SYNTHESIS OF 1,3,5-TRIAZINE DERIVATIVES ON THE BASIS OF CARBOXYLIC ACID IMINO ESTERS (REVIEW)

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Data on methods for the synthesis of 1,3,5-triazine derivatives by cyclotrimerization and cyclocondensation reactions with the participation of carboxylic acid imino esters are systematized in the review.

The last decades have been marked by significant advances in the development of theoretical and applied principles for the synthesis of 1,3,5-triazine derivatives. 2,4,6-Trichloro-1,3,5-triazine is usually employed as the starting material to obtain the most valuable substances in this series [1, 2]. At the same time, various 1,3,5-triazine derivatives can be synthesized by cyclotrimerization and cyclocondensation reactions with the participation of functional derivatives of carboxylic acids — chlorides, anhydrides, esters, nitriles, imino esters, amidines, etc. These reactions have expanded the synthetic possibilities for obtaining diverse compounds of the 1,3,5-triazine series with valuable application properties.

A significant amount of material on the synthesis of 1,3,5-triazines on the basis of carboxylic acid derivatives has been accumulated in the literature; this material has been correlated in a number of previously published monographs [1, 3] and reviews [4, 5]. Reactions involving the cyclotrimerization of nitriles and other cyano-containing compounds have been illuminated in quite some detail in reviews [6, 7].

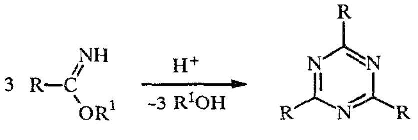
In the present review we attempted to correlate and systematize the literature data on methods for the synthesis of compounds of the 1,3,5-triazine series on the basis of reactive imino esters.

1. SYNTHESIS OF 2,4,6-TRIALKYL(ARYL, HETERYL)-1,3,5-TRIAZINES

This transformation of imino esters was described for the first time in 1877 by Pinner and Klein [8], who isolated 2,4,6-triphenyl-1,3,5-triazine (kyaphenine) in an attempt to obtain benzamidine by the reaction of benzoic acid isobutyl imino ester with ammonia.

Individual data on the conversion of imino esters to 1,3,5-triazines were also subsequently published [9-12]; however, the reactions generally proceeded very slowly, and the yields of the final products were low.

A convenient preparative method for obtaining 2,4,6-trisubstituted 1,3,5-triazines I by cyclotrimerization of imino esters in the presence of acidic catalysts was developed in 1961-1964 [13-20].



I

R = alkyl, aryl, heteryl; R^1 = Me, Et, Bu, PhCH$_2$

It was established [13, 14] that acetic acid ethyl imino ester undergoes complete decomposition in a few months at 20°C. The principal decomposition products are acetonitrile and ethanol, although ~20-30% of the imino ester was converted to 2,4,6-trimethyl-1,3,5-triazine (II). However, an exothermic reaction to give 1,3,5-triazine II, the yield of which reached

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TABLE 1. 2,4,6-Trisubstituted 1,3,5-Triazines I Obtained by Cyclotrimerization of Carboxylic Acid Imino Esters

Starting imino ester		Reaction conditions			Yield, %	Literature
R	R^1	catalyst (mole %)	T, °C	time, h		
Me	Et	AcOH (8)	25	16	85...90	[13]
Me	Et	HC (3)	25 50...80	24 2	68	[15]
Me	Et	HC (10)	25 50...80	24 2	79	[15]
Me	Et	NH_4Cl (3)	25 50...80	24 2	66	[15]
Me	$PhCH_2$	HC (3)	100	4	91	[15]
Me	$PhCH_2$	$Et_3N \cdot HCl$ (10)	100	4	53	[15]
Me	Bu	HC (3)	25 50...80	24 2	73	[15]
Et	Et	AcOH (9)	25	24	74	[13]
Et	Et	HC (3)	25 50...80	24 2	53	[15]
Pr	Et	HC (3)	20 50...80	24 2	68,5	[15]
Pr	Et	NH_4Cl (3)	20 50...80	24 2	18	[15]
i-Pr	Et	AcOH (6)	25	24	75	[13]
Bu	Et	HC (3)	25 50...80	24 2	56,5	[15]
$C_{10}H_{21}$	Et	HC (3)	85...90	20...25	83	[22—24]
$C_{14}H_{29}$	Et	HC (3)	85...90	20...25	85	[22—24]
$C_{17}H_{35}$	Et	HC (3)	85...90	20...25	84	[22—24]
Cl_3C	Me	AcOH (25)	80	6,5	80	[13]
Cl_3C	Me	AcOH (100)	25	45days	40...60	[13]
F_3C	Me	CF_3COOH (5)	50...70	7	25	[20]
MeCHCl	Et	AcOH (12)	50	20	86	[13]
$HOCH_2CH_2$	Et	HC (15)	25	48	63	[25]
$ROCH_2CH_2$	Et	HC (3)	25 70...80	16 3	60...78	[25]
$EtSCH_2CH_2$	Et	HC (5)	40	48	90	[25]
$Me_2C(NO_2)CH_2CH_2$	Me	HC (5)	70	2	100	[26]
$MeC(NO_2)_2CH_2CH_2$	Me	HC (5)	140	0,5	95	[27]
Ph	Me	AcOH (46)	25	72	79	[13]
Ph	Et	HC (3)	80	240	25	[15]
$4\text{-}MeOC_6H_4$	Me	AcOH (50)	70...90	2	68	[13]
$4\text{-}NO_2C_6H_4$	Me	AcOH (100)	70...80	4	54	[13]
$3\text{-}NO_2C_6H_4$	Me	AcOH (150)	70...90	2,5	79	[13]
$3\text{-}NO_2C_6H_4$	Et	AcOH (125)	70...80	4	68	[13]
Ar**	Et	CF_3COOH (10)	60	24	32	[28, 29]
Ar**	Et	HC (3)	120	100	15	[24, 28, 29]
$PhCH_2$	Et	AcOH (12)	25	16	50	[13]
$PhCH_2$	Et	HC (3)	25 80	24 2	63	[15]
$ArCH_2$**	Et	HC (3)	90	24	84	[28, 29]
$ArSCH_2CH_2$**	Et	HC (3)	90	24	80	[24, 28, 29]
3-Indolylmethyl	Me	HC (5)	80...85	20	75	[30—32]
2-Furyl	Et	CF_3COOH (10)	60	5...7	85	[31—34]
5-Methyl-2-furyl	Et	CF_3COOH (10)	60	5...7	81	[31, 34]
5-Nitro-2-furyl	Et	HC (3)	85	12	78	[31, 33]

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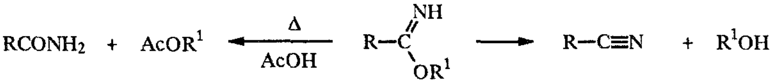
*HC = the imino ester hydrochloride

**Ar = $4\text{-}HO\text{-}3,5\text{-}tert\text{-}Bu_2C_6H_2$.

90%, proceeds rapidly in the presence of 10 mole % glacial AcOH [13]. Smaller amounts of AcOH can also be used, but a large amount of the catalyst — 100 mole % or more — was required in individual cases.

Under similar conditions, aromatic acid imino esters are converted to 1,3,5-triazines with much greater difficulty than aliphatic acid imino esters; the yields of 2,4,6-triaryl-1,3,5-triazines are, in all likelihood, lower due to the competitive conversion of the imino ester to an aromatic nitrile and an alcohol. It was also shown that the reaction proceeds faster in refluxing methanol than at room temperature, but the increased temperature promotes decomposition of the imino ester to the nitrile and alcohol and conversion of it to the amide (the Pinner rearrangement) [21].



$$RCONH_2 + AcOR^1 \xleftarrow[AcOH]{\Delta} R{-}C(=NH)OR^1 \longrightarrow R{-}C{\equiv}N + R^1OH$$

Yakubovich and others [15-20] investigated the effect of salts of various bases on the cyclization of imino esters. It was found that 1,3,5-triazine II is formed in 92% yield when acetic acid benzyl imino ester is heated with 3 mole % of its hydrochloride, whereas it is formed in 57% yield when a solution of the imino ester is saturated with carbon dioxide. A study of the transformations of imino esters of other acids in the presence of their hydrochlorides showed that various 2,4,6-trisubstituted 1,3,5-triazines I can be obtained in 53-70% yields in this way.

Examples of cyclotrimerization reactions of imino esters of various acids in the presence of acidic catalysts are presented in Table 1.

Although a distinct correlation between the structure of the acidic part of the imino ester molecule and the yield of the corresponding 1,3,5-triazine is not presented in the literature, one can observe some qualitative principles of this transformation from the available data. For example, aromatic acid imino esters undergo cyclotrimerization under more severe conditions than aliphatic acid imino esters and give the products in lower yields.

Attempts to accomplish the cyclotrimerization of indole-3-carboxylic acid methyl imino ester [31] and adamantane-1-carboxylic acid methyl imino ester [35] were unsuccessful. Only the corresponding nitriles were obtained after heating these imino esters with 3-5 mole % of their hydrochlorides at 160-180°C. The inability of these imino esters to undergo cyclotrimerization to 1,3,5-triazines was explained by the effect of electron-donor indolyl and adamantyl radicals, which decrease the electrophilic reactivity of the imino ester grouping and thereby hinder cyclotrimerization. The steric hindrance caused by these bulky radicals undoubtedly also plays a definite role.

The cyclotrimerization of 4-hydroxy-3,5-di-tert-butylbenzoic acid ethyl imino ester, in which the reactivity of the imino ester fragment is decreased due to the effect of the hydroxyaryl radical, takes place with great difficulty [36]. Thus 2,4,6-tris(4-hydroxy-3,5-tert-butylphenyl)-1,3,5-triazine was isolated in 12-15% yield from the reaction mixture, along with the starting imino ester and the corresponding nitrile, after heating (120°C, 100 h) this imino ester with 3 mole % of its hydrochloride [28, 29].

Attempts to synthesize 1,3,5-triazines from chloro-, amino-, and hydroxyacetic acid imino esters [37], as well as from β-(diethylamino)propionic acid [25] and 4,4,4-trinitrobutyric acid [38] imino esters, were unsuccessful. Pronounced resinification of the reaction mixtures, from which the desired 1,3,5-triazines could not be isolated, was observed.

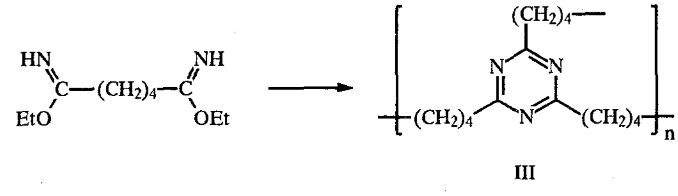
Trifluoroacetic acid methyl imino ester undergoes cyclization only in the presence of CF_3COOH; 2,4,6-tris(trifluoromethyl)-1,3,5-triazine is formed in low yield — 25% based on the imino ester subjected to the reaction and 60% based on the unchanged imino ester [20]. Under similar conditions, perfluorobutyric acid methyl imino ester undergoes virtually no cyclotrimerization. The low degree of conversion of fluorinated imino esters to 1,3,5-triazines is evidently due to the difficulty in the formation and the significant rate of decomposition of the imino ester salts, which are catalysts of this reaction, to perfluorocarboxylic acid amides [20].

Instances of the spontaneous cyclotrimerization of imino esters that contain strong electron-acceptor groupings in the acidic part of the molecule are known. For example, 4-nitro-4-methylvaleric acid [26] and 4,4-dinitrovaleric acid [27] imino esters undergo gradual trimerization to the corresponding 1,3,5-triazines when they are stored at 20°C.

The cyclotrimerization of the bis(imino esters) of some dicarboxylic acids has been reported [20, 39, 40]. For example, adipic acid diethyl bis(imino ester) is converted to a structured polytriazine with methylene bridges in the presence of catalytic amounts of the bis(imino ester) salt [39-41].

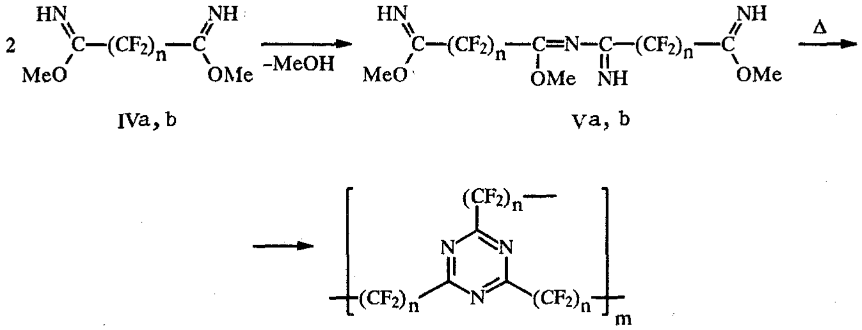
TABLE 2. Dependence of the Composition of Mixtures of 2,4,6-Trisubstituted 1,3,5-Triazines II and XIII-XV on the Ratio of Acetic Acid Ethyl Imino Ester (XI) and Butyric Acid Ethyl Imino Ester (XII) [16, 17]

XXXXI:XII molar ratio	Overall yield, %	Composition of the reaction products, %			
		II	XIII	XIV	XV
1 : 1	67,5	10,5	40,5	49	1
1 : 2	66	1,5	34,5	45,5	18,5
2 : 1	70	49	24,5	26,5	—



III

In a study of the cyclization of perfluoroglutaric acid dimethyl bis(imino ester) (IVa) and perfluoroadipic acid dimethyl bis(imino ester) (IVb) it was established that products Va, b of condensation of two molecules of bis(imino esters) Va, b are formed at 20°C in the presence of acetic or trifluoroacetic acid. Structured polytriazines VIa, b with fluoromethylene bridges are obtained when these "dimers" are heated to 150-180°C [20, 41].



IVa, b

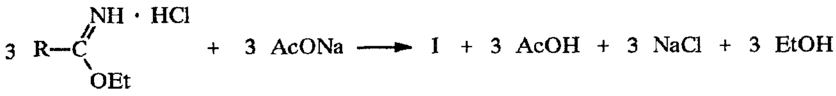
Va, b

VI a, b

IV-VI a n=3, b n=4

The authors note that the cyclization of bis(imino ester) IVb and its "dimer" Vb requires a significantly longer time and higher temperatures than the cyclization of bis(imino ester) IVa or Va (n = 3).

It was established [13] that an exothermic reaction occurs when the imino ester hydrochloride is mixed with an equivalent amount of sodium acetate, and 2,4,6-trisubstituted 1,3,5-triazines I are formed in 50-60% yields.



$$3\ \mathrm{R{-}C}\begin{matrix}\mathrm{NH\cdot HCl}\\ \mathrm{OEt}\end{matrix} + 3\ \mathrm{AcONa} \longrightarrow \mathrm{I} + 3\ \mathrm{AcOH} + 3\ \mathrm{NaCl} + 3\ \mathrm{EtOH}$$

I R = H, Me, Et, $ClCH_2$, MeCHCl, EtOOC

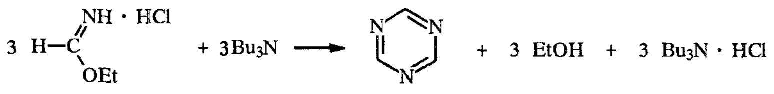
This method can be recommended for obtaining 1,3,5-triazines from unstable imino esters or imino esters that are difficult to isolate in the base form. For example, it was used successfully to obtain unsubstituted 1,3,5-triazine (VII) from formic acid ethyl imino ester hydrochloride. Among the various bases used in this reaction (NaOH, CaO, NH_3, K_2CO_3, EtONa, AcONa, and tertiary amines), the best results were obtained in the case of tributylamine [13] — 1,3,5-triazine (VII) is formed in 80% yield after 2 h at 20°C.

TABLE 3. Monosubstituted 1,3,5-Triazines XVIII and 2,4-Disubstituted 1,3,5-Triazines XIX Obtained from Ethyl Imino Esters and 1,3,5-Triazine (VII) [49]

R	Reaction conditions			Yield, %	
	imino ester:VII ratio (moles)	T, °C	time, h	XVIII	XIX
Me	3 : 2	45	172	75	—
Me	3 : 2	80	8	66	18
Me	3 : 1	25	260	90	—
Me	2 : 1	50	2,5	50	16
Me	3 : 1	75	4	50	8
Et	3 : 2	80	4,5	50	7
Ph	2 : 1	80...110	32	94	—
4-$NO_2C_6H_4$	1 : 1	78	3	82	—
3-$NO_2C_6H_4$	1 : 1	78	3	42	—
$PhCH_2$	3 : 2	80	1	38	7

TABLE 4. 2,4-Dimethyl-6-R-1,3,5-triazines XXII Obtained from 2,4,6-Trimethyl-1,3,5-triazine (II), Nitriles, and Methanol under Pressure (100°C, 30 h) [47]

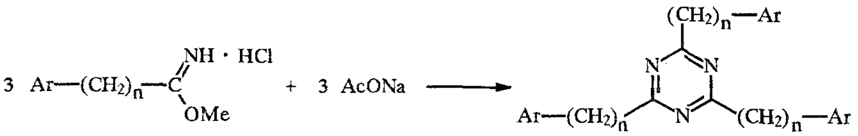
R	$P \cdot 10^{-3}$, atm	Yield, mole %	
		XXII	XXIII
Et	6	28,0	9,2
Ph	2	18,1	—
Ph	4	65,7	1,4
Ph	6	94,7	3,0
4-MeC_6H_4	6	95,2	1,7
4-ClC_6H_4	6	92,0	2,2
2-Naphthyl	8	70,6	—
4-Pyridyl	8	75,1	4,5



VII

In [42] it is recommended that 1,3,5-triazines II and VII (R = Me, H) be obtained by heating the benzyl imino ester hydrochlorides of the corresponding acids with N,N-diethylaniline in vacuo; the yields of 1,3,5-triazines in this case ranged from 50% to 63%.

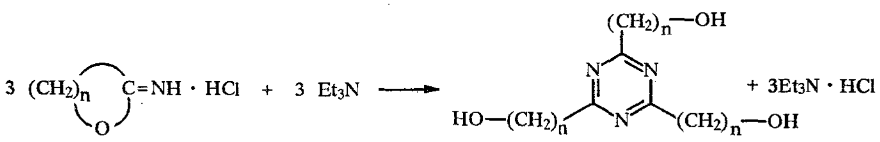
2,4,6-Trisubstituted 1,3,5-triazines VIII, which contain fragments of a sterically hindered phenol, were similarly synthesized in the presence of sodium acetate [43].



VIII

VIII Ar = 4-OH-3,5-$Me_2C_6H_2$, 4-OH-3,5-tert-$Bu_2C_6H_2$; n = 1, 2

2,4,6-Tris(ω-hydroxyalkyl)-1,3,5-triazines IX were synthesized in 53-70% yields by treatment of the hydrochlorides of cyclic imino esters with triethylamine [44].



IX

IX n = 3—5

TABLE 5. Production of 2,4,6-Trisubstituted 1,3,5-Triazines by the Joint Cyclotrimerization of Amidine Hydrochlorides with Imino Esters* [50]

R in the starting amidine	Reaction conditions		Yield, %	
	T, °C	time, h	XXIV	XXV
H	65...75	3,5		
	25	18	50****	
H	35...40	1,5	65****	
	25	18		
H**	40...60	2	54****	
H***	25	16	87,5	—
i-Pr	80	0,5		
	25	18	45	12
Cl_3C**	25	20	64	—
Cl_2CH	25	96	40	11
MeCHCl	15	4		
	25	18	50	26
Ph	60	2		
	25	18	55	—
4-ClC_6H_4	30...45	2		
	80	0,5	88	—
4-$NO_2C_6H_4$	60	3,5		
	25	18	60	—
2-Pyridyl	50	0,5		
	25	96	81	—
$PhCH_2$	25	120	58	20
EtOOC	50	0,5		
	25	96	39	13

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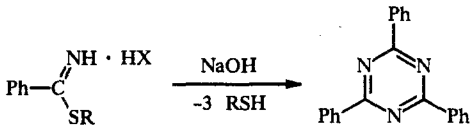
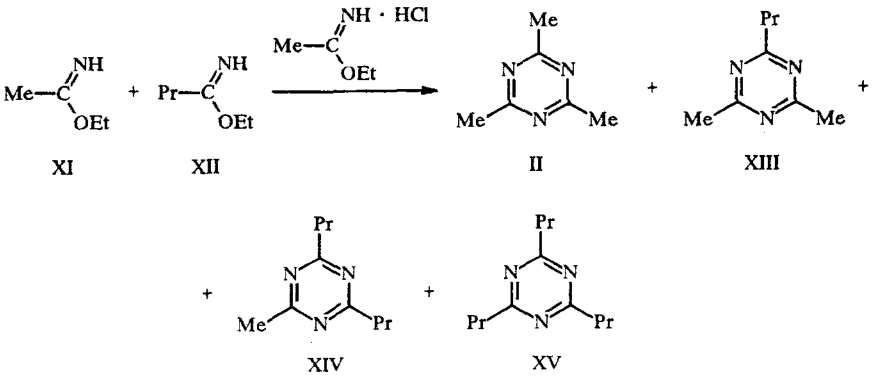
*R^1 = Me. **R^1 = Et. ***R^1 = 4-pyridyl. ****Overall yield. Imino thioester hydrohalides X are converted to 2,4,6-triphenyl-1,3,5-triazine on treatment with aqueous alkali solution [45].



X

X R=Et, $PhCH_2$; X=Cl, Br

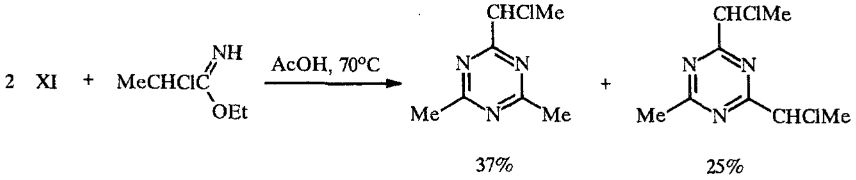
The cyclotrimerization of imino esters in the presence of acidic catalysts can also be used to obtain 2,4,6-trisubstituted 1,3,5-triazines with mixed structures that are formed by joint cyclization of imino esters of different acids [16, 17, 46]. For example, a mixture of four 1,3,5-triazines II and XIII-XV (in an overall yield of 67-70%) is formed in the cyclization of a mixture of acetic acid ethyl imino ester (XI) and butyric acid ethyl imino ester (XII) in the presence of 6 mole % XI hydrochloride [16, 17].

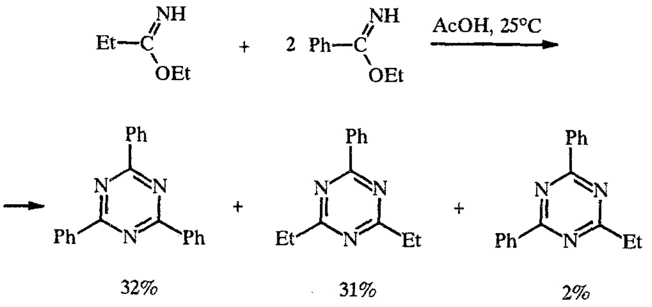

XI XII II XIII XIV XV

The composition of this mixture varies considerably as a function of the ratio of the starting imino esters (see Table 2).

2,4,6-Trimethyl- (II), 2,4-dimethyl-6-ethyl-, 2-methyl-4,6-diethyl-, and 2,4,6-triethyl-1,3,5-triazine are formed in a ratio of 1:0.9:0.8:3.1 in the joint cyclotrimerization of an equimolar mixture of imino ester XI and propionic acid ethyl imino ester in the presence of 15 mole % AcOH (20°C, 24 h) [47].

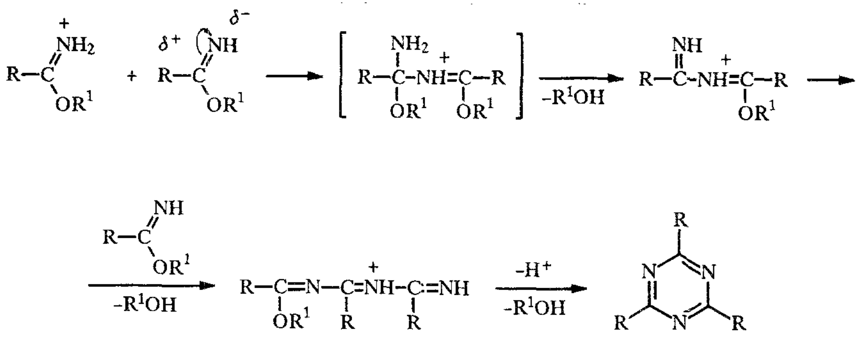
Imino esters that differ markedly with respect to their character and reactivities can participate in joint cyclotrimerization; this is illustrated by the following examples [46]:





The mechanism of the formation of 1,3,5-triazines by the acid-catalyzed cyclotrimerization of imino esters can be represented in the following way. It is assumed [13, 15, 20] that the acidic catalyst promotes the reaction by forming an imino ester salt in which the electrophilicity of the carbon atom of the functional group increases significantly as a consequence of the high polarization of the C=N bond.

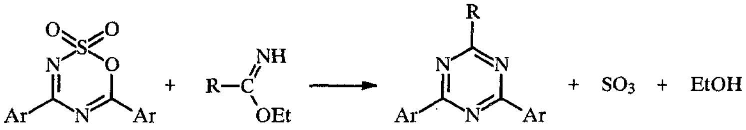
The activated molecule of the imino ester salt is attacked by a second molecule of the imino ester to give a dimeric intermediate, which is then converted to salt XVI of a linear "trimer." The salt undergoes cyclization to the resonance-stabilized triazine system.



XVI

The electrophilicity of the carbon atom in the imino esters is evidently insufficient to ensure the effective addition of a second molecule of the imino ester to the C=N bond, and cyclization of the imino ester bases therefore does not occur. The isolation of dimeric intermediates V in the case of perfluorocarboxylic acid imino esters [20] and their subsequent cyclization to 1,3,5-triazines confirm this reaction mechanism.

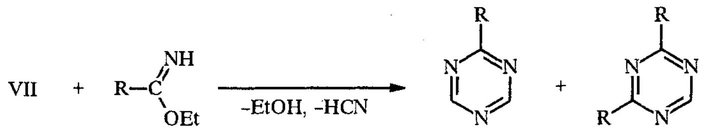
An interesting method for the synthesis of 2,4,6-trisubstituted 1,3,5-triazines with mixed structures has been proposed [48]: they are obtained in good yields (53-68%) in the reaction of imino esters with 4,6-diaryl-1,2,3,5-oxathiadiazine 2,2-dioxides XVII.



XVII

XVII Ar = Ph, 3-MeC$_6$H$_4$; R = Me, Cl$_3$C, Ph, 1-chloroanthraquinon-3-yl

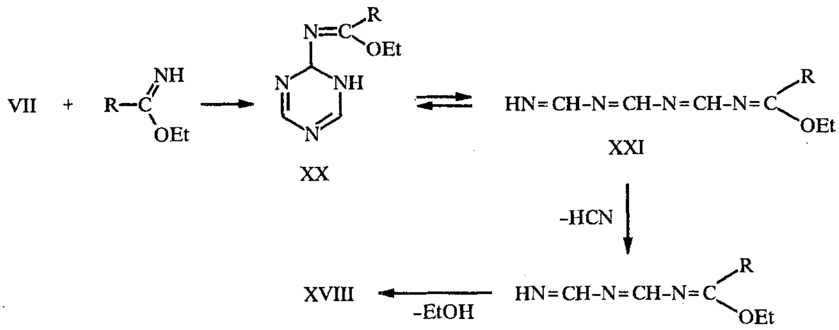
It was established [49] that monosubstituted 1,3,5-triazines XVIII and 2,4-disubstituted 1,3,5-triazines XIX are formed when imino esters are heated (40-80°C) with 1,3,5-triazine (VII) (see Table 3).



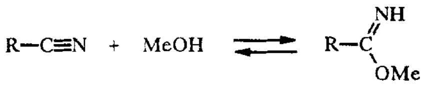
XVIII XIX

XVIII, XIX R = Me, Et, Ph, PhCH$_2$, 4-NO$_2$C$_6$H$_4$, 3-NO$_2$C$_6$H$_4$

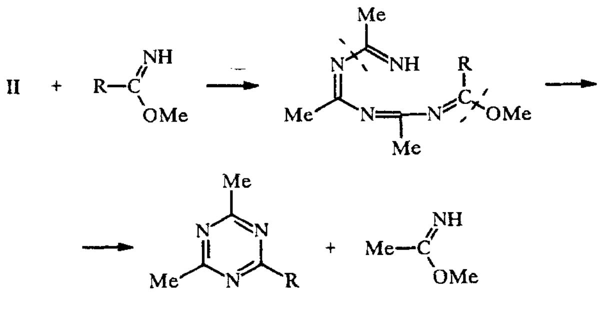
The reaction proceeds via a scheme involving nucleophilic addition to the C=N bond of 1,3,5-triazine (VII) [13, 49]. Intermediate XX, which is formed as a result of the addition of one molecule of the imino ester to VII, exists in equilibrium with linear isomer XXI. The latter is stabilized by cyclization with the prior elimination of HCN and ethanol. This results in the formation of monosubstituted 1,3,5-triazine XVIII, which can react with a second molecule of the imino ester, thereby undergoing a similar transformation to 2,4-disubstituted 1,3,5-triazine XIX.



2,4-Dimethyl-6-R-1,3,5-triazines XXII are formed in high yields, along with small amounts (2-9%) of 2-methyl-4,6-R$_2$-1,3,5-triazines XXIII, in the reaction (100-150°C, 30 h) of equimolar amounts of 1,3,5-triazine (II), a nitrile, and methanol under a pressure of (4-6)·10^3 atm (see Table 4) [47]. Intermediates in this process are imino esters of the corresponding acids, which are generated in the mixture of the nitrile and methanol under pressure [6].

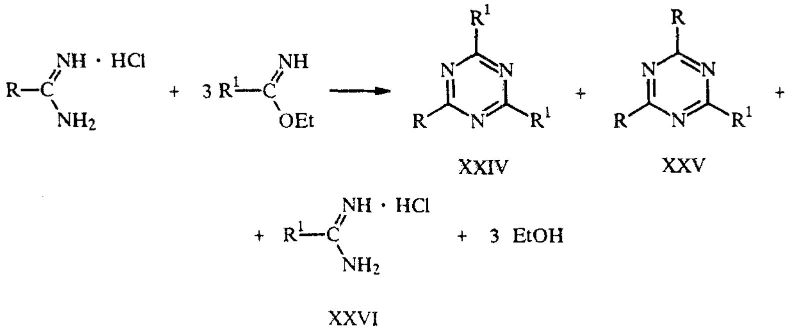


$$\mathrm{R{-}C{\equiv}N + MeOH \rightleftharpoons R{-}C({=}NH)OMe}$$



XXII

Imino esters can undergo joint cyclotrimerization with amidines. It was established [50] that amidine hydrochlorides react with imino esters (in a molar ratio of 1:3) to give a mixture of two 2,4,6-trisubstituted 1,3,5-triazines XXIV and XXV, in which XXIV, which contains two radicals from the imino ester, predominates (see Table 5).

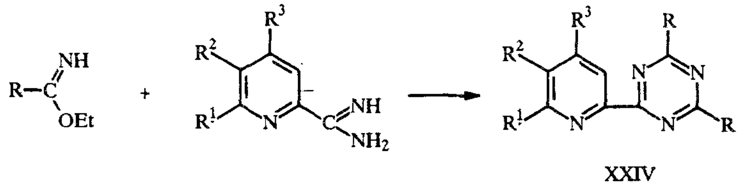


XXIV—XXVI R = H, alkyl, aryl, heteryl ; R^1 = Me, Et, 4-pyridyl

New amidine hydrochloride XXVI is formed as a side product. Although Schaeffer [50] notes that the reaction proceeds well only with the simplest aliphatic imino esters, it has been reported [51] that 2,4-bis(4-pyridyl)-1,3,5-triazines (XXIV, R = H, R^1 = 4-pyridyl) was obtained in 87% yield from isonicotinic acid methyl imino ester and formamidine hydrochloride.

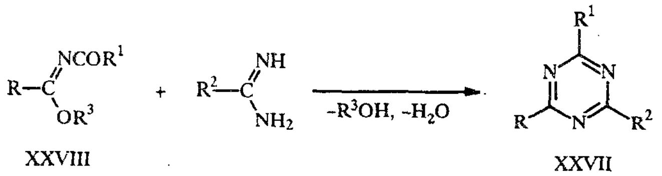
The yields of 1,3,5-triazines with mixed structures XXIV and XXV are sometimes reduced significantly due to the formation of the simplest trimers, viz., 2,4,6-trimethyl- (II) or 2,4,6-triethyl-1,3,5-triazine, which is a result of the competitive cyclotrimerization of the imino ester with side amidine XXVI. Aliphatic amidines react with imino esters with low selectivity, as evidenced by the formation of significant amounts of 1,3,5-triazine XXV.

The condensation (60°C, 0.5 h) of imino esters of aliphatic acids with the hydrochlorides of amidines of substituted pyridine-2-carboxylic acids, leading to 2,4-dialkyl-6-(2-pyridyl)-1,3,5-triazines XXIV, which are effective fungicides, has been described [52].



XXIV R = alkyl C_1-C_4; R^1 = alkyl C_1-C_7, substituted phenyl ; R^2, R^3 = H, alkyl C_1-C_3

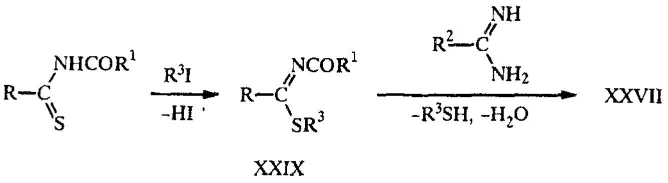
An original method for obtaining 1,3,5-triazines XXVII containing three different radicals by the reaction of equimolar amounts of N-acylimino esters XXVIII and amidines has been proposed [46, 53]. It should be noted that N-acylimino esters XXVIII are formed in high yields in the acylation of imino esters with acid chlorides in the presence of triethylamine at 0°C [54, 55].



XXVII, XXVIII R = Et, Ph; R^1 = Me, Et, Ph, $PhCH_2$, PhCH=CH; R^2 = H, Me, Ph; R^3 = Et, Pr

However, the yields of 1,3,5-triazines of this type were low as a consequence of the formation of various side products, among which amidines and esters, as well as other 1,3,5-triazines, were found.

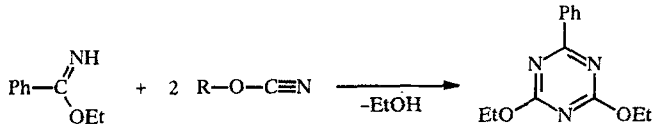
It was subsequently shown [56, 57] that the yields of 1,3,5-triazines XXVII can be raised to 75-93% if N-acylimino thioesters XXIX, which are readily formed by alkylation of N-acylthioamides with alkyl halides, are used instead of N-acylimino esters XXVIII in the condensation with amidines.



XXVII, XXIX R = H, Me, Ph, 4-MeC_6H_4, EtO; R^1 = Ph, 4-MeC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$; R^2 = Me, Ph, NH_2; R^3 = Me, Et

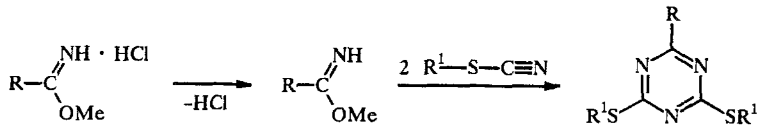
2. SYNTHESIS OF FUNCTIONAL DERIVATIVES OF 1,3,5-TRIAZINE

Imino esters have also been used as starting substances to obtain some functional derivatives of 1,3,5-triazine. For example, 2,4-dialkoxy(aroxy)-6-phenyl-1,3,5-triazines, which are promising pesticides, were synthesized by the reaction of benzoic acid ethyl imino ester with alkyl and aryl cyanates (in a molar ratio of 1:2) [58].



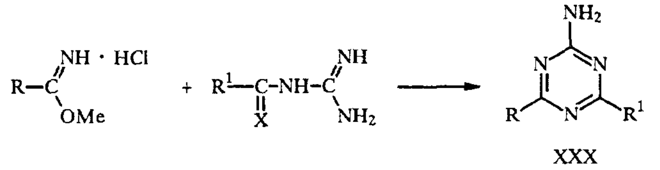
R = Cl_3CCH_2, Ph, 2,4-$Me_2C_6H_3$, 4-ClC_6H_4

6-Substituted 2,4-dialkyl(aryl)thio-1,3,5-triazines were synthesized by the reaction of methyl imino esters (generated in situ by treatment of imino ester hydrochlorides with triethylamine) with thiocyanates [28, 31, 32, 59, 60].



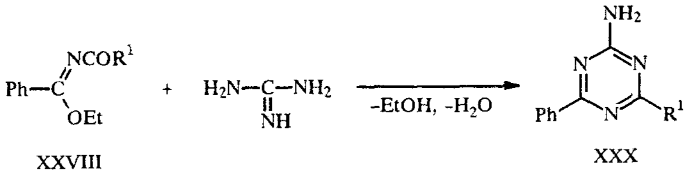
R = Me, Ph, $PhCH_2$, Cl_3C, 2-furyl, 5-nitro-2-furyl, 3-indolyl; R^1 = Me, $PhCH_2$, 3,5-tert-Bu_2-4-HOC_6H_2, tetrahydrofuryl, $Ac(CH_2)_3$

2-Amino-4,6-disubstituted 1,3,5-triazines XXX are formed in high yields (80-92%) as a result of the condensation of the hydrochlorides of imino esters of various acids with N-acylguanidines or N-imidoylguanidines [24, 61-67].



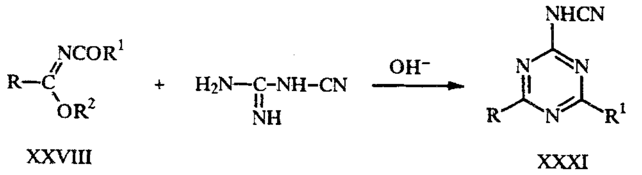
XXX R = Me, $ClCH_2$, $PhCH_2$, 3,5-tert-Bu_2-4-HOC_6H_2, 3,5-tert-Bu_2-4-$HOC_6H_2SCH_2$, 3-indolyl, 3-pyridyl, 5-nitro-2-furyl; R^1 = Cl_3C, Ph, 3-indolylmethyl, 2-furyl, 3-pyridyl
X = O, NH

2-Amino-1,3,5-triazines XXX were obtained in the reaction of benzoic acid N-acylimino esters XXVIII with guanidine [68].



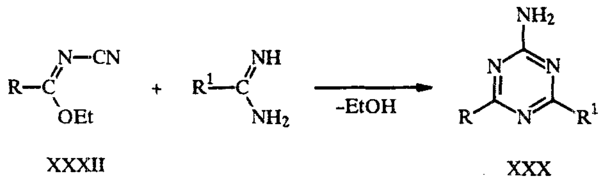
XXVIII, XXX R^1 = Me, Ph

The condensation of N-acylimino esters XXVIII with dicyanodiamide in the presence of strong bases (potassium tert-butoxide, for example) in inert solvents at −40°C to 150°C leads to 4,6-disubstituted 2-cyanamino-1,3,5-triazines XXXI, which are used as intermediates to obtain herbicides [69].



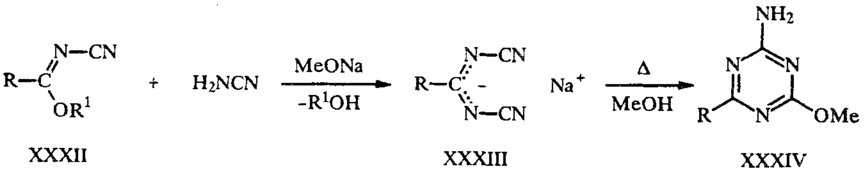
XXVIII, XXXI R, R^1 – alkyl, haloalkyl, cycloalkyl, arylalkyl ; R^2 – alkyl C_1-C_3

The easily obtained and reactive N-cyanoimino esters XXXII are convenient starting substances for obtaining functionally substituted 1,3,5-triazines [70, 71]. For example, 2-amino-1,3,5-triazines XXX were synthesized in 38-84% yields by condensation of N-cyanoimino esters with amidines at 20-30°C for several hours [72, 73].



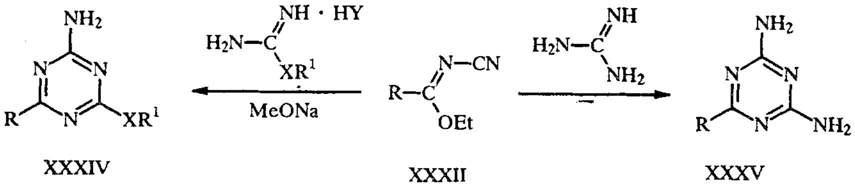
XXX, XXXII R – H, Me, $ClCH_2$, Ph; R^1 – Me, Ph, 4-$NO_2C_6H_4$, $AlkOOCCH_2$

The reaction of N-cyanoimino esters XXXII with cyanamide and sodium methoxide (in a molar ratio of 1-1.1:2.0) in absolute methanol at 20°C gives Na salts XXXIII, which are converted to 6-substituted 2-amino-4-methoxy-1,3,5-triazines XXXIV in 33-54% yields by refluxing (for 5 days) in methanol [74].



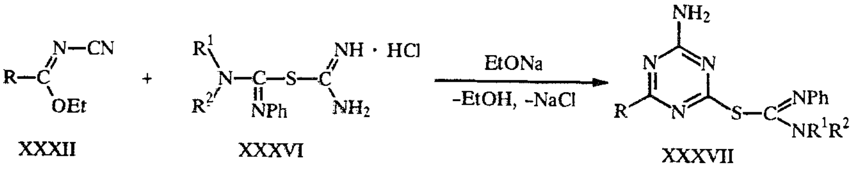
XXXII—XXXIV R – H, Me, Ph; R^1 – Me, Et

6-Substituted 2,4-diamino-1,3,5-triazines XXXV and 6-substituted 2-amino-4-alkoxy(alkylthio)-1,3,5-triazines XXXIV, respectively, were synthesized in 60-98% yields by condensation of N-cyanoimino esters XXXII with guanidine [72, 73] or with salts of O-alkylisoureas [73, 75] and S-alkylisothioureas [75] in the presence of sodium methoxide at 20°C.



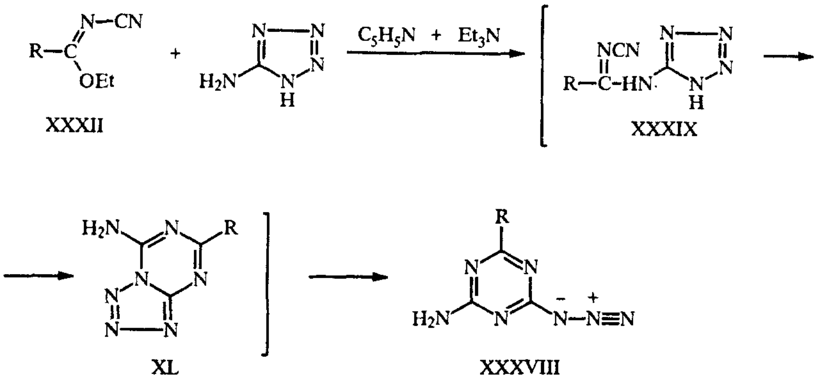
XXXIV, XXXV R – H, alkyl C_1-C_4, $ClCH_2$; R^1 – alkyl C_1-C_3; X – O, S; Y – Cl, HSO_4, NO_3

S-Substituted 2-amino-4-mercapto-1,3,5-triazines XXXVII were obtained in 54-88% yields in the reaction of N-cyanoimino esters XXXII with trisubstituted thiobis(formamidine) salts XXXVI in the presence of sodium ethoxide [76].



XXXII, XXXVI, XXXVII R – H, Me; R^1 – H, alkyl C_1-C_3; R^2 – alkyl C_1-C_3, cyclohexyl;
$R^1 + R^2$ – $(CH_2)_4$

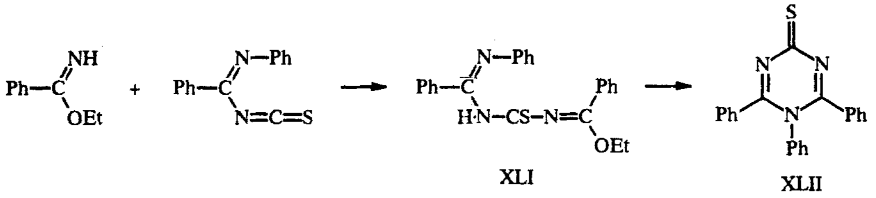
It has been reported [77] that 6-substituted 2-amino-4-azido-1,3,5-triazines XXXVIII are obtained (in 35-60% yields) in the reaction (20°C, 11 h) of N-cyanoimino esters XXXII with 5-aminotetrazole in the presence of triethylamine and pyridine.



XXXII, XXXVIII—XL R = Me, Ph

The authors assume that the intermediate in this reaction is N,N-disubstituted amidine XXXIX, which subsequently undergoes cyclization to labile tetrazolotriazine XL.

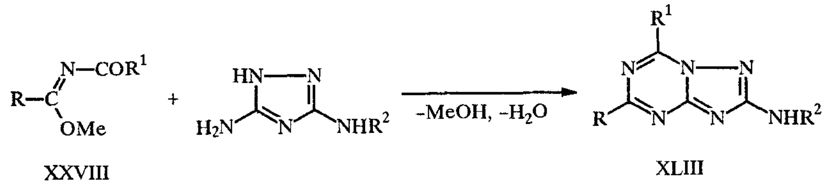
The reaction of equimolar amounts of a benzoic acid imino ester and N-phenylbenzimidoyl isothiocyanate in benzene at 20°C gives unstable adduct XLI, which undergoes cyclization to 1,2,6-triphenyl-1,4-dihydro-1,3,5-triazine-4-thione (XLII) (in 26.4% yield) under the reaction conditions [78].



3. SYNTHESIS OF CONDENSED 1,3,5-TRIAZINE SYSTEMS

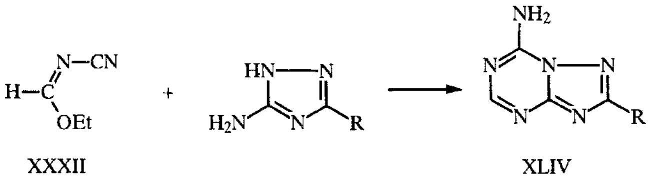
N-Acylimino esters XXVIII and N-cyanoimino esters XXXII are used as synthones in obtaining condensed heterocyclic systems that include 1,3,5-triazine fragments.

For example, the condensation of N-acylimino esters XXVIII with 5-amino-1H-1,2,4-triazoles leads to 2-amino-1,2,4-triazolo[1,5-*a*]-1,3,5-triazine derivatives XLIII, which are intermediates for obtaining herbicides [79].



XXVIII, XLIII R, R^1 = H, alkyl C_1-C_4, haloalkyl, haloalkoxy ., R^2 = H, acyl, alkenyl, alkynyl

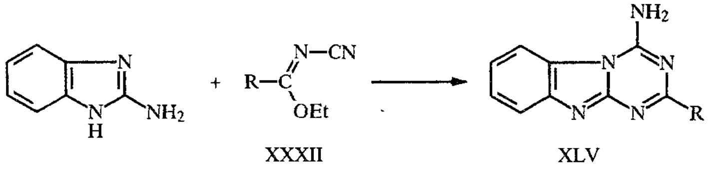
5-Amino-2-R-1,2,4-triazolo[1,5-*a*]-1,3,5-triazines (5-azaadenines) XLIV were synthesized in 66-93% yields by the reaction of formic acid N-cyanoimino ester (XXXII, R = H) with 4-substituted 5-amino-1H-1,2,4-triazoles (in a molar ratio of 2:1) in methanol (refluxing, 1 h) [80].



XXXII XLIV

XLIV R = H, Me, Et, Ph

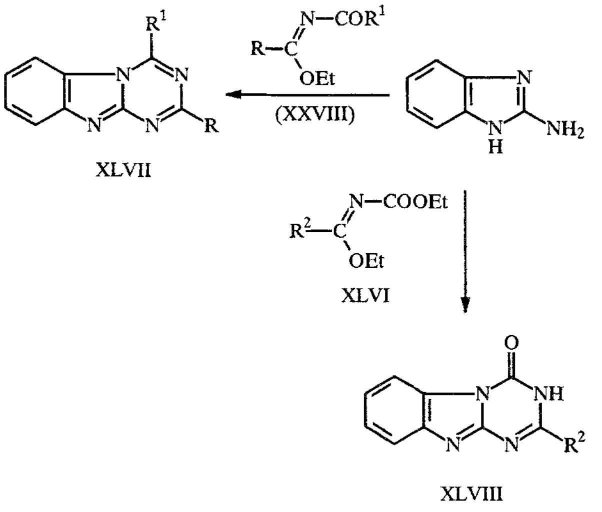
2-Substituted 4-aminobenzimidazolo[1,2-*a*]-1,3,5-triazines XLV were obtained in 68-73% yields under similar conditions from N-cyanoimino esters XXXII and 2-aminobenzimidazole [80].



XXXII XLV

XXXII, XLV R = H, Me, Ph

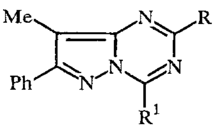
It has been reported [81] that the condensation of equimolar amounts of 2-aminobenzimidazole and N-acylimino esters XXVIII or N-(ethoxycarbonyl)imino esters XLVI in methanol (refluxing for 16-24 h) gives, respectively, 2,4-disubstituted benzimidazolotriazines XLVII or benzimidazolotriazin-4-ones XLVIII in ~80% yields.



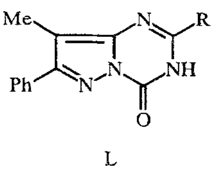
XLVII XLVIII

XXVIII, XLVII R = Ph, 4-MeOC$_6$H$_4$; R^1 = Me, Et; XLVI, XLVIII R^2 = *i*-Pr, Ph

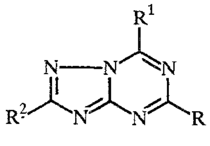
Pyrazolotriazines XLIX (in 85% yields), pyrazolotriazinones L (in 85% yields), 1,2,4-triazolotriazines LI (in 75% yields), and 1,2,4-triazolotriazinones LII (in 84% yields), respectively, were synthesized under similar conditions from N-substituted imino esters XXVIII and XLVI and 3-amino-4-methyl-5-phenylpyrazole or 3-amino-5-R-1H-1,2,4-triazoles [81].



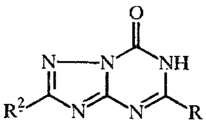
XLIX



L



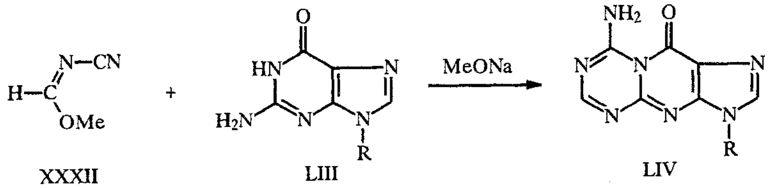
LI



LII

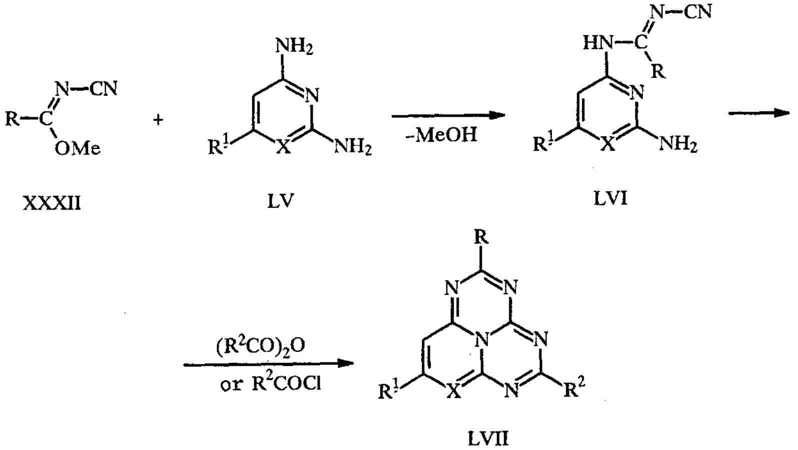
XLIX—LII R = Ph, 4-ClC$_6$H$_4$CH$_2$, PhCH$_2$; XLIX, LI R^1 = Me, *i*-Pr; LI, LII R^2 = H, Et

IA'-Metamorphosine (LIV) — a fluorescent three-ring analog of adenosine — was obtained in 39% yield by the reaction of excess formic acid N-cyanoimino ester (XXXII) with guanosine (LIII) in the presence of sodium methoxide in methanol (20°C, 24 h) [82].



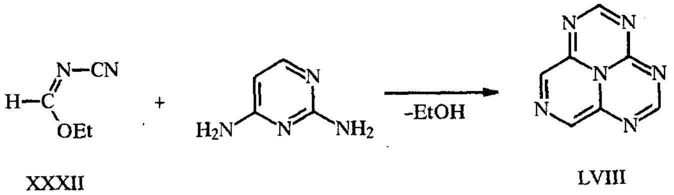
LIII, LIV R = β-D-ribofuranoside

Refluxing (for 2-3 h) N-cyanoimino esters XXXII with heterocyclic diamines LV (in a molar ratio of 1:1) in glyme leads to N,N-disubstituted amidines LVI (in 70-73% yields), which on treatment with acid anhydrides or chlorides (refluxing for 18 h) are converted in 29-94% yields to 1,3,4,6,9-pentaazaphenalene derivatives (LVII, X = CH) or 1,3,4,6,7,9-hexaazaphenalene derivatives (LVII, X = N) [83].

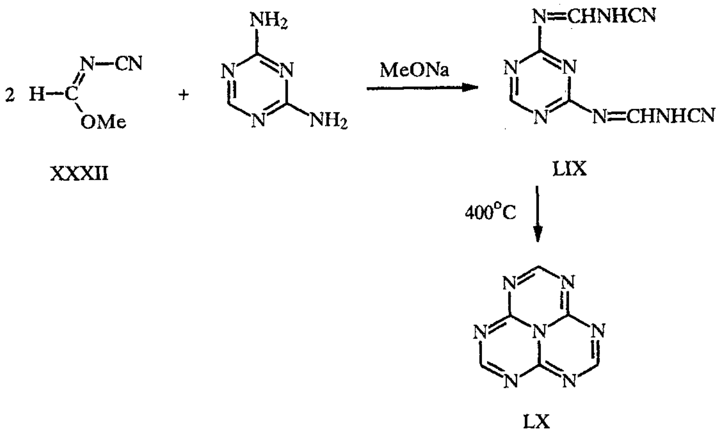


XXXII, LVI, LVII R = H, Me; LV—LVII R^1 = H, Me; LVII R^2 = Me, Et, n-Pr, F_3C, $ClCH_2$, Ph, $HOOC(CH_2)_2$, 2-$HOOCC_6H_4$; LV—LVII X = CH, N

1,3,4,6,8,9-Hexaazaphenalene (LVIII) was obtained in 40% yield by condensation of formic acid N-cyanoimino ester (XXXII) with 2,4-diaminopyrimidine (in a molar ratio of 2.4:1) in DMFA (95°C, 4 h) [84].



2,4-Bis(N-cyano-N-formamido)-1,3,5-triazine (LIX) was synthesized in 60% yield by the reaction of 2,4-diamino-1,3,5-triazine with excess N-cyanoimino ester XXXII in the presence of sodium methoxide in methanol—DMSO at 20°C. The thermolysis (400°C, 0.025 mm, 2 min) of bis(amidine) LIX leads to 1,3,4,6,7,9,9b-heptaazaphenalene (cyanmelurine) (LX) in 60% yield [85].



The material presented in this review provides evidence for the promising character of the use of imino esters as synthones in the preparative synthesis of 1,3,5-triazines with various structures. From a theoretical and applied point of view the possibilities of imino esters are evidently still far from having been exhausted, and the continuation of research in this direction is expedient.

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