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REVIEW

Dedicated to the memory of Prof. Yu.S. Andreichikov

Synthesis and Chemical Transformations of Mono- and Disubstituted Cyanamides

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Abstract—The review briefly discusses the known methods for the preparation of substituted cyanamides, their typical transformations, and some aspects of practical applications of these compounds in medicine, various branches of industry, and agriculture.

I. INTRODUCTION

The first information on cyanamide was published as early as 1851, i.e., at the dawn of organic chemistry [1]. Three years after, mono- and disubstituted cyanamides were synthesized [2]. Substituted cyanamides are very reactive compounds, and a number of their transformation products are widely used or are very promising for use in industry. Reactions of cyanamides often give rise to compounds which cannot be obtained by other methods.

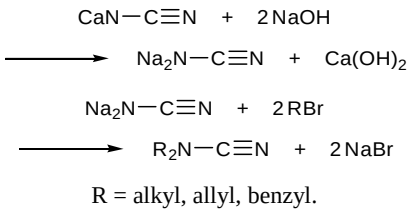
The review on unsubstituted cyanamide, published in 1948 by Barskii [3], is out of date. In 1984, Weis [4] proposed a classification for reactions of cyanamides; however, no relevant published data were given. The present review is the first attempt to summarize and systematize published data on the synthesis and chemical transformations of substituted cyanamides. It should be noted that citing of all references concerning properties and application of cyanamides seems to be impossible in the framework of a single publication. Processes involving heterocyclization of cyanamides will be the subject of a separate review article.

II. METHODS OF SYNTHESIS

II.1. Alkylation and Acylation of Cyanamide

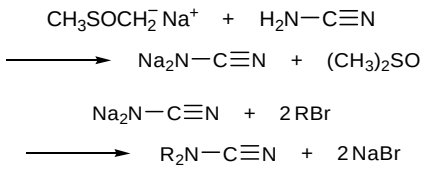
The most widely known and extensively used method for the synthesis of dialkylcyanamides is based on the alkylation of cyanamide sodium (potassium) or

calcium salt in ethanol or aqueous ethanol, sometimes in the presence of sodium hydroxide [5–8].

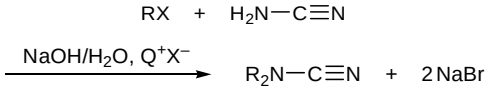


R = alkyl, allyl, benzyl.

The alkylation is usually carried out by heating for 2.5–3 h. The procedure is advantageous due to its simplicity and accessibility of initial cyanamide calcium salt. However, low yields of the target dialkylcyanamides and laboriousness of this method stimulated search for ways to improve it. For example, the use of dimethyl sulfoxide as solvent and sodium methylsulfenylmethylide as reagent allowed the reaction to occur at a lower temperature and within a shorter period of time; as a result, the yield of the final product increased [9].

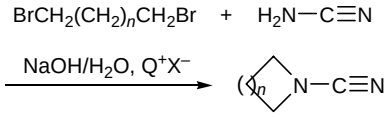


Disubstituted cyanamides were obtained in high yields by alkylation of cyanamide under conditions of phase-transfer catalysis in the presence of quaternary ammonium salts [10].



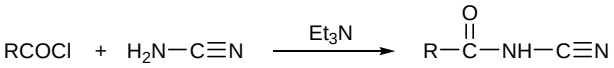
X = Cl, Br; Q^+ is a quaternary ammonium ion.

An advantage of this procedure is that α,ω-dihaloalkanes can be used as alkylating agents [11].



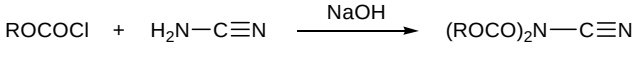
A wide variety of cyanamides available in this way and simple experimental procedure make the method promising for large-scale applications. However, the procedures based on alkylation of cyanamide cannot be applied to the synthesis of monosubstituted cyanamides and those containing two different substituents on the nitrogen atom. Apart from alkyl halides, dialkyl sulfates are used as alkylating agents; in this respect, dimethyl sulfate is the most important [12].

Acylation of cyanamide is usually effected with carboxylic acid chlorides in an inert solvent, and the reaction gives the corresponding acylcyanamides.



R = CH_3, C_2H_5, C_3H_7, C_4H_9, C_6H_{13}, C_7H_{15}, C_8H_{17}, $C_{16}H_{33}$.

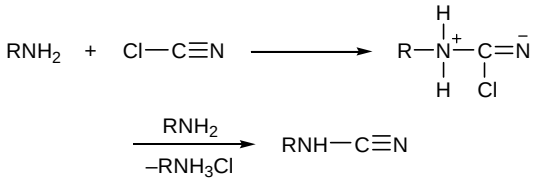
Triethylamine is commonly added as hydrogen chloride acceptor [13]. Cyanamide reacts with alkyl chloroformates in the presence of sodium hydroxide to afford the corresponding bis(alkoxycarbonyl) derivatives.



R = CH_3, C_2H_5.

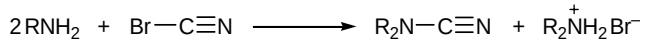
II.2. Cyanation of Amines and Their Derivatives

Methods involving introduction of a cyano group into molecules of amines and their derivatives are widely used for the synthesis of substituted cyanamides. Cyanogen halides, potassium and sodium cyanides, stable *N*-cyanotrialkylammonium salts, cyanic and thiocyanic acid esters, arenesulfonyl cyanides, etc., are suitable cyanating agents. Cyanogen halides react with primary, secondary, and tertiary amines. In the first case, monosubstituted cyanamides are formed, while secondary and tertiary amines give rise to disubstituted cyanamides. The mechanism of cyanation of amines was shown to follow the addition–elimination pattern. In the reaction of primary amines with cyanogen chloride, the first stage is addition of cyanogen chloride at the amino group with formation of resonance-stabilized cation [15]. The latter is more electrophilic than cyanogen halide, and it reacts with the second amine molecule, yielding the corresponding ammonium salt and monosubstituted cyanamide.



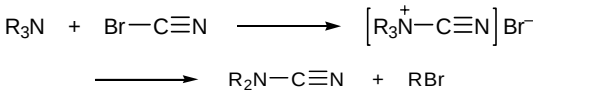
The mechanism of reactions of secondary amines with cyanogen halides was not studied in detail; however, these reactions are likely to involve similar

processes. In the general case, the reaction may be written as follows:



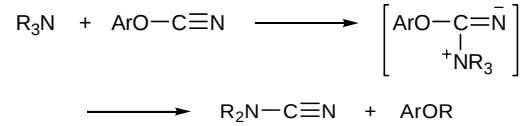
The products are disubstituted cyanamide and dialkylammonium salt [16–18]. Ammonium salts formed in the cyanation of amines are capable of reacting with cyanamides to give guanidine derivatives; as a result, the yield of the target product decreases. To avoid this process, it is advisable to carry out the reaction under effective cooling. Addition of various hydrogen halide acceptors (such as DMF, K_2CO_3, NaOH, etc.) prevents formation of ammonium salts, and the yield of substituted cyanamide can be raised twofold [19, 20].

The reaction of tertiary amines with cyanogen bromide was reported for the first time in 1900 by Braun [21].

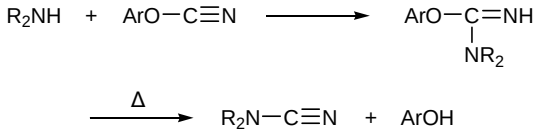


Unlike primary and secondary amines, tertiary amines react with cyanogen bromide through intermediate formation of *N*-cyanotrialkylammonium bromide which decomposes to disubstituted cyanamide and alkyl bromide. Analysis of vast experimental data showed that alkyl radicals form the following series with respect to the ease of their departure as alkyl halide: allyl > benzyl > methyl > ethyl, etc. [22, 23].

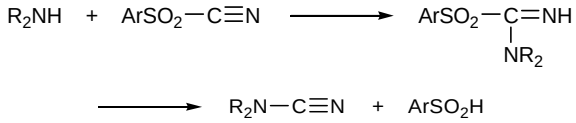
The above method is advantageous due to the possibility for synthesizing cyanamides with two different substituents on the nitrogen. When a disubstituted cyanamide is available via reaction of cyanogen bromide with both secondary and tertiary amine, the Braun reaction is usually preferred, for it ensures a considerably better yield of the product. Purygin and co-workers synthesized 1-cyanobenzimidazole by the Braun reaction [23]. However, high toxicity of cyanogen halides strongly restricts their wide application in the synthesis of cyanamides. Therefore, a number of new reagents were proposed in the recent years. Among these, cyanic acid esters occupy an important place. For instance, aryl cyanates react with tertiary amines to afford dialkylcyanamides and alkyl aryl ethers [24].



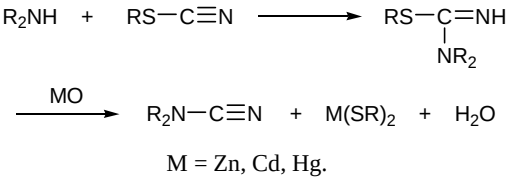
These reactions follow the same pattern as the Braun reaction. The yields of dialkylcyanamides range from 40 to 60%. Like cyanogen halides, aryl cyanates react with secondary amines to afford the corresponding dialkylcyanamides [25]. Here, intermediate products are unstable *O*-arylisoureas which decompose to dialkylcyanamide and phenol. The use of aryl cyanates as cyanating agents ensures preparation of substituted cyanamides in good yields and imposes no limits on the reaction temperature.



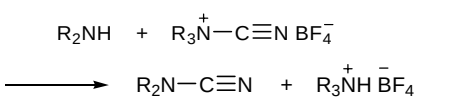
Apart from aryl cyanates, arenesulfonyl cyanides act as good cyano group carriers. Their reactions with dialkylamines lead to formation of 60–70% of the corresponding dialkylcyanamides. As in the above reactions, cyano group transfer occurs as a result of addition–elimination sequence [26].



Thiocyanates react in a similar way [27]. In the first stage, isothiourea derivatives are formed. In order to constrain the reaction toward formation of cyanamides, zinc, cadmium, and mercury oxides are added as acceptors of the liberated sulfur compound. The greatest yields were obtained in the presence of cadmium oxide. The accessibility of thiocyanates and arenesulfonyl cyanides and their excellent cyanating properties make these reagents promising for wide use in the synthesis of disubstituted cyanamides.

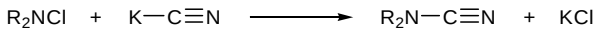


N-Cyanotrialkylammonium tetrafluoroborates were also proposed as efficient cyanating agents. Nucleophilic attack by amine on the alkyl group in *N*-cyanotrialkylammonium salt leads to elimination of one

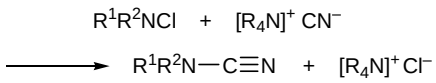


alkyl group (as in the Braun reaction) and formation of dialkylcyanamide and trialkylammonium tetrafluoroborate. The procedure ensures high yields of disubstituted cyanamides [28].

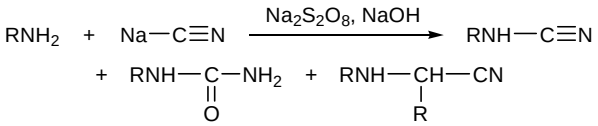
The most widely used method for the preparation of dialkylcyanamides is based on nucleophilic replacement of the halogen atom in *N*-chloro amines by cyanide ion [29, 30].



With a view to improve the efficiency of this procedure, new reagents and reaction conditions favoring the nucleophilic substitution process were sought for. In particular, tetraalkylammonium cyanides were proposed as cyanating agents [31]. These salts are more advantageous than alkali metal cyanides due to their solubility in organic solvents, which makes it possible to shorten the reaction time and obtain cyanamides in 50–90% yield.

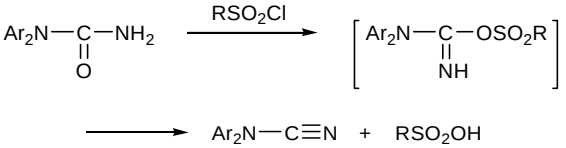


Relatively recently, Troyanskii *et al*. [32, 33] reported a procedure for the synthesis of monosubstituted cyanamides by oxidative cyanation of amines. The authors used a reagent system consisting of sodium peroxydisulfate, sodium cyanide, and sodium hydroxide. However, the formation of alkylureas and α-amino nitriles as by-products reduces the preparative value of the proposed method.

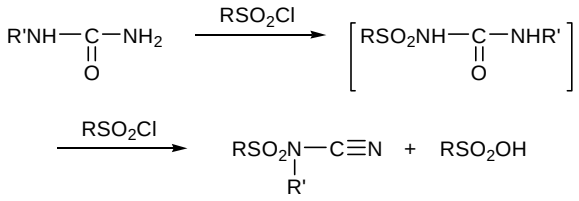


II.3. Dehydration of Urea and Amide Oximes

Reactions of this type underlie methods of synthesis of disubstituted cyanamides. An example is direct dehydration of *N*,*N*-diarylureas by the action of arenesulfonyl chlorides in pyridine [34, 35].

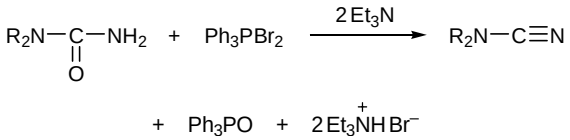


Despite severe reaction conditions, the yields of diarylcyanamides are fairly high. Analogous reactions with *N*-arylureas lead to formation of substituted arylsulfonylcyanamides [36, 37].

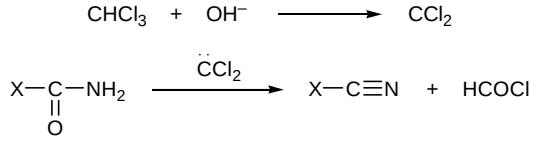


In the first stage *N*-aryl-*N'*-arylsulfonylurea is formed, and it immediately undergoes dehydration with arenesulfonyl chloride to give *N*-aryl-*N*-arylsulfonylcyanamide. The yields of the products do not exceed 40–50%.

Dibromo(triphenyl)phosphorane in the presence of triethylamine was also used to convert *N*,*N*-dialkylureas into cyanamides [38].



Schroth *et al*. [39, 40] reported on successful transformation of both substituted and unsubstituted ureas into the corresponding cyanamides by the action of dichlorocarbene in the presence of bases.

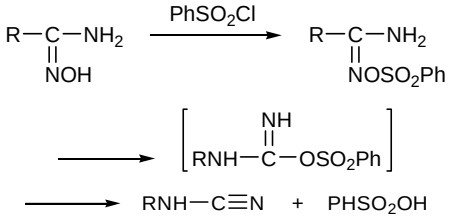


$X = NH_2$, NHR, NR^1R^2.

The reactions were carried out in a two-phase system using benzyltriethylammonium chloride as phase-transfer catalyst. The procedure ensures good yields of cyanamides, and its simplicity and general character favor its wide application.

Less common methods for the synthesis of cyanamides include, e.g., dehydration of amide oximes. As with ureas, the dehydration is effected by the action of arenesulfonyl chlorides or phosphoryl chloride in the presence of a base (such as pyridine) [41, 42]. In the first stage, the corresponding *O*-phenylsulfonyl derivative is formed. It then undergoes Beckmann rearrangement either spontaneously or on slight heating and decomposes into substituted cyanamide and benzenesulfonic acid. Taking into account that monosubstituted cyanamides tend to undergo trimerization, the proce-

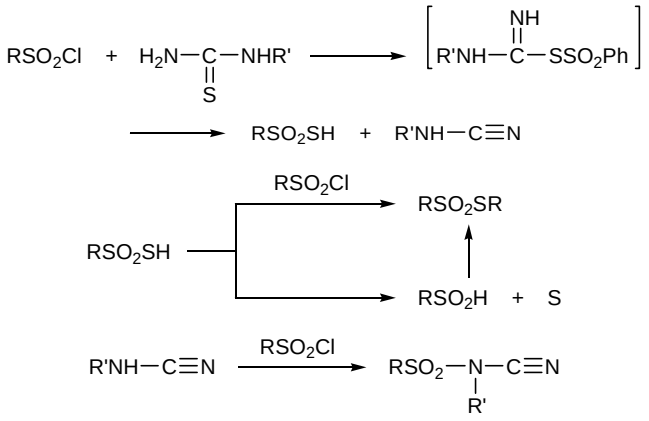
dure cannot be regarded as convenient. Dehydration of heterocyclic amide oximes by the action of phosphoryl chloride is characterized by greater yields of cyanamides (40–50%) [43].



The mechanism of this process was not studied. Presumably, better yields of heterocyclic monosubstituted cyanamides originate from stronger difficulties in the trimerization of these compounds.

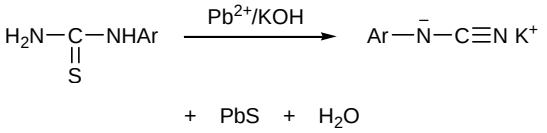
II.4. Elimination of Hydrogen Sulfide from Thiourea

Methods for the preparation of cyanamides via elimination of hydrogen sulfide from thioureas are related to those discussed in the preceding section. Elimination of hydrogen sulfide from thioureas can be effected by the action of excess arenesulfonyl chloride in the presence of pyridine [44].

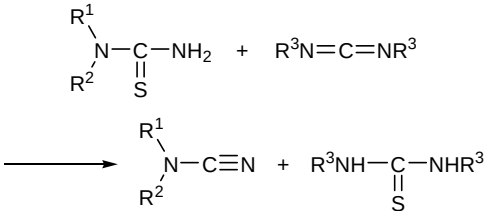


Depending on the conditions and reactant ratio, the major products are either arylcyanamides or *N*-aryl-*N*-arylsulfonylcyanamides. Concomitant arenethiosulfonic acid partially decomposes to give arenesulfinic acid and sulfur and partially reacts with excess arenesulfonyl chloride to afford *S*-aryl arenethiosulfonate. The procedure has not found wide application owing to formation of by-products, which considerably reduces the yield of cyanamides and complicates their isolation.

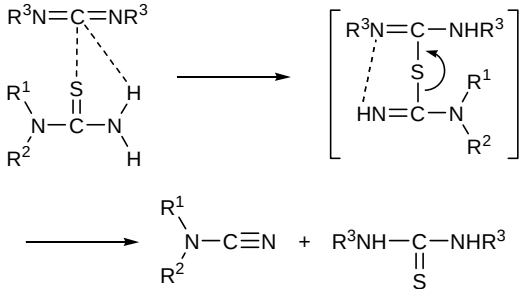
Oxidative desulfurization of thiourea by the action of lead oxides was reported in [34, 45]. Acidification of the initially formed arylcyanamide salt gives monosubstituted cyanamide. Despite severe reaction conditions, the procedure is used fairly widely, for arylcyanamide salts formed in the first stage do not undergo trimerization and the yields of cyanamides are good.



Carbodiimides can also be used as efficient desulfurizing agents [46].

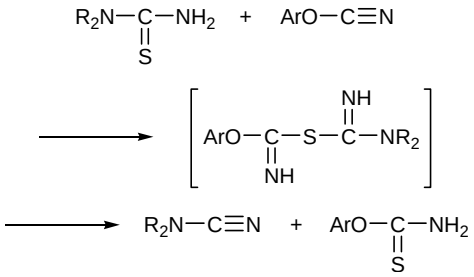


The mechanism of this reaction was not studied in detail, but it was presumed that the initial stage of the process involves nucleophilic attack by the sulfur atom in thiourea on the carbon atom in carbodiimide. Electron density redistribution in the intermediate thus formed promotes successive transfer of two hydrogen atoms from thiourea to carbodiimide. Cleavage of the weakest carbon–sulfur bond leads to formation of disubstituted cyanamide and monosubstituted thiourea.



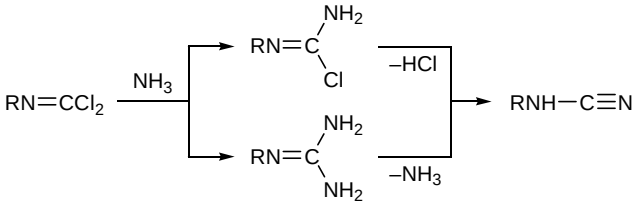
The procedure is suitable for the synthesis of only disubstituted cyanamides. Desulfurization of unsubstituted thiourea gives cyanamide which instantaneously undergoes dimerization to dicyanamide, while monosubstituted cyanamides derived from N-substituted ureas undergo trimerization.

Like carbodiimides, aryl cyanates also act as desulfurizing agents toward ureas [47]. As in the above reactions, cyanamides can be obtained only from N,N-disubstituted thioureas; the yields of cyanamides vary over a wide range.

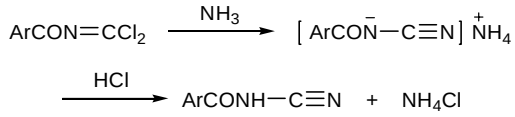


II.5. Aminolysis of Carbonimidic Dichlorides and Salts Derived Therefrom

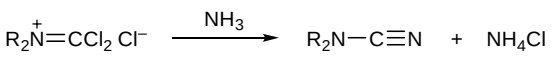
Arylcarbonimidic dichlorides react with ammonia to give monosubstituted arylcyanamides in high yield [48]. The reaction was presumed to involve intermediate formation of guanidine or chloroformamidine.



Unlike arylcarbonimidic dichlorides, aroylcarbonimidic dichlorides give rise to aroylcyanamide ammonium salts which are converted into aroylcyanamides by treatment with an acid [49].



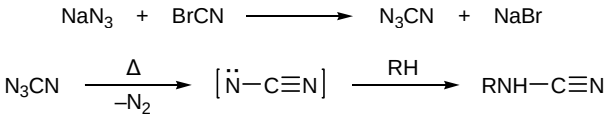
The aminolysis of *N*-(dichloromethylene)ammonium salts leads to disubstituted cyanamides [50].



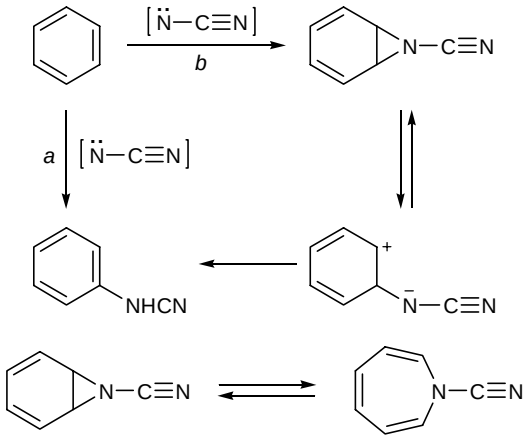
In all cases, the yields of cyanamides attain 70–80%; however, the application of this procedure is limited due to toxicity of carbonimidic dichlorides.

II.6. Addition of Cyanonitrene to Hydrocarbons

A new step in the development of synthetic routes to cyanamides was the use of cyanonitrene reported in [51]. Presumably, this is the only publication which describes the synthesis of monosubstituted cyanamides from hydrocarbons. Cyanonitrene is generated *in situ* by thermal decomposition of cyanogen azide. When a hydrocarbon is present in the mixture, insertion of cyanonitrene into the C–H bond occurs.



As might be expected, the insertion becomes more difficult in going from tertiary to secondary and then to primary C–H bond. Following this procedure, *N*-(1-methyl-1-ethylpropyl)cyanamide was obtained in 41% yield from 3-methylpentane. Apart from insertion into C–H bonds, cyanonitrene is capable of adding at double bonds in alkenes. In such a way some *N*-cyanoaziridines were synthesized [52, 53]. Cyanamides are also formed by cycloaddition of cyanonitrene at an aromatic system, followed by isomerization [54].



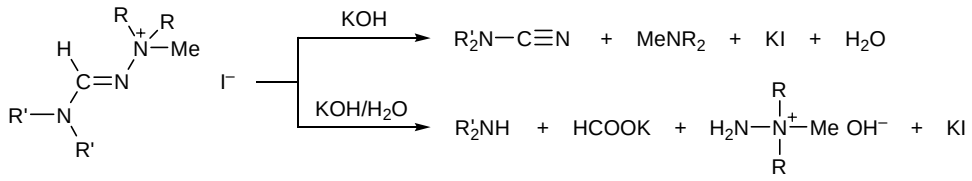
The formation of substitution products can follow several paths: via electrophilic substitution by singlet nitrene, radical substitution, direct insertion, abstraction–recombination of aromatic C–H bonds, and rearrangement of cyclic adduct. Such products can be formed either directly (path *a*) or indirectly (path *b*). The yields of the corresponding cyanamides are almost quantitative, but explosive properties of cyanogen azide strongly restrict its application for preparative purposes.

II.7. Other Methods

Cyanamides can be obtained, sometimes in good yields, via elimination of amine from amidrazonium salt on heating or by the action of bases. For example, treatment of quaternary amidrazonium iodides with alkali afforded dialkylcyanamides and tertiary amines as the major products [55] (Scheme 1).

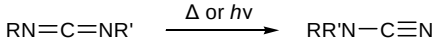
Severe reaction conditions are necessary because of donor properties of the dialkylamino group which reduces the mobility of the C–H proton. In addition,

Scheme 1.

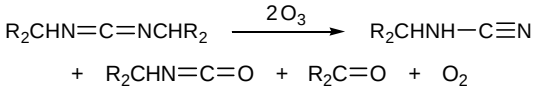


the yield of cyanamides decreases owing to concurrent alkaline hydrolysis of amidrazonium salts.

Cyanamides are isomeric to carbodiimides, and the former can be obtained from the latter by thermal or photochemical rearrangement. Boyer and Frints [56] reported on the isomerization of carbodiimides into cyanamides in a high yield on heating or irradiation.

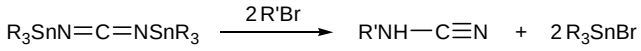


According to the authors, cyanamides are formed via either cleavage of one C–N bond and interaction of the resulting radicals or intramolecular reorganization of σ- and π-bonds. Ozonation of carbodiimides was also found to afford cyanamides [57].

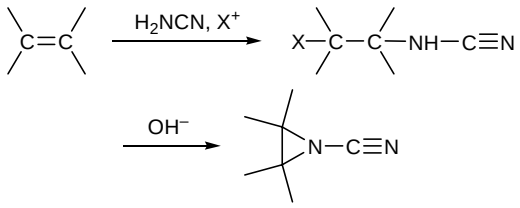


Apart from cyanamides, the reaction gives isocyanates, ketones, and oxygen. A wide variety of the products makes the procedure hardly suitable for preparative purposes.

Heteroelement-containing carbodiimides react with alkyl halides in a quite specific fashion. Reactions of alkyl halides with organotin carbodiimides are accompanied by cleavage of the Sn–N bond with formation of the corresponding dialkylcyanamide and trialkylstannyl halide [58]. The yields of cyanamides range from 50 to 60%.



β-Haloalkylcyanamides are formed in 20–65% yield by conjugate addition of cyanamide and positively charged halogen species (*N*-bromosuccinimide, dichlorocarbamate, *tert*-butyl hypochlorite) at the double bond of alkenes.



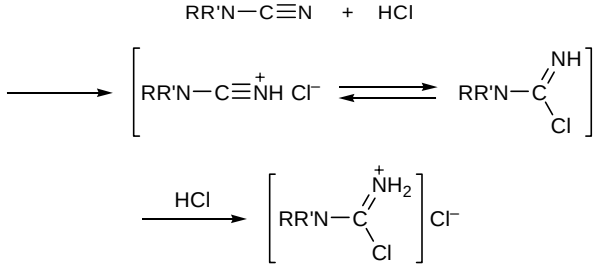
Treatment of the primary adducts with alkali promotes their transformation into *N*-cyanoaziridines [59]. However, halocyanamides turned out to be the most important in the synthesis of vicinal diamines [60, 61]. Elimination of hydrogen sulfide from *N*-phenylthiourea in pyridine gave 82% of phenylcyanamide [62]. The same product was obtained by alkaline hydrolysis of 1-phenyltetrazole [63] and by treatment of 5-chloro-1-phenyltetrazole with butyllithium [64].

III. CHEMICAL PROPERTIES

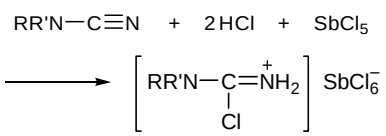
The reactivity of cyanamides originates from chemical properties of the amino and cyano groups. Most reactions involving the amino group are analogous to reactions of other amines with reduced nucleophilicity. Reactions with participation of the cyano group are more versatile, and in some cases they occur in a specific fashion. The most important reactions at the cyano group are addition, cycloaddition, cyclotrimerization, and complex formation.

III.1. Reactions of Cyanamides at the Amino Group

A number of reactions occurring at the amino group of cyanamides follow a different pattern than those typical of common amines. Thus, typical amines react with acids to give ammonium salts. The basicity of the amino nitrogen atom in cyanamides is strongly reduced due to conjugation of its lone electron pair with the triple carbon–nitrogen bond. Therefore, proton adds at the cyano nitrogen atom rather than at the amino group [65]. According to the IR data, initially formed cyanamide salt gives rise to tautomeric equilibrium with chloroformamidine.

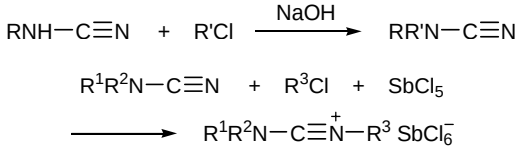


The latter is sufficiently basic to take up the second hydrogen chloride molecule with formation of chloroformamidinium chloride [66]. Protonation in the presence of Lewis acids also leads to formamidinium halides [67]. As in the above cases, the reaction involves nitrogen atom of the cyano group.



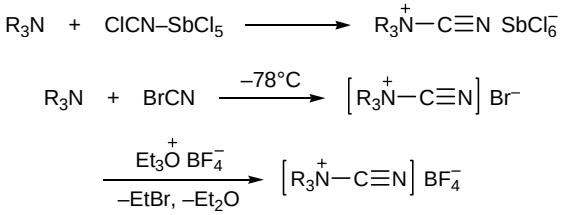
Amines also exhibit properties of weak NH acids. The presence of phenyl and cyano groups in phenylcyanamide makes the amino hydrogen atoms more acidic and thus facilitates formation of cyanamide metal salts like ArN(Na)C≡N [45].

Substituents also affect other reactions of cyanamides. The alkylation of monosubstituted cyanamides occurs at the amino nitrogen atom [68], whereas disubstituted cyanamides react at the cyano group.

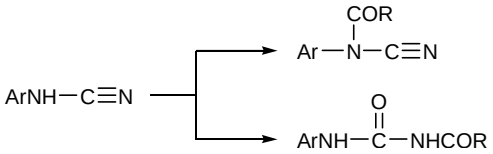


In the latter case, the primary products are nitrilium salts which usually cannot be isolated. In most reactions of cyanamides such salts are formed as intermediates.

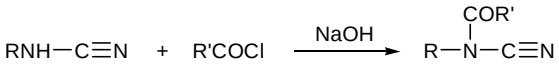
Presumably, direct quaternization of disubstituted cyanamides at the amino nitrogen atom is impossible because of low stability of *N*-cyanotrialkylammonium halides [69]. *N*-Cyanotrialkylammonium salts with less nucleophilic BF_4^- or $SbCl_6^-$ anion were synthesized by reaction of tertiary amines with the complex cyanogen chloride–antimony(V) chloride [70], as well as by the low-temperature Braun reaction in the presence of triethyloxonium tetrafluoroborate [28].



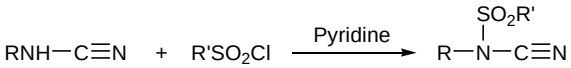
The acylation of cyanamides also occurs in a specific fashion. Acetic anhydride reacts with arylcyanamides to give either *N*-acetyl-*N*-arylcyanamide or *N*-acetyl-*N'*-arylurea [70]. The second pathway requires the presence of concentrated sulfuric acid.



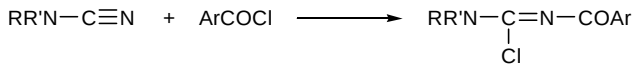
In the acylation of amines with acyl chlorides, excess amine is usually taken to bind liberated hydrogen chloride. Insofar as the basicity of the amino nitrogen atom in cyanamides is reduced, addition of alkali metal hydroxide or carbonate is necessary to bind HCl and displace the equilibrium toward *N*-acylcyanamide [71, 72].



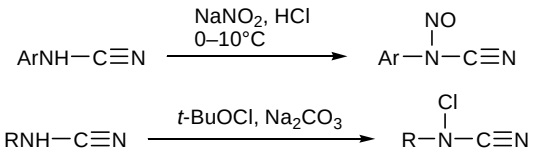
Pyridine was used as hydrogen chloride acceptor in the acylation of monosubstituted cyanamides with arenesulfonyl chlorides [36].



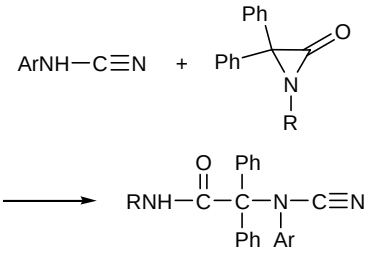
Reactions of dialkylcyanamides with acyl chlorides follow the nucleophilic addition pattern at the triple carbon–nitrogen bond to give chloroformamidine derivatives [73, 74]. This process will be discussed in more detail while considering chemical transformations of cyanamides at the cyano group.



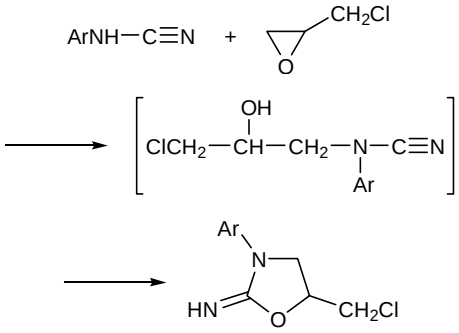
Like secondary amines, monosubstituted cyanamides undergo nitrosation and halogenation by the action of sodium nitrite and *tert*-butyl hypochlorite, respectively. The products are *N*-nitrosocyanamides [45] and *N*-halocyanamides.



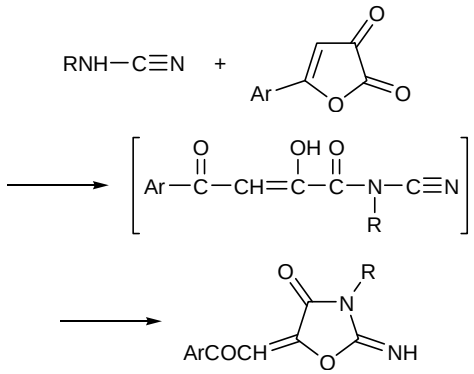
Although the nucleophilicity of the amino group in cyanamides is lower as compared to amines, it nevertheless remains sufficient to open strained rings. For example, arylcyanamides react with aziridines to give disubstituted cyanamide [75].



In the reaction with oxiranes, the process does not stop at the stage of formation β-hydroxyalkylcyanamide [76]. Intramolecular addition of the hydroxy group to the cyano group leads to ring closure, yielding 2-iminooxazolidine derivative.

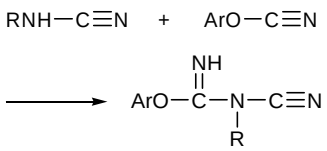


Likewise, monosubstituted cyanamides react with 5-aryl-2,3-dihydrofuran-2,3-diones. The products are 2-imino-5-(aroylmethylene)oxazolidin-4-ones [77]. This reaction was reviewed in detail in [78].



Ar = *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-ClC_6H_4; R = *o*-ClC_6H_4.

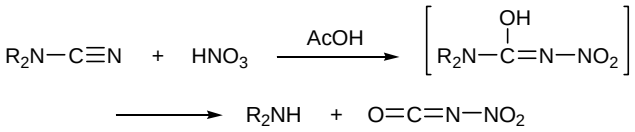
As well as amines, cyanamides react with aryl cyanates at the triple carbon–nitrogen bond in the latter to afford *O*-aryl-*N*-cyanoisourea derivatives [79].



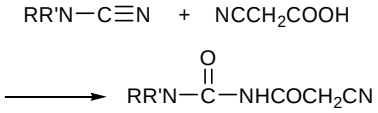
III.2. Reactions of Cyanamides at the Cyano Group

Taking into account unsaturated character of the C≡N bond, addition reactions should be most typical of cyanamides. The electron density on the nitrogen atom of the cyano group is greater than on the carbon atom; therefore, both electrophilic and nucleophilic reagents are capable of adding thereto. Conjugation between the lone electron pair on the amino nitrogen atom and the triple carbon–nitrogen bond favors reactions with electrophiles. Apart from addition processes at the cyano group, cyanamides can be involved in cycloaddition, trimerization, reduction, complex formation, and other reactions.

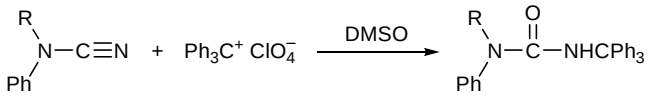
III.2.1. Addition of electrophilic reagents. Reactions of this type include addition of acids. In the preceding section we considered the reaction of cyanamides with hydrogen halides, which leads to formation of haloformamidinium halides. Treatment of disubstituted cyanamides with nitric acid induces their decomposition to secondary amines. The latter were presumed to result from attack by nitronium cation on the nitrogen atom of the cyano group, followed by addition of hydroxy group. Intermediate enol is unstable, and it decomposes into secondary amine and nitryl isocyanate [80].



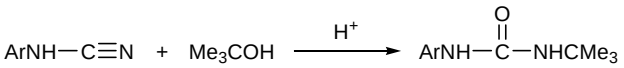
Organic acids, in particular cyanoacetic acid, react with substituted cyanamides to give the corresponding *N*-alkyl- or *N*,*N*-dialkyl-*N*′-cyanoacetylureas [81, 82].



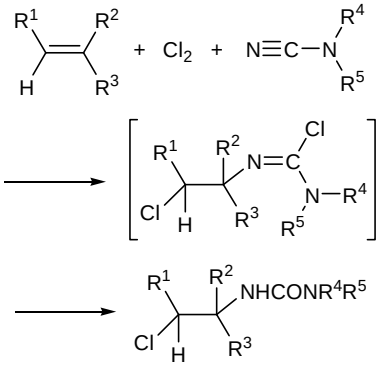
Carbenium ions generated *in situ* from alcohols, olefins, etc., often act as electrophilic reagents toward cyanamides. Alkylation of the cyano nitrogen atom with such species, e.g., with triphenylmethyl cation, yields *N*,*N*′-substituted ureas [83].



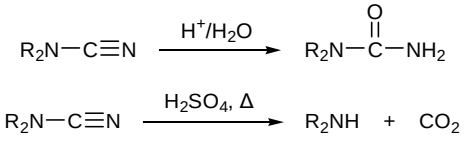
Analogous products were obtained by the Ritter reaction [71, 72].



Electrophilic addition of halogens to alkenes in the presence of disubstituted cyanamides gives *N*-(β-haloalkyl)haloformamidines whose hydrolysis leads to formation of *N*-(β-haloalkyl)-*N*,*N*′-dialkylureas [84].

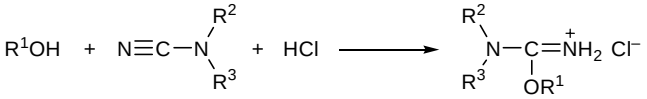


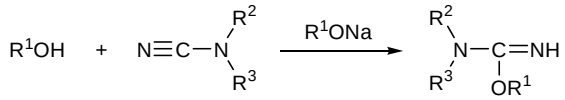
III.2.2. Addition of nucleophilic reagents. The addition of nucleophiles to cyanamides is more difficult, as compared to electrophile addition, and such reactions usually require the presence of a catalyst. As the latter, acids and bases are used most frequently. The simplest example is hydrolysis in dilute hydrochloric or sulfuric acid, which produces substituted ureas [85]. The hydrolysis in the presence of concentrated acids leads to dialkylamines as a result of hydrolytic cleavage of the corresponding ureas [5]. Analogous reactions occur by the action of a concentrated solution of potassium or sodium hydroxide [86].



Addition of hydrogen sulfide and hydrogen selenide to cyanamides is catalyzed, respectively, by hydrogen sulfide or hydrogen selenide ion and yields thio- [16, 87] and selenoureas [88, 89].

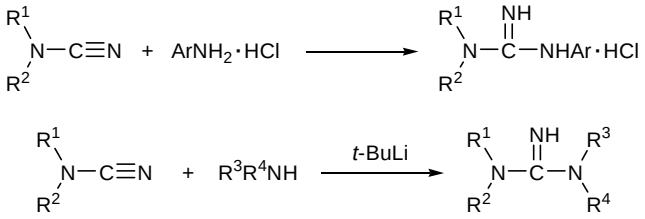
Reactions of cyanamides with alcohols have been extensively studied [17, 90–92]. These reactions give rise to isothiourea derivatives. Monosubstituted cyanamides react with alcohols only in the presence of hydrogen chloride, while disubstituted cyanamides take up alcohols in the presence of HCl or alkali [93].



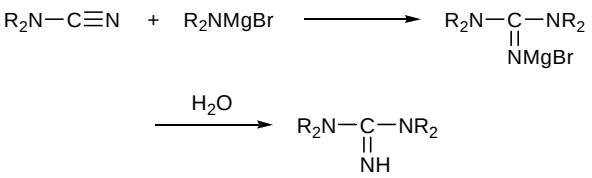


It should be noted that lower dialkylcyanamides react with alcohols in the presence of a catalytic amount of alkali metal alkoxide, whereas the addition of alcohols to higher dialkylcyanamides requires excess alkali metal alkoxide. When an alcohol contains one more functional group, heterocyclic compounds are obtained. For example, reactions of cyanamides with α-hydroxy esters and α-hydroxy ketones result in formation of 2-amino-4,5-dihydrooxazol-4-ones [94] and 2-aminooxazoles [95], respectively. In the first case, the reaction is catalyzed by sodium hydride, and in the second, by sodium hydroxide.

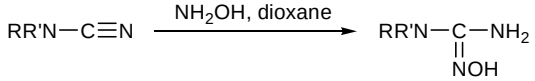
Amines do not add at the C≡N bond of cyanamides in the absence of a catalyst. As in reactions with alcohols, both acids and bases catalyze the addition. The most frequently used catalysts are amine hydrochlorides and alkali metal dialkylamides, the latter sometimes being obtained *in situ* [96–100].

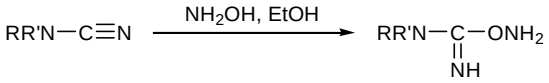


Addition of amines to cyanamides with formation of tetraalkyl-substituted guanidines was also effected with dialkylaminomagnesium bromide [101].

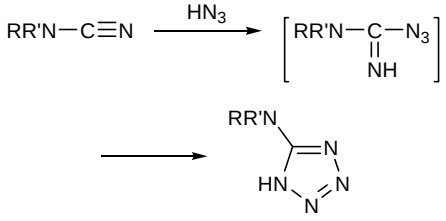


Unlike amines, hydroxylamine is sufficiently nucleophilic to add to both mono- [102] and disubstituted cyanamides [103] in the absence of a catalyst. Depending on the solvent, the addition involves either amino or hydroxy group of hydroxylamine [104], leading to hydroxyguanidine or formamidine derivatives, respectively.

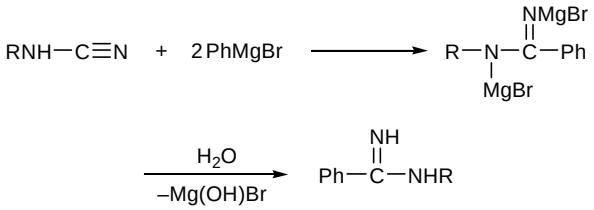




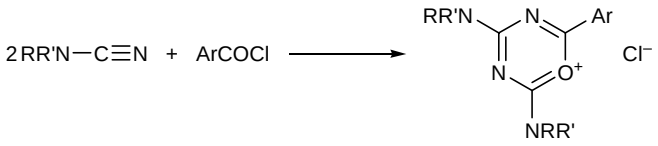
An example of addition of anionic species at the C≡N bond of cyanamides is their reaction with azide ion, which yields 5-aminotetrazoles, presumably through intermediate guanyl azide [18, 105–107].



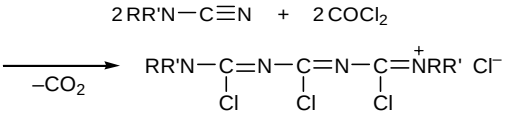
Monosubstituted cyanamides react with Grignard compounds to afford N-substituted amidines [108]. Analogous reactions with dialkylcyanamides give rise to *N*,*N*-dialkylamidines [109].



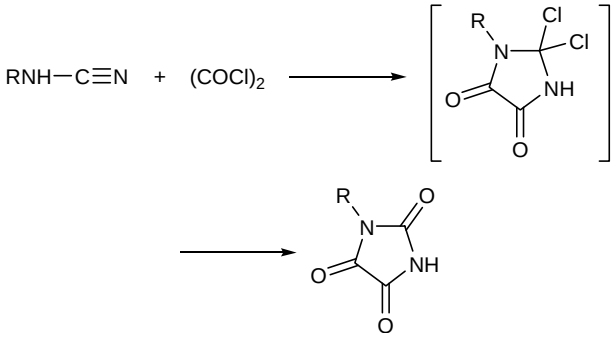
Various reactions occur between cyanamides and acyl chlorides. Monosubstituted cyanamides are acylated at the amino nitrogen atom, while disubstituted cyanamides react at the nitrogen atom of the cyano group; the products are the corresponding *N*-acylcyanamides and chloroformamidine derivatives. Reactions of acyl chlorides with 2 equiv of disubstituted cyanamide give diazapyrylium salts [73].



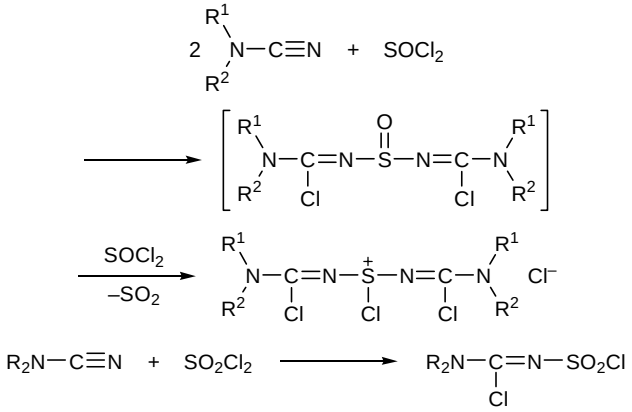
Products of the reactions of disubstituted cyanamides with dibasic acid chlorides, such as phosgene and oxalyl chloride, are derivatives of dialkyl(1,3,5-trichloro-5-dialkylamino-2,4-diaza-2,4-pentadienylidene)-ammonium chloride [73, 110]. Dimethylcyanamide reacts most smoothly. Increase in the size of substituents in cyanamide, as well as participation of the lone electron pair on the amino nitrogen atom in conjugation, makes the process more difficult to occur.



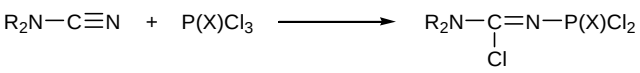
In the reaction with oxalyl chloride, the latter undergoes decarbonylation to phosgene, so that identical products are obtained from $(COCl)_2$ and $COCl_2$. Monosubstituted cyanamides react with oxalyl chloride to give unstable 2,2-dichloroimidazolidine-4,5-diones which undergo hydrolysis to imidazolidine-2,4,5-triones [111, 112].



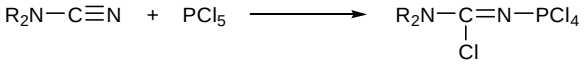
The reaction of thionyl chloride with 2 equiv of disubstituted cyanamides gives bis[dialkylamino-(chloro)methyleneamino]sulfonium chloride; and the product of analogous reaction with sulfuryl chloride is *N*,*N*-dialkyl-*N'*-(chlorosulfonyl)chloroformamidine [113, 114].



Chloroformamidine derivatives are also formed by reactions of disubstituted cyanamides with phosphoryl chloride and thiophosphoryl chloride [114, 115]. Phosphorus pentachloride gives rise to *N*,*N*-dialkyl-*N'*-(tetrachlorophosphoranyl)chloroformamidine [116].

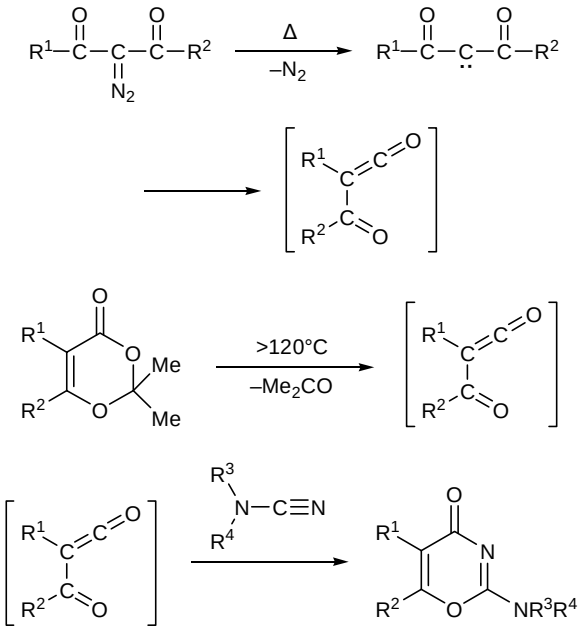


X = O, S.

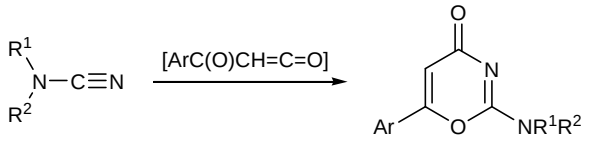


III.3. Cycloaddition Reactions

The triple carbon–nitrogen bond in cyanamides can act as dienophile in [4+2]-cycloaddition (hetero-Diels–Alder) reactions with 1,3-dienes. An example of such reactions is the addition of cyanamides to acylketenes generated from 2-diazo-1,3-diketones [117] and 1,3-dioxin-4-ones [118–120], which leads to 2-amino-1,3-oxazin-4-one derivatives.



Analogous products were obtained by reaction of cyanamides with diketene [121–123] and aroylketenes [124, 125].

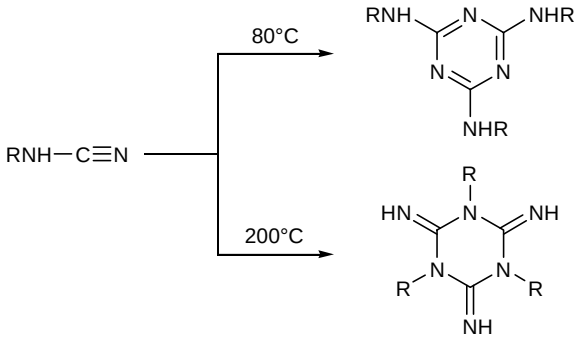


Ar = *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-ClC_6H_4.

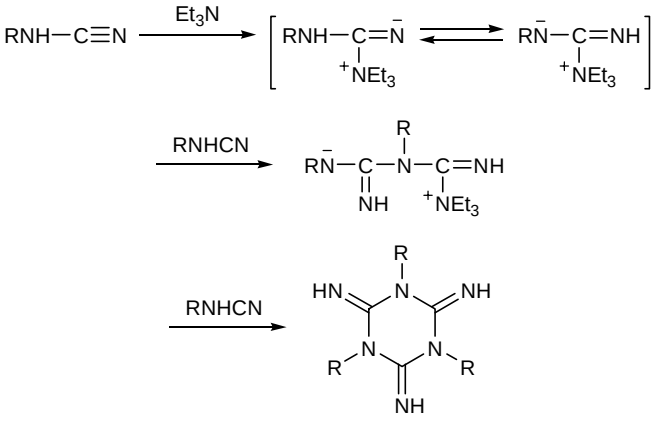
Reactions of cyanamides with aza heterodienes were reviewed in [126].

III.4. Cyclotrimerization

Disubstituted cyanamides do not tend to undergo cyclotrimerization; they are fairly stable to storage and heating. On the other hand, monosubstituted cyanamides undergo spontaneous cyclotrimerization to give 1,3,5-triazines either during their synthesis or on heating for a short time [34, 127, 128]. Raising the temperature accelerates the trimerization process; moreover, the product structure depends on the temperature. At 80°C, 2,4,6-triamino-1,3,5-triazines are formed, while at 200°C the products are 1,3,5-trialkylhexahydro-1,3,5-triazine-2,4,6-triimines [129].



The structure of the cyclotrimerization products is also determined by the nature of the catalyst: Lewis acids favor formation of melamine derivatives, while basic catalysts give rise to isomelamine derivatives. Lewis acids with cyanamides form RNH–C≡N·MX complexes with increased polarity of the C≡N bond; as a result, the rate of cyclotrimerization increases, and the product is 2,4,6-triamino-1,3,5-triazine. In the catalysis by bases, e.g., by triethylamine, intermediate adduct is formed via attack by the nitrogen atom of the tertiary amine on the electrophilic carbon atom of the cyano group in cyanamide. Successive addition of two more cyanamide molecules gives hexahydro-1,3,5-triazine-2,4,6-triimine derivative [130].

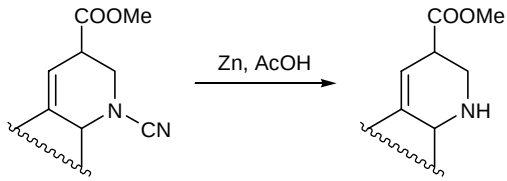


Cyclotrimerization of compounds having several cyanamide groups underlies the synthesis of heat-resistant polymers with a network structure due to formation of triazine rings [131]. Joint polycyclotri-

merization of mono- and bis-cyanamides can be used to obtain polymeric products with different degrees of cross-linking, up to preparation of fusible and soluble polymers [132, 133].

III.5. Reduction of the Cyano Group

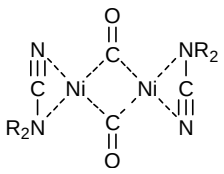
The cyano group in cyanamides can be reduced with various reducing agents, including metal–proton donor systems [134], complex metal hydrides, and hydrogen in the presence of catalysts [135]. Fehr *et al*. [136] reported on the reduction of cyanamide derived from lysergic acid with zinc dust in 80% acetic acid.



Analogous transformation can be effected by the action of hydrogen over Raney nickel. Lithium tetrahydridoaluminate is not suitable, for the cyanamide molecule contains a readily reducible ester moiety. It should be noted that reduction of cyanamides is usually accompanied by a series of side reactions; however, the major product is always the corresponding secondary amine.

III.6. Complex Formation

Participation of cyanamides in complex formation with metals is interesting. Heating of dialkylcyanamides with nickel carbonate gives dialkylcyanamide carbonyl Ni(0) complexes of the general formula $Ni_2(CO)_2(R_2NC{\equiv}N)_2$ [137]. According to spectral data and other physical properties of the complex, the zero-valent nickel atom therein coordinates not only to the cyano group (π-coordination) but also to the amino nitrogen atom at the lone electron pair on the latter [138].



Structurally related complexes were obtained from chromium and molybdenum carbonates [139]. Complexes formed by cyanamides and Sb, Fe, and Al salts are stable only at low temperature [140].

IV. SOME ASPECTS OF PRACTICAL APPLICATION

While speaking about practical application of cyanamides, first of all their importance from the viewpoint of synthesis of various compounds of the aliphatic, aromatic, and heterocyclic series should be noted. In addition, these compounds are widely used as condensing agents in the synthesis of peptides [141, 142] and nucleotides [143]. There are prospects in using cyanamides in the preparation of polymeric materials. For example, polymerization of alkylenedicyanamides afforded polymers possessing valuable adhesive properties [124]. Polymers characterized by high resistance to acidic and basic reagents were obtained on the basis of unsaturated cyanamides and alcohols. Such products can be used as anticorrosion agents. Catsiff *et al*. [144] recently showed the possibility of using methylenebis(phenylcyanamide) as highly efficient curing agent for epoxy resins. Cyanamides can find wide application in textile industry as activators of hydrogen peroxide bleaching [145]. Dialkylcyanamides were also proposed as depressor additives to diesel fuel [146]. Of particular interest is the use of cyanamides in agriculture and medicine. Various cyanamide derivatives exhibit biological activity; examples are adamantylcyanamide possessing antiviral activity [147] and some acylcyanamides which affect central nervous system [148]. In some cases, cyanamides are intermediate products in the synthesis of biologically active derivatives of isourea [93], oxazolidines [149], guanidines [97–99, 147], etc. The latter were proposed to use as herbicides [100]. Dialkylcyanamides are used as aprotic solvents [150].

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