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Reviews

Trichloroisocyanuric Acid: A Safe and Efficient Oxidant

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Abstract:

The literature on trichloroisocyanuric acid (TCCA) has been reviewed. TCCA is a safe and efficient reagent, useful for chlorination and oxidation even on large scale.

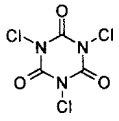
Introduction

Trichloroisocyanuric acid, 1,3,5-trichloro-1,3,5-2,4,6,-(1H,3H,5H)-trione (TCCA, **1**) (Scheme 1) with the commonly used trade names, Symclosene, ACL-85, or Chloreal,[1] was first reported in 1902 by Chattaway and Wadmore. The authors describe that trichloriminocyanuric acid is obtained in a quantitative yield from the reaction of the potassium salt of cyanuric acid (**2**) with chlorine gas[2] (Scheme 2). Later Birckenbach and Linhard described the synthesis of TCCA through cyclization of *N*′-carbonyl-*N*,*N*-dichlorourea.[3] After the microbiological activity of TCCA was discovered, Hands and Whitt reported the synthesis of TCCA through chlorination of cyanuric acid (**2**) with chlorine gas in aqueous NaOH. Thereafter, TCCA and its monosodium salt DCCA became industrially important.[4] In 1952 Monsanto obtained a patent on the synthesis of TCCA.[5] In 1960 W.R. Grace obtained a second patent on the synthesis of TCCA.[6] Purex obtained in 1958 a patent on a method for the purification of TCCA through dissololution in concentrated H_2SO_4 and dilution with ice water.[7]

Over the years there has been some confusion about the correct structure of TCCA. In earlier volumes of Fieser and Fieser the structure of TCCA was confused with cyanuric chloride (**3**) the acid chloride of cyanuric acid (**2**) Scheme 3).

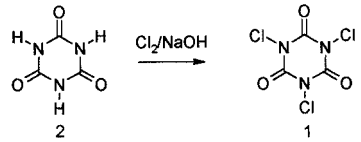
As seen from the structure TCCA belongs to the large group of *N*-chloroimides and amides which is a subgroup of the more general *N*-chloroamines. *N*-chloroamines are inorganic or organic nitrogen compounds with at least one chlorine atom attached to nitrogen. The oldest example is monochloroamine NH_2Cl known since the beginning of the 19th century. The solvent-free material, isolated at −70 °C, disproportionates violently at −50 °C to ammonium chloride and the explosive nitrogen trichloride.[8]

Scheme 1. **Trichloroisocyanuric acid (1)**



1

Scheme 2. **Synthesis of TCCA**



2 **1**

Scheme 3. **Structure of TCCA (1) versus cyanuric chloride (3)**

1 **3**

Chloroamines are used as bleaching agents, disinfectants, and bactericides, due to their function as chlorinating agents and oxidants. A few of them are also commonly used as chlorinating reagents and oxidants in organic synthesis. Many of the chloroamines show unstable or explosive properities. Many of their reactions are also extremely violent, for example, the reaction of *N*-chlorosuccinimide with aliphatic alcohols.[9] Since chloroamines are easier to handle than chlorine gas or metal hypochlorites, they are widely used in the purification of drinking water and as sanitizing agents in swimming pools. Since the first large-scale manufacture of TCCA and its monosodium salt DCCA, they have gained a continuously growing share of these markets as important replacements of calcium hypochlorite, 1,3-dichloro-5,5-dimethylhydantoin (NDDH), and chloramine T.

The chemical synthesis of TCCA has not been that successful. The most commonly used reagent is *N*-chlorosuccinimide (NCS) **4**. Another reagent commonly used is 1,3-dichloro-5,5-dimethylhydantoin (NDDH) **5**[10] (Scheme 4).

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(1) (a) Ura, Y.; Sakata, G. *Ullmann's Encyclopedia of Industrial Chemistry*, 6th ed.; Wiley−VCH: Weinheim, 2001. (b) *Merck Index;* Merck & Co.: Whitehouse Station, NJ, 1996.
(2) Chattaway, F. D.; Wadmore, J. M. *J. Chem. Soc.* **1902**, *81*, 191.
(3) Birckenbach, L. *Chem. Ber.* **1930**, *63*, 2528.
(4) Hands, W. *J. Soc. Chem. Ind.* **1948**, *67*, 66.
(5) Hardy, U.S. Patent 2,607,738, 1952.
(6) Christian, U.S. Patent 2,956,056, 1960.
(7) Lorenz, U.S. Patent 2,828,308, 1958.
(8) Bretherick, L. *Handbook of Reactive Chemical Hazards*, 5th ed.; Butterworth−Heinemann Ltd.: London, 1995; Vol. 1, Entry 3857, p 1259.
(9) Bretherick, L., *Handbook of Reactive Chemical Hazards*, 5th ed.; Butterworth−Heinemann Ltd.: London, 1995; Vol. 2, p 158.

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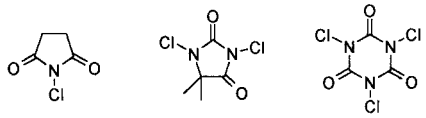
10.1021/op010103h CCC: $22.00

Scheme 4. **Structure of NCS (4), NDDH (5), and TCCA (1)**



4 5 1

Table 1. **Properties**

reagent	NCS	NDDH	TCCA
physical properties	white solid 150−151 °C dec	white solid 132 °C dec	white solid 234 °C dec
active chlorine content	51%	78%	91.5%
oxidizing ability	5.82	4.40	4.84
decomposition enthalpy kJ/mol active chlorine	−129,8	−120,3	−120.0
toxicological properties (LD_{50})	2700*	542	1300
cost USD/kg active chlorine	164	58	44

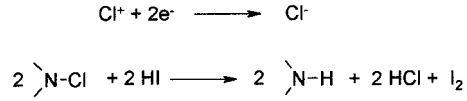
For chlorination and oxidation *tert*-butylhypochlorite has also been a very commonly used reagent. However, the use of *tert*-butylhypochlorite has been slowly vanishing over the last years due to reports of decomposition during transportation and explosions during production. The use of aqueous hypochlorite is still very common for various oxidations although only in cases where the use of an aqueous solution does not interfere with the reaction or the product. In organic synthesis the hypochlorites could also be substituted with *N*-chloroamines, especially when anhydrous conditions are necessary.

Properties of *N*-Chloroamines. At this point, it is important to state that all *N*-chloroamines are thermally unstable and can explode at elevated temperature. They can also react violently with amines, strong acids and bases, and easily oxidised organic material. *N*-Chlorosuccinimide has been reported to react violently with alcohols and benzylamine, 1,3-dichloro-5,5-dimethylhydantoin reacts violently with xylene, and trichloroisocyanuric acid has been reported to generate explosive nitrogen trichloride in concentrated acidic aqueous solution due to the attack of formed hypochlorous acid on the imine bond.[11]

To get a comparative picture of the optimal use of different *N*-chloroamines in organic synthesis we have compared some of the properties of NCS, NDDH, and TCCA (see Table 1). In all *N*-chloroamines all chlorines are active, and in the case of TCCA we have found that all chlorines have comparable reactivity

All three *N*-chloroamines are white solids which decompose at elevated temperature. NDDH has a melting point with decomposition at 132 °C, NCS, at 150 °C, and TCCA, at 234 °C (Scheme 5). *N*-Chloroamines can act as oxidants by absorbing two electrons. Thus, *N*-chloroamine oxidises hydroiodic acid to liberate iodine which is used for quantitative analysis of the activity.

Scheme 5. **Oxidation mechanism**



The theoretical available chlorine content is expressed as twice the mass fraction of chlorine in the molecule or for practical purposes, the equivalent of elemental chlorine. This is a value for the atom efficiency of these reagents. The amount of active chlorine in NCS is 51%, in NDDH 78%, and TCCA has the highest amount of active chlorine with 91.5%.

The quantitative hydrolysis constant *K* is used to express the bactericidal power of *N*-chloroamines, which depends on the ability to generate hypochlorous acid in water. It is expressed as the total amount of hypochlorous acid produced through quantitative hydrolysis of the *N*-chloroamine in water, is expressed by the equation below, and is normally in the range $10^{-4}-10^{-10}$; expressed as the p*K*-value, it is between 4 and 10. Among the three reagents NDDH has the highest oxidation potential with 4.40, TCCA with 4.84, and NCS with 5.82, which also indicates another property of these reagents. They are rather slowly hydrolysed in water. A well-known method for purification of NCS is through recrystallization from water.

$$K = \frac{C_{RR'NH} \cdot C_{HOCl}}{C_{RR'NCl}}$$

The bulk price of the different *N*-chloroamines in relationship to the amount of active chlorine is also important for large-scale synthesis. The price of NCS (164/kg) is almost 4 times the price of TCCA ($44 $/kg). The price of NDDH is also in a moderate range with $58 $/kg.

The toxicity of *N*-chloroamines is very important because of their widespread use in drinking water, swimming pools, and food processing. The toxicological data for TCCA, NCA, and NDDH are summarised in Table 1.[12]

Last, but not least important, is the solubility of reagents in organic solvents which is an important factor for scale-up and manufacture. During our research in the field of β-carbolines we determined the solubilities of these three reagents in various solvents.

In organic solvents TCCA has the highest solubility of the three reagents. TCCA has a high solubility in acetone (350 g/L) and ethyl acetate (385 g/L) and a moderate solubility in toluene (70 g/L). In comparison the solubilty of NCS in organic solvents is much lower than for TCCA (see Table 2). The difference in solubility between NCS and TCCA becomes even more striking when one compares the amount of active chlorine which is possible to dissolve per liter of solvent. After dissolving TCCA in ethyl acetate the solution is 5.0 M in active chlorine in comparison with NCS which only gives a 0.44 M solution. The picture is the same in acetone and other organic solvents where TCCA gives highly concentrated solutions, and NCS gives much more diluted ones.

(10) Larock, R. C. *Comprehensive Organic Transformations, A Guide to Functional Group Preparations*; VCH Publishers Inc.: New York, 1989.
(11) Bretherick, L. *Handbook of Reactive Chemical Hazards*, 5th ed.; Butterworth−Heinemann Ltd.: London, 1995.
(12) Ura, Y.; Sakata, G. *Ullmann's Encyclopedia of Industrial Chemistry*, 6th ed.; Wiley−VCH: Weinheim, 2001.

Table 2. **Solubility**

solvent (g/L) (mol active chlorine/L)	TCCA	NCS	NDDH
water	10 (0.13)	43 (0.32)	9 (0.09)
acetone	350 (4.56)	183 (1.37)	211 (1.83)
ethyl acetate	385 (5.02)	59 (0.44)	131 (1.14)
toluene	70 (0.91)	15 (0.07)	62 (0.53)

As it is possible to chlorinate ketones and esters in the α-position with TCCA, we investigated during our solubility test if any chlorination of the solvent could be determined. We did not observe any chlorination but it is still not recommended to store solutions of *N*-chloroamines in organic solvents.

The Main Use of TCCA. The worldwide production of TCCA and DCCA is about 100.000 t/year. The demand is increasing by 8−10% per year for swimming pools and 3−5% for food processing. They are used for many purposes such as disinfecting swimming pools, nonshrinking treatment of wool, cleaning and sterilizing bathrooms, and using in laundry bleach as well as for removing oil and protein in stainless steel. They are also recommended for dishwashing in hotels, hospitals, restaurants, and food factories; however, as reagents for organic synthesis the examples are rather rare.

Trichloroisocyanuric Acid in Organic Synthesis. Although TCCA has been produced on large scale for use in household and industry since the 1950s, it has never had a real breakthrough in organic chemistry laboratories. It also has not found its way into textbooks in organic chemistry and even books on heterocyclic chemistry fail to mention this very useful reagent. This probably has something to do with the early chlorination experiments which indicated a rather uncontrolled chlorination with TCCA in comparison to that using NCS and NBS.

The main part of this contribution will concentrate on the chemistry of TCCA in organic synthesis that has been reported up to now. We do not intend to give a complete review over all reports that have been published on chemical synthesis with this reagent. When possible the uses of NCS and NDDH are compared, and the possibilities to substituting *tert*-butyl hypochlorite with TCCA are shown.

This part will be divided into:

A. Chlorination

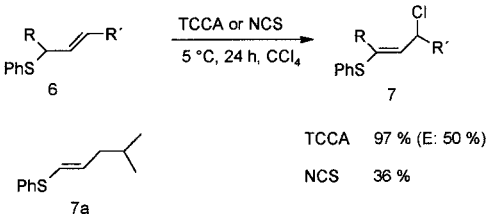
B. Oxidation

C. Miscellaneous

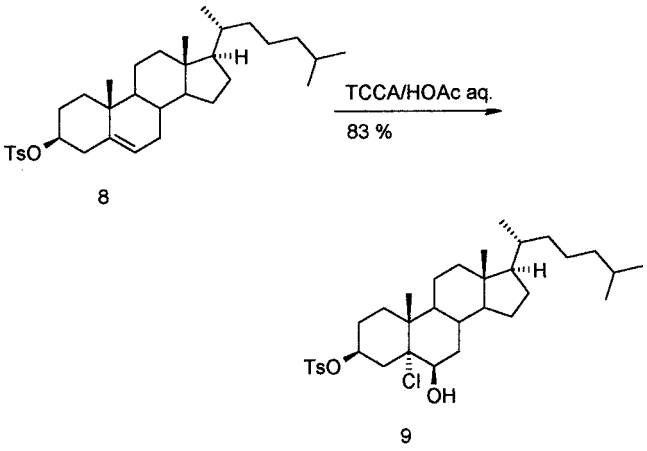
A. Chlorination. In 1942 Ziegler and co-workers[13] reported for the first time the use of trichloroisocyanuric acid as a reagent in organic synthesis for the α-chlorination of alkenes. During a detailed study about the allylic halogenation with different reagents TCCA was also studied under standard reaction conditions. The authors reported a very exothermic reaction with cyclohexene producing a mixture of products. The main product 3-chlorocyclohexene was obtained in a yield of 29%. No optimization of the reaction conditions was performed.

(13) Ziegler, K.; Späth, A.; Schaaf, E.; Schumann, W.; Winkelmann, E. *Anal. Chem.* **1942,** *551*, 80.

Scheme 6. **Allylic chlorination of allylphenylsulfides**



Scheme 7. **Hypohalogenation of an alkene**



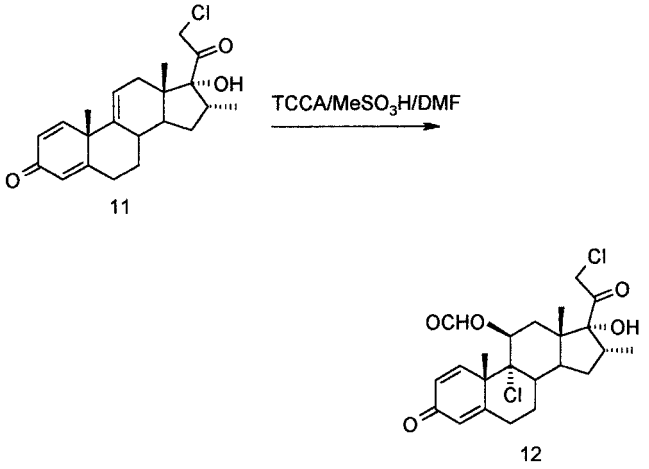
In 1975 an allylic chlorination was used by Cohen et al.[14] for the synthesis of 1-thiophenoxy-3-chloroalkenes (**7)** from allyl phenyl sulphides (**6**). The authors commented that the yield with TCCA approached quantitative in comparison to that of the far more expensive reagent *N*-chlorosuccinimide which was considerably less effective. When R = alkyl, the reaction conditions using NCS afforded mainly unreacted starting material. The yield of **7a** was found to be quantitative with TCCA although as 1:1 mixture of *E*/*Z* (Scheme 6). The authors observed, though, that for substrates which reacted with NCS the stereoselectivity was better.

Under aqueous conditions in acetic acid it was possible to do a hypohalogenation to a Δ-5,6 double bond in a cholestanol derivative.[15] Hypohalogenation has mainly been reported from the reaction of sodium hypochlorite reaction with alkenes (see, for instance, ref 16) or chlorine gas (see, for instance, ref 17) (Scheme 7). Also for the preparation of 9α-chloro-11-*β*-formyloxypregnan derivative, **11**, a type of hypohalogenation was used[18] (Scheme 8).

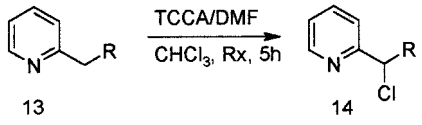
A benzylic chlorination of *N*-heterocycles has been reported by Jeromin et al.[19] Alkyl pyridine and methylquinoline which are normally difficult to chlorinate in the side chain were easily chlorinated with TCCA. In comparison to the fast and exothermic chlorination in chlorinated solvent with TCCA, the use of NCS or NDDH gave no complete reactions. The major product was always the monochloro derivative when TCCA was used in a stoichiometric amount.

(14) Mura, A. J., Jr.; Bennett, D. A.; Cohen, T. *Tetrahedron Lett.* **1975**, *50*, 4433.
(15) Mukawa, F. *Nippon Kagaku Zasshi* **1957**, *78*, 450; *Chem. Abstr.* **1960**, *53*, 5338.
(16) Colonge, J.; Cumet, L. *Bull. Soc. Chim. Fr.* **1947**, 838.
(17) Mills, J. S. *J. Chem. Soc.* **1966**, 2261.
(18) Draper, R. W.; Vater, E. J. U.S. Patent 5,602,248 A, 1995.
(19) Jeromin, G. E.; Orth, W.; Rapp, B.; Weiss, W. *Chem. Ber.* **1987**, *120*, 649.

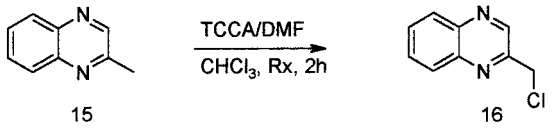
Scheme 8. **Hypohalogenation of a pregnan derivative**



Scheme 9. **Benzylic chlorination of pyridines**



Scheme 10. **Benzylic chlorination of chinoxalin**



Surprisingly no ring chlorination was observed under the reaction conditions (Scheme 9).

The authors found that adding a radical starter did not have any significant effect on the reaction which rules out a radical mechanism. Instead it was found that the addition of carboxylic amide like benzamide or DMF was beneficial for the start of the reaction. 2-Chloromethyl pyridines were obtained in fairly good yields. Another independent study of the benzylic chlorination of **13** (R = H) with NCS gave only 25% of **14** combined with 20% of the dichloro derivative.[20]

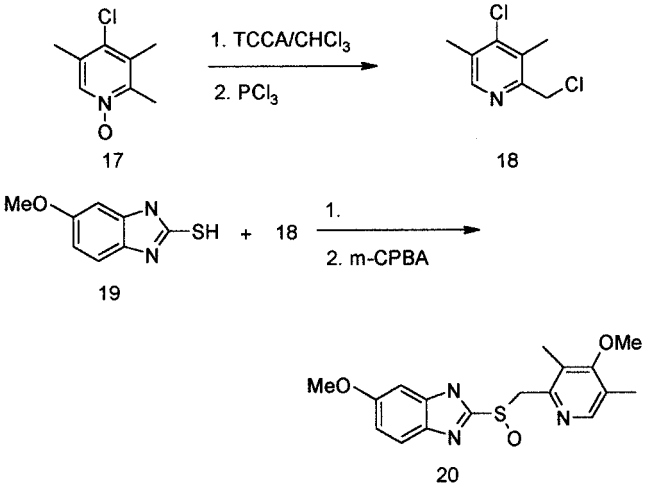
Also other alkyl-substituted *N*-heterocycles could be chlorinated, for instance, 2-methylchinoxalin (**15**), from which it was possible to obtain the monochloro derivative **16** in 75% (Scheme 10).

In this chlorination study only electron-deficient *N*-heterocycles were studied. Until now no benzylic chlorination of electron-rich heterocycles with TCCA has been reported.

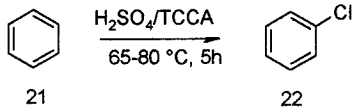
As part of the synthesis of omeprazole, the antiulcer drug from AstraZeneca, the benzylic chlorination of a pyridine derivative was the central transformation in a patented synthesis of A. Palomo Coll[21] (Scheme 11).

As part of their continued study of the use of TCCA as a safe and convenient substitute for chlorine, Juenge et al.[22] also observed that trichloroisocyanuric acid could be used for the chlorination of aromatic systems under polar and free radical conditions. When 50% H_2SO_4 was used as catalyst,

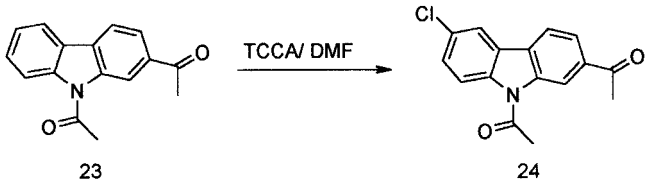
Scheme 11. **Synthesis of omeprazole**



Scheme 12. **Aromatic chlorination**



Scheme 13. **Chlorination of a carbazole**



it was possible to obtain a fairly good yield of chlorobenzene (80%) after 5 h at 65−80 °C.

Toluene gave the 2- and 4-chlorotoluenes under acidic reaction conditions (66%). The main regioisomer was the 4-chlorotoluene. With phenol and aniline the yield was lower, giving mainly the para isomer. With electron-withdrawing groups no reaction occurred (Scheme 12). Alternately, when benzoylperoxide was used as radical initiator, benzylchloride was obtained in 44% from toluene.

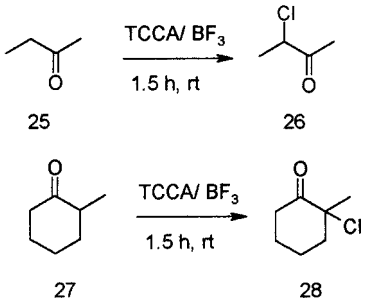
J. Rosevear and J. F. K. Wilshire reported in 1980 a study of the chlorination of some *N*,*N*-dimethylanilines with TCCA.[23] Under the reaction conditions, concentrated sulfuric acid at room temperature overnight, the reaction produced a complex mixture of chlorinated products. No attempt was made to optimise the reaction conditions.

In 1994 Manschand et al.[24] reported a selective chlorination in the 7-position of the carbazole **23** using TCCA in DMF or triethylphosphate at room temperature. Using these conditions a moderate yield of the chlorinated carbazole **24** was obtained. The authors claimed this to be the most selective chlorination system for this substrate (Scheme 13).

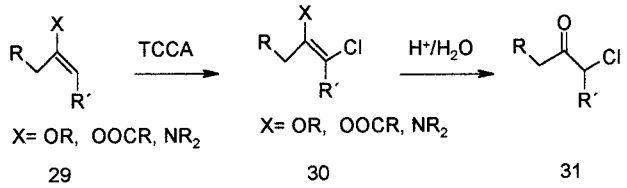
H. Suzuki published in 1998 a method for the chlorination of phenylphosphonic acid with TCCA in concentrated sulfuric acid.[25] Using this method it was also possible to

(20) Newkome, G. R.; Kiefer, G. E.; Xia, Y. J.; Gupta, V. K. *Synthesis* **1984**, 676.
(21) Palomo Coll, A. Eur. Pat. 0484265, 1992.
(22) Juenge, E. C.; Beal, D. A.; Duncan, W. P. *J. Org. Chem.* **1970**, *35*, 719.
(23) Rosevear, J.; Wilshire, J. F. K. *Aust. J. Chem.* **1980**, *33*, 843.
(24) Manschand, P. S.; Coffen, D. L.; Belica, P. S.; Wong, F.; Wong, H. S.; Berger, L. *Heterocycles* **1994**, *39*, 833.
(25) Suzuki, H. Japanese Patent 10045779 A2, 1998. *Chem. Abstr.* **1998**, *128*, 154222.

Scheme 14. **Chlorination of ketones**



Scheme 15. **Chlorination of substituted alkenes**



prepare tetrachlorophthalic anhydride from phthalic anhydride in 93.2% yield.[26]

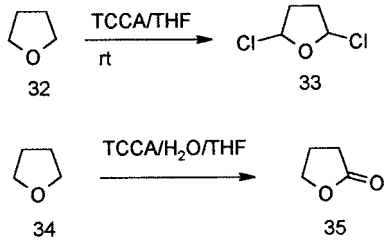
In 1985 Hiegel et al. reported for the first time the use of TCCA for the α- chlorination of ketones. The chlorination was performed under acid catalysis using BF_3−etherate as catalyst. Under these conditions a monochlorination of the most substituted side chain was obtained in moderate-to-high yields. A drawback of this method is that the ketone has to be used in large excess. In the case of 2-propanone (**25**) a 17.4 excess was used, giving 58% of chloroketone **26**. In the case of 2-methylcyclohexanone (**27**) a 1.98 excess was necessary to obtain the chloroketone **28** in 87% yield (Scheme 14).

In 1998 H. Rayle and R. Roemmele reported the chlorination of substituted alkenes **29** using trichloroisocyanuric acid.[27] The alkenes used were enolethers, enolesters, and enamines, and after hydrolysis the corresponding monosubstituted chloroketone **31** was obtained in good yield without using a large excess of the starting material (Scheme 15).

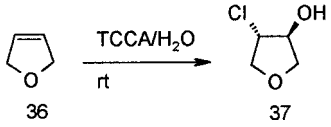
Juenge et al.[28] also reported in 1966 the chlorination of cyclic ethers. They investigated the reaction between tetrahydrofuran or tetrahydropyran with trichloroisocyanuric acid at 0 °C. The reaction afforded mainly *trans*-2,5 dichlorotetrahydrofuran (**33**) in 26% or *trans*-2,6-dichloro-tetrahydropyran 28% yield. By a simple modification of the reaction conditions, namely, the addition of water, the reaction afforded instead γ-butyrolactone (**35)** from THF and δ-valerolactone from THP as the major product after an α-methylene oxidation probably via a hypochlorous acid oxidation. The liberation of hypochlorous acid from TCCA in contact with water is well-known[29] (Scheme 16).

Hypohalogenation was also found by Juenge et al. to occur with TCCA in the presence of water in the reaction with unsaturated cyclic ethers such as 2,5-dihydrofuran. By

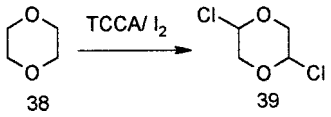
Scheme 16. **Chlorination of cyclic ethers**



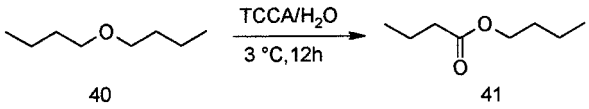
Scheme 17. **Hypohalogenation of unsaturated ethers**



Scheme 18. **α-Chlorination of ethers**



Scheme 19. **Oxidation of ethers**



the reaction *trans*-3-chlor-4-hydroxy-tetrahydrofuran was obtained in about 30% yield. In this case no α-chlorination of the cyclic ether was observed (Scheme 17).

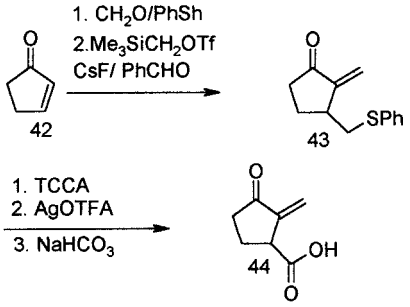
Later the scope and limitation of the chlorination of cyclic ethers was reported by Duncan et al.[30] studying also *p*-dioxane. The chlorination of dioxane at 80−85 °C with TCCA in dioxane as solvent and I_2 as catalyst was found to give a 9:1 mixture of *trans*- and *cis*-2,5-dichloro-*p*-dioxane (**39**) in 72% yield. The catalysis with $ZnCl_2$ also gave a rise in yield compared to that of the uncatalysed reaction although not as high as with iodine catalysis. It was also possible through iodine catalysis of the reaction with THF and THP to raise the yield of the dichloro derivatives to 54 and 56%, respectively (Scheme 18).

B. Oxidation. Oxidation of Ethers. In 1968 Juenge et al.[31] described the direct oxidation of aliphatic ethers to esters utilizing TCCA in aqueous ether solution. The yield from the reaction was found to be extremely dependent on the structure of the ether. From diethyl ether ethyl acetate was obtained in 49%, but from dibutyl ether (**40)** butylvalerate (**41)** was obtained in a quantitative yield. From benzyl ethers the major product was benzaldehyde. As it is necessary to have at least 3 equiv of water compared to TCCA in the mixture to start the reaction, the actual oxidant is probably hypochlorous acid as described earlier for the synthesis of lactones from cyclic ethers (Scheme 19).

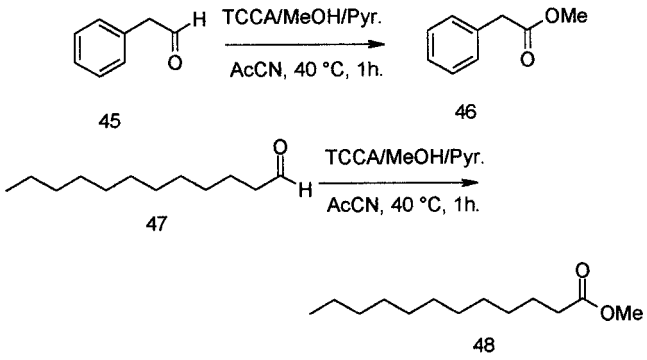
The oxidation of a thioether in a two-step process with TCCA and AgTFA for a short synthesis of sarkomycin (**44)** from cyclopentenone (**42**) has also been reported.[32] (Scheme 20).

(26) Suzuki, H. Japanese Patent 09067359 A2, 1997. *Chem. Abstr.* **1997**, *126*, 277382.
(27) Rayle, H. L.; Roemmele, R. C. Eur. Pat. 0872463A1, 1998.
(28) Juenge, E. C.; Spangler, P. L.; Duncan, W. P. *J. Org. Chem.* **1966**, *31*, 3836.
(29) Brady, A. P.; Sancier, K. M.; Sirine, G. *J. Am. Chem. Soc.* **1963**, *85*, 3101.
(30) Duncan, W. P.; Strate, G. D.; Adcock, B. G. *Org. Prepr. Proced. Int.* **1971**, *3*, 149.
(31) Juenge, E. C.; Beal, D. A. *Tetrahedron Lett.* **1968**, *55*, 5819.

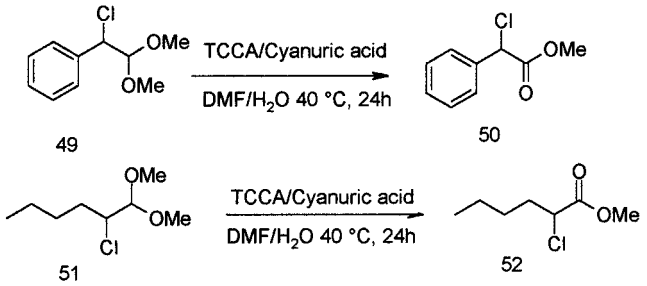
Scheme 20. **Synthesis of sarkomycin**



Scheme 21. **Oxidation of aldehydes**



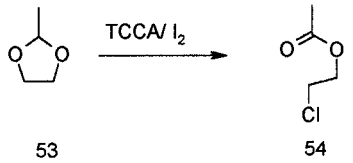
Scheme 22. **Oxidation of 2-chloroacetals**



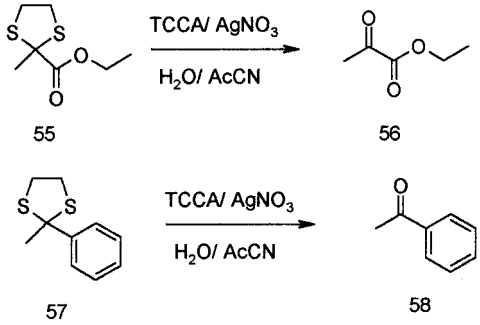
Oxidation of Aldehydes and Acetals. In 1980 Hiegel et al.[33] presented a simple method for the oxidation of aldehydes to methyl esters. A solution of TCCA, the aldehyde, methanol, and pyridine in acetonitrile gave the corresponding methylester. The authors suggested that the reaction probably goes through a hemiacetal which can be oxidised as a secondary alcohol. The methylesters were obtained from all examples in fairly good yields with yields ranging from methyl 2-phenylethanoate (**46**) in 68% yield to methyl dodecanoate (**48**) in 93% yield (Scheme 21). The oxidation of 2-chloroacetals with TCCA has also been reported to give the corresponding 2-chloroesters[34] (Scheme 22).

The reaction gives yields in the range from 42% of methyl 2-chloro-2-phenylethanoate (**50**) to 92% of methyl 2-chlorohexanoate. The authors reported that the addition of cyanuric acid to the reaction mixture was necessary to get the reaction started. The cyanuric acid probably functions as an acid catalyst for the formation of the hemiacetal which can be oxidised as a secondary alcohol.

Scheme 23. **Cleavage of acetal**



Scheme 24. **Cleavage of thioketal**



Also the oxidation of α-acetoxyacetals has been reported by Ghelfi et al.[35] The reaction was performed under the same reaction conditions as with the chloro acetal except that no cyanuric acid was added to the reaction. The yields are also comparable with those obtained with the chloroacetals.

The α-chlorination of cyclic ethers with TCCA has also been used to open up cyclic acetals to the corresponding chlorine-substituted esters. In 1974 Gelas and Petrequin developed this reaction as an alternative for cleavage of acetals in sugar chemistry.[36] (Scheme 23)

The authors reported a 70% yield of **54** after distillation. The low yield was found to be due to the instability of the product during distillation. Prior to purification a yield of 90% was observed. The authors also compared the use of NCS for the reaction. It was found that the yield was much lower around 40−50%.

Later G. Olah et al. used the α- chlorination of sulfides with TCCA as a mild cleavage of ethandiyl *S*,*S*-acetals. The authors used an excess of TCCA together with silver nitrate in aqueous acetonitrile. The corresponding carbonyl compound was obtained in excellent yield after a reaction time of only 10 min (Scheme 24).

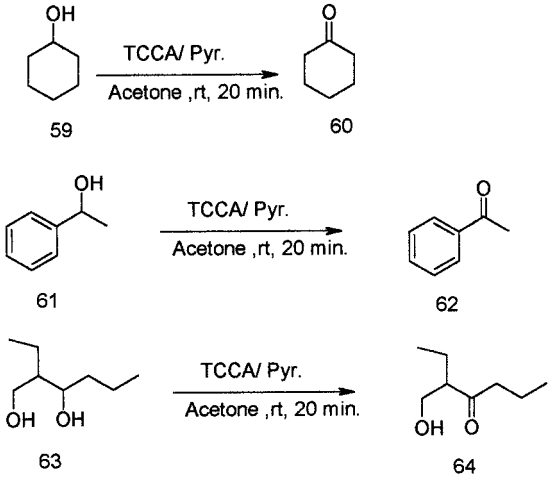
From the reaction it was possible to obtain ethyl pyruvate (**56**) in an almost quantitative yield (95%). The lowest yield was obtained from acetophenone (**58**) 93%. α-Chlorination of thioethers has also been reported to occur with NCS although in modest yield.[37]

Oxidation of Alcohols. In 1957 the first use of TCCA for the oxidation of alcohols was reported.[15] This was a small study over oxidation of steroid and terpene alcohols using TCCA.

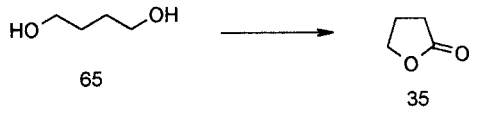
In 1992 Hiegel and Nalbandy[38] reported a more detailed study over the use of TCCA for the oxidation of alcohols. They studied the oxidation of secondary alcohols in acetone

(32) Cohen, T.; Kosarych, Z.; Suzuki, K.; Yu, L.-C. *J. Org. Chem.* **1985**, *50*, 2965.
(33) Hiegel, G. A.; Bayne, C. D.; Donde, Y.; Tamshiro, G. S.; Hiberath, L. A. *Synth. Commun.* **1996**, *26*, 2633.
(34) Boni, M.; Ghelfi, F.; Pagoni, U. M.; Pinetti, A. *Bull. Soc. Chem. Jpn.* **1994**, *67*, 156.
(35) Benicasa, M.; Grandi, R.; Ghelfi, F.; Pagnoni, U. M. *Synth. Commun.* **1995**, *25*, 3463.
(36) Gelas, J.; Petraquin, D. *Carbohydr. Res.* **1974**, *36*, 227.
(37) Muthusubramanian, L.; Mitra, R. B.; Rao V. S. S.; Raghavan, K. V. *Indian J. Chem., Sect. B* **1996**, *35*, 1331.
(38) Hiegel, G. A.; Nalbandy, M. *Synth. Commun.* **1992**, *22*, 1589.

Scheme 25. **Oxidation of secondary alcohols**



Scheme 26. **Oxidation of diols**



with TCCA and pyridine as base to scavenge the released hydrochloric acid. All ketones were obtained in good yields after 20 min at room temperature. During the course of the reaction in acetone only very limited amounts of chlorinated products were observed. When the reaction was run in acetonitrile, more chlorinated products were observed.

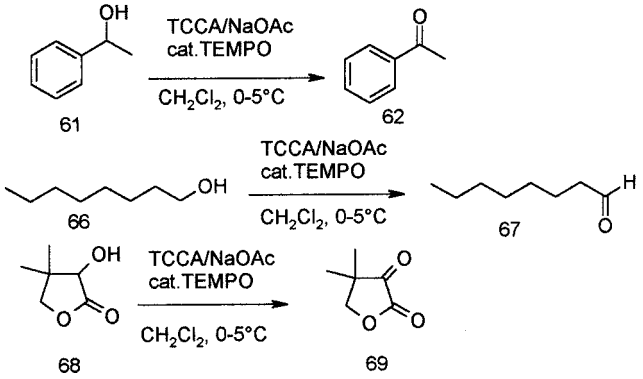
The authors also observed that secondary alcohols were oxidised considerably faster than primary alcohols in the presence of TCCA which allowed a selective oxidation of secondary alcohols in the presence of primary (Scheme 25).

The yield of ketone was more or less independent of the structure. The lowest yield of 68% was obtained from cyclohexanone (**60**), and the best, from acetophenone (**62**) with 90%. 2-Ethyl-1-hydroxy-3-hexanone was obtained in 72%.

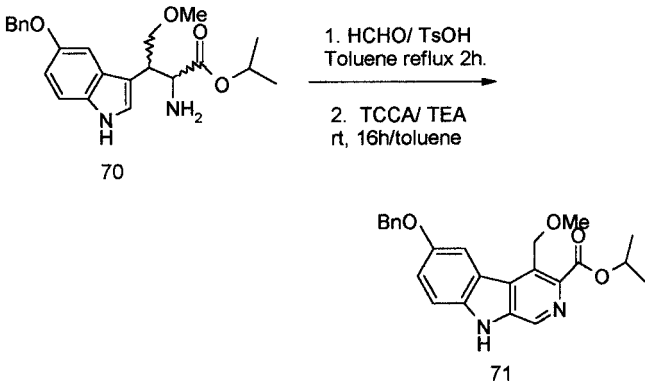
Kondo et al.[39] reported in 1995 the oxidation of diols for the synthesis of lactones using *N*-haloamides. The reaction was initially optimised with NCS. The optimal conditions for the reaction with 1,4-butanediol (**65**) were found to be room temperature in methylene chloride for 5 h. Under these conditions γ-butyrolactone (**35**) was obtained in 88% yield. The authors found that the reaction did not work at all in the presence of pyridine. For the reaction 3 equiv of NCS was necessary to force the reaction to completion. Using the optimum conditions other *N*-haloamides were compared to NCS. In these studies TCCA was the best, giving **35** in 85% yield. *N*-Bromoacetamide and *N*,*N*-dichlorobenzenesulfonamide also gave yields over 80%. With NBS the reaction did not work well, giving only 57% of **35** (Scheme 26).

A TEMPO-catalysed oxidation of alcohols with TCCA as primary oxidant has also been reported.[40] With this method it is possible to oxidise primary and secondary alcohols to the corresponding carbonyl compound in good-to-excellent

Scheme 27. **TEMPO-catalysed oxidation of alcohols.**



Scheme 28. **Dehydrogenation of tetrahydro-β-carbolines**



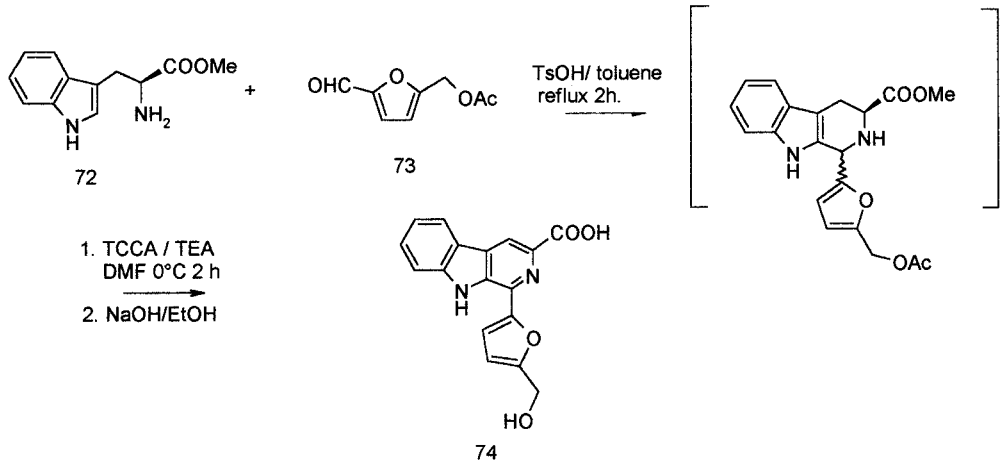
yields. The standard procedure for the TEMPO-catalysed oxidation of alcohols utilises aqueous sodium hypochlorite as the primary oxidant.[41] The major drawback of the standard method is that it is not possible to prepare aldehydes and ketones which are sensitive towards aqueous alkaline conditions. With the new method no water is necessary to reoxidise TEMPO (Scheme 27). The authors reported that after purification by distillation they obtained acetophenone (**62**) in 69% yield, octanal (**67**) in 91%, and 2-ketopantolacton (**69**) in 86% yield. Instead of TCCA dichlorodimethyl hydantoin NDDH could also be used without any difference in yield of the prepared product.

The TEMPO-catalysed oxidation of primary and secondary alcohols has also been reported for NCS.[42]

Dehydrogenation of Amines. In 1998 we reported the use of TCCA in combination with triethylamine for the dehydrogenation of 3-carboxytetrahydro-β-carbolines.[43] The method was developed during scale-up of the β-carboline abecarnil, **71**. Due to reported problems of explosions during transport of *tert*-butyl hypochlorite, the method of choice for lab scale, it was decided to search for an alternative method. During this study two reagents were found to give high transformations: NCS and TCCA. Although NCS gave a very high yield of crude product, it was not possible to obtain a purified product after recrystallization due to the fact that the byproduct succinimide cocrystallises with **71**. It was only possible to eliminate succinimide from the crude product through a chromatographic purification (Scheme 28).

(39) Kondo, S.; Kawasoe, S.; Kunisada, H.; Yuki, Y. *Synth. Commun*. **1995**, *25*, 719.
(40) Jenny, C. J.; Lohri, B.; Schlageter, M. Eur. Pat. 775684, 1997.
(41) Anneli, P. C.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559.
(42) Einhorn, J.; Einhorn, C.; Ratajczak, F.; Pierre, J.-L. *J. Org. Chem*. **1996**, *61*, 7452.
(43) Haffer, G.; Nickisch, K.; Tilstam, U. *Heterocycles* **1998**, *48*, 993.

Scheme 29. **Synthesis of flazin**



Using TCCA it was possible in the laboratory to obtain the **71** in 82% yield from the tryptophane derivative, **70**. For the sequence the yield from **71** using *t*-BuOCl as oxidant was 80%. The method was transferred to the pilot plant and could be safely scaled up to a 100-kg scale. During hazards evaluation of the process it was found that the addition of TCCA to the reaction mixture was best dose-controlled. The addition of TCCA to the reaction mixture was found to have a heat of reaction of −210 kJ/mol.

After the successful transfer to the pilot plant the scope and limitations of the process for the dehydrogenation of various tetrahydro-β-carbolines were evaluated. During this evaluation it was also possible to perform a total synthesis of flazin (**74**) a natural product found in Japanese soy sauce.[44] The original aromatization was performed with Pt/C and oxygen in refluxing toluene (Scheme 29).

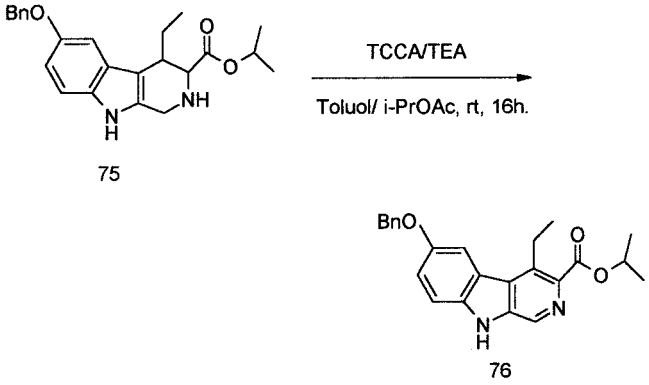
Tryptophan methyl ester was condensed with 5-(acetoxymethyl)furaldehyde under TsOH catalysis in refluxing toluene. The yield of flazin (**74**) from tryptophan methyl ester (**72**) was 85%. No benzylic oxidation or aromatic chlorination was observed under the reaction conditions, although the system contains an electron-rich benzylic position and two electron-rich heterocycles.

Also in another development project the aromatization of a tetrahydro-β-carboline (**75**) with TCCA and TEA was successfully used for scale-up to 15-kg scale in the pilot plant (Scheme 30). The aromatization method has lately also been reported for the synthesis of β-carbolines on solid phase.[45]

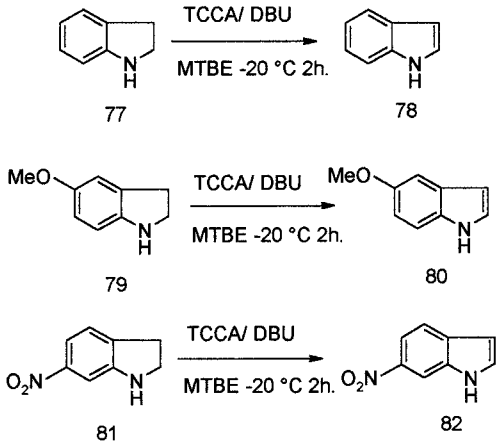
The conversion of indolines to indoles has been the subject of many oxidation studies over the years.[46] This theme seems to be trivial but has not been satisfactorily solved until we utilised TCCA for the conversion[47] (Scheme 31).

The reaction was optimised for indole (**78**); from this study it was found that the amount of oxidant and base for a complete conversion of indoline to indole was found to be a 10% molar excess of TCCA with 2 equiv of DBU. The best solvent being MtBE. Utilizing these reaction conditions

Scheme 30. **Large-scale dehydrogenation**



Scheme 31. **Dehydrogenation of indolines**

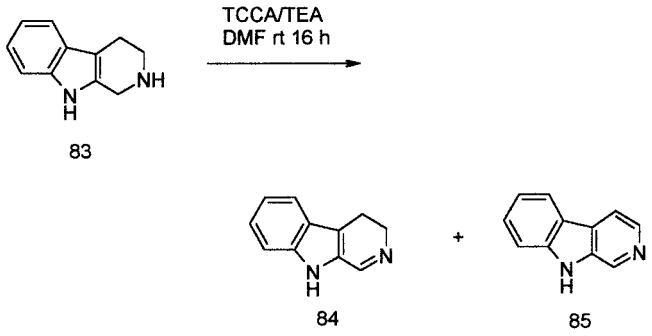


it was possible to obtain indole in 89% yield after workup and crystallization from petrol ether. Under these conditions it was possible to obtain 5-methoxyindole (**80**) in 83% yield and the electron-poor 6-nitro-indole (**82**) in 76% yield (Scheme 32).

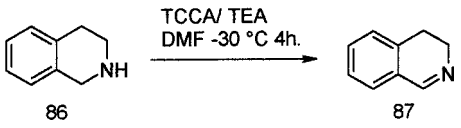
During our laboratory investigation of dehydrogenation of β-carbolines we also investigated the aromatization of the core system (**83**). Under these reaction conditions the dihydro-β-carboline (**84**) was the main product, although accompanied by the starting material and the β-carboline (**85**). This is probably due to disproportionation of the dihydro-β-carboline (**84**).

(44) Gessner, W. P.; Brossi, A. *Arch. Pharm. (Weinheim)* **1988**, *321*, 95.
(45) Jing Xin, Z.; Xiao Chuan, T.; Liang, P.; Xiao Tian, L. *Chin. Chem. Lett.* **2000**, *11*, 955.
(46) Gribble, G. *J. Chem. Soc., Perkin Trans.* **2000**, *1*, 1045.
(47) Tilstam, U.; Harre, M.; Heckrodt, T.; Weinmann, H. *Tetrahedron Lett.* **2001**, *42*, 5385.

Scheme 32. **Dehydrogenation of tetrahydro-β-carboline**



Scheme 33. **Dehydrogenation of tetrahydroisoquinoline**



Under the used reaction conditions it was not possible to obtain the β-carboline (**85**) selectively. This resistance of tryptamine derivatives towards oxidation is known from the literature.[48]

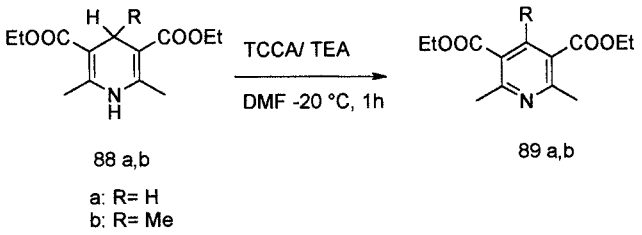
3,4-Dihydroisoquinoline (**87)** is a useful precursor for the synthesis of isoquinoline alkaloids. Using TCCA/TEA 3,4-dihydroisoquinoline (**86**) could easily be obtained in high yield under mild conditions without being contaminated with larger amounts of the corresponding isoquinoline or the 1,2,3,4-tetrahydroisoquinoline-1-one normally seen in oxidations of tetrahydroisoquinoline[49] (Scheme 33). 3,4-Dihydroisoquinoline (**87**) was obtained in 88% yield.

1,4-Dihydropyridines are intermediates in the Hantzsch pyridine synthesis, one of the most useful pyridine ring synthesis, and there is a demand for a general and convenient method for their oxidation to the corresponding pyridines. A variety of oxidizing agents, viz. HNO_3, PCC, $KMnO_4$, CAN, and *tert*-butylhydroperoxide, at elevated temperature have been reported.[50]

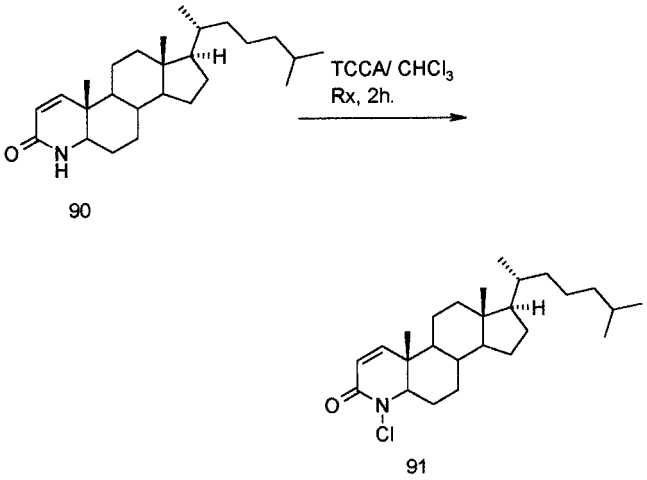
The use of TCCA/TEA was found to be very efficient for the dehydrogenation of 1,4-dihydropyridines.[51] Until now we have studied two cases, **89a** and **b**. In both cases we obtained almost a quantitative yield of the pyridine derivative **89a** (92%) and **89b** (95%). In the case of **89b** no demethylation was observed, a major obstacle reported with other methods (Scheme 34).

C. Miscellaneous. In 1991 Back et al.[52] reported the synthesis of some novel *N*-chloro-Δ^1-4-azasteroids by efficient N-chlorination with TCCA. The authors compared the reaction time and the amount of reagent necessary for the reaction for TCCA and NCS. For instance for the chlorination of the azasteroid **90** 0.5 mol equiv of TCCA was necessary to prepare the *N*-chloro-derivative **91** in 99% yield within 2 h in refluxing chloroform. With NCS 5.2 mol equiv was necessary for the conversion, which then took 12 h in refluxing chloroform. The yield of **91** from the reaction with NCS was 85%. Due to the huge excess a tedious chromatographic workup was necessary. The authors found also for other derivatives that TCCA is superior to NCS from the point of view of efficiency and convenience (Scheme 35). Matsugi et al. reported the use of various chlorine- and bromine-containing oxidants together with (−)-menthol for an enantioselective oxidation of sulfides to sulfoxides[53] (Scheme 36).

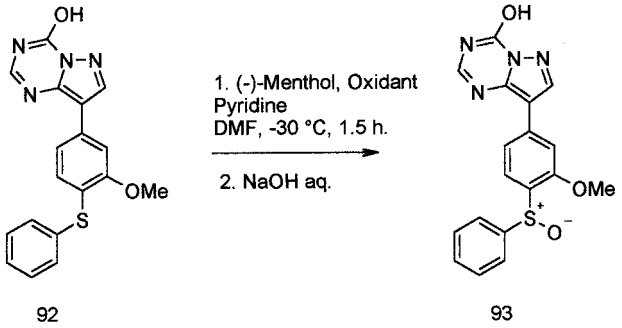
Scheme 34. **Aromatization of dihydropyridines**



Scheme 35. **N-Chlorination of azasteroids**



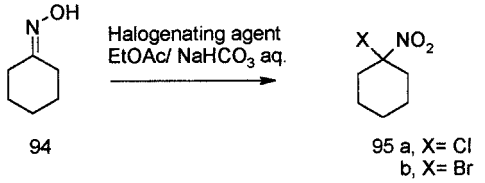
Scheme 36. **Sulfide oxidation**



The reaction was studied on the pyrazolotriazine system **92** for the preparation of BOF-4272 (**93**), a potent xanthine oxidase/xanthine dehydrogenase antagonist. The method was first reported by Oae's group using *tert*-butylhypochlorite as oxidant and pyridine as base.[54] In the study from Matsugi et al. the influence of the type of oxidant, chiral alcohol, pyridine base, and solvent on the reaction was studied as a starting point. The best oxidant was selected from *tert*-butylhypochlorite, *N*-chlorobenzotriazole, TCCA, *N*-bro-

(48) Love, B. E. *Org. Prep. Proced. Int.* **1996**, *28*, 1.
(49) Moriarty, R. M. et al. *Tetrahedron Lett.* **1988**, *29*, 6913.
(50) Ko, K.-Y.; Kim, J.-Y. *Tetrahedron Lett.* **1999**, *40*, 3207.
(51) Tilstam, U. Unpublished results.
(52) Back, T. G.; Chau, J. H.-L.; Dyck, B. P.; Gladstone, P. L. *Can. J. Chem.* **1991**, *69*, 1482.
(53) Matsugi, M.; Hashimoto, K.; Inai, M.; Fukuda, N.; Furuta, T.; Minamikawa, J.; Otsuka, S. *Tetrahedron: Asymmetry* **1995**, *6*, 2991.
(54) Moriyama, M.; Yoshimura, T.; Furukawa, N.; Numata, T.; Oae, S. *Tetrahedron* **1976**, *32*, 3003.

Scheme 37. **Oxidation of oximes**



mobenzotriazole and NCS. *N*-bromobenzotriazole and NCS did not give the expected product. The other three gave almost the same yield and ee: *N*-chlorobenzotriazole (yield 87%, 43% ee), TCCA (yield 83%, 39% ee), and *tert*-butylhypochlorite (yield 87%, 38% ee). From these results *N*-chlorobenzotriazole was chosen for further optimization. DMF was found to be the best solvent, and 4-cyanopyridine was used as base. As chiral auxiliary 2-substituted cyclohexanols were effective. From (1*R*,2*S*)-(−)-2-phenylcyclohexanol an ee of 73% was obtained.

Later it was found that the best conditions were to isolate the intermediate menthoxy sulfonium salt from ethyl acetate (> 99% de) which afterwards was separately treated with sodium hydroxide.

In 1991 the use of DCCA, the monosodium salt of TCCA, *N*,*N*-dibromocyanuric acid and dibromodimethyl-hydantoin were studied for the oxidation of hydroxylamines to *gem*-halonitro compounds (Scheme 37).[55]

The chloro compound **95a** was obtained in 78% yield independently if TCCA or the monosodium salt was used as these are under the reaction conditions convertible. The bromo derivative **95b** was obtained in 69% yield, utilizing dibromocyanuric acid.

Alkyl chlorides, acid chlorides, and vinyl chlorides can be prepared from alcohols, carboxylic acids, and 1,3-diketones, respectively, by using phosphorus pentachloride, phosphorus trichloride, sulfuryl choride, or dichlorotriphenylphosphorane ($(C_6H_5)_3PCl_2$). The same reagents can also convert amides into nitriles.[56] Hiegels group reported in 1999 that a mixture of TCCA and triphenylphosphine in anhydrous acetonitrile effectively carries out the same kinds of reactions described above[57] (Scheme 38).

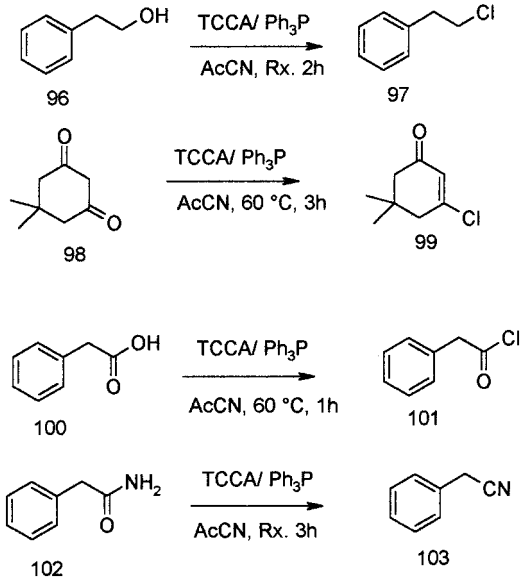
All derivatives were obtained in fairly good yields after chromatographic purification except that the yield for the nitrile **103** was only 39%. 2-Phenylethyl chloride (**97**) was obtained in 74% yield, the vinyl chloride **99** in 82% yield, and the acid chloride **101** in 95% yield.

The most important advantage of this new method is that the two reagents triphenylphosphine and TCCA are stable until combined in anhydrous acetonitrile which makes the method attractive for large-scale preparations.

Chlorine-substitution reactions with alcohols has also been reported for NCS in combination with dimethyl sulfide.[58]

(55) Walters, T. R.; Zajac, W. W., Jr.; Woods, J. M. *J. Org. Chem.* **1991**, *56*, 316.
(56) Larock, R. C. *Comprehensive Organic Transformations*; VCH Publishers: New York, 1989.
(57) Hiegel, G. A.; Ramirez, J.; Barr, R. K. *Synth. Commun.* **1999**, *29*, 1415.
(58) Werner, M.; Stephenson, D. S.; Szeimies, G. *Liebigs Ann. Chem.* **1996**, 1705.

Scheme 38. **Chlorine-substitution reactions**



Conclusions

In this literature review we have shown that trichloroisocyanuric acid (TCCA) is a safe and efficient reagent, useful for chlorination and oxidation reactions also on large scale.

Depending on the reaction conditions employed, it is possible to obtain either a selective chlorination (acidic conditions) or an oxidation (alkaline conditions).

For use in reactions all three chlorine atoms are active. In comparison to NCS, the most-used *N*-haloamide, TCCA is more atom economical and is also highly soluble in organic solvents as well as more economical, thus making it the better reagent for large-scale use.

TCCA shows in benzylic chlorinations a remarkable selectivity for the monochlorination of different electron-poor heterocycles. The selectivity for the monochlorination of cyclic ethers is also quite good, affording rather good yields of monochlorinated cyclic ethers when used in combination with a catalytic amount of iodine. The α-chlorination of ethers has also been successfully used for the ring-opening of acetals and thioketals. In combination with water, TCCA is a good reagent for hypohalogenation of alkenes. The monochlorination of ketones affords the more substituted α-chloroketone.

The use of TCCA for the oxidation of secondary alcohols has been shown to be a method to consider. The combination with TEMPO has been shown to be a remarkably good method for the oxidation of primary and secondary alcohols under nonaqeous conditions.

The use of TCCA for the dehydrogenation of various *N*-heterocycles has been shown to be not only selective but also very high-yielding.

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