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Isoureas: synthesis, properties, and applications

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Abstract. Data on the methods of synthesis, chemical properties, and applications of isoureas are surveyed. Promising ways of using isoureas in organic synthesis are demonstrated. The bibliography includes 166 references.

I. Introduction

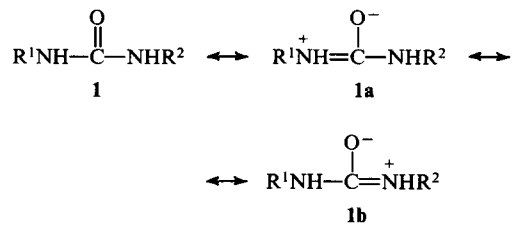
Ureas and isoureas (urea derivatives with *O*-functional-group substituents) are genetically related classes of organic compounds. This claim is based on the fact that they can be obtained from the same starting materials (carbodiimides, cyanamides, and organic cyanates) and also on their ability to be interconverted.

One of the promising aspects of the chemistry of ureas is their synthesis from compounds of different classes with an amide group activated beforehand. A transition of this kind from the amide to the iminoester group has already yielded excellent results. Thus imidates have been obtained from amides,[1,2] while lactim esters have been obtained from lactams.[3] The lactim esters were subsequently used in new ways which had not been employed before. There are virtually no reviews on the chemistry of isoureas apart from Hegarty's paper,[4] but the description of the methods of synthesis of isoureas in the latter is more in the way of a summary. This led to the writing of the present review in which information about the methods of synthesis, chemical properties, and applications of isoureas is compiled.

II. Methods of synthesis of isoureas

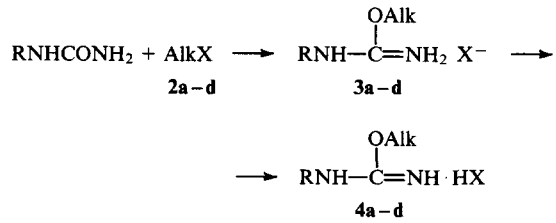
1. Syntheses from ureas

The delocalisation of π electrons in the R^1N-C-O and R^2N-C-O fragments in the ureas **1** is responsible for their weak basicity. The structure of the ground state of ureas can be expressed as a hybrid of the resonance forms **1**, **1a**, and **1b**.



1 **1a** **1b**

Nevertheless, among the multiplicity of the reactions which ureas tend to undergo, the most characteristic are those involving nucleophilic attack on the oxygen or nitrogen atom of the ureas **1** by electrophiles or neutral reagents, the resonance forms **1a** and **1b** being the most probable reactive species in these reactions. One of the specific examples of nucleophilic attack on the oxygen atom of ureas is provided by the direct *O*-alkylation of urea by various alkylating agents **2a–d**. The isoureas **4a–d** are apparently formed via the isouronium intermediates **3a–d**.



2a–d **3a–d** **4a–d**

R = H, Alk, Ar;

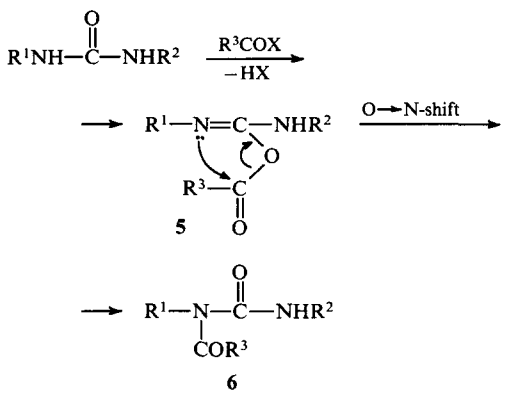
X = $AlkSO_4^-$ (**a**), $NaSO_3^-$ (**b**), I^- (**c**), $AlkSO_3^-$ (**d**).

The reaction involving the *O*-alkylation of ureas is carried out as a rule in neutral media at low temperatures (up to 100 °C), because the alkylating agents AlkX are extremely reactive. Alkyl sulfates **2a**,[5–7] alkanesulfonates **2b**,[5] alkyl iodides **2c**,[8] and aryl alkanesulfonates **2d**[5] are usually employed as the *O*-alkylating agents for ureas. *O*-Alkylisoureas **4a–d** are as a rule isolated as the corresponding salts, but in some cases the free bases can also be obtained by careful neutralisation. The isoureas **4** with easily removeable groups ($AlkO^-$) tend to undergo elimination readily in a basic medium.

Many investigators believe[9–13] that the *N*-acylation of ureas proceeds via the initial *O*-acylated intermediate **5**.

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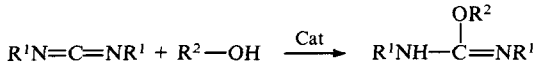
6

However, the kinetically controlled adduct **5** has not so far been isolated in the classical acylation reactions of ureas, only the *N*-acylureas **6** being found among the reaction products.[14-16] *N*-Acylureas **6** are formed as a result of the intramolecular thermodynamically more favourable O → N shift (migration) of the acyl group. For example, the acylation of *N*-methylurea by acetyl chloride affords *N*-acetyl-*N*-methylurea **6**,[13] which agrees with the formation of the *O*-acetyl intermediate **5**, although the secondary nitrogen atom should be more nucleophilic in the direct attack by the acylating agent.

2. Synthesis from carbodiimides

Carbodiimides (CDI) constitute one of the most important types of unsaturated compounds with a heterocumulated bond system. By virtue of thoroughly developed and reliable methods of synthesis, CDI have found extensive applications, mainly in peptide synthesis and for the immobilisation of biomolecules.[17,18] The close relationship between CDI and ureas is emphasised by the fact that ureas are one of the traditional sources of CDI[17-22] and the latter can be readily converted, in their turn, into ureas. CDI are obtained from 1,3-disubstituted ureas by dehydration with P_2O_5,[19] metal carbonyls [$Fe(CO)_5$, $Fe_2(CO)_4CNPh$, $Fe_2(CO)_9$, $W(CO)_6$, $Mo(CO)_6$],[20] triphenylphosphine dibromide,[21] or triphenylphosphine[22] in triethylamine and aromatic sulfonic acid chlorides under conditions of phase transfer catalysis,[23] or by the interaction of *N*-alkylideneureas with PCl_5.[24]

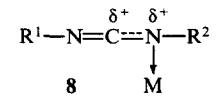
By virtue of their comparatively ready availability and high reactivity in reactions with nucleophiles, CDI have proved to be perhaps the principal synthons for the synthesis of *O*-alkyl(aryl)isoureas. The reactions of CDI with alcohols and certain phenols in the presence of specific catalysts or alkoxides in the synthesis of *O*-alkyl(aryl)isoureas do not even require heating.[25-32] The noncatalytic addition of alcohols and phenols to CDI is relatively ineffective because of the weak nucleophilic properties of these reagents.



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R^1, R^2 = Alk, Ar.

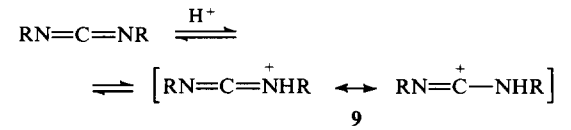
The relatively low nucleophilicity of alcohols (phenols), on the one hand, and the known tendency of CDI to undergo spontaneous or initiated polymerisation[33] during the synthesis of isoureas **7**, on the other, can be readily overcome by employing a series of synthetic procedures designed to increase the electrophilicity of the heterocumulene fragment of the CDI towards nucleophiles. In this part of the review, we shall quote only the studies which were published after the reviews of Bocharov[34] and Pankratov,[35] where reactions involving CDI, including the reactions of CDI with alcohols, were surveyed. The interaction of CDI with alcohols (phenols) is usually catalysed by copper salts (CuCl, $CuCl_2$, Cu_2O) or Zn^{2+}.[36-41] The catalytic action of metal ions apparently consists in the formation of a coordination complex between the CDI and the metal ion (via the imine nitrogen atom).



8

M = Cu(I), Cu(II), Zn(II).

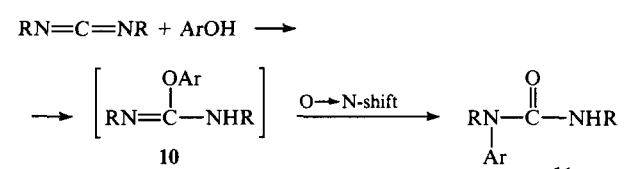
The formation of the coordination complex **8** leads to an increase in the electrophilicity of the central carbon atom of the CDI. Another method for the activation of CDI in reactions with nucleophiles, including alcohols, involves the use of proton-donors.[42,43] The protonation of CDI results in the formation of the electrophilic species **9**.



9

The preliminary *N*-functionalisation of the CDI by electron-accepting groups (acyl, sulfoxyl, and phosphoryl) significantly facilitates subsequent nucleophilic addition.[44]

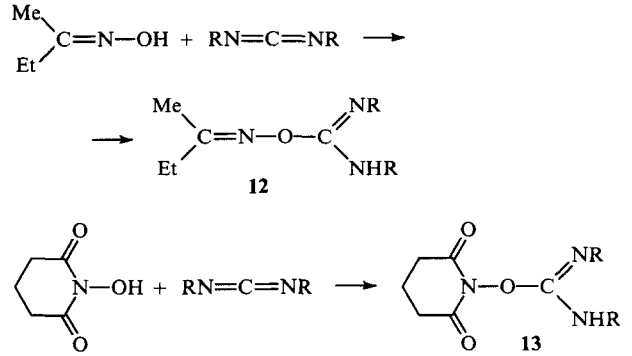
Proceeding now to certain characteristic features of the reactions of CDI with alcohols (phenols), we note in the first place that the interaction of CDI with alcohols affords the corresponding isoureas **7**, whilst the analogous reactions with phenols do not proceed unambiguously. The usual phenols react with CDI to form in most cases *N*-arylureas **11**[45-48] and many workers are inclined to assume that these reactions proceed via the *O*-aryl intermediate **10**, although there is no reliable evidence for this.



10 11

The fact that phenols with distinct acid properties react with CDI to form stable *O*-arylisoureas **10** may serve as indirect evidence in support of the existence of the intermediate **10**.[49-55] Such compounds have been isolated in the reactions of CDI with 2,6-dichloronitrophenol,[55] pentachlorophenol,[51,52] and 2-carboxy-4,6-dinitrophenol. It has been postulated that *ortho* substituents in the phenols mentioned above inhibit the usual O → N shift as a result of their steric influence on the reaction centre.

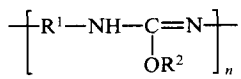
It has been shown in a number of studies[37,56-59] that the non-traditional isoureas **12** and **13** can be obtained from CDI and *N*-hydroxy-compounds.



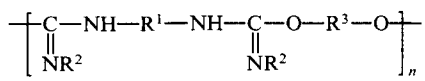
12 13

R = Alk, Ar.

Polycarbodiimides react with aliphatic alcohols to form the corresponding poly-*O*-alkylisoureas with structures **14** and **15**.[60–63]



14

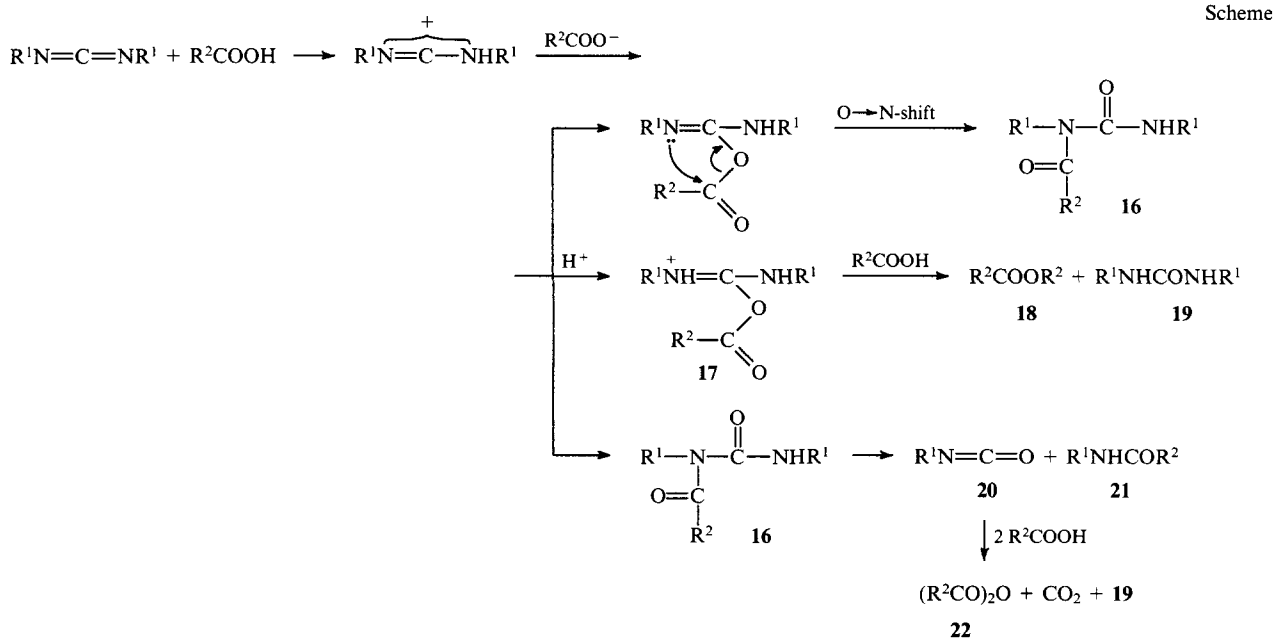


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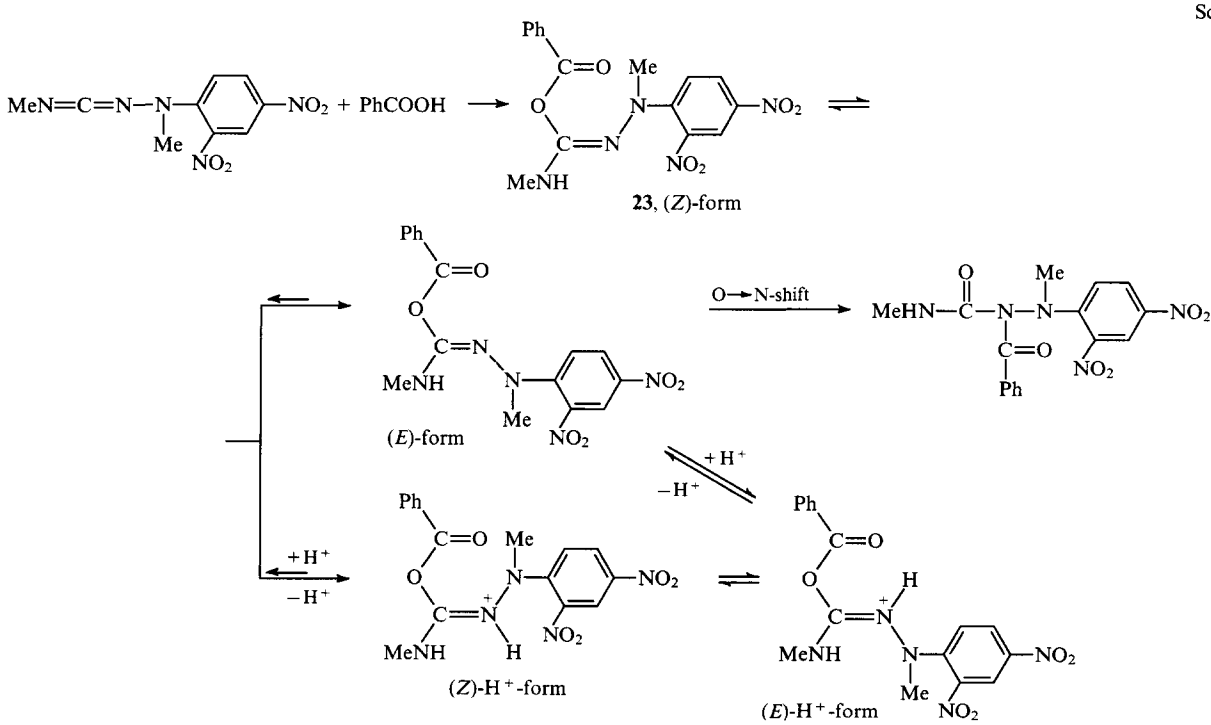
It is of interest that the polyisoureas **14** and **15** are more soluble and have lower melting points than the initial polycarbodiimides.

The attractive features of CDI in peptide synthesis stimulated detailed investigation of the reactions of CDI with carboxylic acids, including the kinetics of these processes.[18,64–70] The reactions of CDI with carboxylic acids (Scheme 1) are completed, depending on the acidity of the medium, temperature, and the amount of reactant, by the formation of either the *N*-acylurea **16**, or of the ester **18** and the urea **19**, or of the amide **21** and the anhydride **22** via the intermediate isocyanate **20**. The formation of the *N*-acylurea **16** is usually observed at elevated temperatures or when the reaction is carried out for a long time.[71] A highly acid medium promotes the formation of the esters **18** via the protonated intermediate **17**; sterically cumbersome groups R^1 or the use of a high temperature lead to decomposition of the *N*-acylurea **16** into the isocyanate **20** and the amide **21**, while the isocyanates **20** react with two molecules of a carboxylic acid to produce two molecules of the urea **19** and the anhydride **22** (Scheme 1).

Scheme 1



Scheme 2



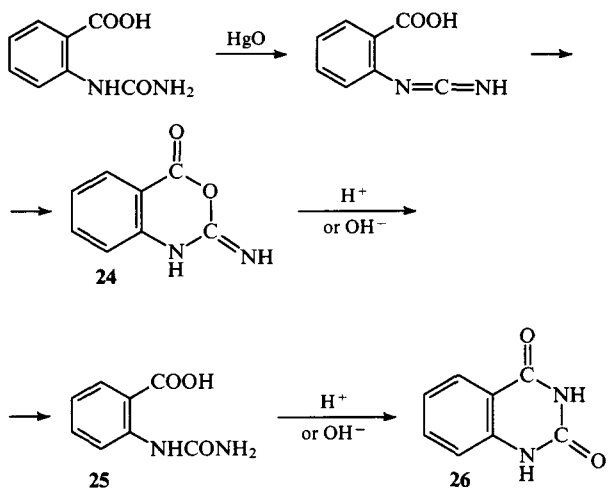
In order to eliminate the racemisation of the acid substrate, which is undesirable in peptide synthesis, and the competing O → N shift in reactions with carboxylic acid, one may employ *N*-hydroxysuccinimide or 1-hydroxybenzotriazole.[72,73]

It is believed[74,75] that poly-*N*-acylureas are formed from polycarbodiimides and carboxylic acids via the corresponding poly-*O*-acylated intermediate.

Comparatively recently, it has been possible to synthesise and isolate the stable *O*-acylisourea **23** (Scheme 2).[76,77]

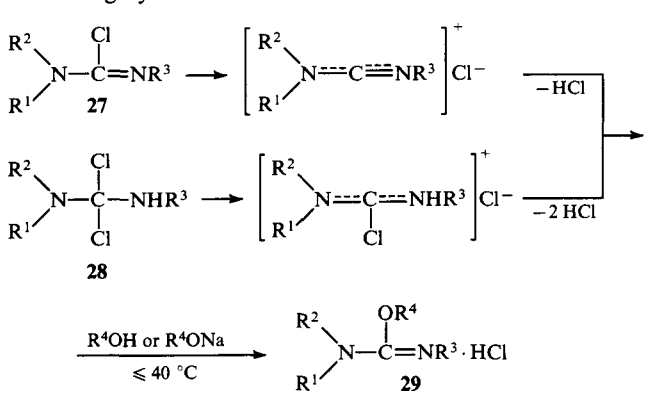
The stability of the *O*-acylisourea **23** is attributed to the (*Z*)-configuration relative to the C=N bond, while the (*E*)-isomer undergoes the spontaneous O → N shift of the acyl group.

The synthesis of 1,2-dihydro-2-imino-3,1,4-*H*-benzoxazolin-4-one **24**, which can be converted into the quinazolinedione **26** via the urea **25**, is a remarkable example of the intramolecular stabilisation of *O*-acylisoureas.[78]



3. Syntheses from chloroformamidines

Mono- and di-chloroformamidines **27** and **28** can be readily synthesised from the corresponding CDI and dry HCl.[17,18,33,34] They are sometimes obtained by treating *N,N,N'*-trisubstituted ureas with PCl_5.[4] Being highly reactive in dissociative reactions, the chloroformamidines **27** and **28** smoothly substitute the chloride anion by alkoxide anions, affording *O*-alkylisoureas **29** in a high yield.[79–82]

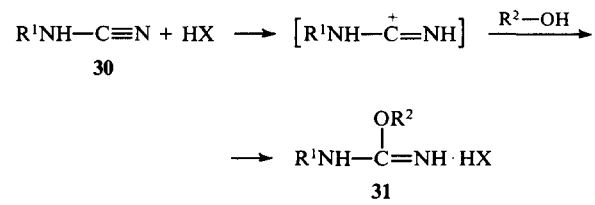


R^1–R^4 = Alk, Ar.

Despite the simplicity of the formation of the isoureas **29**, the methods of their synthesis based on chloroformamidines have not come to be widely used in preparative chemistry, which is evidently associated with the greater availability of CDI and ureas, although in certain cases (for trisubstituted isoureas) chloroformamidines are preferable.

4. Syntheses from cyanamides

The close relationship between ureas and cyanamides **30** can be seen on the basis of their interconversion: the dehydration of *N*-substituted ureas in basic media results in the formation of cyanamides **30**, whilst the reverse reaction affords ureas.[82] Cyanamides may be regarded also as a tautomeric form of CDI and the latter, as noted above, are 'genetically' close to ureas. Consequently cyanamides **30** tend to undergo the same addition reactions as CDI. As was in fact expected, cyanamides **30** react with alcohols in the presence of acids to form the isoureas **31** with a free imine group.[83–88]

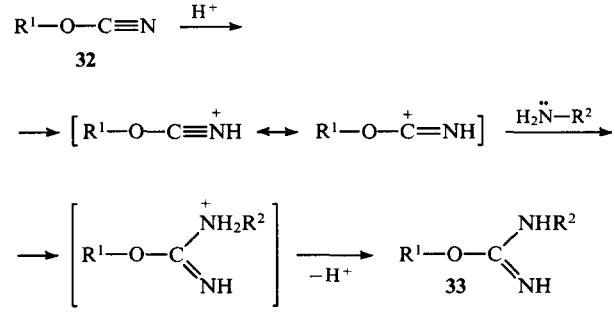


R^1, R^2 = Alk, Ar.

Both inorganic and organic acids are used as proton catalysts, whilst the isoureas **31** are isolated respectively as the halides and the sulfate, phosphate, carbonate, and nitrate salts or in the form of aliphatic and aromatic carboxylates.[83–88] ^{14}C-Labelled *O*-methylisourea has been obtained for biochemical research from the corresponding cyanamide and methanol in the presence of hydrogen chloride.[89]

5. Syntheses from organic cyanates

The methods of synthesis of isoureas examined above were based on the initial attack by nucleophilic alcohols (alkoxides) on the electrophilic carbon of the substrates, while the formation of isoureas from organic cyanates **32** is based on attack by a nucleophilic amine.



R^1, R^2 = Alk, Ar.

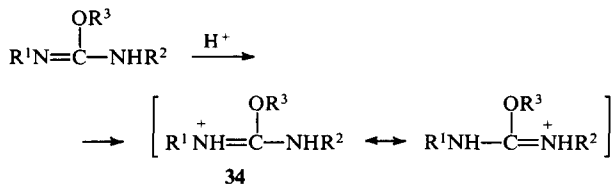
The reactions of organic cyanates **32** with amines or their salts are carried out as a rule in inert organic solvents at −50 to +150 °C, the best yields of the isoureas **33** being attained for equimolar proportions of the substrate and the reagent.[90–93]

6. Other methods of synthesis of isoureas

A series of examples of the synthesis of isoureas, not related directly to the methods of synthesis examined above, have been described in the literature.[94–97] However, analysis of these methods showed[94–97] that they definitely imply the intermediate formation of species the conversion of which into isoureas was examined above. Bearing this factor in mind and taking into account the fact that these examples of the synthesis of isoureas[94–97] represent isolated instances, we believe that they do not require detailed comments.

III. Chemical properties

Isoureas, which contain the iminoester functional group, are stronger bases (the pK_a values for isoureas are from 6 to 10) than ureas. Thus pK_a for *O*-methylisourea is 9.80, while that for the isomeric *N*-methylurea is 0.82.[98,99] The increased basicity of isoureas can be accounted for by the higher stability of their conjugate acids as a result of the resonance of the isouronium cation **34**, which gives rise to a fundamental difference between isoureas and *N*-substituted ureas.



34

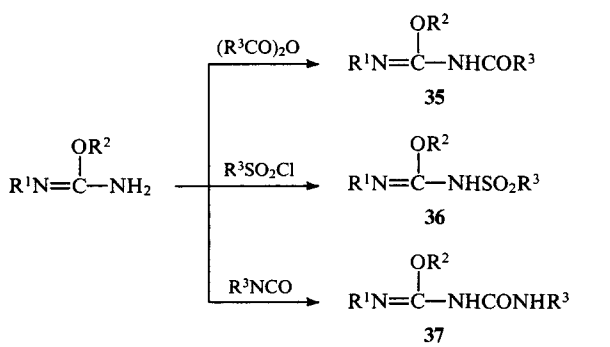
R^1-R^3 = Alk, Ar.

As was to be expected, isoureas are extremely reactive with respect to nucleophiles, but their free bases are themselves effective nucleophiles. The above general properties of isoureas make it possible to specify certain characteristic reactions which isoureas tend to undergo.

1. Reactions with participation of a nucleophilic nitrogen atom

In synthetic practice, *N*-acylation processes (Scheme 3) have been most widely investigated among the reactions of isoureas with widely the particpation of a nucleophilic nitrogen atom.[100-106]

Scheme 3



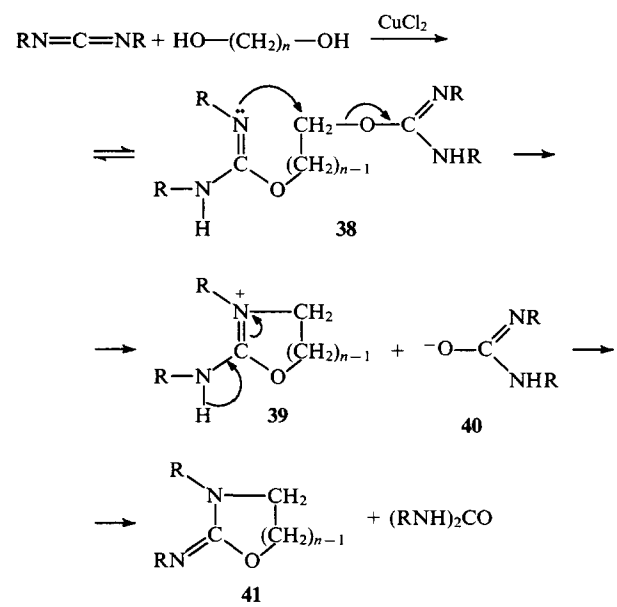
35 **36** **37**

R^1, R^3 = Alk, Ar; R^2 = Alk.

Examples of the synthesis of derivatives of bisisourea from phthalic acid dichloride and the corresponding isoureas are known.

N-Acylisoureas **35-37** are as a rule formed smoothly and in high yields, the procedure for their isolation not requiring special conditions. The key stage in the formation of type **41** 1,3-oxazolidines involves nucleophilic attack by the imine nitrogen atom on the methylene group. Thus the interaction of glycols with CDI, catalysed by copper chloride,[107,108] is completed by the cyclisation of the intermediate bisisoureas **38** via intramolecular nucleophilic attack by the imine nitrogen atom on the terminal methylene group and the transfer of the proton in the cyclic isouronium ion **39** to the highly basic anion **40**.

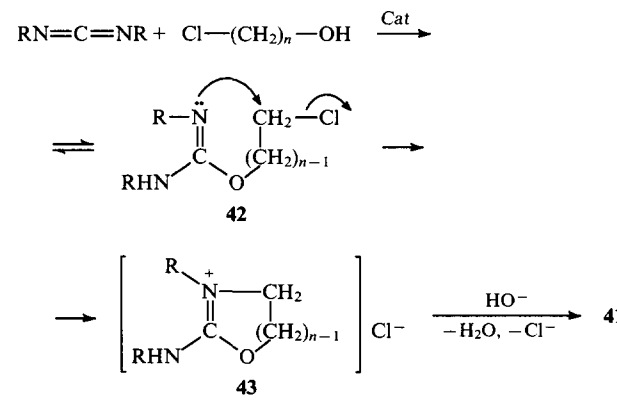
The reactions of cyclohexanediols with CDI afford the corresponding oxazolidines with the *trans*-configuration.[109] It has been established that the type **41** oxazolidines are also formed in the reaction of CDI with certain haloalcohols.[103,105]



38 **39** **40** **41**

R = Alk, Ar; n = 2, 3.

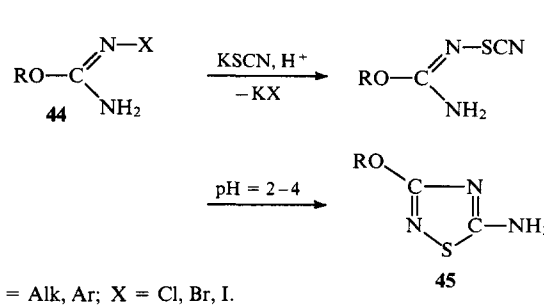
It has been suggested that the hydrochloride **43** is formed as a result of intramolecular nucleophilic substitution of the chlorine atom by the imine nitrogen in the isourea **42** and the subsequent dehydrochlorination in a basic medium leads to the oxazolidines **41**.[110]



42 **43**

R = Alk, Ar; n = 2,3; Cat = $CuCl_2$,[103] HBF_4.[105]

Another example of the cyclisation of isoureas has been demonstrated by Goerdeler and Bechlars.[111] It was established that the isoureas **44** react with thiocyanates under the influence of inorganic acids to form 3-alkoxy(aryloxy)-5-amino-1,2,4-thiadiazoles **45**.

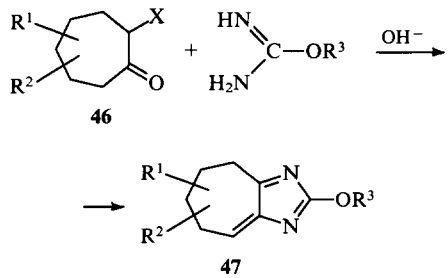


44 **45**

R = Alk, Ar; X = Cl, Br, I.

The thiadiazoles **45** proved to be extremely stable compounds, which are readily acylated and give rise to nitrosoamines capable of azo-coupling in an acid medium.[111]

The reactions of derivatives of the tropones **46** having functional-group substituents in the 2-position with isoureas or their salts in the presence of bases result in the formation of the cyclic 2-alkoxyimidazole derivatives **47**.[112]

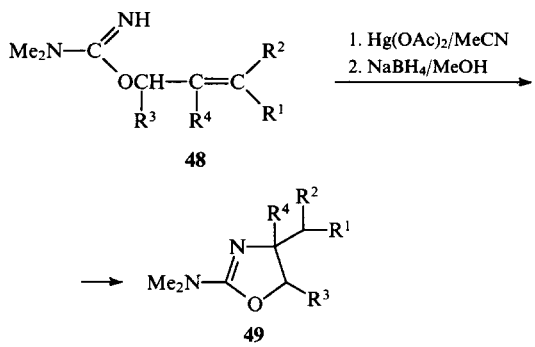


46 **47**

$R^1 = R^2$ = H, Alk, Ar, $PhCH_2$, Hal, OH, CN, NHY;

X = Br, Cl, AlkO, TsO; R^3 = Me, Et.

The intramolecular electrophilic cyclisation of alkyl-substituted 1,1-dimethylisoureas **48**, obtained from the corresponding alcohols and cyanamide, leads to the formation of the oxazole derivatives **49**.[113]



48 **49**

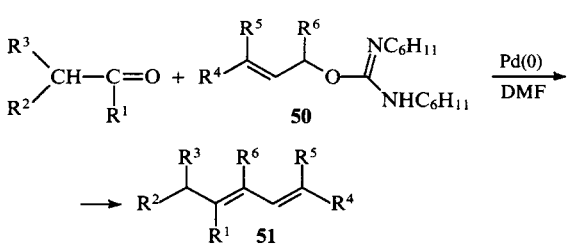
R^1–R^4 = H, Ar, Alk.

The relatively unstable *N*-haloisoureas RO–C(=NX)–NH_2 have been synthesised.[111] Their relative stability was found to depend on the nature of the substituent R (Me < Et < β-ClC_2H_4 < Ph < $PhCH_2$ ≪ cyclo-C_6H_{11}) and on the halogen X (I < Br < Cl). It was shown that the condensation of *O*-alkylisoureas with cyanamide gives rise to *O*-alkyl-*N*-cyanoisoureas and dicyandiamide.[114]

2. Reactions accompanied by the elimination of the *O*-alkyl(aryl) fragment

a. *C*-Alkylation

There are few examples of the *C*-alkylation of *O*-alkylisoureas in the literature. A convenient method of synthesis of alkenes employing 2-allyl-isoureas **50** as an effective agent for the direct α-allylation of ketones and aldehydes in the presence of zerovalent palladium or with added triphenylphosphine (for aldehydes) has been developed comparatively recently.[115,116]

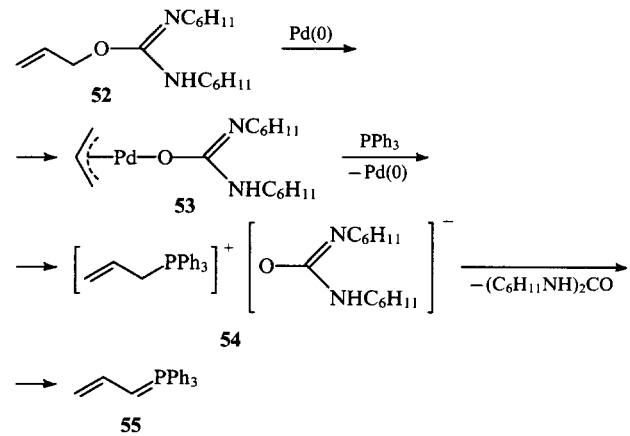


50 **51**

R^1 = H, Alk, Ph; R^2, R^3 = H, Alk, Ph;

R^4–R^6 = H, Me, Pr, C_6H_{11}, Ph.

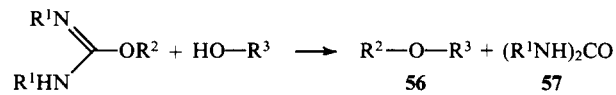
It has been suggested that the oxidative coupling of the isourea **52** with zerovalent palladium results in the formation of the π-allyl intermediate **53**. When triphenylphosphine is employed, the intermediate **53** reacts with the latter as a nucleophile, affording the phosphonium salt **54**. As a strong base, the isourea anion in compound **54** abstracts an α-proton, affording the allylidenetriphenylphosphorane **55** and the latter is then used as an agent for the introduction of the allylidene group into benzaldehydes via a Wittig type reaction.



52 **53** **54** **55**

b. *O*-Alkylation (arylation)

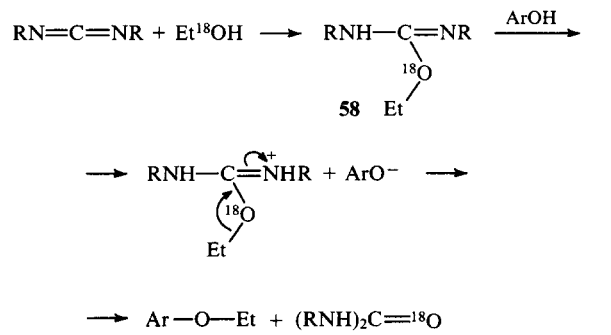
Isoureas react smoothly with alcohols or phenols, giving rise to the ethers **56**; the leaving groups are the ureas **57**.[108, 117–119]



56 **57**

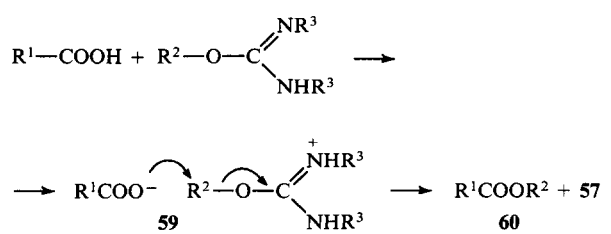
R^3 = Alk, Ar.

It has been established that type **56** ethers are formed in the interaction of ^{18}O-labelled ethanol with CDI by attack of the alkoxide or aryloxide anions on the alkyl group of the intermediate *O*-alkylisoureas **58**.[120]



58

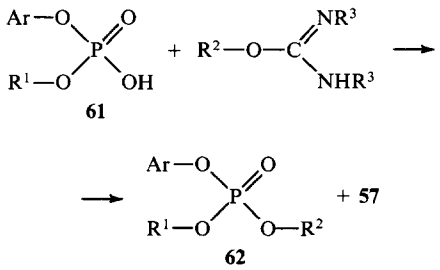
The esters **60** can be obtained in high yields by the reaction of *O*-alkylisoureas with carboxylic acids.[121,122]



59 **60**

The existing ideas about the mechanisms of the reactions of isoureas with carboxylic acids are based on the fact that the isoureas are initially protonated to give the intermediate **59** and the latter is then attacked by the carboxylate anion at the alkoxy-group with formation of a tetrahedral intermediate.

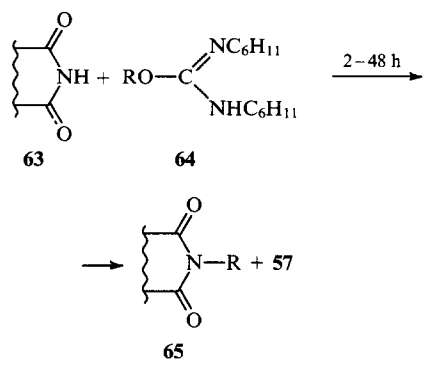
The phosphates **61** react readily with *O*-alkylisoureas to form the corresponding esters **62**.[123]



R^1, R^2 = H, Alk.

c. *N*-Alkylation

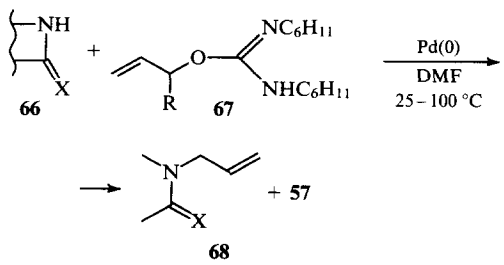
It has been found comparatively recently[124,125] that the refluxing of cyclic imides **63** with *O*-alkyldicyclohexylisoureas **64** in dimethylformamide (DMF) makes it possible to synthesise the *N*-alkylimides **65** in satisfactory yields.



R = Me, Bu, (±)-Bu^s, (±)-$C_6H_{13}CHMe$, $C_{12}H_{25}$.

According to the authors, the reaction proceeds via an S_N2 mechanism with 98% inversion of the configuration. This has been confirmed by the reaction of [(*R*)-(−)-1-methylheptyl]-isourea **64** with phthalimide, which leads to [(+)-1-methyl-heptyl]phthalimide. On treatment with hydrazine hydrate, the latter is converted into [(*S*)-(+)-1-methylheptyl]-amine.

The zerovalent palladium-catalysed direct *N*-allylation of amides, thioamides, and certain lactams **66** by *O*-allylisoureas **67** has been achieved.[126]



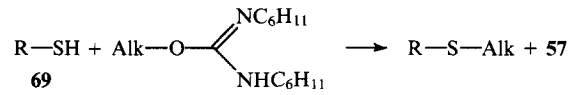
X = O, S.

The yields of the *N*-allyl derivatives **68** are in the range 27%–87%.

In the allylation of certain heterocyclic bases (thymine, thymidine, uridine) by *O*-alkylisoureas, it was established that this entails the exclusive *N*-alkylation of the azaheterocycles, while the isomeric *O*-alkyl derivatives were not detected even in trace amounts.[127,128]

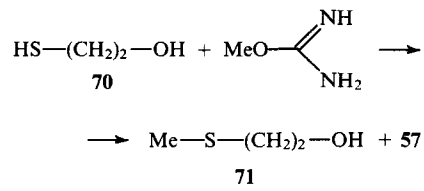
d. *S*-Alkylation

It has been shown in a number of studies[129,130] that *O*-alkyl-isoureas are excellent *S*-alkylating agents for mercaptans and thiophenols **69**.

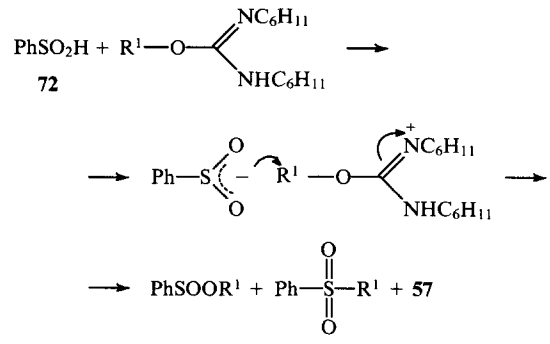


R = Alk, Ar.

It is remarkable that the reaction of *O*-methylisourea with 2-mercaptoethanol **70** affords selectively the *S*-methylated product **71**.[130]



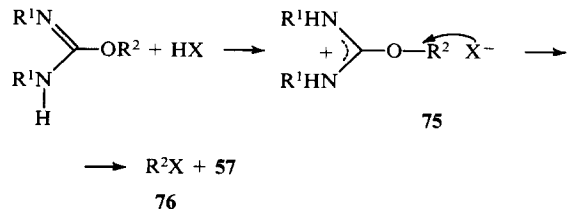
The interaction of *O*-alkylcyclohexylisoureas with benzene-sulfinic acid **72** leads to the preferential formation of the sulfinates **73** (*O*-alkylation products), although the formation of appreciable amounts of the sulfones **74** (*S*-alkylation products) has also been observed.[131]



The overall yield of the alkylation products was 60%–90%. The ratio of the sulfinates **73** and the sulfones **74**, determined from ^{1}H NMR spectroscopic data, depends on the nature of the group R and the solvent employed, branched groups R inducing the virtually 100% formation of the sulfinates **73**.

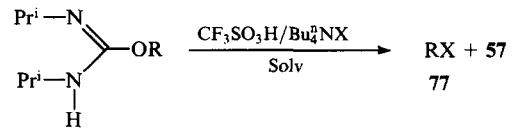
e. Synthesis of alkyl halides

Nucleophilic substitution in the protonated urea **75** on heating with hydrogen halides, where the leaving groups are neutral ureas **57** and alkyl halides **76** are the products, has long been known.[132–135]



X = Cl, Br, I.

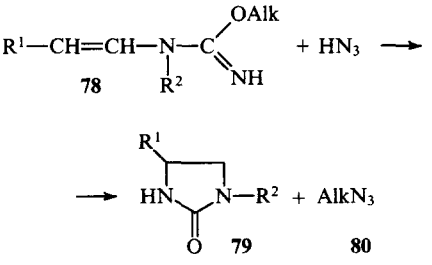
Since the traditional methods of synthesis of alkyl halides **76**, especially the bromides, frequently involve the formation of insufficiently pure target products, an effective modification of this reaction has been proposed,[136] permitting the synthesis, together with the usual alkyl halides, also of the unsaturated alkyl halides **77** in 57%–90% yields.



X = Br, I.

The use of trifluoromethanesulfonic acid instead of the traditional hydrogen halides made it possible to regulate accurately the amount of acid and to eliminate nucleophilic competition between the added halide and the acid residue. Kinetic study showed that this is a first-order reaction and that its rate depends on the concentration of the *O*-alkylisourea salt **75**. It has been established that, depending on the substituent, the reactivity of isoureas decreases in the following sequence: allyl = propargyl = benzyl > primary > secondary. Although the reaction involving nucleophilic substitution in solution in hexamethylphosphoramide and DMF proceeds more effectively, it is preparatively more convenient to employ dichloromethane or chloroform.

It has been shown[137] that the reaction of *O*-alkyl-*N*-alkenyl-isoureas **78** with hydrazoic acid does not lead to the expected aminotetrazoles, as in the case of iminoesters,[1] but affords *N*-alkylimidazolidin-2-ones **79** and alkyl azides **80**.



$R^1 = R^2$ = Alk, Ar.

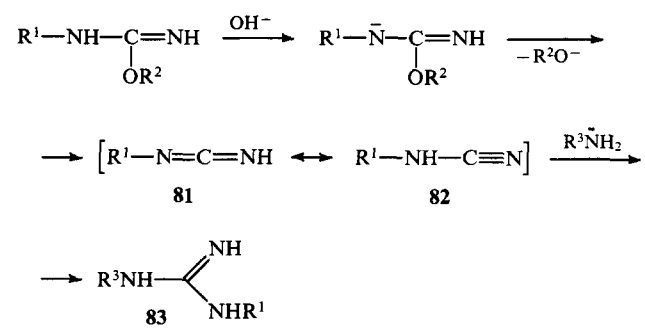
It has been suggested[137] that the heterolytic dissociation of the O–Alk bond accompanied by nucleophilic substitution by the azide anion takes place in the hydrazoate salt of the isourea **78**. The isourea residue undergoes heterocyclisation to compound **79** apparently via intramolecular electrophilic addition to the double bond.

The formation of *N*-substituted ureas **57** has been observed in a number of instances on heating *O*-alkylisoureas.[125,136] Compounds **57** are obtained by elimination of an alkene from the *O*-alkylisoureas.

3. Reactions accompanied by the elimination of the alkoxy-fragment

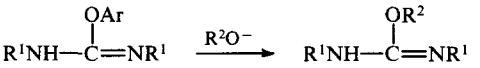
Among reactions of this type, the reactions of isoureas with amines, leading to guanidines, are best known.[83,138]

It has been suggested that the CDI **81** is formed initially via β-elimination and then undergoes a tautomeric transformation into the cyanamide **82**. The cyanamide undergoes nucleophilic attack by the amine.



R^1–R^3 = Alk, Ar.

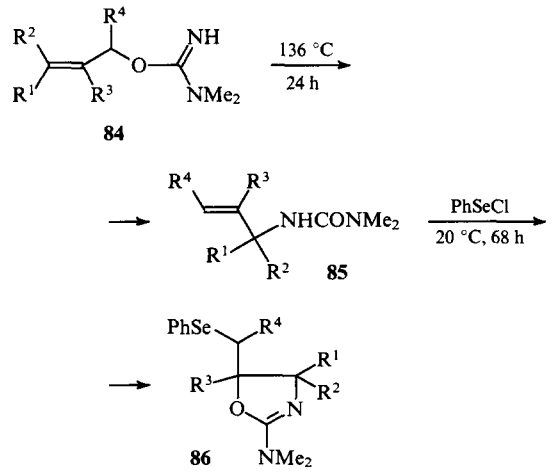
The exchange of the aryloxy-group for an alkoxy-group sometimes occurs in *O*-arylisoureas. It takes place on heating in the presence of the R^2O^- alkoxide ion via a mechanism involving a process similar to elimination-addition.[4]



It has been established that *N*-alkyl- and *O*-aryl-isoureas give rise to the corresponding alkanes and arenes on reduction with hydrogen over palladium.[139–141] Consequently, these reactions can be regarded as a general method for the reduction of alcohols and phenols to hydrocarbons. In a strongly basic medium, *N*-acylisoureas give rise to *N*-acylcyanamides,[142] whilst a high-temperature treatment of isoureas (250–300 °C) leads to the formation of isocyanates.[143]

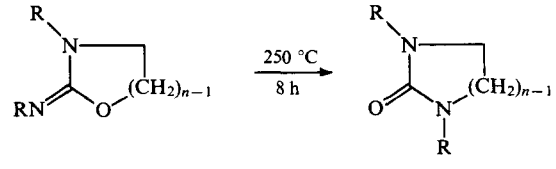
4. Other reactions

The isomerisation of the isoureas **84** on refluxing in xylene leads to the formation of *N*-substituted ureas **85**, which are converted into the oxazolines **86** on treatment with PhSeCl in chloroform in the presence of silica gel.[113]



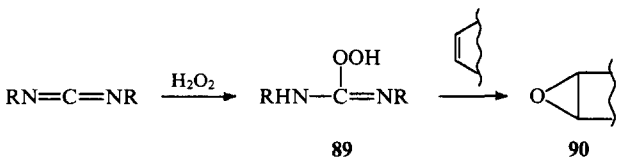
R^1–R^4 = H, Alk, Ar.

On heating to 250 °C, the isoureas **87** rearrange to the cyclic ureas **88**.[144]



n = 2, 3.

The interaction of CDI with hydrogen peroxide leads to the peroxycarboximidic acids **89**, which are effective agents for the oxidation of alkenes and especially arenes to the corresponding epoxides **90**.[145]



89 **90**

IV. Applications of isoureas

The principal fields in which isoureas are employed are agriculture, medicine, and biochemistry. Isoureas are used to a somewhat lesser extent in polymer and analytical chemistry.

Thus isoureas exhibit a high herbicidal activity,[146–148] are used as plant growth regulators,[146–153] and promote the acceleration of the growth of wool, improvement in the production of meat and milk from animals, and improvement in the assimilation of animal feed.[154]

The study of the biological activity of *O*-alkylisoureas established their stimulating effect on smooth muscles.[155] Certain isoureas are used as antiinflammatory medicinal drugs.[156] A few possess an anticancer activity.[157] Isoureas linked to purine or pyrimidine bases and containing fluorescent labels are used to detect deoxyribonucleic and ribonucleic acids and their fragments.[158]

Isoureas are employed in the synthesis of auxiliary agents for the dyeing of textiles and polymers[159] and for the synthesis of copolymers with a specified fibre shape.[60–63]

The pronounced basicity of isoureas made it possible to synthesise from them a large number of coloured coordination compounds and to investigate their properties.[160–166]

V. Conclusion

Unfortunately, new studies on the development of general methods of synthesis of isoureas have not been published recently. However, more vigorous investigation of the chemical properties of isoureas promises to yield important results both synthetically and theoretically. In this context, one of the promising procedures involves the study of the reactions of isoureas with various amino-derivatives which are potentially capable of giving rise to the synthesis of new heterocyclic systems. Analysis of literature data has shown that the reactions of isoureas with organometallic compounds, especially with Grignard reagents, have not been investigated. For example, the possibility of the addition of a Grignard reagent to the C=N bond and of the direct substitution of the alkoxy-group in isoureas by an alkyl residue may lead to interesting results, as has been shown for iminoesters.

The fairly large set and availability of the synthons for the preparation of a wide variety of isoureas have been by no means fully made use of, in our view, for the needs of medicine, biochemistry, and other purposes.

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