-\pi_1$	$7A_1-n_1\sigma_{CN}$	$1\pi_g--$	5A—π
$1E--\pi_{CH_2}$	$1B_2-\pi_{CH_2}$	$1B_1-\pi_1$	$1\pi_u--$	4B—π
$3B_2-\sigma_{CC}\sigma_{CH_2}$	$7A_1-n,\sigma_{CC}$	$1B_2-\pi_{CH_2}$	$3\sigma_u-$	3B—$\sigma_{NC}\sigma_{NH}$
$4A_1-\sigma_{CH_2}\sigma_{CC}$	$6A_1-\sigma_{CH_2}\sigma_{CC}$	$6A_1-\sigma$	$4\sigma_g-$	4A—$\sigma_{NH}\sigma_{NC}$
$2B_2-\sigma_{CH_2}$	$5A_1-\sigma_{CC}\sigma_{CH_2}$	$5A_1-\sigma$	$2\sigma_{CC}-$	2B—σ_{NH}
$3A_1-\sigma_{CC}$	$4A_1-\sigma_{CO}$	$4A_1-\sigma_{NN}\sigma_{CN}$	$3\sigma_g-$	3A—σ_{NC}

C. Stereochemistry

Molecular orbital theory has been applied to the problem of racemization of carbodiimides. Since carbodiimides are analogous to allenes, they should in principle be resolvable. An ab initio SCF LCAO MO study of nitrogen inversion in carbodiimide indicates a barrier to racemization of some 8.4 kcal/mol.[161] An INDO study which also minimized geometry to give a dihedral angle of 94° calculated the energies of structures of carbodiimide on possible paths of racemization.[162] Two paths exist—the rotational and the inversion—both with very similar energies; Table III collects the energies for fluorocarbodiimide and carbodiimide.

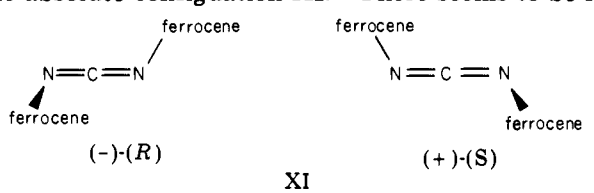
It was concluded that the CNR valence angles opened out slightly in the planar (rotational) transition state. The lowest triplet state is 60 kcal/mol higher than ground, effectively ruling out such a mechanism for racemization. An interesting point is that the difluorocarbodiimide with energy for racemization of about 22 kcal/mol should be resolvable. The low energy for racemization of the parent of 8 kcal/mol is comparable with that for NH_3 inversion; the high energy of the FNCNF racemization parallels the high barrier for inversion at NF_3.[162] Similar low barriers for racemization have been calculated for dimethylcarbodiimide (5 kcal/mol for *inversion* and 4.5 kcal/mol for *rotation*).[163] The dicyanocarbodiimide structure is flexible, with even less barrier for racemization than regular carbodiimides, and a linear resonance structure is proposed (X).[163]

$$N{\equiv}C{-}N{=}C{=}N{-}C{\equiv}N \leftrightarrow N{\equiv}C{-}N{=}\overset{+}{C}{-}\overset{-}{N}{=}C{=}N \leftrightarrow$$
$$\overset{-}{N}{=}C{=}N{-}\overset{+}{C}{=}N{-}C{\equiv}N$$

X

The diaminocarbodiimide has a (calculated) barrier to *inversion* of 18.5 and to *rotation* of 41.5 kcal/mol.[163] A semiempirical method confirms the low barrier to racemization in carbodiimides of <10 kcal/mol.[164]

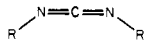
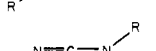
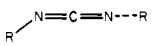
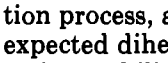
The problem of the configurational instability of carbodiimides has recently been reviewed.[165] Despite the low barriers to the optical isomerization calculated for regular carbodiimides, bisferrocenylcarbodiimide has been partially resolved;[166] application of Lowe's rule for allenes[167] indicates that the resolved components have the absolute configuation XI. There seems to be no



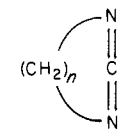
XI

reason why the ferrocenyl derivative should be any different from the parent with regard to the racemization process, and we suggest that the relatively small expected dihedral angle of about 90° allows an interaction stabilizing either of the ground-state forms to occur. Such an interaction has been already proposed as the cause of the ∠N=C=N and ∠C=C=C buckling. The species bis(methylphenyl)methylcarbodiimide has also been resolved by using partially acetylated cellulose.[168] Application of the Brewster model applied to chiral allenes[169] in conjunction with Lowe's rule[167] allows assignment of configuration.

TABLE III. Energies of Difluorocarbodiimide and Carbodiimide[162]

	R = H		R = F	
	dihedral/deg	E/(kcal mol^{-1}	dihedral/deg	E/(kcal mol^{-1}
R—N=C=N—R		16.8		51.4
	0	15.7	0	46.6
		8.1		22.4
	180	7.8	180	22.8
	94	0	93	0

Optically active endocyclic carbodiimides have been resolved on partially acetylated cellulose;[168] the homologue with $n = 7$ (XII) is resolvable, but that with $n =$



XII

11 is not. The cause of the relatively high barrier to racemization is the restraint effected by the medium-sized ring ($n = 7$); as these restraints are lifted ($n = 11$), rotation or inversion become possible.

Measurements of the energy barrier of racemization have been made by using NMR techniques[169,170] and found to be in the range 6–9 kcal/mol, in remarkable agreement with theory.

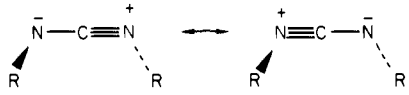
D. Nuclear Magnetic Resonance

The use of NMR techniques has been mainly aimed at the racemization problem as above, but structural problems have been attacked. ^{13}C NMR chemical shift studies have shown that the resonance of the central carbon of carbodiimides occurs at an unusually high field ($g = 140$ ppm) whereas that of allenes is at about 210 ppm.[171] *N,N'*-Disilylcarbodiimide has a ^{13}C resonance at 130 ppm[172] and that of the ^{29}Si at −0.8 ppm.[173] Thus ^{15}N resonances of carbodiimides occur (like those of ^{13}C) at high fields due possibly to the contribution from polar resonance structures which increase the

TABLE IV. *A* Value of Groups Attached to Cyclohexane

substituent	*A*
$-NCNC_6H_{11}$	1.00
-NCO	0.51
-NCS	0.28
$-N{=}C$	0.21
$-NO_2$	1.05
$-CHCH_2$	1.35
$-C{\equiv}CH$	0.41

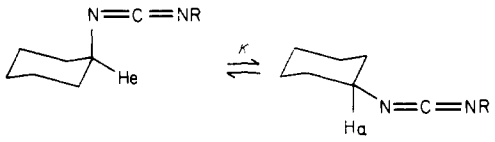
shielding of nitrogens and the central carbon of the carbodiimide (XIII).[174] Polar solvents have little effect



XIII

on the ^{13}C chemical shift of the central carbon but significantly alter that of the ^{15}N resonance.[174] This is probably related to the ability to solvate at the nitrogen and its lack at the carbon.

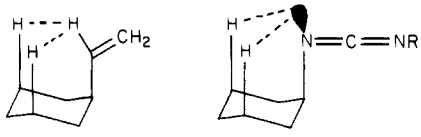
The *A* value of carbodiimide attached to a cyclohexane ring has been estimated by NMR techniques with CS_2 solvent (eq 56).[175] The value of *A* is compared



(56)

$$A = RT \ln K/1000$$

with that of other substituents (Table IV). The conformational requirement of the nonbonded lone pair on the nitrogen of the carbodiimide is not as severe as that of the hydrogen in the vinyl group (XIV).



XIV

The ^{15}N resonance in carbodiimides is half way between that of CN and NR_2 in cyanamides.[176] NMR studies with *N*-ethyl-*N'*-[(dimethylamino)propyl]-carbodiimide indicate the presence of a cyclic species in solution,[174,177] and we shall return to this problem later.

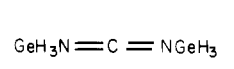
E. Infrared Spectroscopy

Low-temperature matrix isolation methods have been used to observe the infrared spectrum of carbodiimide and its deuterio analogue for the first time.[178] The 27 fundamental vibrations in dimethylcarbodiimide have been assigned by analyzing the infrared spectrum of vapor, liquid, and crystalline form together with Raman spectroscopy.[178-181] The asymmetric vibrational frequency of carbodiimide with aryl substituents may be correlated with the appropriate Hammett σ or σ^+ values.[182,183] The Hammett substituent constants have been determined for the NCNPh group on a phenyl ring making use of the relationship of eq 57[184] where *A* is

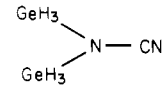
$$\sigma_R^\circ = 0.0079A^{1/2} - 0.027 \qquad (57)$$

the area under the peak for the ν_{16} ring band in monosubstituted benzene.[185]

The vibronic spectrum of digermylcarbodiimide indicates that the structure is a carbodiimide and not a cyanamide (XV and XVI).[125] The selection rules are



XV



XVI

consistent with a linear heavy atom skeleton. The spectrum is similar to that of bis(trimethylsilyl)carbodiimide.[125]

The structure and lattice dynamics of bis(triphenylstannyl)carbodiimide have been studied by using Raman ^{119}Sn Mössbauer correlational spectroscopy (Raman frequency ω = 26 cm^{-1}).[185] The infrared spectrum of dicyclohexylcarbodiimide has been investigated.[186]

F. Photoelectron Spectroscopy

He(I) photoelectron spectra of dialkylcarbodiimides have been studied.[187,188] A distinct peak due to lone-pair character is separated from the rest of the ionizations. Dimethylcarbodiimide shows bands at 9.5, 11.55, and 12.26 eV; the first maximum consists of two ionizations representing two orbitals on the NCN part with both π and n character. The 9.5-eV bands represent orbitals of B character and are probably assigned to the n orbitals described in Table II.[160]

G. Ultraviolet Spectroscopy

The ultraviolet spectra of several alkyl- and arylcarbodiimides have been measured.[189-191] The absorption spectrum of dimethylcarbodiimide in the vapor phase has a maximum at 191 nm, a shoulder at 207–210 nm, and three maxima at 246.4, 252.5, and 258.4 nm; in heptane solution there is a strong band at 206.6 nm and three at 247.5, 254, and 260 nm due to the allowed $n-\pi^*$ transitions polarized perpendicularly to the plane of the CNC angle.[181] The near-UV absorption spectrum of *N,N'*-diphenylcarbodiimide is sensitive to substituent effects and varies systematically with σ.[192]

H. Mass Spectroscopy

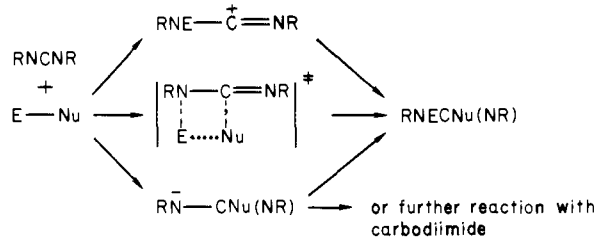
The mass spectra of both alkyl- and arylcarbodiimides have been investigated.[193] Diarylcarbodiimides have relatively stable molecular ions; there is a little fragmentation decomposition via the rearranged benzimidazole for 4- or 3-substituted phenyl groups. The dialkylcarbodiimides have weaker molecular ions which suffer *N*-alkyl cleavage and α-cleavage fragmentation.[193] The fragmentation pattern of bis(trimethylsilyl)- and -(trimethylgermyl)carbodiimides are similar.[194] Bis(trifluoromethyl)carbodiimide fragments to yield $C_3F_6N_2$, C_2F_4N, C_2F_4, $C_2F_2N_2$, C_2F_2N, C_2FN_2, CF_3, CFN, CN, and CF.[195]

I. Miscellaneous Physical Properties

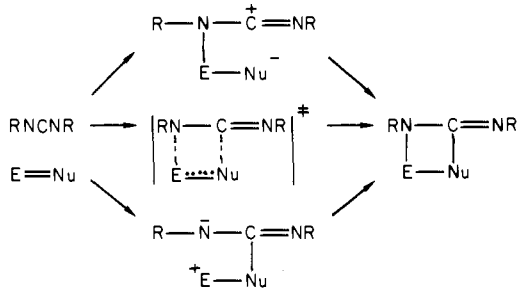
Physicochemical properties (viscosity, surface tension, refractive index, and parachor) have been measured for bis(tributylstannyl)carbodiimide.[196] The Sn–N bond energy is of the order of 100 kcal/mol, as determined

TABLE V. Pathways for Reactions of Carbodiimides

Addition



Electrocyclic Addition



from heats of formation in the liquid and gaseous states and the heats of atomization for bis(tributylstannyl)-carbodiimide.[197] The dipole moment of bis(triethylstannyl)carbodiimide is 2.79 D.[198]

IV. Chemical Properties

A. General Properties

The carbodiimide molecule has two centers of reactivity; the central carbon atom is electrophilic and the terminal nitrogens electron rich. By far the most important reactions involve nucleophilic attack of a reagent E–Nu which may add by stepwise or concerted paths (Table V). The reaction essentially occurs by interaction of the highest occupied molecular orbital of the reagent and the lowest vacant orbital on the carbodiimide which has a large coefficient on the central carbon.

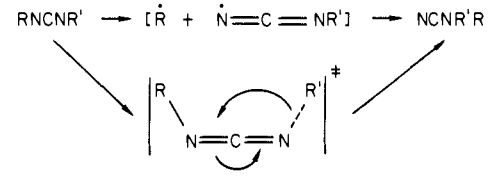
Table VI illustrates a comparison between reactivity of a series of heterocumulenes and nucleophiles; as might be expected, the oxygen analogues, carbon dioxide and isocyanate, are much more reactive than carbodiimide.

B. Isomerization

The isomerization of *N*-phenyl-*N*-tritylcyanamide to carbodiimide has been studied kinetically (eq 58),[199,200]

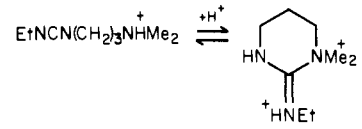
$$PhN(CPh_3)CN \rightarrow PhNCNCPh_3 \qquad (58)$$

and an ionic mechanism was postulated to account for the accelerated rate constant in polar solvents. The formation of cyanamides from carbodiimides was also studied, but the mechanism is uncertain.[201] Possibilities involve radicals reacting in cages or an intramolecular cyclic reorganization of σ or π electrons (eq 59).[201]



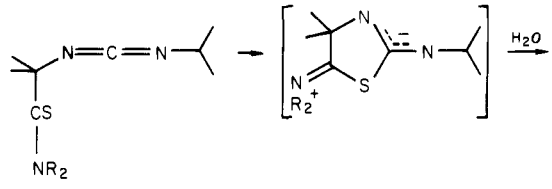
(59)

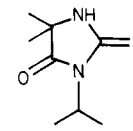
Ring–chain tautormerism has been demonstrated in the well-known water-soluble carbodiimide 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (eq 60).[202] At



(60)

neutral pH the cyclic form contributes some 7% of the total material. A similar form of tautomerism is deduced from the unusual product of hydrolysis of a thiocarbamidocarbodiimide (eq 61)[203,204] where intra-

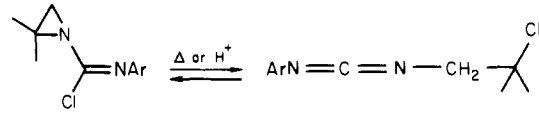




(61)

molecular rearrangement yields a thiazolidine which extrudes the secondary amine (NHR_2) to yield a thiohydantoin.

A novel form of tautomerism has been observed between aziridines and carbodiimide (eq 62).[205]



(62)

Bis(trifluoromethyl)carbodiimide may be prepared by isomerization of perfluoro-2,4-diaza-1,4-pentadiene (eq 63).[206]

$$CF_2{=}NCF_2N{=}CF_2 \rightleftarrows CF_3NCNCF_3 \qquad (63)$$

C. Addition of HX

a. Water and Alcohols

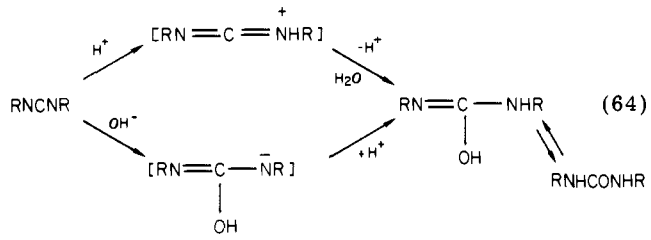
The hydrolysis of carbodiimides is a relatively slow

TABLE VI. Reactivity of Some Heterocumulenes to Nucleophiles[a]

heterocumulene	$k_H/(M^{-1}\ s^{-1})$	$k_{OH}/(M^{-1}\ s^{-1})$	k_{H_2O}/s^{-1}	$k_{RNH_2}/(M^{-1}\ s^{-1})$
HNCO	0.16	980	0.079	1300[b]
n-PrNCNPr-*n*	630	0.014	$<10^{-6}$	0.015[c]
O=C=O		4000[d]	0.0145[e]	9810[d]
O=C=S		4.2[f]		12000[g]
S=C=S		1.1×10^{-3}[f]		1.7
n-BuN=C=S		0.0268		4.2×10^{-2}[b]

[a] 25 °C aqueous solution. [b] Methylamine. [c] Ethylamine. [d] M. B. Jensen, *Acta Chem. Scand.*, 13, 289 (1959). [e] B. R. W. Pinsent, L. Pearson, and F. J. W. Roughton, *Trans. Faraday Soc.*, **52**, 1512 (1956). [f] B. Philipp and H. Dautzenberg, *Z. Phys. Chem.* (*Leipzig*), 231, 270 (1966). [g] B. Philipp and H. Dautzenberg, *Faserforsch. Textiltech.*, 19, 23 (1968).

reaction but is catalyzed by oxonium ions and hydroxide ions; the mechanisms are proposed to involve cationic and anionic intermediates, respectively (eq 64).[207,208]



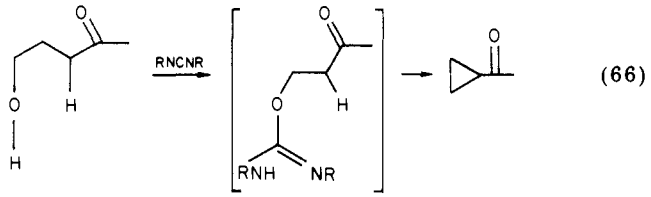
(64)

Carbodiimides of the group 4 elements are readily hydrolyzed or reacted with alcohols to yield cyanamide, its dimer, or melamine (eq 65).[209,210,211]

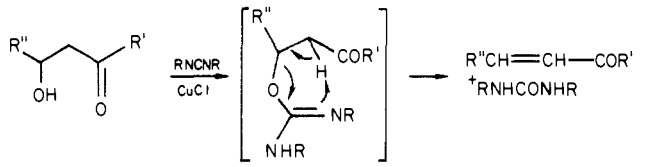
$$R_3MN{=}C{=}NMR_3 \xrightarrow{2R'H} 2R_3MR' + NH_2CN \text{ or } 0.5(NH_2C(NH)NHCN) \quad (65)$$

Carbodiimides react with alcohols to yield *O*-alkylisoureas. The reaction is carried out with the alkoxide,[212-214] without catalyst,[215-217] with copper salts as catalyst,[218-225] and with HBF_4,[226] $ZnCl_2$,[227] or Pd^{II} halides.[228] The product *O*-alkylisourea has been used in situ as an alkylating agent.[213,215-217,220] The alkylation of phenols with alcohols in the presence of carbodiimides has been shown to progress through the *O*-alkylisourea; ^{18}O-enriched alcohol transfers the isotopic label to the oxygen of the final urea product.[215]

Dicyclohexylcarbodiimide may be used as an intramolecular dehydration reagent for ketols (eq 66, 67).[229,230]

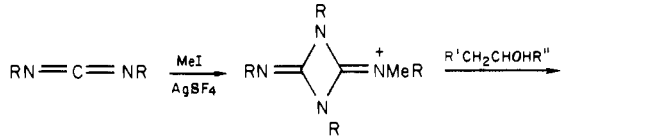


(66)



(67)

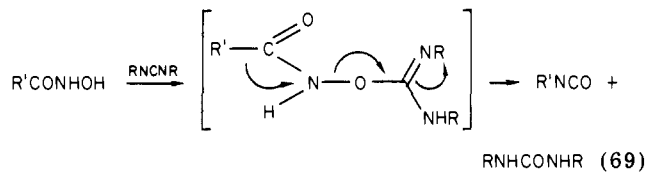
Carbodiimidium compounds[231] may also be used in alcohol dehydration (eq 68). The syn elimination in-



(68)

dicates the existence of an intramolecular pathway.[231a] Carbodiimides have also been used as dehydrating agents.[231b]

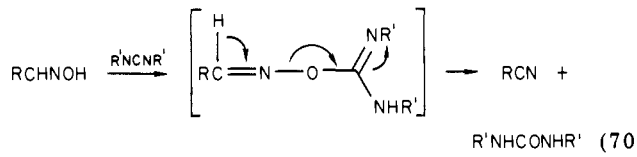
Addition of the alcohol portion of an hydroxamic acid



(69)

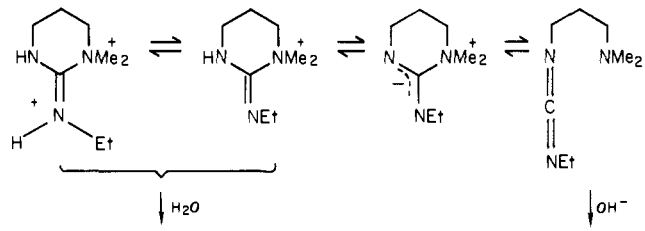
results in elimination with rearrangement to yield isocyanate (eq 69).[232]

Oximes eliminate water to yield nitriles (eq 70)[233]



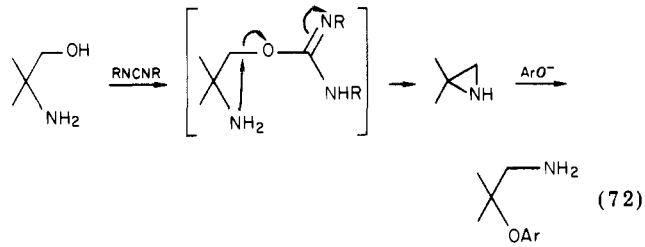
(70)

Comparison of the reactivity to hydrolysis of the water-soluble carbodiimide (1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide with that of the quaternary ammonium derivative indicates that the carbodiimide form is only involved in the hydroxide-catalyzed hydrolysis.[234] Hydrolysis at neutral and acid pH involves attack on the cyclic tautomer (eq 71).



(71)

Reaction of carbodiimide with 2-amino alcohols in the presence of phenolate ion leads to aziridine formation followed by alkylation of the phenol (eq 72).[235]



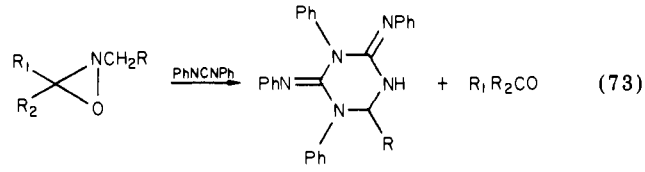
(72)

The epimerization reaction reported in the earlier review[2] has been extended to galactose.[236]

b. Nitrogen Nucleophiles

Reaction with amines to form guanidines in general requires no catalyst.[23-240] Tetrafluoroboric acid has been used as a catalyst for reaction with amines and hydrazines.[241] Piperidinylguanidines from 4-aminopiperidines and dicyclohexylcarbodiimides have been used as stabilizers for polymers.[239,240]

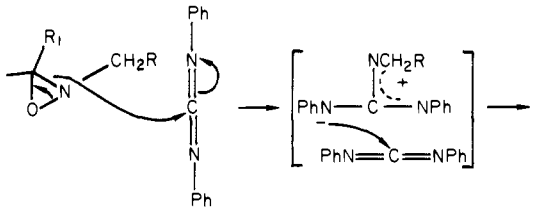
An interesting reaction occurs with the tertiary amine oxaziridine (eq 73).[242] The reaction is thought to in-

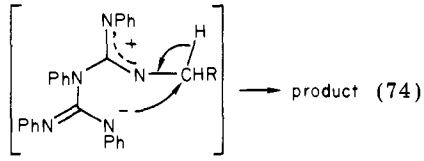


(73)

volve amine attack on the carbodiimide (eq 74),[242] but it is possible that the initial step involves a cycloaddition (eq 75) since the oxaziridine has marked π-bond character.

Nitrogen attacking as its anion is observed in the reaction of nitramine with dicyclohexylcarbodiimide.[243] Urea, nitrousoxide, and an olefin result (eq 76).





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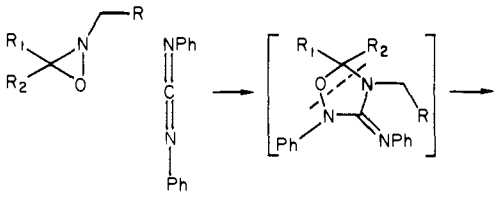

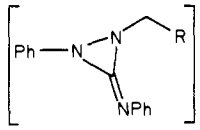

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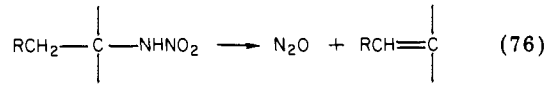
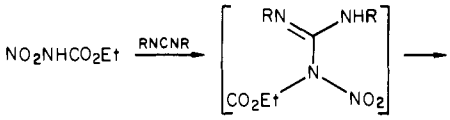
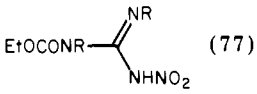


(76)

Other reactions with nitramine nucleophiles involve the formation of a nitroguanide from *N*-nitrourethane (eq 77),[244] presumably via an acyl-shift reaction from



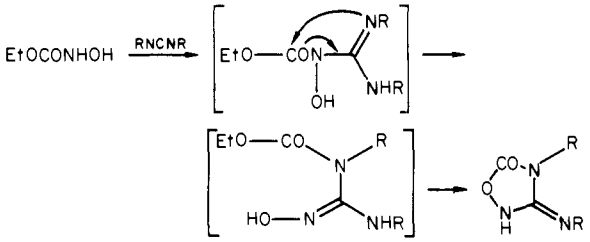


(77)

the initially formed adduct. *O*-Alkylhydroxylamines yield the corresponding oxyguanidines (eq 78),[245] and

$$NH_2OEt \xrightarrow{RNCNR} RNHC(NHR)NOEt \quad (78)$$

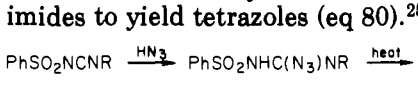
N-(ethoxycarbonyl)hydroxylamine yields a 1,2,4-oxadiazolin-5-one (eq 79),[246] probably through attack of

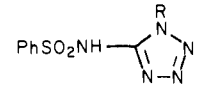


(79)

nitrogen on the central carbon followed by an acyl shift and a cyclization. Reactions of carbodiimides with other hydroxylamines are noted.[247-250]

Cyanoguanidines may be formed from cyanamide and carbodiimides.[251] Hydrazoic acid reacts with carbodiimides to yield tetrazoles (eq 80).[252] Reaction of carbodiimides with tosylazide is catalyzed by copper powder (eq 81),[253] and reaction with sulfonamides gives

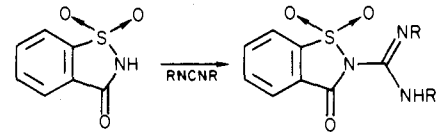




(80)

$$TsN_3 \xrightarrow[HCl]{Cu/RNCNR} RNHC(NTs)NHR \quad (81)$$

substituted guanidines (eq 82).[254] 1,2-Disubstituted

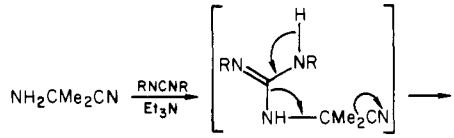


(82)

biguanidines may be prepared from carbodiimides and guanidine (eq 83).[255,256]

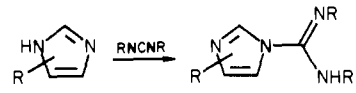
$$RNCNR \xrightarrow{NH_2C(NH)NH_2} NH_2C(NH)NHC(NR)NHR \quad (83)$$

Anilines react with carbodiimides to give the corresponding *N*-arylguanidine[257,258] and (dimethylamino)-acetonitrile reacts to give α-cyano-*N*,*N*'-dialkylformamidine, probably through an initial guanidine adduct (eq 84).[259] Imidazole and its derivatives react with



$$RNCNR + HCN + Me_2C{=}NH \longrightarrow RNC(CN)NHR \quad (84)$$

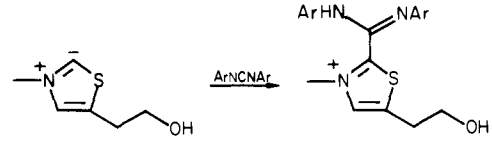
carbodiimides to the corresponding guanidine (eq 85).[260a] Polyguanidines have been prepared by the addition of biscarbodiimides with diamines.[260b]



(85)

c. Carbon Nucleophiles

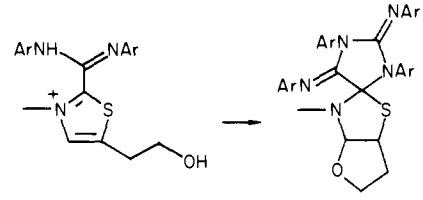
Carbon nucleophiles form C–C bonds with carbodiimides. Reaction with thiazolium salts yields a 1:1 adduct, presumably through the ylide (eq 86),[261] and a 1:2



(86)

adduct is obtained with concomitant saturation of the thiazoline ring (eq 87).

Similar addition reactions occur between indolizine, Meldrum's acids, and carbodiimides (eq 88 and 89).[262,263]



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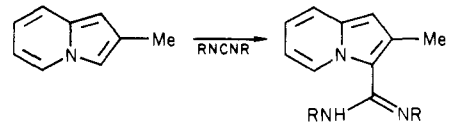

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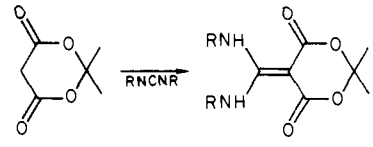


(89)

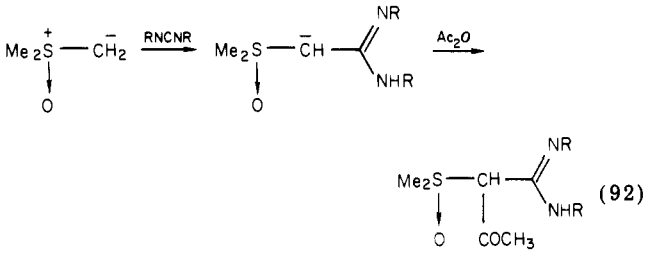
Grignard type reagents react with the central carbons of carbodiimides (eq 90).[264,265] A similar reaction is

$$R'Li(MgBr, ZnBr) \xrightarrow[2.\ H_2O]{1.\ RNCNR} RN{=}C(R')NHR \quad (90)$$

observed with alkylniobium(V) and tantalum(V) chlorides (eq 91).[286] Reaction of the dimethyl sulfoxide

$$R'_xMCl_{5-x}\ (M = Nb, Ta;\ x = 1, 2, \text{or } 3) \xrightarrow{RNCNR} MCl_4[RNC(R')NR]^- \quad (91)$$

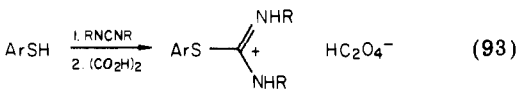
alkyl ylide yields a C–C bond with carbodiimides (eq 92).[267]



(92)

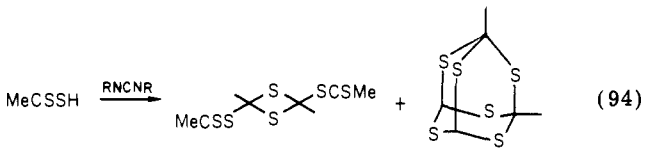
d. Sulfur Nucleophiles

Thiophenols react directly with carbodiimides to yield *S*-arylisothioureas (eq 93)[268] which may be conveniently



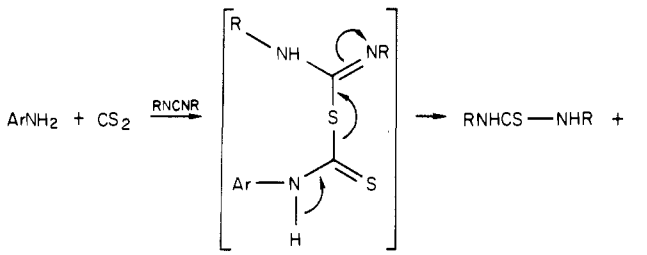
(93)

isolated as the oxalate salts. Reaction of monothiocarboxylic acids with carbodiimides yield the monothioanhydrides,[269] and dithioacetic acid yields *trans*-2,4-dimethyl-2,4-bis(thioacetylthio)-1,2-dithietane (eq 94).[270]



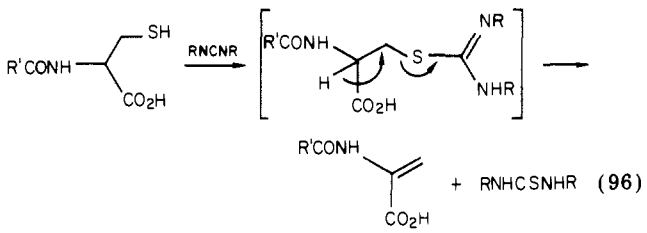
(94)

Dithiocarbamates from carbon disulfide and anilines undergo elimination of the elements of hydrogen sulfide to give isothiocyanates (eq 95).[271,272] Direct attack of



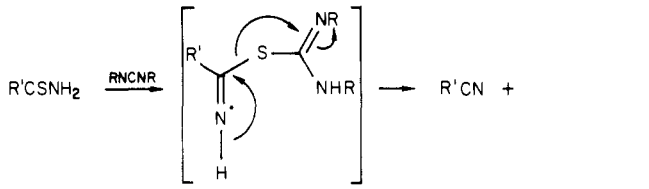
ArNCS (95)

thiol on carbodiimide is followed by elimination of thiourea if a suitably acidic β hydrogen is available (eq 96).[273] Thioamides react with carbodiimides to yield



(96)

the nitrile (eq 97).[274,275] Ammonium thiocyanate reacts with two molecules of carbodiimide to give thiourea and α-cyanoguanidine.[276]

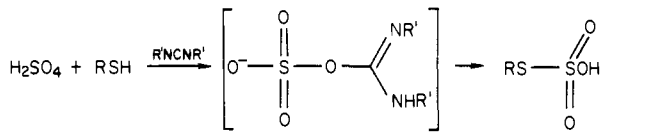


RNHCSNHR (97)

A further elimination reaction promoted by carbodiimides involves exchange with thioureas and provides a possible synthetic route to carbodiimides (limited by the favorability of the equilibrium constant) (eq 98).[275]

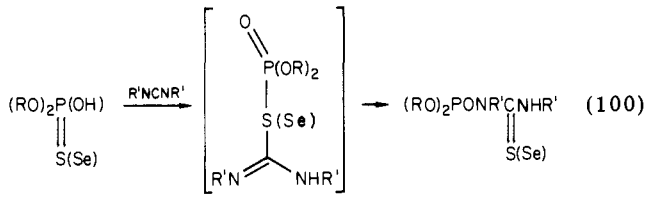
$$R'NHCSNHR'' \xrightarrow{RNCNR} R'NCNR'' + RNHCSNHR \quad (98)$$

The reaction of thiols with sulfuric acid in the presence of dicyclohexylcarbodiimide probably involves oxygen attack (eq 99)[277] rather than that of sulfur.



(99)

Phosphorothio(seleno)ic acid forms the *N*-phosphothio(seleno)urea via an isourea intermediate (eq 100)[278]

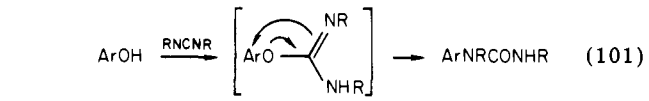


(100)

which has been detected by using low-temperature FT ^{31}P NMR spectroscopy. Adducts of phosphorodithioate and carbodiimides have been used as antioxidants.[279]

e. Phenols

Acidic phenols add to carbodiimides to give the *N*-phenylurea (eq 101).[280–282] Some acidic phenols yield



(101)

O-phenylisourea products,[283–289] and well-defined crystalline *O*-arylisoureas are obtained from pentachloro-[286,287] and 2,6-dichloronitrophenol.[283] It has been suggested that the bulky o-chloro substituents are involved in preventing the usual O→N shift in the latter compounds.[283] The *O*-arylisoureas from reaction of phenols with carbodiimide may be hydrogenolyzed over Pd/charcoal to yield the aromatic species (eq 102).[284]

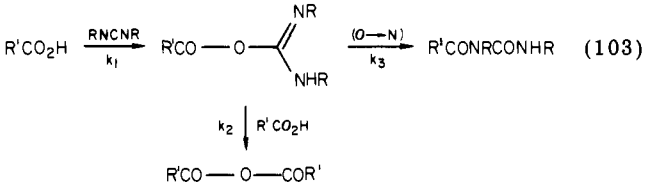
$$ArOH \xrightarrow{RNCNR} RNHC(NR)OAr \xrightarrow{H_2/Pd} RNHCONHR + ArH \quad (102)$$

Acetyltyrosine ethyl ester reacts with 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide to yield the *O*-arylisourea rather than the *N*-arylurea.[285] Picric acid yields *N*-arylurea with carbodiimide, although the

mechanism probably involves an *O*-arylisourea intermediate.[290]

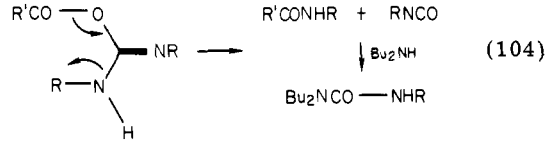
f. Carboxylic Acids

The reaction of carboxylic acids with carbodiimides is a very important precursor to the synthesis of peptide links. The kinetics of reaction of carbodiimides with mono- and dicarboxylic acids have been extensively investigated.[234,291-298] Reactivity, in general, increases with acid strength.[296] The reaction sequence involves formation of the anhydride through an *O*-acylisourea (eq 103) and is complicated by an O→N shift. A further complication in the sequence (eq 103) is the formation



(103)

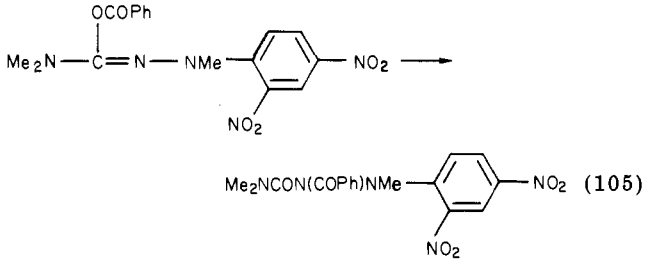
of an isocyanate (RNCO) from the intermediate probably via the mechanism of eq 104;[229] di-*n*-butylamine



(104)

was employed as a trap for the isocyanate (eq 104).[299]

Evidence for the *O*-acylisourea intermediate is sparse; phenols yield the *O*-phenylisourea, and by analogy it is reasonable that the intermediate is formed. An analogue of the *O*-acylisourea has been isolated, and the kinetics of decomposition to the *N*-acylurea have been studied (eq 105).[300] Intramolecular analogues of the

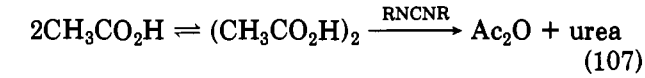


(105)

O-acylisourea have been prepared and their reactions investigated (eq 106).[301-303] Evidence for an *S*-phosphonylisothiourea has already been mentioned.[278]

The products of reaction of acetic acid with dicyclohexylcarbodiimide in acetonitrile and carbon tetrachloride are acetic anhydride, *N,N'*-dicyclohexylurea, and *N*-acetyl-*N,N'*-dicyclohexylurea.[304-306] The kinetics are interpreted according to (eq 103), and in acetonitrile the ratio $k_2/k_3 = 60\ M^{-1}$ and in carbon tetrachloride 400 M^{-1}. The order of reaction in carbon tetrachloride is slightly higher than unity in acetic acid concentration.

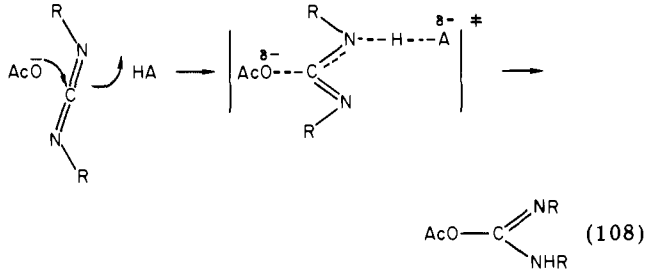
A mechanism (eq 107) involving reaction of acetic acid dimer with carbodiimide was postulated. The



(107)

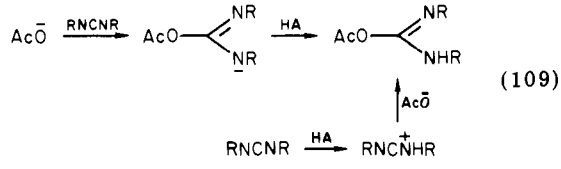
reaction in acetonitrile is slower than that in carbon tetrachloride, consistent with acetic acid being largely dimeric in the latter solvent. The possibility that an *N*-acetylurea is obtained from acetylation of the carbodiimide by acetic anhydride is excluded by control reactions.

Spectroscopic and kinetic evidence for the formation of *O*-acetylisourea has been obtained in the reaction of 1-ethyl-3-[3'-(trimethylammonio)propyl]carbodiimide perchlorate with acetate buffers.[298] The formation of intermediate is followed by monitoring the absorption at 250 nm when an increase followed by an exponential decay is observed.[298] Kinetics of formation of the intermediate and its decay were studied and the former shown to be general acid catalysed (eq 108).[298]



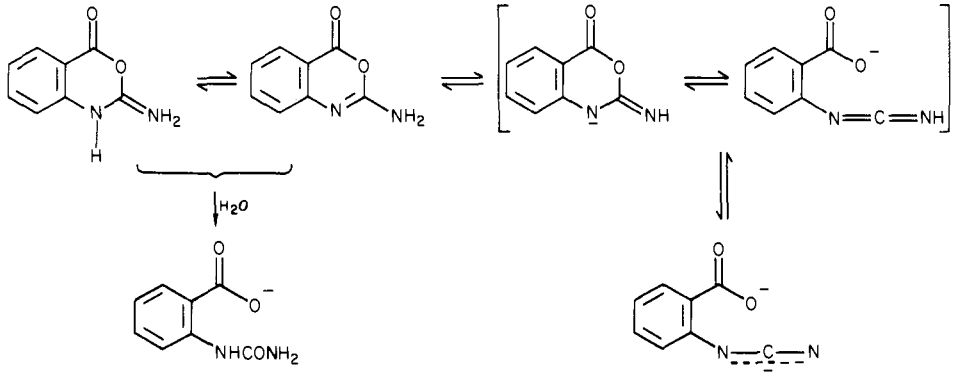
(108)

The existence of a concerted proton transfer in aqueous solutions is rationalized on the grounds that both stepwise mechanisms (eq 109) involve highly



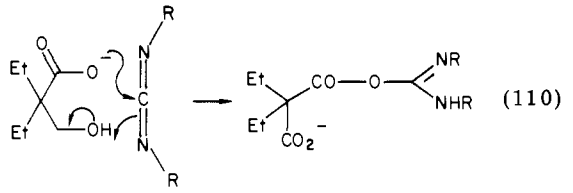
(109)

unstable charged intermediates and would give Brønsted α values of either 0 or −1.0 instead of the observed value ($\alpha = -0.67$).[298] The mechanism has particular relevance throughout carbodiimide chemistry, as the charged intermediates (eq 109) are even less likely to form in nonprotic solvents normally used in their reactions. Intramolecular proton transfer has been



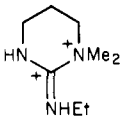
(106)

observed in the reaction of dicarboxylic acids with carbodiimides (eq 110).[298]



(110)

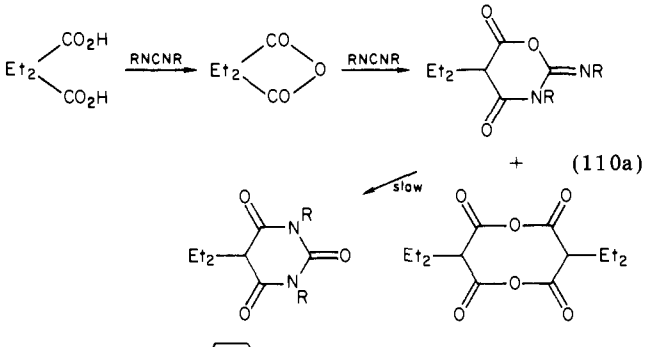
The water-soluble carbodiimide 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide has been shown to react with acetic acid through the cyclic tautomer XVII



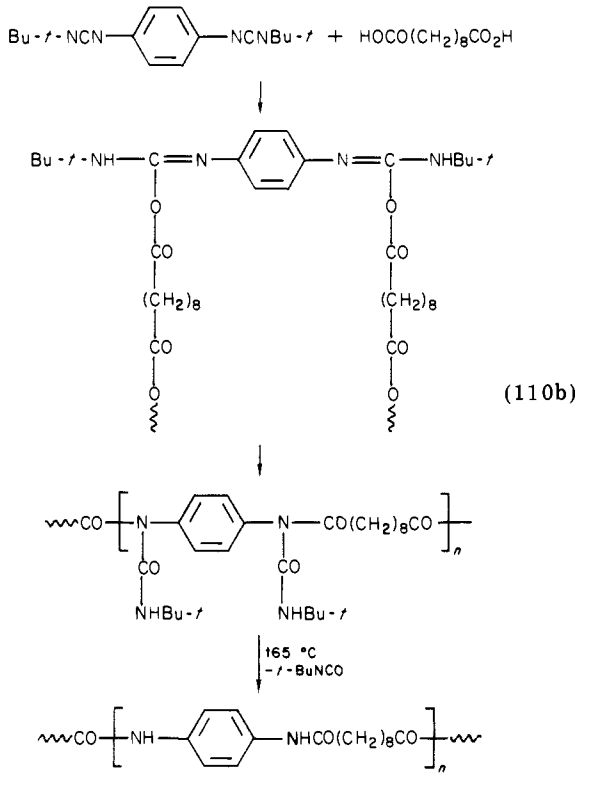
XVII

by comparison of the reactivity with that of the quaternary ammonium analogue 1-ethyl-3-[3-(trimethylammonio)propyl]carbodiimide.[234] This reaction pathway has relevance to the mode of action of the tautomeric carbodiimide as a modification agent for biological polymers.

Diethylmalonic acid anhydride has been detected spectroscopically in the reaction of the acid with dicyclohexylcarbodiimide (eq 110a).[307a]



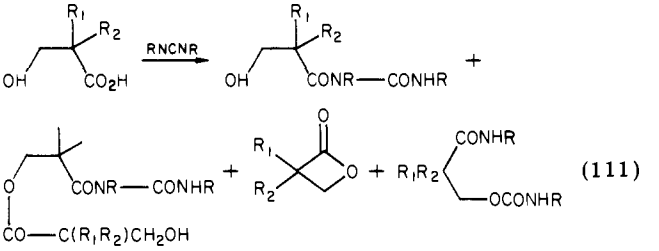
(110a)



(110b)

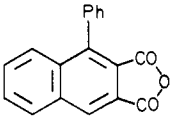
An interesting synthesis of a polymer is obtained from reacting a biscarbodiimide with dicarboxylic acids; the synthesis exploits the O→N acyl shift reaction (eq 110b).[307b]

Reaction of 2,2-disubstituted 3-hydroxypropionic acids with aliphatic carbodiimides in tetrahydrofuran yields a variety of rearranged products (eq 111).[308]



(111)

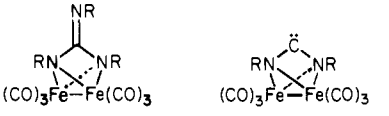
Phenylpropiolic acid undergoes a novel cyclization reaction in the presence of carbodiimide to yield 1-phenylnaphthalene-2,3-dicarboxylic anhydride by a mechanism which is not yet understood (XVIII).[309] The reaction is also initiated by acetic anhydride.[309]



XVIII

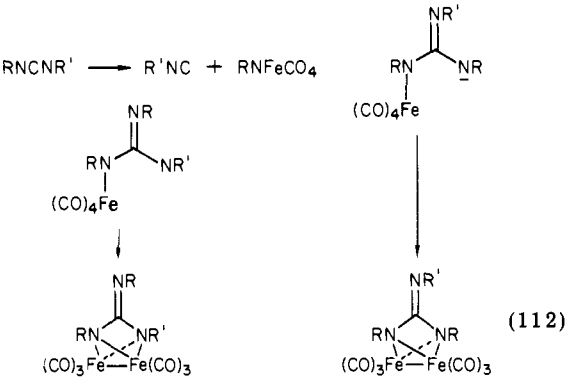
g. Reactions with Metals

There has been considerable work on the coordination of carbodiimides with iron pentacarbonyl to yield XIX.[310,311] Experiments using unsymmetrical carbo-



XIX XX

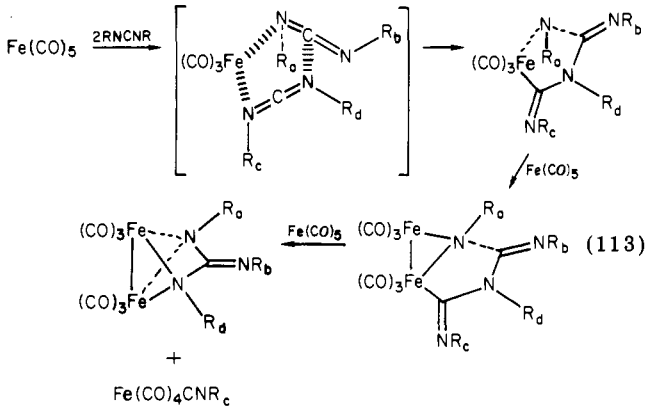
diimides[310] allow the exclusion of the symmetrical intermediate XX.[311] The observation that some dehydroguanidino complexes have both coordinated nitrogen bearing the same substituent is not consistent with the above intermediate, and a mechanism (eq 112) involving



(112)

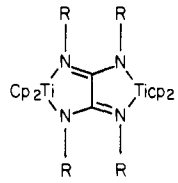
a metal–nitrene intermediate[310] is proposed. An alternative mechanism eliminates one-half of the carbodiimide unit as isocyanide in the form of a complex ($Fe(CO)_4CNR$) (eq 113).[312]

Carbodiimides may act as ligands to metals, and structures XXI[313] and XXII[314,315] have been confirmed by X-ray crystallography.

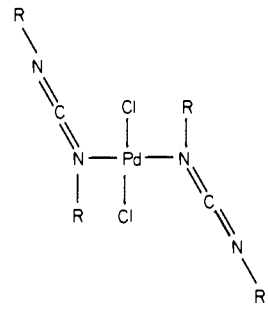


(113)

Reaction of chromium pentacarbonyl with diphenylcarbodiimide yields a product which possibly



XXI

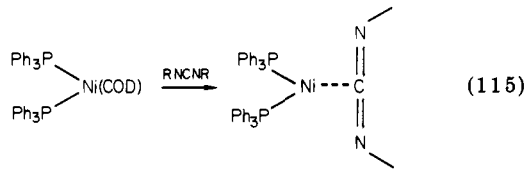


XXII

contains a metal–carbon bond;[316] reaction of phosgene with the product yields an isocyanide complex with liberation of phenyl isocyanate (eq 114).

$$\text{PhNCNPh} \xrightarrow{\text{Cr(CO)}_5} \text{Cr(CO)}_5\text{C(NPh)}_2 \xrightarrow{\text{COCl}_2} \text{PhNCO} + \text{(CO)}_5\text{CrCNPh} \quad (114)$$

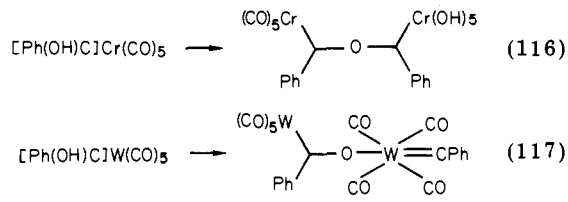
A further type of complex has been observed with a three-center bond (eq 115);[317] analogous complexes are



(115)

observed with isocyanates and ketenes.

Carbodiimides effect some interesting coupling reactions between metal complexes, in some cases attacking via the metal (eq 116[318] and 117[319]).



(116)

(117)

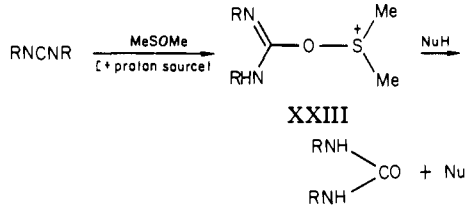
Simple displacement of ligands on group 4 carbodiimides has been observed (eq 118).[320a]

$$(Et_3SnN)_2C \xrightarrow{CuSO_4} Cu_2(NCN) \quad (118)$$

The formation of isocyanates from carbodiimides and CO_2 or CO has been claimed to be catalyzed by $RhCl_3$ and V_2O_5.[320b]

h. Reactions Involving Dimethyl Sulfoxide

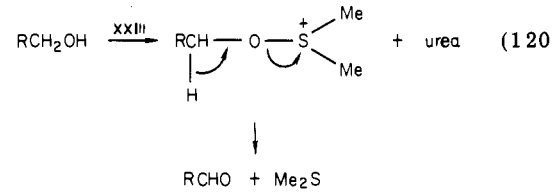
Dimethyl sulfoxide is thought to yield an electrophilic adduct with carbodiimide (XXIII, eq 119); this adduct



XXIII

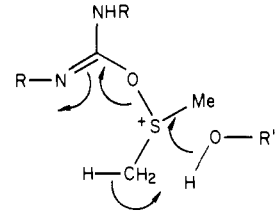
(119)

reacts with nucleophiles in a number of interesting and useful ways.[321,322] Probably the most important reaction is with an alcohol to give an intermediate which subsequently eliminates dimethyl sulfide to give an aldehyde or a ketone (eq 120). The reaction is selective

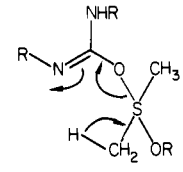


(120)

to yield the carbonyl derivative, and overoxidation does not occur.[321,322] The oxidation of 5α-lanost-8-en-3β-ol to 5α-lanost-8-ene-3-one does *not* involve allylic oxidation.[323] The mechanism is similar to the Pummerer reaction which utilizes dimethyl sulfoxide and acetic anhydride; the function of the carbodiimide is solely to provide a good leaving group. The mechanism of the transfer of the sulfur atom from the carbodiimide adduct probably involves intramolecular hydrogen transfer from the methyl group (XXIV or XXV) be-



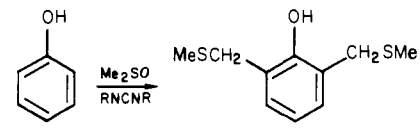
XXIV



XXV

cause fully deuterated dimethyl sulfoxide transfers *one* deuteron to the product urea.[324,325] A three-body mechanism postulated to account for the deuteron transfer[326] is probably not valid.[327]

Aromatic substitution at phenols has been observed with the dimethyl sulfoxide/carbodiimide reagent (eq 121).[328-332] The mechanism probably involves intra-



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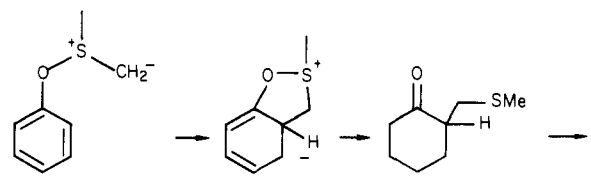
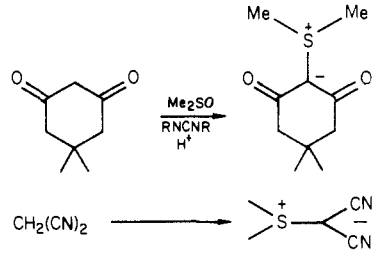


product (122)

molecular attack via an ylide (eq 122) rather than action of the methylenemethylsulfonium ion (CH_2=SMe^+);

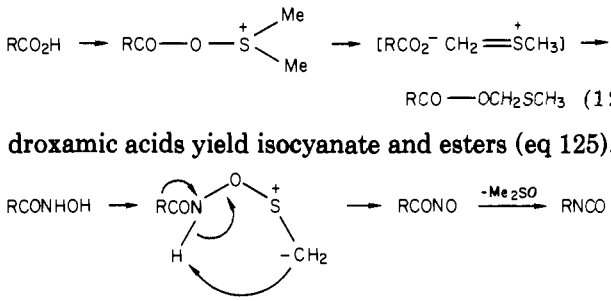
the latter sulfonium ion is thought to be involved in para substitution.[329]

Stabilized carbon nucleophiles yield sulfonium ylides (eq 123).[333] Carboxylic acids react with carbodiimide



(123)

and dimethyl sulfoxide to give esters (eq 124).[334] Hydroxamic acids yield isocyanate and esters (eq 125).[334]

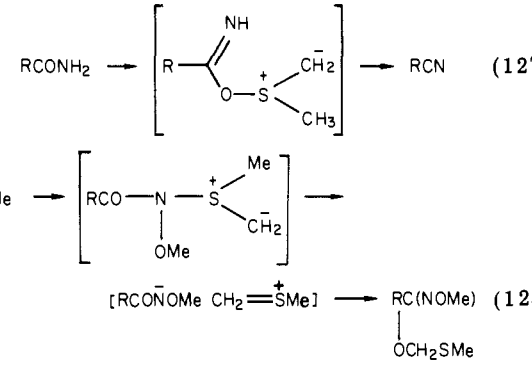


(124)

(125)

(126)

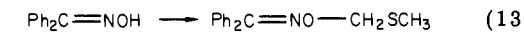
Amides yield nitriles (eq 127)[334] and O-methylhydroxamic acids give imino esters (eq 128).[334] Sulfonamides



(127)

(128)

react with Me_2SO/carbodiimide reagent to yield S–N ylides (eq 129).[254] Ketoximes yield *O*-alkyloximes (eq 130) and arylhydroxylamines yield azoxy aromatic species (eq 131).[335] Amines yield an S–N ylide with



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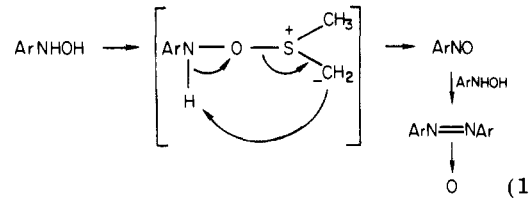
(130)

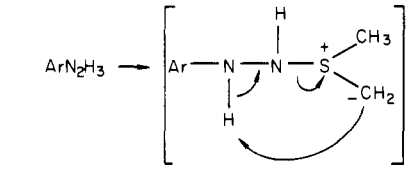


(131)

Me_2SO/carbodiimide reagent (eq 132)[336] and aromatic hydrazines undergo a complicated series of reactions (eq 133).[336]

The oxidation of carbohydrate derivatives is an obvious extension of the use of the mild and selective Me_2SO/carbodiimide reagent and has been extensively reviewed.[337-340]

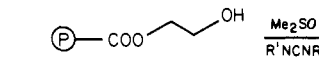
(132)



(133)

l. Solid-Phase Oxidations

Polymers with pendant or chain-incorporated carbodiimide groups have been prepared for action as solid-phase reagents in the oxidation of alcohols with Me_2SO.[341-344] Hydroxyalkyl methacrylate gels have been treated with Me_2SO/carbodiimide to yield a polymer gel to act as a carrier for biologically active compounds (eq 134).[345]

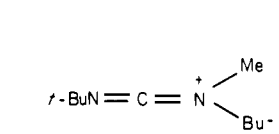


(134)

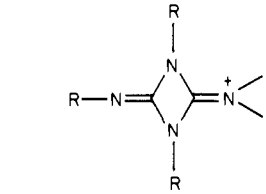
D. Reactions of Carbodiimide Involving the Nitrogen as a Nucleophile

a. Alkylation

Di-*tert*-butylcarbodiimide may be methylated to give *N*-*tert*-butyl-*N'*-butyl-*N'*-methylcarbodiimidinium iodide.[346-350] Only the highly hindered carbodiimides yield the monomeric species XVI. Less hindered carbodiimides form the dimeric type of product (XXVII).[231,347,348,350] Both products have been used as the basis for novel dehydrating reagents.



XXVI



XXVII

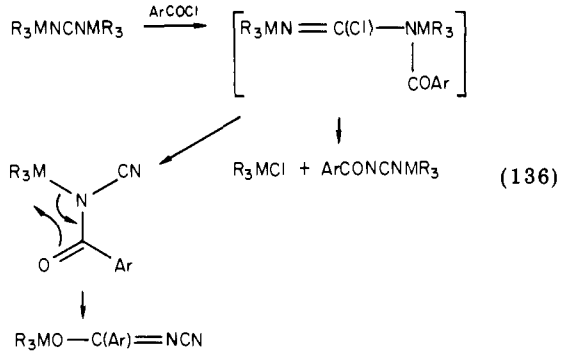
Group 4 element carbodiimides react with alkyl halides with the expulsion of the element already on the nitrogen as its halide (eq 135).[124,351-355] This reaction

$$PhNCNSiMe_3 \xrightarrow{CF_3CRClNSO} PhN{=}C{=}NCR(CF_3)NSO + Me_3SiCl \quad (135)$$

is the basis of the exchange method of carbodiimide synthesis (see earlier).

b. Acylation

Group 4 element carbodiimides react with "acidic" electrophiles such as halides or anhydrides to eliminate the group 4 element (eq 136).[356-361] Anthranil reacts with carbodiimide to yield a quinazoline by a novel reaction probably involving electrophilic attack on the carbodiimide nitrogen (eq 137).[362] Sulfenyl halides



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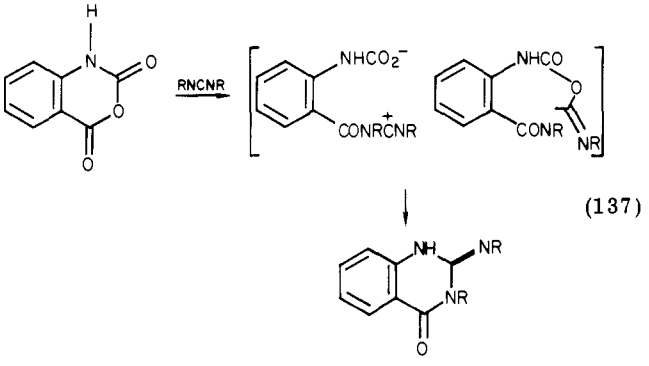
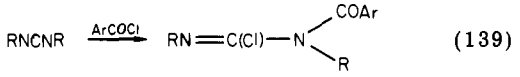


(137)

yield the expected sulfenylated carbodiimide (eq 138).[356]

$$BuNCNSiMe_3 \xrightarrow{R_2NSCl} BuNCNSNR_2 + Me_3SiCl \quad (138)$$

Alkyl- or aryl-substituted carbodiimides react with acyl halides to yield a chloroformamidine (XXVIII, eq 139)[363-365] which has been used as a reagent for re-



(139)

XXVIII

moving the elements of hydrogen sulfide from sulfur-containing species (eq 140–143).[363]

$$R'CSNH_2 \xrightarrow{XXVIII} R'CN + RNHCSN(COAr)R \quad (140)$$

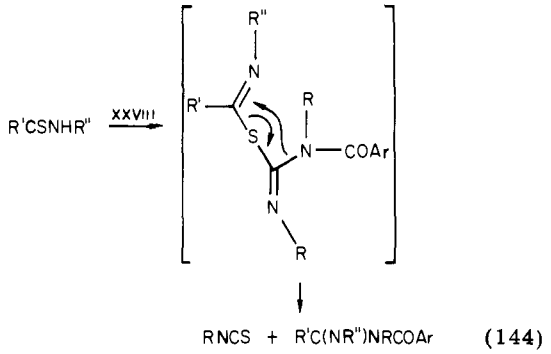
$$R'NHCSNHR'' \xrightarrow{XXVIII} R'NCNR'' \quad (141)$$

$$(EtSO_2)_2CCSNHR \xrightarrow{XXVIII} (EtSO_2)_2C{=}C{=}NR \quad (142)$$

$$HCSNHR \xrightarrow{XXVIII} RNC \quad (143)$$

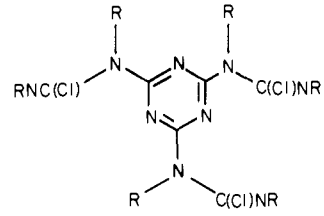
A further reaction of the chloroformamidine leads via a rearrangement to isothiocyanate (eq 144).[363]

Cyanuric chloride reacts with dicyclohexylcarbodi-



(144)

imide to give a chloroformamidine adduct (XXIX, R = cyclohexyl).[366]



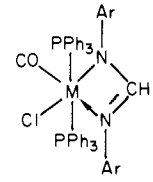
XXIX

E. Reduction

Direct formation of the formamidine from carbodiimides has been effected with sodium borohydride[367] trialkylsilanes in the presence of palladium or rhodium complexes (eq 145).[368,369] Ruthenium or osmium hy-

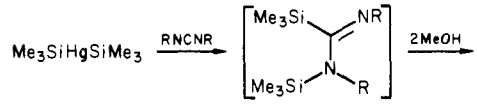
$$RNCNR \xrightarrow[PdCl_2]{Me_3SiH} [RN(SiMe_3)CH{=}NR] \xrightarrow{H_2O} RNH{-}CH{=}NR \xrightarrow{AcCl} RN(COMe)CH{=}NH \quad (145)$$

dride complexes react with diarylcarbodiimides to give diarylformamidinato complexes (XXX, M = Os or Ru).[370] Trimethylsilylmercury salts add to carbodi-



XXX

imide and the adduct on methanolysis yields the formamidine (eq 146).[371]



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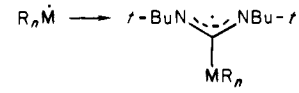
F. Miscellaneous Reactions

Radical addition to carbodiimides has been little studied; radicals attack the central carbon atom of di-*tert*-butylcarbodiimide to yield an unstable product (eq 147).[372]

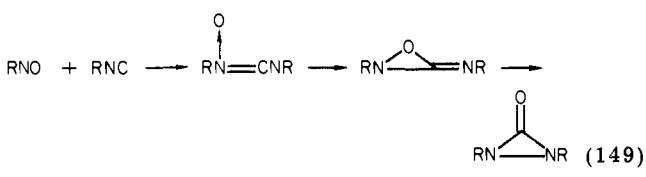


(147)

Ozonolysis yields as main products ketone, isocyanate, cyanamide, and oxygen (eq 148).[373] The

$$R_2CHNCNCHR_2 \xrightarrow{2O_3} R_2CHNHCN + R_2CHNCO + R_2CO + 2O_2 \quad (148)$$

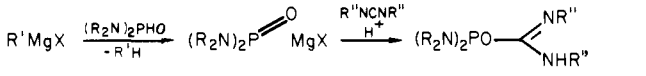
possible intermediacy of a carbodiimide *N*-oxide has been postulated in the reaction of nitroso groups and isocyanides, resulting in the formation of a diaziridinone (eq 149).[374,375] An isocyanate trapping agent diverts the product from diaziridinone.[375] Carbodiimides may also



(149)

be oxidized with 3-chlorobenzoyl peroxide[376] and hydrogen peroxide[377] to yield diaziridinone. Oxidation may be effected with trifluoroacetyl peroxide.[378]

Reaction with phosphorus as a nucleophile has been effected with a phosphorus magnesium salt (eq 150).[379]



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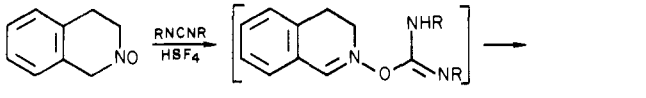
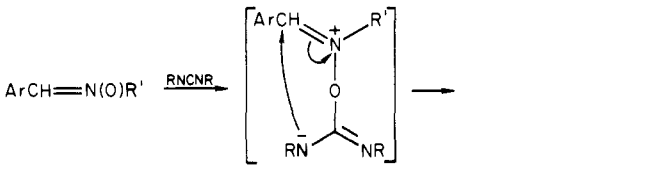
Nitrones react with carbodiimides in the presence of tetrafluoroboric acid catalyst (eq 151, 152; R = *t*-Bu).[380]



+ RNHCONHR (151)



RNCH(NR'Ar) + RNCO (152)

Protic reagents act on trimethyl silylcarbodiimides and germyl analogues to yield dicyanamide (presumably from the parent carbodiimide) (eq 153, 154; M = Ge, Si).[381-384]

$$Me_3SiNCNSiMe_3 \xrightarrow{BuSeH} Me_3SiSeBu + {}^1/_2(NH_2CN) \quad (153)$$

$$Me_3MNCNMMe_3 \xrightarrow{HNO_3} Me_3MONO_2 + {}^1/_2(NH_2CN) \quad (154)$$

V. Metal Insertion Reactions

Organometallic insertion reactions at the carbodiimide conform to the general reaction type proposed in Table V; the electrophilic component "E" is usually a proton but can be other functions such as RCO-. In the present case a family of reactions is reviewed where E = metal or metalloid species. Reviews of metal insertion reactions at heterocumulene derivatives have appeared,[385] and the carbodiimide reactivity is in general in the order carbodiimide > isocyanate > isothiocyanate.[385]

Insertion into boron compounds has been studied extensively and the following scheme elucidated for diarylcarbodiimides (eq 155).[386,387]

$$\begin{aligned} BCl_3 &\rightarrow ClB[NArC(NAr)Cl]_2 \\ RBCl_2 &\rightarrow RB[NArC(NAr)Cl]_2 \\ R_2BCl &\rightarrow R_2BNAr(NAr)Cl \\ R_2BX &\rightarrow R_2BNAr(NAr)X \quad (155) \\ R = RO;\ X &= NR_2, OR, SR \end{aligned}$$

Titanium(IV) amides and alkoxides insert into carbodiimides (eq 156).[388,389] Lead and tin compounds

$$\begin{aligned} Ti(NMe_2)_4 &\xrightarrow{ArNCNAr} (Me_2N)_2Ti[NArC(NAr)NMe_2]_2 \\ Ti(OR)_4 &\rightarrow (RO)_2Ti[NArC(NAr)OR]_2 \quad (156) \end{aligned}$$

undergo insertion reactions with carbodiimides (eq 157,[390] 158,[391,392] 159,[391,392] 160[393,394]).

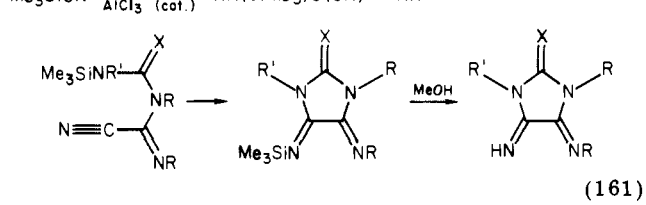
$$Ph_3PbOMe \xrightarrow{ArNCNAr} Ph_3PbNArC(NAr)OMe \quad (157)$$

$$Bu_3SnOMe \rightarrow Bu_3SnNArC(NAr)OMe \quad (158)$$

$$(Bu_3Sn)_2O \rightarrow Bu_3SnNArC(NAr)OSnBu_3 \quad (159)$$

$$Me_3SnNMe_2 \rightarrow Me_3SnNArC(NAr)NMe_2 \quad (160)$$

Trimethylsilyl cyanide reacts with carbodiimides in the presence of a catalytic amount of aluminum trichloride to give an insertion product which cyclizes (eq 161).[395,396]



(161)

The second reaction is, in effect, a further insertion and is followed by a ring-forming insertion. *N*-Benzoyl-*N'-tert*-butylcarbodiimides have been shown to react with silyl and germyl compounds to yield the respective insertion products.[397] Organomercury species react with carbodiimides to yield insertion products which decompose to isocyanides (eq 162).[398]

$$PhHgCCl_2Br \xrightarrow{RNCNR} [PhHg\text{–}NR\text{–}C(NR)CCl_2Br] \rightarrow RNCCl_2 + RNC + PhHgBr \quad (162)$$

Carbodiimides have been shown to insert into cuprous chloride. The product reacts with alcohols to yield *O*-alkylisoureas; the reaction scheme (eq 163)[399] probably accounts for the catalytic effect of copper salts on the reaction of alcohols with carbodiimides.

$$RNCNR \xrightarrow{CuCl} [CuNR\text{–}C(NR)Cl] \xrightarrow{R'OH} RNHC(OR')NR \quad (163)$$

Other examples of "metal" insertion reactions with carbodiimides and Grignard reagents have been discussed earlier.

VI. Formation of Heterocycles

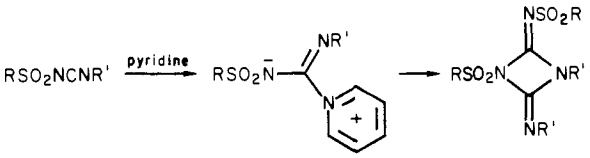
A. Cycloaddition Reactions

Cycloaddition reactions of carbodiimides are now very well documented and may occur to yield 1:1 or 2:1 adducts. The 1:1 cycloaddition may be concerted or stepwise (see Table V), and there is evidence for both pathways. Carbodiimides are involved in 1,2-, 1,3-, and 1,4-cycloaddition reactions.

a. Condensation with C=N

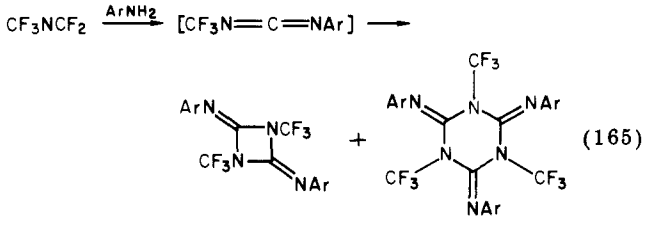
Self-condensation leads to dimers and trimers. The dimerization of a sulfonylcarbodiimide is catalyzed by

pyridine through an addition complex, probably a zwitterion (eq 164).[400]



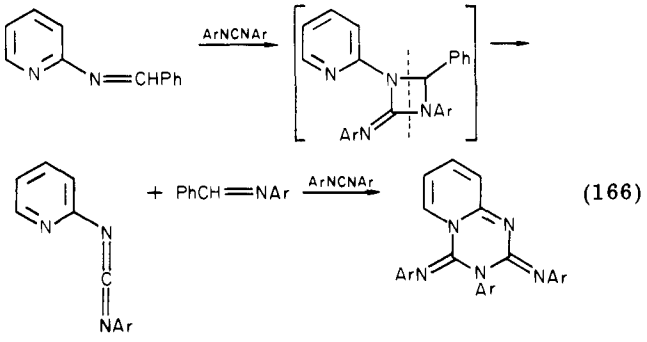
(164)

Recent work on the alkylation of carbodiimides has indicated[401,402] that unless both the nitrogens in the carbodiimide possess very bulky groups such as *tert*-butyl the product is the diazetidinium ion rather than the linear alkylated species (see structures XXVI and XXVII and ref 231, 347, 348, and 350). Dimer and trimer are obtained in the synthesis of *N*-aryl-*N*-(trifluoromethyl)carbodiimides from aniline and perfluoroazapropene (eq 165);[403] the carbodiimide is too



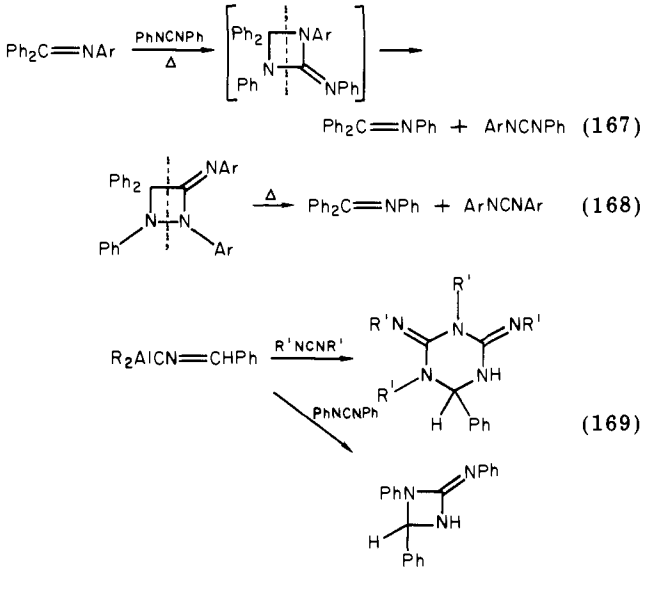
(165)

unstable to isolate. Azomethines undergo cycloaddition with carbodiimides with the expulsion of the *transferred* group (eq 166).[404]



(166)

Evidence has been provided for an imine–carbodiimide 1,2-cycloaddition adduct from the nature of the disproportionation products of the coupling in eq 167.[405]



(167)

(168)

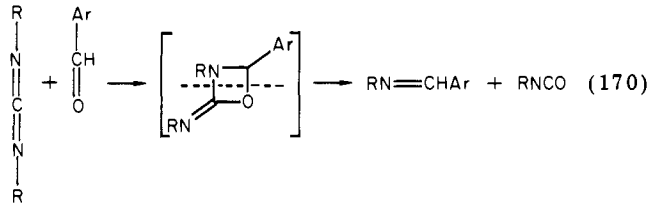
(169)

An interesting retro cycloaddition from a 1,2-diazetidine imine is reported (eq 168).[406]

There is a report of the synthesis of the diphenylcarbodiimide using tri-*n*-butylphosphine catalyst[406] and of the cycloaddition of carbodiimide to *N*-benzylidenealuminium amides (eq 169).[407]

b. Condensation with C=O

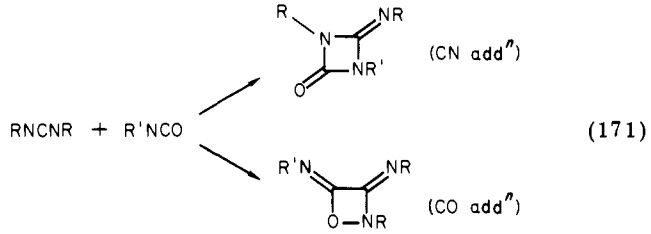
Carbodiimides react with aromatic aldehydes to yield isocyanates and the corresponding imine (eq 170).[408]



(170)

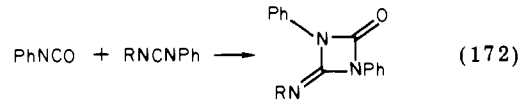
c. Condensation with Isocyanates

Condensation (1:1) with isocyanates involves a regioselectivity problem where CN or CO addition takes place (eq 171). The oxaazetidine product has not been



(171)

reported, and it is thought that the diazetidines (uretidinones) are the major products (eq 172).[409]



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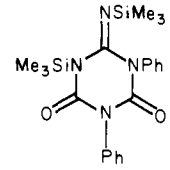
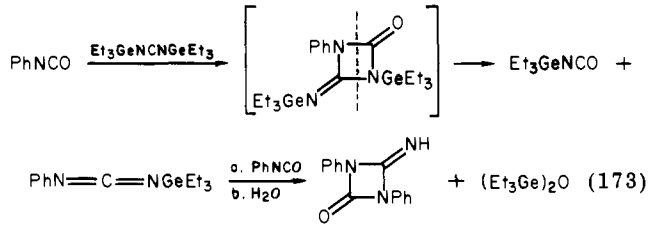
Phenyl isocyanate reacts with (trimethylsilyl)carbodiimides to yield the 2:1 cyanurate product (XXXI),[410]



XXXI

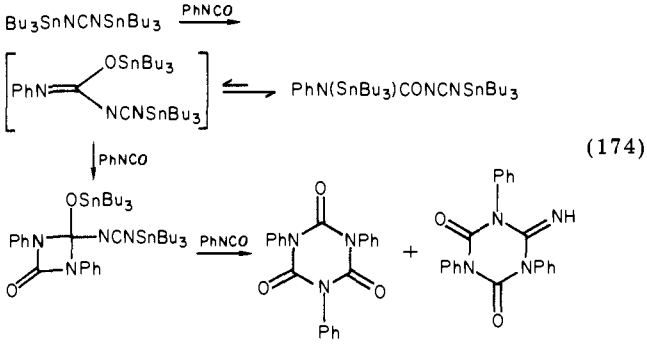
but with (triethylgermyl)carbodiimide exchange occurs, presumably through the uretidinone, and further cycloaddition and hydrolysis results in a 1,3-diphenyluretidinone (eq 173).[410]



(173)

Phenyl isocyanate inserts into (tributylstannyl)carbodiimide and the CN product cycloadds to a further isocyanate molecule to yield a 2:1 uretidinone derivative

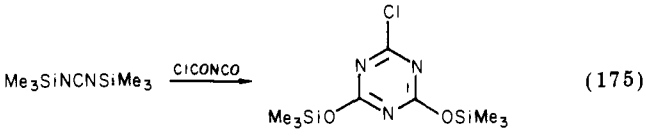
(eq 174).[411] Yet further phenyl isocyanate gives the 3:1 cyanurate (eq 174).[411]



(174)

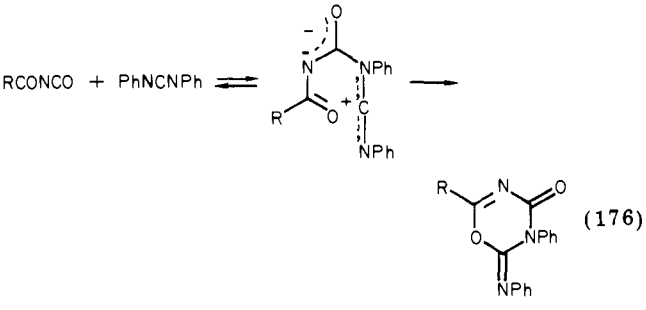
d. Condensation with Acyl Isocyanates

A 1,3 cycloaddition occurs between chloroformyl isocyanate and bis(trimethylsilyl)carbodiimide to yield the chlorotriazine (eq 175)[412] in 64% yield. Other acyl



(175)

isocyanates react to give oxadiazinones presumably via a zwitterionic intermediate (eq 176).[413,414]



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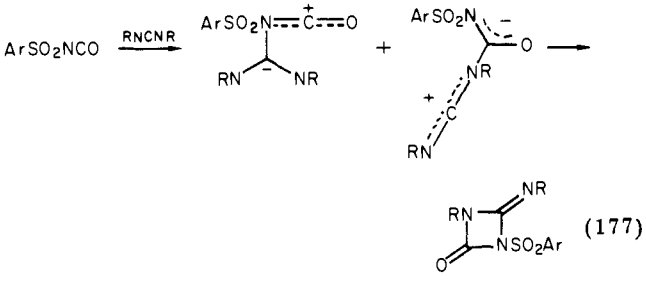
e. Condensation with Sulfonyl Isocyanates

Evidence has been advanced for the stepwise addition of sulfonyl isocyanates to carbodiimide (eq 177).[415,416]

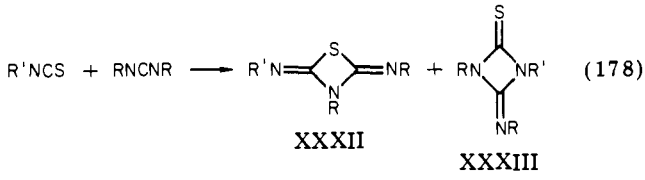


(177)

Infrared absorption peaks at 1869 and 1724 cm^{-1} appear on addition of carbodiimide to isocyanate[415,416] followed by their slow disappearance. Addition of tolyl isocyanate to *N*-*tert*-butyl-*N'*-methylcarbodiimide results in a shift in the *N*-methyl NMR signal from 2.9 to 3.32 ppm; this signal slowly decays and is replaced by new ones at 2.9 and 3.6 ppm. The acyclic intermediate consistent with these observations may be intercepted by a dipolarophile to yield a six-membered heterocycle, and this is the basis of the synthesis of several triazine derivatives.[417-419]

f. Condensation with Isothiocyanates

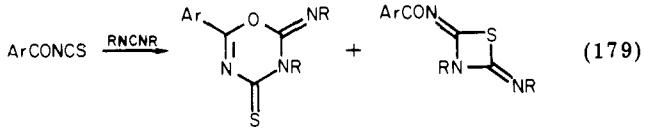
The regioselectivity in the addition of carbodiimides to isothiocyanates in the 1:1 stoichiometry results in thiazetidine formation (XXXXII)[420-423] as well as the diazetidinethione (XXXIII)[424,425] (eq 178). Benzoyl



(178)

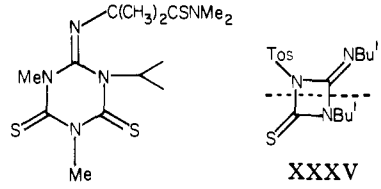
XXXII XXXIII

isothiocyanates add to carbodiimides to yield thiazetidine and 1,3,5-oxadiazine (eq 179)[426] in a 1,2- and



(179)

1,4-cycloaddition, respectively. The cycloaddition of methyl isothiocyanate to *N*-isopropyl-*N'*-((*N*,*N*-dimethylthiocarbamoyl)dimethylmethyl)carbodiimide yields a triazine (XXXIV) derivative which is shown

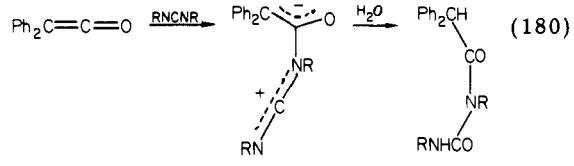


XXXIV XXXV

to have a boat conformation.[427] *tert*-Butylcarbodiimide and tosyl isothiocyanate interact to yield *tert*-butyl isothiocyanate and tosyl-*tert*-butylcarbodiimide, presumably through the diazetidinethione XXXV.[428]

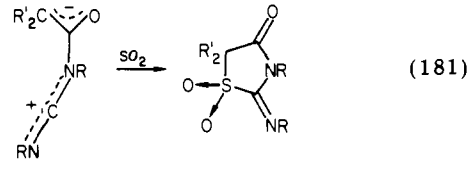
g. Condensation with C=C

Ketenes react with carbodiimides to yield a variety of products. The evidence that there is an acyclic intermediate in the reaction with diphenylketene is that quenching the reaction with water yields an acyclic amide (eq 180).[429] In sulfur dioxide as solvent the



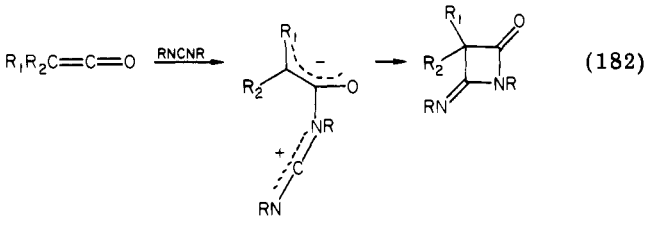
(180)

reaction is diverted to a thiazolidinone *S*,*S*-dioxide (eq 181).[430-432] In the absence of dipolarophiles the cor-

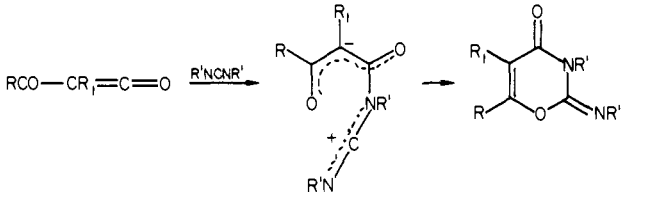


(181)

responding azetidinone is formed (eq 182).[433-439] Regioselectivity to yield the oxaazetidine is not observed. Reaction of acylketenes with carbodiimides has been shown to yield the aminooxazinone, presumably by intramolecular trapping of an intermediate zwitterion (eq 183).[440]

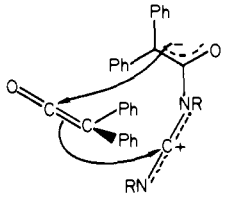


(182)



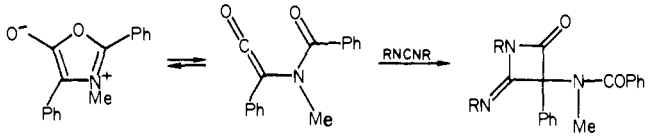
(183)

Addition of diphenylketene with carbodiimides in a 2:1 ratio has not been observed,[441] probably due to steric inhibition of the bulky adduct to a bulky dipolarophile (XXXVI).



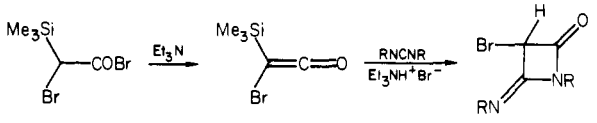
XXXVI

The reactivity of mesoionic 5-oxazolone with carbodiimides is probably due to the small equilibrium percentage of ketene (eq 184).[437] Carbodiimide traps the



(184)

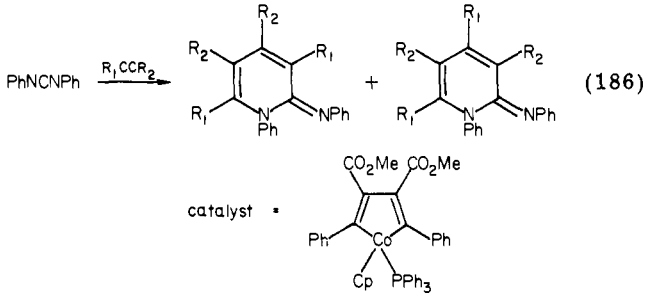
ketene from the interaction of base with (trimethylsilyl)bromoacetyl bromide (eq 185)[438a] and that from the



(185)

interaction with chloroacetyl clorides.[438b]

Cycloaddition of acetylenes with carbodiimides to yield pyridine derivatives is catalyzed by cobalt complexes (XXXVII) (eq 186).[442,443] The reaction is also catalyzed by nickel(0) complexes such as $(Ph_3P)_2NiC_2H_4$.[444]

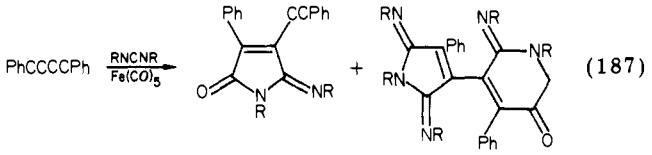


(186)

XXXVII

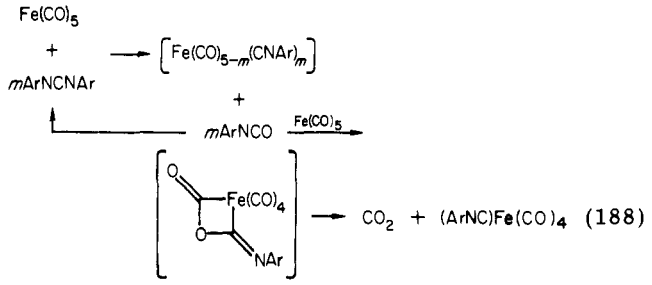
(Cp = cyclopentadienyl)

Iron pentacarbonyl catalyzes the addition of carbodiimide across diphenylbutadiyne to give iminopyrrolidin-2-ones and 2,5-bisaryliminopyrrolines (eq 187).[445] The complex $RCN{\cdot}Fe(CO)_4$ is also obtained,

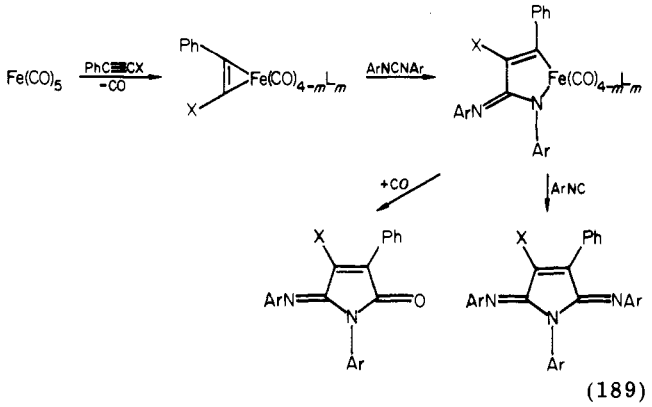


(187)

but in small yield, and the mechanism is thought to be as in eq 188 and 189.[445,446] Reaction of X (as —C≡



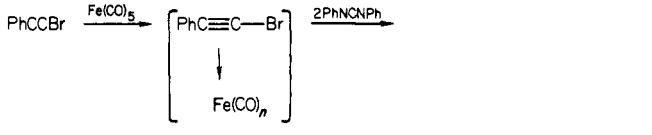
(188)



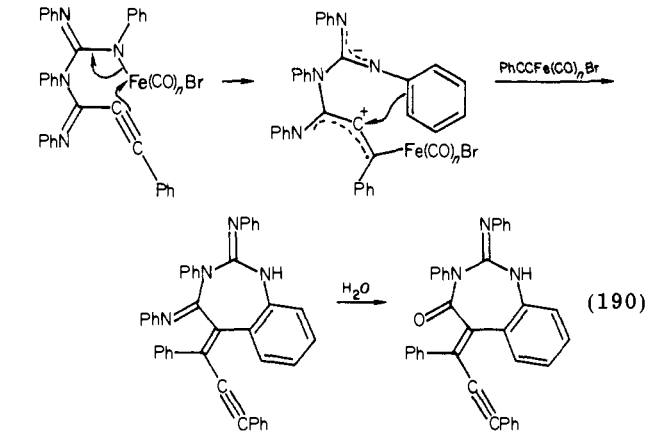
(189)

C—Ph) in eq 189 with further ArNCNAr and $Fe(CO)_5$ gives the bis(pyrroline).

Phenylacetylene bromide with diphenylcarbodiimide in the presence of iron pentacarbonyl yields benzodiazepinone (eq 190).[442] The diyne is produced via the acetylene adduct (XXXVIII) which reacts with carbodiimide to give the benzodiazepinimine (XXXIX); the



XXXVIII



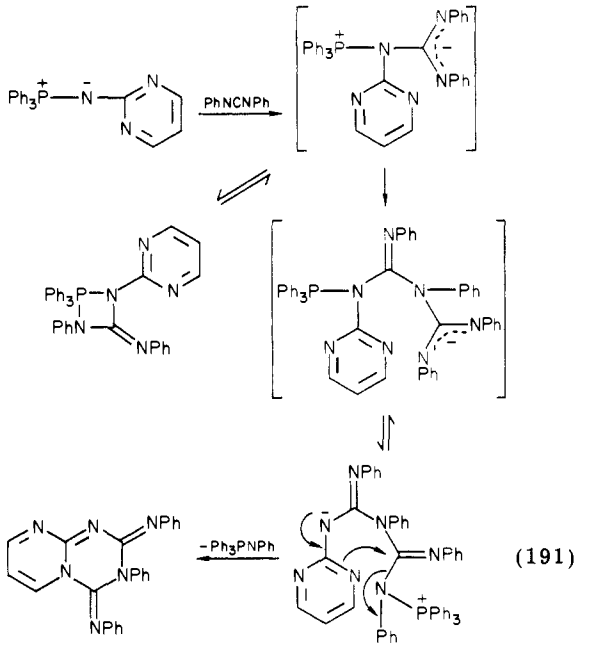
(190)

XXXIX XL

latter undergoing hydrolysis on work up with water to yield the benzodiazepinone (XL).[447]

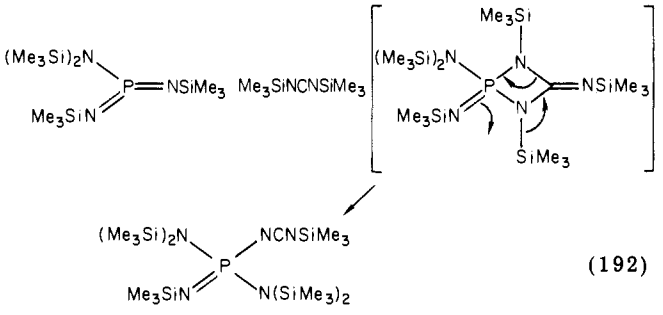
h. Condensation with PN and PC

The ylide Ph_3PNR adds to diphenylcarbodiimide (eq 191)[448,449] via zwitterionic intermediates. Tetrakis(tri-



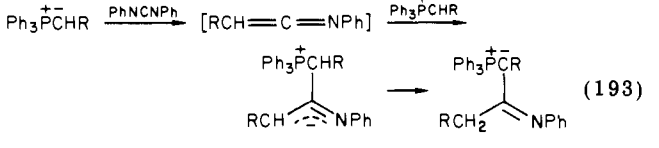
(191)

methylsilyl)aminodiiminophosphorane reacts with bis(trimethylsilyl)carbodiimides to yield phosphocarbodiimides through cycloaddition (eq 192).[450] The



(192)

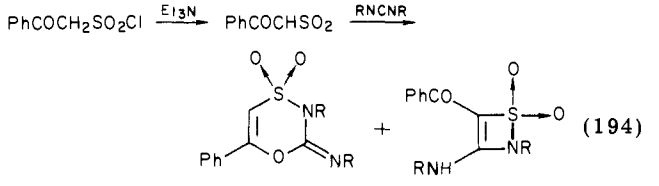
"Wittig" reagent (Ph_3PCHR) acts on diphenylcarbodiimide to yield an iminophosphorane after a cycloaddition reaction to form a ketenimine (eq 193).[451]



(193)

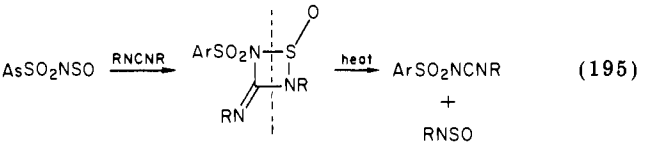
i. Miscellaneous Cycloaddition Reactions

Sulfenes produced by the action of tertiary amine base on sulfonyl chlorides are trapped by carbodiimides to give four- and six-membered heterocycles (eq 194).[452] Nonactivated sulfenes do not undergo cycloaddition with dialkylcarbodiimides. *N*-Sulfinylamines yield



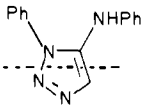
(194)

thiadiazetidine *S*-oxides which may be split by heating to yield the transferred carbodiimide (eq 195).[428,453]



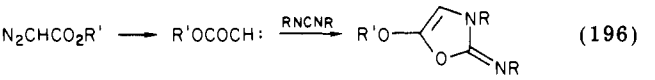
(195)

Reaction of carbodiimides with diazoalkanes can involve 1,3-addition to yield a 1,2,3-triazole (XLI)[454] or



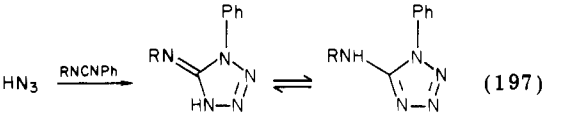
XLI

nitrogen may be eliminated in the diazoester case to give an iminooxazoline (eq 196);[455-457] the reaction is



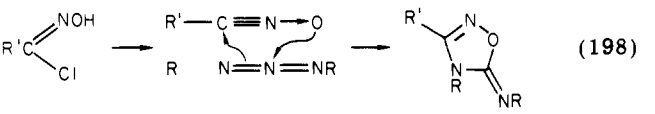
(196)

catalyzed by copper triflate and may involve a carbene. Aminotetrazoles are formed from hydrazoic acid and carbodiimidees (eq 197).[458-460]



(197)

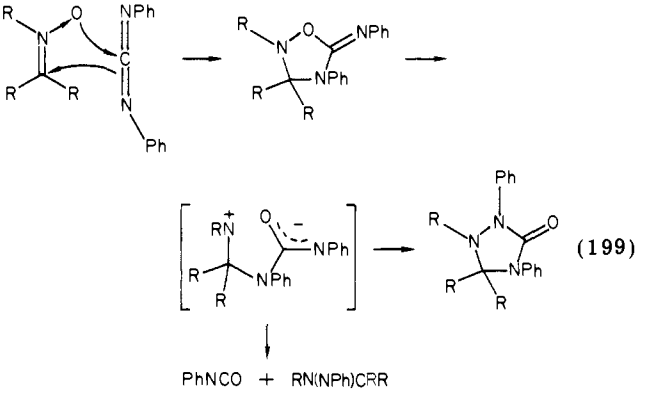
The addition of the C–N–O unit to carbodiimides yields isoxazoles; hydroxamoylchloride reacts to give the nitrile oxide which then adds to the carbodiimide (eq 198).[461] Nitrones act similarly, but the oxadiazolidine



(198)

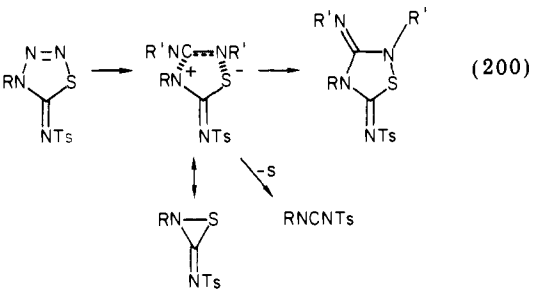
product rearranges to a triazolidinone (eq 199).[462a]

1,2,3,4-Thiatriazoline yields a 1,3-dipole which reacts



(199)

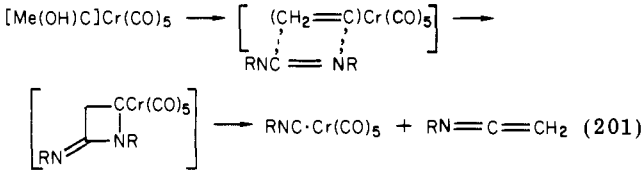
with carbodiimide to give an iminodithiazolidine (eq 200).[462b-465] In the absence of carbodiimide sulfur is



(200)

also extruded to yield a carbodiimide.[514,515] Trapping experiments are not conclusive for the thiaziridinimine intermediate.

Pentacarbonyl(hydroxymethylcarbene)chromium(0) reacts with dicyclohexylcarbodiimide, possibly through the dehydrated species (eq 201), to yield the isonitrile complex and ketenimine.[466]



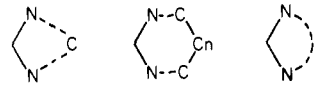
(201)

B. Incorporation of Carbodiimides into Heterocycles

In this section we review the synthesis of heterocycles where carbodiimide is incorporated in the ring. The carbodiimide nucleus has been found to incorporate all three atoms, two, or only one in the ring, and the chapter is divided accordingly. We shall not deal with those syntheses yielding four-membered heterocycles where these result from cycloaddition reactions as these are covered in the previous section; there is of necessity a little overlap between the sections.

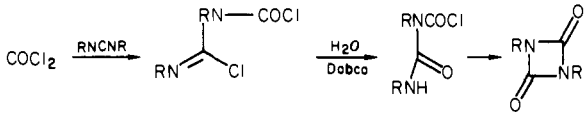
a. Full Incorporation

Heterocyclic syntheses involving full incorporation have been noted for systems such as XLII and XLIII.



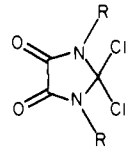
XLII XLIII XLIV

An example of XLII involves the interaction of phosgene with carbodiimide in acetone to yield a chloroformamidine which cyclizes in the presence of diazabicyclooctane (Dabco) to give a 1,3-dialkylazetidinone (eq 202).[467]



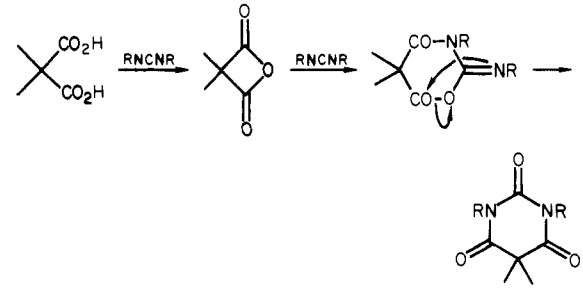
(202)

Oxalyl chloride yields 2,2-dichloroimidazoline-4,5-diones with carbodiimides (XLV).[468,469]

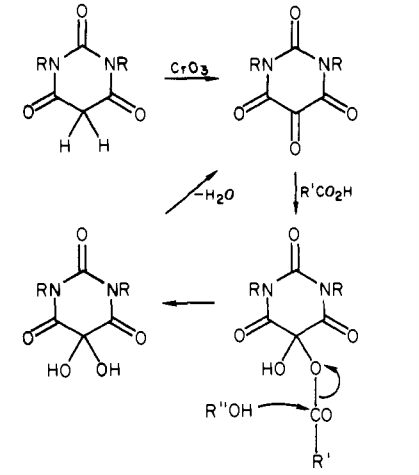


XLV

Malonic acids react through the scheme represented by XLIII (n = 1) to yield alloxans.[470,471] It is thought that the carbodiimide first dehydrates the malonic acid;[471] the anhydride then acylates the carbodiimide in the usual way and the acyclic intermediate presumably is further dehydrated by extra carbodiimide (eq 203). The alloxan product has been utilized as a coupling agent for ester formation (eq 204).[471]

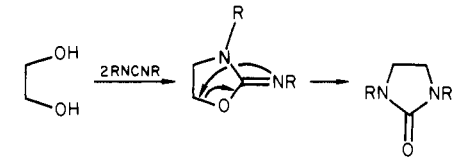


(203)



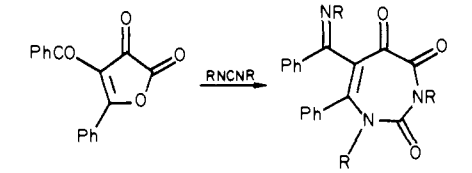
(204)

Diols yield iminooxazolidines with carbodiimides in the presence of CuCl catalyst. The products rearrange to give imidazolidinones (eq 205).[472,473] Tetrahydro-



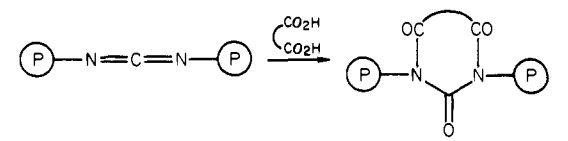
(205)

diazepinetriones may be prepared through interaction of carbodiimides with furandione (eq 206).[474] Poly-



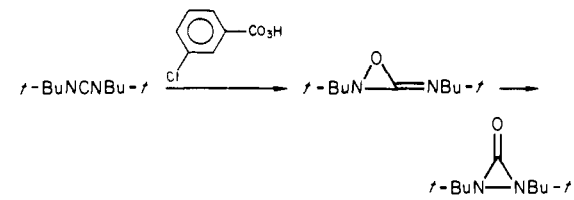
(206)

ureides have been prepared from polycarbodiimides through reaction with dicarboxylic acids at 100–160 °C (eq 207).[475] Diaziridinones (XLIV) are prepared by



(207)

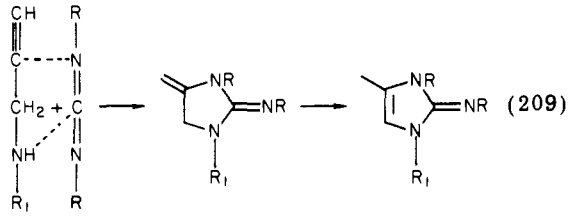
peracid oxidation of carbodiimides possibly through an oxyaziridine imine (eq 208).[476]



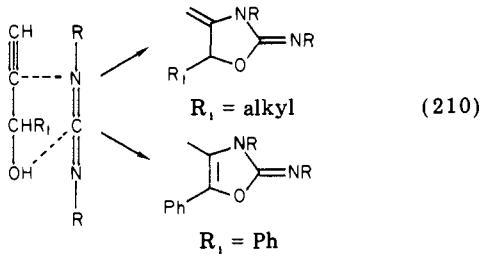
(208)

b. Incorporation of CN

Table VII illustrates schematically the synthetic schemes which have been noted. Coupling of CCN and CCO with carbodiimides yields alkylimidazolines (eq 209)[476] and oxazolidines (eq 210),[477] respectively.

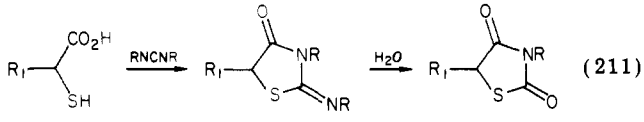


(209)



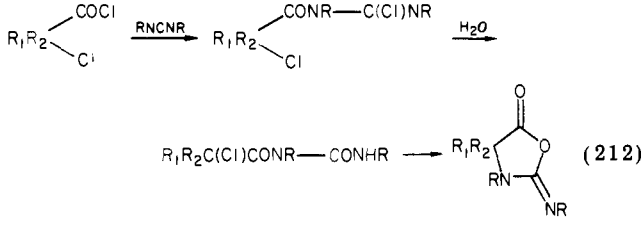
(210)

Thioglycolic acid gives thiazolidinones and thiazolidinediones with carbodiimides (eq 211).[478] Reaction



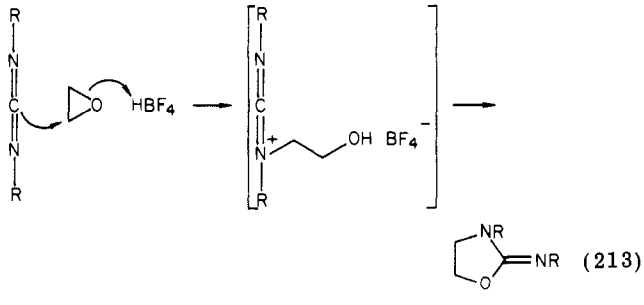
(211)

of carbodiimide with halo acid chloride (in the absence of base) yields an *N*-acylchloroformamidine which cyclizes to a 5-oxazolidinone (eq 212).[479] Tetrafluoroboric



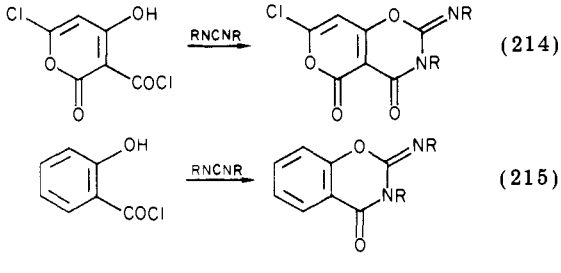
(212)

acid catalyzes the addition of epoxides to carbodiimide, possibly through ring opening (eq 213).[480]



(213)

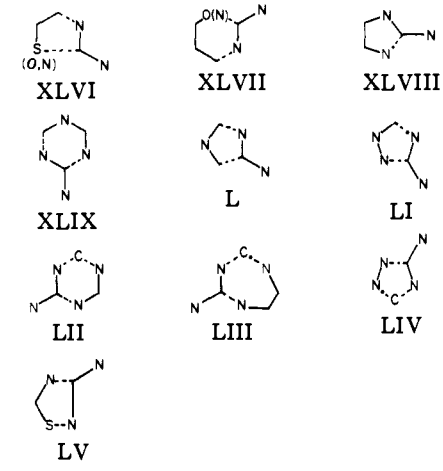
1,3-Benzoxazines may be synthesized through XLVII from 2-hydroxyaroyl halides and carbodiimides (eq 214, 215).[481,482] Similar products are obtained from 2-



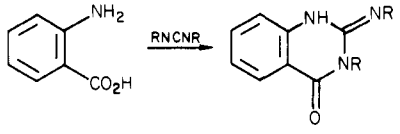
(214)

(215)

TABLE VII. Schemes for Incorporation of C-N of Carbodiimide into Heterocycles

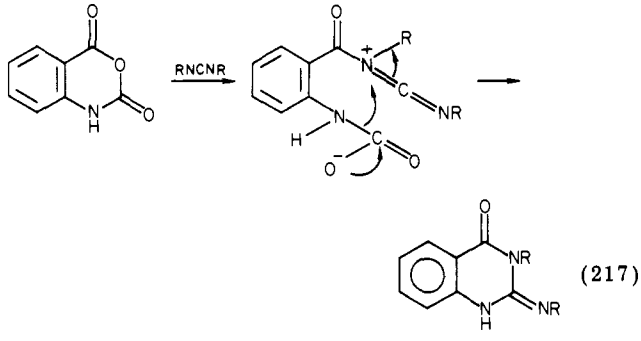


hydroxycarboxylic acids, and these are probably formed through the anhydride.[483,484] Quinazolines may be prepared through XLVII by the interaction of anthranilic acid and carbodiimide (eq 216).[485] Synthesis



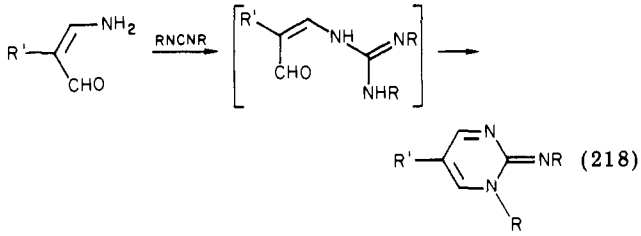
(216)

of a quinazoline through isatoic anhydride may involve acylation of the carbodiimide at nitrogen as a first step (eq 217).[486]



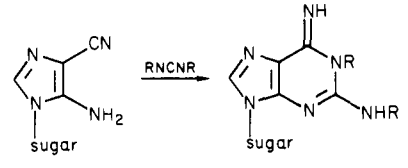
(217)

Pyrimidine derivatives may be synthesized through interaction of carbodiimide and β-aminovinyl compounds (eq 218).[487] The purine, 2,6-diaminonebularine,



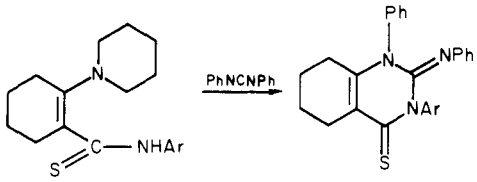
(218)

has been prepared from a 4,5-aminocyanoimidazole (eq 219).[486] Cyclohexene enamines react with diphenyl-



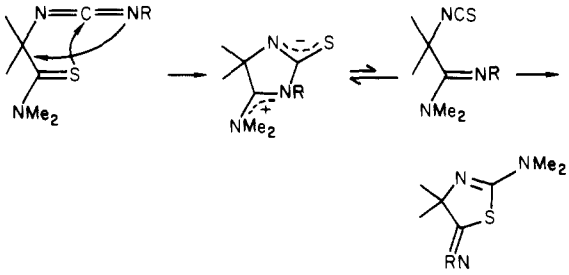
(219)

carbodiimide to give pyrimidine derivatives through XLVII (eq 220).[489] Intramolecular formation of thia-



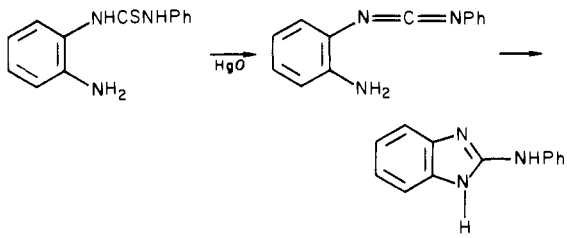
(220)

zolidines and oxazolidines has been carrried out through XLVIII (eq 221);[439] reaction is thought to proceed



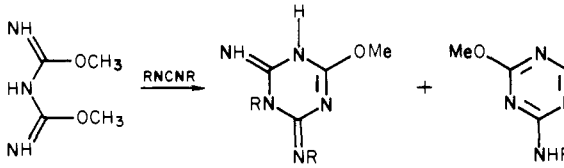
(221)

through the isothiocyanate. Benzimidazoles have been synthesized from thiourea through carbodiimide (eq 222).[490]



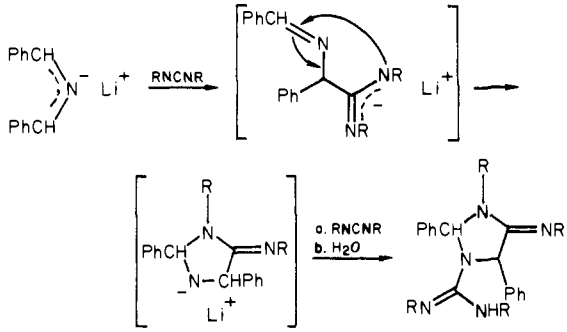
(222)

Thiazines may be synthesized through XLIX from dimethyl iminobiscarbimidate (eq 223).[491]



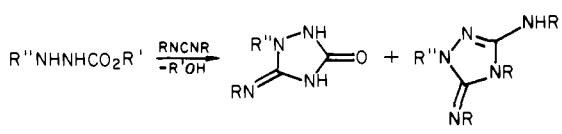
(223)

L has been reported for the synthesis of an imidazoline species (eq 224)[492] from carbodiimides and (1,3-diphenyl-2-azaallyl)lithium.



(224)

There has been considerable activity in heterocyclic syntheses through L. The NNC moiety in these syntheses is a hydrazide grouping, and the reactions are illustrated below; 1,2,4-triazolidines result (eq 225,[493] 226,[494] and 227[495-497]).



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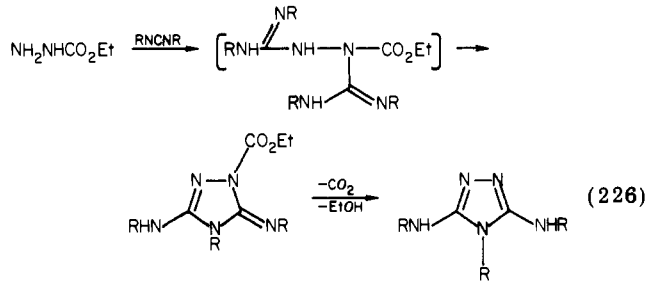

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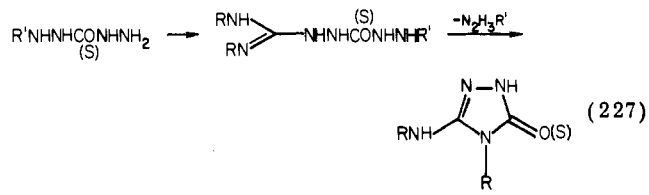
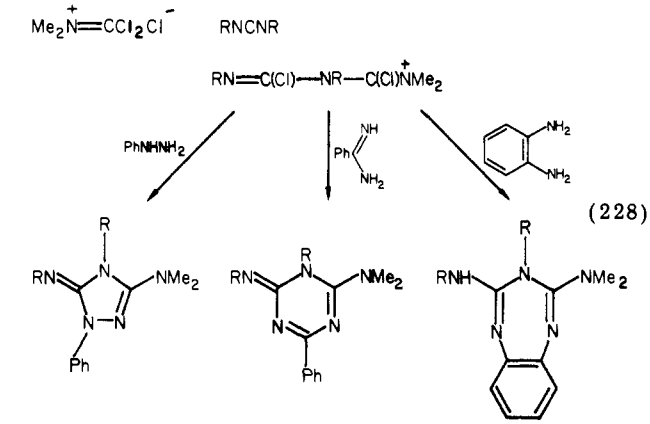


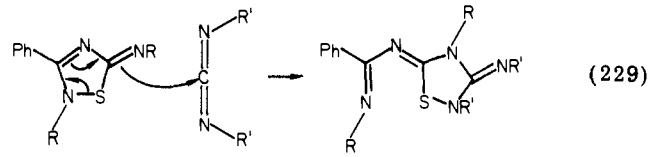
(227)

Examples of LII–LIV have been reported.[498] The carbon element comes from phosgeneiminium salts (eq 228).



(228)

Reaction of 5-imino-Δ^3-1,2,4-thiadiazolines with carbodiimide is an example of a synthesis using LV (eq 229).[499]

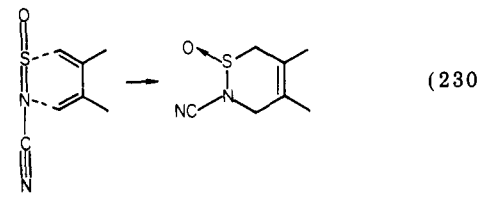


(229)

c. Incorporation of One Element

The schemes of Table VIII have been observed for incorporation of one element from the carbodiimide skeleton. The atom involved is usually C but can be N.

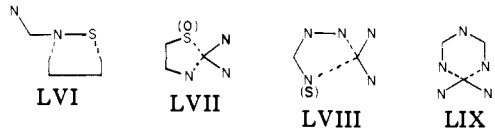
LVI is observed in the explosive decomposition of a mixture of thionyl cyanamide with 2,3-dimethylbutadiene to give a six-membered adduct (eq 230).[500]



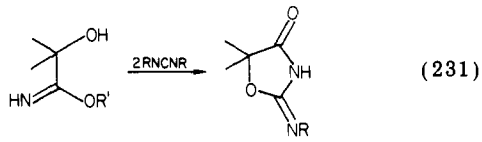
(230)

LVII is involved in the synthesis of iminooxazolidinones (eq 231)[501] catalyzed by Cu_2Cl_2. The reaction path probably involves an *O*-alkylisourea as an intermediate since the reaction is copper catalyzed. Reaction of am-

TABLE VIII. Schemes for Incorporation into Heterocycles One Element from the Carbodiimide Skeleton

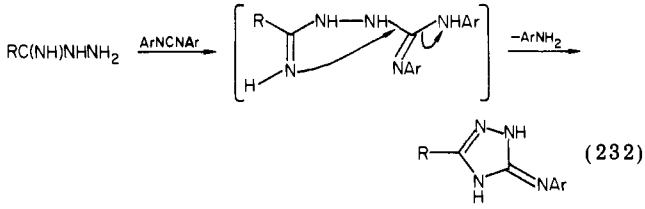


LVI LVII LVIII LIX



(231)

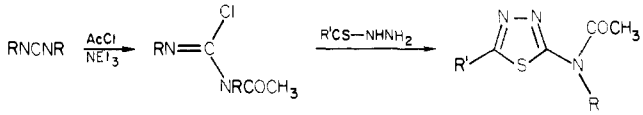
idrazones with carbodiimide follows LVIII to yield 3-substituted 5-(arylamino)-1,2,4-triazoles (eq 232).[502,503]



(232)

Dimethyl iminobiscarbimidate reacts with diarylcarbodiimides via LIX to yield triazines (eq 223).[491]

1,3,4-Thiadiazoles may be prepared by the interaction of acetylated carbodiimides with thioacylhydrazides (LVIII, eq 233).[504]



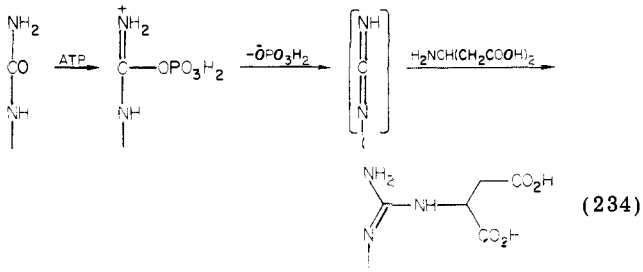
(233)

VII. Carbodiimides in Biological Chemistry

A. General

The synthetic usefulness of carbodiimides was first recognized because of their application to peptide and nucleotide chemistry; other biological properties were not very well-known at the time of the previous comprehensive review,[2] and only five references were recorded of work directly related to physiology. It has since been recognized that carbodiimides may play a role as effectors in biology other than that of synthetic tools, for example, as protein-modifying agents or as site-directed modifiers.

The carbodiimide moiety has never been postulated as an intermediate in biological transformations; however, it is probable, in view of previous work on ElcB mechanisms,[505] that carbodiimides play a role in the urea cycle reactions. The synthesis of arginine from citrulline ATP and argininosuccinate synthetase is likely to involve a carbodiimide (eq 234).



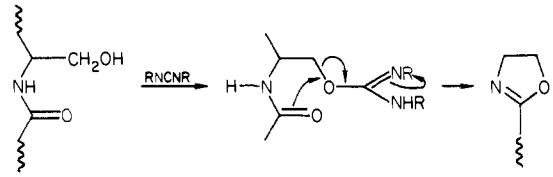
(234)

argininosuccinic acid

It is, however, unlikely that the carbodiimide would enjoy a free existence but would most probably be bound in an enzyme complex.

B. Modification and Inactivation of Proteins and Enzymes

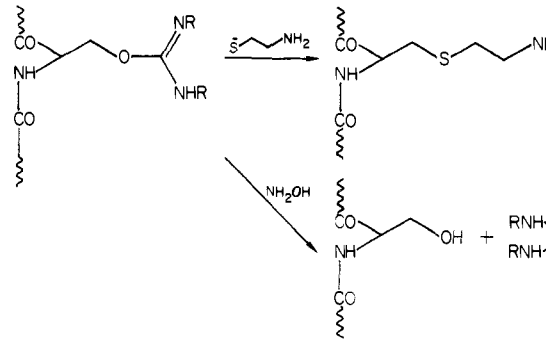
Proteins carry a normal complement of reactive groups and therefore will react with carbodiimides largely in the same fashion as with simple nucleophiles (see earlier). α-Chymotrypsin has been inactivated with a water-soluble carbodiimide which reacts with the active-site serine (residue 195) (eq 235).[506] The *O*-



(235)

Ser-195

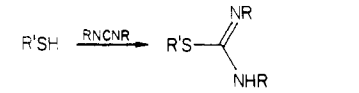
acylisourea also reacts with cysteamine (eq 236) and hydroxylamine (eq 237); the inhibition is analogous to that caused by cyanate and isocyanate.[507]



(236)

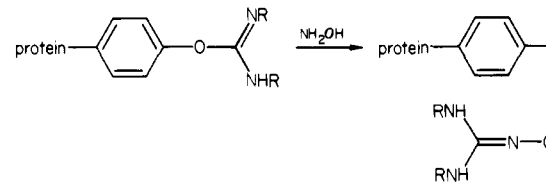
(237)

Protein thiol groups react with water-soluble carbodiimides;[508-510] papain is modified at residue cysteine-25,[508] and the free thiol group of buckwheat α-glucosidase is protected (eq 238).[509]



(238)

Tyrosine residues may be modified by carbodiimides,[285,511] and the inactivation of yeast hexokinase is reversed by hydroxylamine which presumably forms the *N*-hydroxyguanidine (eq 239).[511]



(239)

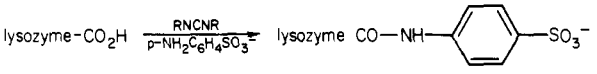
For the possibility of other pendant groups reacting with carbodiimides (e.g., imidazoles, amines), see the section on chemical properties.

C. Modification of Carboxyl Groups in Proteins

Carboxyl groups may be modified by using carbodiimide and a nucleophile such as an amine. Glycinamide has been attached to the carboxyl groups of cell walls to remove the negative charge (eq 240).[512] Radioactive

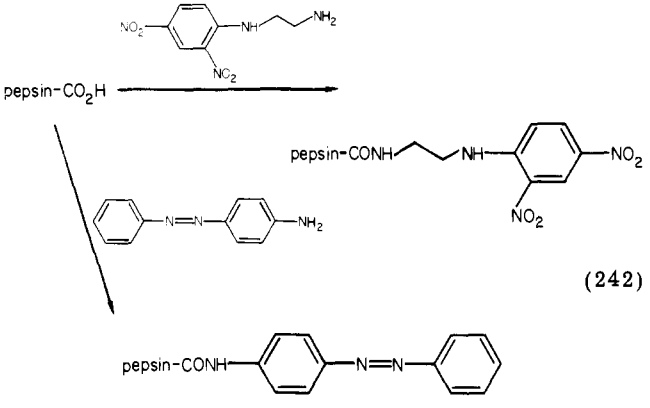
$$\text{cell wall-}CO_2H \xrightarrow[NH_2CH_2CONH_2]{RNCNR} \text{cell wall-}CONHCH_2CONH_2 \qquad (240)$$

glycine has been used to label carboxyl groups in blood coagulation Factor VIII through carbodiimide[513] and glycine ethyl ester or *N*-(2,4-dinitrophenyl)diaminoethane have been coupled to carboxyl groups in rabbit muscle phosphorylase.[514] The carboxyl groups of lysozyme have been modified with glycine[515] and sulfanilic acid (eq 241).[516]



(241)

Pepsin has been coupled to colored hydrophobic amines (eq 242).[517] Reaction of yeast hexokinase with

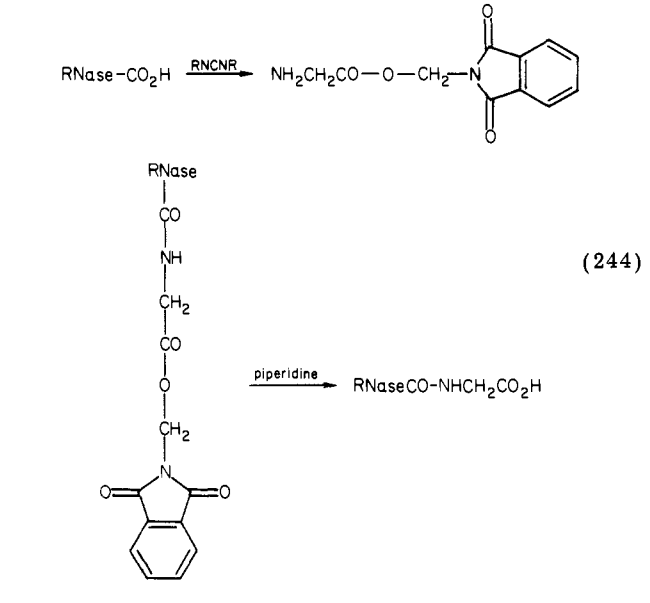


(242)

nitrotyrosyl ethyl ester and carbodiimide gives inactive protein when two carboxyls have been modified.[518] Modification of bovine collagen fiber with carbodiimide and diaminoethane as a cross-linking agent leaves the fiber structure unchanged.[519] Exposed aspartyl and glutamyl residues in proteins may be converted to asparaginyl and glutaminyl residues with carbodiimide and ammonia (eq 243).[520]

$$R'CH_2CO_2H \xrightarrow[NH_3]{RNCNR} R'CH_2CONH_2 \qquad (243)$$

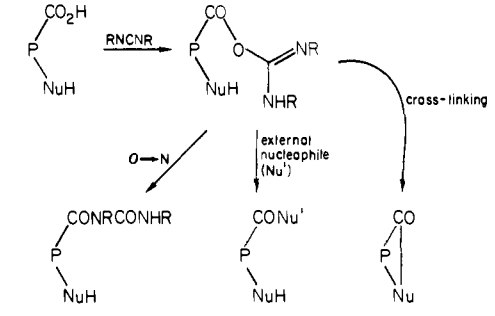
Active-site carboxyl groups may be protected by substrate or inhibitor at saturating concentrations,[521,522] and the carboxyl group may be modified as in ribonuclease (RNASE) but retaining its negative charge (eq 244).[523]



(244)

The total number of carboxyl groups in a protein may be determined by treating the material with a denaturant, coupling with glycinamide or glycine methyl ester (using carbodiimide coupling agent) and then comparing the amino acid analysis with that of the original protein.[524] Buried carboxyl groups may be detected by reacting the natural protein and the denaturated protein with glycinamide in the presence of carbodiimide.[525-527] Fifteen of the seventeen carboxyl groups in α-chymotrypsin have been coupled to ethyl glycinate through a water-soluble carbodiimide.[528] Bovine trypsin has been modified with semicarbazide (probably at its carboxyl functions) in the presence of a carbodiimide.[529]

The reaction of carbodiimides *alone* with the carboxyl group in proteins can lead to inhibition; this can be caused by either interaction of neighboring nucleophiles or through the O→N acyl shift (eq 245). If the external



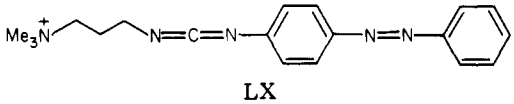
(245)

nucleophile (eq 245) is water, then the enzyme is regenerated. The *O*-acylisourea is relatively labile to hydrolysis back to active enzyme, and permanent modification must involve one of the other paths.[530]

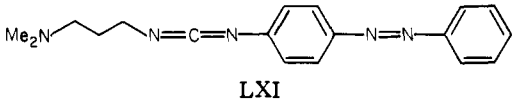
Another carboxyl modification reaction involves that of yeast enolase by water-soluble carbodiimides.[531] The interesting observation was made[531] that noninhibitor or nonsubstrates such as phosphate or glucose 6-phosphate protected the enzyme against inactivation; these species were assumed to react with the carbodiimide in competition with the protein.[531] An insect mid-gut trehalase,[532] acetylcholinesterase,[533] bovine β-lactoglobulin A,[534] bovine serum albumin,[535] casein,[536] L-glutamate dehydrogenase,[537] and an acid proteinase from *Aspergillus awamori*[538] have been modified at essential carboxyl groups with carbodiimide.

Pepsinogen is modified with dicyclohexylcarbodiimide at four sites and pepsin at three.[539] One of the carbodiimides is attached at the N-terminal of pepsinogen and is removed (together with a peptide) when the precursor is activated.[539]

Two colored carbodiimides have been synthesized (LX, LXI) and used in modifications of pepsin, pepsinogen, and aspergillopepsin A.[540-543]



LX



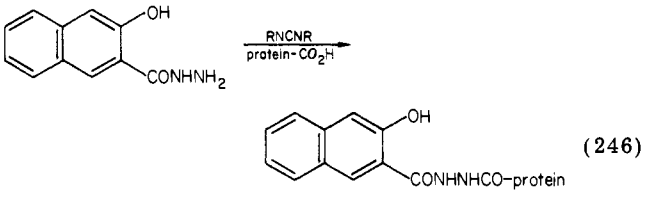
LXI

Carbodiimides have been utilized in the histochemical detection, using a fluorescent coupled group, of carboxyl groups in proteins (eq 246).[544-546] It has been pointed

TABLE IX. Collection of Sequences of Some F_0 Lipoproteins

organism	No.[d]	N[e]	carboxyl sequence	C[f]
Neurospora crassa[a]	81	Tyr	Ala-Phe-Val-*Glu*-Ala-Ile-Gly	Thr
bovine heart[a]	75	Asp	Ala-Leu-Ser-*Glu*-Ala-Met-Gly	Met
Saccharomyces cerevisiae[a]	76	fMet	Ala-Leu-Ser-*Glu*-Ala-Thr-Gly	Val
spinach[b]	81	fMet	Ala-Phe-Met-*Glu*-Ala-Leu-Thr	Val
E. coli[c]	79	fMet	Gly-Leu-Val-*Asp*-Ala-Ile-Pro	Ala
PS-3[c]	72	fMet	Ala-Leu-Val-*Glu*-Ala-Leu-Pro	Arg

[a] Mitochondria. [b] Chloroplast. [c] Bacterial plasma membrane. [d] Residues in protein. [e] N terminal. [f] C terminal.



(246)

(fluorescent)

out that since proteins contain both amine and carboxyl side chains, the possibility of polymerization may be realized in protein modification studies;[547] we shall turn later to a similar fixation phenomenon which is utilized in electron microscopy. Two to three carboxyl residues of serine pepsin have been shown to be modified by tritium-labeled dicyclohexylcarbodiimide with the loss of approximately 70–80% of the activity to hemoglobin.[548]

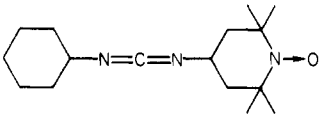
D. Modification of Carboxyl Groups in ATPases

Since it was discovered some 13 years ago,[549] there has been increasing activity in studies on the inhibition of membrane ATPase by carbodiimides. There is considerable interest in ATPases as the mitochondrial enzyme system is an important coupling factor in oxidative phosphorylation; it has a role in muscle contraction and in the transport of ions across membranes.[550]

The inhibition of ATPases was early shown to be associated with membrane lipoprotein,[551] and carbodiimide binding proteins were isolated from mitochondrial membranes.[552,553] The lipoprotein (F_0) which binds carbodiimide in mitrochondrial membranes was shown to have a molecular weight of about 10 000.[554] Work in the early 1970s succeeded in isolating the F_0 lipoproteins and established the amino acid sequence for these from several species; it showed that a glutamate or aspartate residue in the central position of the F_0 proteins is responsible for the proton translocation and energy-transducing properties of the ATPase complex.[554-559a] Table IX[559b] collects the amino acid sequence of some isolated F_0 proteins.

Carbodiimide binding proteins have now been isolated and purified from a large number of sources including bacterial membranes,[560-567] chloroplasts,[568-570] animal liver mitrochondria,[571,572] bovine heart mitochondria,[573] moulds,[574] and yeasts.[575]

Spin-labeled carbodiimide (LXII) has been utilized to bind to the ATPase complex, and EPR studies have indicated a distance between the ATP binding site for Mn^{2+} and the inhibitor site in the F_0 protein of the order of 20 Å. The inhibitor site in mitochondrial ATPase has characteristics of low polarity, and there is a strong restraint on rotational motion of the probe.[576-578] The site of carbodiimide attack in the F_0 protein is probably in a hydrophobic region as only lipophilic



LXII

carbodiimides are effectve inhibitors.[579]

Carbodiimides act as inhibitors of ATPase as an ATP-driven proton "pump" in mitochondria and chloroplasts[580-585] in electron transport[579,586] and in calcium[587,588] and alkali metal transport.[589-592] Ion permeability is also affected by carbodiimide inhibition of ATPase.

ATPase complexes have been isolated and studied.[597-604] The complex consists of a fragment (F_1) and two peptides (F_0) of molecular weight approximately 10 000.[597] The F_1 fragment is insensitive to carbodimides whereas F_0 is.[597]

The chemistry of the F_0 subunits has been the subject of intensive research. Mutant strains of *E. coli* bacteria resistant to carbodiimides have been shown to possess an altered aspartate in the F_0 protein and blocked proton translocation.[605] Mutant strains on other organisms resistant to carbodiimide have been studied, and the F_0 protein has been isolated.[606-614] The protection by Ca^{2+} of ATPase from sarcoplasmic reticulum toward carbodiimide inhibition has been advanced as evidence for a Ca^{2+} binding site in the hydrophobic region of the F_0 protein.[615] Water-soluble carbodiimides inhibit the ATPase of mitochondria, but not at the F_0 site.[616]

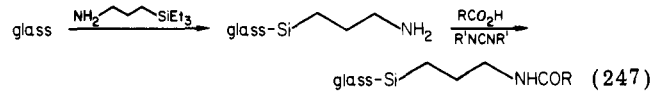
The addition of methyl glycinate protects erythrocyte membrane ATPase against inhibition by carbodiimides.[617] The mechanism of the inhibition process is thought to be formation of the *O*-acylisourea species followed by attack of an adjacent nucleophile to cause loss of urea, covalent binding of the nucleophile with the binding site to produce cross-linking, and no loss of inhibition.[617] Protection of the enzyme by methyl glycinate only occurs when this nucleophile is added simultaneously with the carbodiimide; subsequent addition to the nucleophile does not cause regeneration. The possibility that methyl glycinate protection is due to the competing reaction of the protecting amine with the carbodiimide was not considered. It is now thought that the inhibitory action of carbodiimide is an O→N acyl shift.[614] The binding sites of carbodiimide in membrane-bound ATPase of *E. coli* and beef heart mitochondria[620,621] have also been characterized.

E. Use of Carbodiimide as a Biological Tool

a. Attachment of Biological Materials to Solid or Polymer Supports

Enzymes such as creatine kinase have been grafted on collagen films by using water-soluble carbodi-

imides,[622] and the carbodiimide method of binding chymotrypsin to carboxymethylcellulose has been evaluated.[623] The pH optimum for coupling collagen to acrylic acid polymers is 4.4, and only accessible carboxyl groups are active.[624,625] Carbodiimides have been employed to couple ovalbumin to mouse spleen cells[626] and melibionic acid to serum albumin.[627] Immunologically active species may be joined to glass through 3-(triethylsilyl)propylamine (eq 247).[628] Carbodiimide has also been employed to coat glass beads or modified polyacrylamide beads with polyamines.[629,630]



(247)

b. Carbodiimide as a "Fixing Agent"

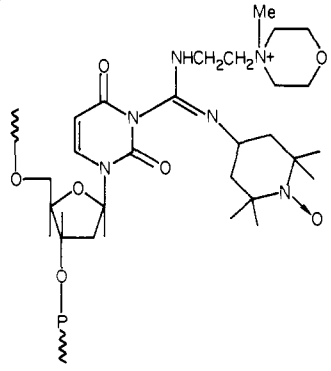
Carbodiimides have been used as fixatives for immunohistochemistry; intestinal glucagon has been preserved and localized by a water-soluble carbodiimide.[631] "Fixation" by carbodiimides is useful as an ultrastructure preservative for electron microscopy,[632] and the quality of the result is similar to that from the action of glutaraldehyde a conventional fixative.[633] The action of the carbodiimide in these processes is probably to effect cross-linking between carboxyl and amino groups.

c. Cross-Linking of Proteins

Lysozyme and α-chymotrypsin when treated with water-soluble carbodiimide undergo *inter*molecular cross-linking to yield thermostable proteins.[634] A similar stability has been induced in hemoglobin used in transfusions by cross-linking with water-soluble carbodiimides.[635] Intermolecular cross-linking caused by carbodiimides leads to an increase in viscosity of collagen fiber.[636a,b] Carbodiimides have been utilized to cross-link wool,[636c] hair (in a permanent wave composition),[637] and bovine lutotropin.[638,639]

d. Spin-Labeling with Carbodiimides

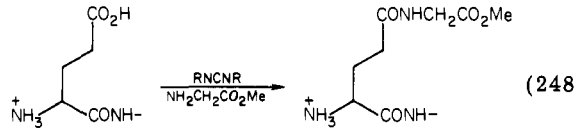
We have already discussed an example of spin-labeling in the problem of carbodiimide binding proteins of ATPases.[626-628] Water-soluble spin-labeled carbodiimides have been synthesized and reacted with nucleosides;[640-642] poly(uridylic acid) is modified on the pyrimidine nitrogen (LXIII).[642]



LXIII

e. Peptide Sequence Determination

N-Terminal glutamic acid or aspartic acid may be modified with carbodiimide and methylglycinate to yield a residue which may be distinguished readily from glutamine or asparagine in the Edman method (eq 248).[643]

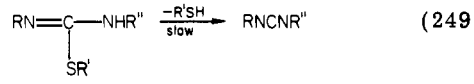


(248)

f. Carbodiimides as Biological Effectors

Carbodiimides have been shown to act as herbicides;[644] involvement of ATPase activity with initiation of germination has been inhibited by carbodiimides.[645] Antifoliant,[646] fungicide,[647] and antitumor[648] activities are all observed with carbodiimides. Carbodiimides may be used in pesticide formulations of thiophosphates to prevent hydrolytic decomposition.[649] Insecticidal and acaricidal[650,651] and ectoparasiticidal[625,653] activities have also been observed with carbodiimides.

Miticidal and lepidoptericidal activities are observed with isothiourea species;[654] this may be due to the operation of a controlled-release mechanism producing carbodiimides (eq 249).



(249)

g. Other Membrane Activities of Carbodiimides

Low concentrations of carbodiimides modify the effector portion of the β-adrenergic receptor of the adenylyl cyclase system in frog erythrocytes.[655] Dicyclohexylcarbodiimide blocks the catecholamine activation of adenylyl cyclase in turkey erythrocytes.[656] Carbodiimide modifies neuromuscular transmission in the frog[657] and has been examined as a possible affinity label for the acetylcholine receptor at the frog neuromuscular junction.[658] Dicyclohexylcarbodiimide has been shown to affect the photoinduced changes in electric potential differences and resistance in plasma membranes of Nitella cells.[659]

h. Action on Nucleotides and Nucleosides

Water-soluble carbodiimides have been shown to inhibit transcription of supercoiled PM2 DNA with *E. coli* B RNA polymerase.[660,661a] Reaction of carbodiimides with cytidine 2′(3′)-phosphate yields an adduct which leads to cyclic 2′,3′-phosphate, hydrolysis product, and *N*′-amidinyl product similar to LXIII.[661b] Uridine reacts to give an N-substituted product (LXIII).[640-642,661c] Polynucleotides react with positively charged water-soluble carbodiimides much faster than do the monomers owing to the electrostatic effect.[661d,e]

VIII. Carbodiimides and Polymer Chemistry

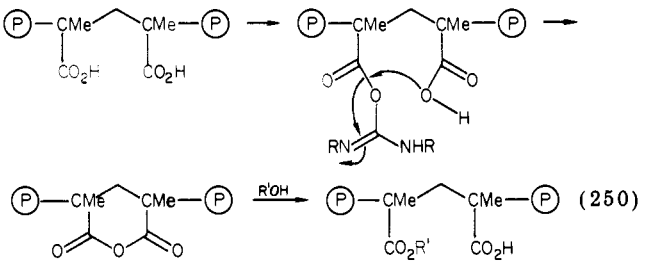
A. General

Since the discovery of catalytic methods for the preparation of carbodiimides from the readily available isocyanates, carbodiimides have been increasingly studied as precursors for polymer materials. At the same time the use of carbodiimides as reagents in polymer chemistry has been increasing, and we have

already dealt with this aspect for biological polymers. Carbodiimides may participate in polymer structures as part of the backbone (chain or cross-link) or as a pendant group. Incorporation in polymers by polymerization of carbodiimides is dealt with elsewhere in the review with regard to dimers and trimers; polymerization by condensation with an appropriate reactive group such as diamine is discussed under chemical properties.

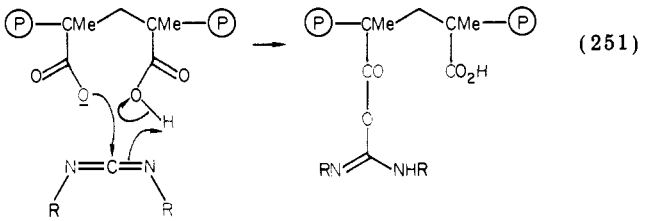
B. Modification of Polymers

Syndiotactic poly(methacrylic acid) is esterified by alcohols in the presence of carbodiimides to give alternate ester links.[662-664] Strong acid catalysts yield random esterification; the explanation is believed to involve anhydride formation from the isomer, yielding one ester for every two carboxyl groups (eq 250). The



(250)

simple explanation (eq 250) can only be partially correct, as it requires the formation of alternating isourea groups. This condition can arise through concerted acid catalysis, as discovered recently (eq 110),[298] and we propose the initial reaction to be as in eq 251.



(251)

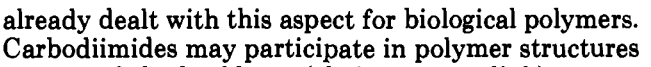
Water-soluble carbodiimides have been used to couple glycine ethyl ester with poly(acrylic acid); it is thought that the reaction proceeds through the carboxylic anhydride.[865]

Carboxyl group site–site interactions have recently been shown to occur in functionalized cross-linked polystyrene resins. Dicyclohexylcarbodiimide treatment of the carboxyl resin was followed by infrared spectroscopy, and the appearance of a band at 1785 cm^{-1} indicates a lower limit for anhydride formation.[666] A band at 1660 cm^{-1} was proposed to be due to the *N*-acylurea group. Previous to this work[666] there was no definitive evidence, and it was generally assumed that there was little or no interaction between groups in cross-linked polymers.

Hardening of amino/carboxyl emulsion polymers has been effected with ditolylcarbodiimide to yield films.[667] Butadiene/acrylonitrile copolymers with 0.09% carboxyl group content have been cross-linked with a bifunctional carbodiimide (LXIV).[868] Water-soluble

$$PhNCN(CH_2)_6NCNPh$$
LXIV

carbodiimides suitable for polymer modification have been synthesized from basic carbodiimides and sultones (eq 252).[869]



(252)

Hemin has been derivatized as amide and ester by using water-soluble carbodiimides.[670] Hydroxyl polymers may be modified to yield more hydrophobic species by using dicyclohexylcarbodiimide with tetrafluoroboric acid through *O*-alkylisourea formation[671] and to contain guanidine groups.[672] The latter species with M_r 400–2000 are useful in the preparation of polyurethanes.[673] Fluoroaliphatic carbodiimides have been used to impart oil- and water-repellent finishes to nylon and polyester fabric[674] and also to leather.[675,676]

C. Polymerization Catalysts and Reagents

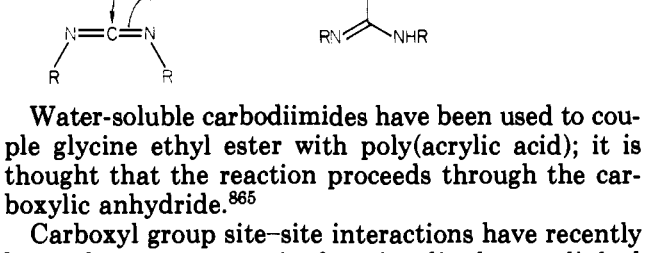
Carbodiimides may be used to polymerize malic acid to yield a possible protease inhibitor (eq 253).[677]

(253)

Protamine sulfate may be polymerized by carbodiimides;[678] dicyclohexylcarbodiimide induces the formation of a tacky fire-resistant polyphosphoramide from diamines and inorganic phosphate.[679] Carbodiimides catalyze the polymerization of lactones;[680] the reaction requires a catalytic amount of sodium.

D. Polymers with Functional Carbodiimides

Polymers with pendant carbodiimides have been prepared and used as dehydrating agents (eq 254[681] and 255[682]).



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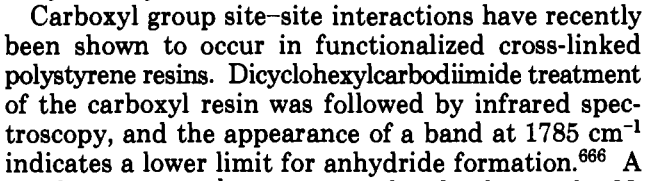
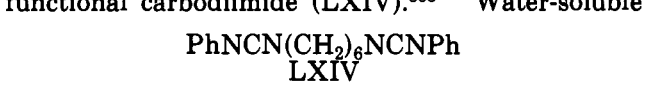


(255)

E. Insulators and Heat-Resistant Plastics

Cross-linked organosilicon carbodiimide polymers have been prepared and found to be useful for electrical insulating coatings and high-temperature paints.[683] Cross-linked carbodiimide polymers with electrical insulating properties may be prepared by using bis(isocyanatophenyl)methane (LXV) and a catalyst.[684] Iso-



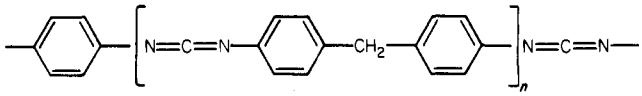
LXV

cyanurate foams[685] and other plastics containing polycarbodiimides are useful as heat-stable materials.[686-689]

The fire resistance of carbodiimide foams based on polyols from trichlorobutene oxide or epichlorohydrin has been reviewed.[690]

F. Reinforcements

Poly(4,4′-diphenylmethanecarbodiimide) (LXVI) at 1% in nylon increases the relative melt strength and viscosity.[691] Polycarbodiimides have been used as fiber



LXVI

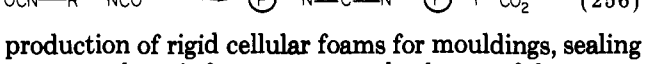
reinforcements[692,693] and in strengthening glass-fiber compositions.[694,695] The strengthening effect probably comes from the rigid nature of the polymer carbodiimide which has relatively few degrees of rotational freedom.

G. Adhesives and Microcapsules

Polycarbodiimides have been used as adhesive primers.[696-698] Film forming carbodiimide homo- or copolymers have been used in microcapsulation techniques for pressure-sensitive copy paper.[699-701]

H. Foams and Microcellular Elastomers

Catalytic formation of polycarbodiimides from bisisocyanate monomers results in carbon dioxide liberation (eq 256); use is made of this phenomenon in the



(256)

production of rigid cellular foams for mouldings, sealing compounds, reinforcements, and other useful purposes.[702-723]

I. Stabilization of Polymers with Carbodiimides

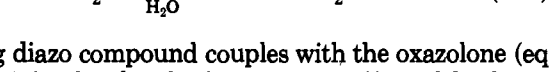
The instability of cross-linked polyesters is due to the hydrolysis of the ester link which is accelerated as the carboxyl groups are formed.[724-727] Scavenging the carboxyl end groups with carbodiimide has been shown to prevent hydrolysis.[724] Monomeric carbodiimides[728-739] and poly(carbodiimides)[740-745] have been suggested as stabilizing additives for polyesters. The blocking function may be due to formation of *N*-acylurea or to formation of ester links with adjacent hydroxyl groups. The stabilizing effect is felt in both aqueous emulsions[731] or solutions[724] of polyester as well as in the bulk polymer.

The storage life of liquid poly(isocyanates) is improved by the addition of carbodiimides which presumably scavenge water.[746-751]

IX. Photography and Related Subjects

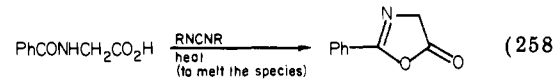
Carbodiimides have been used extensively as gelatin hardeners;[752-766] the action of the carbodiimide is to link carboxyl and amino groups on the gelatin chains, effectively cross-linking the polymer.[766] Carbodiimides also have application as "antifoggants".[767,768]

Applications for carbodiimides have been found in the generation of azo-dye images from light-sensitive heat-developable diazotype compositions. These compositions comprise a light-sensitive diazonium compound, a normally solid carbodiimide, and a normally solid diazo-coupler precursor. The latter is converted to a reactive coupler by dehydration with the carbodiimide (effected by melting). The light process converts diazo species to a phenol (eq 257), and the re-



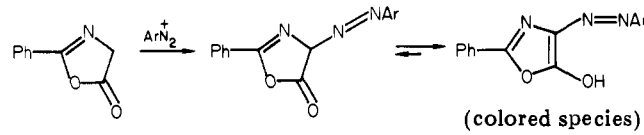
(257)

maining diazo compound couples with the oxazolone (eq 258, 259) in the developing process effected by heat.



(258)

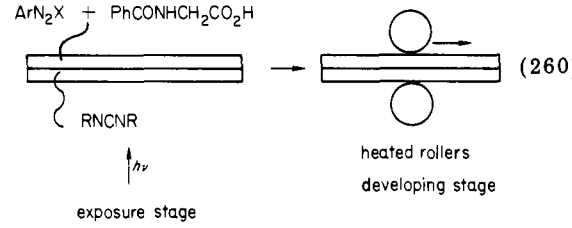
Diazo coupling:



(colored species)

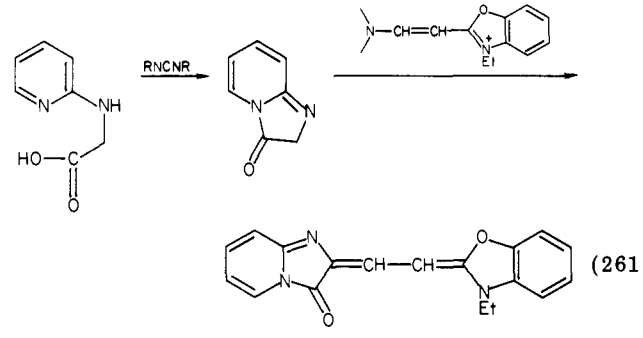
(259)

The process may be envisaged as in eq 260; the light-exposed areas are colorless.[769]



(260)

A thermographic process involves printing by infrared radiation; the heat warms and mixes solid carbodiimide with the dye precursor which cyclizes to give the dye (eq 261).[770]

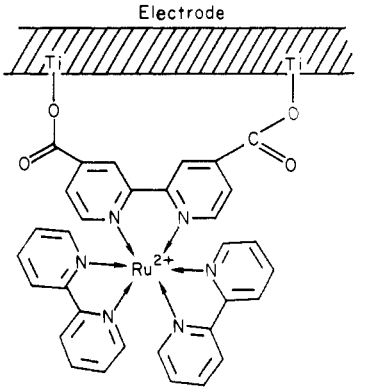


(261)

magenta color

Carbodiimides have been used as stabilizing agents for a photosensitive polymer composed of cinnamate attached to a polyether chain through ester links. The carbodiimide presumably acts as a water scavenger.[771] Adhesion of the gelatinous photographic material to polyethylene terephthalate supports has been improved through the addition of carbodiimides; the mechanism probably involves the formation of ester linkages.[772]

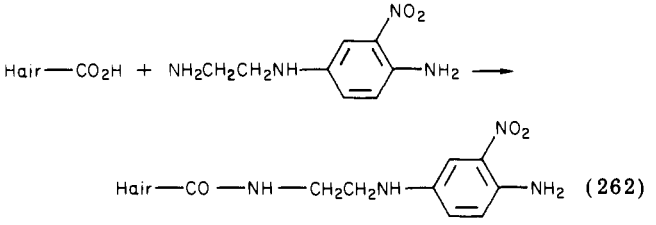
Titanium(IV) oxide electrodes may be dye sensitized by coupling with a bipyridylruthenium complex; ester links are formed from the TiOH group and carboxyl groups through the action of carbodiimide (LXVII).[773]



LXVII

X. Dyeing and Related Subjects

Most of the applications of carbodiimides to dyeing refer to improving the wash-fastness of the dye. Wool[774,775] and hair[775] dyeing is improved by treatment with carbodiimides. 1-Ethyl-3-[3-(trimethylammonio)propyl]carbodiimide fixes the red dye [2-nitro-4-[(β-aminoethyl)amino]aniline] to hair, probably via an amide link (eq 262).[776] Neutral or acid conditions may be used to couple a phosphorus dyestuff with a cellulosic material by using carbodiimide (LXVIII).[777]



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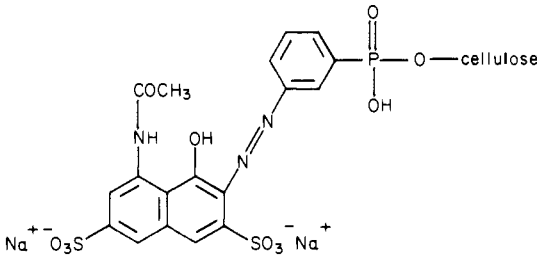


LXVIII

The cosmetic qualities of bleached human hair may be improved, presumably by some form of internal cross-linking, by treatment with 1-cyclohexyl-3-(*N*-methylmorpholino)carbodiimide.[778]

XI. Analysis

A. Assays for Carbodiimide

The estimation of carbodiimides has been relatively unsatisfactory in that no reliable, sensitive, color assay has been available. Despite increasing use of carbodiimides at low concentrations as biological effectors, the only assays available until the present involved the estimation of carbon monoxide from oxalic acid under anhydrous conditions or of excesss oxalic acid by back-titration (eq 263).[2] The latter method was used

$$RNCNR + (CO_2H)_2 \rightarrow RNHCONHR + CO + CO_2 \quad (263)$$

to determine carbodiimide in polymer supports[779] and in other analyses.[780,781] GLPC analysis[781] and infrared absorption spectroscopy[782] have been used as assays for carbodiimides. An interesting technique for polymer-supported carbodiimides involved reaction with acetic acid to give an equivalent amount of acetic anhydride which was then analyzed by GLPC.[783] Paper or thin-layer chromatograms of free dicyclohexylcarbodiimide were exposed to iodine vapor; colored spots formed at the carbodiimide which disappeared in the free atmosphere.[784]

Recently a sensitive method for estimation of carbodiimides has been reported to involve a color development (400 nm) when the water-soluble carbodiimide is added to a pyridine buffer at pH 7 containing ethylenediamine.[785] The cause of the color is not apparent, but concentrations in the assay mixture down to 50 μM of carbodiimide may be estimated.

Two methods of assay based on the known chemistry of carbodiimides have been developed.[786] The first method involves guanidine formation by reaction of the carbodiimide with 1 M anilinium hydrochloride followed by quenching in 1 M HCl and reading the absorption at 230 nm (eq 264). The phenylguanidine

$$PhNH_3^+ \xrightarrow{RNCNR} PhN{=}C(NHR)_2{\cdot}HCl \quad (264)$$

spectrum has a very large absorbance at 235 nm, and the large extinction coefficient at 230 nm (ϵ 1 × 10^4) allows concentrations to be measured down to 0.2 μM. The second technique[786] relies on the formation of an amount of acetic anhydride equivalent to the carbodiimide by addition of acetic acid. The acetic anhydride is quenched in alkaline hydroxylamine and the color developed (at 540 nm) with ferric chloride solution (eq 265).[786] The sensitivity of this method is close to that

$$RNCNR \xrightarrow{AcOH} Ac_2O \xrightarrow{NH_2OH} AcNHOH \xrightarrow{FeCl_3} \text{colored ferric complex} \quad (265)$$

claimed for the pyridine/ethylenediamine technique.[785]

B. Determination of Carboxylic Acids

Carboxylic acids have been assayed by using carbodiimide to promote ester formation followed by GLPC analysis.[787] A colorimetric method utilizes carbodiimide as a coupling agent to yield hydroxamic acid with hydroxylamine; color is developed with ferric chloride,[788-795] and the chemical basis of the method is as described in eq 265. The assay of carboxylic acids in biological polymers is dealt with earlier.

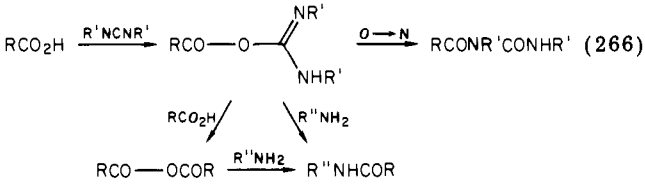
C. Carbodiimide in Biological Assays

Carbodiimides have been used as coupling agents to form conjugates between steroids and chemiluminescent species; these act as the basis for an assay of plasma progesterone through antibody-enhanced chemiluminescense.[796] Conjugate formation through carbodiimides is the basis of the immunoassay of secretin and IBG.[797,798] Antibodies have been coupled to carboxymethylcellulose through carbodiimide to form the basis of an immunoassay.[799] The preparation of tritium-labeled dicyclohexylcarbodiimide for the assay of biological species has been described.[800]

XII. Uses of Carbodiimide in Synthesis

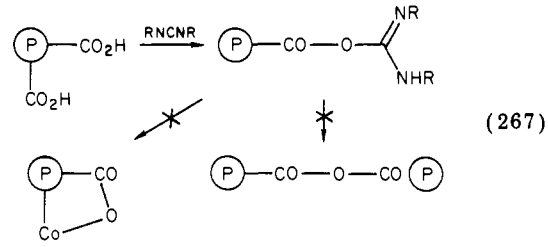
A. Peptide Synthesis

Peptide synthesis continues to utilize the carbodiimide "method" and its major coupling procedure.[801-808] The mechanism of peptide coupling involves the overall scheme given in eq 266 (see also eq 103). There are two



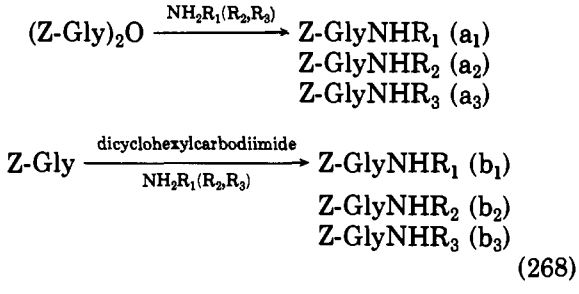
(266)

main side reactions, namely, the O→N acyl shift to give *N*-acylurea and racemization. The anhydride and *O*-acylurea pathways to peptide remain as protagonists. Reaction of dicyclohexylcarbodiimide couples monomer amines to a cross-linked polymer containing pendant carboxyl groups; it is unlikely that anhydride formation could occur between polymer acids even in an *intra*polymer reaction (eq 267).[809] However linear poly-



(267)

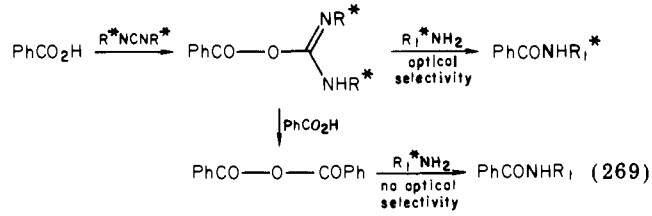
(acrylic acids) appear to form anhydrides readily,[665] and even some carboxyl functionalized polystyrenes form *intra*molecular anhydrides.[666] The product distribution in the reaction of a mixture of three amino acid amines with benzyloxycarboxylglycine anhydride ($(Z\text{-}Gly)_2O$) and benzyloxycarbonylglycine (Z-Gly) with carbodiimide is different under identical conditions; this indicates that the *O*-acylisourea path predominates for the carbodiimide method in solution (eq 268).[810] A



(268)

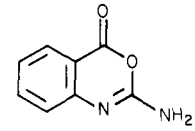
$$(a_1{:}a_2{:}a_3 :: b_1{:}b_2{:}b_3)$$

similar method involves the use of an optically active carbodiimide coupling on optically inactive acid ($PhCO_2H$) with an optically active amine. The anhydride pathway should involve no optical selectivity because the anhydride is symmetrical. The *O*-acylisourea, however, is an asymmetric molecule, and the observation of optical selectivity in the synthesis indicates that the *O*-acylisourea pathway is being followed (eq 269).[811] Carbodiimides with only one optically active substituent have been found to be weakly selective in the coupling of cyclohexylamine with racemic carboxylic acids.[812] The presence of excess acid in the coupling



(269)

reaction leads to anhydride being the major path; when acid is present in equimolar amount with respect to carbodiimide, the *O*-acylisourea pathway predominates.[811] The isolation of the *O*-acylisourea has been claimed during a peptide synthesis in solution.[813] The anhydride path is not a necessary requirement as the benzoxazine analogue of the *O*-acylisourea (LXIX) does

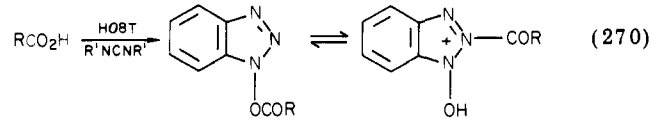


LXIX

not require the action of a carboxyl group in order to acylate amines.[301-303] Under the conditions of solid-phase peptide synthesis using a resin-bound amino acid as the amino group the mechanism which predominates is the anhydride.[814] The solution studies indicate that neither mechanism is necessarily predominant but depends on the conditions employed. The relatively slower reactions with solid-phase amine will presumably allow the *O*-acylisourea to react with the usually less nucleophilic carboxyl group to yield the anhydride which then becomes the major acylator. The latter conditions may also be reached by increasing the carboxylic acid concentration.[811] The evidence for the two pathways has been reviewed.[815,816]

The overall reaction of leucylleucine synthesis in aqueous solution effected by 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide involves a maximal yield at 0.1 M HCl;[817] the reason for this result is not clear.

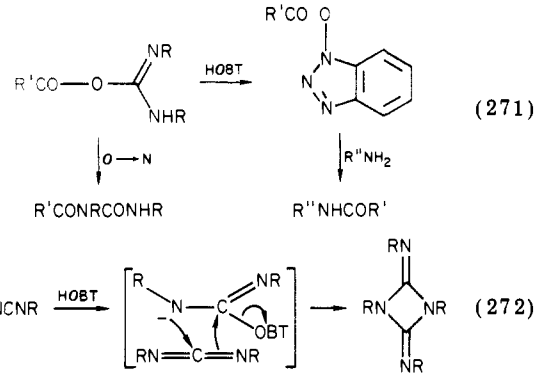
The racemization problem is acute in carbodiimide-mediated coupling. Racemization decreases according to carbodiimide structure in the order $C_6H_{11}NCNC_6H_{11}$ > $PhCH_2NCNEt$ > $4\text{-}CH_3C_6H_4NCNEt$ > $PhNCNEt$.[818] Coupling with carbodiimides is accelerated by catalysts such as *N*-hydroxybenzotriazole and *N*-hydroxysuccinimide which also tend to suppress racemization.[819-833] The action of these catalysts is probably as a transfer agent (eq 270), but it is not certain which group in, for



(270)

example, hydroxybenzotriazole (HOBT) is acylated (eq 270).

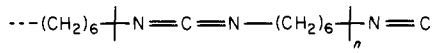
The problem of *N*-acylurea formation arises especially when long reaction times are involved,[834-837] as in solid-phase methods. This problem can be resolved if a reactive nucleophile such as HOBT is added to react with the *O*-acylisourea to yield a secondary reacting species (eq 271). *N*-Hydroxybenzotriazole catalyzes the formation of a further byproduct, namely, the diazetidine (eq 272), in a peptide synthesis[838] probably by a stepwise cycloaddition reaction involving the acyl hydroxybenzotriazole.



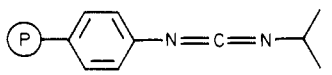
(271)

(272)

Solid-phase carbodiimides have been utilized as dehydrating agents in peptide coupling; both long-chain polymers[839] and pendent side chains[840-842] have been used (LXX[839] and LXXI[840]). The cyclic peptide



LXX



LXXI

gramicidin S has been synthesized by using a resin-bound carbodiimide with HOBT additive.[842]

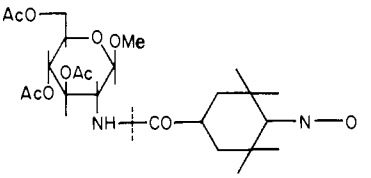
Solid-phase peptide synthesis has utilized carbodiimides for coupling; reaction with radioactive dicyclohexylcarbodiimide has shown that less than 0.2% of the polymer-bound amine reacts directly with the reagent.[843] Studies have been made of the availability of carbodiimide-activated N-protected amino acids in solid-phase synthesis.[644,845] Carbodiimide has been shown to be superior to the mixed anhydride or Woodward method of peptide coupling in solid-phase synthesis.[646] The evaluation of carbodiimide stoichiometry in the reaction of glycine with amino acid has been made by "resin probe" analysis (eq 273a). The

$$\text{resin-}(OCOCH_2NH_2)_n + \text{amino acid} \xrightarrow{\text{RNCNR}} \text{resin-}(OCOCH_2NHCO\text{–}CHR'NH_2)_x \xrightarrow[(-OCOCH_2NH_2)_{n-x}]{NaOCH_3} \text{resin-OH} + (n-x)\text{Gly} + x\text{Gly} \quad (273a)$$

glycyl-resin is reacted with amino acid derivative in the presence of dicyclohexylcarbodiimide and the product cleaved from the resin; the ratio of free glycine to glycyl peptide as determined by amino acid analysis gives a measure of the stoichiometry of the reaction. The method of course suffers from the grave disadvantage that some of the glycine esters will be protected from reaction by the polymer architecture. A pentapeptide fragment of substance P has been synthesized by using Sephadex LH-20 as the polymer support.[848]

B. Amide Synthesis

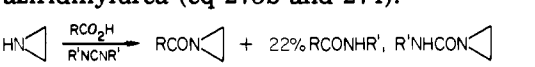
Dicyclohexylcarbodiimide has been used to couple nitroxide spin-labeled species with monosaccharides (LXXII).[849] Carbodiimide has been used as a reagent (albeit an expensive one) for coupling amine and acid groups to synthesize potential local anesthetics from benzocaine,[850] analgesic and antiinflammation drugs from 2-aminobenzothiazoles,[851] and ureas direct from carbon dioxide and amines.[852]



LXXII

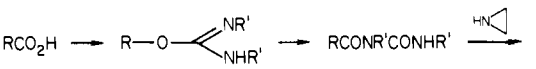
Kinetic studies on *N*-arylamide formation indicate that anhydride production is the rate-limiting step.[853]

A complicating feature in amide synthesis is a side reaction, presumably caused by the attack of amine on the *N*-acylurea. In the dicyclohexylcarbodiimide coupling of an aziridine with a fatty acid some 22% of the product is *N*-cyclohexylamide and *N*-cyclohexyl-*N'*-aziridinylurea (eq 273b and 274).[854]



(273b)

R' = cyclohexyl



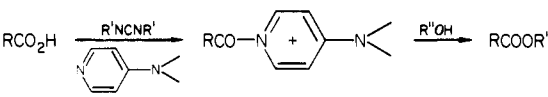
$$\text{RCONHR'} + C_2H_4NCONHR' \quad (274)$$

The very high nucleophilility ("supernucleophile") of the aziridine moiety[855] probably accounts for the cleavage of the *N*-acylurea; we would therefore not regard this problem as generally very troublesome, as most amines are not "supernucleophiles". A new technique for formylating sensitive amino acids has been reported to work efficiently (eq 275).[856]

$$2HCO_2H \xrightarrow{\text{RNCNR}} \text{HCO–O–COH} \xrightarrow{\text{amino acid}} \text{HCONH–CHRCO}_2\text{H} \quad (275)$$

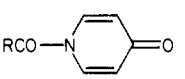
C. Ester and Anhydride Formation

Carbodiimide continues to provide a useful route to ester; the preparation of thiol esters has been exemplified[857] and the difficulty experienced with simple alcohols may be relieved by the use of pyridine catalysts[858-860] which probably act by formation of acylpyridinium intermediates (eq 276). An alternative



(276)

pyridine derivative is the 4-hydroxy species; acylation still occurs at nitrogen to give the *N*-acyl-4-pyridine species (LXXIII).[861-863]



LXXIII

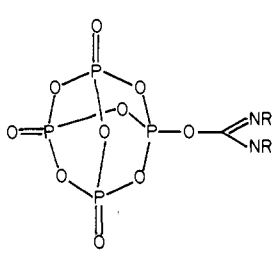
Toluenesulfonic acid has been employed as a catalyst for ester formation using carbodiimides;[864] the esterification method is generally used for exotic esters on account of the cost of the reagent.[865,866]

Carbodiimides have been used as reagents for the synthesis of rare symmetrical anhydrides[867-869] and formic anhydride.[856]

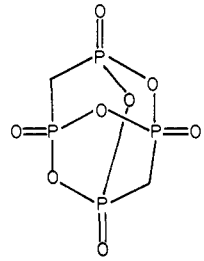
D. Phosphorus Esters

Reaction of dicyclohexylcarbodiimide with phos-

phoric acid leads to an anhydride complex analogous to phosphorus pentoxide (P_4O_{10}, LXXIV).[870,871] Me-

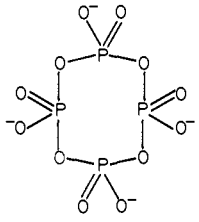


LXXIV

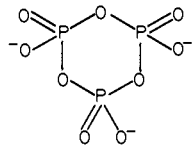


LXXV

thylenephosphonic acid ($H_2O_3PCH_2PO_3H_2$) yields the methylene analogue of P_4O_{10} (LXXV).[870] The esterification of phosphonic acid mediated by carbodiimides involves phosphonic acid anhydrides (LXXVI); in the

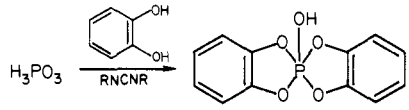


LXXVI



LXXVII

presence of tertiary amine the trimer LXXVII is the major intermediate.[872] The stepwise esterification of phosphate competes with condensation to form polymeric phosphoric acids and their esters. Esterification is promoted by increased acidity, smaller size, and increased concentration of the alcohol.[873] Pyridinephosphonic acids have been esterified by the use of carbodiimide[874] and the pentacoordinate phosphorane (eq 277) from phosphorous acid.[875] Carbodiimides

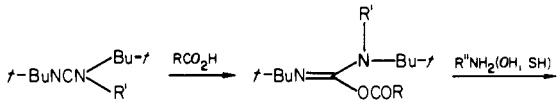


(277)

continue to be used in nucleotide synthesis,[876-882] and several reports have indicated phosphonic anhydride intermediates.[876-879]

E. Miscellaneous Dehydration Reactions

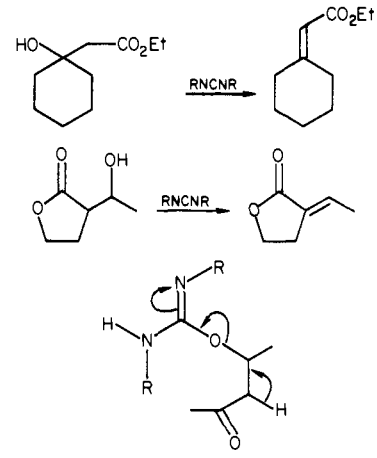
Toluenesulfonic esters have been synthesized from toluenesulfinic acids and alcohols.[883] A very powerful agent for a number of dehydration reactions involves the linear N-alkylated di-*tert*-butylcarbodiimide (XXVI) or the dimeric analogue (XXVII)[231,346-350] (eq 278).



amide, ester, thioester (278)

Carbodiimides effect the dehydration of β-hydroxycarbonyl moieties (eq 279),[884] presumably through the intermediate LXXVIII.

An intermediate similar to LXXVIII is probably involved in the formation of a tertiary amine from carbazole and *N*-(2-hydroxymethyl)acrylamide in the presence of toluenesulfonic acid (eq 280).



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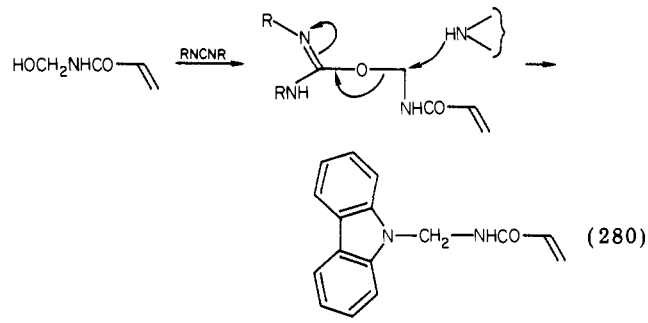
LXXVIII



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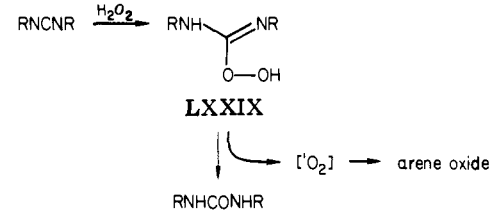
F. Use in Oxidation

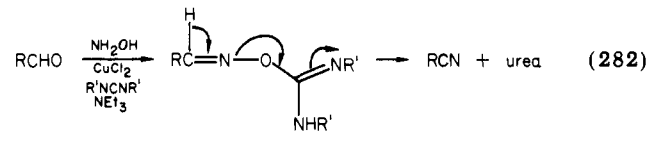
We dealt with the considerable literature on the dimethyl sulfoxide–carbodiimide method for oxidizing alcohols to carbonyl moieties earlier in this review. Hydrogen peroxide with carbodiimide has been shown to react with polycyclic aromatic hydrocarbons to form arene oxides which are possible intermediates responsible for the carcinogenicity and mutagenicity of polycyclic aromatic hydrocarbons.[886,887] The mechanism is shown to involve an intermediate (LXXIX) which degrades to urea and oxidation products (eq 281). The



(281)

oxidation is supposed to involve singlet oxygen.[888]

Aldehydes may be oxidized to the acid level oxidation state by a process involving dehydration of an oxime (eq 282).[889,890] o-Hydroxy substituents block the oxidation.[889]



(282)

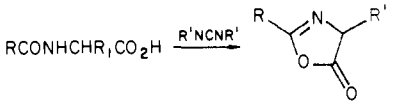
G. Diazoketone Synthesis

The synthesis of diazoketones from acid chlorides with diazomethane is not always possible due to the

sensitivity of the acid; acylamino acid chlorides give the oxazolinone. Interaction of diazoalkane with a mixture of acid and carbodiimide effects the synthesis.[891,892] The reaction probably involves the anhydride as an intermediate in the case of simple acids.[892]

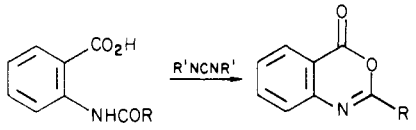
H. Heterocycle Formation through Dehydration

Oxazolinones are well-known as troublesome intermediates in peptide syntheses through the N→C terminal strategy and have been prepared from *N*-acylamino acids by interaction with carbodiimides (eq 283).[893-898] Carbodiimides have also been used in



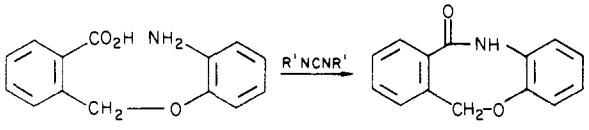
(283)

benzoxazinone synthesis (eq 284).[899,900] The synthesis



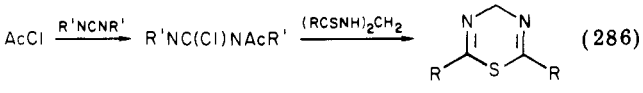
(284)

of dibenzoxazocines has been accomplished for 2-carboxybenzyl 2-aminophenyl ether (eq 285)[901] using carbodiimide. Intramolecular elimination of hydrogen



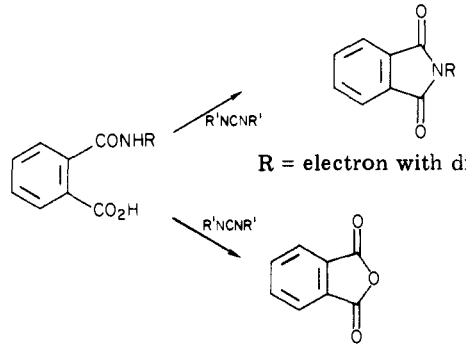
(285)

sulfide has been effected from bis(thionacylamidomethane) using an acetylated carbodiimide (eq 286).[902]



(286)

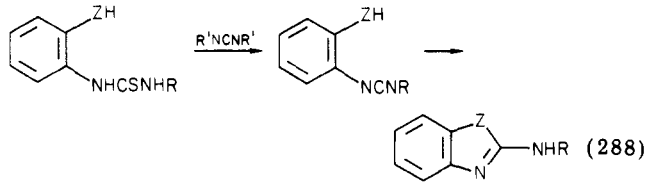
The dehydration of phthalamic acids yields the *isophthalimide* if the nitrogen substituent is methyl or phenyl and the *imide* when the substituent is electron withdrawing (eq 287).[903] Benzimidazoles, benz-



(287)

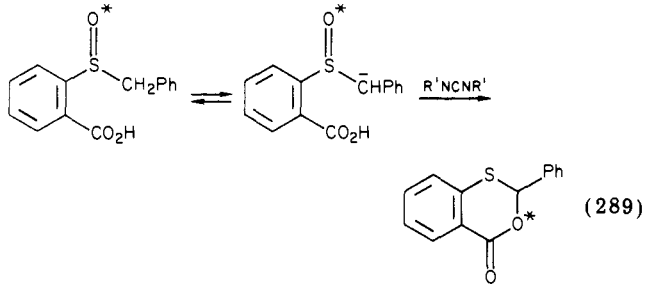
thiazoles, and benzoxazoles have been obtained by desulfurization of thioamides.[904] The reaction probably involves the formation of a carbodiimide intermediate (eq 288; see, e.g., eq 141[363]).

Dicyclohexylcarbodiimide effects an intramolecular Pummerer reaction in a sulfone to yield the 1,3-benzthioxan-4-one LXXX. Oxygen-18 transfer takes place (eq 289).[905]



(288)

Z = O, NH, or S



(289)

LXXX

I. Alkylation Reactions

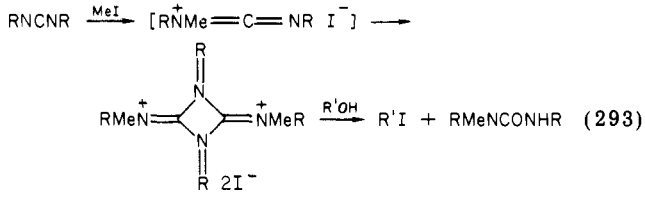
Carbodiimides have been employed as precursors of *O*-alkylisoureas which are proving to be valuable alkylating agents.[213,215-217,220] A recent review[906] indicates that *O*-alkylisoureas may be used in the formation of esters (eq 290), phenyl esters (eq 291), and phosphate esters (eq 292). The driving force of these reactions

$$R'CO_2H + R''OC(NR)NHR \rightarrow R'CO\text{–}OR'' + RNHCONHR \quad (290)$$

$$ArOH + R''OC(NR)NHR \rightarrow ArOR'' + RNHCONHR \quad (291)$$

$$(RO)_2PO_2H + R''OC(NR)NHR \rightarrow (RO)_2POOR'' + RNHCONHR \quad (292)$$

is the thermodynamic stability of the urea; sulfur, nitrogen, and carbon may also be alkylated. N-Alkylated carbodiimides (which are probably dimers) may be used as alkylating agents (eq 293).[349]



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