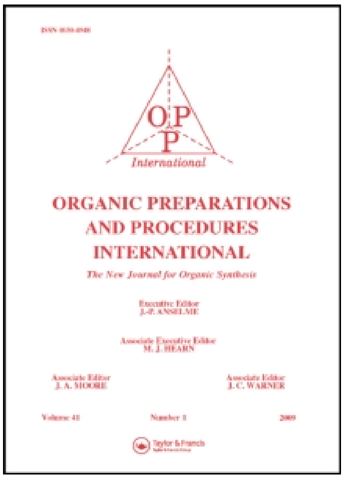

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SYNTHETIC APPLICATIONS OF ISOUREAS. A REVIEW

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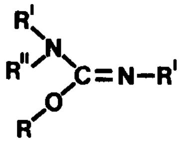
Dedicated to Professor C.G. Overberger on the Occasion of his 60th Birthday

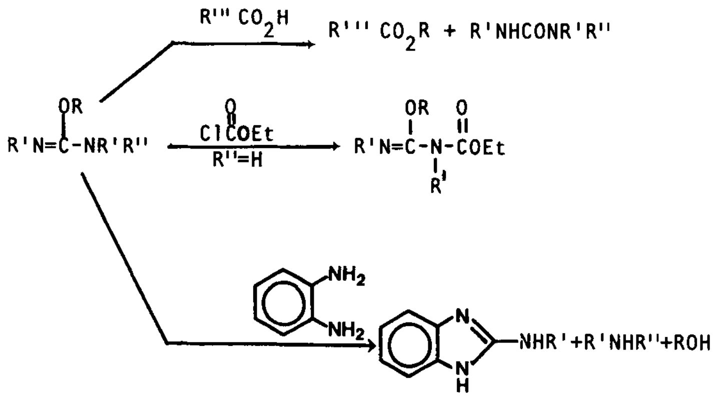
INTRODUCTION

Isoureas (or pseudoureas) are a unique and highly reactive class of reagents possessing many demonstrated and potential applications in organic synthesis. Their reactivity stems, in part, from their isomeric relation-



ship to ureas. Many reactions (Eq. 1) are based on the facile loss or rearrangement of the O-substituent to give the thermodynamically more stable urea. In this respect, the isoureas are excellent alkylation and esterification agents. Other reactions are based on the nucleophilicity of the isourea nitrogens (Eq. 2) or on exchange of the nitrogen and oxygen groups of the isourea (Eq. 3).

A previous review[1] described the large number of applications of various isoureas (R = 1°, 2° or 3° alkyl) as alkylating agents. These applications include the formation of esters of carboxylic acids and phsophoric acids, N-alkylated amino acid betaines, N-alkylated heterocycles, and phenolic and thiol ethers. All but a few of these uses involved N,N'-disubstituted isoureas obtained by the copper-catalyzed addition of alcohols to

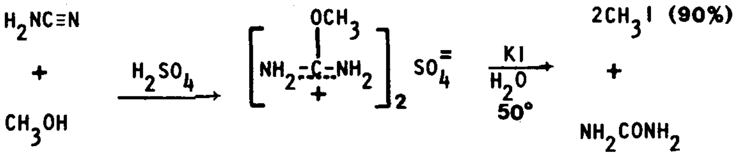


carbodiimides[2,3] such as the commercially available diisopropyl or dicyclohexyl deravitives.

In addition to alkylations, isoureas are intermediates or reagents for a number of unique and synthetically useful reactions. These include a variety of conversions such as that of methanol to methyl iodide,cyanamide to secondary amides, aldehydes to nitriles,and alcohols and phenols to the alkanes and arenes. Knowledge of these reactions of isoureas requires reassessment of two accepted derivatization procedures, one involving cyanogen bromide activation of carbohydrates for amine coupling, the other resulting in peptide guanidination with O-methylisourea. Isoureas also find extensive application in the formation of heterocycles such as pyrimidines. This review will survey these uses with the purpose of increasing the general awareness of isoureas and, hopefully, sparking new and extended applications of isoureas to synthetic problems. While a majority of the procedures to be discussed employed symmetrically disubstituted isoureas (Eq. 1-3, R'' = H; R' = isopropyl, cyclohexyl, phenyl or tolyl), other deravitives such as the N,N'-unsubstituted compounds (R' = R'' = H) have also been used. The entire range of derivatives have been reported including both alkyl- and aryl-substituted compounds. The synthetic availability of the five basic families is currently being reviewed.[4] It should be noted that several isoureas may now be obtained commercially.[1]

1. Methyl Iodide Synthesis

A brief description has appeared on the overall conversion of methanol to methyl iodide via the parent isourea (Eq. 4).

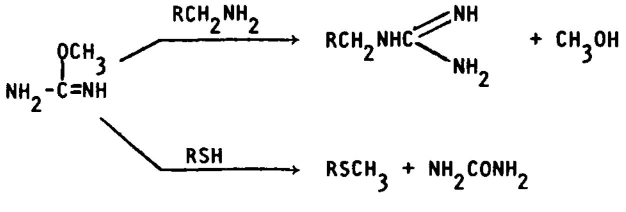


$$H_2NC{\equiv}N + CH_3OH \xrightarrow{H_2SO_4} \left[NH_2\text{-}\overset{OCH_3}{\underset{+}{C}}\text{-}NH_2\right]_2 SO_4^{=} \xrightarrow[50^\circ]{KI,\ H_2O} 2CH_3I\ (90\%) + NH_2CONH_2 \quad (4)$$

The excellent yield and mild conditions reported suggest that further investigation of the generality of this reaction should be carried out with respect to other O-alkyl substitutents and other classes of isoureas. Specifically, the N,N'-dialkylisoureas should be examined since they are readily available in essentially quantitative yield from the alcohol and carbodiimide. One valuable application of this procedure would be to the synthesis of $^{13}CH_3I$ specifically, and isotopically labelled alkyl iodides in general. High-yield conversion of the less expensive $^{13}CH_3OH$ to the iodide would be economically advantageous.

2. Guanidination

One of the most important uses of isoureas in biochemical studies is that of the commercially available O—methylisourea for conversion of side-chain amine groups of amino acids and peptides to guanidine moieties



$$NH_2\text{-}\overset{OCH_3}{C}{=}NH \xrightarrow{RCH_2NH_2} RCH_2NHC({=}NH)NH_2 + CH_3OH \quad (5)$$

$$NH_2\text{-}\overset{OCH_3}{C}{=}NH \xrightarrow{RSH} RSCH_3 + NH_2CONH_2 \quad (6)$$

(Eq. 5). This has long been considered a clean, straightforward procedure.[6] Recent reports of competing reactions with amine, acid and thiol groups indicate, however, that this is not always the case.[1] Competing reactions should be especially evident for peptides and enzymes which contain a great deal of diverse side-chain functionality. A specific example involves the inactivation of papain with O-methylisourea in which the inactivating process was shown to be sulfur alkylation at the active site as in Eq. 6.[7] It is important that these additional reactions of isoureas be considered before attempting guanidination.

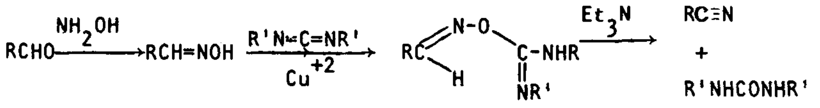
3. Cyanogen Bromide Activation of Carbohydrates

One of the more common methods of introducing reactive functionality in carbohydrate oligomers and polymers involves initial treatment of these substrates with cyanogen bromide (CNB) followed by coupling of various amine groups to the resulting cyanate ester (R-O-CN). This has been important for drug incorporation into dressings, cellulose modification, and anchoring or "insolubilization" of a variety of enzymes. While the procedure does result in chemically bound species, the nature of the binding group was only recently clarified. Through spectroscopic analysis and isoelectric focusing experiments, the tether moiety was found to be the isourea;[8] that is, the $RO\text{-}C{\equiv}N$ group converted to the $RO\text{-}\overset{NH}{\overset{\|}{C}}\text{-}NHR'$ species on reaction with amines. Since this procedure is widely used, current knowledge of the reactivity of the resulting isourea with carboxylic acid, amine and thiol groups demands a reassessment of the method. Specifically, gradual release of the bound group may be occurring with loss of the substituted urea derivative. For polymer-bound drugs, enzymes and affinity labels, such slow release will be of immediate concern and must be carefully evaluated. On the other hand, intentional reaction of these isourea moieties *via* loss of the urea may allow incorporation of a variety of heterocycle, ester and thiol ether groups into the carbohydrate substrate.[1] This method could thus lead to variouslysubstituted derivatives of the polysaccharides, for example, which would be of synthetic and medicinal interest.

A further consideraiton is the nucleophilicity of the isourea nitrogens. The isoureas obtained from CNB treatment of agarose followed by reaction with alkyl amines possess pKa values very similar to the free alkyl amines. They were found to be very reactive in releasing the phenolate anion from p-nitrophenyl acetate;[9] the parent O-methylisourea behaved similarly. While this reaction was developed as an analytical tool for determining the amount of isourea incorporation, the nucleophilicity displayed will have importance with respect to side-reactions involving modification or application of polymer-bound enzymes, affinity labels and reagents.

4. Nitrile Synthesis

Vowinkel has extended his previous investigation[1] of the synthetic applications of isoureas to include two new areas, the first of which is nitrile synthesis. The overall process (Eq. 7) involves conversion of an aldehyde to the oxime, formation of the oxime isourea and finally urea elimination to give the nitrile.[10] Isolation of the oxime and the isourea is not required and a one-pot synthesis thus results. The oxime is obtained with hydroxylamine hydrochloride in a pyridine-water mixture. A two-phase system is then developed by addition of CH_2Cl_2 along with Et_3N and $CuSO_4$. Finally, a CH_2Cl_2 solution of dicyclohexylcarbodiimide is added and the mixture stirred for several hours at room temperature. Work-up and purification gives generally excellent yields (>90%) of the nitriles.

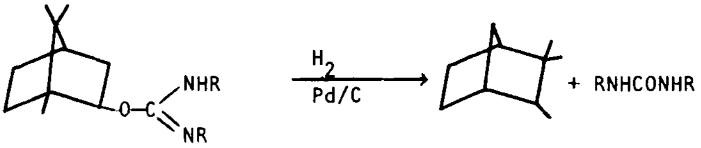


(7)

The reaction works well for a wide variety of alkyl and aryl aldehydes. The procedure is mild, clean and easy to carry out. Functional groups which would competitively react with the diimide must, of course, be excluded.[1] Nonetheless, this application of isoureas as intermediates in the dehydrative synthesis of nitriles offers a valuable and general alternative to previous methods.

5. Dehydroxylation of Alcohols and Phenols

Vowinkel's second recent development in isourea chemistry allows the overall reductive removal of HO-groups. Hydrogenolysis of a series of O-alkylisoureas (obtained in nearly quantitative yield from dicyclohexylcarbodiimide and the alcohol) led to excellent yields of the alkanes in most cases.[11] Generally, low pressure conditions at room temperature required 0.5-30 hrs.; however, for the menthyl- and bornyl-compounds longer reaction times were required, skeletal rearrangements occurred and low yields were obtained (Eq. 8). The method worked well for 1°, 2° and 3° alcohol derivatives and especially well for benzyl alcohols.

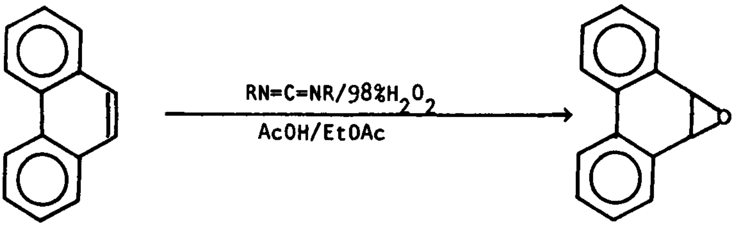


(8)

The procedure was also applied to dehydroxylation of phenols and related compounds.[12],[13] Formation of the O-arylisoureas involved either uncatalyzed addition of the phenols to an excess of various N,N'-dialkyl- or N,N'diarylcarbodiimides[12] (method A) or sequential formation of the aryl cyanate and the isourea by treatment of the phenol with cyonogen bromide followed by addition of a secondary amine (method B).[13] Although the O-alkylisoureas were obtained almost quantitatively, yields of the O-aryl derivatives were in the range of 54-80% with method A and ≥ 86% with method B. Isolation of the O-arylisoureas was sometimes preformed by formation of the picrate or oxalate salts. Hydrogenolysis with Pd/C at room temperature and low pressure was normally complete after 1-9 hrs. Overall yields of the arenes were generally good to excellent. Limitations include groups which react with either carbodiimide or isourea as well as aromatic halides which are susceptible to hydrogenolysis. The dehydroxylation reaction via isoureas is thus general for both alkyl and aromatic hydroxyl groups and provides a useful addition to the synthetic arsenal of the organic chemist.

6. Arene Oxide Synthesis

An application of isoureas to oxide formation has recently been described which is nearly the reverse of the dehydroxylation reaction. This application involves the direct epoxidation of phenanthrene and pyrene with a mixture of N,N'-dialkylcarbodiimide, H_2O_2 and acetic acid in ethyl acetate (Eq. 9).[14] While the yields are not high (28% and 27%, respectively, based on reacted arene), the reaction is mild and seems to mimic the biological pathways which are implicated in the carcinogenicity of these compounds. The epoxidation was shown not to proceed through the peroxyacetic acid, thus suggesting the peroxyisourea as the active reagent. The method is also reported to give alkene epoxidation under mild conditions; further description of this and the arene oxide synthesis was promised.



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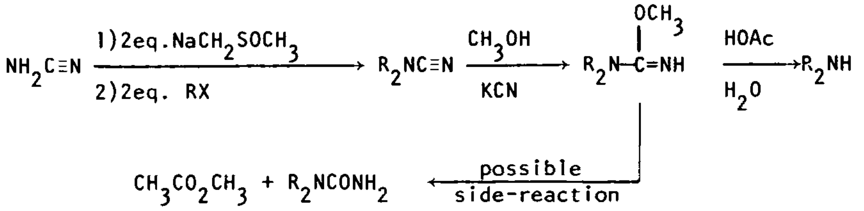
7. Secondary Amine Synthesis

A recently-available synthesis of secondary amines was based on the dialkylation of cyanamide followed by removal of the cyano group (Eq. 10). The latter was frequently a difficult reaction until the introduction of a



$$NH_2C\equiv N \xrightarrow[2)\,2eq.\ RX]{1)\,2eq.\,NaCH_2SOCH_3} R_2NC\equiv N \xrightarrow[KCN]{CH_3OH} R_2N{-}\overset{\overset{OCH_3}{|}}{C}{=}NH \xrightarrow[H_2O]{HOAc} R_2NH \quad (10)$$

$$CH_3CO_2CH_3 + R_2NCONH_2 \xleftarrow[\text{side-reaction}]{\text{possible}} R_2N{-}\overset{\overset{OCH_3}{|}}{C}{=}NH$$

two-step procedure involving the intermediate isourea.[15] A series of allylic and benzylic groups were incorporated into the cyanamide in 55-90% yields respectively. The yield of the hydrolysis step might be improved by use of inorganic acid catalysis since carboxylic acids may be involved in methyl ester formation with concomittant release of the N,N-dialkylurea.[1] This points out the additional possibility of the use of the intermediate isoureas for the directed synthesis of the ureas in the absence of water via ready loss of the O-methyl group.

8. Heterocycle Synthesis

Other than alkylations and esterifications,[1] the use of isoureas for the formation of a variety of heterocyclic compounds has received the most widespread attention. Three general areas exist:

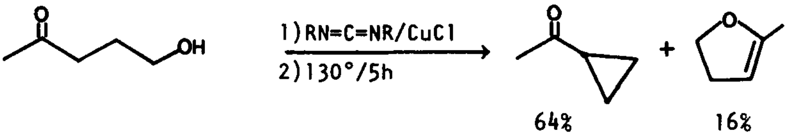
(1) ring-closures in which all or part of the isourea is eliminated.

(2) condensations in which both isourea nitrogens are included directly or indirectly into the heterocycle.

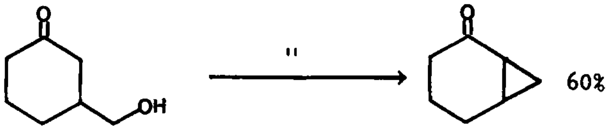
(3) reactions giving heterocycles containing the oxygen and one of the two isourea nitrogens, the other being exocyclic.

a. Involving Loss of Isourea

The first elimination resulted in competitive cyclopropane and enol ether formation. The synthesis involved initially the N,N'dicyclohexylisoureas of δ-hydroxy ketones which were then pyrolyzed. Loss of the urea involved C-C or C-O bond formation as shown in Eq. 11:[16]

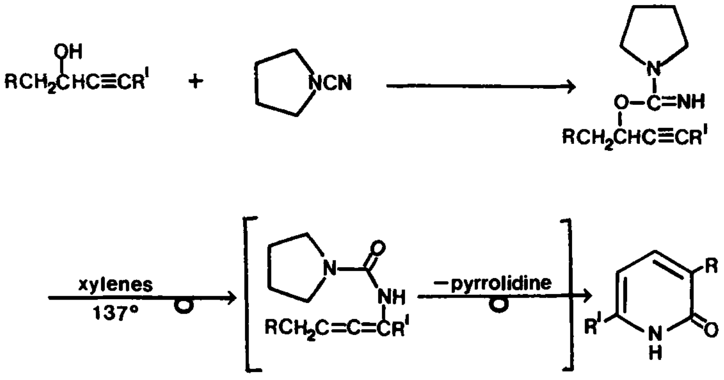


(11)



(12)

When applied to 2-(β-hydroxyethyl)cyclohexanone, the cyclopropyl ketone and the enol ether were obtained in about 20% and 60% yields, respectively. However, when 3-(hydroxymethyl)cyclohexanone was used, only the fused cyclopropyl compound was isolated (Eq. 12). The overall reaction here is formally dehydration, although the formation of C-C bonds <u>via</u> the isoureas is rare compared to heteroatom attack at the α-carbon to the oxygen of the isourea. However, a related report involving a thermolysis of cyclohexanol isourea involved urea loss to give cyclohexene.[17]

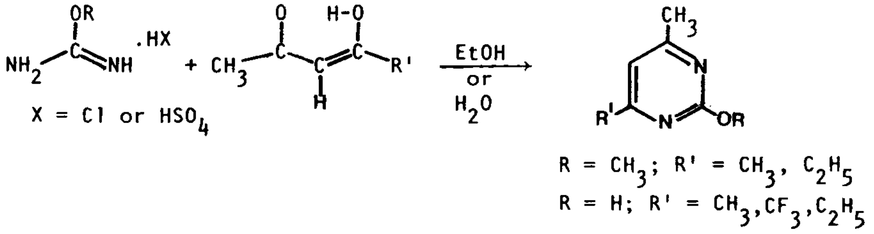


(13)

2-Pyridone synthesis (Eq. 13) involved initial base catalyzed addition of propargyl alcohols to 1-cyanopyrrolidine to give the intermediate isourea. Thermolysis was suggested to lead initially to the N-substituted allene, which through hydrogen migrations and loss of pyrrolidine gave the 2-pyridone products. Yields were generally $\geq$ 60% and R and R' were various combinations of H, CH_3, C_2H_5, n- and i-C_3H_7, t- C_4H_5 and phenyl. The reaction gave low yields when R = R'= Ph and R = C_2H_5, R' = H; a competitive cyclization occurs which will be discussed in section c.

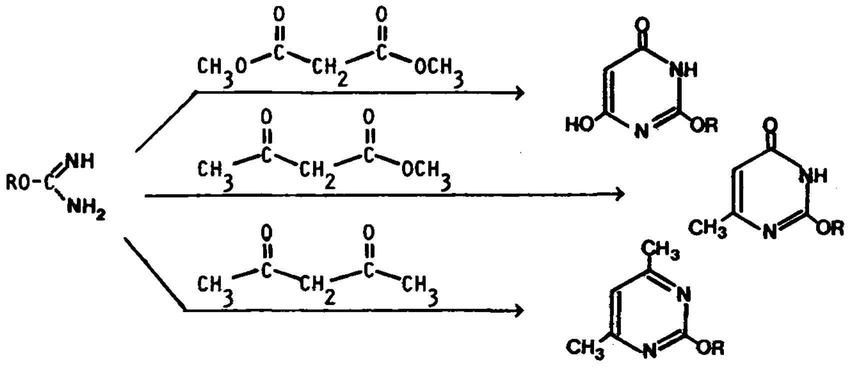
b. Involving Incorporation of Both Nitrogens

The reaction of O-methylisourea with several β-diketones led to either the 2-hydroxy- or 2-methoxypyrimidines (Eq. 14).[19] In refluxing ethanol with the HCl salt, ring formation and loss of the methyl group gave the 2-hydroxy compounds. The sulfate, however, reacted in aqueous K_2CO_3 at room temperature to give the 2-methoxy derivatives. The latter were readily demethylated in both aqueous and ethanolic solutions of HCl. These pyrimidines, along with their 2-methylthio analogs, are potential anti-tumor agents.[19]



(14)

A much earlier and more thorough investigation of this synthesis involved a series of papers in which the reactions of a whole family of O-alkylisoureas were reported.[20-24] The oxygen substituents included most of the C_1-C_5 alkanes as well as allyl, benzyl and β-phenylethyl groups. A few condensations with α-diketones were reported, but the major effort was with β-diketoesters and malonates (Equations 15-17) to give barbituric acid, uracil and pyrimidine products.

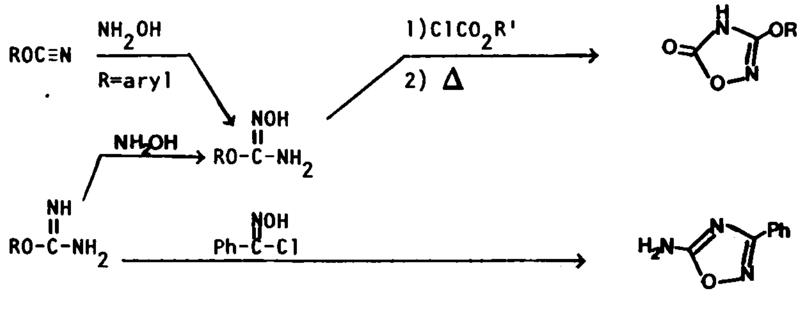


(15)

(16)

(17)

Finally, hydroxylamine reacted with a series of O-alkylisoureas through replacement of one of the nitrogens (Eq. 18).[25] The corresponding O-aryl derivatives were obtained by an alternative procedure involving addition of hydroxylamine to arylcyanates:[26]



(18)

(19)

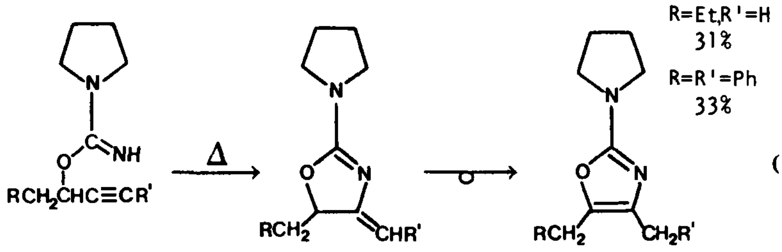
Subsequent reaction with alkyl or aryl chloroformates followed by thermal ring closure gave the 3-aryloxy- or 3-alkoxy-1,2,4-oxadiazolones. The oxadiazole ring could also be formed by condensation of the isourea with the acid chloride of benzhydroximic acid (Eq. 19). This procedure resulted in the presence of an amino substitutent on the ring in place of the carbonyl.[25]

c. Involving O- and N-Incorporation

This is the most thoroughly investigated of the heterocycle reactions and is based on the relatively high nucleophilicity of the isourea nitrogens.

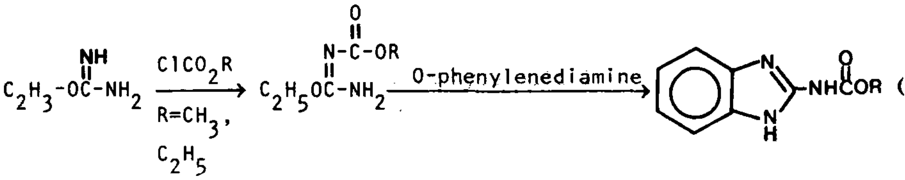
The isoureas were either isoluble or transient intermediates in which subsequent intramolecular nitrogen attack lead to the cyclic compounds.

The 2-pyridone synthesis described in section 8a gave low yields when R' (Eq. 20) was H or Ph. Apparently, competitive imine addition to the triple bond followed by aromatization gave the oxazoles which were isolated in moderate yields. While it was suggested that gas phase thermolysis should suppress this reaction, means of improving the yield for oxazole synthesis were not postulated.[18]



(20)

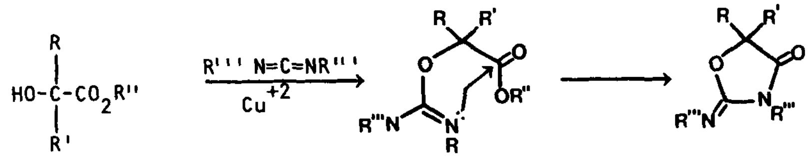
An unusual benzimidazole synthesis (Eq 21) involved the monocarbamate of ethylisourea in condensation with o-phenylenediamine.[27] The one-pot reaction starting from the isourea proceeded in 70% overall yield for the R = CH_3 derivative. This method offers a valuable alternative to carbamate formation from the 2-aminobenzimidazole where ring acylation may compete. These compounds were reported to display fungicidal activity.



(21)

The most widely observed type of cyclization reaction occurs with polyfunctional alcohols. Reaction takes place in two steps in which isourea formation produces the nucleophilic nitrogens capable of subsequent intramolecular displacement reactions. Dabritz has discussed many of these reactions in detail;[17] selected examples are included here of typical cyclizations.

Esters of α-hydroxy acids (Eq. 22) readily formed isoureas via copper-catalyzed addition to carbodiimides.[17] These compounds underwent immediate ring-closure involving ester group cleavage to give the 2-imino-4-oxazolidones in excellent yields. A related reaction was observed in which unexpected formation of a six-membered ring compound occurred in the attempted synthesis of N-alkoxamides from β-hydroxy acids.[28] At the reaction temperature employed, the initially formed O-acylisourea rearranged to the N-acylurea (Eq. 23). Subsequent loss of cyclohexylamine gave the heterocycle as a side product in the desired synthesis with the α,α-diphenyl derivative. Other β-hydroxy acid derivatives apparently did not give appreciable amounts of the corresponding compounds. This reaction is unique in that CN-bond breakage with CO-bond formation on cyclization of isoureas is rare.



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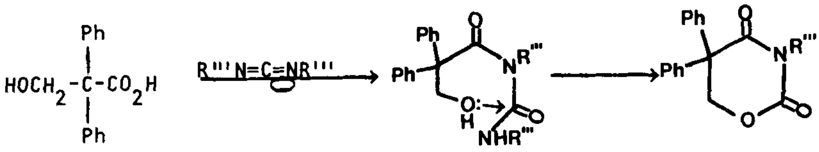
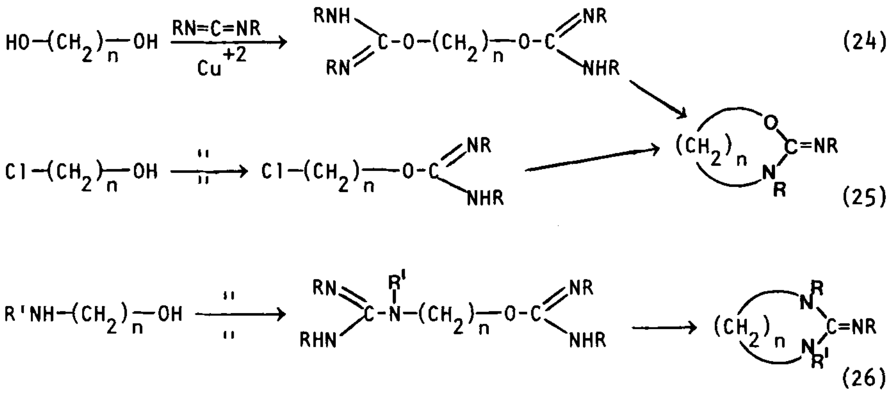


(23)

Synthesis of several groups of isoureas from substituted alcohols containing 2,3 and sometimes 4 carbon atoms between substitutents often led to 5, 6, and 7-membered heterocycles as in Equations 24-26.[17] The guanidine

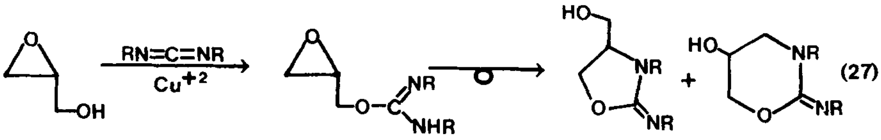


(24)

(25)

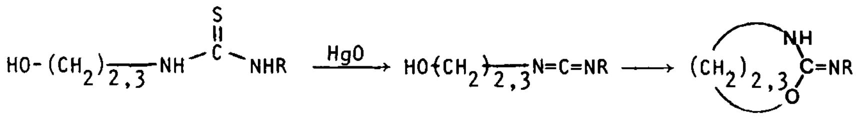
(26)

formed in Eq. 26 indicates the preference for the elemination of urea over loss of guanidine from the intermediate. A related reaction of hydroxyalkyloxiranes and the analogous oxetanes lead to opening of the 3- or 4-membered oxygen rings by intramolecular nitrogen attack to give the 5- or 6-membered cyclic isoureas containing hydroxy substituents as shown is Eq. 27.[17]



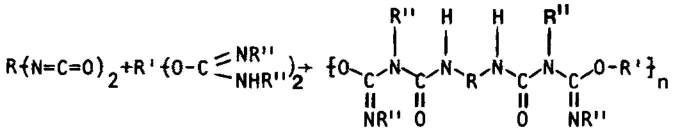
(27)

Cyclic isoureas related to those shown in Eqs. 24 and 25 may be obtained by an alternative method starting from the β-hydroxyethyl- or δ-hydroxypropylthioureas (Eq. 28).[29] The intermediate carbodiimides were reported to be isolable, especially that of the δ-hydroxypropyl compound which took months to cyclize to the oxazine. While only the R=allyl derivatives were investigated, this procedure should be general and complementary to that described by Dabritz.[17]



(28)

Several other reactions of isoureas have been reported which take advantage of the active nitrogens.[30] These include substitution via sodium hypochlorite or cyanamide, and addition to or attack on acid chlorides. Diisocyanates lead to linear polymers with repeat units as drawn in eq. 29. None of these reactions, however, has been extensively explored or developed.



$$R\{N{=}C{=}O\}_2 + R'\{O{-}C(=NR'')NHR''\}_2 \rightarrow \{O{-}C(=NR''){-}N(R''){-}C(=O){-}N(H){-}R{-}N(H){-}C(=O){-}N(R''){-}C(=NR''){-}O{-}R'\}_n \qquad (29)$$

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