THE CHEMISTRY OF TRICHLOROACETONITRILE

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Abstract- Trichloroacetonitrile (TCAN) is a versatile reagent in organic synthesis which has drawn the interest of synthetic and theortical chemists. In this review, literature reports are organized to fill what was an obvious gap by providing an overview of the subject.

CONTENTS

1. INTRODUCTION

Trichloroacetonitrile (TCAN) can be viewed as a species containing two functional groups, cyano and trichloromethyl functions. Their mutual activity extends the synthetic capabilities of TCAN as a compound with dual reactivity. It can be used as an important versatile reagent in organic synthesis. Although over a fifty years has been passed since the discovery of trichloroacetonitrile by Petri,[1] and also new horizons in its chemistry are being opened up till now, there is no review article has been reported on the utility of this reagent in organic synthesis. However, reviews covering the chemistry of trichloroacetonitrile adducts[2,3] and chloral hydrate,[4] have been appeared. It is hoped that this review will remedy the lack of a comprehensive review by providing an up-to-date coverage of the recent literature.

2. SCOPE AND LIMITATION OF THE REVIEW

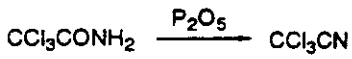
In this review all aspects of the chemistry of trichloroacetonitrile (**1**), irrespective of its biological study, will be discussed. Because of their importance as synthetic intermediates, trichloroacetonitrile adducts with active methylene reagents and their further reactions with a variety of reagents are also incorporated in this report. Patents are only cited if they contain valuable synthetic informations which otherwise has not been published.

3. METHODS OF PREPARATIONS

Petri[1] in his patent was the first to prepare TCAN (**1**) by passing chlorine gas through chloroacetonitrile (**2**).

$$\underset{\mathbf{2}}{ClCH_2CN} \xrightarrow[60^\circ C]{Cl_2} \underset{\mathbf{1}}{CCl_3CN}$$

TCAN was also obtained by passing dry HCl gas [5,6] or Cl_2-O_2 mixture over AgCl at 395°C through acetonitrile.[7] The best results were achieved by dehydration of trichloroacetamide (3) with P_2O_5 or cyanuric acid.[8,9]



3 1

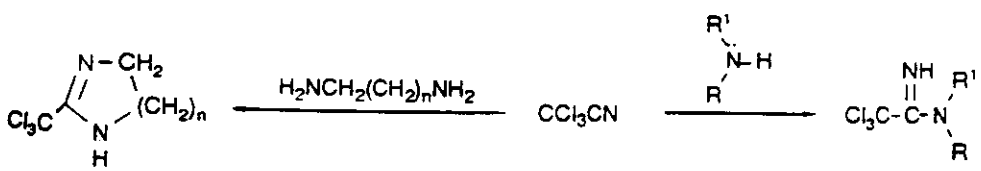
4. CHEMICAL PROPERTIES

Trichloroacetonitrile (TCAN) is a simple and highly reactive derivative of acetic acid. The trichloromethyl and cyano groups selectively participate in chemical reactions with a very strong electrophilic characters. This gives a simple way for the synthesis of a variety of unique organic compounds from amines, alcohols, phenols, thiols and other nucleophilic reagents. The combination of both functional groups allows the use of TCAN on a wide scale for cyclization proceeding under mild conditions.

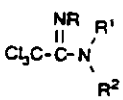
4.1. Interaction with Protic Nucleophiles

4.1.1. Interaction with Amines

Many patents are devoted to obtaining trichloroacetamidine derivatives by the addition of amines to TCAN for the purpose of producing biologically active compounds and drugs. TCAN reacts easily with amines either with or without catalysis. As a rule, the products are trichloroacetamidines in case of both aliphatic[10-20] and aromatic amines.[21-24] All of the *N*-substituted and *N,N*-disubstituted amidines (4), Table 1,[12] were prepared by addition of the corresponding amine to TCAN, preferably in C_6H_6, $(CH_3)_2SO$ or DMF at or below room temperature. Cyclic *N,N*-disubstituted amidines (5) were obtained from the reaction of TCAN with molar equivalent of the mono-*p*-toluenesulfonic acid salt of the appropriate diamine in methanol.[12]



5 1 4

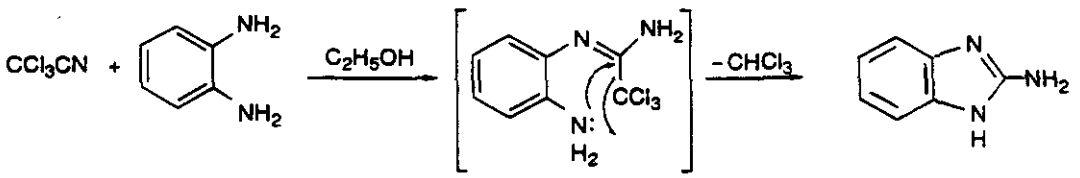
Table 1. Trichloroacetamidines 4. 

R	R^1	R^2	mp °C	Yield (%)
H	H	CH_3	223-232 decomp.	21
H	H	*n*-C_3H_7	210.5-212.5 decomp.	38

Table 1. Cont'd.

R	R^1	R^2	mp °C	Yield (%)
H	H	H	210-220 decomp.	52
-$CH_2CH_2CH_2$-		H	113.8-116.8	60
H	H	$CH_2CH{=}CH_2$	177.8-181.8 decomp.	85
CH_3	H	$CH_2CH{=}CH_2$	83-87 decomp.	47
H	H	$CH_2C_6H_4$-*o*-OCH_3	242-245 decomp.	59
-CH_2CH_2-		H	85 decomp.	13
H	H	$CH_2CH(OAc)CH_2$-*o*-C_6H_5	157.8-161.8 decomp.	84
H	H	$CH_2C_6H_4$-*p*-OCH_3	227.5-229.5 decomp.	76
H	CH_3	$CH_2CH{=}CH_2$	101-106	86
H	H	$(CH_2)_2OH$	74.5-76.5	52
H	H	$CH_2C_6H_4$-*p*-CH_3	241-243	55
H	CH_3	CH_3	191-194	49
H	H	$(CH_2)_2C_6H_4$-*p*-OH	94-95	50
H	H	$CH_2CH(OH)C_6H_5$	104-106	72
CH_3	CH_3	CH_3	103-107	83
H	H	$(CH_2)_3OH$	136 decomp.	41
H	H	$CH_2C_6H_4$-*m*-OCH_3	203-207 decomp.	16
H	H	$CH_2C_6H_4$-*o*-CH_2OH	110-112	32
H	H	$CH_2CH(OH)CH_2$-OC_6H_5	86-87	87

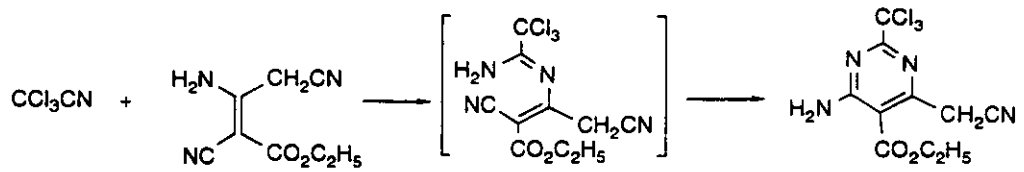
TCAN reacted with *o*-phenylenediamine (**6**) to afford 2-aminobenzimidazole (**8**) *via* intermediacy of **7**.[25]



1 **6** **7** **8**

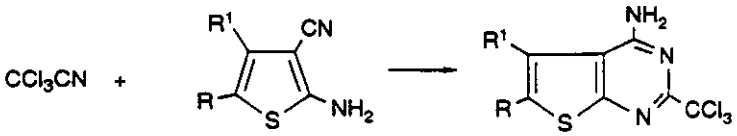
4.1.2. Interaction with ß-Enaminonitriles

3-Amino-2-ethoxycarbonylpentendinitrile (**9**) reacted with TCAN in dry toluene in the presence of sodium metal to give 2-trichloromethylpyrimidine derivative (**11**) *via* intermediacy of **10**.[26]



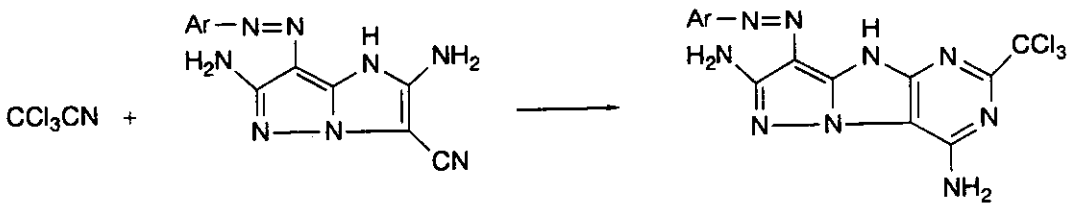
1 9 10 11

The thiophene derivative (**12**) reacted with TCAN to give the thieno[2,3-*d*]pyrimidine derivative (**13**).[27,28]



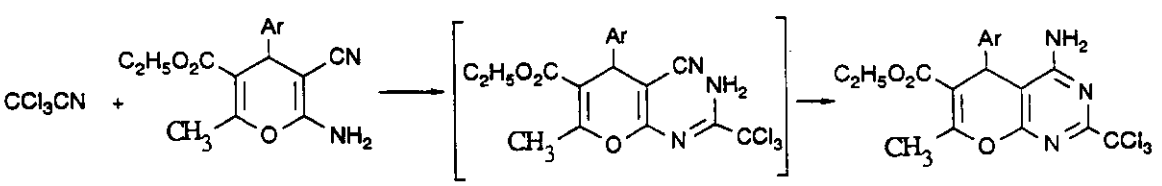
1 12 13

6-Arylazo-2,5-diamino-1*H*-imidazo[1,2-*b*]pyrazole-3-carbonitriles (**14**) reacted with TCAN in DMF containing $(C_2H_5)_3N$ to give the corresponding 2-trichloromethylpyrazolo[5`,1`:1,2]imidazo[4,5-*b*]-pyrimidine-4,7-diamine derivatives (**15**).[29,30]



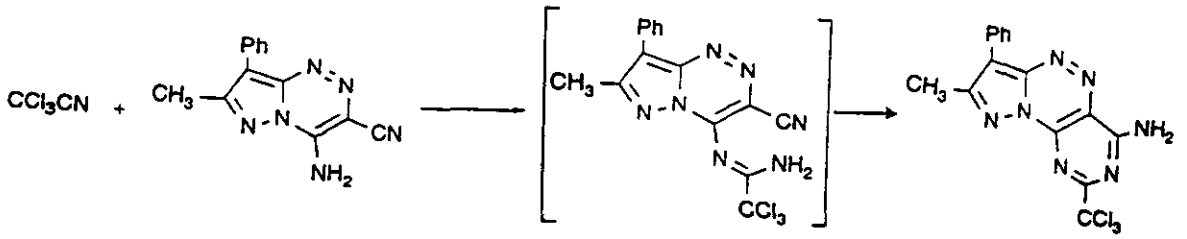
1 14 15

The pyrano[2,3-*d*]pyrimidines (**18**) could be obtained *via* the reaction of ethyl 2-amino-3-cyanopyran-5-carboxylates (**16**) with TCAN. The reaction proceeded *via* intermediacy of the adduct (**17**).[31,32]



1 16 17 18

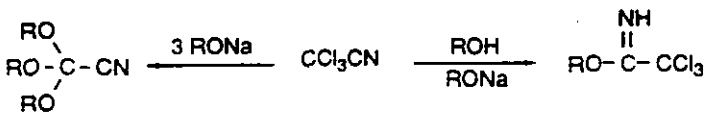
The ß-enaminonitrile moiety in **19** reacted with TCAN to yield the adduct (**20**) which subsequently cyclized into **21**.[33]



1 **19** **20** **21**

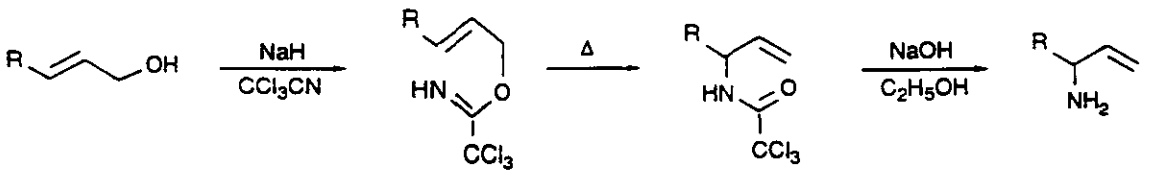
4.1.3. Interaction with Alcohols and Phenols

TCAN reacted with equimolar amount of ROH/RONa to give the corresponding alkyl trichloroacetimidates (**22**). Reaction of TCAN with three-fold molar equivalent of RONa gave the corresponding trialkoxyacetonitriles (**23**).[34-37]



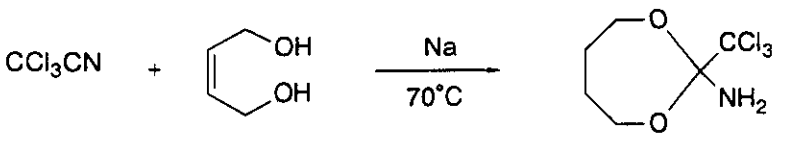
23 **1** **22**

Primary allylic amines (**27**) were obtained in good yields by Overman rearrangement[38,39] and by others.[40-45] Thus, treating the allyl alcohols (**24**) with NaH and TCAN gave the corresponding allylic trichloroacetimidates (**25**). The latter under thermal rearrangement followed by hydrolysis afforded **27**.[46]



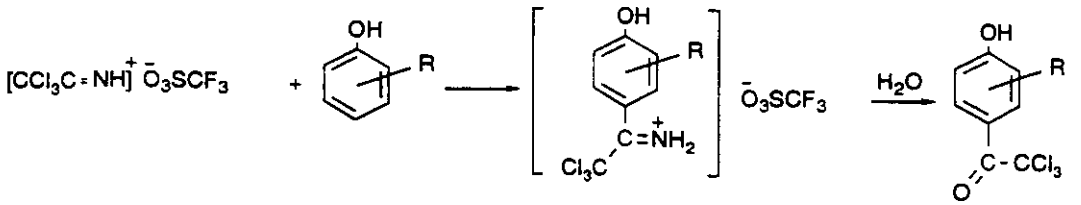
24 **25** **26** **27**

2-Amino-2-trichloromethyl-1,3,4,7-tetrahydro-1,3-dioxepin (**29**) was obtained *via* the reaction of TCAN with but-2-en-1,4-diol (**28**).[47]



1 **28** **29**

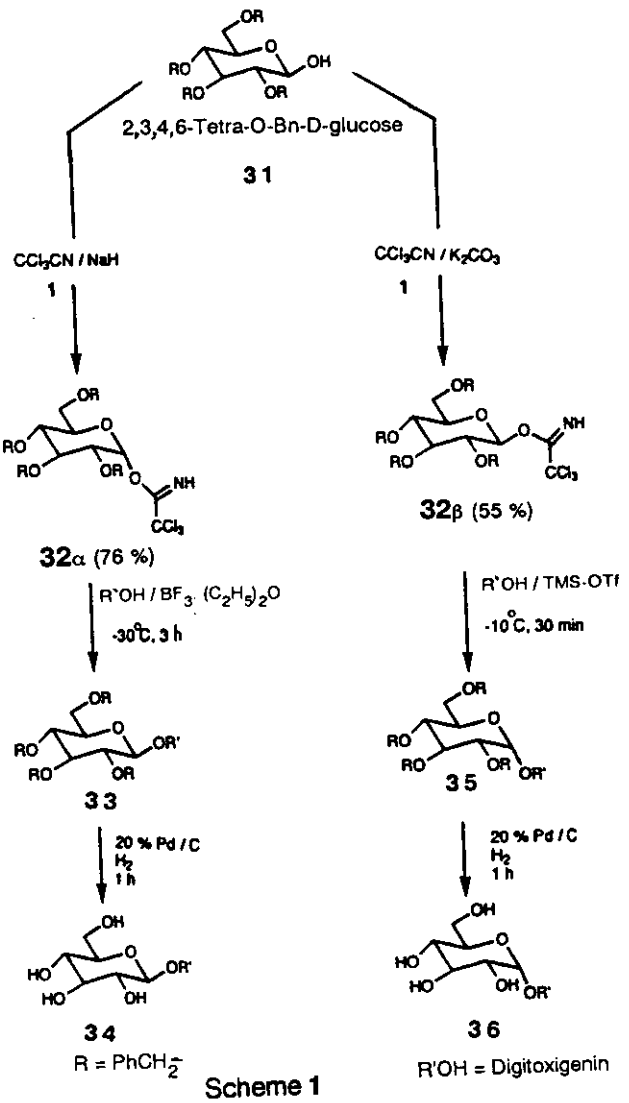
TCAN, in the presence of trifluromethanesulphonic acid has been found by Booth *et al.*[48] to react with mono-, di-, and tri- substituted phenols at room temperature to give ketones (**30**) after hydrolysis of the reaction mixture.



30

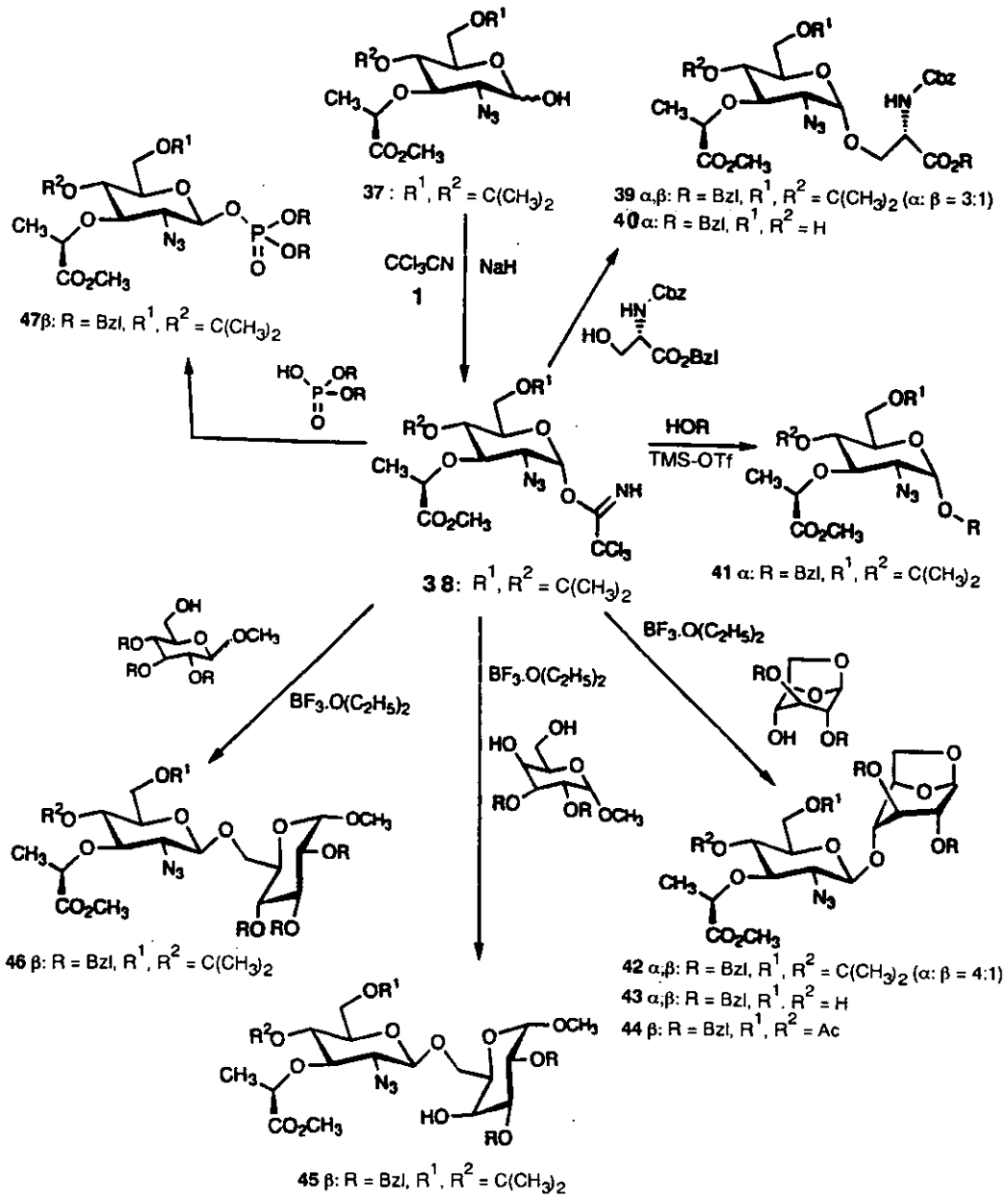
4.1.4. Interaction with Carbohydrates

TCAN has been used in the synthesis of several cardiac glycosides.[49-54] The outline in Scheme 1 illustrates an efficient route to digitoxigenin α-D-, ß-D-glycosides (**34**) and (**36**), respectively.[55]



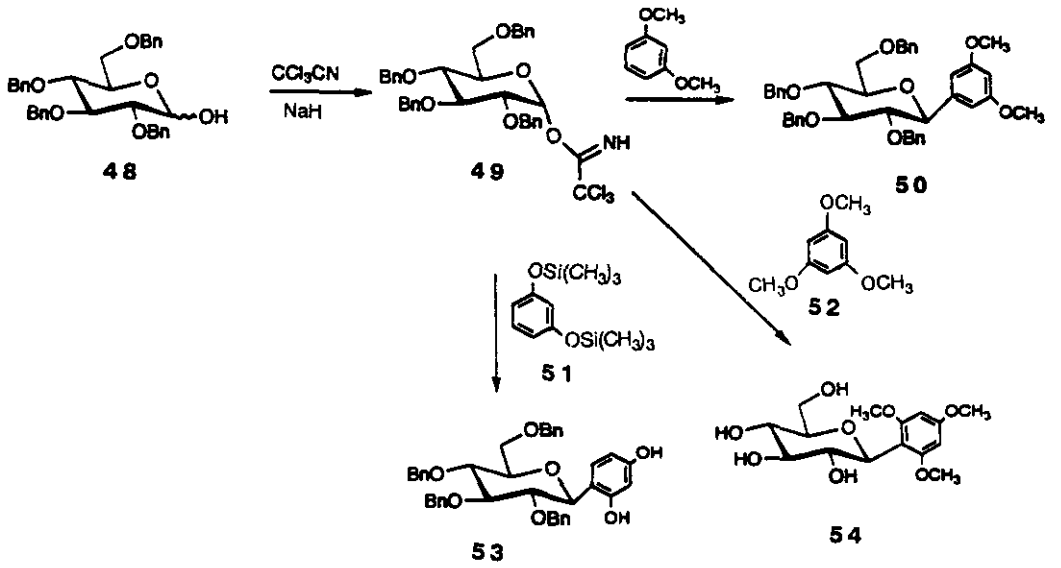
Scheme 1

Schmidt *et al.*[56-61] have observed that 2-azido-2-deoxy-D-glucose derivative (**37**) reacted with TCAN in the presence of NaH to give the imidate (**38**). The latter provided a good muramic acid glycosyl donor. With various glycosyl acceptors depending on the catalyst and the reaction conditions either ß-or α-glycosides and disaccharides (**39-47**) were obtained selectively (Scheme 2).[62]



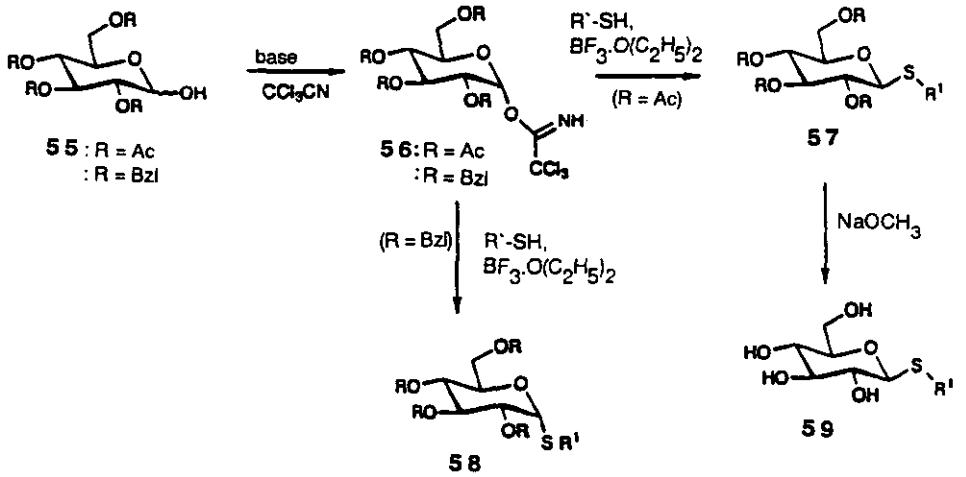
Scheme 2

Schmidt *et al.*[63-66] have also observed that from *O*-glycosyl trichloroacetimidates (**49**) and activated benzene derivatives, *C*-arylglycosides (**50, 53, 54**) were obtained by mild Lewis acid catalysis (Scheme 3). Similarly, an important intermediates for glycosphingolipids were prepared by Ogawa *et al.*[67-69]



Scheme 3

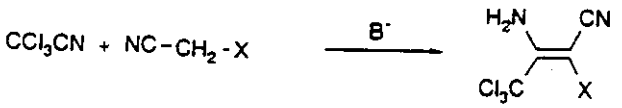
The reactive acetyl-protected *O*-(α-D-glycopyranosyl)trichloroacetimidates (**56**) reacted with sulphur nucleophiles in the presence of trifluoroborane ether as catalyst to yield 1-thio-ß-D-glucopyranosides with inversion of the configuration. The corresponding benzyl-protected α-trichloroacetimidate afforded, with retention of the configuration, alkyl 1-thio-α-D-glucopyranosides (Scheme 4).[70-74]



Scheme 4

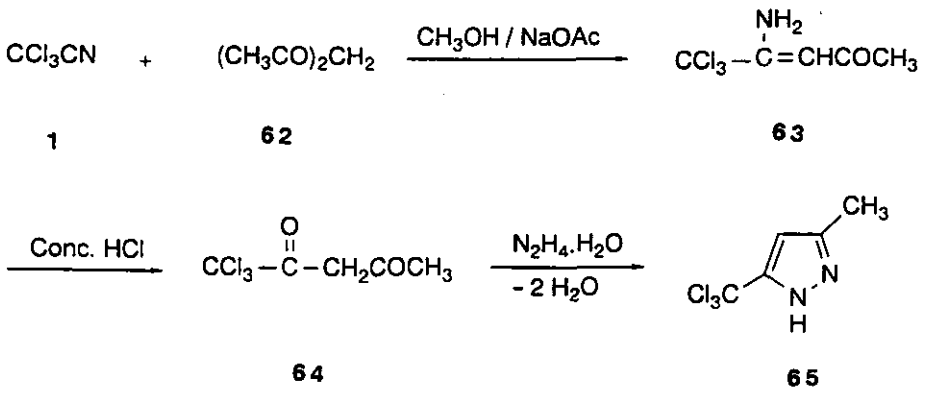
4.2. Interaction with Active Methylenes and Methyl Ketones

The condensation of active methylenecarbonitriles (**60**) (X = CN, CO_2R; COPh) with TCAN in presence of a base as catalyst afforded the corresponding 3-amino-2-substituted 4,4,4-trichlorocarbonitriles (**61**) in good yields after only short reaction time.[75-81]



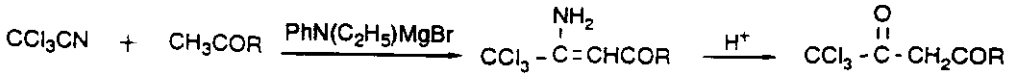
1 **60** **61**

The adduct (**63**), obtained from the condensation of acetylacetone (**62**) with TCAN, was converted to 1,3-diketone (**64**), from which substituted pyrazole derivative (**65**) was obtained by the action of hydrazine hydrate.[82]



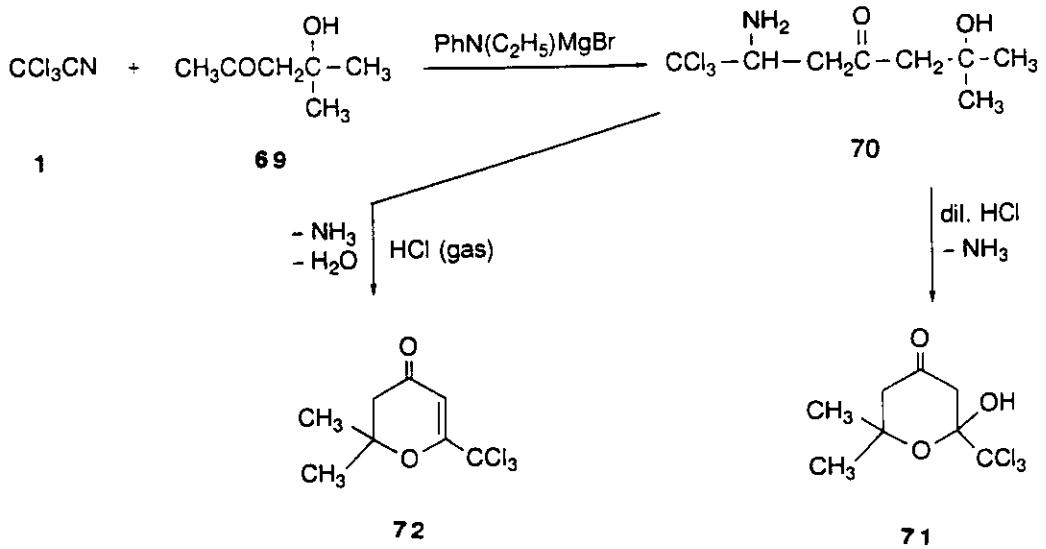
1 **62** **63** **64** **65**

Treatment of TCAN with methyl ketones (**66**) in the presence of $PhN(C_2H_5)MgBr$ afforded aminovinyl ketones (**67**). The latter underwent acid hydrolysis to give ß-diketones (**68**).[83]

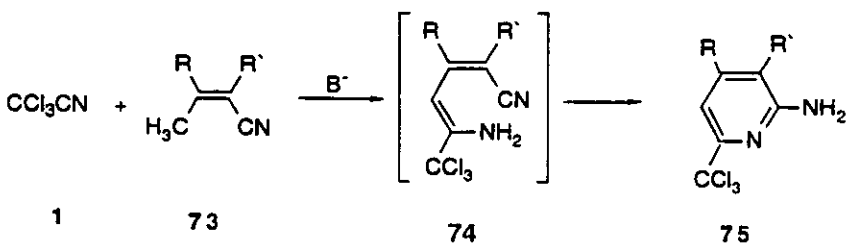


1 **66** **67** **68**

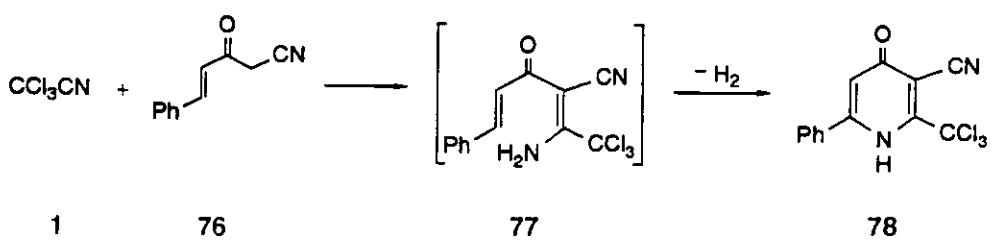
Depending on the reaction conditions, (**69**) reacted with TCAN to yield either the tetrahydro-γ-pyrone derivative (**71**) or the dihydro-γ-pyrone derivative (**72**). The reaction proceeded *via* intermediacy of the adduct (**70**).[84]



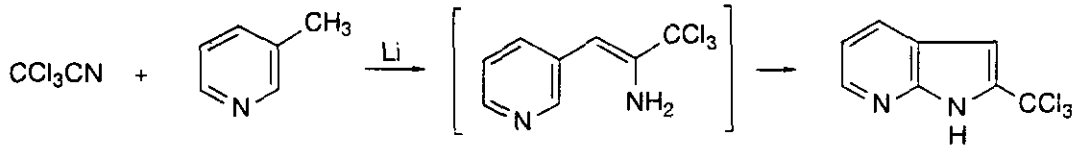
A general method for the synthesis of a wide variety of trichloromethylpyridines (**75**) from nitriles (**73**) was reported by Gewald and Hain.[85] The reaction involves addition of the methyl group in **73** to TCAN and subsequent cyclization of the adduct (**74**).



Cinnamoylacetonitrile (**76**) reacted with TCAN to give the 2-trichloromethylpyridone (**78**).[86]



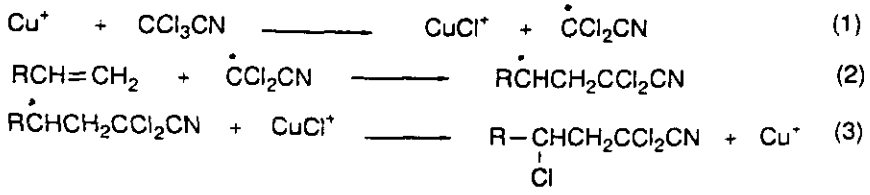
The carbanion obtained by the action of lithium metal on 3-picoline (**79**) reacted with TCAN to give 2-trichloromethyl-[1*H*]-pyrrolo[2,3-*b*]pyridine (**81**) *via* intermediacy of (**80**).[87]



1 79 80 81

4.3. Addition to Polar Multiple Bonds

Addition of TCAN to olefins were reported in floods of papers.[88-99] An outline of the reaction mechanism is shown below.[88]

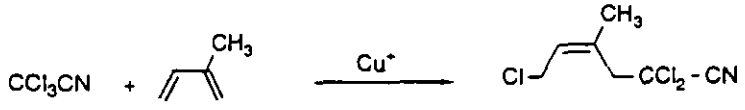


(1)

(2)

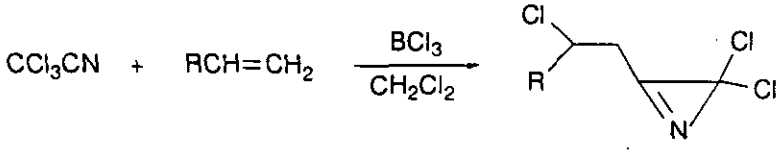
(3)

For example, the addition of TCAN to substituted 1,3-butadiene (82) gave the halogenated alkene (83).[88]



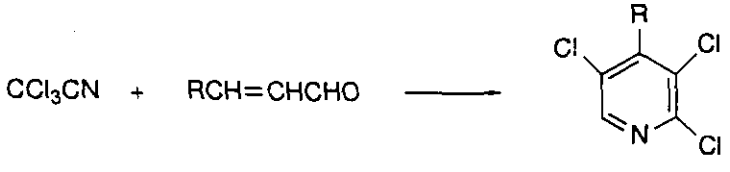
1 82 83

The reaction of olefins (84) with TCAN in presence of BCl_3 at -87°C, under argon atmosphere, gave the corresponding azirine derivatives (85).[100]



1 84 85

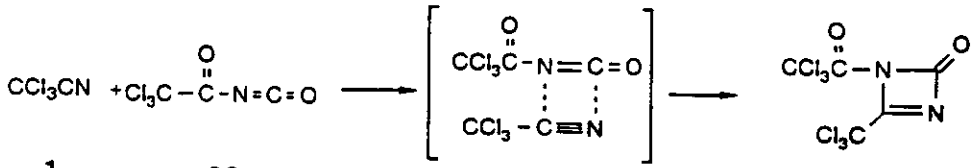
The pyridine derivatives (87) were obtained when TCAN was heated with α,ß-unsaturated aldehydes (86) in presence of CuCl or Cu.[101]



1 86 87

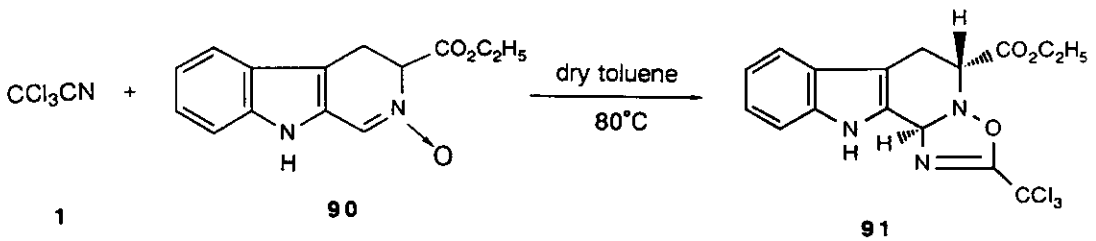
4.4. Cycloaddition Reactions

The important anticancer 1-trichloroacetyl-2-trichloromethyl-1,3-diaza-2-cyclobuten-4-one (**89**) was prepared by the [2+2] cycloaddition reaction of trichloroacetyl isocyanate (**88**) with TCAN.[102]

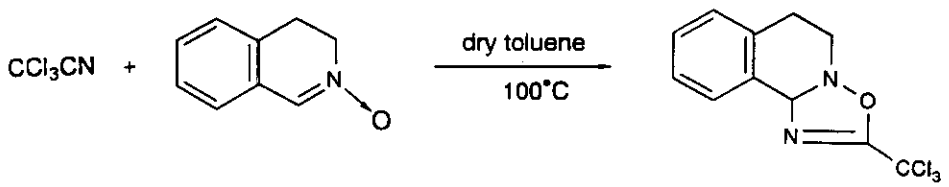


1 **88** **89**

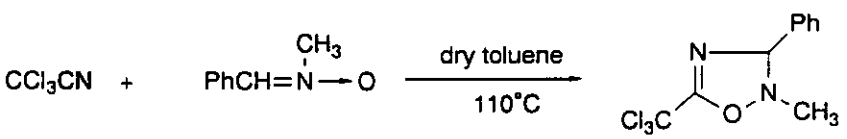
1,2,4-Oxadiazole derivatives (**91**), (**93**) and (**95**) were synthesized in quantitative yields by 1,3-dipolar cycloaddition of TCAN with the nitrile oxide compounds (**90**), (**92**) and (**94**), respectively.[103]



1 **90** **91**

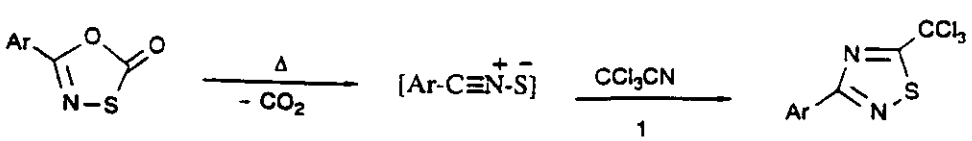


1 **92** **93**



1 **94** **95**

Nitrile sulfides (**97**), generated by thermal decarboxylation of oxathiazolones (**96**), underwent 1,3-diploar cycloaddition with TCAN to yield trichloromethylthiadiazoles (**98**).[104] Similarly, but independently, the same reaction was reported by Krayushkin *et al.* [105]



96 **97** **98**

5. UTILITY IN HETEROCYCLIC SYNTHESIS

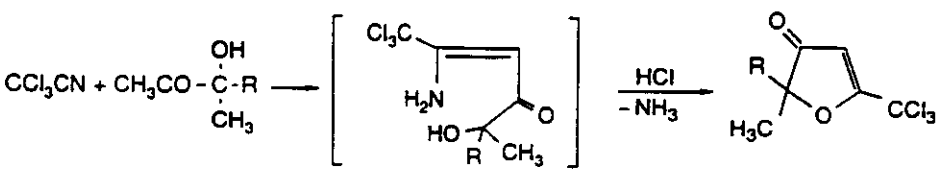
Reaction of TCAN with bidentate reagents yields heterocyclic and condensed systems. These reactions proceed under mild conditions in the presence of base or by heating in an inert solvent. These cyclocondensations are also used for the synthesis of nucleosides containing condensed heterocycles.[106,107] Among the products of these reactions, biologically active compounds were found which included some herbicides[108] and antitumour agents.[109] Thus, we will discuss the utility of TCAN in heterocyclic synthesis in separate section. Some of heterocyclic systems have been previously discused and will not be discussed further.

5.1. Synthesis of Five-Membered Rings

5.1.1. With One Heteroatom

5.1.1.1. Furans

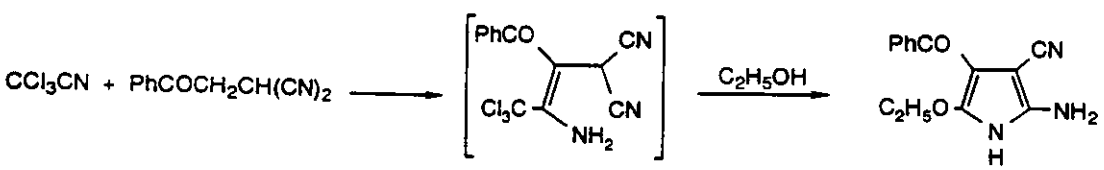
The condensation of TCAN with alkylacetyl carbinols (**99**) in the presence of $PhN(C_2H_5)MgBr$ gave the adducts (**100**). The latter were cyclized by HCl to give furanones (**101**) in about 93% yields.[110]



1 **99** **100** **101**

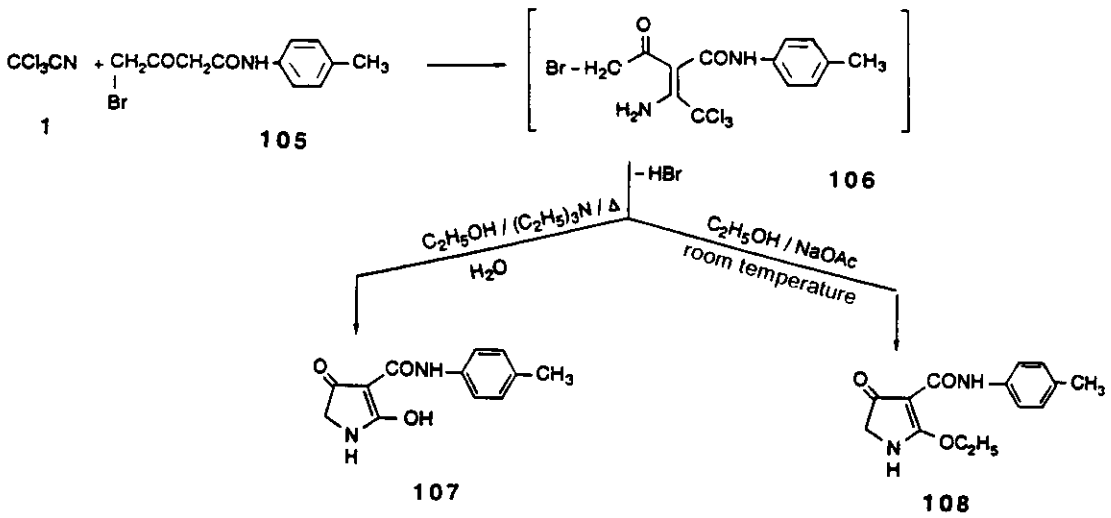
4.2.1.2. Pyrroles

The pyrrole derivative (**104**) could be prepared by the cycloaddition reaction of TCAN with phenacylmalononitrile (**102**).[111]

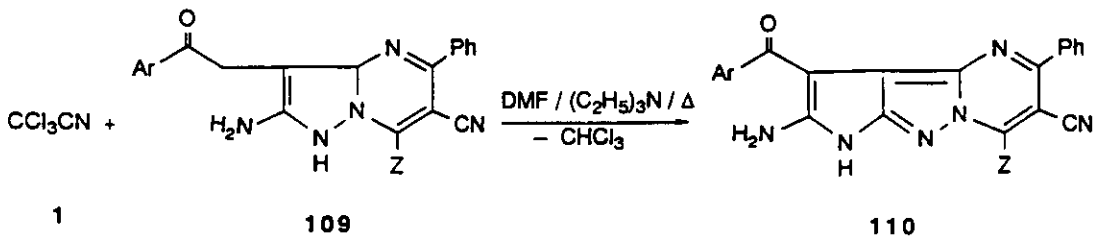


1 **102** **103** **104**

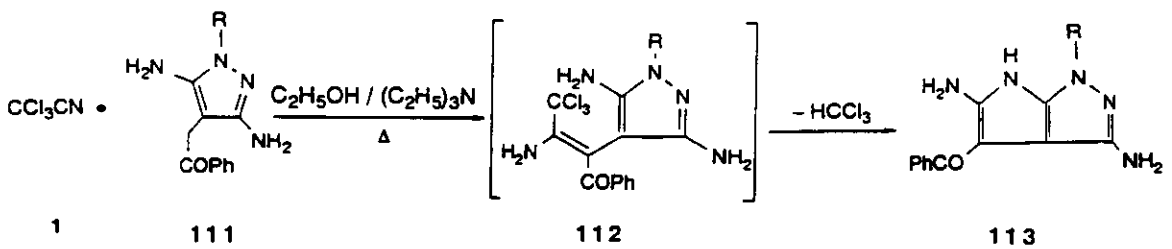
Depending on the reaction conditions, γ-bromoacetylaceto-*p*-toluidide (**105**) reacted with TCAN to yield either the hydroxypyrrole derivative (**107**) or the ethoxypyrrole derivative (**108**). The reaction proceeded *via* intermediacy of the adduct (**106**).[112]



The fused pyrrolo[2`,3`:3,4]pyrazolo[1,5-*a*]pyrimidine derivatives (**110**) could be prepared *via* the Michael addition of the active methylene protons in **109** to the activated CN function in TCAN followed by elimination of chloroform.[113]



Similarly, 1,6-dihydropyrrolo[2,3-*c*]pyrazole derivatives (**113**) could be prepared starting from the pyrazole derivatives (**111**). The reaction was believed to proceed *via* intermediacy of the adduct (**112**).[114]

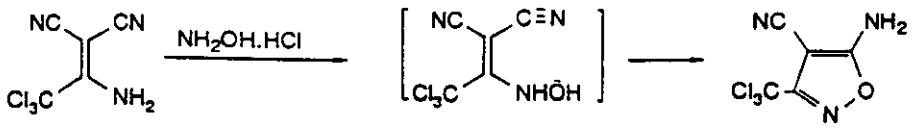


5.1.2. With Two Heteroatoms

5.1.2.1. Oxazoles

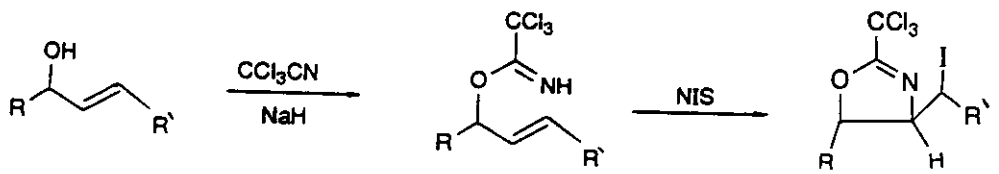
3-Amino-4-trichloro-2-cyanocrotonitrile (**114**), prepared from the addition of TCAN to malononitrile, reacted with hydroxylamine to yield the 1,2-oxazole derivative (**116**). This compound was assumed to be

formed by the addition of the hydroxylamine to the α,ß-unsaturated linkage followed by cyclization.[115,116]



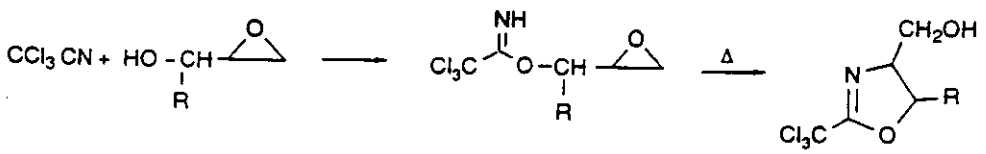
114 115 116

A general method for the synthesis of a wide variety of 1,3-oxazoles from allylic alcohols by using TCAN as a key precourser was reported by Cardillo *et al.* [117,118] The reaction involved addition of the hydroxyl group in the allylic alcohols (**117**) to the cyano group in TCAN to yield the allylic imidates (**118**). The latter were treated with *N*-iodosuccinimide to give the 1,3-oxazoles (**119**).



117 118 119

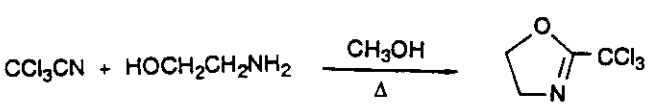
Condensation of TCAN with epoxypropanols (**120**) in the presence of base gave the adducts 1-trichloroacetamidyloxy-2,3-epoxypropanes (**121**) in 70% yields. The latter underwent thermal intramolecular cylcization to afford the 1,3-oxazoles (**122**) in excellent yields.[119,120]



1 120 121 122

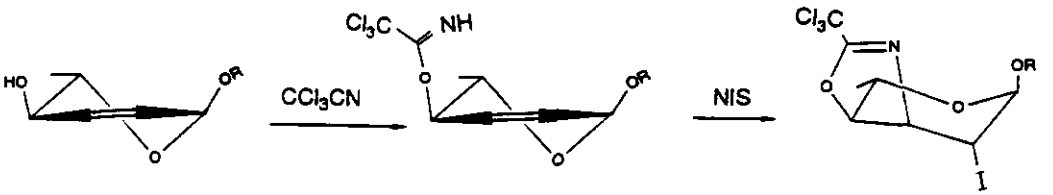
R = H, cyclohexyl

Reaction of ethanolamine (**123**) with TCAN afforded the corresponding 1,3-oxazoline (**124**) which proved to exert an antidotal activity for the defense of crops against the toxic action of nonselective herbicides.[121]



1 123 124

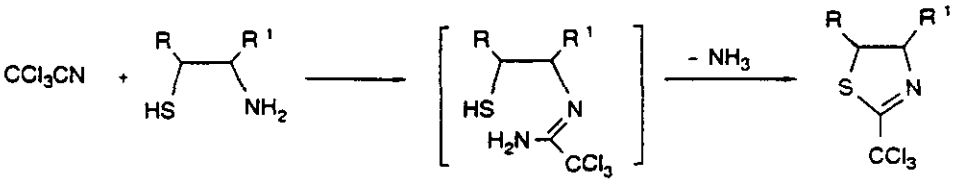
The reaction of methyl 2,3,6-trideoxy-α-L-threo-hex-2-enopyranosides (**125**) with TCAN afforded the imidates (**126**). The latter underwent iodonium ion-induced intramolecular cyclization to yield the corresponding condensed 1,3-oxazoles (**127**).[122]



125 **126** **127**

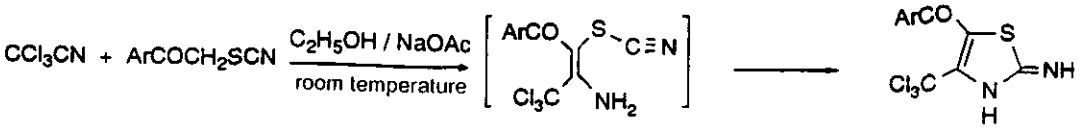
5.1.2.2. Thiazoles

An important antidotal active 1,3-thiazoline derivatives (**130**) were prepared by treating TCAN with **128** in refluxing methanol.[123]



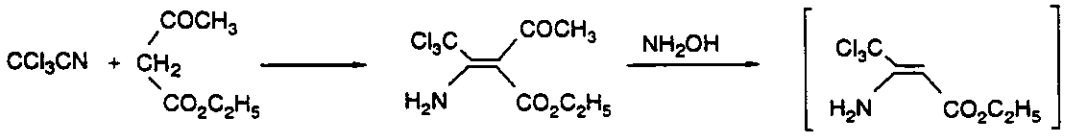
1 **128** **129** **130**

Treating TCAN with **131** in refluxing ethanolic-sodium acetate solution at room temperature afforded the 2-iminothiazoline derivatives (**133**) *via* intermediacy of **132**.[124]

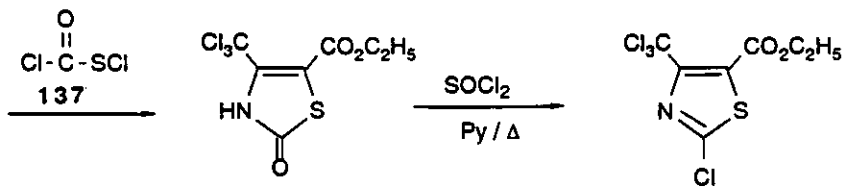


1 **131** **132** **133**

An important thiazole carboxylic acid derivative (**139**), used as protectant against herbicide damage, was obtained by treating TCAN with ethyl acetoacetate (**134**) which was deacetylated by NH_2OH to the intermediate (**136**), cyclocondensed with **137** to afford the thiazolone (**138**). The latter treated with thionyl chloride in pyridine solution to afford the desired thiazole (**139**).[125]



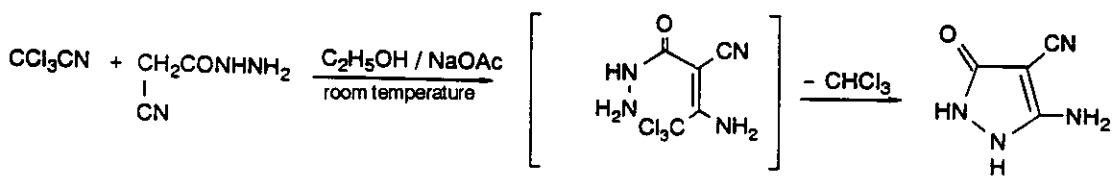
1 134 135 136



138 139

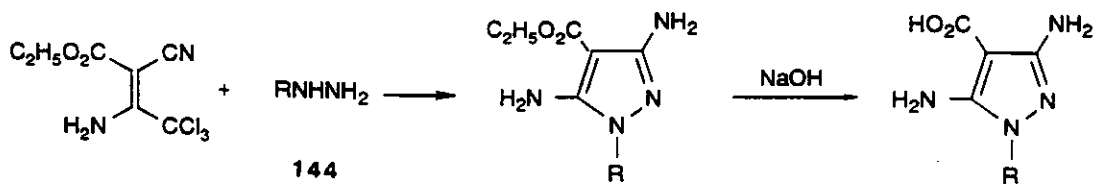
5.1.2.3. Pyrazoles

The addition of the active methylene moiety of cyanoacethydrazide (**140**) to the cyano group of TCAN afforded the acyclic intermediate (**141**). The latter cyclized with loss of $CHCl_3$ to give the pyrazolinone derivative (**142**).[112]



1 140 141 142

The important antibacterial pyrazolecarboxylic acid derivatives (**146**) were prepared by the cyclization of the TCAN adduct (**143**) with hydrazines (**144**). The latter were hydrolyzed by aqueous sodium hydroxide at room temperature to give **146**.[126]



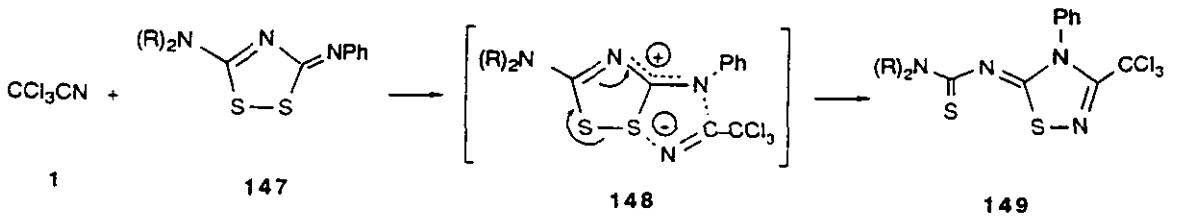
143 144 145 146

R =CH_3, $HOCH_2CH_2$

5.1.3. With Three Heteroatoms

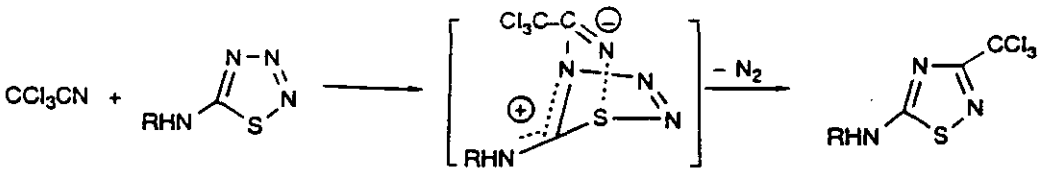
5.1.3.1. Thiadiazoles

A series of 4,5-dihydro-5-thiocarbamylimino-4-phenyl-1,2,4-thiadizolines (**149**) was prepared by ring-opening cycloaddition of some imino-1,2,4-dithiazoles (**147**). The reaction proceeded *via* the intermediacy of the dipolar intermediates (**148**).[127]



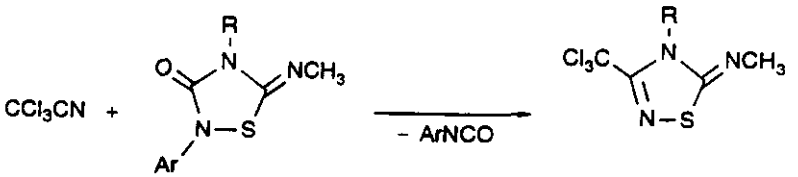
1 **147** **148** **149**

Amino-1,2,3,4-thiatriazoles (**150**) were effectively converted to 1,2,4-thiadiazoles (**152**) when treated with TCAN *via* the cycloadduct polar intermediates (**151**).[128]



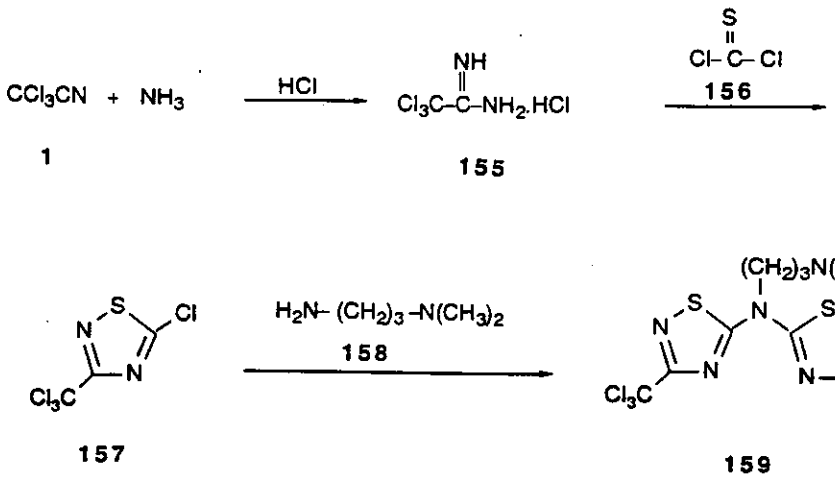
1 **150** **151** **152**

Similarly, iminothiadiazolines (**154**) were prepared by using 5-imino-1,2,4-thiadiazolidin-3-ones (**153**) as masked 1,3-dipoles starting materials.[129,130]



1 **153** **154**

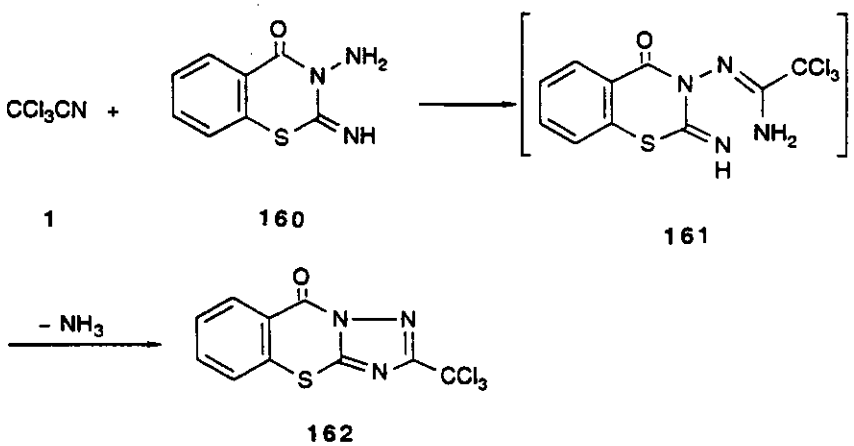
The antimalarial agent (**159**) was synthesized via the reaction of TCAN with liquid ammonia to give trichloroacetamidine (**155**). The latter was treated with thiophosgene (**156**) to give 5-chloro-3-trichloromethyl-1,2,4-thiadiazole (**157**) which after condensation with *N,N*-dimethyl-1,3-propanediamine (**158**) yields the desired antimalarial drug (**159**).[131,132]



1 155 157 159

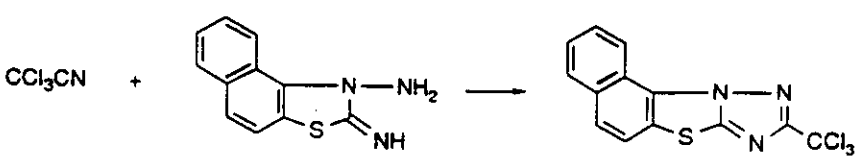
5.1.3.2. Triazoles

Heating 3-amino-3,4-dihydro-2-imino-2*H*-1,3-benzothiazine-4-one (**160**) with TCAN afforded triazolo-[5,1-*b*][1,3]benzothiazine (**162**). The reaction was initiated by the condensation of the amino group in **160** with TCAN to give the adduct (**161**) followed by cyclization *via* ammonia elimination.[133]



1 160 161 162

Similarly, the naphthothiazolotriazole derivative (**164**) was prepared from the reaction of 2-iminothiazole (**163**) with TCAN.[134]

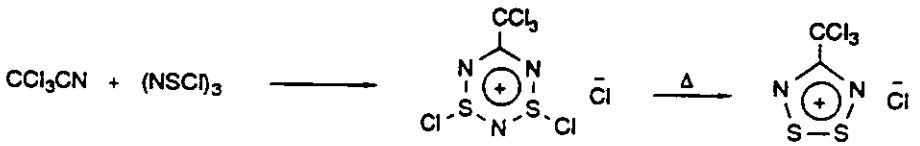


1 163 164

5.1.4. With Four Heteroatoms

5.1.4.1. Dithiadiazoles

The reaction of TCAN with $(NSCl)_3$ at 23°C produces good yield of dithiatriazine (**165**). The latter was heated to give the dithiadiazolium chloride (**166**).[135,136]



1 **165** **166**

5.1.4.2. Tetrazoles

The tetrazole derivatives (**168**) were prepared in 90% yields *via* cycloaddition reaction of alkyl azides (**167**) to TCAN at high temperature.[137-140]

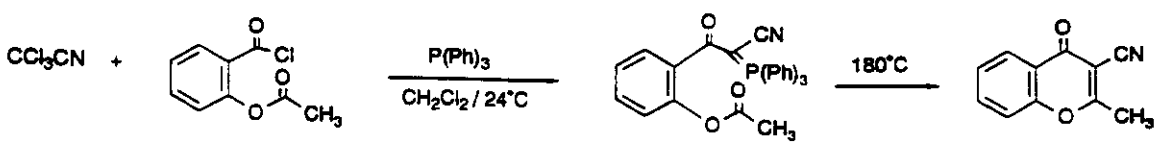
1 **167** **168**

5.2. Synthesis of Six-Membered Rings

5.2.1. With One Heteroatom

5.2.1.1. Flavones

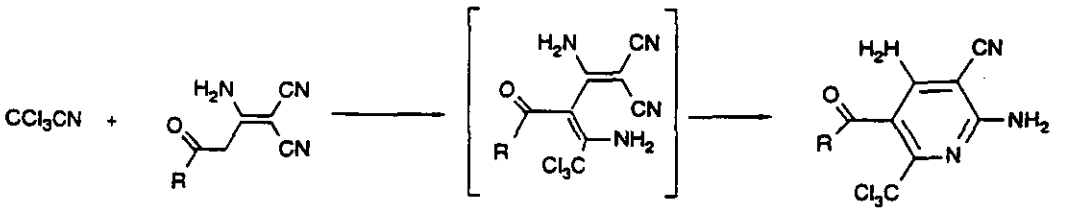
2-Acetoxybenzoyl chloride (**169**) reacted with $CCl_3CN/P(Ph)_3$ in CH_2Cl_2 at 24°C to give 48% of 3-(2-acetoxyphenyl)-2-triphenylphosphorylidene-3-oxopropionitrile (**170**) which was cyclized on heating at 180°C in 1,2-dichlorobenzene to afford 2-methyl-3-cyanoflavone (**171**) in 65% yield.[141]



1 **169** **170** **171**

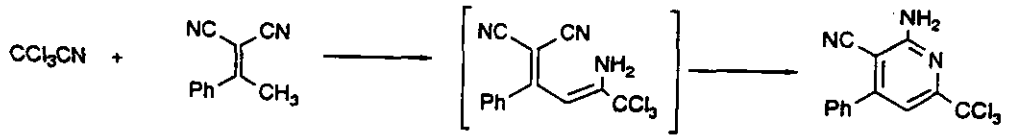
5.2.1.2. Pyridines

Cyclocondensation of **172** with TCAN gave the pyridines (**174**) *via* intermediacy of the adduct (**173**).[142,143]



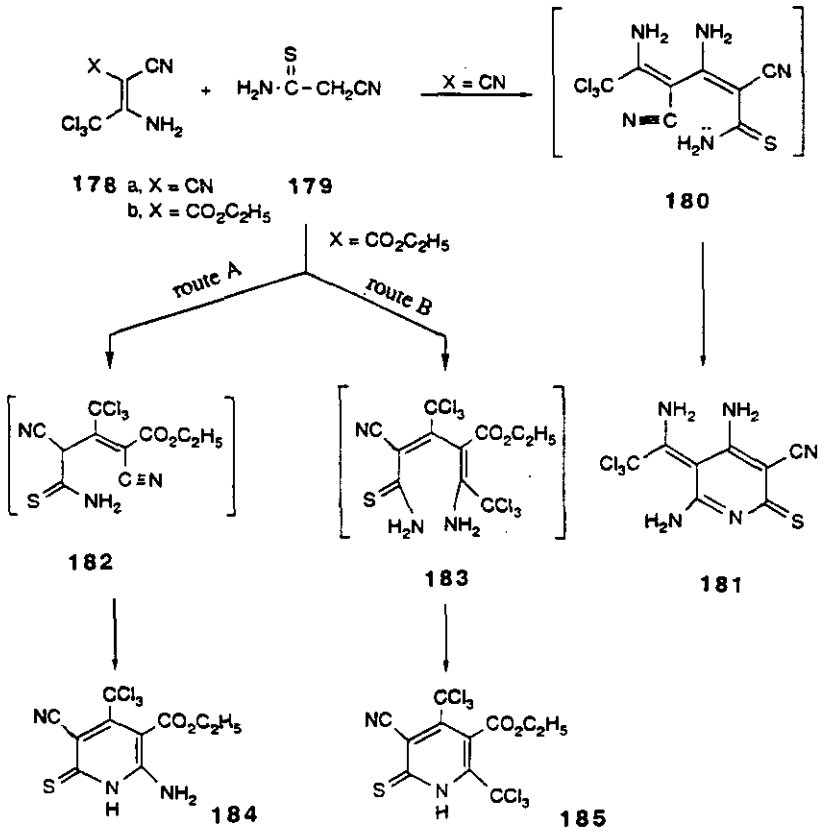
1 172 173 174

The activated methyl group in **175** reacted with TCAN to yield the 2-aminopyridine (**177**) *via* intermediacy of the adduct (**176**).[144]



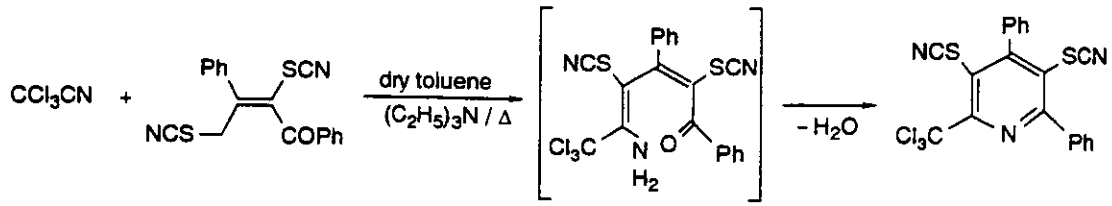
1 175 176 177

ß-Enaminonitrile (**178a**) (X = CN), prepared from the reaction of TCAN with the appropriate active methylene compound, reacted with cyanothioacetamide (**179**) to yield the adduct (**180**) that cyclizes to **181**. Compound (**178b**) (X = $CO_2C_2H_5$) reacted with **179** to yield a mixture of **184** and **185**. Compounds (**182**) and (**183**) are assumed to be intermediates for the formation of these products.[145]



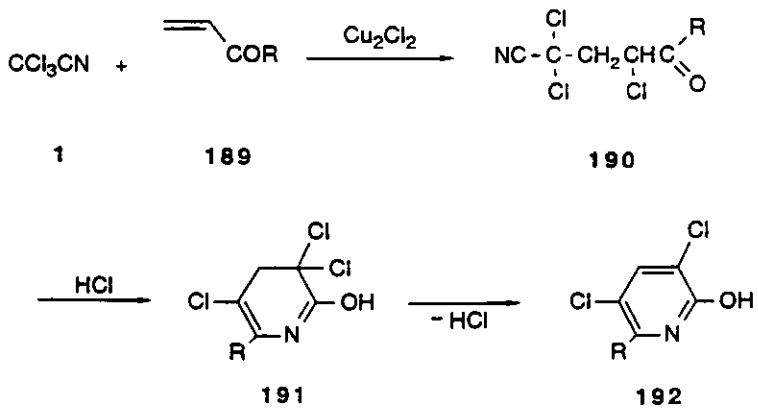
178 a, X = CN; b, X = $CO_2C_2H_5$ 179 180 182 183 181 184 185

The pyridine derivative (**188**) was effectively prepared when phenacyl thiocyanate dimer (**186**) was treated with TCAN.[111]



1 **186** **187** **188**

The reaction of olefins (**189**) with TCAN in the presence of Cu_2Cl_2 gave **190** which cyclized in Bu_2O containing HCl to give the pyridinols (**191**). Dehydrochlorination of **191** gave 3,5-dichloro-2-pyridinols (**192**).[146-148]

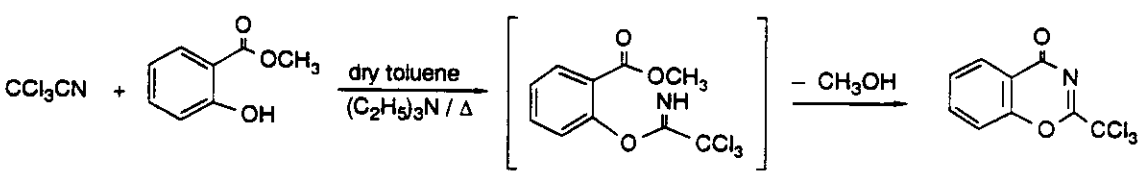


1 **189** **190** **191** **192**

5.2.2. With Two Heteroatoms

5.2.2.1. Oxozines

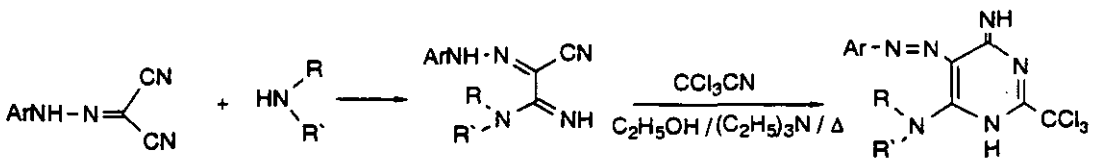
Methyl salicylate (**193**) reacted with TCAN to give the intermediate adduct (**194**) which subsequently cyclized *via* loss of methanol to yield the benzoxazine (**195**).[25]



1 **193** **194** **195**

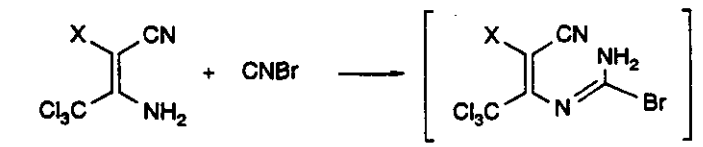
5.2.2.2. Pyrimidines

Arylhydrazomalononitriles (**196**) reacted with secondary amines to give the acetamidines (**197**), which in turn reacted with TCAN to yield the pyrimidines (**198**).[149]



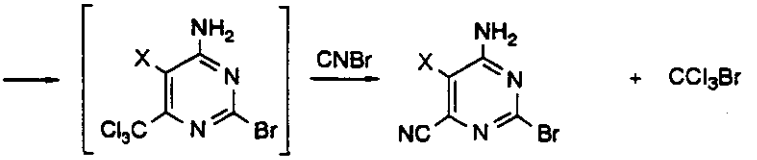
196 **197** **198**

ß-Enaminonitriles such as **178a-c**, prepared from the reaction of TCAN with the appropriate active methylene compound, yielded 2-bromopyrimidines (**202**) when treated wtih cyanogen bromide (**199**). Compounds (**202**) were assumed to be formed *via* the addition of the amino function in **178** to the cyano group in BrCN to yield the adduct (**200**) which readily cyclized into **201**. The latter then underwent nucleophilic displacement of the trichloromethyl moiety by the CN group to give **202**.[150]



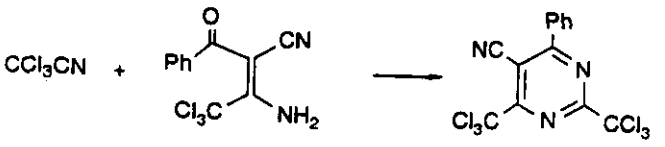
178 a, X = CN
b, X = $CO_2C_2H_5$
c, X = COPh

199 **200**



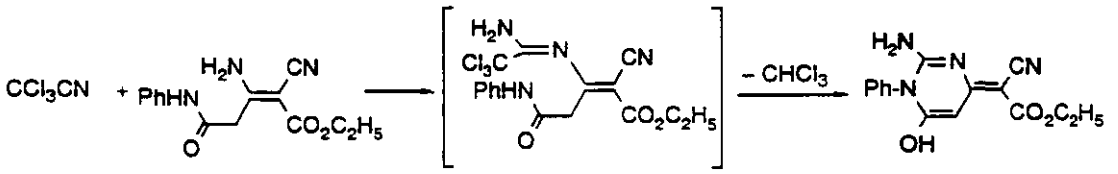
201 **202**

Elnagdi *et al.*[151] reported the preparation of pyrimidine (**203**) by condensing TCAN with the enaminonitrile (**178c**).



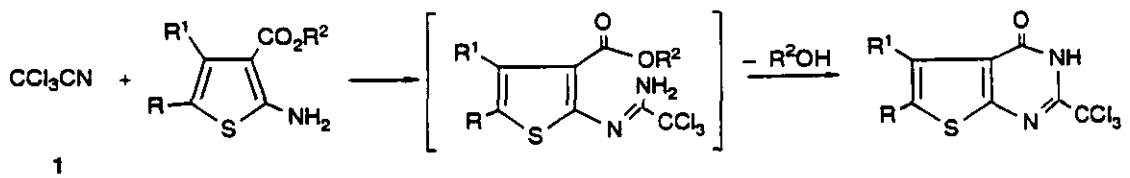
1 **178c** **203**

Similarly, the amide derivative (**204**) reacted with TCAN to give the adduct (**205**) which spontenously cyclized into **206** *via* loss of chloroform.[143]



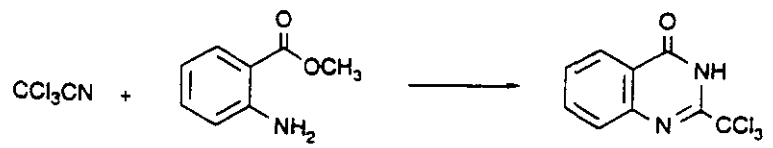
1 **204** **205** **206**

The antiallergy agents thieno[2,3-*d*]pyrimidines (**209**) were synthesized *via* the reaction of thiophenes (**207**) with TCAN to yield the adduct (**208**) which cyclized readily to give the final isolable products (**209**).[152,153]



1 **207** **208** **209**

Methyl anthranilate (**210**) reacted with TCAN in dry toluene in the presence of $(C_2H_5)_3N$ to yield the *quinoxalinone* (**211**) *in good yield.*[25]

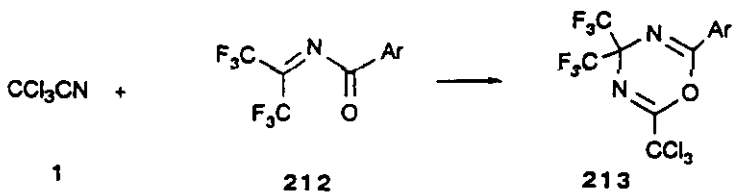


1 **210** **211**

5.2.3. With Three Heteroatoms

5.2.3.1. Oxadiazines

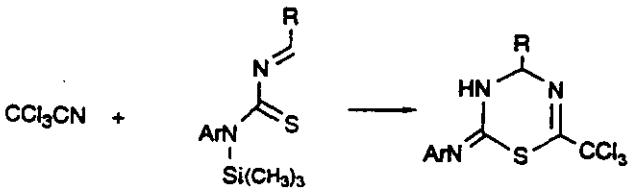
Burger *et al.*[154] have observed that TCAN behaves as electron-deficient dienophile in cycloaddition reactions. The [4+2] cycloaddition of **212** with the cyano group of TCAN yielded the cycloadduct (**213**).[154]



1 **212** **213**

5.2.3.2. Thiadiazines

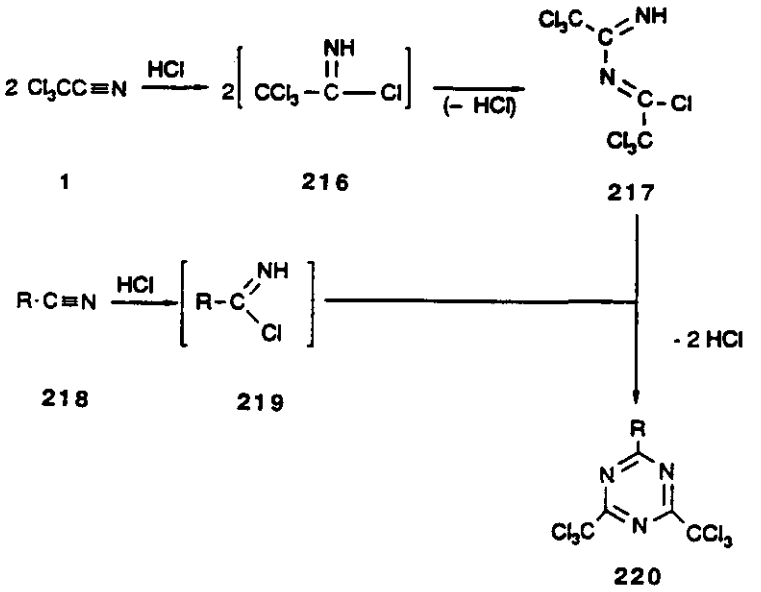
An efficient one-pot synthesis of 3,4-dihydro-1,3,5-thiadiazines (**215**) has been achieved *via* [4+2] cycloaddition of 1-thia-3-azadienes (**214**) with TCAN.[155]



1 **214** **215**

5.2.3.3. Triazines

Syntheses of the light-sensitive composition bis(halomethyl)triazines (**220**) were reported in floods of patents[156-164] and papers[165-175] *via* the reaction of TCAN with aryl, alkyl nitriles or even itself **218**. (Table 2). An outline of the reaction mechanism is shown below.



1 **216** **217**

218 **219** **220**

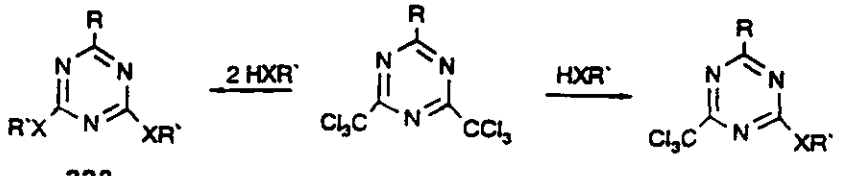
Table 2. Cotrimerization of CCl_3CN with some nitriles.[170]

R	Yield (%)	mp °C	R	Yield (%)	mp °C
CH_3	95	96-97	2-Naphthyl	78	210-212
C_6H_5	94	97-98	C_2H_5	92	34-36

Table 2. Cont'd.

R	Yield (%)	mp °C	R	Yield (%)	mp °C
2-ClC_6H_4	91	120-122	*n*-C_3H_7	93	136-138
3-ClC_6H_4	93	125-127	*i*-C_3H_7	87	170-175
4-ClC_6H_4	92	158-159	*n*-C_4H_9	90	157-159
2,4-$Cl_2C_6H_3$	88	143-145	*i*-C_4H_9	82	154-156
3,4-$Cl_2C_6H_3$	90	139-140	*s*-C_4H_9	81	142-146
2,4,5-$Cl_3C_6H_2$	85	153-155	*t*-C_4H_9	56	154-157
4-BrC_6H_4	92	161-163	*n*-C_5H_{11}	95	175-177
4-$CH_3C_6H_4$	95	122-123	*n*-C_9H_{19}	78	192-194
3-$NO_2C_6H_4$	74	103-104	*n*-$C_{17}H_{35}$	92	210-215
4-$CH_3OC_6H_4$	90	144-145	CH_2ClCH_2	69	65-67
1-Naphthyl	83	216-218	CH_2ClCCl_2	87	47-48

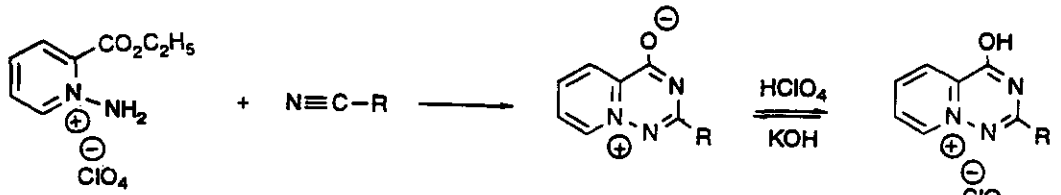
The trichloromethyl moiety in **220** showed high reactivity as leaving group with nucleophilic reagents. Treating triazines (**220**) with amines, phenols or carbanions afforded mono or disubstituted derivatives, depending on the reaction conditions.[176,177]



222 **220** **221**

X = NH, O, S, CHR"

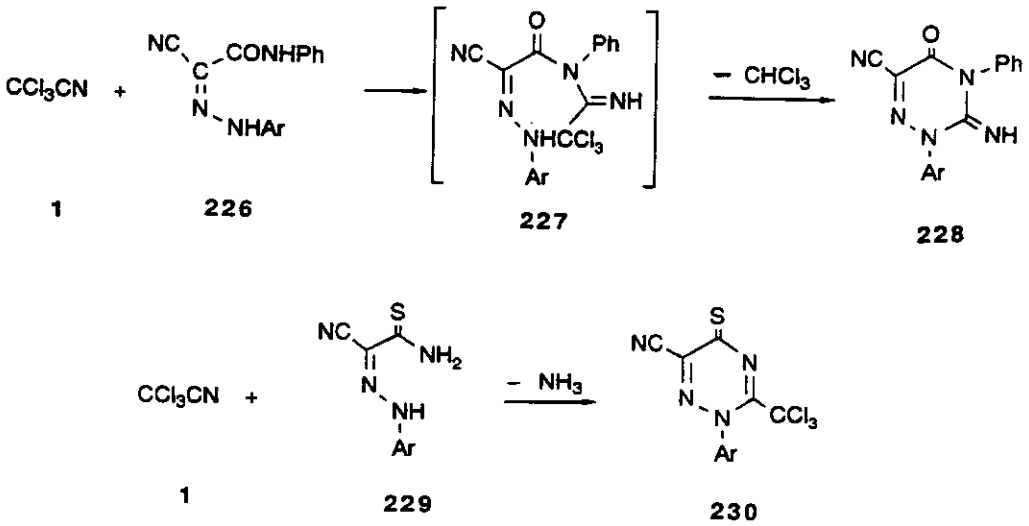
A general synthetic route for pyrido[2,1-*f*]-*as*-triazines such as **225** starting from ethyl picolinate *N*-ammonium perchlorate (**223**) with alkyl or aryl cyanide was reported by Batori *et al.*[178]



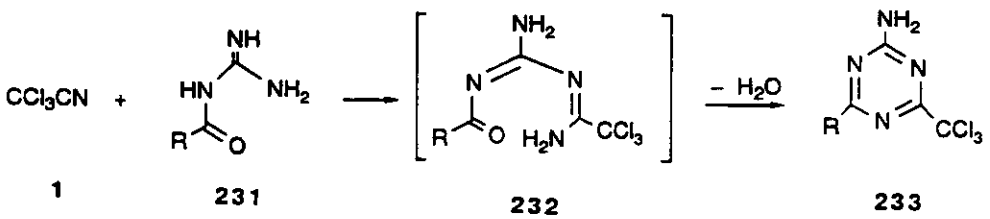
223 **218** **224** **225**

R = CCl_3, aryl, alkyl

The reaction of arylhydrazones (**226**) with TCAN in the presence of piperidine afforded 1,2,4-triazines (**228**) *via* the intermediate (**227**).[179] In a similar manner, TCAN reacted with the hydrazones (**229**) to afford high yields of the triazines (**230**).[180]



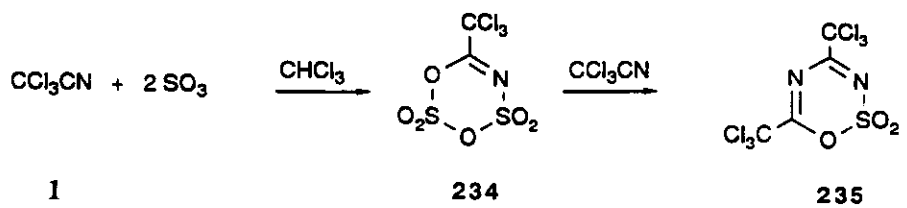
Kelarev *et al.*[175] reported the preparation of *s*-triazines (**233**) by condensing TCAN with *N*-carbonylguanidines (**231**).



5.2.4. With Four Heteroatoms

5.2.4.1. Dioxadithiazines and Oxathiadiazines

Dioxadithiazine tetraoxide (**234**) were obtained in high yields by treatment of TCAN with 2 moles SO_3 in $CHCl_3$. Treatment of **234** with another molecule of TCAN gave **235**.[181,182]



6. CONCLUSIONS AND PROSPECTS

There has been a rapid growth in the research activities in the chemistry of TCAN. This trend will continue in future not only because of the proporties of TCAN but also, because synthetic applications to the construction of unique and complex molecules are possible. Through this review, it is hoped that understanding of TCAN potential in the synthesis of glycosphingolipids, heterocycles, biologically active compounds and drugs will results. Recently, the floods of papers and patents concerning the biologically active trichloroacetamidines (**4**)[10-20, 49-54] and the light-sensitive composition triazines (**220**)[156-175] testify to its terrific potential. Finally, it is hoped that this review will fill what was an obvious gap by providing an overview of the subject.

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