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Synthesis of five- and six-membered nitrogen-containing heterocyclic compounds from carboxylic acid iminoesters

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Abstract. The review surveys and gives a systematic account of literature data concerning the application of carboxylic acid iminoesters in the synthesis of five- and six-membered nitrogen-containing heterocycles with several heteroatoms as well as heterocycles containing in the ring oxygen and sulfur atoms together with nitrogen atoms. The bibliography includes 350 references.

I. Introduction

Carboxylic acid iminoesters (imidates) and their salts, first obtained and described by Pinner[1] as early as the end of the previous century, have been attracting increasing attention by investigators, in view of their high reactivity, as synthons in the preparation of compounds of various classes — esters, amides, orthoesters, amidines, amidrazones, hydrazidines, amidoximes, etc. However, iminoesters and their salts are of special interest as key compounds in the syntheses of a wide variety of five- and six-membered nitrogen-containing heterocycles — imidazoles, benzimidazoles, 1,2,4-triazoles, pyrimidines, triazines, etc., as well as heterocycles containing nitrogen, oxygen, and sulfur atoms (oxazoles, oxazines, oxadiazoles, thiadiazoles, etc.).

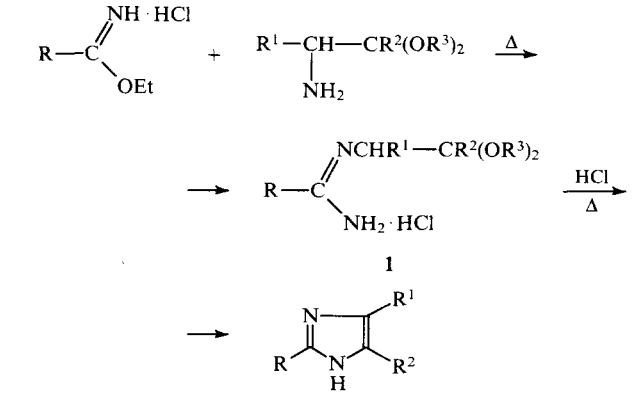
The available information about the synthesis, structures, and chemical reactions of iminoesters and their salts is described in monographs[2-4] and reviews.[5,6] However, the data concerning the reactions of iminoesters which lead to the formation of heterocyclic structures, examined in the above communications, are far from complete from our point of view and the systematic treatment employed there requires improvement. We may note, in particular, that a review devoted to the synthesis of compounds of the 1,3,5-triazine series from carboxylic acid iminoesters was published in 1992.[7] In addition, new effective methods have been developed for the synthesis from iminoesters of heterocyclic compounds possessing practically useful properties. Thus, there has been recently a considerable growth of the number of publications on this field. In the present review, we have attempted to give a systematic account and to examine critically the information on the use of iminoesters in the synthesis of heterocycles, which has appeared during the period between 1975 and 1994. Earlier data concerning the preparation of heterocycles from iminoesters may be found in a monograph[4] published in 1975. We shall make use of them only when necessary.

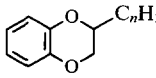
We have arranged the relevant data in terms of the type of the heterocycle formed — initially five- and six-membered nitrogen-containing heterocycles in order of increasing ring size and increasing number of nitrogen atoms in the ring and then five- and six-membered nitrogen heterocycles containing also oxygen and sulfur atoms. Such systematic treatment provides a clear idea about the synthetic possibilities of the method and may be useful in selecting the direction of further research.

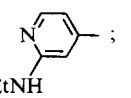
II. Synthesis of five- and six-membered nitrogen-containing heterocycles

1. Synthesis of substituted imidazoles and Δ^2-imidazolines

When the hydrochlorides of the iminoesters of various acids are condensed with the acetals of α-aminoketones in ethanol (refluxing for 1 – 6 h), the hydrochlorides of *N*-substituted amidines **1** are formed. On treatment with hydrochloric acid (50 – 100 °C, 0.5 – 6 h), these cyclise to substituted imidazoles (yield 30% – 85%)[8-16]



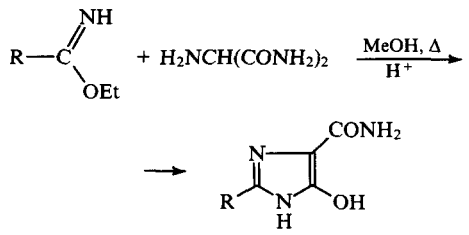
R = Me, Ar, $ArOCH_2$,  ;

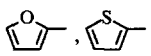
R^1 = H, Me; R^2 = H,  ; R^3 = Me, Et.

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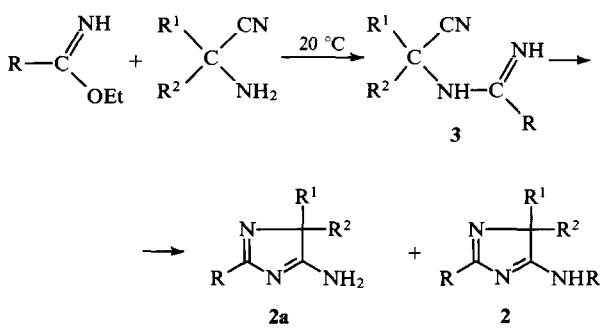
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Uspekhi Khimii **64** (4) 339 – 372 (1995); translated by A K Grzybowski

According to patent data,[17-19] the interaction of carboxylic acid iminoesters with aminomalonic acid diamide leads to the amides of 2-substituted 5-hydroxy-1*H*-imidazole-4-carboxylic acids, which exhibit an immunostimulating activity.



R = H, Alk, cyclo-(C_3–C_7), 1-Ad, Ar, $PhCH_2$, Ph_2CH, 3-Py, 

It has been reported[20] that the interaction of equimolecular amounts of α-aminonitriles with the iminoesters of pyridine-2-carboxylic and ethoxycarbonylformic acids results in the formation of 5-amino-4*H*-imidazoles **2a** in 44%–86% yield together with insignificant amounts (4%–10%) of *N*-substituted 5-amino-4*H*-imidazoles **2**.

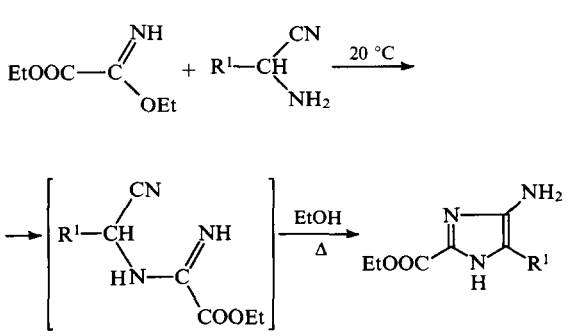


R = 2-Py, EtOOC; $R^1 = R^2$ = Me;

R^1 = Me, R^2 = Et; $R^1 + R^2 = -(CH_2)_4-$, $-(CH_2)_5-$

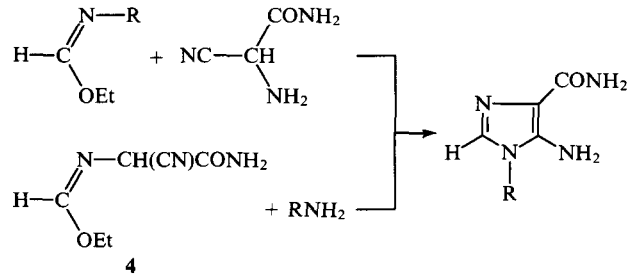
The authors suggest that the *N*-substituted amidine **3** is an intermediate in this reaction and also note that the iminoesters of other acids (R = Me, Ph, Cl_3C, 4-$NO_2C_6H_4$) do not form the imidazoles **2a** at all, but in certain cases afford *N*-substituted 5-amino-4*H*-imidazoles **2** in a low yield (4%–12%).

The condensation of the ethyl iminoester of ethoxycarbonylformic acid with α-substituted α-aminonitriles in ether leads to the amidines **3** (R = EtOOC), which cyclise on refluxing in alcohol to the ethyl esters of 4-amino-5-substituted 1*H*-imidazole-2-carboxylic acids (yield 51%–92%).[21,22]



R^1 = H, Me, EtOOC, H_2NCO, Ar

The condensation of *N*-substituted formic acid iminoesters with α-aminocyanoacetamide or the condensation of the *N*-substituted iminoester **4** with aromatic amines have been used to synthesise the amides of 1-substituted 5-amino-1*H*-imidazole-4-carboxylic acids.[23]

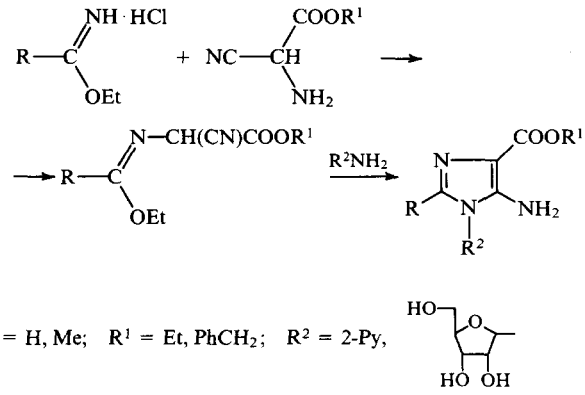


4

R = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4

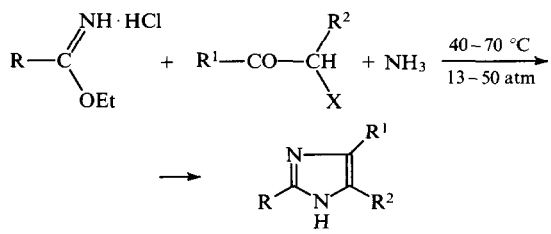
The iminoester **A** was obtained in its turn from the hydrochloride of the iminoester of formic acid with α-aminocyanoacetamide.

English investigators[24,25] used the latter method to obtain the esters of 1-substituted 5-amino-1*H*-imidazole-4 carboxylic acids, which are key compounds in the synthesis of purines.



R = H, Me; R^1 = Et, $PhCH_2$; R^2 = 2-Py,

In 1973, German investigators[26] proposed a convenient method of synthesis of imidazoles, which consists in the interaction of equimolecular amounts of the hydrochloride of an iminoester and of an α-substituted carbonyl compound in liquid ammonia under pressure. The carbonyl compounds employed in this reaction were 1,3-dihydroxyacetone,[26,27,29-31] α-hydroxyketones,[28,31] α-haloketones,[28,32] and α-acetoxyketones.[28] The reactions were carried out by heating the reactants (40–70 °C) under a pressure of 13–50 atm for 3–48 h; the yields of the target 2,4,5-trisubstituted 1*H*-imidazoles were then 10%–90% (Table 1).



(1)

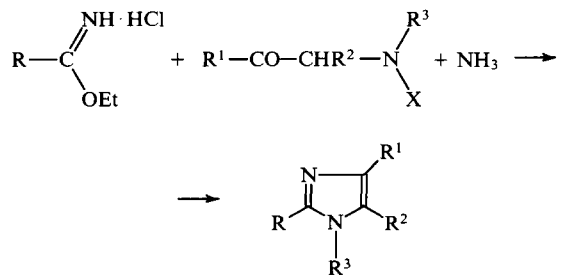
R = H, Me, Pr^i, Ar, $PhCH_2$, α-$C_{10}H_7CH_2$, cyclo-C_6H_{11}, Py, $ClCH_2CH_2$, $TsNHCH_2CH_2$, Me_2NCH_2, $Me_2NCH_2CH_2$, cyclo-$C_5H_{10}NCH_2CH_2$;

R^1 = H, $HOCH_2$, $HOCH_2CH_2$, Alk, Ph;

R^2 = H, Me, Ph, $MeOCH_2$; $R^1 + R^2 = -(CH_2)_4-$;

X = HO, Br, Cl, AcO.

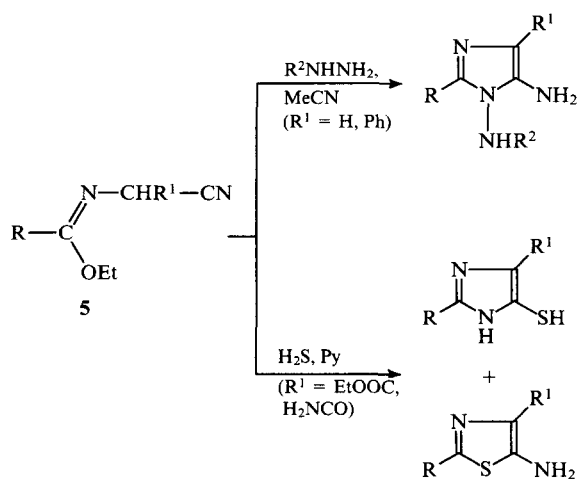
It was shown subsequently that *N*-substituted 1*H*-imidazoles are formed in a satisfactory yield from α-amino- and α-acylamino-ketones under similar conditions (80 °C, 35 atm, 15 h).[33,34]



R = Me, Ar, 4-$ClC_6H_4CH_2$, cyclo-C_6H_{11}, 3-Py;
R^1 = Alk, Ph;
R^2 = H, Alk, Ph, $PhCH_2$, $MeSCH_2CH_2$;
R^3 = H, Me, Ph, cyclo-C_6H_{11}; X = H, Ac.

The *N*-cyanomethylimidates **5** are convenient intermediates in the synthesis of 1*H*-imidazoles with functional group substituents. For example, treatment of compound **5** (R^1 = H, Ph) with hydrazine or phenylhydrazine afforded 1,5-diamino-1*H*-imidazoles — key compounds in the synthesis of azaindoline heterocycles.[35] The interaction of compounds **5** (R^1 = EtOOC, H_2NCO) with hydrogen sulfide in pyridine results in the formation of 5-mercapto-1*H*-imidazoles (yield 20%–35%) together with 5-aminothiazoles (yield 10%–20%, see Scheme 1).[36]

Scheme 1



R = H, Me, Ph, $PhCH_2$;
R^1 = H, Ph, EtOOC, H_2NCO; R^2 = H, Ph.

Table 1. Synthesis of 2,4,5-trisubstituted 1*H*-imidazoles by the condensation of iminoester hydrochlorides with α-substituted carbonyl compounds reaction (1) in liquid ammonia.[26–30]

R	R^1	R^2	Reaction conditions			Yield (%)
			P/atm	*T*/°C	*t*/h	
H	$HOCH_2$	H	20	70	5	35
H	H	H	25	50	5	20
H	Me	Me	25	50–60	10	43
H	Ph	H	25	50–60	10	16
Me	$HOCH_2$	H	45–50	60–70	6	68
Pr^i	$HOCH_2$	H	30	68	3	48
Ph	$HOCH_2$	H	20	70	5	73
Ph	Ph	Ph	25	50–60	15	25
Ph	Me	H	25	50–60	5–15	50
Ph	Ph	H	25	50–60	5–15	10
Ph	Ph	H	25	50	5	50
Ph	Ph	H	30	50–60	5–15	10
4-MeC_6H_4	$HOCH_2$	H	18	60	15	69
4-$MeOC_6H_4$	$HOCH_2$	H	29	70	4	76
$PhCH_2$	$HOCH_2$	H	15	50	20	85
4-$ClC_6H_4CH_2$	$HOCH_2$	H	20	70	15	42
cyclo-C_6H_{11}	$HOCH_2$	H	20	70	15	63
$PhCH_2$	$HOCH_2$	H	18	60	20	59
3-Py	$HOCH_2$	H	28	68	3	63
4-Py	$HOCH_2$	H	28	68	3	39
Ph	$HOCH_2CH_2$	H	13	40	48	61
Ph	$-(CH_2)_2-$		25	50–60	15	62
4-MeC_6H_4	Me	H	25	50–60	10	90

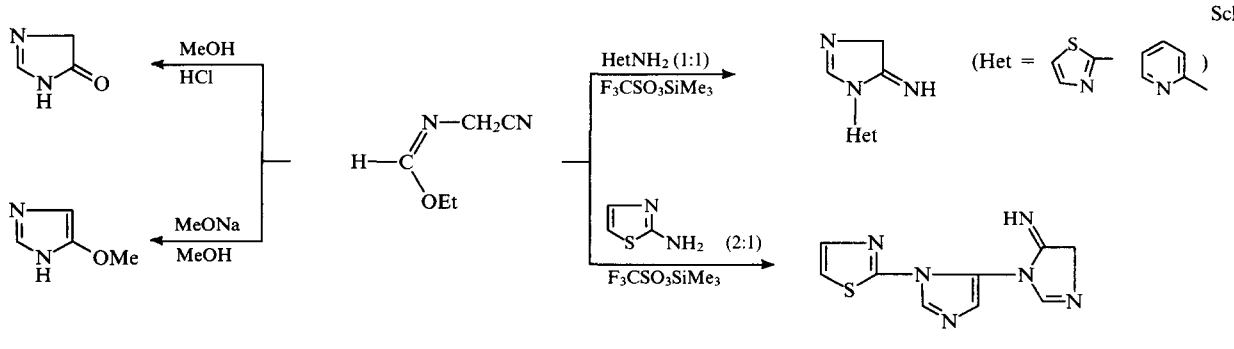
The reaction of the *N*-cyanomethyliminoester of formic acid with a methanol solution of HCl (20 °C, 0.5 h) leads to Δ^2-imidazolin-4(5)-one (yield 90%),[37,38] whilst refluxing with sodium methoxide in methanol gives rise to 4(5)-methoxyimidazole (yield 60%, see Scheme 2).[38]

The interaction of the same *N*-cyanomethyliminoester with heterocyclic amines (in molar proportions of 1 : 1) in the presence of trimethylsilyl triflate in acetonitrile (20 °C, 2 h) led to the synthesis of 1-heteroaryl-5-imino-Δ^2-imidazolines in 82%–91% yield.[38,39] On the other hand, the reaction of 2-aminothiazole with two equivalents of the *N*-cyanomethylimidate under similar conditions leads to the formation of the 1,5-disubstituted imidazole **6**.[38,39]

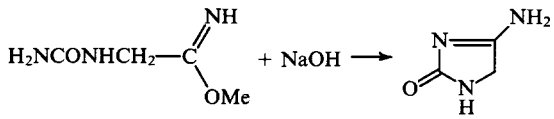
The condensation of the iminoester of ethoxycarbonylformic acid with *N*-phenylurea in tetrahydrofuran (THF) in the presence of HCl results in the formation of 3-phenylimidazolidine-2,4,5-trione (yield 56%).[22]

According to patent data,[40] 4-amino-Δ^3-imidazolin-2-one is formed in 95% yield on refluxing the iminoester of uredioacetic acid with alkali in aqueous alcohol.

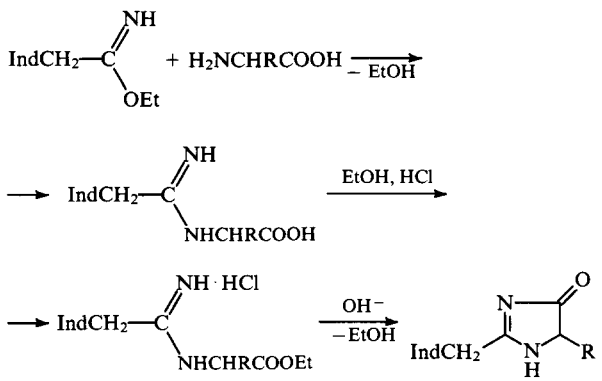
Scheme 2



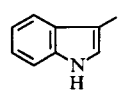
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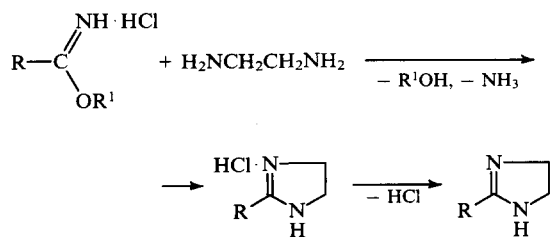
Fel'dman et al.[41] synthesised 2-(3-indolylmethyl)-Δ^2-imidazolin-4-ones, which are unstable under the usual conditions, from the ethyl iminoester of 3-indolylacetic acid and α-aminoacids in accordance with the following scheme:



R = H, Pr^i, Bu^i, Bu^s, $IndCH_2$;

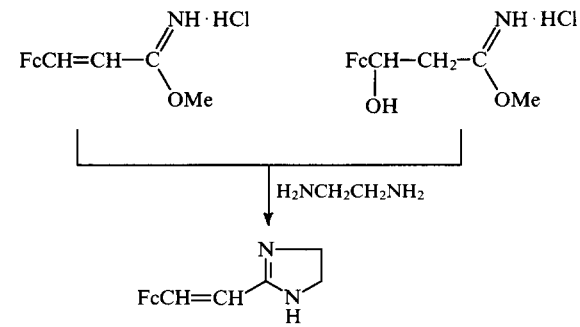
Ind = 

Some of the most interesting derivatives of the imidazole series are 2-substituted Δ^2-imidazolines, in view of their high and varied biological activity and valuable applied properties.[42,43] Compounds of this type are formed on condensation of iminoester salts with aliphatic 1,2-diamines.[4,5,42] It is noteworthy that investigators have devoted considerable attention in recent years to the synthesis of Δ^2-imidazolines from the hydrochlorides of ring-substituted iminoesters of benzoic,[44-49] phenylacetic,[44,47-49] 3,4-dihydro- and 1,2,3,4-tetrahydro-naphthalene-2-carboxylic acids,[50] adamantane-1-carboxylic acid,[51,52] ferrocenecarboxylic acid,[53] heterocyclic acids derived from furan,[54-57] benzofuran,[58] indole,[55,59-64] benzimidazole,[55] pyridine,[55] 4,5,6,7-tetrahydrobenzothiophene,[55] imidazo[1,2-a]-pyrazine,[65] isoxazoline,[66] etc., as well as aliphatic acids with functional-group substituents containing nitro-groups,[67-69] silylalkyl groups,[70-72] *N*-acylamino-groups,[73] alkoxy- and aryloxy-groups,[74-77] alkylthio- and arylthio-groups,[49,78] and organophosphorus fragments,[79,80] sterically hindered phenols,[81] etc.



R = Alk, cyclo-C_nH_{2n-1}, 1-Ad, $AlkOCH_2CH_2$, $ArOCH_2$, $MeC(NO_2)_2CH_2CH_2$, $Me_2C(NO_2)CH_2CH_2$, $Me_3SiCH_2CH_2$, $PhCH_2$, $XC_6H_4CH_2$, Ar, $ArCH_2SCH_2CH_2$, $(EtO)_2P(O)CH_2$, $(AlkO)_2P(O)CH_2CH_2$, Het; R^1 = Me, Et, $MeOCH_2CH_2$.

There are also isolated literature data concerning the synthesis of 2-substituted Δ^2-imidazolines from the iminoesters of α,β-unsaturated acids and their hydrochlorides. For example, (*E*)- and (*Z*)-2-(β-ferrocenylvinyl)-Δ^2-imidazolines **7** have been synthesised in 82%–88% yield by the reaction of the hydrochlorides of the methyl iminoesters of (*E*)- and (*Z*)-β-ferrocenylacrylic acids with ethylenediamine (0 °C, 0.5 h; 50–60 °C, 2 h).[82]



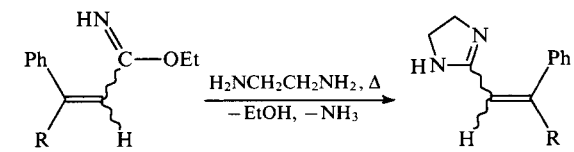
(*E*)- and (*Z*)-**7**

Fc = $(\eta^5\text{-}C_5H_5)Fe(\eta^5\text{-}C_5H_4)$–

The same workers showed[83] that a 3:1 mixture of the (*E*)- and (*Z*)-isomers **7** is formed under similar conditions from the hydrochloride of the methyl iminoester of 3-hydroxy-3-ferrocenylpropionic acid.

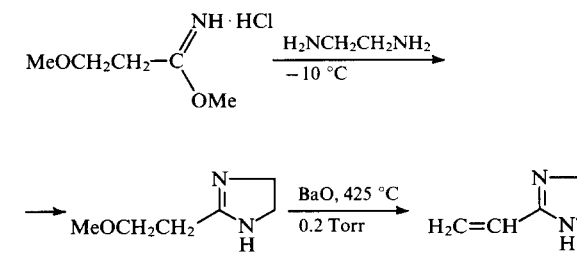
The *p*-tosylate of 2-[β-(5-nitro-2-furyl)vinyl]-Δ^2-imidazoline, which inhibits the growth of pathogenic bacteria, has been obtained in 83% yield by the reaction of the iminoester of β-(5-nitro-2-furyl)acrylic acid with the di-*p*-tosylate of ethylenediamine in ethanol (50–55 °C, 18 h).[84,85]

Ishikawa[86] synthesised (*E*)- and (*Z*)-(β-R-styryl)-Δ^2-imidazolines in 54%–88% yield by refluxing the ethyl iminoesters of (*E*)- and (*Z*)-β-R-cinnamic acids with ethylenediamine (molar ratio 1:2) in ethanol. These compounds exhibit a hypoglycemic activity.

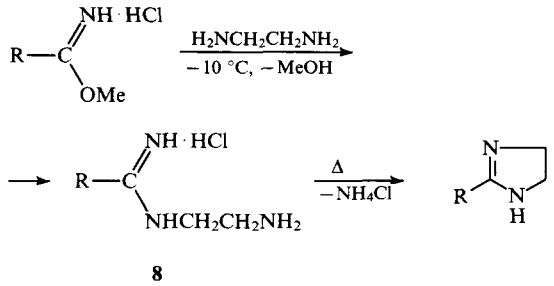


R = Ph, Py

We may note that 2-vinyl-Δ^2-imidazoline, which is used as the monomer in the synthesis of water-soluble polymers, may be synthesised in a high yield from 2-(β-methoxyethyl)-Δ^2-imidazoline.[74-77,87]

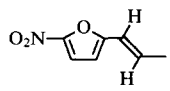


Despite the extensive application of the condensation of iminoester salts with ethylenediamine for the synthesis of Δ^2-imidazolines, there is hitherto hardly any information about the mechanism of this reaction. The condensation apparently proceeds with the intermediate formation of the hydrochlorides of *N*-(2-aminoethyl)amidines **8**, which subsequently cyclise to Δ^2-imidazolines.[88] In certain cases, when the reaction was carried out at −10 °C, it was possible to isolate and identify intermediates of this type, which on refluxing in ethanol (2–3 h) were converted quantitatively into 2-substituted Δ^2-imidazolines.[89]



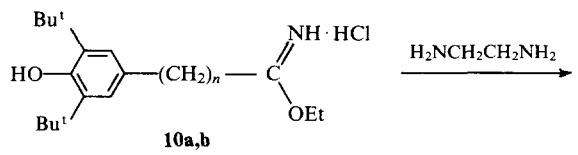
8

R = PhCH(OH), 4-$O_2NC_6H_4$, Ind, 3-Py,

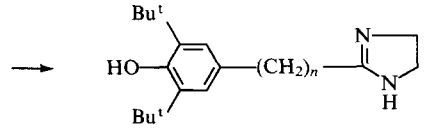


Since the first stage of the reaction proceeds with evolution of heat, the hydrochlorides of the iminoesters are mixed with ethylenediamine in an anhydrous solvent (methanol, ethanol, dioxane, methylene chloride, etc.) whilst cooling the system (0–10 °C). In order to complete the cyclisation, the reaction mixture is heated (40–78 °C) for several hours. The hydrochlorides of Δ^2-imidazolines formed under these conditions are converted into the free bases by treatment with a solution of sodium alkoxide in methanol or ethanol and also with a saturated solution of alkali whilst cooling. This results in the formation of the target 2-substituted Δ^2-imidazolines in fairly high yields (73%–95%) and without impurities.

There are only isolated literature data on the correlation between the structure of the acid components of the iminoester molecule, the reaction time, and the yields of the corresponding Δ^2-imidazolines. For example, the synthesis of the Δ^2-imidazoline **9a** from the hydrochloride of the iminoester of 3,5-di-*tert*-butyl-4-hydroxybenzoic acid **10a** requires prolonged heating (8–10 h), whereas the formation of the Δ^2-imidazoline **9b** from the hydrochloride of the iminoester of 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionic acid **10b** is completed in 1.5–2 h.[44,45,81]



10a,b



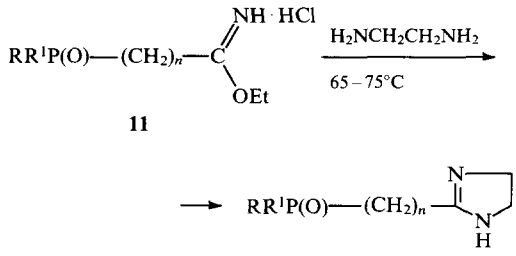
9a,b

n = 0 (**a**), 2 (**b**).

The lower reactivity of the iminoester hydrochloride **10a** with respect to ethylenediamine can be accounted for by the influence of the electron-donating hydroxyaryl group, which diminishes the positive charge on the carbon atom of the iminoester group and lowers its electrophilicity. In the case of the iminoester hydrochloride **10b**, the influence of this group is much smaller, since the groups are separated by two methylene units.[44,45]

A similar behaviour was found in a study of the condensation of ethylenediamine with the hydrochlorides of the iminoesters of indole-3-carboxylic and 3-indolylacetic acids containing the electron-donating indolyl group.[61]

It has been noted,[79] that the hydrochlorides of the iminoesters of β-phosphorylated propionic acids **11** (n=2) react with ethylenediamine twice as slowly as the corresponding acetic acid derivatives **11** (n=1).



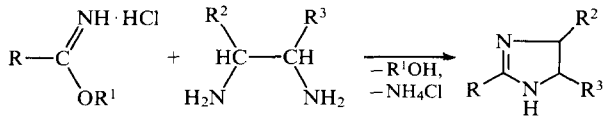
11

R = Ph, AlkO; R^1 = AlkO; n = 1, 2.

The authors explained this by the fact that the approach of the electron-accepting phosphoryl group to the reaction centre increases its electrophilicity, which facilitates the reaction with ethylenediamine.

One should also note that iminoester hydrochlorides are much more reactive in the reaction with ethylenediamine than the iminoesters themselves. In the latter case, the formation of Δ^2-imidazolines in a satisfactory yield requires prolonged (10–22 h) refluxing of the reactants in ethanol or in another suitable solvent,[52,59,73] while the iminoesters of phosphorylated acids do not react with ethylenediamine at all.[79] This finding can be explained by the increase in the electrophilicity of the carbon atom of the C=N group in the iminoester hydrochlorides as a consequence of the greater shift of the π-electron pair of the double bond towards the nitrogen atom of the iminoester group.[4]

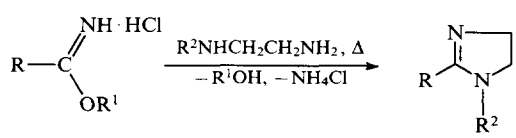
Apart from ethylenediamine, other aliphatic 1,2-diamines have been condensed with iminoesters and their hydrochlorides, for example, 1,2-diaminopropane,[90,91] 2,3-diaminopropan-1-ol,[49] and erythro-1,2-diamino-4,4,4-trifluoro-1-phenylbutane.[46] The 2,4-disubstituted or 2,4,5-trisubstituted Δ^2-imidazolines formed as a result of these reactions exhibit hypotensive,[92] hypertensive,[49] analgesic, and anti-inflammatory[46] activities.



R = Et, Ar, $PhCH_2OCH_2$,
$PhCHR^4CH_2$ (R^4 = Ph, cyclo-C_6H_{11}, 4-Py);
R^1 = Me, Et; R^2 = Me, $HOCH_2$, Ph; R^3 = H, F_3CCH_2.

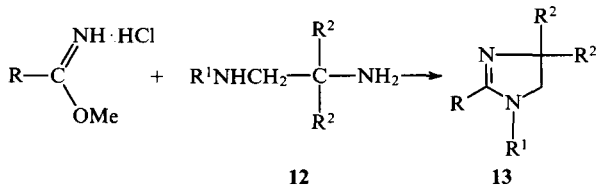
The condensation of iminoester hydrochlorides with *N*-monosubstituted ethylenediamines, leading to 1,2-disubstituted Δ^2-imidazolines which are difficult to obtain by other methods, is of definite interest.[42]

There are literature data on the condensation of iminoester hydrochlorides with *N*-alkyl-,[48,81] *N*-(2-cyanoethyl)-,[55,61,62,89,93] *N*-(1-adamantylmethyl)-,[52] *N*-(trimethylsilylmethyl)-,[71,94] *N*-aryl-,[95–97] *N*-benzyl-,[54,55,61,62,81,89,98] *N*-(2-aryl-2-hydroxyethyl)-,[99] *N*-furfuryl-,[54,55,64,89,100] *N*-tetrahydrofurfuryl-,[64,100] *N*-(2-thienylmethyl)-,[54,89] *N*-(4-phenyl-2-thiazolyl)-, *N*-(2-benzothiazolyl)-,[89,101] and *N*-(1-benzotriazolylmethyl)-ethylenediamines.[89]



R = Alk, $HOCH_2$, Ph, $PhCH_2$, $XC_6H_4CH_2$,
cyclo-C_nH_{2n-1}, Het, 1-Ad;
R^1 = Me, Et; R^2 = Alk, Ar, $PhCH_2$, Het.

The interaction of iminoester hydrochlorides with the 1,2-diamines **12** — ethylenediamine, *N*-(trimethylsilylmethyl)-ethylenediamine, and 2-amino-2-methyl-1-(trimethylsilylmethyl)aminopropane — has been studied in detail.[71,94]

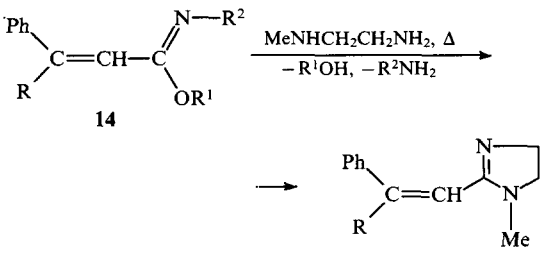


12 **13**

R = Me, Ph, $PhCH_2$, $Me_3SiCH_2CH_2$;
R^1 = H, Me_3SiCH_2; R^2 = H, Me.

It was established that the yield of the Δ^2-imidazolines **13** depend to a greater extent on the structure of the initial 1,2-diamine and to a much lesser extent on the structure of the iminoester hydrochlorides. This fact can evidently be accounted for by the steric hindrance generated by the presence of bulky substituents next to the reaction centres in the 1,2-diamine. The yields of the Δ^2-imidazolines **13** decrease from ethylenediamine (yield 68%–90%) to the *N*-substituted ethylenediamine **12** ($R^1 = Me_2SiCH_2$, R^2 = H; yield 53%–58%) and to the *N*-substituted 1,2-diaminopropane **12** (R^1-Me_3SiCH_2, R^2 = Me) (yield 23%–34%).

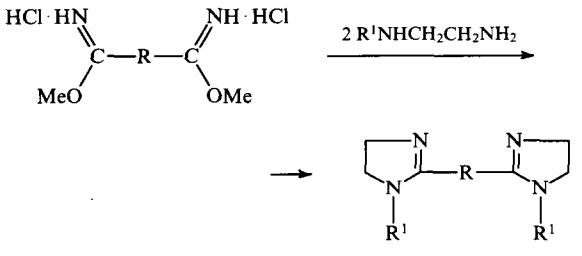
Heating of the *N*-substituted iminoesters **14** with *N*-methylethylenediamine (120–130 °C, 1.5 h) leads to 1-methyl-2-(β-R-styryl)-Δ^2-imidazolines, which exhibit a hypoglycemic activity.[102]



14

R = Me, Ph, Py; R^1 = Alk; R^2 = Pr^i, Bu^t.

There are also literature data on the condensation of the dihydrochlorides of the bisiminoesters of dicarboxylic acids with ethylenediamine[103,104] and *N*-(1-adamantylmethyl)ethylenediamine,[52] which leads to the bisimidazolines **15** in 80%–97% yield.

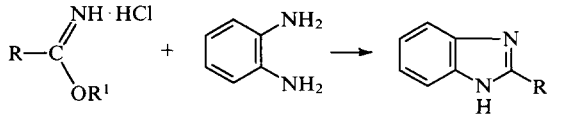


15

R = $-CH_2CH_2CMe(NO_2)CH_2CH_2-$,
$-CH_2CH_2C(NO_2)_2CH_2CH_2-$,
$-CH_2CH_2OCH_2C{\equiv}CCH_2OCH_2CH_2-$;
R^1 = H, 1-$AdCH_2$.

2. Synthesis of substituted benzimidazoles

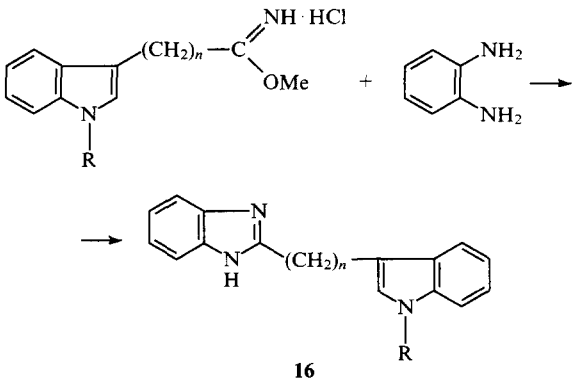
The condensation of the hydrochlorides of the iminoesters of aliphatic, aromatic, and heterocyclic acids with *o*-phenylenediamine leads to 2-substituted benzimidazoles.[4,42,44,51,52,55,57,61,62,69,71,72,80,82,89,103,105–114] Reactions of this type are usually carried out by refluxing (for 1.5–5 h) equimolecular amounts of the reactants in methanol or ethanol; the benzimidazoles are then formed in 36%–92% yields.



R = Me, $EtOOCCH_2$, $Me_2C(NO_2)CH_2CH_2$, $MeC(NO_2)_2CH_2CH_2$, $(O_2N)_3CCH_2CH_2$, $Ac(CH_2)_3$, $Me_3SiCH_2CH_2$, $ArNHCH_2CH_2$, 4-HO-3,5-$Bu^t_2C_6H_2(CH_2)_n$ (n = 0, 2), Ar, $PhCH_2$, Fc, 1-Ad, Het;
R^1 = Me, Et, $MeOCH_2CH_2$.

It has been noted[115,116] that the interaction of iminoesters with *o*-phenylenediamine is rapid only when the reaction is carried out in an acid medium. For example, when the iminoester of *N*-phenylalanine was heated with *o*-phenylenediamine in dioxane or isopentyl alcohol (140 °C, 3 h), the yield of 2-(2-phenylaminoethyl)benzimidazole reached only 55%, whereas the reaction with the dihydrochloride of this iminoester proceeds exothermically and the yield of benzimidazole is 70%–80%.[116]

The 2-substituted benzimidazoles **16**, containing indole fragments, are formed in 85%–92% yield on refluxing equimolecular amounts of the hydrochlorides of the iminoesters of acids of the indole series and *o*-phenylenediamine in ethanol for 4–6 h.[55,61,62,89]

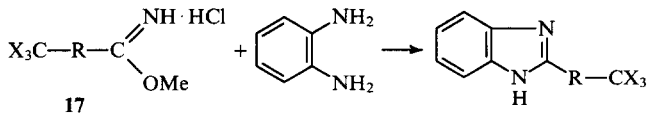


16

R = H, Me; n = 0, 1.

The benzimidazoles **16** have also been synthesised by condensing the iminoesters of the above acids with *o*-phenylenediamine. These reactions were carried out under more severe conditions — at 140–150 °C in dimethylformamide (DMF) for 15–20 h, but the yield of the target products did not then exceed 44%–52%.[89] In view of this, iminoester hydrochlorides are employed as a rule as the initial compounds in the synthesis of benzimidazoles by the above procedure. In those cases where the iminoester hydrochlorides are difficult to obtain or are unstable (for example, the hydrochlorides of the iminoesters of trichloroacetic acid[117]), the hydrochloride of *o*-phenylenediamine is condensed with the iminoesters. For example, 2-trichloromethylbenzimidazole is formed in 85%–95% yield on interaction of the iminoester of trichloroacetic acid with the monohydrochloride of *o*-phenylenediamine in ethanol[118] or in acetic acid.[119]

The condensation of equimolecular amounts of the hydrochlorides of the iminoesters of polyhalogenated carboxylic acids **17** and *o*-phenylenediamine in methanol (refluxing for 1–2 h) afforded 2-polyhaloalkylbenzimidazoles in 45%–86% yields.[114]

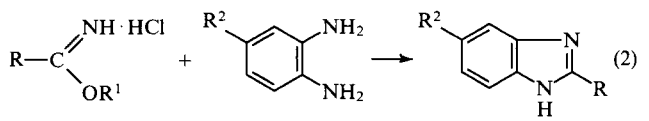


17

X = Br, R = $-(CH_2)_2-$;
X = Cl, R = $-CH_2CHCl-$, $-(CH_2)_2-$.

At the same time, the authors[114] noted that they were unable to synthesise the corresponding benzimidazoles from the hydrochlorides of the iminoesters of 2,4,4,4-tetrabromobutyric acid **17** (X = Br, R = $-CH_2CHBr-$), 4,4,4-tribromobut-2-enoic acid **17** (X = Br, R = $-CH=CH-$), and 4,4,4-trichlorobut-2-enoic acid **17** (X = Cl, R = $-CH=CH-$). According to the authors, the presence of the double bond in the α-position relative to the carbon atom of the iminoester group lowers its electrophilicity, which prevents the occurrence of the target reaction.

The condensation of the hydrochlorides of the iminoesters of various acids with 4-substituted 1,2-diaminobenzenes containing both electron-donating and electron-accepting groups has been widely used in recent years for the synthesis of 2,5(6)-disubstituted benzimidazoles.[107,112,113,120-127]



(2)

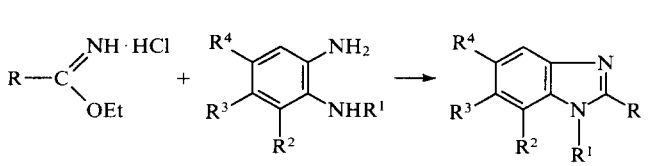
R = $PhCH_2$, $XC_6H_4CH_2$, Ar, Het;
R^1 = Me, Et, $MeOCH_2CH_2$;
R^2 = Alk, AlkO, ArO, O_2N, NC, MeOOC, F_3C, Het.

The above reactions were carried out by refluxing (for 2–8 h) equimolecular amounts of the reactants in methanol, ethanol, dioxane, or acetic acid, the yield of the target benzimidazoles amounting to 30%–62% depending on the structures of the initial iminoester hydrochlorides and on the nature of the substituents R^2 in the *o*-phenylenediamine (Table 2, see over).

It has been noted[121-123,125] that, when the methoxyethyl iminoesters of aromatic acids are condensed with 4-substituted 1,2-diaminobenzene, the yield of the target benzimidazoles increases appreciably compared with the methyl and ethyl iminoesters.

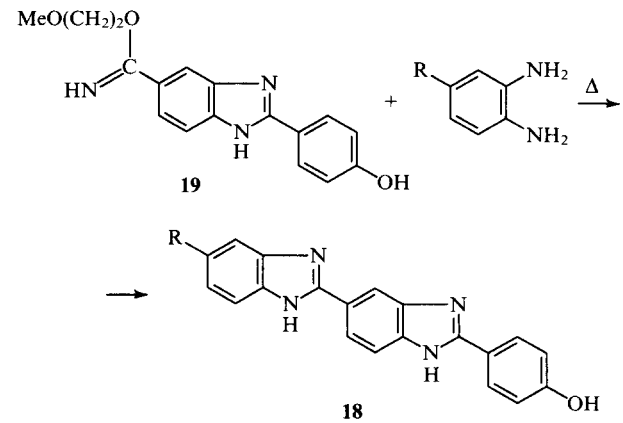
Some of the 2,5(6)-disubstituted benzimidazoles synthesised from the iminoester hydrochlorides possess antihelminthic and fungicidal properties,[107] exhibit antihypertensive, spasmolytic, and vasodilating activities,[120] as well as high cytotoxic,[123] antiproteolytic,[125] analgesic, and anti-inflammatory activities.[127]

The condensation of iminoester hydrochlorides with *N*-monosubstituted *o*-phenylenediamines leads to 1,2-disubstituted benzimidazoles. For example, when the hydrochlorides of aliphatic acid iminoesters are refluxed with *N*-alkyl-*o*-phenylenediamines in ethanol, polysubstituted benzimidazoles are formed in 58%–79% yields. They can be used as selective herbicides.[128-132]

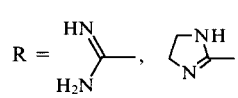


R = H, Alk, $HOCH_2$;
R^1 = Alk; R^2, R^3 = H, Hal, NO_2, NH_2, MeNH, MeO, Me_2N;
R^4 = Alk, cyclo-(C_3–C_6), F_3C, F_2CHSO_2.

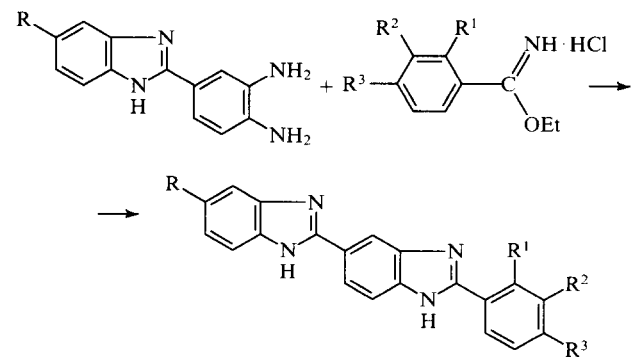
Derivatives of 2,5-bisbenzimidazolyl **18** are of definite interest from the standpoint of the search for new substances with antiproteolytic[125] and chemotherapeutic[126] activities. For example, when the methoxyethyl iminoester **19** is condensed with 4-R-*o*-phenylenediamines in methanol (refluxing for 3 h), 5-(5-R-2-benzimidazolyl)-2-(4-hydroxyphenyl)benzimidazoles **18** are formed in 25%–28% yields.[125]

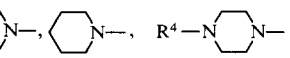


19 **18**

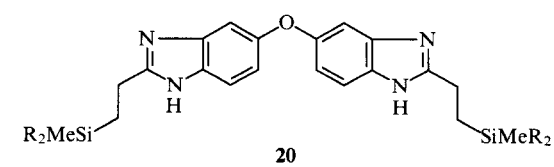


The corresponding bisbenzimidazolyls have also been synthesised in 55%–83% yields by the interaction of 2-(3,4-diaminophenyl)-5-R-benzimidazoles with the hydrochlorides of aromatic acid iminoesters in ethanol (refluxing for 3–5 h).[126]



R = Et_2N, ;
R^1 = H, HO; R^2 = H, Cl, Me, NO_2, MeO;
R^3 = H, AlkO, Me, Cl, Ph, PhO, NH_2;
R^1 + R^2 = OCH_2O; R^4 = Alk, $PhCH_2$, $HOCH_2CH_2$, Ph, Et_2NCO.

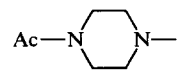
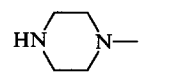
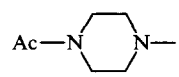
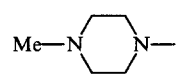
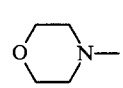
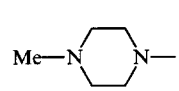
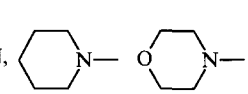
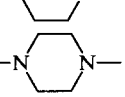
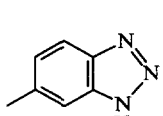
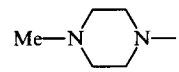
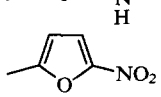
The condensation of the hydrochlorides of the iminoesters of β-trialkylsilylpropionic acids with di(3,4-diaminophenyl) ether (molar ratio 2 : 1) afforded a 70%–72% yield of the organosilicon dibenzimidazolyl ether **20**.[72]



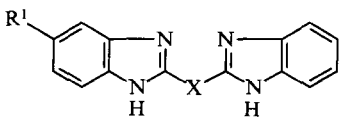
20

R = Me, Et.

Table 2. Synthesis of benzimidazoles from iminoester hydrochlorides and 4-substituted 1,2-diaminobenzenes [reaction (2)].

R	R^1	R^2	Yield (%)	Ref.
Ph	$MeOCH_2CH_2$		48	122
4-HOC_6H_4	$MeOCH_2CH_2$	$Me_2N(CH_2)_3NHCO$	65	121
	$MeOCH_2CH_2$		69	122
	$MeOCH_2CH_2$		74	122
	Me		68	124
	Me	Me	54	124
	Me	Cl	58	124
	Me	NC	75	125
4-$O_2NC_6H_4$	$MeOCH_2CH_2$	$HOOC(CH_2)_5NHCO$	78	119
	$MeOCH_2CH_2$	Me_2N	92	122
4-$AcNHC_6H_4$	$MeOCH_2CH_2$	$Me_2N(CH_2)_3NHCO$	70	119
4-HO-3,5-$Bu^t_2C_6H_2$	$MeOCH_2CH_2$		75	121
	$MeOCH_2CH_2$	$HOCH_2CH_2NH$	82	121
	$MeOCH_2CH_2$		72	121
4-HO-3-IC_6H_3	Me	Me	30	124
4-H_2N-3-$O_2NC_6H_3$	Et	Et_2N,   (R³ = Alk, Ph, $PhCH_2$, $HOCH_2CH_2$)	54–78	126
$PhCH_2$	Et	NO_2	77	107
2,4-$(O_2N)_2C_6H_3CH_2$	Et	Me	68	113
	Et	MeO	75	113
	$MeOCH_2CH_2$		70	122
	Et	Cl	46	112
	Et	MeOOC	25	112
$R^3NHCH(OH)CH_2OC_6H_3R^4$ (R³ = Alk, cyclo-C_nH_{2n-1}; R⁴ = H, F, Cl, Br, Alk, AlkO)	Et	Alk, AlkO, F, Cl, Br	54–72	120

The interaction of the bisiminoesters of dicarboxylic acids or their hydrochlorides with *o*-phenylenediamine or 4-substituted 1,2-diaminobenzenes (molar ratio 1 : 2) results in the formation of the derivatives **21**, in which the benzimidazole fragments are separated by a chain of carbon atoms or by an aromatic or a heterocyclic group.[52,103,104,125,133]

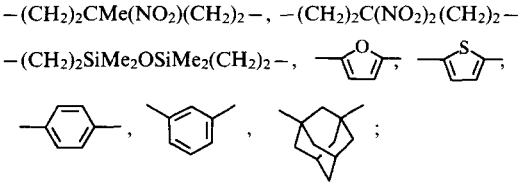


21

X = $-(CH_2)_n-$, where n = 1–3, 5, 6, 8;

$-(CH_2)_2CMe(NO_2)(CH_2)_2-$, $-(CH_2)_2C(NO_2)_2(CH_2)_2-$,

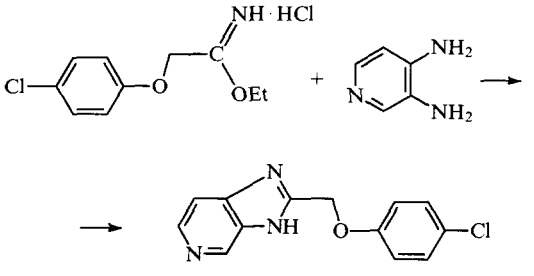
$-(CH_2)_2SiMe_2OSiMe_2(CH_2)_2-$,



R^1 = H, $-C(NH)NH_2$, $-C(NBu)NH_2$,

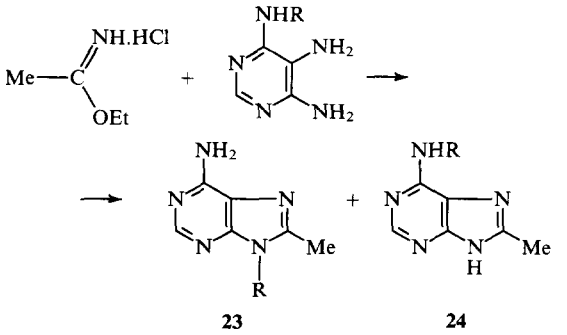


The condensation of iminoester hydrochlorides with heterocyclic *o*-diamines leads to condensed imidazole systems. For example, the interaction of the hydrochloride of the (4-chlorophenoxy)acetic acid iminoester with 3,4-diaminopyridine in ethanol (refluxing for 20 h) gives rise to the imidazo[4,5-*c*]pyrimidine derivative **22** (yield 20%), which exhibits an antihypotoxic activity.[134]



22

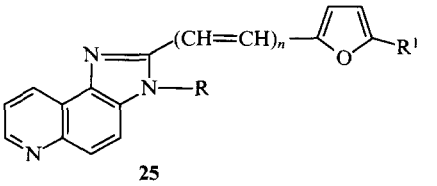
The ring closure in the reaction of 4-*N*-substituted 4,5,6-triaminopyrimidines with the hydrochloride of the acetic acid iminoester proceeds much more readily with participation of the secondary 5-amino-group and not the primary 6-amino-group.[135] This results in a 70%–85% yield of 6-amino-9-R-8-methylpurines **23** together with 6-*N*-substituted 6-amino-8-methylpurines **24** (yield 6%–17%).



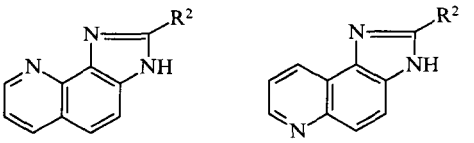
23 **24**

R = Ph, $PhCH_2$.

The condensation of *N*-substituted 5,6-diaminoquinolines with the hydrochlorides of the iminoesters of acids derived from furan afforded 40%–75% yields of 2-(5-R^1-2-furyl)- and 2-[β-(5-R^1-2-furyl)vinyl]-3-substituted 3*H*-imidazo[4,5-*f*]quinolines **25**.[136]



25



26 **27**

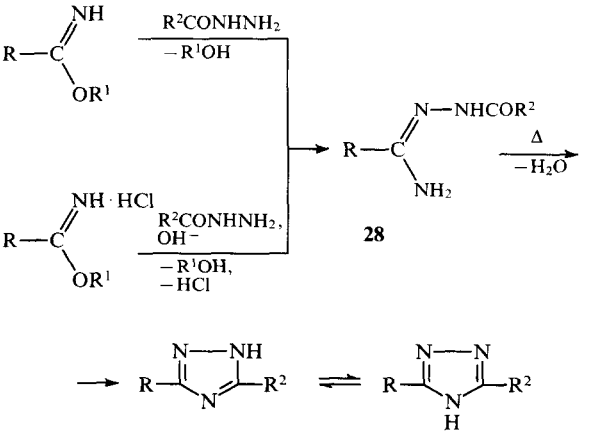
R = H, Me; R^1 = H, Br, NO_2; n = 0, 1; R^2 = Me, Ph, $PhCH_2$.

Refluxing of equimolecular amounts of 7,8-diaminoquinoline and the hydrochlorides of carboxylic acid iminoesters in ethanol gives rise to 60%–67% yields of 2-R-3*H*-imidazo[4,5-*h*]quinolines **26**.[137] 2-R-3*H*-imidazo[4,5-*f*]quinoline **27** have been synthesised from 5,6-diaminoquinoline under similar conditions.

3. Synthesis of substituted 1,2,4-triazoles and derivatives of 1,2,4-triazole with functional group substituents

The interactions of carboxylic acid iminoesters of *N*-acylhydrazines (acid hydrazides) are known to give rise to carboxylic acid *N*-acylamidrazones **28**, which can serve as convenient intermediates in the synthesis of 3,5-disubstituted 1*H*-1,2,4-triazoles.[4,5,138–142]

The *N*-acylamidrazones **28** are formed in high yields (70%–94%) when equimolecular amounts of an iminoester and an acid hydrazide are refluxed in methanol or ethanol[89,142–146] (in the case of *N*-formylhydrazine, the reaction is carried out at 0 °C)[140] or when iminoester hydrochlorides interact with acid hydrazides in the presence of bases—triethylamine,[147,148] aqueous NaOH solution,[139] or sodium ethoxide in absolute ethanol.[149]



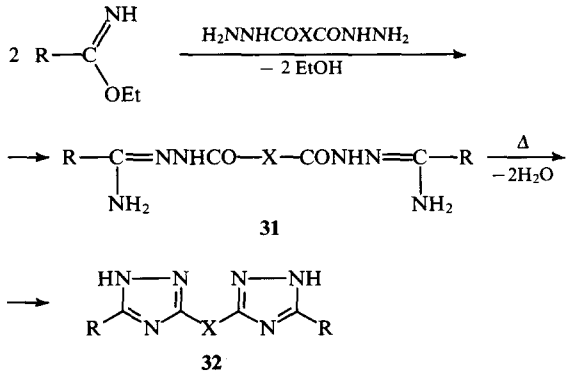
29 **30**

R = Alk, $Me_3SiCH_2CH_2$, $PhCH_2$, $PhCH_2OCONHCH_2$, EtOOC, Ar, Het;

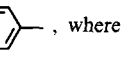
R^1 = Me, Et; R^2 = H, Alk, Ar, Het.

The *N*-acylamidrazones **28** readily undergo cyclodehydration to 3,5-disubstituted 1*H*-1,2,4-triazoles **29**, which can exist in the form of the tautomeric 4*H*-1,2,4-triazoles **30**.[150,151] The cyclodehydration of the *N*-acylamidrazones **28** takes place on heating to a temperature higher by 5–10 °C than the melting point for several minutes[20,89,143–146] and in certain cases on heating in vacuo[142] and in high-boiling solvents (toluene, DMSO).[147,149]

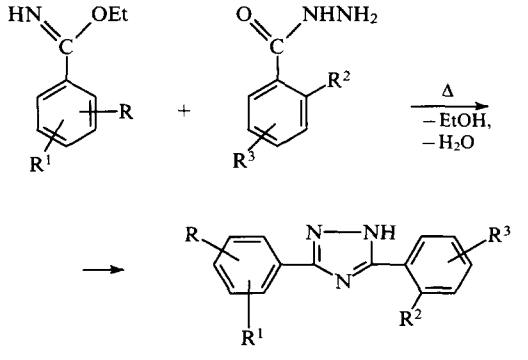
When iminoesters interact with dicarboxylic acid dihydrazides (molar ratio 2:1), the bis-*N*-acylamidrazones **31** are formed. On heating to 200–220 °C in vacuo, the latter give rise to 3,5-disubstituted bis-1*H*-1,2,4-triazoles **32** (yields 31%–74%).[142,149]



R = Me, $Me_3SiCH_2CH_2$, Ph, $PhCH_2$, 4-MeC_6H_4;

X = $-(CH_2)_n-$, , where n = 0, 1, 4.

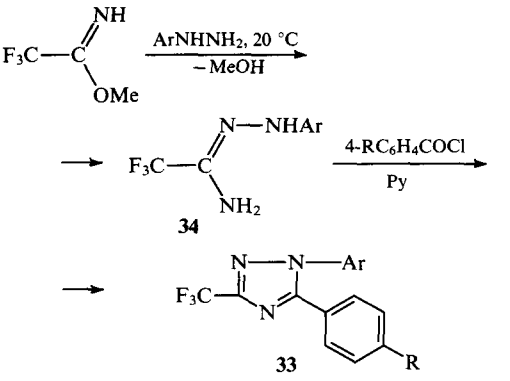
There are literature data concerning the synthesis of 3,5-disubstituted 1*H*-1,2,4-triazoles **29** from acid iminoesters and hydrazides without the isolation of the intermediate *N*-acylamidrazones **28**. For example, when substituted benzoic acid iminoesters were heated with aromatic acid hydrazines (110–125 °C, 10–24 h), 3,5-diaryl-1*H*-1,2,4-triazoles were synthesised in satisfactory yields. They exhibit high sedative and contraceptive activities.[152–155]



R = H, F, Cl, Alk, AlkO, Me_2N, Ph, F_3C;
R^1 = H, F, Cl, Alk; R + R^1 = OCH_2CH_2;
R^2 = Alk; R^3 = H, F, Cl, Alk, AlkO.

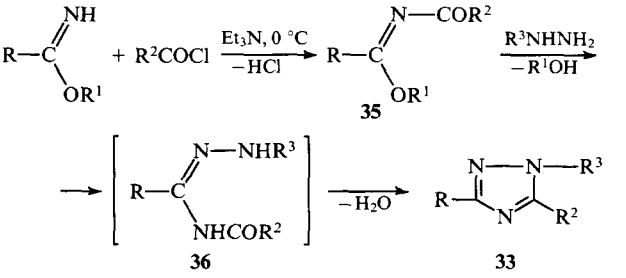
Certain 1*H*-1,2,4-triazoles are also formed in 30%–80% yields when iminoesters are refluxed in ethanol or methanol with reactive hydrazides — *N*-formylhydrazine,[139,156] the hydrazides of carboxylic hydroxyacids,[157,158] and the hydrazides of cyano-,[159,160] methoxy-,[159] and dimethoxy-acetic acids.[159]

As a result of the search for promising substances with anti-inflammatory activity, Hungarian investigators[161,162] proposed a method of synthesis of 1,3,5-trisubstituted 1*H*-1,2,4-triazoles **33** (yield 16%–28%), which involves treatment of the *N*-substituted amidrazones **34** with acid chlorides in dioxane in the presence of pyridine.



R = H, Cl, F.

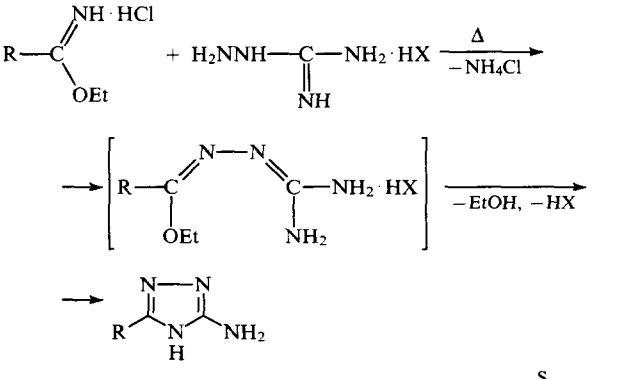
The interaction of the reactive *N*-acyliminoesters **35** with hydrazine or *N*-substituted hydrazines at 20 °C is apparently a more promising method of synthesis of 1,3,5-trisubstituted 1*H*-1,2,4-triazoles **33**.[163,164] The initial *N*-acyliminoesters **35** are formed in satisfactory yields (54%–95%) when iminoesters are acylated by acid chlorides in the presence of triethylamine at 0 °C.[163,165]



R = Me, Ar, Het; R^1 = Me, Et;
R^2 = Me, Ph, 4-ClC_6H_4, 2-$F_3CC_6H_4$;
R^3 = H, Me, Ph, C_nH_{2n-1}.

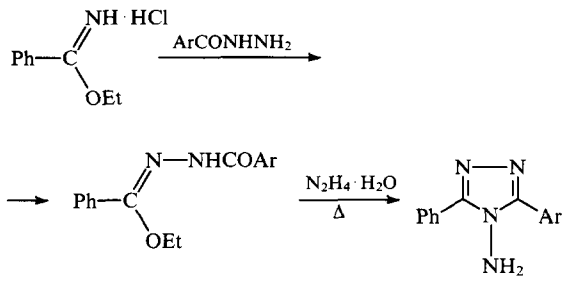
It has been suggested[163] that the intermediate **36** is formed initially as a result of the attack by the NH_2 group of the substituted hydrazine on the carbon atom of the iminoester. The intermediate cyclises at a temperature as low as 20 °C to the 1,2,4-triazole **33** with elimination of a water molecule. When the reaction is carried out under the conditions indicated, the yield of the target 1*H*-1,2,4-triazoles is 55%–87%.

Carboxylic acid iminoesters are also used as the reactants in the synthesis of 1*H*-1,2,4-triazole derivatives with functional group substituents. For example, when the iminoester hydrochlorides were refluxed with aminoguanidine hydrochloride or nitrate in pyridine or tripropylamine, 3-amino-5-substituted 4*H*-1,2,4-triazoles were synthesised in 35%–86% yields.[166,167]



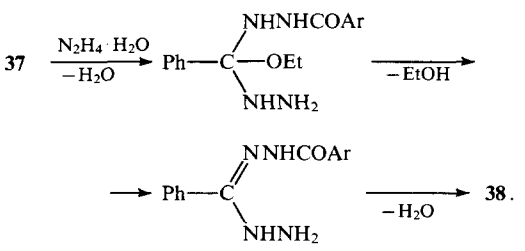
R = Me, Et, Ph, 4-$O_2NC_6H_4$, $Me_3SiCH_2CH_2$, cyclo-C_6H_{11}, .

French investigators isolated the benzoic acid *N*-acylhydrazones **37** in 65%–90% yields after the interaction of the benzoic acid iminoester hydrochloride with aromatic acid hydrazides in ethanol at 0 °C.[168] On refluxing with hydrazine hydrate in 1-propanol, the *N*-acylhydrazones were converted into 4-amino-4*H*-1,2,4-triazoles **38** in 52%–83% yields.



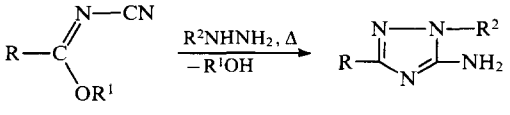
37 **38**

The authors proposed the following mechanism of the formation of 4-amino-1,2,4-triazoles **38** from the *N*-acylhydrazones **37** and hydrazine hydrate:

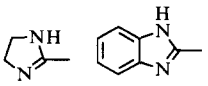


The reactive carboxylic acid *N*-cyanoiminoesters **39** are convenient compounds for the synthesis of amino-1*H*-1,2,4-triazoles. The *N*-cyanoiminoesters are formed when iminoester hydrochlorides react with chlorocyanogen[169] in the presence of triethylamine (yield 70%–80%) or with cyanamide in water in the presence of phosphate buffer (yield 34%–74%).[170]

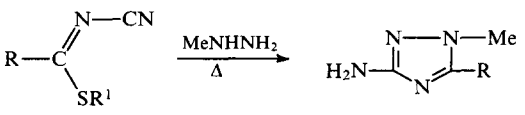
For example, the condensation of the *N*-cyanoiminoester **39** with *N*-substituted hydrazines in ethanol (refluxing for 1–2 h) afforded 73%–82% yields of 1,3-disubstituted 5-amino-1*H*-1,2,4-triazoles.[171–173]



39

R = H, Me, $EtOOCCH_2$; R^2 = Me, .

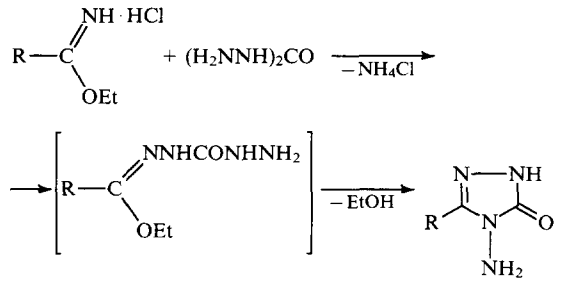
On the other hand, 3-amino-1-methyl-5-substituted 1*H*-1,2,4-triazoles are formed regioselectively in 82%–84% yield on refluxing the *N*-cyanoiminothioesters **40** with methylhydrazine in chloroform.[171]



40

R = Me, Pr^i; R^1 = Me, Et.

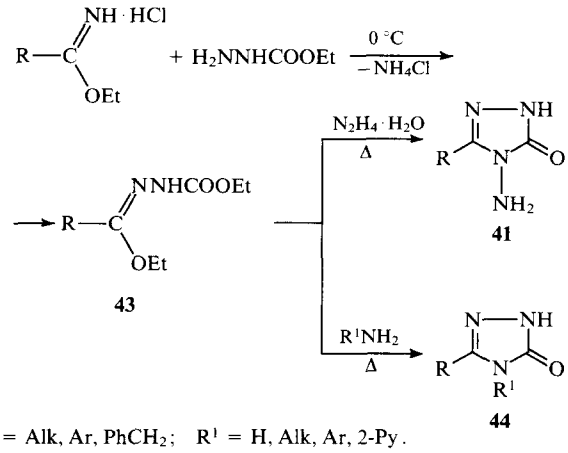
The condensation of equimolecular amounts of iminoester hydrochlorides and carbodihydrazide in ethanol (refluxing for 48 h) leads to 40%–45% yields of 4-amino-3-substituted 1*H*-Δ^2-1,2,4-triazolin-5-ones **41**.[174,175] The intermediate formation of the *N*-substituted hydrazones **42** in this reaction has been postulated.[174]



42 **41**

R = Me, Bu^t.

The interaction of iminoester hydrochlorides with *N*-(ethoxycarbonyl)hydrazine at 0 °C in ethanol affords 60%–85% yields of carboxylic acid ester N^2-(ethoxy-carbonyl)hydrazones **43**, which are convenient intermediates for the synthesis of Δ^2-1*H*-1,2,4-triazolin-5-ones.[174,176,177]

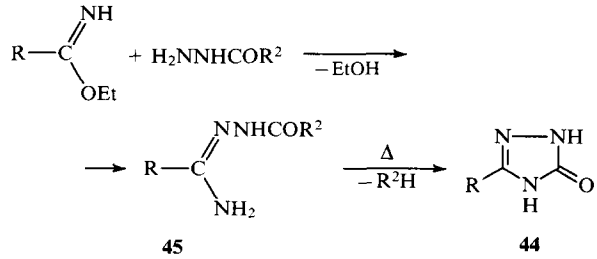


43 **41** **44**

R = Alk, Ar, $PhCH_2$; R^1 = H, Alk, Ar, 2-Py.

On heating with ammonia or primary amines, the hydrazones **43** are converted into 3,4-disubstituted Δ^2-1*H*-1,2,4-triazolin-5-ones **44**,[176,177] while on prolonged refluxing (30 h) with hydrazine hydrate in 1-butanol they cyclise to 4-amino-Δ^2-1,2,4-triazolin-5-ones **41** (yield 62%–95%).[174]

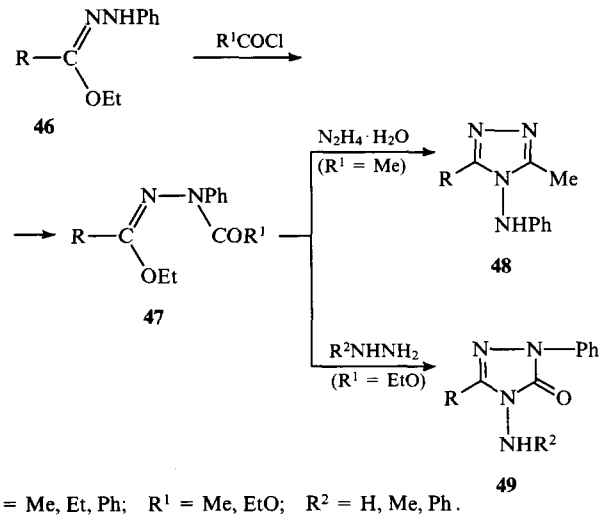
It is noteworthy that reactions of iminoester bases with *N*-(ethoxycarbonyl)hydrazines and semicarbazides give *N*-(R-carbonyl)amidrazones **45**, which cyclise on heating to 3-substituted Δ^2-1*H*-1,2,4-triazolin-5-ones **44** (R^2 = H).[22,176,178,179]



45 **44**

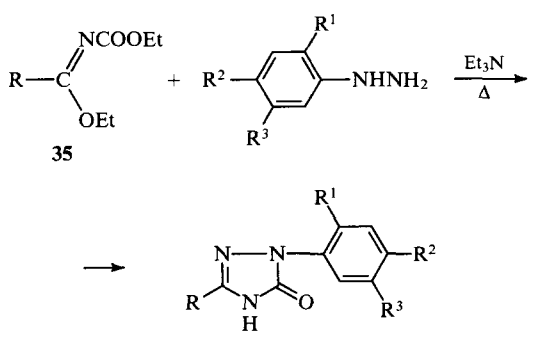
R = Alk, Ar, EtOOC; R^2 = EtO, NH_2, PhNH

The interaction of carboxylic acid *N*-phenylhydrazones **46** with ethyl chloroformate or acetyl chloride in the presence of pyridine or triethylamine gives rise to the formation of the *N*-disubstituted hydrazones **47**, the reactions of which with hydrazine hydrate and monosubstituted hydrazines in methanol lead to 4-phenylamino-4*H*-1,2,4-triazoles **48** or to 1,3-disubstituted 4-amino-Δ^2-1,2,4-triazolin-5-ones **49**.[180,181]



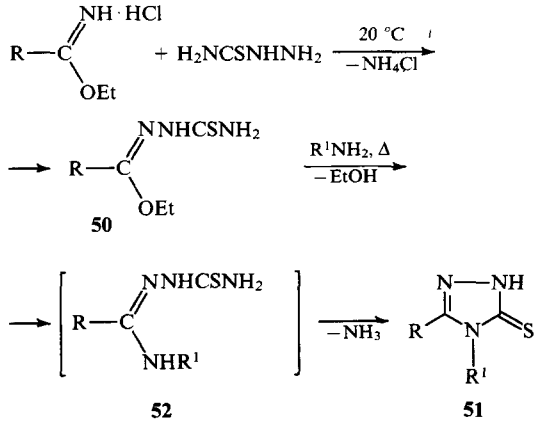
R = Me, Et, Ph; R^1 = Me, EtO; R^2 = H, Me, Ph.

According to patent data,[182-187] 1,3-disubstituted Δ^2-1*H*-1,2,4-triazolin-5-ones, used as intermediates in the synthesis of herbicides, are formed in 50%–95% yields on heating equimolecular amounts of the *N*-(ethoxycarbonyl)iminoesters **35**, *N*-arylhydrazines, and triethylamine (40–90 °C, 3–12 h).



R = H, Alk; R^1 = H, Cl, F, NO_2; R^2 = H, Cl, F, HO, AlkO; R^3 = H, NO_2, COOH, $NCCH_2O$.

The interaction of iminoester hydrochlorides and thiosemicarbazide in DMF at 20 °C affords carboxylic acid ester thiosemicarbazones **50** in 53%–74% yields.[188,189] On heating with primary amines or arylhydrazines in DMF for 2–3 h, the latter are converted into 4,5-disubstituted Δ^2-1*H*-1,2,4-triazoline-5-thiones **51** (yield 20%–95%). The authors suggest that this involves the intermediate formation of the *N*-(thiocarbamoyl)-amidrazones **52**.[188]



R = Alk, Ar, $PhCH_2$;
R^1 = $PhCH_2$, $HOCH_2CH_2$, Ar, 2-Py, cyclo-C_6H_{11}, ArNH.

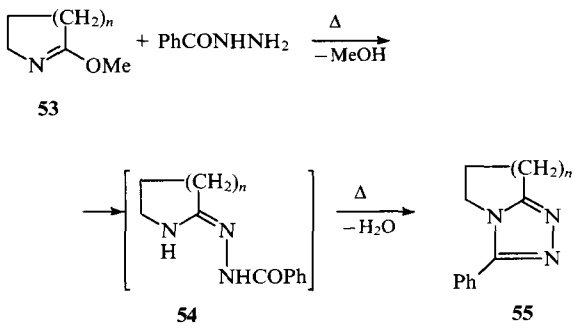
3-Substituted 4-phenyl-Δ^2-1,2,4-triazoline-5-thiones have been obtained in 42%–65% yields by condensing iminoester hydrochlorides with 4-phenylthiosemicarbazide in the presence of bases (pyridine, tripropylamine).[89,167,190,191]

Iminoester hydrochlorides are also convenient key compounds in the synthesis of condensed heterocyclic systems incorporating 1,2,4-triazole fragments.

Refluxing of the 5-chlorovaleric iminoester hydrochloride with aromatic acid hydrazides and triethylamine (molar ratios 1:1:2) in ethanol leads to 2-aryl-5,6,7,8-tetrahydro-1,2,4-triazolo[5,1-*a*]pyridines (yield 26%–35%).[8]

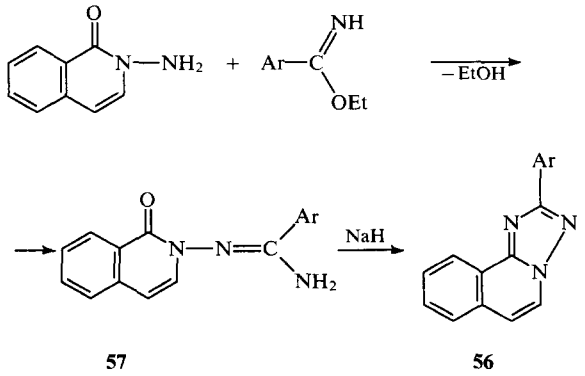


The condensation of the cyclic iminoesters **53** with benzoic acid hydrazide results in the formation of the *N*-acylamidrazones **54**, which, on refluxing in acetic acid (n = 1) or in xylene (n = 2), undergo intramolecular cyclisation to 3-phenyl-6,7-dihydro-5*H*-pyrrolo[2,1-*c*]-1,2,4-triazole **55** (n = 1) or 3-phenyl-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyridine **55** (n = 2).[8]

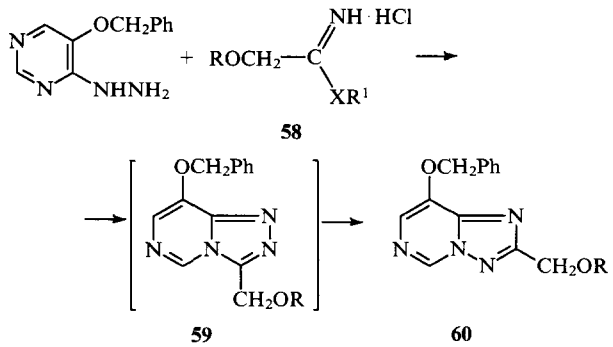


n = 1, 2.

The synthesis of 2-aryl-1,2,4-triazolo[5,1-*a*]isoquinolines **56** by the reaction of 2-amino-2*H*-isoquinolin-1-one with aromatic acid iminoesters and subsequent cyclisation of the intermediate amidrazones **57** on treatment with sodium hydride has been described in patents.[192,193]

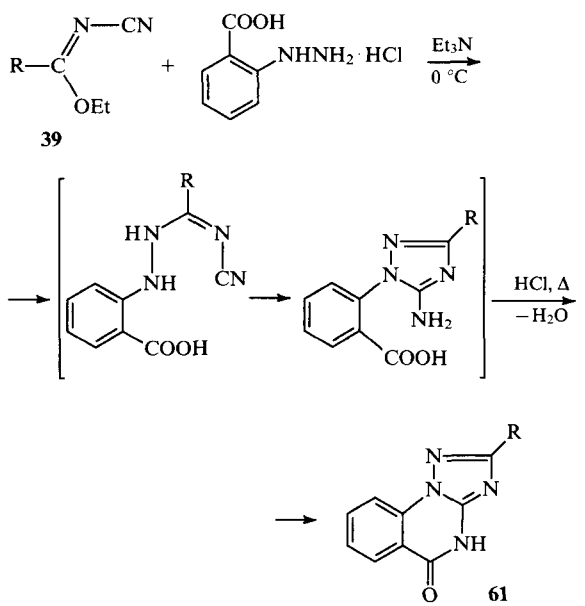


The interaction of 5-benzyloxy-4-hydrazinopyrimidine with the iminoester or iminothioester hydrochlorides **58** in pyridine (80 °C, 3 h) leads initially to 1,2,4-triazolo[4,3-*c*]pyrimidine **59**, which is converted into 2-substituted 8-benzyloxy-1,2,4-triazolo[5,1-*c*]pyrimidine **60** (yield 32%–53%) as a result of the Dimroth rearrangement.[194]



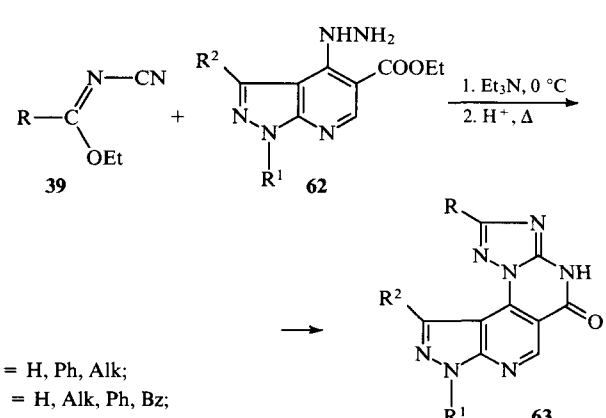
R = $PhCOOCH_2CH_2$; R^1 = Me, Et; X = O, S

2-R-1,2,4-triazolo[5,1-*a*]quinazolin-5(4*H*)-ones **61** have been synthesised in 70%–94% yields by condensing the hydrochloride of 2-hydrazinobenzoic acid with the *N*-cyanoiminoesters **39** and triethylamine (molar ratios 1:1.2:3) in ethanol at 0 °C and subsequent treatment with aqueous HCl (80 °C).[195]



R = H, Me, $NCCH_2$.

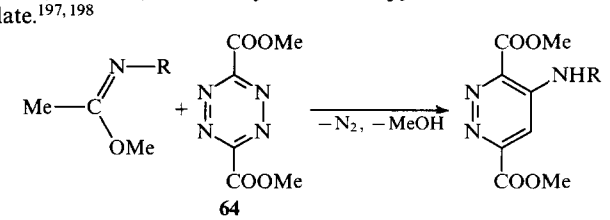
Derivatives of pyrazolo[4',3':5,6]pyrido[3,4-e]-1,2,4-triazolo-[1,5-*a*]pyrimidine **63**, which exhibit an anti-inflammatory activity and a depressant activity on the central nervous system, have been obtained under similar conditions from the *N*-cyano-iminoesters **39** and the 4-hydrazino-derivatives of pyrazolo-[3,4-*e*]pyridine-3-carboxylic acid esters **62**.[196]



R = H, Ph, Alk;
R^1 = H, Alk, Ph, Bz;
R^2 = H, Ph, Alk.

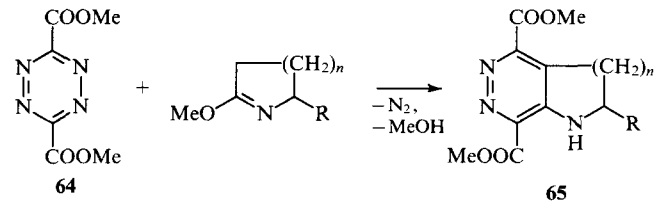
4. Synthesis of pyridazine, pyrazine, and quinoxaline derivatives

Only isolated data on the syntheses of pyridazine, pyrazine, and quinoxaline from iminoesters are so far available in the literature. Thus the interaction of *N*-substituted acetic acid iminoesters with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate **64** leads to a low yield (9%–12%) of dimethyl 4-R-aminopyridazine-3,6-dicarboxylate.[197,198]



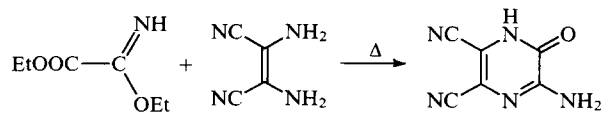
R = Me, Ph

The condensed pyridazines **65** have been synthesised similarly from the *sym*-tetrazine **64** and cyclic iminoesters (yield 8%–47%).[197]

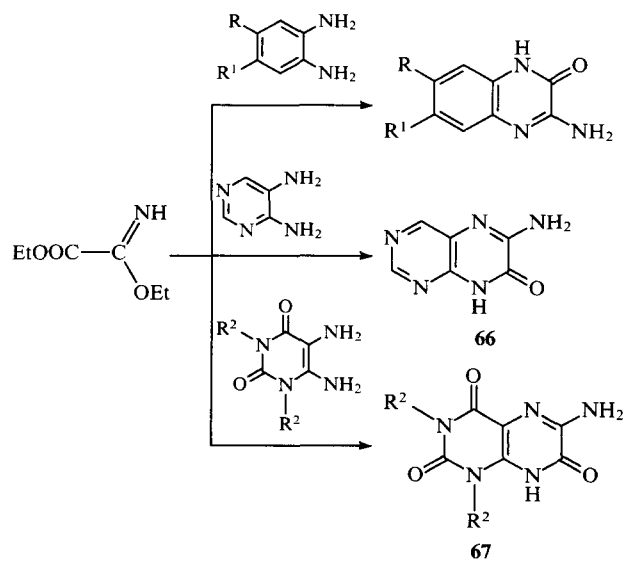


R = H, Me; n = 1–3.

When the ethoxycarbonylformic acid iminoester was refluxed with 1,2-diamino-1,2-dicyanoethene in ethanol, 3-amino-5,6-dicyano-1*H*-pyrazine-2-one was isolated in 72% yield.[21,22]



The interaction of this iminoester with aromatic and heterocyclic 1,2-diamines afforded derivatives of quinoxaline and pteridine.[21,22] For example, on refluxing with substituted *o*-phenylenediamines in ethanol, 6,7-disubstituted 3-amino-1*H*-quinoxalin-2-ones are formed in 58%–99% yield.

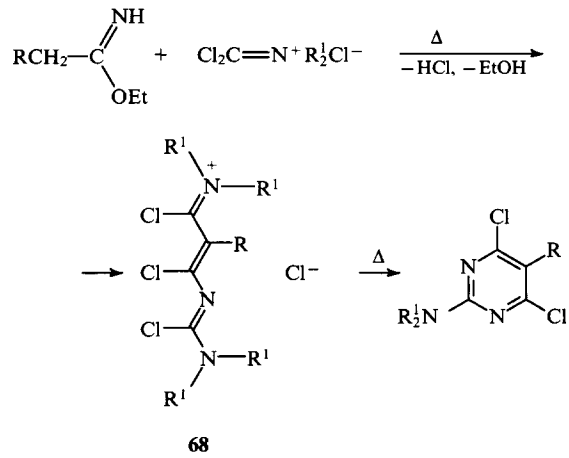


R = H, Me, Cl; R^1 = H, Me, Cl, NO_2; R^2 = H, Me.

6-Amino-8*H*-pteridin-7-one **66** was obtained in 80% yield under similar conditions from 4,5-diaminopyrimidine and trioxopteridines **67** have been synthesised from 5,6-diaminouracils (yield 60%–94%).

5. Synthesis of pyrimidine and quinazoline derivatives

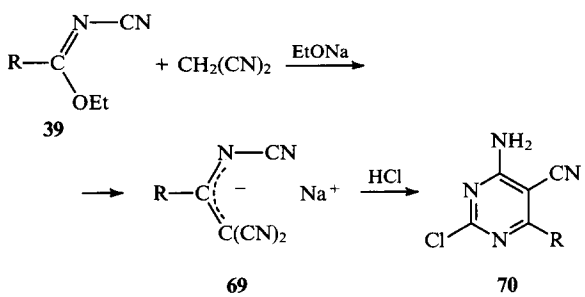
When aliphatic acid iminoesters interact with phosgene iminium salts (molar ratio 1:3) in chloroform (refluxing for 3–4 h), 2,4,6-trichloro-1,3,7-triazaheptatrienium chlorides **68** are formed in 85%–87% yield. On heating in vacuo, these products cyclise to 2-dialkylamino-4,6-dichloro-5-R-pyrimidines (yield 33%–90%).[199]



68

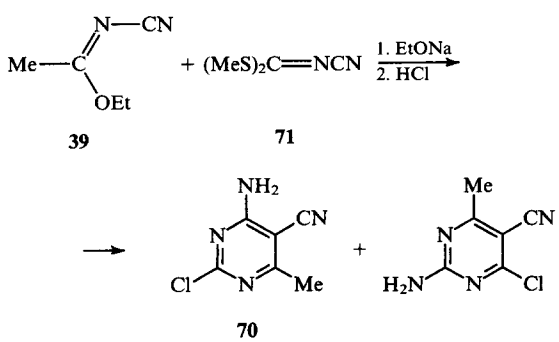
R = H, Me; R^1 = Me, Et.

By treating malonodinitrile with the *N*-cyanoiminoesters **39** in the presence of sodium ethoxide at 20 °C, Kristiansson obtained the reactive sodium salts **69**, which, on treatment with an ethereal solution of HCl, were converted into 4-amino-5-cyano-2-chloro-6-R-pyrimidines **70** in 83%–87% yield.[200]



39 **69** **70**

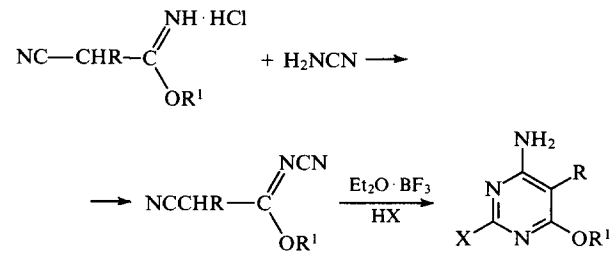
A 2:3 mixture of the 2-chloropyrimidine **70** (R = Me) and 2-amino-6-chloro-5-cyano-4-methylpyrimidine is formed in 88% yield under similar conditions from the acetic acid *N*-cyanoiminoester **39** (R = Me) and the *N*-substituted cyanamide **71**.



39 **71** **70**

On the other hand, it has been reported[201] that, when the *N*-cyanoiminoesters **39** were refluxed with malonodinitrile in methanol in the presence of sodium methoxide (molar ratios 1:1:2), 2-amino-5-cyano-4-methoxy-6-R-pyrimidines (R = H, Me, Ph) were synthesised in 17%–40% yield.

Japanese investigators established[202–205] that the interaction of the hydrochlorides of the iminoesters of carboxylic α-cyanoacids with cyanamide in benzene in the presence of 4 Å molecular sieves (25 °C, 4 h) leads to the formation of the *N*-cyanoiminoesters **72**. On treatment with boron trifluoride etherate and a hydrogen halide in nonpolar solvents (ether, benzene), the latter cyclise to 6-alkoxy-4-amino-2-halo-5-R-pyrimidines in 70%–92% yield.

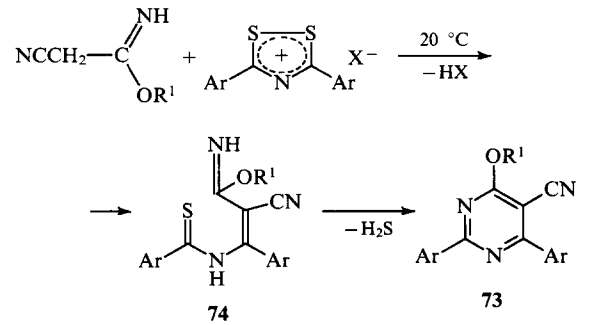


72

R = H, Me, Ph; R^1 = Alk; X = Cl, Br.

It is worth noting that, when the *N*-cyanoiminoester **72** (R = H, R^1 = Me) is treated with gaseous HCl at −15 °C, 2-amino-6-chloro-4-methoxypyrimidine is formed in 70% yield.[206]

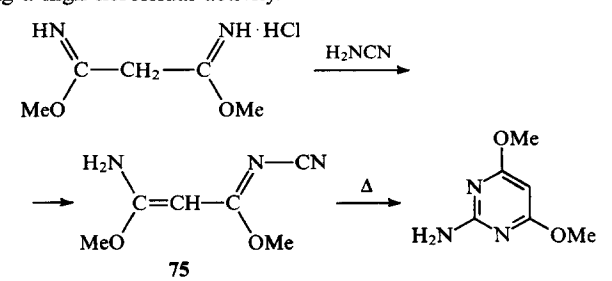
4-Alkoxy-5-cyanopyrimidines **73**, which are intermediates for the synthesis of biologically active compounds, have been obtained in 36%–71% yields by the reaction of cyanoacetic acid iminoesters with 3,5-diaryl-1,2,4-dithiazolium salts in aqueous acetonitrile in the presence of alkali (20 °C, 10 min).[207,208] The authors suggest that the ring in the dithiazolium salt is initially opened with formation of the intermediate **74**, which subsequently cyclises to the pyrimidine **73**.



74 **73**

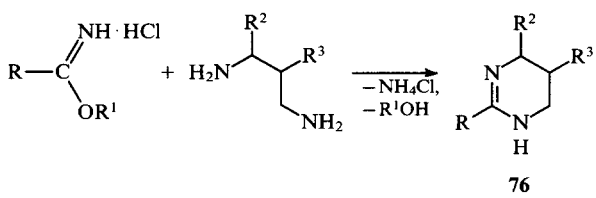
R^1 = Alk; X = ClO_4, I_3, Cl, Br, $FeCl_4$.

The interaction of the monohydrochloride of malonic acid bisiminoester with cyanamide leads to the *N*-cyanoiminoester of 3-amino-3-methoxyprop-2-enoic acid **75**, which, on refluxing in toluene or on heating to the melting point, is converted quantitatively into 2-amino-4,6-dimethoxypyrimidine, exhibiting a high herbicidal activity.[209–211]



75

The cyclocondensation of the hydrochlorides of various carboxylic acid iminoesters with aliphatic 1,3-diamines is a convenient method of synthesis of 2-substituted 1,4,5,6-tetrahydropyrimidines **76**.[47,212,213] These reactions are analogous to the synthesis of 2-substituted Δ^2-imidazolines from 1,2-diamines (see above) and are carried out by refluxing the reactants in ethanol (4–12 h); the yield of the tetrahydropyrimidines **76** is then 50%–86%.

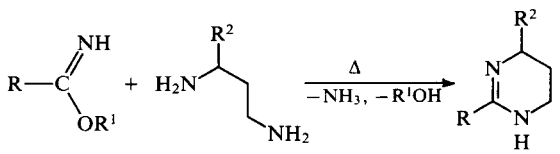


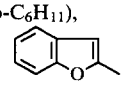
76

R = PhC(OH)Me, ArCH(OH), 2,4,5,6-$Me_4C_6HCH_2$, 2,4,5,6-$Me_4C_6HSCH_2$, , Ar—CH=CH—;

R^1 = Me, Et; R^2 = H, Me; R^3 = H, OH.

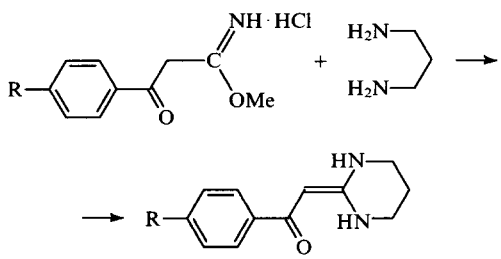
2-Substituted tetrahydropyrimidines have also been obtained in 50%–80% yield by heating iminoesters with 1,3-diamines (80–150 °C, 2–10 h).[58,88,214]



R = $PhCHR^3CH_2$ (R^3 = Ph, 2-Py, cyclo-C_6H_{11}), 4-$R^4C_6H_4CH_2$ (R^4 = Cl, Br, NO_2), 

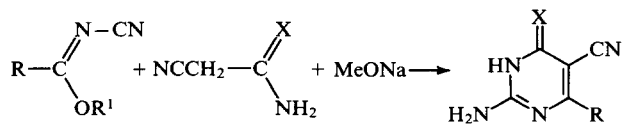
R^1 = Me, Et; R^2 = H, Me.

It has been reported[214] that the condensation of the hydrochlorides of benzoylacetic acid esters with 1,3-diaminopropane in ethanol (refluxing for 10 h) leads to the formation of 2-(benzoylmethylene)perhydropyrimidines in 35%–56% yield.



R = H, Cl, Br, MeO.

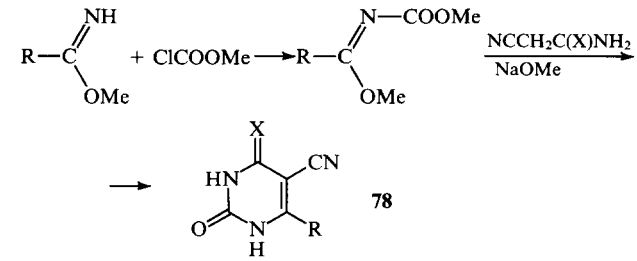
Cyclocondensation of the *N*-cyanoiminoesters **39** with the amide or thioamide of cyanoacetic acid and sodium methoxide [molar ratios 1 : 1 (1.1–2)] in methanol (refluxing for 2–3 h) gives 41%–77% yields of 2-amino-5-cyano-3,4-dihydropyrimidin-4-ones and the corresponding 4-thiones **77**.[176]



39 **77**

R = H, Me, Et, $PhCH_2$, Ar; R^1 = Me, Et; X = O, S.

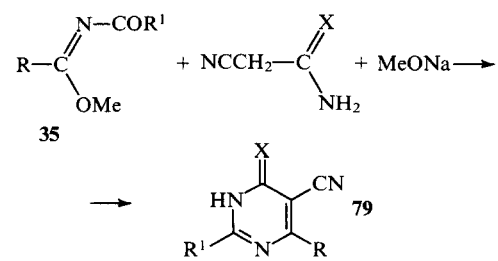
The reaction of iminoesters with methyl chloroformate in hexane in the presence of 2,4,6-trimethylpyrimidine leads to the reactive *N*-(methoxycarbonyl)iminoesters. On heating with equimolecular amounts of cyanoacetic acid derivatives and sodium methoxide in methanol, the latter cyclise to 2,4-dioxo- or 2-oxo-4-thioxo-derivatives of 5-cyano-1,2,3,4-tetrahydropyrimidines **78** (X = O, S) in 38%–98% yield.[215]



78

R = Et, Ph, $PhCH_2$, 4-$MeOC_6H_4$; X = O;
R = Ph, $PhCH_2$; X = S.

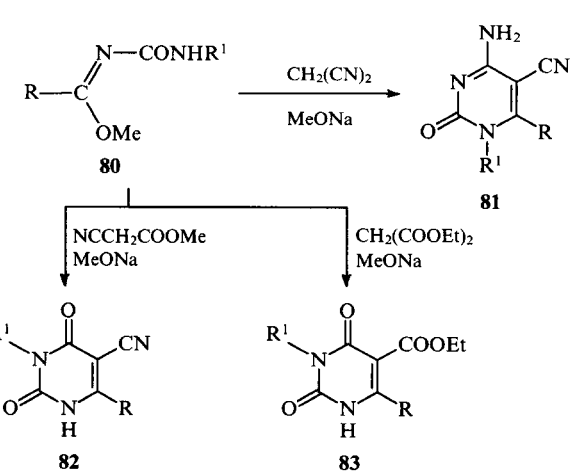
2,6-Disubstituted 5-cyano-4-oxo(or 4-thioxo)-3,4-dihydropyrimidines **79** (X = O, S) have been synthesised in 45%–77% yields under similar conditions from the *N*-acyliminoesters **35**.[215]



35 **79**

R = Me, Et, Ph; R^1 = Me, Bu^t, Ph, 4-ClC_6H_4; X = O, S.

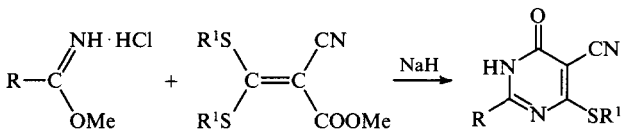
The interaction of iminoesters with isocyanates leads to *N*-substituted aminocarbonyliminoesters **80**, which in the presence of equimolecular amounts of sodium methoxide in methanol condense with malonodinitrile (20 °C, 14 h), cyanoacetic acid ester (refluxing for 15 h), and malonic ester (refluxing for 7 days) to form the corresponding 6-substituted 4-amino-5-cyano-2,3-dihydropyrimidin-2-ones **81** (yield 20%–89%), 3,6-disubstituted 5-cyano-2,4-dioxo-1,2,3,4-tetrahydropyrimidines **82** (yield 56%–70%), and 5-ethoxycarbonyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidines **83** (yield 35%–60%).[216]



80 **81** **82** **83**

R = Et, Ph, 4-MeC_6H_4, 4-ClC_6H_4; R^1 = Et, Ph.

The synthesis of 2-substituted 6-alkylthio-5-cyano-3,4-dihydropyrimidin-4-ones by the reaction of iminoester hydrochlorides with sodium hydride and cyanoacetic acid ester derivatives **84** in DMF (0 °C; 20 °C, 1 h) has been described in a patent.[217]

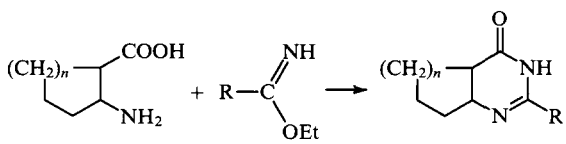


84

R = Alk, cyclo-(C_3-C_6), $PhCH_2$, Ar,  ;

R^1 = Alk, cyclo-(C_4-C_7), Ph, $PhCH_2$.

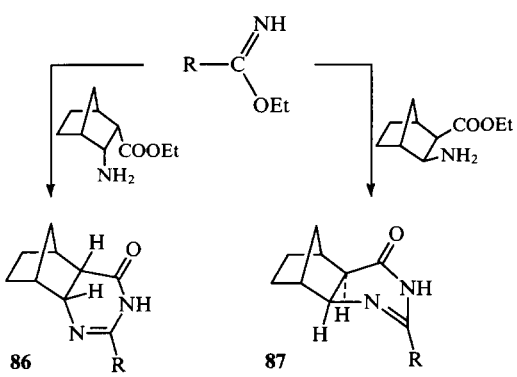
5,6-Dihydro-3*H*-pyrimidin-4-one derivatives **85**, exhibiting anti-inflammatory, antipyretic, and analgesic activities, have been synthesised by condensing *cis*-2-aminocycloalkanecarboxylic acids with iminoesters.[218,219]



85

R = H, Alk, cyclo-C_nH_{2n-1}, Ar, $PhCH_2$, 4-Py.

Hungarian investigators[220,221] studied in detail the condensation of the esters of the stereoisomeric aminonorbornanecarboxylic and aminonorbornenecarboxylic acids with the iminoesters of aromatic and cycloalkanecarboxylic acids. It was established that the interaction of the ester of *endo*-3-aminobicyclo[2.2.1]heptane-2-carboxylic acid with the iminoesters in ethanol (refluxing for 10 h) results in the formation of 2-substituted 4*ar*,5*t*,6,7,8*t*,8*ac*-hexahydro-3*H*-5,8-methano-3-*H*-quinazolin-4-ones **86** in 53%–81% yield.

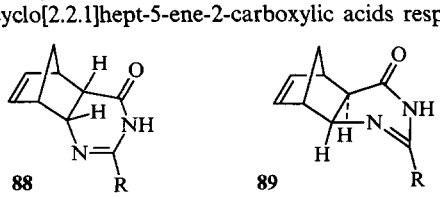


86 **87**

R = Ar, cyclo-C_6H_{11}.

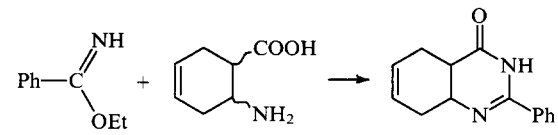
The ester of *exo*-3-aminobicyclo[2.2.1]heptane-2-carboxylic acid reacts with the iminoesters, affording 58%–69% yields of 2-substituted 4*ar*,5*c*,6,7,8*c*,8*ac*-hexahydro-3*H*-5,8-methanquinazolin-4-ones **87**.[220,221]

2-Substituted 4*ar*,5*t*,8*t*,8*ac*-tetrahydro-3*H*-5,8-methanoquinazolin-4-ones **88** (yield 54%–68%) and 4*ar*,5*c*,8*c*,8*ac*-tetrahydro-3*H*-5,8-methanoquinazolin-4-ones **89** (yield 56% to 74%) have been synthesised from the esters of *endo*- and *exo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acids respectively.[220,221]

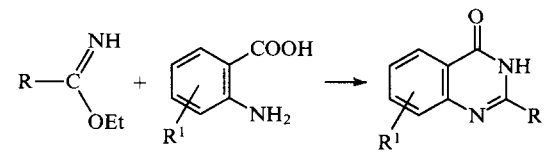


88 **89**

By refluxing equimolecular amounts of the benzoic acid iminoester with *cis*- or *trans*-2-aminocyclohex-4-enecarboxylic acid in chlorobenzene, the same workers obtained 2-phenyl-4*a*,5,8,8*a*, tetrahydro-3*H*-quinazolin-4-one in 62%–65% yield.[222]



The condensation of iminoesters with substituted anthranilic acids in methanol (20 °C, 2 h) resulted in the formation of 6- and 7-substituted 2R-3*H*-quinazolin-4-ones **90** in 21%–51% yields.[223]

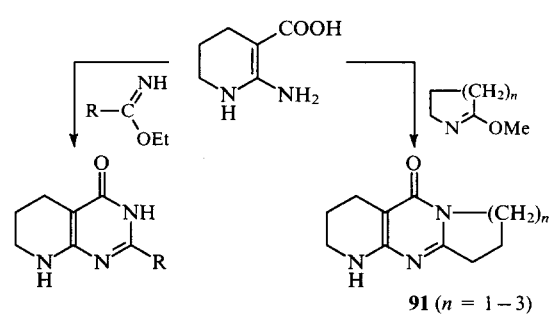


90

R = $PhCH_2$, 4-MeC_6H_4;
R^1 = H, 6-Me, 7-Cl.

The authors note that this reaction is a convenient method of synthesis of the quinazoline alkaloid glucozymine **90** (R = $PhCH_2$, R^1 = H) and related compounds with a high biological activity.

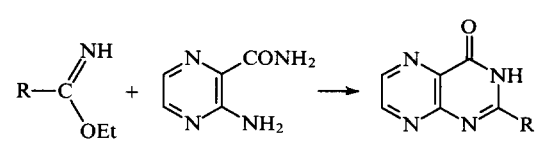
The interaction of iminoesters with heterocyclic *o*-aminoacids or their derivatives leads to the formation of condensed systems incorporating pyrimidine fragments. For example, when the ester of 2-amino-1,4,5,6-tetrahydropyrimidine-3-carboxylic acid was heated with iminoesters in polyphosphoric acid, 2-R-5,6,7,8-tetrahydro-3*H*-pyrido[2,3-*d*]pyrimidin-4-ones were obtained in 47%–48% yields.[224] Under similar conditions, cyclic iminoesters afford the tricyclic systems **91** (yield 58%–68%).



91 (*n* = 1–3)

R = Ph, $PhCH_2$.

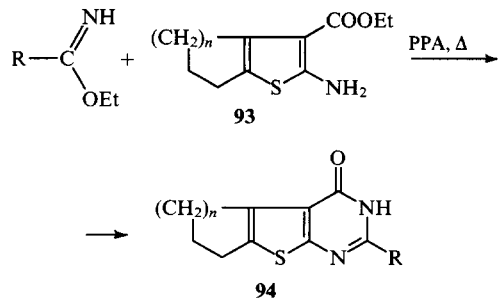
The preparation of 2-substituted 3*H*-pteridin-4-ones **92** by the reaction of iminoesters with the amide of 2-aminopyrazine-3-carboxylic acid has been described in a patent.[225]



92

R = Alk, CHEtCH = CH_2, cyclo-C_3H_5.

Refluxing of iminoesters with the esters of heterocyclic *o*-aminoacids **93** (molar ratio 3:1) in chlorobenzene in the presence of polyphosphoric acid (PPA) leads to derivatives of thieno[2,3-*d*]pyrimidin-4-one **94**.[226]



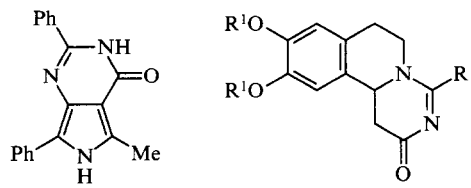
93

94

R = Ph, 3-ClC_6H_4; n = 1, 3.

Italian investigators synthesised derivatives of pyrrolo-[3,4-*d*]pyrimidin-4-one **95** (yield 15%), exhibiting an appreciable anti-inflammatory activity, by heating the benzoic acid iminoester with the ester of 3-amino-5-methyl-2-phenylpyrrole-4-carboxylic acid (140 °C, 18 h).[227]

In the search for new effective substances with analgesic activity, 4-substituted 9,10-dialkoxy-1,6,7,11-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-2-ones **96** have been obtained by condensing iminoesters with the esters of 6,7-dialkoxy-1,2,3,4-tetrahydro-1-isoquinolinylacetic acids.[228]

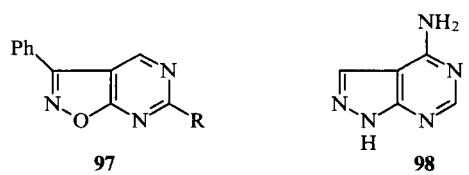


95 **96**

R = Alk, Ar, 4-$ClC_6H_4CH_2$;
R^1 = Me, Et.

The authors note that the pyrimidoisoquinolin-2-ones **96** are formed in 28%–58% yields on refluxing (for 24 h) equimolecular amounts of the reactants in chlorobenzene or are obtained in 40%–70% yields on refluxing (for 16 h) the reactants (molar ratio 10:1) in benzene in the presence of acetic acid.

Japanese investigators synthesised 6-substituted 3-phenylisoxazolo[5,4-*d*]pyrimidines **97** by the reaction of 5-amino-3-phenylisoxazole-4-carbaldehyde with the iminoesters of various acids.[229,230] It is best to carry out the condensation without a solvent at 40–50 °C; under these conditions, the yield of the target isoxazolopyrimidines **97** was 46%–75%.

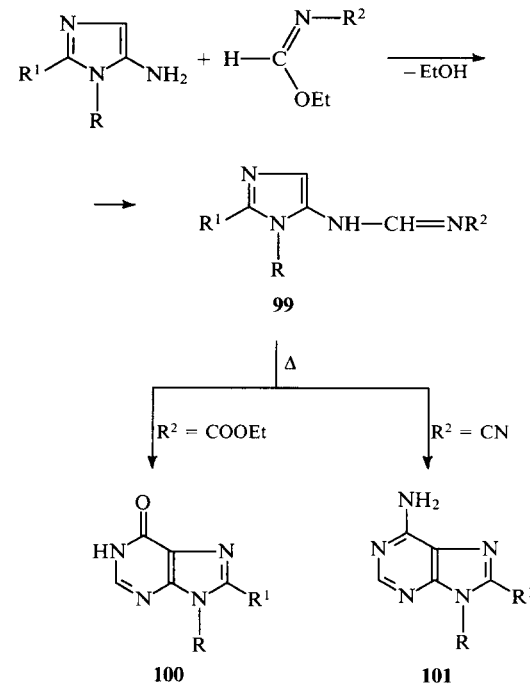


97 **98**

R = Alk, Ph, $PhCH_2$.

Iminoesters are convenient starting materials for the synthesis of purines {imidazo[4,5-*d*]pyrimidines} and their analogues. For example, the synthesis of adenine **98** in 42% yield by the condensation of the formic acid iminoester with 5-(alkoxycarbonylamino)-4-cyanoimidazole in DMF has been described in a patent.[231]

The interaction of 1,2-disubstituted 5-aminoimidazoles with the formic acid *N*-(ethoxycarbonyl)iminoester or *N*-cyanoiminoester leads to the *N,N*-disubstituted amidines **99** (yield 33%–52%), which cyclise to the 8,9-disubstituted hypoxanthines **100** (R^2 = EtOOC) (yield 65%–91%) or to the 9-R-adenines **101** (R^2 = CN) (yield 10%–20%) on heating to 190–260 °C.[232]

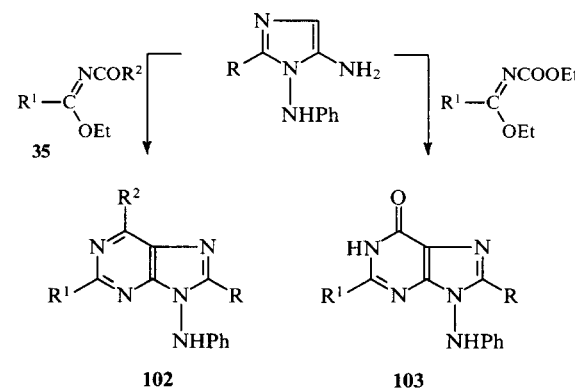


99

100 **101**

R = Me, $HOCH_2CH_2$; R^1 = H, Me; R^2 = EtOOC, NC.

The synthesis of the purine derivatives **102** and the hypoxanthine derivatives **103** by the reaction of 2-substituted 5-amino-1-phenylaminoimidazoles respectively with the *N*-acyliminoesters **35** or with *N*-(ethoxycarbonyl)iminoesters in xylene (refluxing for 1–3 h) has been reported.[233]



35

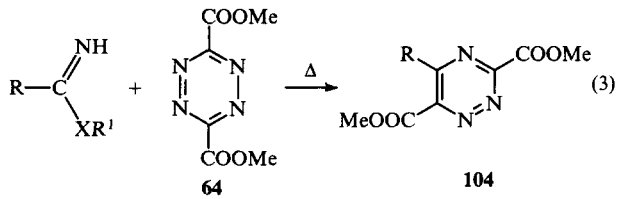
102 **103**

R = Pr^i, Ar, $PhCH_2$, 4-$ClC_6H_4CH_2$;
R^1 = Ph, $PhCH_2$; R^2 = Me, Et.

6. Synthesis of 1,2,4-triazine derivatives

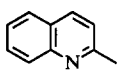
There are hitherto only limited literature data on the synthesis of compounds of the 1,2,4-triazine series using carboxylic acid iminoesters as starting materials.[234]

Boger and Panek obtained the dimethyl esters of 5-aryl-(heteroaryl)-1,2,4-triazine-3,6-dicarboxylic acids **104** (Table 3) as a result of the interaction of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate **64** with the iminoesters or iminothioesters of aromatic and heterocyclic acids (molar ratio 2:1) in dioxane at 60–80 °C.[235,236]



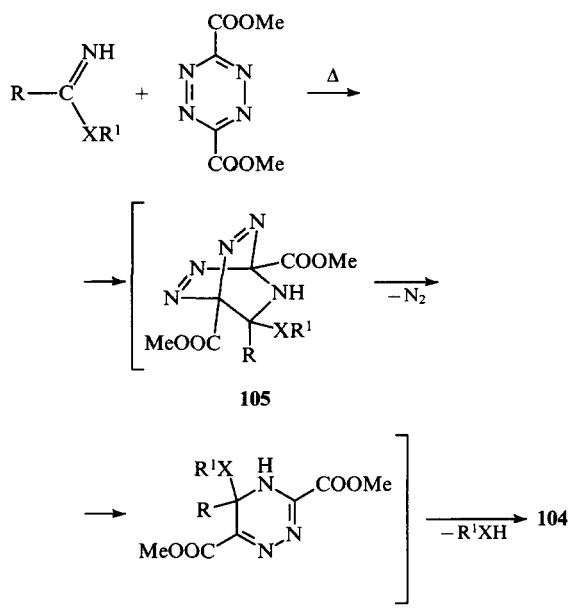
(3)

64 104

R = Ph, 2-Py,  ;

R^1 = Me, Et; X = O, S.

The authors assumed that the initial stage of the reaction is the thermal cycloaddition of the diester **64** to the C=N bond of the iminoester or iminothioester, which in this case are regarded as heterodienophiles. The cyclic adducts **105** formed in this reaction eliminate in succession a nitrogen molecule and an alcohol or mercaptan molecule, being converted into the 1,2,4-triazine derivatives **104.**

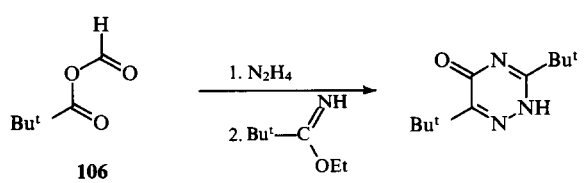


105

The authors note that carboxylic acid amidines and nitriles do not react with the diester **64** under the conditions indicated. Table 3 presents data concerning the influence of the structures of the initial iminoesters and of the reaction time on the yields of the 1,2,4-triazines **104.**

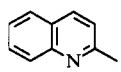
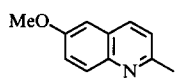
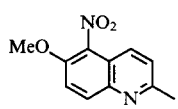
It is noteworthy that the 1,2,4-triazine **104** (R = 6-methoxy-5-nitro-2-quinolinyl) formed in the reaction of the diester **64** with the iminothioester of 6-methoxy-5-nitroquinoline-2-carboxylic acid is a key compound in the total synthesis of the antibiotic streptonigrin.[237]

The successive interaction of equimolecular amounts of the mixed anhydride **106** with anhydrous hydrazine in ethanol (20 °C, 2 h) and then with pivalic acid iminoester (refluxing for 12 h) leads to 3,6-di-*tert*-butyl-1,2,4-triazin-5(2*H*)-one in 40% yield.[238]



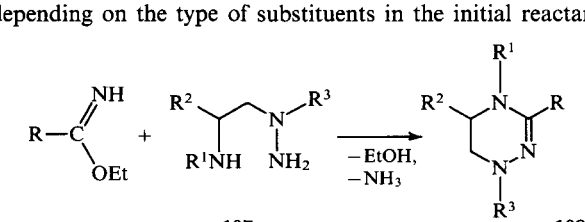
106

Table 3. Synthesis of the dimethyl esters of 5-substituted 1,2,4-triazine-3,6-dicarboxylic acids **104** by the reaction of the dimethyl ester of 1,2,4,5-tetrazine-3,6-dicarboxylic acid **64** with iminoesters or iminothioesters (under a N_2 atmosphere) [reaction (3)].[235,236]

R	R^1X	Reaction conditions		Yield
		T/°C	t/h	(%)
Ph	EtO	60	10	27
	MeS	80	24	64
2-Py	EtO	80	8–12	37
	MeS	80	20	68
	EtO	80	20	33
	MeS	80	4	70
	MeS	80	4	78
	MeS	80	20–24	72–82

The ethyl ester of 3-methyl-5-oxo-2*H*-1,2,4-triazine-6-carboxylic acid has been synthesised in 70% yield by condensing the acetic acid iminoester with the oxomalonic ester hydrazone.[239]

The reactions of *N*-(β-aminoalkyl)hydrazines **107** with iminoester hydrochlorides[240] or iminoesters[241] in ethanol (refluxing for 3–20 h) lead to substituted 1,4,5,6-tetrahydro-1,2,4-triazines **108**, the yield of which varies from 13% to 68% depending on the type of substituents in the initial reactants.

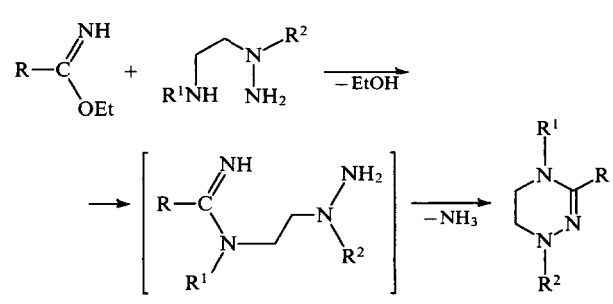


107 108

R = Alk, $Me_3Si(CH_2)_n$ (n = 2, 3), Ph_2CH, Ph_2CHCH_2, $PhCH_2CHPh$, $PhCH_2CH_2$;

R^1 = H, Me; R^2 = H, $HO(CH_2)_2$; R^3 = H, Me.

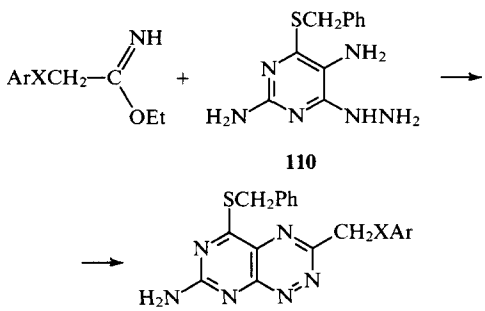
It has been suggested[241] that the electrophilic carbon atom of the iminoester group is attacked by the amine nitrogen atom with formation of the amidine **109**, which cyclises to 1,2,4-triazine with elimination of an ammonia molecule.



109 108

The interaction of equimolecular amounts of aliphatic acid iminoesters and ethylenedihydrazine in ethanol (refluxing for 10 h) led to the synthesis of 3-alkyl-4-amino-1,4,5,6-tetrahydro-1,2,4-triazines in 79%–83% yields.[241]

The condensation of substituted acetic acid iminoesters with 2,5-diamino-6-hydrazinopyrimidine **110** in dioxane at 20 °C results in the formation of derivatives of pyrimido[5,4-*e*]1,2,4-triazine **111** in 37%–64% yields.[242]



110

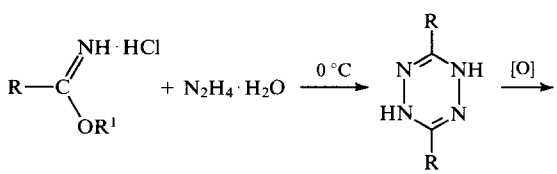
111

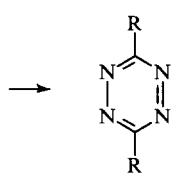
Ar = 4-ClC_6H_4, 3,4-$Cl_2C_6H_3$; X = S, NH.

The authors note that the pyrimidotriazines **111** are selective antagonists of folic acid and its analogues.

7. Synthesis of 1,2,4,5-tetrazine derivatives

The interaction of iminoester hydrochlorides with hydrazine hydrate at 0 °C is known[4,5,243–245] to afford 3,6-disubstituted 1,4-dihydro-1,2,4,5-tetrazines, the oxidation of which by atmospheric oxygen, nitrous acid, pentyl nitrite, iron(III) chloride, or hydrogen peroxide leads to symmetrical 3,6-disubstituted 1,2,4,5-tetrazines **112**, the yield of which does not, however, exceed 25%–35%.



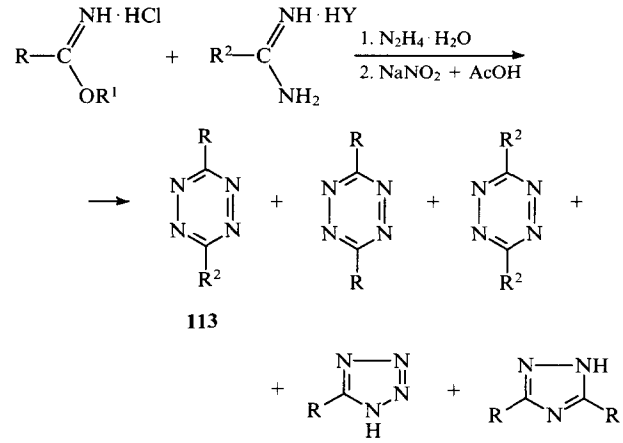


112

R = Alk, Ar, Het.

Investigators have devoted particular attention during the last decades to the development of methods of synthesis of asymmetric 3,6-disubstituted 1,2,4,5-tetrazines **113**, since substances with valuable applied properties have been found among compounds of this type.[198]

In 1975, American investigators[246–248] proposed a method of synthesis of 1,2,4,5-tetrazines **113**, which consists in the condensation of iminoester hydrochlorides with the hydrochlorides or acetates of amidines and hydrazine hydrate in absolute ethanol at −10 to 20 °C (2–3 h) with subsequent oxidation of the intermediate 1,4-dihydro-1,2,4,5-tetrazines (without isolation) by nitrous acid at 5–10 °C. Under these conditions, the target 1,2,4,5-tetrazines **113** are formed in 9%–55% yields together with symmetrical 3,6-disubstituted 1,2,4,5-tetrazines **112**, 5-substituted tetrazoles, and 3,5-disubstituted 1*H*-1,2,4-triazoles.



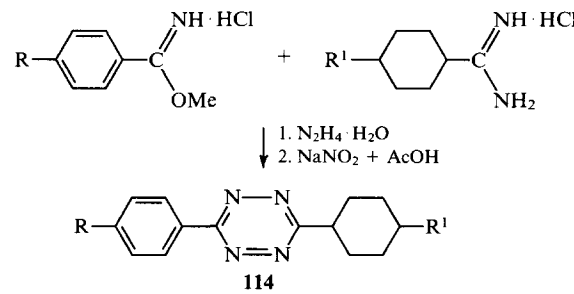
113

R = Bu^t, Ar, 1-Naphth, $PhCH_2$, cyclo-C_6H_{11}, Het; R^1 = Me, Et; R^2 = H, Me, Et, XCH_2 (X = MeO, PhO, MeS, PhS, $PhSO_2$, Cl, HO), $PhCH_2$, 1-Ad, Het; Y = Cl, AcO.

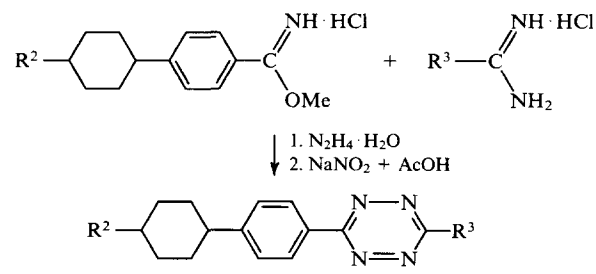
R	R^1	Yield (%)	Ref.
Ph	H	30	246
Ph	Me	11	249
Ph	Et	13	249
4-ClC_6H_4	H	45	246
4-ClC_6H_4	Me	32	246
3-$CF_3C_6H_4$	H	18	246
3-$CF_3C_6H_4$	Me	16	246
4-$MeOC_6H_4$	Me	27	246
4-FC_6H_4	Et	22	246
Bu^t	H	4.5	250
3-$O_2NC_6H_4$	H	25	251

Van der Plas and coworkers[249,250] oxidised the intermediate 1,4-dihydro-1,2,4,5-tetrazines by atmospheric oxygen in solution in methylene chloride or chloroform.

The use of the above method for the synthesis of 3,6-disubstituted 1,2,4,5-tetrazines **114** and **115**, incorporating cyclohexane fragments and alkyl groups with a normal structure, has been described in patents.[251,252]



114



115

R = Alk (C_3–C_5), BuO; R^1, R^2, R^3 = Alk (C_3–C_8).

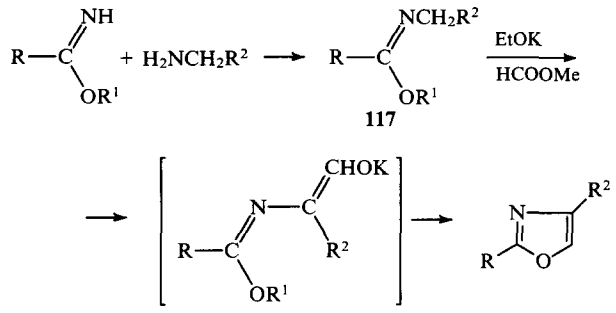
The 1,2,4,5-tetrazines **114** and **115** are used as components of nematic liquid-crystal phases.

III. Synthesis of five- and six-membered heterocycles containing nitrogen and oxygen atoms

1. Synthesis of oxazole and Δ^2-oxazoline derivatives

There are limited data in the literature concerning the synthesis of oxazoles from iminoesters as the initial compounds. This method has found an application only in the synthesis of 2-substituted oxazole-4-carboxylic acids **116** with functional group substitutents.[253,254]

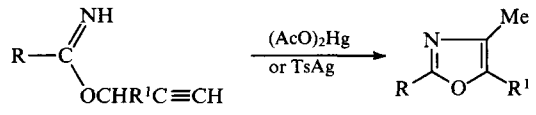
The interaction of iminoesters with aminoacid derivatives — esters, amides, *N*-substituted amides, and nitriles — is known[4,5] to afford the *N*-substituted iminoesters **117**. On treatment with methyl formate and potassium ethoxide (0–20 °C), the latter are converted into the unstable intermediates **118**, which cyclise to derivatives of oxazole-4-carboxylic acids **116**.[4,5,255–257]



117 **118** **116**

R = H, Me, Pr, cyclo-C_6H_{11}, Ar; R^1 = Et, Pr^i;
R^2 = EtOOC, NC, H_2NCO, R^3NHCO; R^3 = Alk.

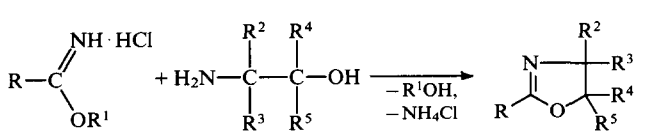
A patent[258] describes the synthesis of trisubstituted oxazoles in 90%–97% yield when propargyl iminoesters are treated with mercury acetate or silver tosylate at 200 °C (1 h).



R = Alk, $Cl(CH_2)_3$, Ph, $PhCH_2$, EtC(OH)Me; R^1 = H, Me.

One of the most important derivatives of the oxazole series are Δ^2-oxazolines, which have been used widely in recent years as intermediates in organic synthesis.[259–262] The cyclocondensation of iminoesters or their hydrochlorides with β-aminoalcohols having different structures is used to obtain ring-substituted Δ^2-oxazolines.[4,5,259,262]

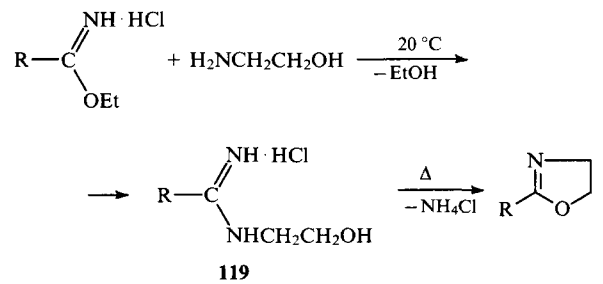
For example, the interaction of equimolecular amounts of iminoester hydrochlorides and β-aminoalcohols in anhydrous solvents (ethanol, methanol, chloroform) affords high yields of substituted Δ^2-oxazolines.[55,62,89,110,263–268]



R = Alk, Ph, PhCH(OH), 4-$MeC_6H_4OCH_2CH(OH)$, 4-HO-3,5-$Bu^t_2C_6H_2(CH_2)_n$ (n = 0, 2), Het;
R^1 = Me, Et; R^2 = H, Me; R^3 = H, Me, EtOOC, $HOCH_2$;
R^4 = H, Me;
R^5 = H, Alk, Ph, (*E*)-$C_{13}H_{27}CH{=}CH$, 4-$MeC_6H_4OCH_2$.

It is noteworthy that the reaction temperature and time as well as the yield of the target Δ^2-oxazolines are determined primarily by the nature of the group in the acid component of the initial iminoester. For example, in the case of iminoester hydrochlorides containing the electron-donating 3-indolyl[55,62,264] or 3,5-di-*tert*-butyl-4-hydroxyphenyl[110] groups, the synthesis of the corresponding Δ^2-oxazolines from ethanolamine in satisfactory yields (46%–62%) requires that the reactants be refluxed in ethanol for 10–12 h. On the other hand, when the hydrochlorides of (3-indolyl)acetic or 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionic acids are used, the cyclisation is completed in 1.5–5 h.

It has been established[266] that the interaction of iminoester hydrochlorides with ethanolamine in methanol at 20 °C (2 h) results in the formation of the hydrochlorides of *N*-substituted amidines **119**, which cyclise on heating to 2-substituted Δ^2-oxazolines in high yields.

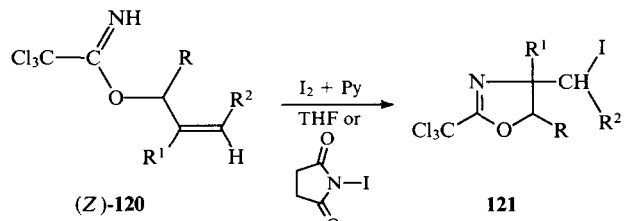


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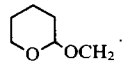
R = Ph, PhCH(OH), 4-$MeC_6H_4OCH_2CH(OH)$.

Substituted Δ^2-oxazolines can also be obtained by condensing iminoester bases with β-aminoalcohols, but in this case the reactions are carried out either with prolonged refluxing in a solvent (chloroform, ethanol)[267] or by heating the reactants without a solvent (160–180 °C) for 16–36 h.[51,264]

Italian investigators have established that the cyclisation of (*Z*)-allyliminoesters of trichloroacetic acid **120** on treatment with iodine and pyridine in THF (20 °C, 12 h)[269] or with *N*-iodosuccinimide in chloroform (20 °C, 12 h)[270,271] leads to the regiospecific formation of 2-trichloromethyl-4-(1-iodoalkyl)-5-R-Δ^2-oxazolines **121** in high yields in the form of a mixture of diastereoisomers. The latter are key compounds in the synthesis of stereoisomeric β-aminoalcohols and certain natural products.[269,270]



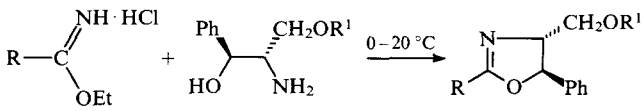
(*Z*)-**120** **121**

R = H, Pr^i, C_5H_{11}, $C_{15}H_{31}$; R^1 = H, Me;
R^2 = H, Et, $C_{15}H_{31}$, $MeOCH_2$, $PhCH_2OCH_2$, .

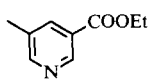
R	R^1	R^2	Yield (%) of **121**
H	Me	H	85
Pr^i	H	H	70
C_5H_{11}	H	H	60
H	H	$C_{15}H_{31}$	90 (*threo*)
$C_{15}H_{31}$	H	H	90 (*cis* : *trans* = 1 : 4)
H	H	Et	88 (*threo*)
H	H	Ph	92
H	H	$MeOCH_2$	87
H	H	CH_2OTHP	81
H	H	$PhCH_2OCH_2$	98

Investigators have devoted much attention in recent years to the synthesis of Δ^2-oxazolines from chiral β-aminoalcohols. The chiral Δ^2-oxazolines formed under these conditions are valuable key intermediates in the asymmetric synthesis of various compounds — 2-hydroxy-, 2-methoxy-, 2-alkyl-, and 2-chloroalkanoic acids, 1,4-dihydropyridines, etc.

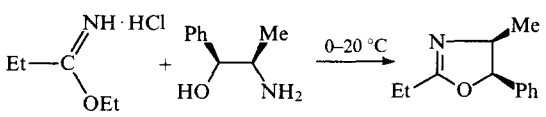
Meyers et al. synthesised (−)-(4*S*,5*S*)-2-substituted 5-phenyl-Δ^2-oxazolines **123** with the *trans*-configuration in 59%–87% yield by the reaction of the hydrochlorides of the iminoesters of various acids with (+)-(1*S*,2*S*)-2-amino-1-phenylpropane-1,3-diol **122** (R^1 = H) or with (+)-(1*S*,2*S*)-2-amino-3-methoxy-1-phenyl-propan-1-ol **122** (R^1 = Me) in methylene chloride (0–20 °C, 6 h).[272–278]



(+)-(1*S*,2*S*)-**122** (−)-(4*S*,5*S*)-**123**

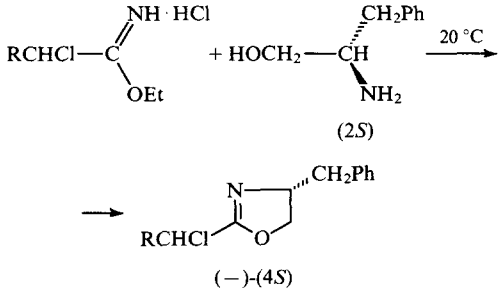
R = Me, Et, Pr, $MeOCH_2$, $ClCH_2$, Ph, $PhCH_2$, 3-Py, 
R^1 = H, Me.

It has been noted[275] that the condensation of the propionic acid iminoester with (+)-(1*S*,2*R*)-2-amino–1-phenylpropan-1-ol in the presence of pyridine in methylene chloride (0 °C; 20 °C, 12 h) affords an 80% yield of (+)-(4*R*,5*S*)-2-ethyl-4-methyl-5-phenyl-Δ^2-oxazoline with the *cis*-configuration.



(+)-(1*S*,2*R*) (+)-(4*R*,5*S*)

Chiral 2-substituted (−)-(4*S*)-4-benzyl-Δ^2-oxazolines have been synthesised in 60%–82% yield by the reaction of equimolecular amounts of 2-chloroalkanoic acid iminoesters with (2*S*)-2-amino-3-phenylpropan-1-ol in methylene chloride at 20 °C.[279,280]



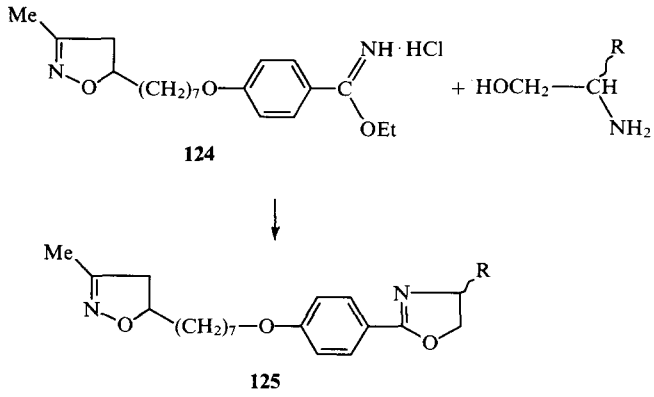
(2*S*)

(−)-(4*S*)

R = Alk.

It has also been noted that, when the phenylacetic acid iminoester is used in this reaction, the corresponding (−)-(4*S*)-2,4-dibenzyl-Δ^2-oxazoline is formed in 71% yield after heating equimolecular amounts of the reactants at 120–130 °C for 12 h without a solvent.[280]

In the search for new effective antiviral preparations — analogues of 3-methyl-5-[7-(4-Δ^2-oxazolin-2-ylphenyloxy)heptyl]isoxazole ('disoxaryl' — an inhibitor of the HPV-14 virus) — individual (4*S*)- and (4*R*)-stereoisomers of the 4-alkyl-Δ^2-oxazolines **125** have been synthesised by condensing the iminoester hydrochlorides **124** with optically active aminoalcohols.[281]

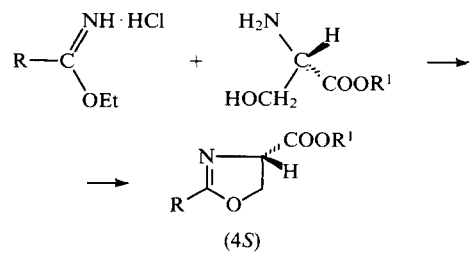


124

125

R = Alk.

The interaction of iminoester hydrochlorides with L-serine esters leads to 75%–76% yields of the chiral esters of 2-substituted (4*S*)-Δ^2-oxazoline-4-carboxylic acids,[282–284] which are used as key compounds in the asymmetric synthesis of 3-substituted alkanoic acids and 3-substituted lactones.[282,283]

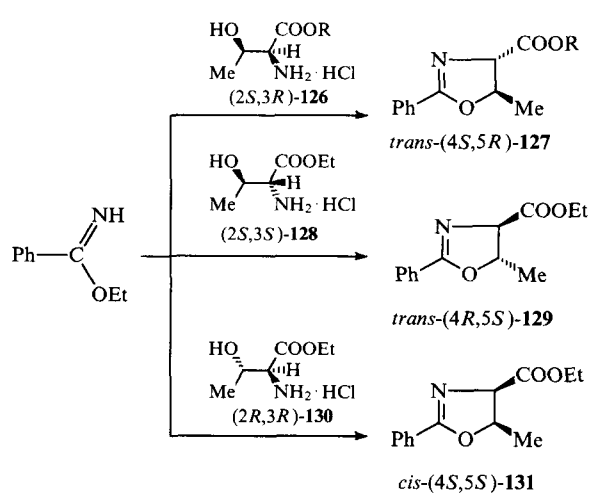


(4*S*)

R = Me, Ph; R^1 = Me, Et.

Racemic esters of 2-phenyl-Δ^2-oxazoline-4-carboxylic acid, which are convenient intermediates in the synthesis of 2-deuterio-D-serine and its derivatives, have been synthesised in 65%–72% yield by condensing the hydrochloride of the benzoic acid iminoester with the hydrochlorides of racemic esters of serine in the presence of triethylamine (molar ratios 1 : 1 : 1) in methylene chloride (20 °C, 8 h).[285,286]

The reaction of the benzoic acid iminoester with the hydrochlorides of L-threonine esters **126** (molar ratio 1 : 1.75) in an ether–water mixture at 20 °C results in the formation of esters of *trans*-(4*S*,5*R*)-5-methyl-2-phenyl-Δ^2-oxazoline-4-carboxylic acid **127** is 70%–72% yield.[287–289]



(2*S*,3*R*)-**126**

trans-(4*S*,5*R*)-**127**

(2*S*,3*S*)-**128**

trans-(4*R*,5*S*)-**129**

(2*R*,3*R*)-**130**

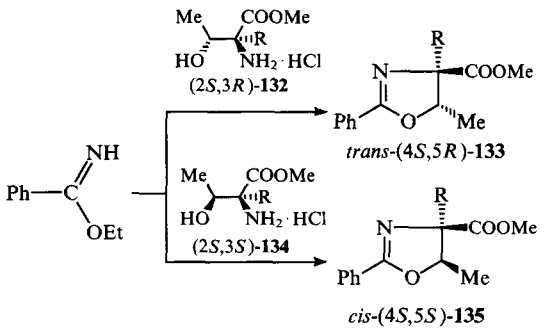
cis-(4*S*,5*S*)-**131**

R = Me, Et.

The ester of *trans*-(4*R*,5*S*)-Δ^2-oxazoline-4-carboxylic acid **129** — a key compound in the enantioselective synthesis of the natural azoxyalkene elaiomycin — has been synthesised in 52% yield under similar conditions from the hydrochloride of the D-threonine ester **128**,[290] while the ester of *cis*-(4*S*,5*R*)-Δ^2-oxazoline-4-carboxylic acid **131** — a key compound in the synthesis of L-threonine — has been obtained from the hydrochloride of the ester **130**.[291]

Japanese investigators[292] synthesised the esters of *trans*-(4*S*,5*R*)-Δ^2-oxazoline-4-carboxylic acid **133** (Scheme 3) by the interaction of the benzoic acid iminoester with the hydrochlorides of (2*S*,3*R*)-2-amino-3-hydroxy-2-R-butyric acids **132** (molar ratio 1.2:1) in methanol (refluxing for 14 h). but the yield of the Δ^2-oxazolines did not exceed 12%–18% under these conditions.

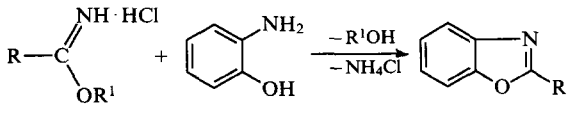
Scheme 3



The esters of *cis*-(4*S*,5*S*)-Δ^2-oxazoline-4-carboxylic acid **135** have been obtained in a low yield (12%–16%) under similar conditions from the hydrochlorides of the esters of (2*S*,3*S*)-2-amino-3-hydroxy-2-R-butyric acid **134** (Scheme 3). The authors note that the Δ^2-oxazolines **133** and **135** are convenient key compounds in the asymmetric synthesis of carboxylic α-alkylamino-β-hydroxyacids.

2. Synthesis of substituted benzoxazoles

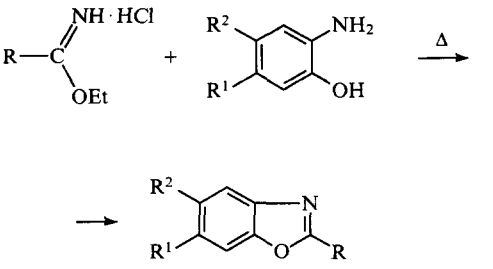
The condensation of carboxylic acid iminoester hydrochlorides with *o*-aminophenyl is known[4,5] to lead to 2-substituted benzoxazoles. It is noteworthy that recently this method has been used most frequently in the synthesis of benzoxazoles from the hydrochlorides of the iminoesters of aliphatic acids with functional-group substituents containing nitro-groups,[67–69] silylalkyl groups,[71,72] halogen atoms,[114,293,294] or an acyl group[106] as well as substituted benzoxazoles,[110] heterocyclic acids,[55,61,62,66,112] and β-substituted acrylic acids.[55,82,295]



R = Alk, $Me_3SiCH_2CH_2$, $Me_2C(NO_2)CH_2CH_2$, $MeC(NO_2)_2CH_2CH_2$, $(O_2N)_3CCH_2CH_2$, $Ac(CH_2)_3$, $Bz(CH_2)_3$, $ClCH_2$, FCH_2, Br_3CCH_2CHBr, $Br_3CCH_2CH_2$, $Cl_3CCH_2CH_2$, $PhCH_2$, Ar, 1-Ad, 4-$O_2NC_6H_4CH$=CH, Het.

Reactions of this type are usually carried out by refluxing equimolecular amounts of the reactants in methanol or ethanol for 5–10 h, whereupon the yield of the target 2-substituted benzoxazoles is 63%–97%. The reaction time in each specific case depends primarily on the nature of the group in the acid part of the initial iminoester hydrochloride.[296] We may note that, in the case of iminoester hydrochlorides containing electron-accepting groups, which reduce the thermal stability of the iminoesters, the reactions are carried out at 0–20 °C.[69]

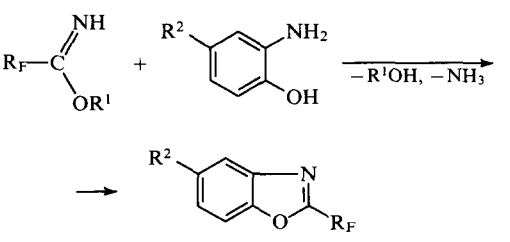
There are isolated literature data on the condensation reactions of iminoester hydrochlorides with ring-substituted *o*-aminophenols, which lead to high yields of 2,5- or 2,6-disubstituted benzoxazoles.[106,297,298]



R = $Ac(CH_2)_3$, $Bz(CH_2)_3$; R^1 = NO_2, R^2 = H;
R = H, Me, Ph, 3-Py, cyclo-C_6H_{11}; R^1 = H, R^2 = NCCH(Me);
R = $ClCH_2$; R^1 = H, R^2 = Alk, cyclo-(C_3-C_6).

The synthesis of 1,5-bis(2-benzoxazolyl)-3,3-dinitropentane in 94% yield by the reaction of the hydrochloride of the diiminoester of 4,4-dinitropimelic acid with *o*-aminophenol (molar ratio 1:2) in methanol at 50 °C (1 h) has been reported.[104]

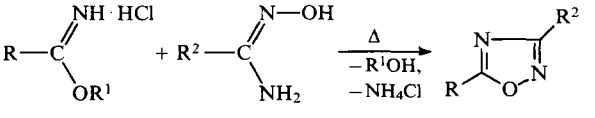
2-Substituted benzoxazoles can also be obtained by condensing iminoester bases with *o*-aminophenol.[296] In the case of iminoesters containing strong electron-accepting groups (for example, the iminoesters of carboxylic perfluoroacids), the condensations take place under mild conditions (20–35 °C, 1–3 h) and the target benzoxazoles are then formed in 75%–86% yields.[296,299]



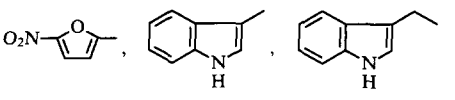
R_F = CF_3, n-C_3F_7, $F_5C_2O(CF_2)_2OCF_2$, n-$C_3F_7O[CF(CF_3)CF_2O]_2CF(CF_3)$;
R^1 = Me, Et; R^2 = H, n-C_3F_7.

3. Synthesis of 3,5-disubstituted 1,2,4-oxadiazoles

Carboxylic acid amidoximes are frequently used as the starting materials for the synthesis of 1,2,4-oxadiazoles.[300] The hydrochlorides of the iminoesters of various carboxylic acids may be used as the second component in the condensation with the amidoximes.[52,56,89,301–305]



R = Alk, Ar, $ClCH_2$, 1-Ad, Het; R^1 = Me, Et;
R^2 = Me, Ph, $ClCH_2$, 4-$O_2NC_6H_4$, $PhCH_2$, 1-Ad,



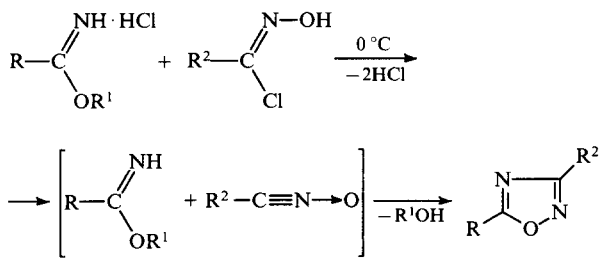
Reactions of this type are usually carried out by refluxing equimolecular amounts of the reactants in ethanol or methanol for 1–12 h, whereupon the yield of the 3,5-disubstituted 1,2,4-oxadiazoles in 38%–92%.

The comparatively low yield (38%–47%) of 3-(3-indolylmethyl)-5,-R-1,2,4-oxadiazoles (R = 3-indolyl, 3-indolylmethyl,

phenyl, *p*-nitrophenyl) has been explained[303] by the thermal instability of the initial amidoxime of (3-indolyl)acetic acid, which decomposes on heating in methanol.

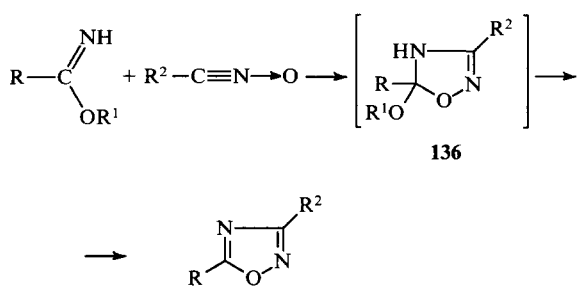
3,5-Disubstituted 1,2,4-oxadiazoles can also be synthesised by the 1,3-dipolar cycloaddition of the *N*-oxides of aromatic and heterocyclic nitriles to the carboxylic acid iminoesters.[107,302,306-312] The 1,3-dipoles (nitrile *N*-oxides) are usually obtained in situ from the chlorides of the corresponding arene- or heteroarene-hydroxamic acids by treatment with bases in the presence of a dipolarophile—the carboxylic acid iminoester. The nitrile *N*-oxides are generated from the hydroxamic acid chlorides by means of either a 5% aqueous solution of sodium carbonate (0–5 °C, 1 h)[302,309] or triethylamine (0–5 °C).[311] In certain cases, the dipolarophile (the iminoester) is also generated from the corresponding iminoester hydrochlorides.[302,308,309]

It has been noted[302,309] that the reactions can be most usefully carried out with a nitrile *N*-oxide : iminoester molar ratio of 1 : (2–2.5) at 0–5 °C for 1 h with subsequent stirring of the reaction mixture at 20 °C for 3 h. When the reactions were performed under the conditions indicated, the yields of 1,2,4-oxadiazoles were 55%–70%.



R = Me, $EtOCH_2CH_2$, 1-Ad, Ar, $PhCH_2$, $PhCH_2CH_2$;
R^1 = Me, Et; R^2 = Ar, .

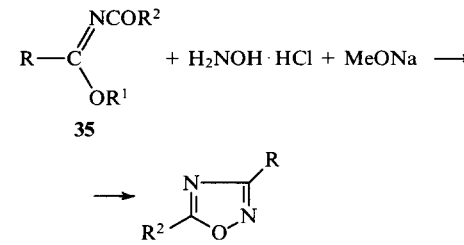
It has been suggested[308,309] that the 1,3-dipolar cycloaddition of nitrile *N*-oxides to the C=N bond of the iminoester involves the formation of Δ^2-1,2,4-oxadiazolines **136** as intermediates, which are subsequently converted into 1,2,4-oxadiazoles as a result of the elimination of an alcohol molecule.



136

An intermediate of this type has been isolated in 34% yield in the reaction of the benzoic acid iminoester with the chloride of 2-methoxycarbonylbenzenehydroxamic acid in the presence of triethylamine.[311] When this intermediate was kept in ether (at 20 °C), it was converted into 3-(2-methoxycarbonylphenyl)-5-phenyl-1,2,4-oxadiazoles in 23% yields.

Certain reactive *N*-substituted iminoesters have also been used as the starting compounds in the synthesis of 1,2,4-oxadiazoles. For example, the interaction of *N*-acyliminoesters with hydroxylamine hydrochloride and sodium methoxide (molar ratios 1 : 1.1 : 1.1) in methanol (20 °C, 12 h; refluxing for 6 h) leads to the formation of 3,5-disubstituted 1,2,4-oxadiazoles in 38%–74% yields.[163]



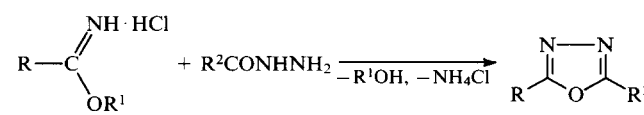
35

R,R^2 = Me, Ar; R^1 = Me, Et.

It is striking that in this case the group R from the acid component of the iminoester occupies the 3-position in the 1,2,4-oxadiazole formed, while the group R^2 from the acyl fragment occupies the 5-position.

4. Synthesis of 2,5-disubstituted 1,3,4-oxadiazoles

It was noted above that on heating with *N*-acylhydrazines (acid hydrazides), carboxylic acid iminoesters give rise either to the *N*-acylamidrazones **28** or to the 3,5-disubstituted 1*H*-1,2,4-triazoles **29**. In 1963, Weidinger and Kranz established[301] that the condensation of the iminoester hydrochlorides with acid hydrazides leads to 2,5-disubstituted 1,3,4-oxadiazoles. Nowadays this method is widely used in the synthesis of 1,3,4-oxadiazoles from iminoester hydrochlorides and the hydrazides of aliphatic, aromatic, and heterocyclic acids.[52,55,56,89,107,168,293,305,313-320]

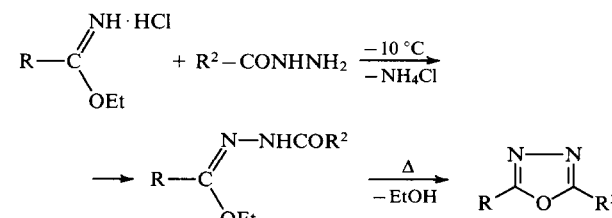


R = Me, $ClCH_2$, $EtOOCCH_2$, $AcCH_2CH_2$, $Me_3SiCH_2CH_2$, cyclo-C_6H_{11}, Ar, PhCH=CH, Het, 1-Ad;
R^1 = Me, Et, Bu; R^2 = H, Me, Ar, cyclo-C_6H_{11}, 1-Ad, Het.

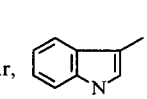
We may note that 1,3,4-oxadiazoles can be obtained by this method in two alternative ways; thus, when the synthesis from two different iminoester hydrochlorides and two hydrazides is planned, the most readily available compounds may be selected.

The condensation of iminoester hydrochlorides with acid hydrazides is carried out as a rule by heating the reactants (78–160 °C) [the iminoester hydrochloride : hydrazide molar ratio is (1–1.35) : 1] in anhydrous solvents—ethanol, DMF, *N*-methylpyrrolidinone, pyridine, or dioxane—for 1–8 h. The yields of the target 1,3,4-oxadiazoles are 55%–94% under these conditions.

The interaction of iminoester hydrochlorides with acid hydrazides involves the formation of the *N*-acylhydrazones of the corresponding esters **137** as intermediates, which in a number of instances have been isolated in 60%–90% yields when the reaction was carried out in ethanol at −10 to 15 °C for 6–24 h.[89,107,168,301,321]



137

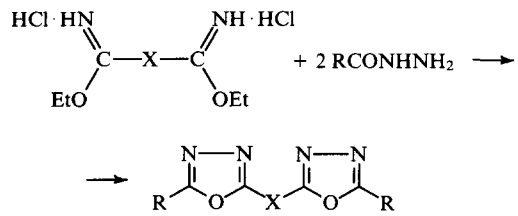
R = Me, Ar, , ;
R^2 = Me, Ar, 4-Py.

On heating to the melting point[89,107,168,301] or on treatment with triethylamine at 20 °C,[321] the esters split off an alcohol molecule and are converted into 1,3,4-oxadiazoles (yield 88%–97%).

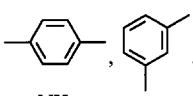
In the search for new substances with anti-inflammatory activity, 2-[ω-(dimethylamino)alkyl]-5-phenyl-1,3,4-oxadiazoles were synthesised by condensing iminoester hydrochlorides with hydrazides.[317] The authors note that, in order to obtain 2-[4-(dimethylamino)butyl]-1,3,4-oxdiazole, it is best to employ the benzoic acid iminoester hydrochloride, while 2-[2-(dimethylamino)ethyl]-1,3,4-oxadiazole is best synthesised from the benzoic acid hydrazide.

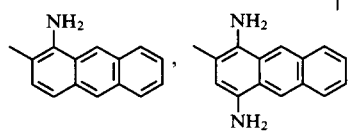
According to patent data,[318–320] the condensation of the hydrochloride of the hydroxyacetic acid iminoester with aromatic acid hydrazides leads to 5-aryl-2-hydroxymethyl-1,3,4-oxadiazoles—important intermediates in the synthesis of compounds with anticonvulsant, analgesic, anti-inflammatory, and diuretic activities.

The condensation of the dihydrochlorides of dicarboxylic acid bisaminoesters with acid hydrazides (molar ratio 1 : 2) results in the formation of bis-1,3,4-oxadiazoles **138**.[301,313]



138

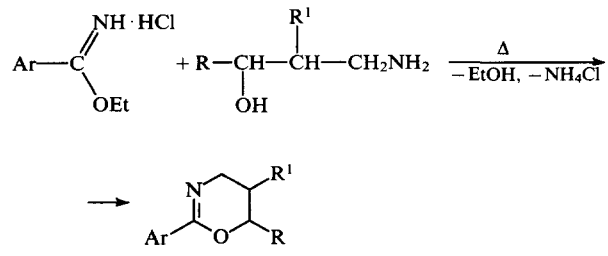
X = $-(CH_2)_n-$ (n = 0, 2, 4), ;

R = Ar, .

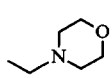
The reactions were carried out by heating the reactants in dioxane, *N*-methylpyrrolidinone, or pyridine and the yield of the bis-1,3,4-oxadiazole **138** was then 40%–80%.

5. Synthesis of 1,3-oxazines and related compounds

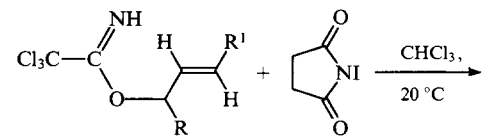
The condensation of aromatic acid iminoester hydrochlorides with substituted 3-aminopropan-1-ols in ethanol (refluxing for 1–2 h) leads to 2,5,6-trisubstituted 5,6-dihydro-4*H*-1,3-oxazines **139**.[322,323]



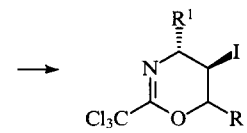
139

R = Ph, ; R^1 = H, Ph.

It was noted above that the cyclisation of (*Z*)-allyl iminoesters of trichloroacetic acid **120** on treatment with *N*-iodosuccinimide in chloroform (20 °C, 12 h) results in the regioselective formation of 4-(1-iodoalkyl)-2-trichloromethyl-5-substituted Δ^2-oxazolines **121**.[269–271] Under similar conditions, (*E*)-allyl iminoesters of trichloroacetic acid **140** cyclise regioselectively to *trans*-5-iodo-2-trichloromethyl-4,6-disubstituted 5,6-dihydro-4*H*-1,3-oxazines **141**.[271,324]



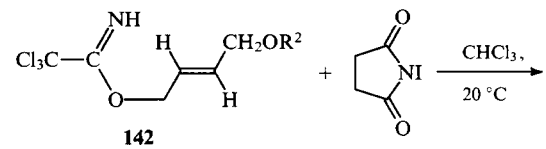
140



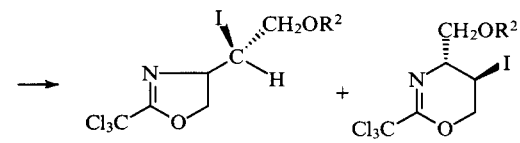
141

R = H, Me; R^1 = Alk, Ph, (*E*)-MeCH=CH, (*E*)-$C_{13}H_{27}$CH=CH.

On the other hand, the (*E*)-allyl iminoesters **142**, containing alkoxy-groups, afford a mixture of Δ^2-oxazolines **121** and 5,6-dihydro-4*H*-1,3-oxazines **141** under the reaction conditions.[318]



142



121 **141**

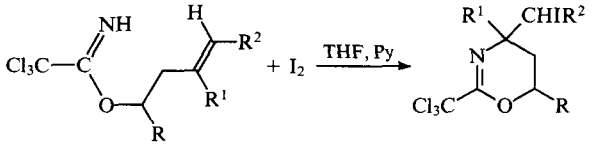
R^2 = Me, $PhCH_2$, .

Examples of the *trans*-5-iodo-5,6-dihydro-4*H*-1,3-oxazines **141** formed on cyclisation of the (*E*)-allyl iminoesters of trichloroacetic acid **140** and **142** are presented below.

R	R^1	Yield of 1,3-oxazine **141** (%)
H	Ph	80
H	(*E*)-MeCH=CH	90
H	(*E*)-$C_{13}H_{27}$CH=CH	95
Me	Me	85
H	n-$C_{15}H_{31}$	70
H	Et	90
H	Pr	87
H	$MeOCH_2$	30 (61% **121**, R^2 = Me)
H	$PhCH_2OCH_2$	18 (75% **121**, R^2 = $PhCH_2$)
H	CH_2OTHP	38 (55% **121**, R^2 = THP)

(THP = tetrahydropyranyl)

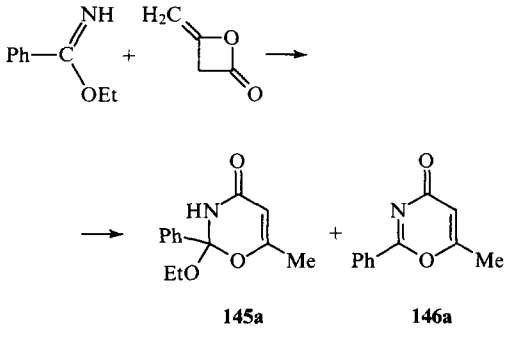
It has been reported[269] that the cyclisation of the homoallyl iminoesters of trichloroacetic acid **143** on treatment with iodine and pyridine in THF (20 °C, 12 h) afforded 4-(1-iodoalkyl)-2-trichloromethyl-5,6-dihydro-4*H*-1,3-oxazines **144** in 65%–90% yields.



143 144

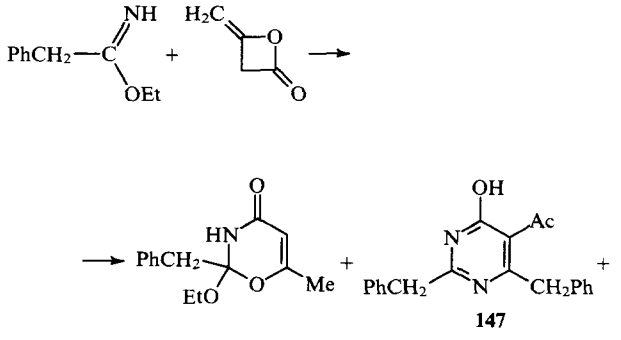
$R = R^2 = H, R^1 = Me$; $R = R^1 = H, R^2 = Et$;
$R = Me, R^1 = R^2 = H$.

A mixture of 2-ethoxy-6-methyl-2-phenyl-3,4-dihydro-2*H*-1,3-oxazin-4-one **145a** (yield 21.3%) and 6-methyl-2-phenyl-4*H*-1,3-oxazin-4-one **146a** (yield 16.0%) was obtained by the reaction of the benzoic acid iminoester with diketene in ether (refluxing for 5 h).[325] The authors note that, on refluxing in benzene, 2-ethoxy-3,4-dihydro-1,3-oxazin-4-one **145a** is converted qualitatively into the 1,3-oxazin-4-one **146a**.



145a **146a**

A mixture of 2-benzyl-2-ethoxy-6-methyl-3,4-dihydro-2*H*-1,3-oxazin-4-one (yield 54.6%), 5-acetyl-2,6-dibenzyl-4-hydroxypyrimidine **147** (yield 27%), and the (*N*-acetoacetyl)amide of phenyl-acetic acid is formed under similar conditions from the phenylacetic iminoester.[325]

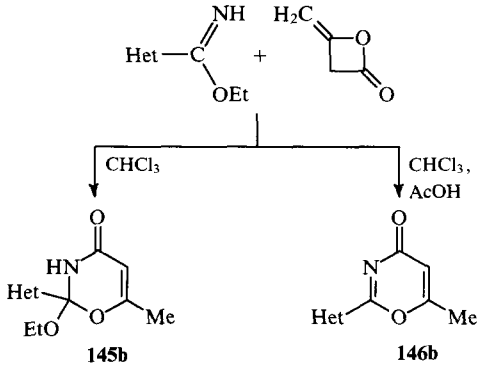


147

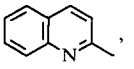
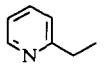
+ $PhCH_2CONHCOCH_2COMe$

On the other hand, the 4*H*-1,3-oxazin-4-one **146a** has been synthesised in 70% yield by refluxing (for 3 h) the benzoic acid iminoester with diketene (molar ratio 1:2) in benzene.[326]

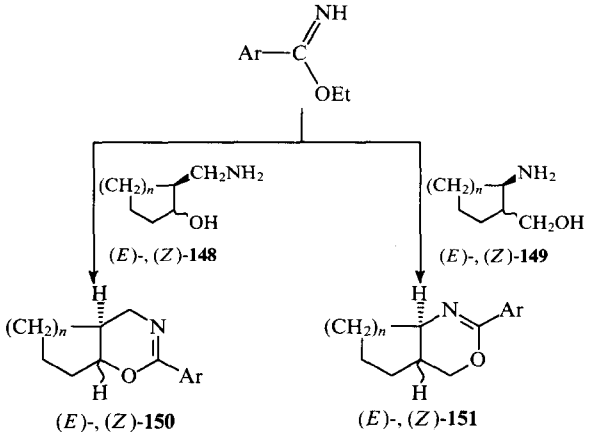
The interaction of the iminoesters of heterocyclic acids with diketene in chloroform in the presence of acetic acid (refluxing for 0.5–2 h) leads to 2-heteroaryl-6-methyl-4*H*-1,3-oxazin-4-ones **146b** in 13%–35% yield.[327] When the reaction is carried out in the absence of acetic acid (20–60 °C, 1–4 h), 2-ethoxy-2*H*-3,4-dihydro-1,3-oxazin-4-ones **145b** are formed in 33%–57% yield.



145b **146b**

Het = 2-Py, 3-Py, 4-Py, , .

Hungarian investigators have studied in detail the condensation of the 4-chlorobenzoic acid iminoester with the stereoisomeric *cis*- and *trans*-2-aminomethylcycloalkanols **148** and 1-amino-2-hydroxymethylcycloalkanes **149**.[328,329] It was established that, when the reactants are heated in ethanol (for 24 h) in the presence of catalytic amounts of HCl, the (*E*)- and (*Z*)-5,6-tetramethylene- or (*E*)- and (*Z*)-5,6-pentamethylene-5,6-dihydro-4*H*-1,3-oxazines **150** are formed respectively in the case of the aminoalcohols **148**.

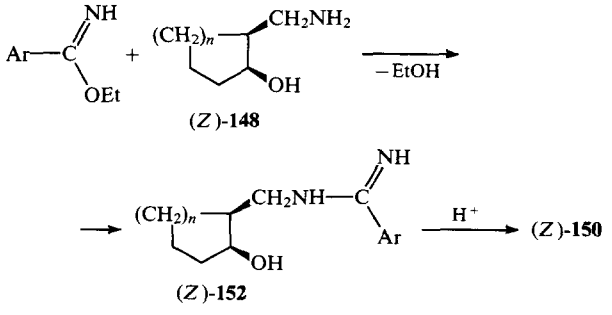


(*E*)-, (*Z*)-**150** (*E*)-, (*Z*)-**151**

$n = 2, 3$; $Ar = 4\text{-}ClC_6H_4$.

Condensation with the stereoisomeric aminoalcohols **149** leads respectively to the (*E*)- and (*Z*)-4,5-tetramethylene- or (*E*)- and (*Z*)-4,5-pentamethylene-4,5-dihydro-6*H*-1,3-oxazines **151** in 70% yield.

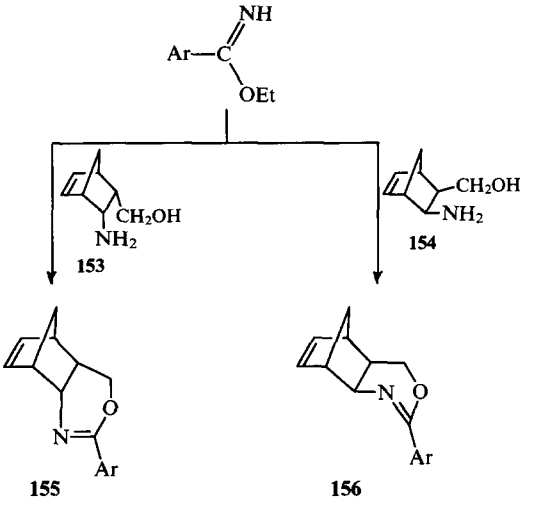
When the (*Z*)-isomers of the aminoalcohols **148** were refluxed (1.5 h) with the 4-chlorobenzoic acid iminoester in ethanol in the absence of an acid catalyst, the *N*-substituted amidines **152** were isolated in 70%–73% yields. On refluxing (for 12 h) in ethanol in the presence of HCl, the amidines are converted into (*Z*)-5,6-dihydro-4*H*-1,3-oxazines **150**.



(*Z*)-**148** (*Z*)-**152**

$Ar = 4\text{-}ClC_6H_4$

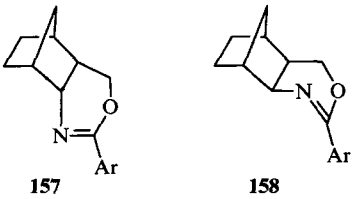
The interaction of equimolecular amounts of aromatic acid iminoesters and 3-*endo*-amino-2-*endo*-(hydroxymethyl)bicyclo-[2.2.1]hept-5-ene **153** or 3-*exo*-amino-2-*exo*-(hydroxymethyl)-bicyclo[2.2.1]hept-5-ene **154** in ethanol in the presence of catalytic amounts of HCl (refluxing for 6–10 h) affords a 32%–48% yield of 2-aryl-5,8-methano-4*ar*,5*t*,8*t*,8*ac*-tetrahydro-4*H*-3,1-benoxazines **155** and 2-aryl-5,8-methano-4*ar*,5*c*,8*c*,8*ac*-tetrahydro-4*H*-3,1-benzoxazines **156** respectively.[330–332]



155 **156**

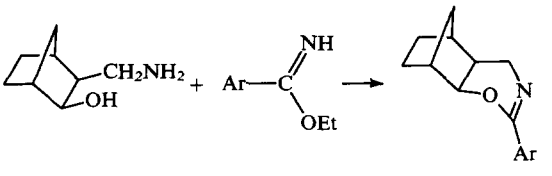
Ar = Ph, 3-ClC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4.

2-Aryl-5,8-methano-4*ar*,5*t*,6,7,8*t*,8*ac*-hexahydro-4*H*-3,1-benzoxazines **157** (yield 34%–45%)[331,332] and 2-aryl-5,8-methano-4*ar*,5*c*,6,7,8*c*,8*ac*-hexahydro-4*H*-3,1-benzoxazines **158** (yield 27% to 38%)[330,332] were synthesised under similar conditions from 3-*endo*-amino-2-*endo*-(hydroxymethyl)bicyclo-[2.2.1]heptane and 3-*exo*-amino-2-*exo*-(hydroxymethyl)bicyclo-[2.2.1]heptane respectively.



157 **158**

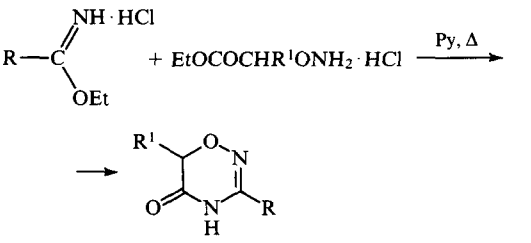
The condensation of aromatic acid aminoesters with *cis,exo*-3-(aminomethyl)bicyclo[2.2.1]heptan-2-ol under the conditions indicated above leads to 2-aryl-5,8-methano-4*ar*,5*c*,6,7,8*c*,8*ac*-hexahydro-4*H*-1,3-benzoxazines **159** in 51%–55% yield.[333]



159

6. Synthesis of 1,2,4-oxadiazine and 1,5,2-dioxazine derivatives

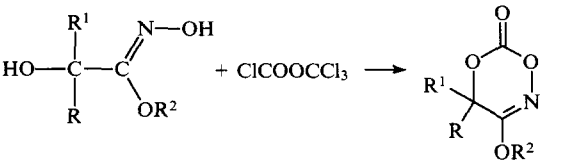
According to patent data,[334] derivatives of 1,2,4-oxadiazin-5-one **160**, which are effective herbicides and plant growth regulators, are formed in satisfactory yields when aromatic and heterocyclic acid iminoester hydrochlorides are refluxed with the hydrochlorides of *O*-substituted hydroxylamine in pyridine.



160

R = Ar, Het; R^1 = H, Me, Et, Ph.

The interaction of the (*E*)-isomers of the *N*-hydroxyiminoesters of carboxylic α-hydroxyacids **161** with trichloromethyl chloroformate at 20 °C leads to 3-alkoxy-4*H*-1,5,2-dioxazin-6-ones **162** in 70%–73% yields.[335]



161 **162**

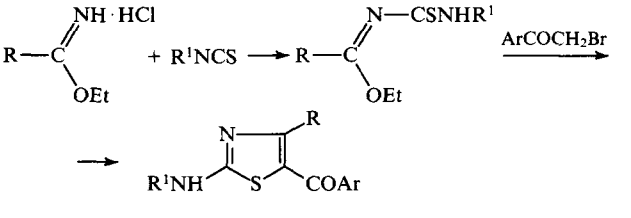
R, R^1 = H, Me, Ph; R + R^1 = $-(CH_2)_5-$; R^2 = Et, $PhCH_2$.

IV. Synthesis of five- and six-membered heterocycles containing nitrogen and sulfur atoms

1. Synthesis of thiazole, Δ^2-thiazoline, and benzothiazole derivatives

It was noted above that the interaction of the *N*-cyanomethyl-iminoesters **5** with hydrogen disulfide in pyridine results in the formation of 5-mercapto-1*H*-imidazoles (yield 20%–35%) together with 5-aminothiazoles (yield 10%–20%).[36]

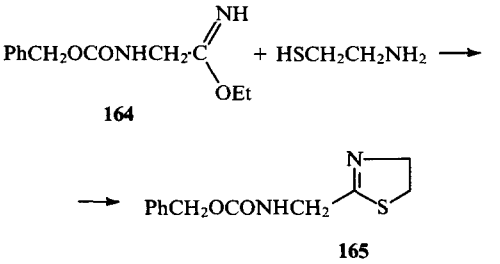
The reactions of aliphatic acid iminoesters with alkyl isothiocyanates lead to *N*-(alkylaminothiocarbonyl)iminoesters, which on treatment with 4-chloro-3-nitrophenylacyl bromide cyclise to 2-aminothiazole derivatives **163** — intermediates in the synthesis of pharmaceutical preparations.[336]



163

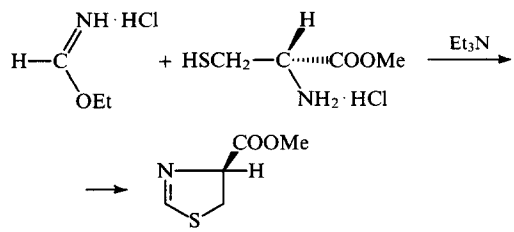
R, R^1 = Alk; Ar = 3-O_2N-4-ClC_6H_3.

The 2-substituted Δ^2-thiazoline **165**, which is a key compound in the synthesis of serine, threonine, allothreonine, and β-hydroxynorvaline, has been synthesised in 75% yield by condensing the *N*-acylated aminoacetic acid iminoester **164** with 2-aminoethanethiol in ethanol (35–50 °C, 3 h).[73]

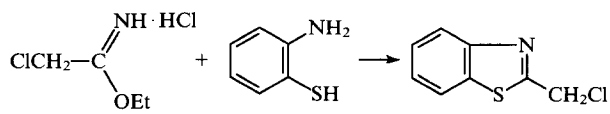


164 **165**

A chiral ester of (4*R*)-Δ^2-thiazoline-4-carboxylic acid has been obtained in 82%–85% yield by the reaction of the formic acid iminoester hydrochloride with the hydrochloride of the methyl ester of D-cysteine in the presence of triethylamine in methylene chloride (20 °C, 3 h).[337,338]

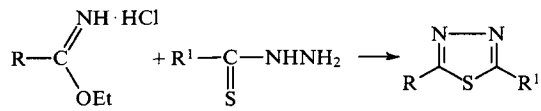


When the chloroacetic acid iminoester hydrochloride is refluxed with *o*-aminothiophenol in chloroform, 2-chloromethylbenzothiazole, which is an intermediate in the synthesis of biologically active substances[339] and functional derivatives of benzothiazole,[293] is formed in 70%–75% yield.[293,339]



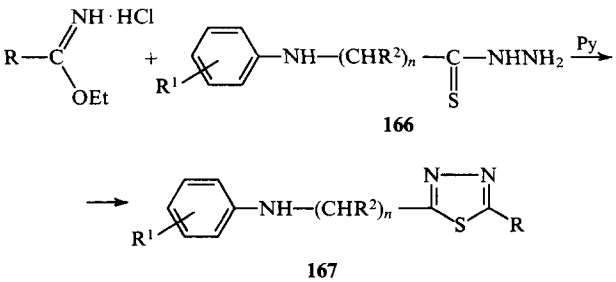
2. Synthesis of 1,3,4-thiadiazole derivatives

In 1963, Weidinger and Kranz[190] proposed a convenient method of synthesis of 2,5-disubstituted 1,3,4-thiadiazoles, which consists in condensing carboxylic acid iminoester hydrochlorides with carboxylic acid thiohydrazides. The reactions were carried out by refluxing equimolar amounts of the reactants in ethanol; under these conditions the yields of 1,3,4-thiadiazoles were 65%–78%.



R = Me, Ar; R^1 = Ar.

The interaction of iminoester hydrochlorides with the thiohydrazides of *N*-substituted aminoacids **166** in pyridine leads to the 1,3,4-thiadiazoles **167**, which possess herbicidal properties.[340]

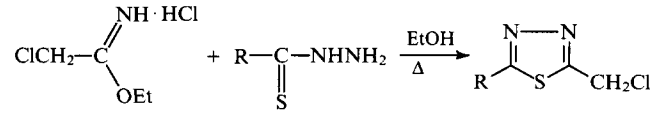


166

167

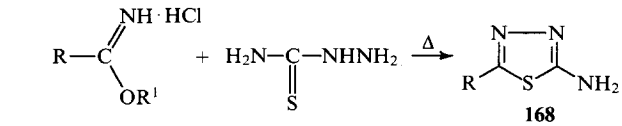
R = H, Me, cyclo-C_nH_{2n-1}, Ar; R^1 = Hal, Alk, AlkO, AlkHal
R^2 = H, Alk; n = 1, 2.

2-Chloromethyl-5-substituted 1,3,4-thiadiazoles, which are intermediates in the synthesis of preparations with an anticonvulsant activity, have been synthesised by the reaction of the chloroacetic acid iminoester hydrochloride with thiohydrazides.[341]

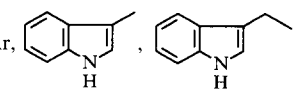


R = Ph, $PhCH_2$, 2-PhC_6H_4, 2-$PhOC_6H_4$, 2-$PhC_6H_4CH_2$.

The condensation of carboxylic acid iminoester hydrochlorides with thiosemicarbazide leads to 2-amino-5-substituted 1,3,4-thiadiazoles **168**.[167,190,191,313,342–345] The reactions were carried out by refluxing the reactants in ethanol, dioxane, or pyridine [molar ratio (1–1.2):1; 1–4 h]; the yields of the 2-amino-1,3,4-thiadiazoles **168** were 34%–92%.

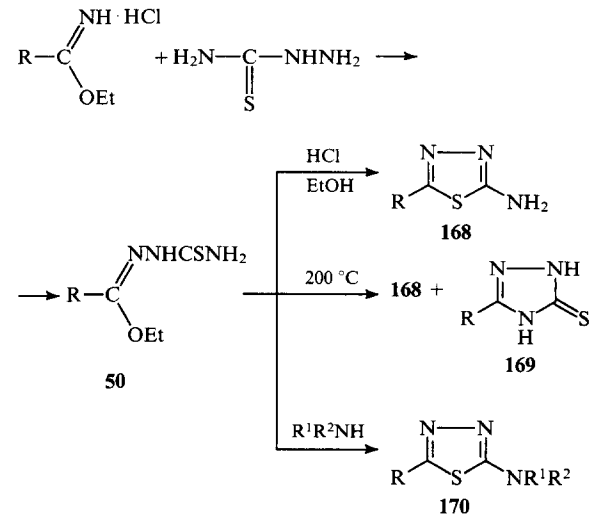


168

R = H, Alk, cyclo-C_6H_{11}, Ar,  ;
R^1 = Me, Et.

It had been noted earlier that the interaction of equimolar amounts of iminoester hydrochlorides and thiosemicarbazide in DMF at 20 °C (20 h) leads to the formation of carboxylic acid ester thiosemicarbazones **50** in 53%–74% yields.[188,189] Under certain conditions, the latter may cyclise to 2-amino-1,3,4-thiadiazoles. For example, 2-amino-5-substituted 1,3,4-thiadiazoles **168** have been synthesised in 31%–85% yields by refluxing the thiosemicarbazones in ethanol (1 h) in the presence of HCl (Scheme 4).

Scheme 4



168

169

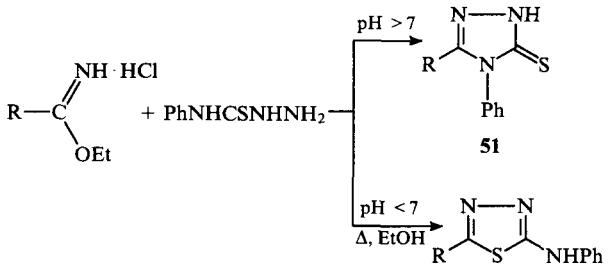
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170

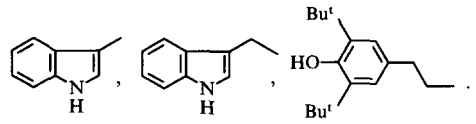
R = Alk, $PhCH_2$, Ar; R^1 = R^2 = Et;
R^1 + R^2 = $-(CH_2)_5-$.

Thermolysis of the thiosemicarbazones (200 °C, 20 min) leads to a mixture of the 2-amino-1,3,4-thiadiazoles **168** (yield 22%–74% and 3-substituted Δ^2-1*H*-1,2,4-triazoline-5-thiones **169** (yield 12%–25%).[188] Substituted 2-amino-1,3,4-thiadiazoles **170** have been obtained in 30%–35% yields by heating the thiosemicarbazone with secondary amines in DMF in a sealed tube (150 °C).[188]

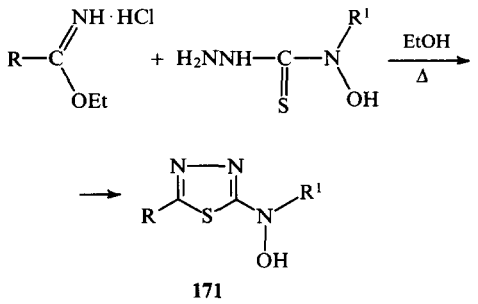
According to literature data,[89,167,190,191,342,343] the mode of the condensation of iminoester hydrochlorides with 4-phenylthiosemicarbazide is determined by the nature of the reaction mixture: in the presence of bases (pyridine, triethylamine, tripropylamine), 3,4-disubstituted Δ^2-1,2,4-triazoline-5-thiones **51** are formed, whereas in an acid medium the products are 2-phenylamino-5-substituted 1,3,4-thiadiazoles (yield 52%–85%).



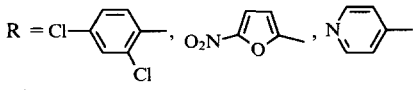
R = Ph, $Me_3SiCH_2CH_2$, $Et_2Si(Me)CH_2CH_2$,



The interaction of equimolar amounts of iminoester hydrochlorides and 4-substituted 4-hydroxythiosemicarbazides in ethanol (refluxing for 0.5 h) leads to 2-hydroxyamino-1,3,4-thiadiazoles **171** in 40%–55% yields.[346]

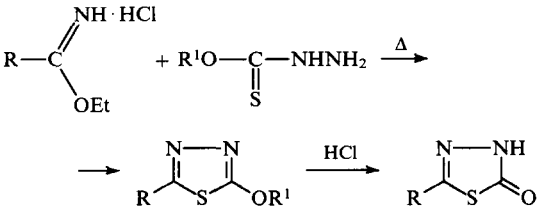


171



R^1 = Me, Ar, All.

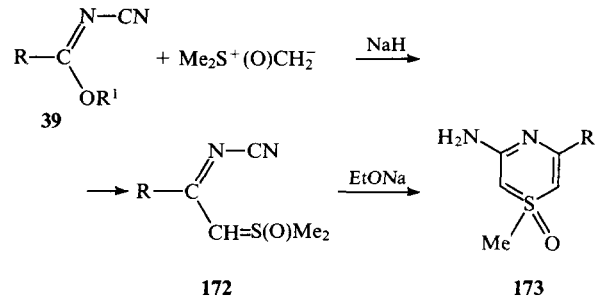
The synthesis of 2-alkoxy-5-substituted 1,3,4-thiadiazoles by the condensation of iminoester hydrochlorides with *O*-alkyl esters of thiocarbazinic acid in ethanol (refluxing for 0.5–1.5 h) has been described in a patent.[347] On treatment with hydrochloric acid, 2-alkoxy-1,3,4-thiadiazoles are converted into 3-substituted Δ^2-1,3,4-thiadiazolin-5-ones, which exhibit insecticidal, acaricidal and fungicidal activities.



R = H, Alk, CH=CH–C_nH_{2n+1} (n = 0–6), Ph;
R^1 = Me, Et, Bu.

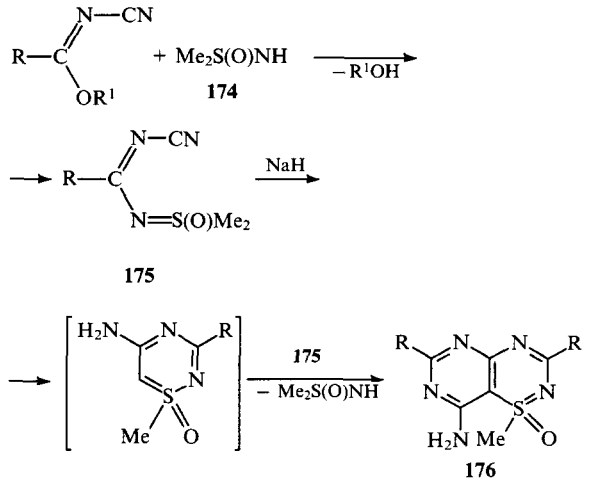
3. Synthesis of thiazine, thiadiazine, and thiatriazine derivatives

It has been reported[348] that the interaction of *N*-cyanoiminoesters with dimethyloxosulfonium methylide (20 °C, 24 h, molar ratio 1:1.2) in DMSO in the presence of sodium hydride leads to the formation of [1-R-2-(dimethyloxo-λ^6-sulfanylidene)ethylidene]cyanamides **172** in 83% yield. On refluxing (for 0.5 h) in ethanol in the presence of sodium ethoxide, the latter cyclise to 3-amino-1-methyl-5-R-1λ^4,4-thiazine 1-oxides **173** (yields 48%–82%).



R = Ar, ;
R^1 = Me, Et.

The condensation of *N*-cyanoiminoesters with the sulfoximide **174** (80 °C, 18 h) leads to *N,N*-disubstituted amidines **175** (yield 27%–91%), which are converted into 3,6-disubstituted 8-amino-1-methylpyrimido[4,5-*e*]-1λ^4,2,4-thiadiazine 1-oxides **176** (yield 39%–57%) on treatment with sodium hydride in DMSO (20 °C).[349]

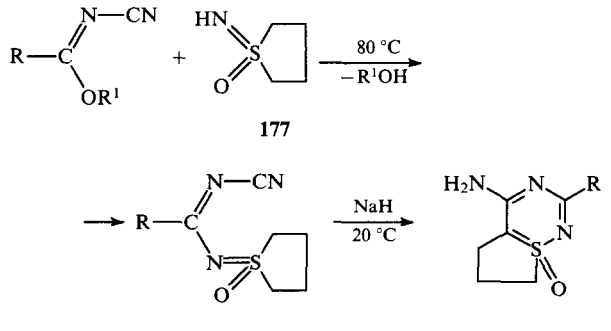


175

176

R = Me, Ar, , ; R^1 = Me, Et.

The *N,N*-disubstituted amidines **178** have been obtained under similar conditions from the sulfoximide **177**. On treatment with sodium hydride, the amidines undergo intramolecular cyclisation to 2-substituted 4-amino-6,7-dihydro-5*H*-thieno-[2,1-*e*]-1λ^4,2,4-thiadiazine *S*-oxides **179** (yield 46%–74%).[349]

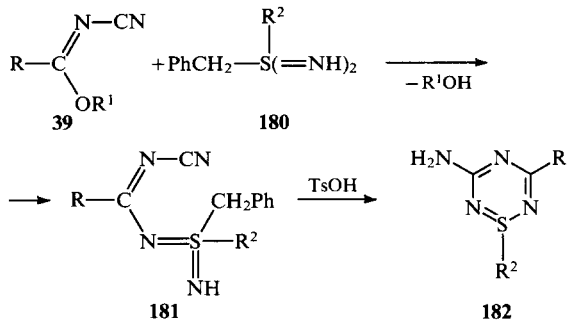


177

178 **179**

R = Me, Ph, 4-MeC_6H_4, .

The reactions of equimolecular amounts of *N*-cyanoiminoesters and *S*-alkyl-*S*-benzylsulfodiimides **180** (60 °C, 16–48 h) afford 43%–90% yields of *N*-(alkylbenzylimino-λ^6-sulfanylidene)-N^2-cyanoamidines **181**.[350]



R = Ar,  ; R^1, R^2 = Me, Et.

On refluxing with toluene-*p*-sulfonic acid in ethanol, the *N,N*-disubstituted amidines **181** are debenzylated with simultaneous cyclisation to 1,5-disubstituted 3-amino-1λ⁴,2,4,6-thiatriazines **182** (yield 48%–71%).

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