

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 theoretical chemists. In this review, literature reports are organized to fill what was an obvious gap by providing an overview of the subject.

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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

Petri¹ in his patent was the first to prepare TCAN (1) by passing chlorine gas through chloroacetonitrile (2).

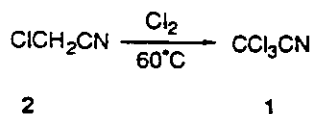
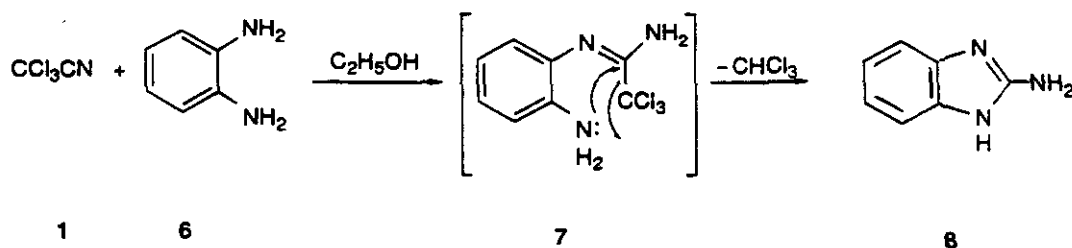


Table 1. Cont'd.

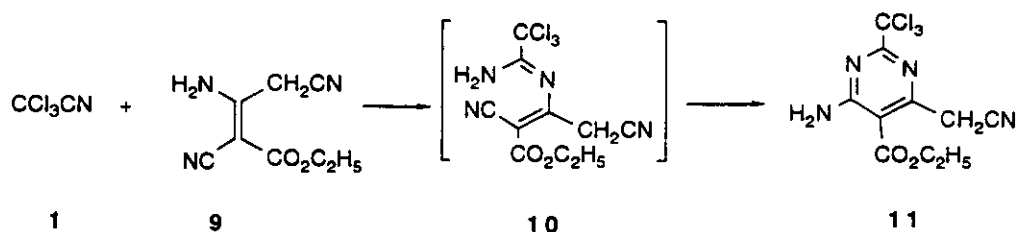
R	R ¹	R ²	mp °C	Yield (%)
H	H	H	210-220 decomp.	52
-CH ₂ CH ₂ CH ₂ -		H	113.8-116.8	60
H	H	CH ₂ CH=CH ₂	177.8-181.8 decomp.	85
CH ₃	H	CH ₂ CH=CH ₂	83-87 decomp.	47
H	H	CH ₂ C ₆ H ₄ - <i>o</i> -OCH ₃	242-245 decomp.	59
-CH ₂ CH ₂ -		H	85 decomp.	13
H	H	CH ₂ CH(OAc)CH ₂ - <i>o</i> -C ₆ H ₅	157.8-161.8 decomp.	84
H	H	CH ₂ C ₆ H ₄ - <i>p</i> -OCH ₃	227.5-229.5 decomp.	76
H	CH ₃	CH ₂ CH=CH ₂	101-106	86
H	H	(CH ₂) ₂ OH	74.5-76.5	52
H	H	CH ₂ C ₆ H ₄ - <i>p</i> -CH ₃	241-243	55
H	CH ₃	CH ₃	191-194	49
H	H	(CH ₂) ₂ C ₆ H ₄ - <i>p</i> -OH	94-95	50
H	H	CH ₂ CH(OH)C ₆ H ₅	104-106	72
CH ₃	CH ₃	CH ₃	103-107	83
H	H	(CH ₂) ₃ OH	136 decomp.	41
H	H	CH ₂ C ₆ H ₄ - <i>m</i> -OCH ₃	203-207 decomp.	16
H	H	CH ₂ C ₆ H ₄ - <i>o</i> -CH ₂ OH	110-112	32
H	H	CH ₂ CH(OH)CH ₂ -OC ₆ H ₅	86-87	87

TCAN reacted with *o*-phenylenediamine (6) to afford 2-aminobenzimidazole (8) via intermediacy of 7.²⁵

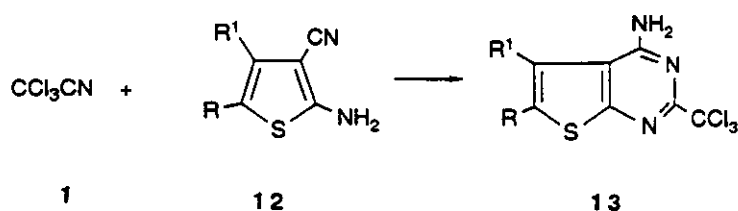


4.1.2. Interaction with β -Enaminonitriles

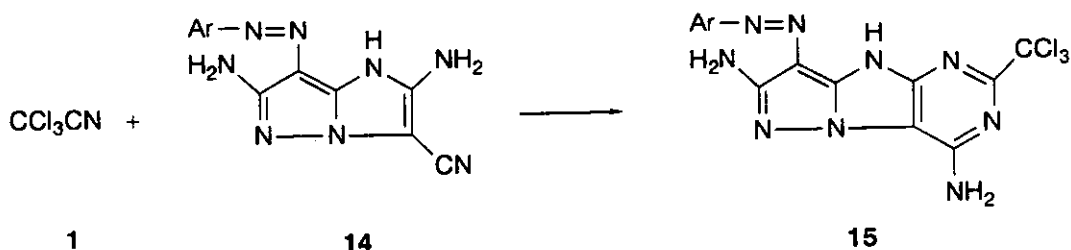
3-Amino-2-ethoxycarbonylpentendinitrile (9) reacted with TCAN in dry toluene in the presence of sodium metal to give 2-trichloromethylpyrimidine derivative (11) via intermediacy of 10.²⁶



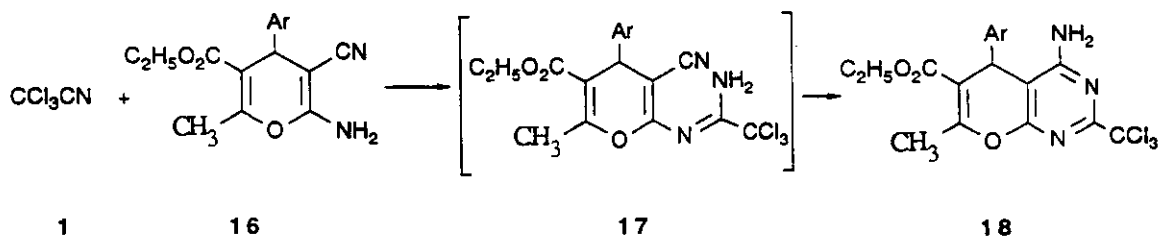
The thiophene derivative (12) reacted with TCAN to give the thieno[2,3-*d*]pyrimidine derivative (13).^{27,28}



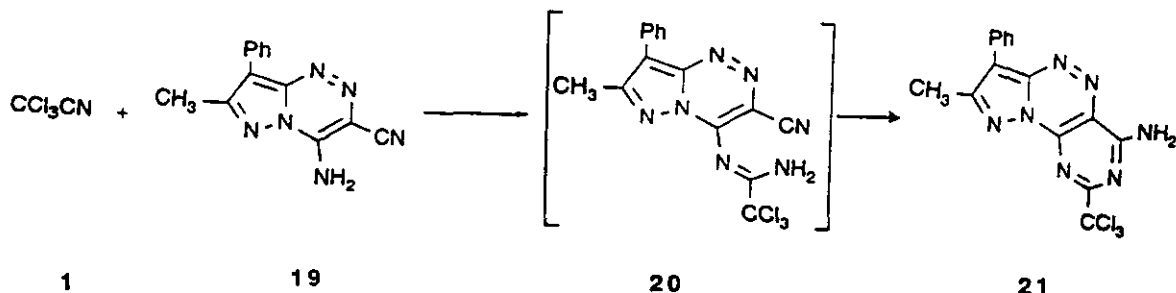
6-Arylazo-2,5-diamino-1*H*-imidazo[1,2-*b*]pyrazole-3-carbonitriles (14) reacted with TCAN in DMF containing $(\text{C}_2\text{H}_5)_3\text{N}$ to give the corresponding 2-trichloromethylpyrazolo[5',1':1,2]imidazo[4,5-*b*]pyrimidine-4,7-diamine derivatives (15).^{29,30}



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}

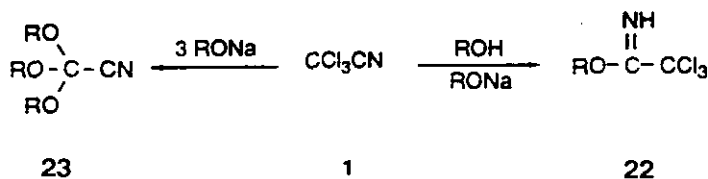


The β -enaminonitrile moiety in **19** reacted with TCAN to yield the adduct (**20**) which subsequently cyclized into **21**.³³

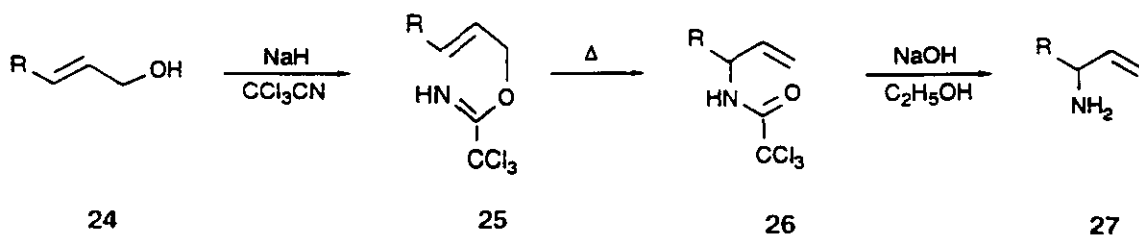


4.1.3. Interaction with Alcohols and Phenols

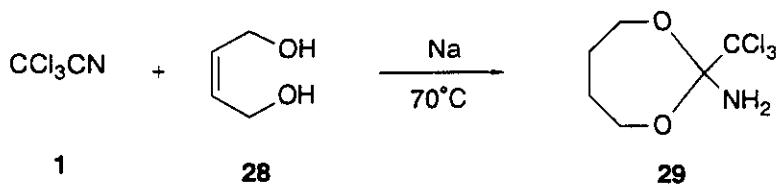
TCAN reacted with equimolar amount of ROH/RONa to give the corresponding alkyl trichloroacetimidates (**22**). Reaction of TCAN with three-fold molar equivalent of RONA gave the corresponding trialkoxyacetoneitriles (**23**).³⁴⁻³⁷



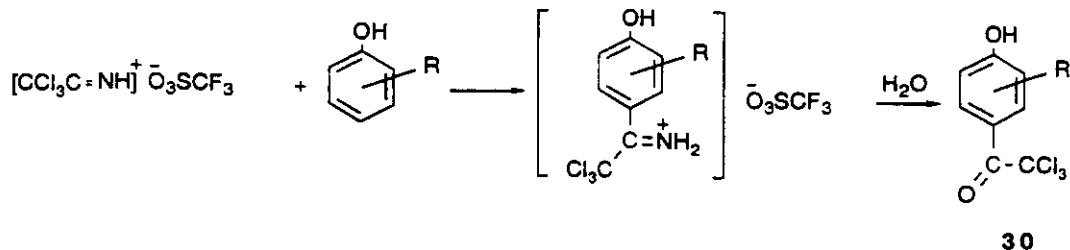
Primary allylic amines (**27**) were obtained in good yields by Overman rearrangement^{38,39} and by others.⁴⁰⁻⁴⁵ Thus, treating the allyl alcohols (**24**) with NaH and TCAN gave the corresponding allylic trichloroacetimidates (**25**). The latter under thermal rearrangement followed by hydrolysis afforded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



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

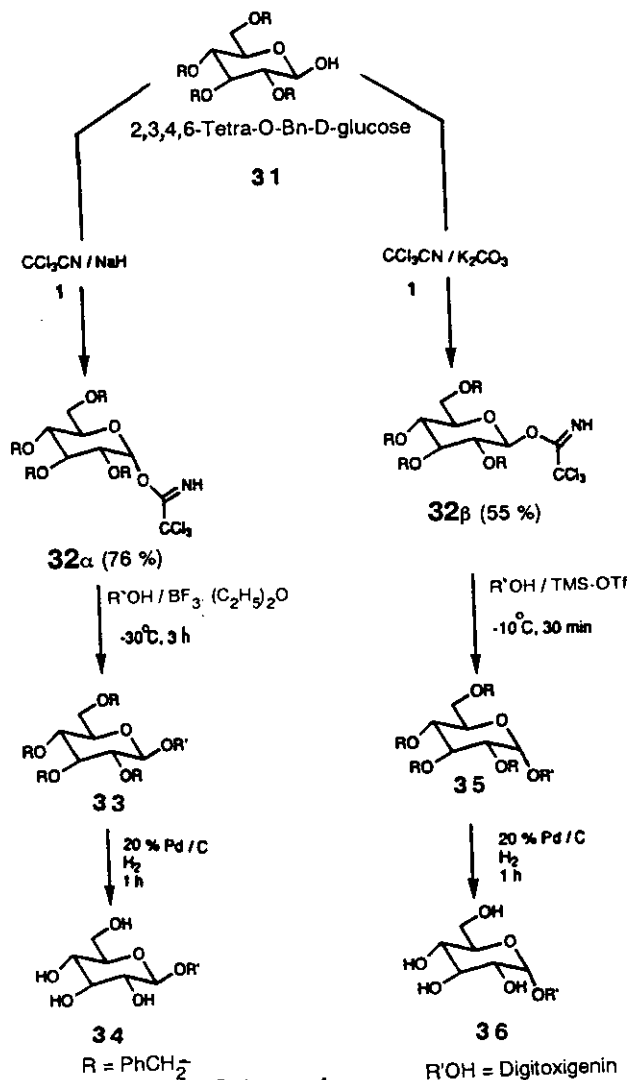


TCAN, in the presence of trifluoromethanesulphonic acid has been found by Booth *et al.*⁴⁸ to react with mono-, di-, and tri- substituted phenols at room temperature to give ketones (30) after hydrolysis of the reaction mixture.



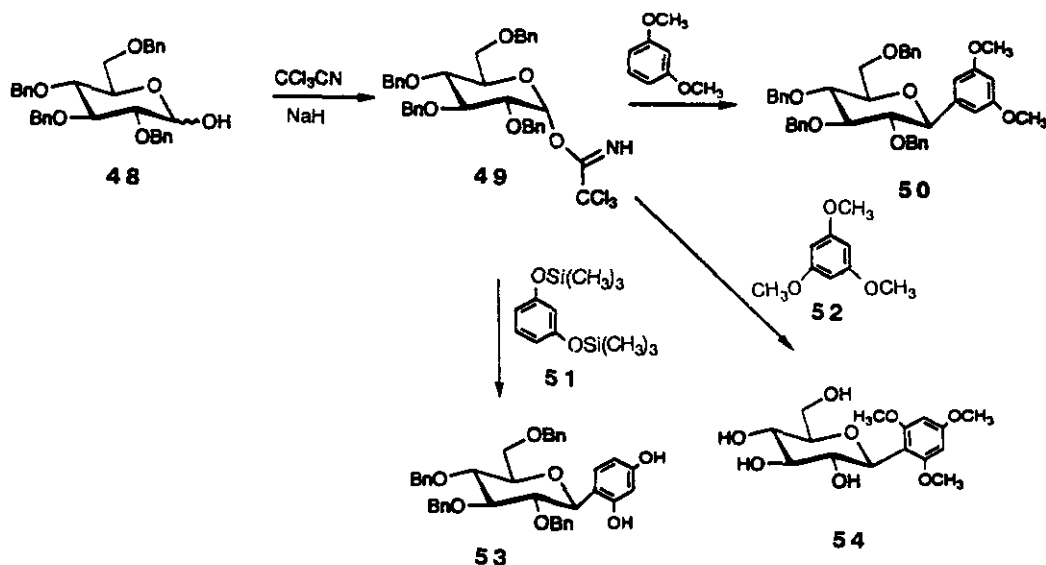
4.1.4. Interaction with Carbohydrates

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-, β -D-glycosides (34) and (36), respectively.⁵⁵



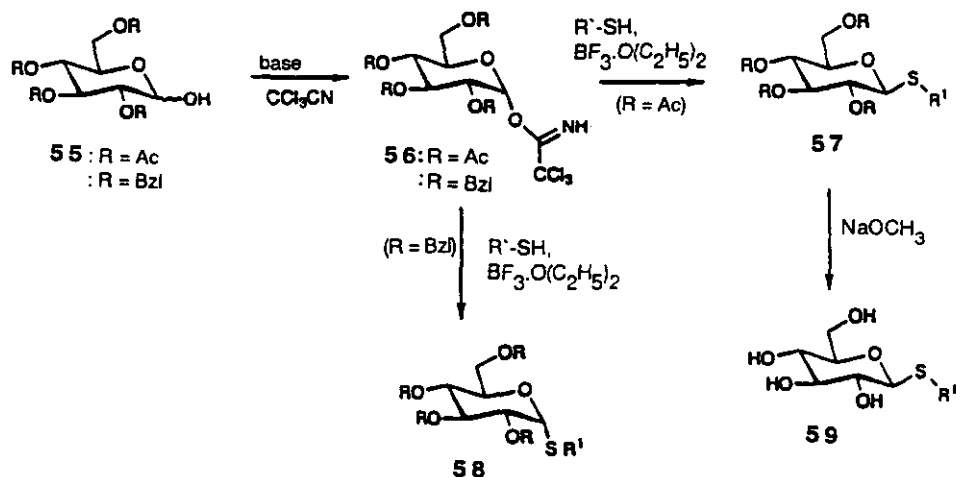
Scheme 1

Schmidt *et al.*⁶³⁻⁶⁶ have also observed that from *O*-glycosyl trichloroacetimidates (49) and activated benzene derivatives, *C*-aryl glycosides (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

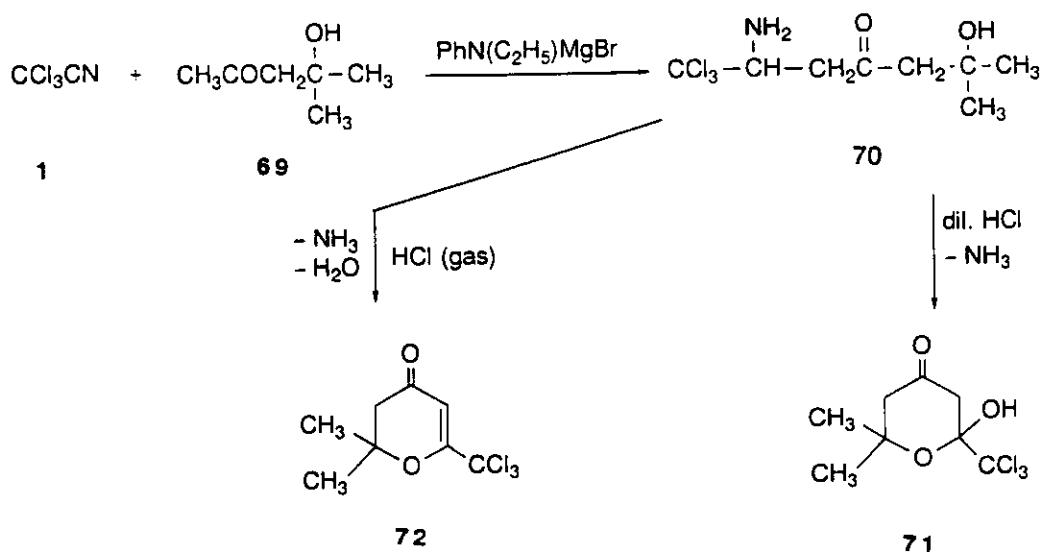


Scheme 3

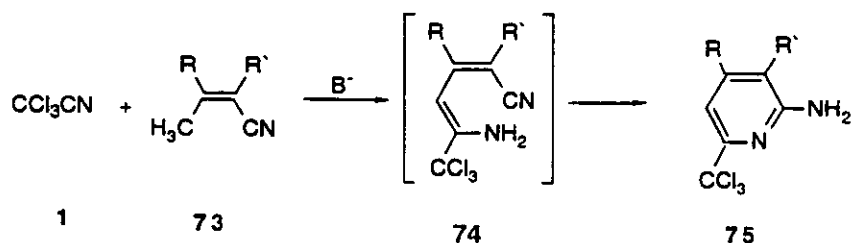
The reactive acetyl-protected *O*-(α -D-glycopyranosyl)trichloroacetimidates (56) reacted with sulphur nucleophiles in the presence of trifluoroborane ether as catalyst to yield 1-thio- β -D-glycopyranosides with inversion of the configuration. The corresponding benzyl-protected α -trichloroacetimidate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



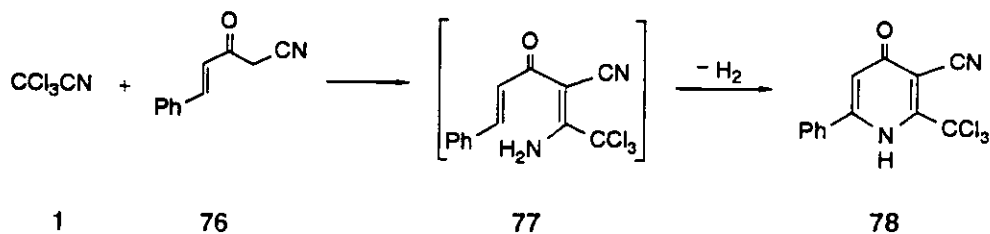
Scheme 4



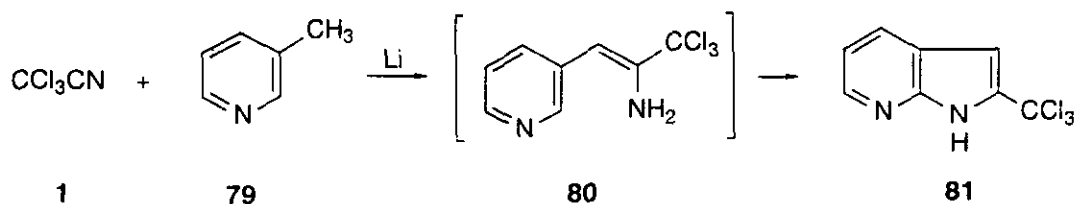
A general method for the synthesis of a wide variety of trichloromethylpyridines (**75**) from nitriles (**73**) was reported by Gewald and Hain.⁸⁵ The reaction involves addition of the methyl group in **73** to TCAN and subsequent cyclization of the adduct (**74**).



Cinnamylacetonitrile (**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-[1H]-pyrrolo[2,3-b]pyridine (**81**) via intermediacy of (**80**).⁸⁷

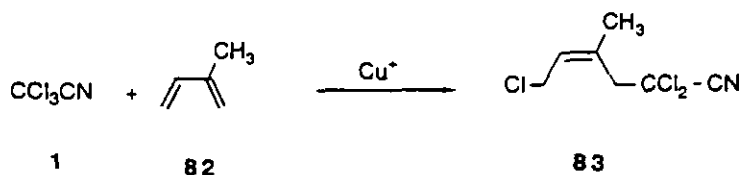


4.3. Addition to Polar Multiple Bonds

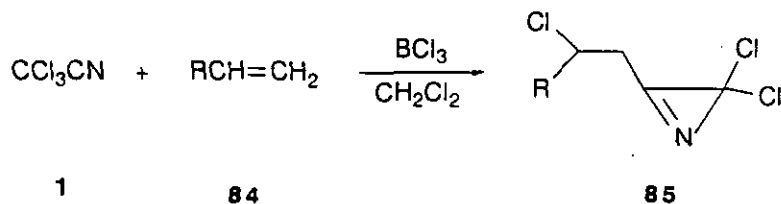
Addition of TCAN to olefins were reported in floods of papers.⁸⁸⁻⁹⁹ An outline of the reaction mechanism is shown below.⁸⁸



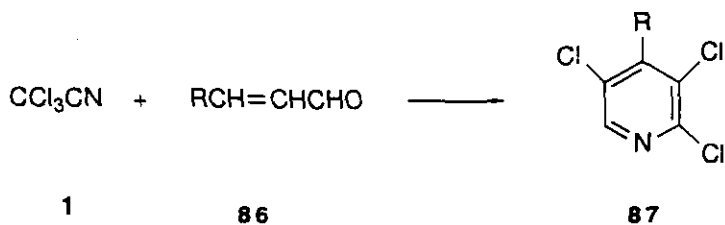
For example, the addition of TCAN to substituted 1,3-butadiene (**82**) gave the halogenated alkene (**83**).⁸⁸



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



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



5. UTILITY IN HETEROCYCLIC SYNTHESIS

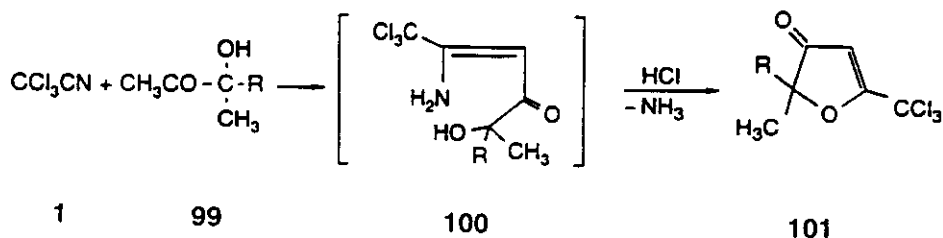
Reaction of TCAN with bidentate reagents yields heterocyclic and condensed systems. These reactions proceed under mild conditions in the presence of base or by heating in an inert solvent. These cyclocondensations are also used for the synthesis of nucleosides containing condensed heterocycles.^{106,107} Among the products of these reactions, biologically active compounds were found which included some herbicides¹⁰⁸ 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 discussed and will not be discussed further.

5.1. Synthesis of Five-Membered Rings

5.1.1. With One Heteroatom

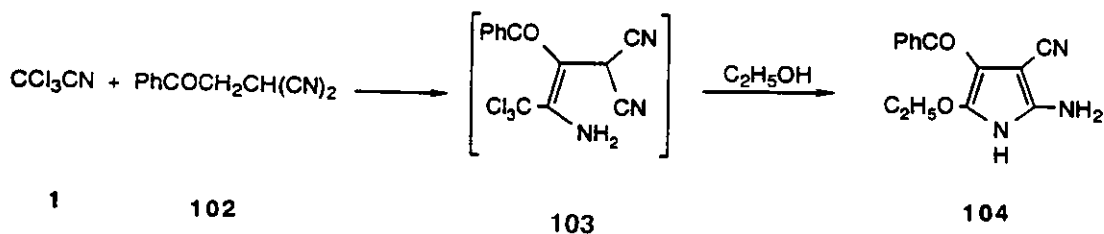
5.1.1.1. Furans

The condensation of TCAN with alkylacetyl carbinols (**99**) in the presence of $\text{PhN}(\text{C}_2\text{H}_5)\text{MgBr}$ gave the adducts (**100**). The latter were cyclized by HCl to give furanones (**101**) in about 93% yields.¹¹⁰

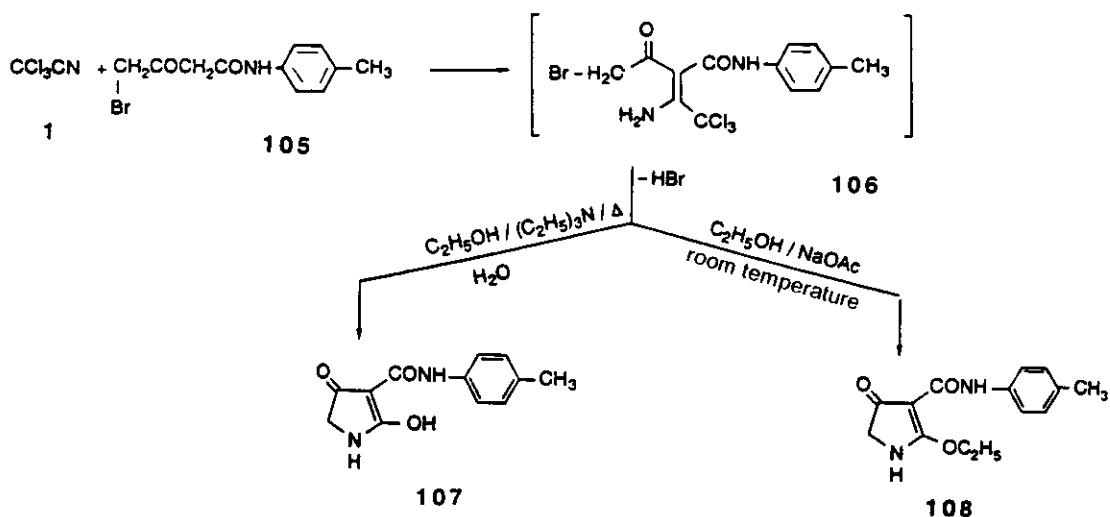


4.2.1.2. Pyrroles

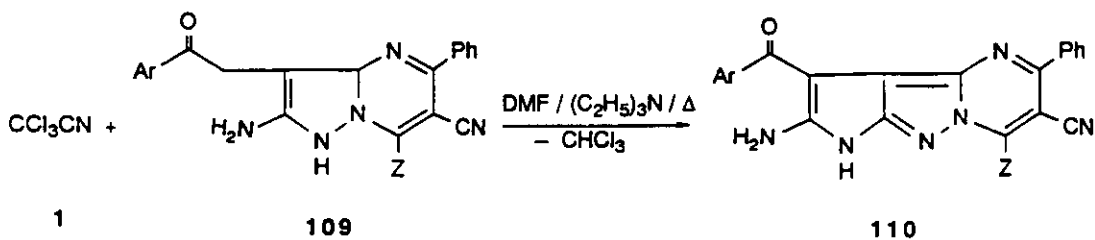
The pyrrole derivative (**104**) could be prepared by the cycloaddition reaction of TCAN with phenacylmalononitrile (**102**).¹¹¹



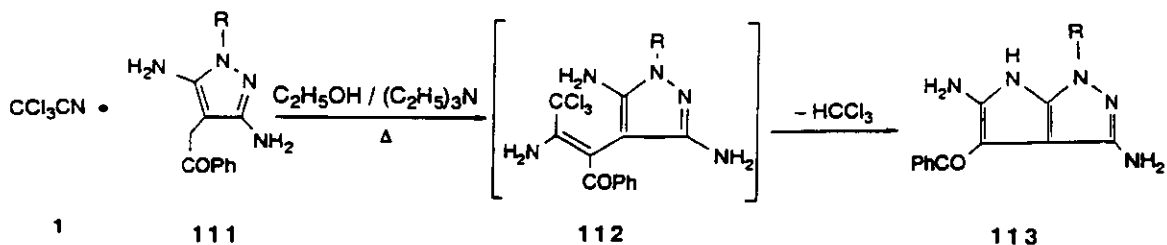
Depending on the reaction conditions, γ -bromoacetylaceto-*p*-toluidide (**105**) reacted with TCAN to yield either the hydroxypyrrole derivative (**107**) or the ethoxypyrrole derivative (**108**). The reaction proceeded *via* intermediacy of the adduct (**106**).¹¹²



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

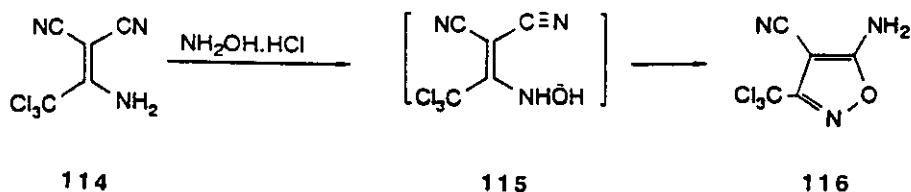


5.1.2. With Two Heteroatoms

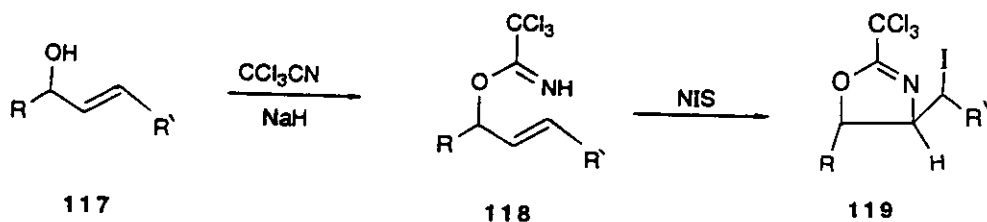
5.1.2.1. Oxazoles

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

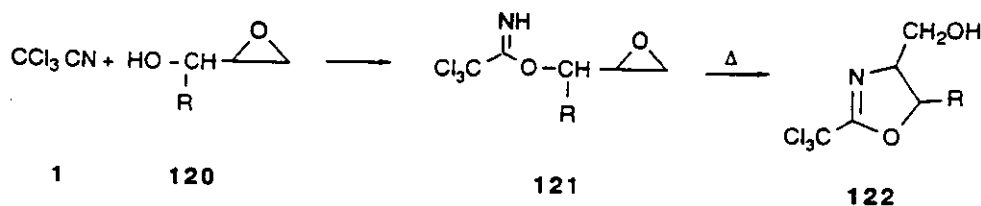
formed by the addition of the hydroxylamine to the α,β -unsaturated linkage followed by cyclization.^{115,116}



A general method for the synthesis of a wide variety of 1,3-oxazoles from allylic alcohols by using TCAN as a key precursor 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).

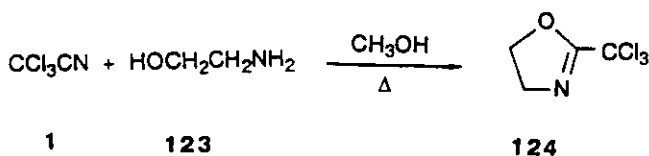


Condensation of TCAN with epoxypropanols (120) in the presence of base gave the adducts 1-trichloroacetamidyoxy-2,3-epoxypropanes (121) in 70% yields. The latter underwent thermal intramolecular cyclization to afford the 1,3-oxazoles (122) in excellent yields.^{119,120}

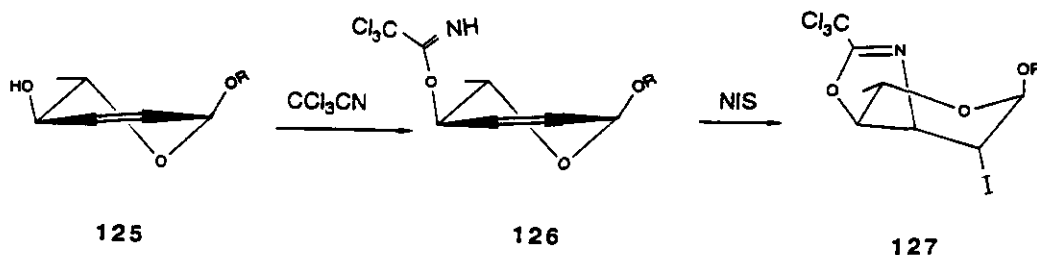


R = H, cyclohexyl

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

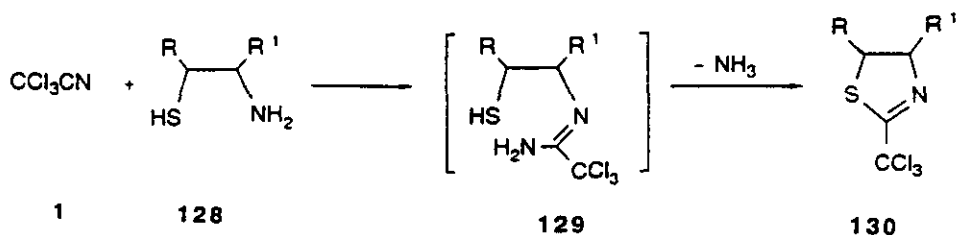


The reaction of methyl 2,3,6-trideoxy- α -L-threo-hex-2-enopyranosides (**125**) with TCAN afforded the imidates (**126**). The latter underwent iodonium ion-induced intramolecular cyclization to yield the corresponding condensed 1,3-oxazoles (**127**).¹²²

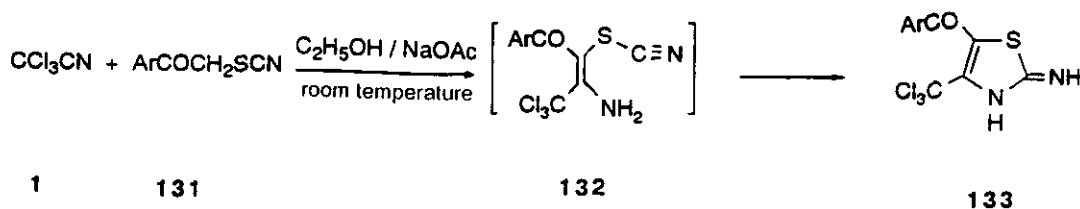


5.1.2.2. Thiazoles

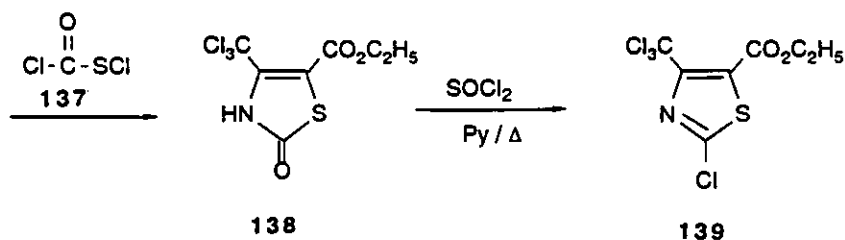
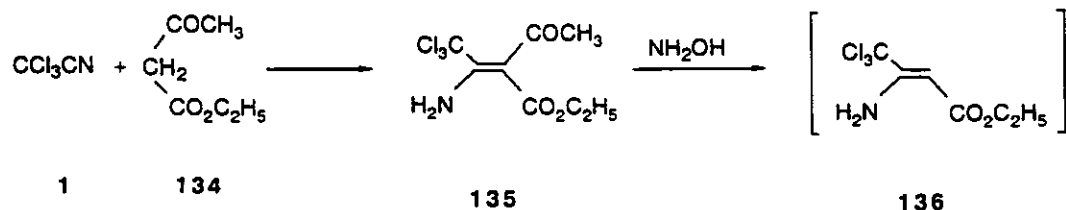
An important antidotal active 1,3-thiazoline derivatives (**130**) were prepared by treating TCAN with **128** in refluxing methanol.¹²³



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

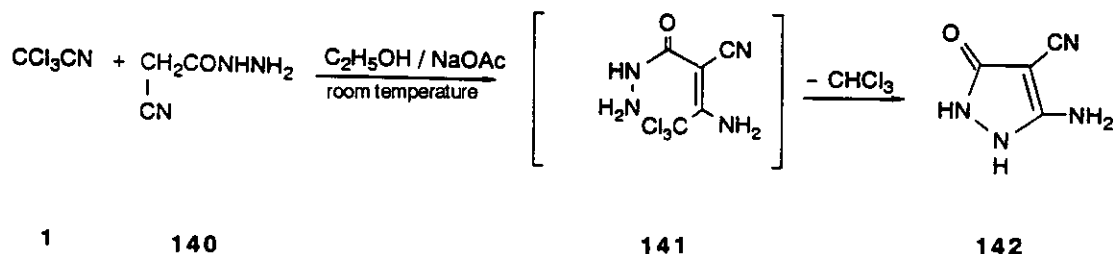


An important thiazole carboxylic acid derivative (**139**), used as protectant against herbicide damage, was obtained by treating TCAN with ethyl acetoacetate (**134**) to give the adduct (**135**) which was deacetylated by NH_2OH to the intermediate (**136**), cyclocondensed with **137** to afford the thiazolone (**138**). The latter treated with thionyl chloride in pyridine solution to afford the desired thiazole (**139**).¹²⁵

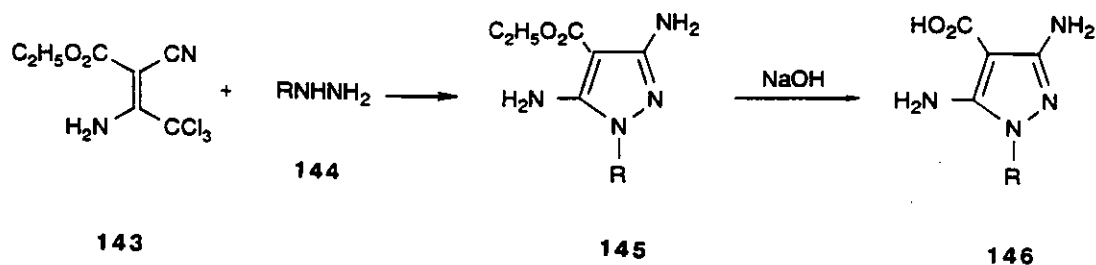


5.1.2.3. Pyrazoles

The addition of the active methylene moiety of cyanoacetylhydrazide (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



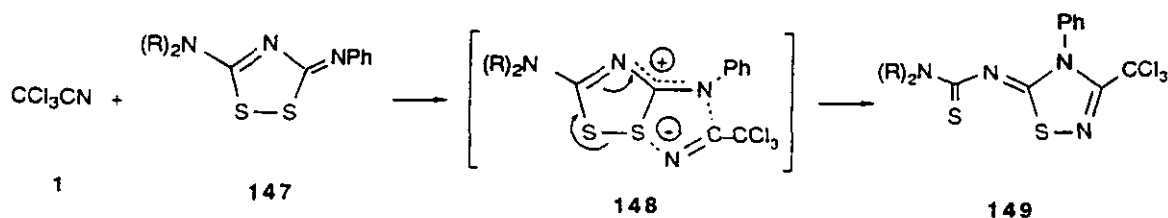
The important antibacterial pyrazolecarboxylic acid derivatives (146) were prepared by the cyclization of the TCAN adduct (143) with hydrazines (144). The latter were hydrolyzed by aqueous sodium hydroxide at room temperature to give 146.¹²⁶



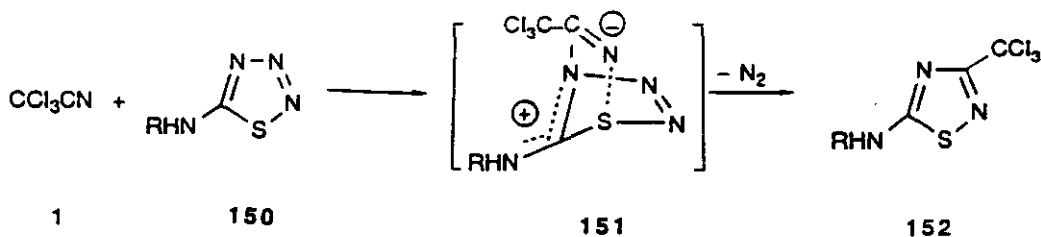
5.1.3. With Three Heteroatoms

5.1.3.1. Thiadiazoles

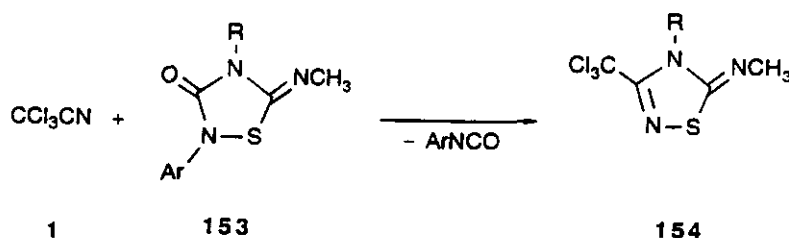
A series of 4,5-dihydro-5-thiocarbamylimino-4-phenyl-1,2,4-thiadiazolines (149) was prepared by ring-opening cycloaddition of some imino-1,2,4-dithiazoles (147). The reaction proceeded *via* the intermediacy of the dipolar intermediates (148).¹²⁷



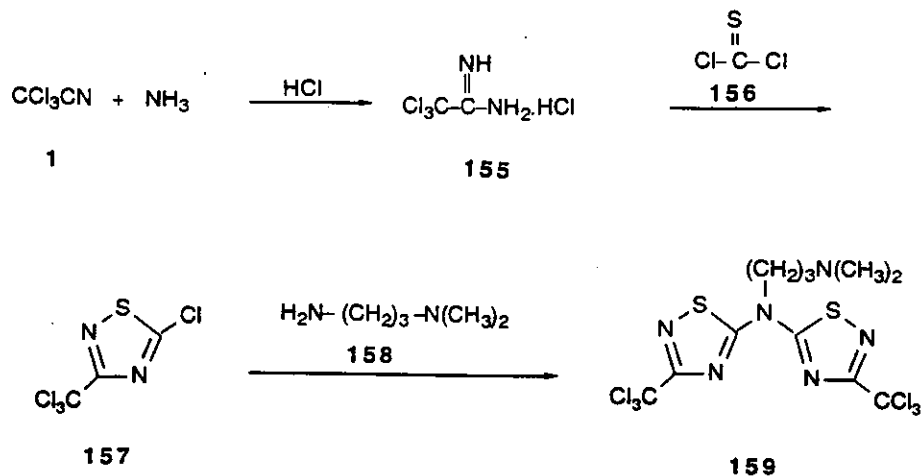
Amino-1,2,3,4-thiadiazoles (150) were effectively converted to 1,2,4-thiadiazoles (152) when treated with TCAN *via* the cycloadduct polar intermediates (151).¹²⁸



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}

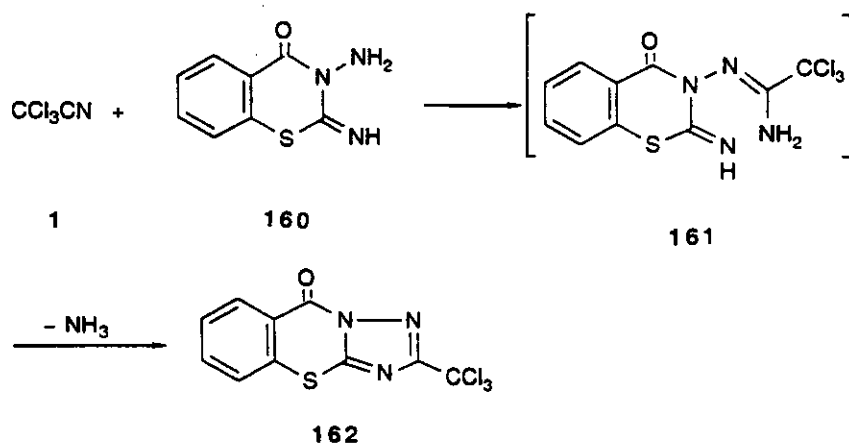


The antimalarial agent (159) was synthesized via the reaction of TCAN with liquid ammonia to give trichloroacetamidine (155). The latter was treated with thiophosgene (156) to give 5-chloro-3-trichloromethyl-1,2,4-thiadiazole (157) which after condensation with *N,N*-dimethyl-1,3-propanediamine (158)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

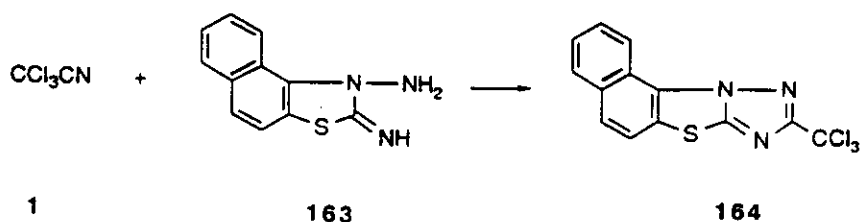


5.1.3.2. Triazoles

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



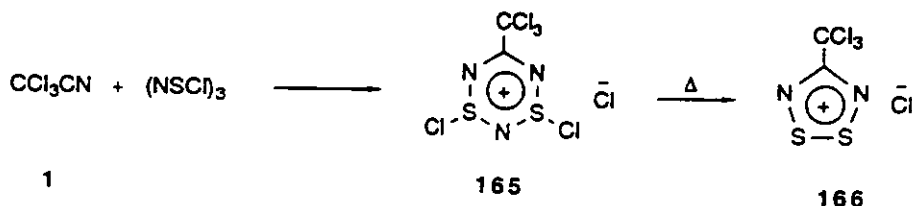
Similarly, the naphthothiazolotriazole derivative (**164**) was prepared from the reaction of 2-iminothiazole (**163**) with TCAN.¹³⁴



5.1.4. With Four Heteroatoms

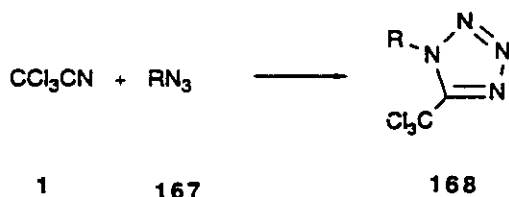
5.1.4.1. Dithiadiazoles

The reaction of TCAN with $(\text{NSCl})_3$ at 23°C produces good yield of dithiatiazine (165). The latter was heated to give the dithiadiazolium chloride (166).^{135,136}



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

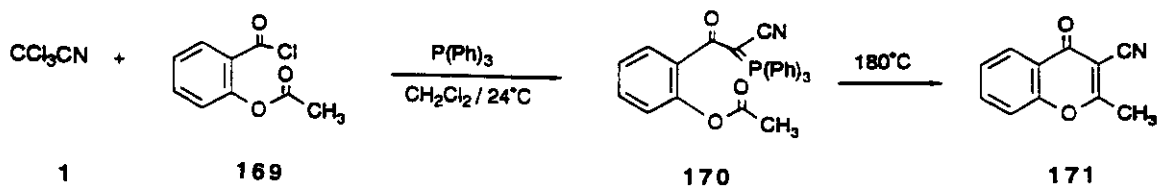


5.2. Synthesis of Six-Membered Rings

5.2.1. With One Heteroatom

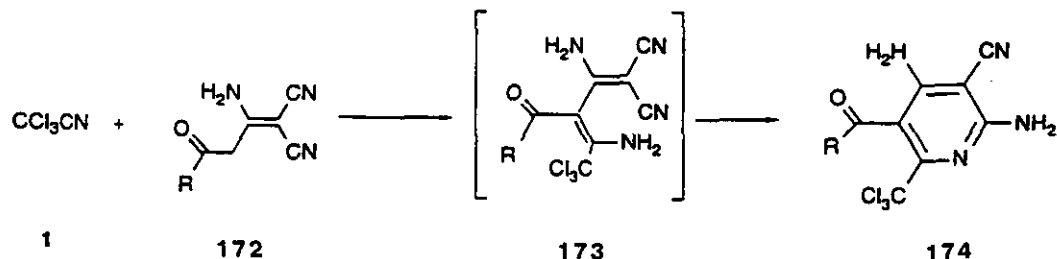
5.2.1.1. Flavones

2-Acetoxybenzoyl chloride (169) reacted with $\text{CCl}_3\text{CN}/\text{P}(\text{Ph})_3$ 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

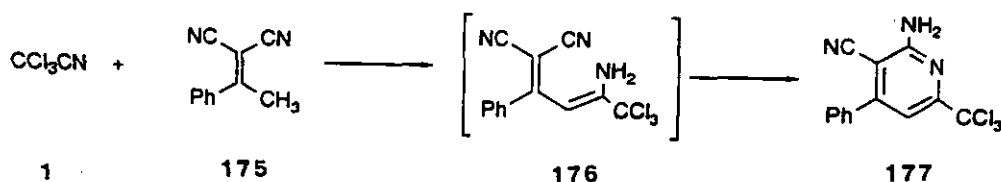


5.2.1.2. Pyridines

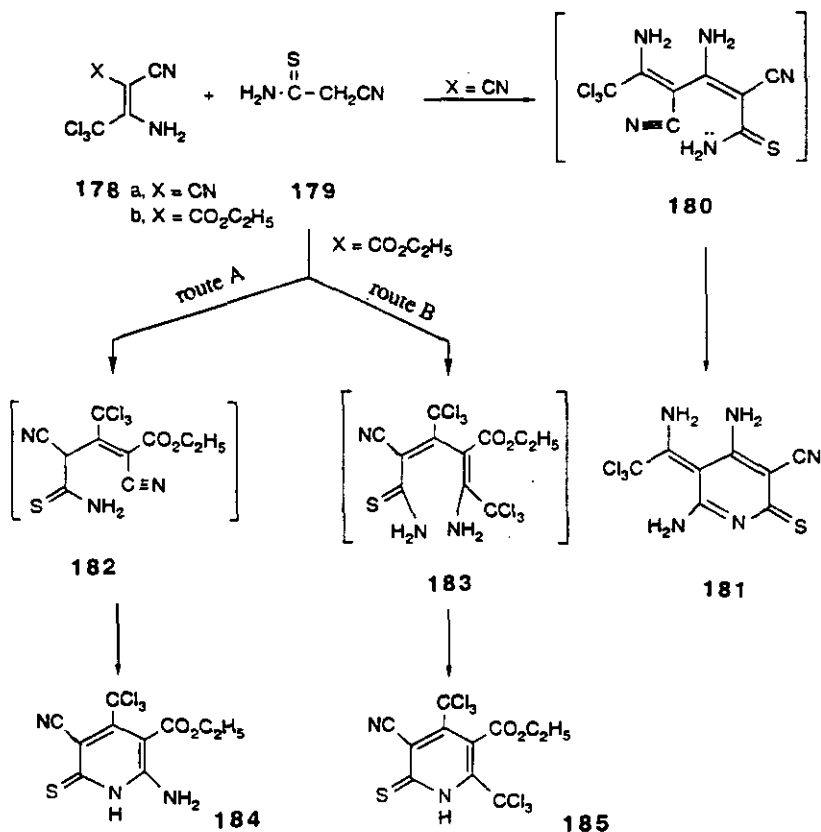
Cyclocondensation of 172 with TCAN gave the pyridines (174) *via* intermediacy of the adduct (173).^{142,143}



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

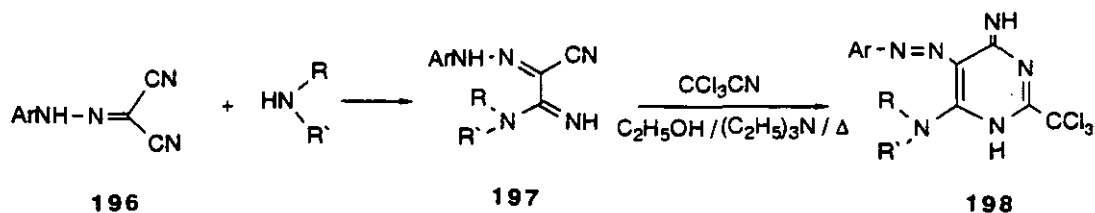


β -Enaminonitrile (178a) ($X = \text{CN}$), prepared from the reaction of TCAN with the appropriate active methylene compound, reacted with cyanothioacetamide (179) to yield the adduct (180) that cyclizes to 181. Compound (178b) ($X = \text{CO}_2\text{C}_2\text{H}_5$) reacted with 179 to yield a mixture of 184 and 185. Compounds (182) and (183) are assumed to be intermediates for the formation of these products.¹⁴⁵

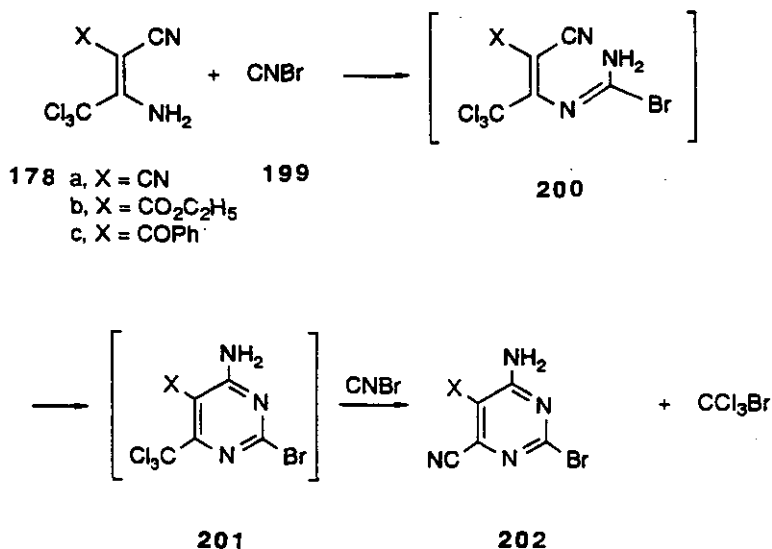


5.2.2.2. Pyrimidines

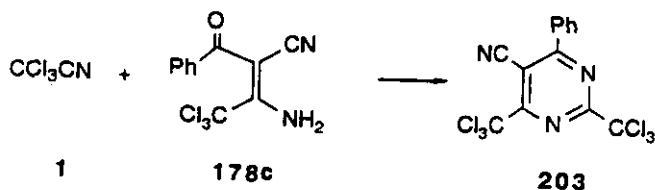
Arylhydrazomalononitriles (196) reacted with secondary amines to give the acetamides (197), which in turn reacted with TCAN to yield the pyrimidines (198).¹⁴⁹



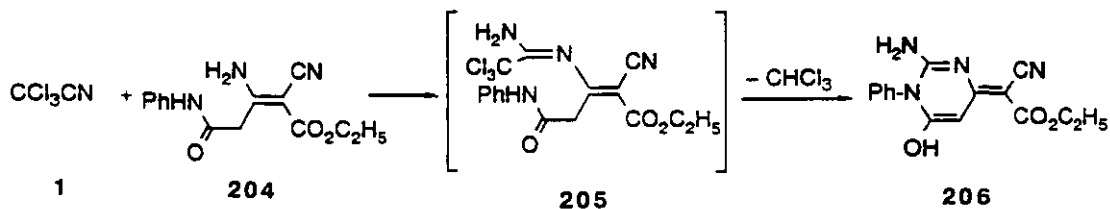
β -Enaminonitriles such as 178a-c, prepared from the reaction of TCAN with the appropriate active methylene compound, yielded 2-bromopyrimidines (202) when treated with cyanogen bromide (199). Compounds (202) were assumed to be formed *via* the addition of the amino function in 178 to the cyano group 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



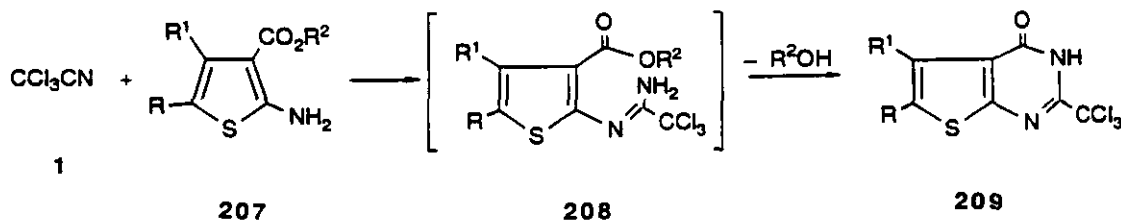
Elnagdi *et al.*¹⁵¹ reported the preparation of pyrimidine (203) by condensing TCAN with the enaminonitrile (178c).



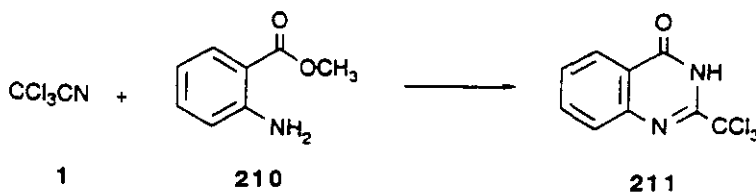
Similarly, the amide derivative (204) reacted with TCAN to give the adduct (205) which spontaneously cyclized into 206 *via* loss of chloroform.¹⁴³



The anti-allergy 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}



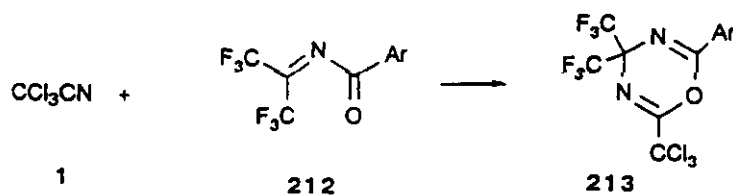
Methyl anthranilate (210) reacted with TCAN in dry toluene in the presence of $(\text{C}_2\text{H}_5)_3\text{N}$ to yield the quinoxalinone (211) in good yield.²⁵



5.2.3. With Three Heteroatoms

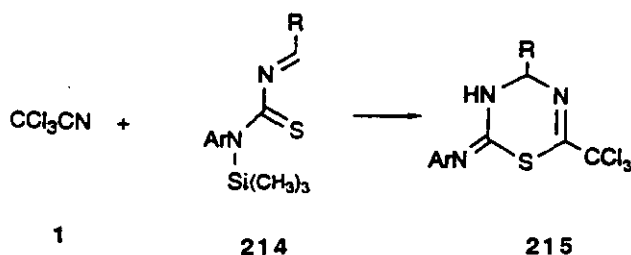
5.2.3.1. Oxadiazines

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



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



5.2.3.3. Triazines

Syntheses of the light-sensitive composition bis(halomethyl)triazines (220) were reported in floods of patents¹⁵⁶⁻¹⁶⁴ and papers¹⁶⁵⁻¹⁷⁵ *via* the reaction of TCAN with aryl, alkyl nitriles or even itself 218. (Table 2). An outline of the reaction mechanism is shown below.

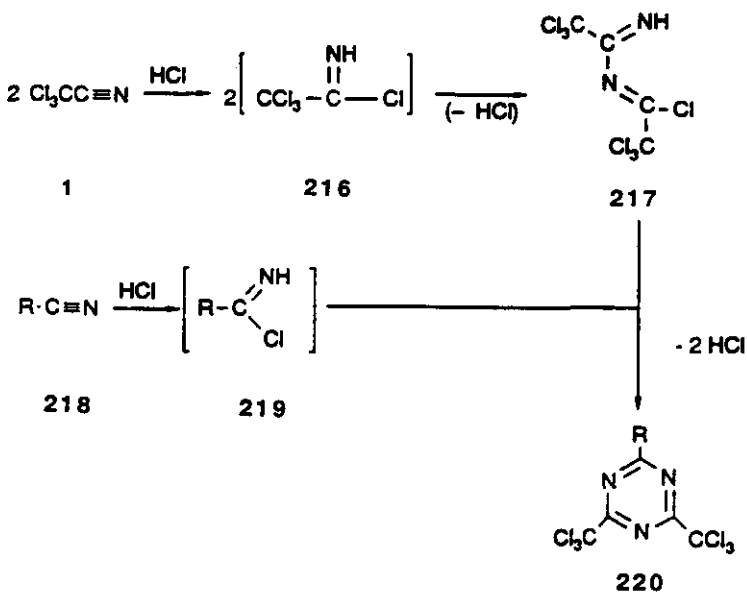


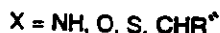
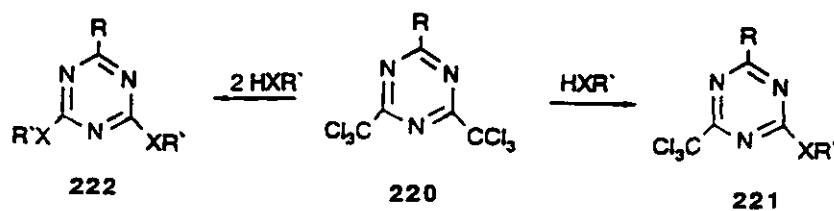
Table 2. Cotrimerization of CCl_3CN with some nitriles.¹⁷⁰

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

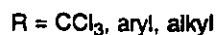
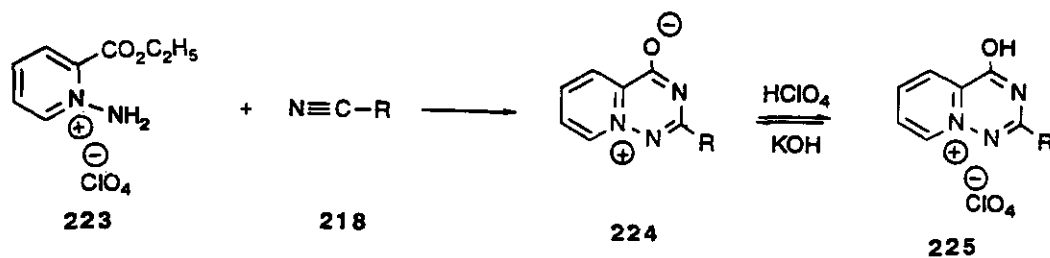
Table 2. Cont'd.

R	Yield (%)	mp °C	R	Yield (%)	mp °C
2-ClC ₆ H ₄	91	120-122	<i>n</i> -C ₃ H ₇	93	136-138
3-ClC ₆ H ₄	93	125-127	<i>i</i> -C ₃ H ₇	87	170-175
4-ClC ₆ H ₄	92	158-159	<i>n</i> -C ₄ H ₉	90	157-159
2,4-Cl ₂ C ₆ H ₃	88	143-145	<i>i</i> -C ₄ H ₉	82	154-156
3,4-Cl ₂ C ₆ H ₃	90	139-140	<i>s</i> -C ₄ H ₉	81	142-146
2,4,5-Cl ₃ C ₆ H ₂	85	153-155	<i>t</i> -C ₄ H ₉	56	154-157
4-BrC ₆ H ₄	92	161-163	<i>n</i> -C ₅ H ₁₁	95	175-177
4-CH ₃ C ₆ H ₄	95	122-123	<i>n</i> -C ₉ H ₁₉	78	192-194
3-NO ₂ C ₆ H ₄	74	103-104	<i>n</i> -C ₁₇ H ₃₅	92	210-215
4-CH ₃ OC ₆ H ₄	90	144-145	CH ₂ ClCH ₂	69	65-67
1-Naphthyl	83	216-218	CH ₂ ClCCl ₂	87	47-48

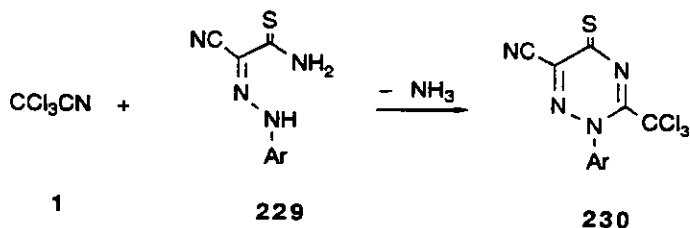
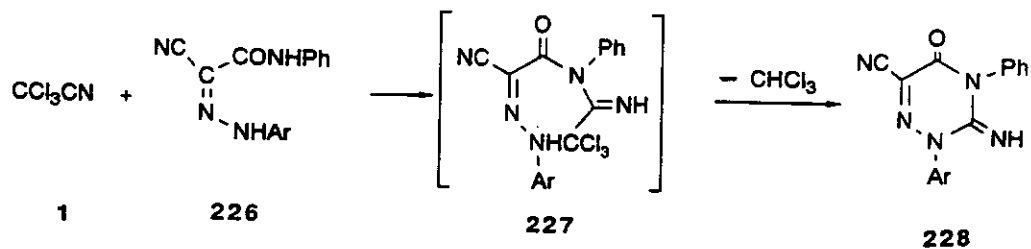
The trichloromethyl moiety in 220 showed high reactivity as leaving group with nucleophilic reagents. Treating triazines (220) with amines, phenols or carbanions afforded mono or disubstituted derivatives, depending on the reaction conditions.^{176,177}



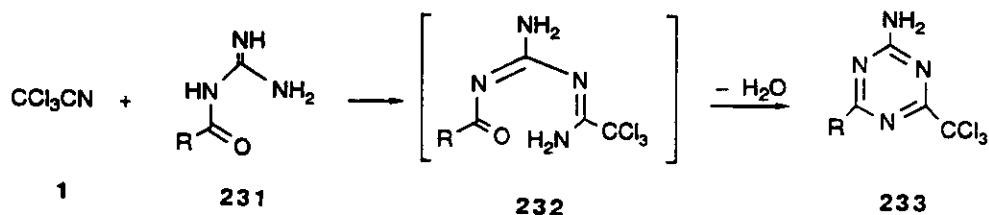
A general synthetic route for pyrido[2,1-*f*]-*as*-triazines such as 225 starting from ethyl picolinate *N*-ammonium perchlorate (223) with alkyl or aryl cyanide was reported by Batori *et al.*¹⁷⁸



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



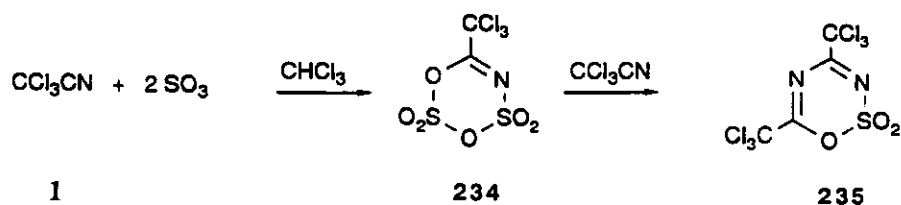
Kelarev *et al.*¹⁷⁵ reported the preparation of *s*-triazines (233) by condensing TCAN with *N*-carbonylguanidines (231).



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 properties 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 result. 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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