Chloramine T and Related *N*-Halogeno-*N*-metallo Reagents

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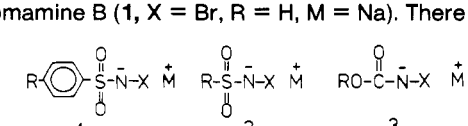
Contents

I. Introduction

The diverse nature of the chemistry of *N*-halogeno-*N*-metallo reagents is a consequence of their ability to act as sources of (a) halonium cations, (b) hypohalite species, (c) N anions (e.g., sulfonamidate or carbamidate anions) which act both as bases and nucleophiles, and (d) nitrenoids in limited cases. As a result, these reagents react with a surprising range of functional groups, effecting an array of molecular transformations. This review will therefore attempt to place in perspective the reactions and utility of the reagents, as gleaned from *Chemical Abstracts* up to late 1976 and other literature sources. Aspects of this chemistry have been reviewed elsewhere,[1] but recent significant developments in the area necessitate a current review.

Several of the *N*-halogeno-*N*-metalloarylsulfonamidates are commonly known by trivial names, e.g., chloramine T (**1**, X = Cl, R = Me, M = Na), chloramine B (**1**, X = Cl, R = H, M = Na), and bromamine B (**1**, X = Br, R = H, M = Na). There has been developed more recently a related series of alkylsulfonamide derivatives **2**. A range of corresponding *N*-halogeno-*N*-metallocarbamates **3** has been prepared, with varying alkyl and aryl groups and *N*-chloro, *N*-bromo, and *N*-iodo substituents, mainly as the sodio and to a lesser extent as the silver salts.



1 **2** **3**

Historically, the important early developments in the area stemmed from the synthesis of chloramine T and related arylsulfonamide derivatives.[2-4] Motivation for the development of these reagents was given by the recognition[4] of their disinfectant and antiseptic properties. Shortly afterward the Great War provided additional impetus to chloramine T chemistry because of the facile reaction with mustard gas $(ClCH_2CH_2)_2S$ to give a relatively innocuous crystalline sulfimide adduct. The multifarious reactions of chloramine T and related sulfonamide derivatives with a range of functional groups have since been investigated, and in the very recent literature important and novel molecular transformations including vicinal hydroxyamination of olefins and allylic amination techniques have emerged. Paralleling the chemistry of these sulfonamide derivatives has been the synthesis and exploitation of the related carbamate derivatives **3**. Although these latter reagents have not yet been as extensively investigated, their potential has recently been realized in such diverse areas as the modification of penicillins and cephalosporins, and in improved methods of olefin hydroxyamination.

This review will deal principally with the preparation and reaction of *N*-halogeno-*N*-metallo reagents with organic, and to a lesser extent, inorganic functional groups. The use of chloramine T in analytical chemistry is extensive and will not be comprehensively covered, although certain informative and important uses, particularly in the chemistry of sulfur and of group 5 derivatives, will be summarized.

No attempt will be made to review the extensive areas of *N,N*-dihalogeno and *N*-monohalogeno reagents, since the reactions of the title compounds are in themselves unique.

II. N-Halogeno-N-metallosulfonamidates

A. Preparation

The first preparation of *N*-halogeno-*N*-metallosulfonamidates[5] was from the treatment of *N,N*-dibromoarylsulfonamides with aqueous base, giving the *N*-bromo-*N*-sodioarylsulfonamidates as hydrates. The second, and subsequently more common, method[3] involved reaction of the arylsulfonamide with sodium or potassium hypochlorite followed by salting out of the derivatives. Most preparations of *N*-chloro, *N*-bromo-, and *N*-iodo metallo salts are based on this method.[4-10] The *N*-chloro-*N*-sodiosulfonamidate salts of xylene, ethylbenzene, bromobenzene, *p*-alkoxybenzene, *o*-tolyl, and a range of other substituted benzene and naphthalene sulfonamides have been described. Recent patents describe a continuous flow process[11] in which chloramines B and T are prepared in 75–95% yield by feeding an aqueous sodium hydroxide solution of the sulfonamidate sodium salt and a stoichiometric quantity of chlorine through a flow reactor, and an alternative[12] preparation in which tolu-

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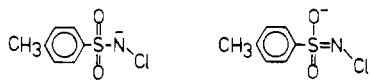
ene-*p*-sulfonamide is dissolved in aqueous sodium hydroxide, extracted with an organic solvent to remove contaminating ditolyl sulfone, and chlorinated to give chloramine T. The silver salt of chloramine T (**1**, X = Cl, R = Me, M = Ag) has been prepared by silver nitrate reaction with chloramine T.[13,14]

In refutation of textbook statements that aliphatic sulfonamides do not react with sodium hypochlorite, it has recently been shown[15] that methane-, ethane, hexane-, and dodecanesulfonamides are rapidly and quantitatively converted to the corresponding *N*-chloro-*N*-sodio derivatives. Sodium hypobromite gave the *N*-bromo-*N*-sodio products. In addition, *N*-chloro-*N*-sodio salts of 3-phenylpropanesulfonamide and cyclohexanesulfamide were prepared.

B. Properties

The structure of chloramine T is most commonly depicted as **4** and occasionally as **5**.[25,56] Bond lengths are not available, and an x-ray crystallographic analysis of the series, sulfonamide, *N*-chlorosulfonamide, and *N*-chloro-*N*-sodiosulfonamide would be desirable.



4 **5**

Chloramine T and related sulfonamide derivatives are stable in aqueous solution. They are strong electrolytes and are strong oxidants in both acidic and alkaline media (chloramine T: E_{red} = 1.138 at pH 0.65 and 0.5 at pH 12).[16] Sulfur is liberated from hydrogen sulfide and iodine from acidified potassium iodide.[17] In aqueous solution chloramine T is thought to exist in a complex series of equilibria (Figure 1).[18,19] The pK_a for *N*-chlorobenzenesulfonamide has been estimated as approximately 9.5.[21]

The *N*-halogeno-*N*-metallosulfonamidates are usually prepared as stable crystalline hydrates (e.g., chloramine T trihydrate) which can be dehydrated on heating to 100 °C or by standing under vacuum over phosphorus pentoxide. Heating chloramine T is, however, hazardous because of explosion.[22] The corresponding alkylsulfonamidates also crystallize in the hydrated form but are more readily dehydrated over phosphorus pentoxide.[15]

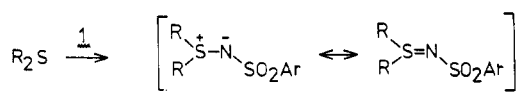
The arylsulfonamide and lower alkylsulfonamide derivatives are very water soluble.[15] Interestingly, *N*-chloro-*N*-sodiododecanesulfonamidate (**2**, R = $C_{12}H_{25}$) is a surfactant.[15]

C. Reactions with Sulfur Compounds

1. Sulfides, Selenides, Sulfoxides, and Sulfimides

a. Sulfides

N-Halogeno-*N*-metallosulfonamidate reactions with sulfides afford a particular facile synthesis of many sulfimides **6**.[191] The



6

area of study was initiated by the reaction of chloramine T with mustard gas to give the sulfimide **7**.[23] A wide range of alkyl and aryl sulfides reacted with chloramine T and related reagents in the form of sodium or potassium salts to give the corresponding sulfimides.[24-33] Cyclic sulfides give sulfimides,[32,33] compound **8** giving the diequatorial isomer **9**.[34] The versatility of the reaction, which is often effected simply by stirring the reactants in alcohol or water, or sometimes as a heterogeneous suspension in nonprotic solvents, is demonstrated by the preparation of modified sulfur-containing polymers,[35] bissulfimides,[25,36,37]

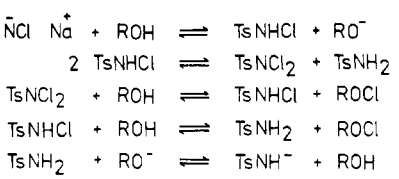
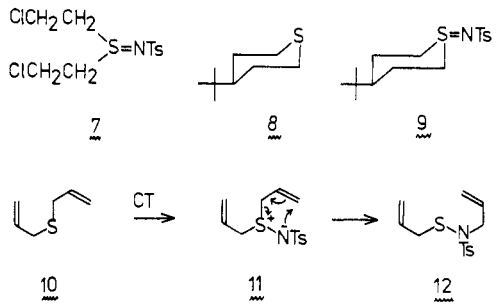


Figure 1.

and allyl sulfimides.[10,38] Diallyl sulfide (**10**), for example, gave a sulfimide **11** which slowly isomerized at room temperature by a [2,3] electrocyclic process to give the sulfenamide **12**, illus-

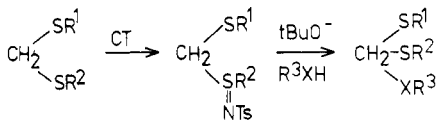


7 **8** **9**

10 **11** **12**

trating a potential use for reagents **1** in the synthesis of sulfenamides. This rearrangement was also observed for allyl sulfimides derived from *N*-chloro-*N*-sodionaphthalene-1-sulfonamidate and *N*-chloro-*N*-sodio-4-methyl-3-nitrobenzenesulfonamidates. Further examples were observed[39,40] with the sulfimides derived from the reaction of chloramine T and cinnamyl phenyl sulfide and benzyl allyl disulfide, and from the reaction of diallyl sulfide with *N*-chloro-*N*-sodio-*p*-acetamidobenzenesulfonamidate.

In a very recent reaction of chloramine T a thioacetal was transformed into the monosulfimide **13**[41] which was subjected to reaction with potassium *tert*-butoxide and trapping of the resultant sulfonium species by alcohol or thiol to give the product (**14**, Y = O or S). Related studies are described in section II.C.9.



13 **14**

An important modification of chloramine T–sulfide reactions resulted from the use of phase-transfer reagents.[19] Advantages over the previously reported single-phase methods were obtained.

The reaction of chloramine T type reagents and sulfides are often performed in water, alcohol, or a mixture, and sulfoxide by-products are often observed. Studies of product distribution and physical parameters such as temperature, pH, solvent polarity, concentration of reactions, and the nature of sulfide substituents have been performed,[42-48] the mechanistic speculation not always being in accord. There is strong support, however, for the equilibrium processes depicted in Figure 1[18,19] including chlorinating species such as *N*-chlorotoluene-*p*-sulfonamide (formed in a fast reaction) and *N,N*-dichlorotoluene-*p*-sulfonamide (formed in a slow reaction). The *N,N*-dichloro species has been noted in another context[49] as being formed readily by disproportionation of chloramine T. Although the *N,N*-dichloro species is not inherently a strong chlorinating agent, it was described[49] as being "kinetically more reactive" than chloramine T and *N*-chlorosuccinimide. The recent key studies[18,19] are in agreement with a reaction pathway as depicted in Figure 2 although in the final step involving displacement of

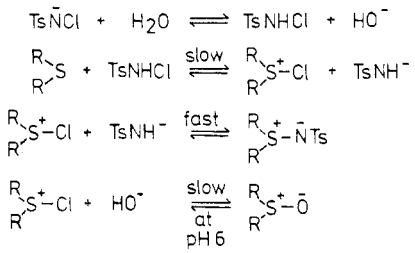
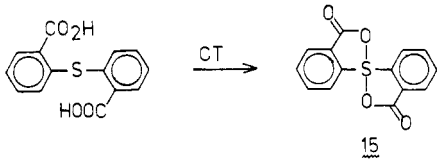


Figure 2.

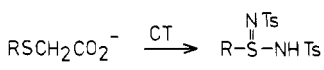
chloride, a sulfurane intermediate may be involved.[20] (In a unique reaction chloramine T reacted with 2,2′-thiodibenzoic acid in dry dioxan to give the dilactone **15**.[20]) It was observed that the



15

reaction of chloramine T with sulfides was second order, and a Hammett correlation showed that the sulfide acted as a nucleophile. Chloramine T was in equilibrium with its protonated form, which was attacked by the sulfide, the rate-determining step being the formation of the chlorosulfonium intermediate. An important finding[19] was that sulfimide formation had a pH optimum of 6 (because toluene-*p*-sulfonamidate anion is protonated at low pH, allowing competitive reaction of the chlorosulfonium intermediate with the aqueous medium), and hence certain sulfimides which are not readily formed under normal reaction conditions may be obtained by adding weak acid to the reaction. In strongly acid media sulfides react with chloramine T to give sulfones in high yield, although sulfides with reactive α or β protons react anomalously.[50]

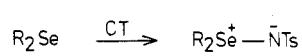
An abnormal reaction was encountered[26,51] when chloramine T was reacted with the sodium salts of ethyl and phenylthioacetic acids (**16**, R = Et or Ph) affording not the expected sulfimide, but the *S*-ethyl- (or phenyl-) *S*-toluene-*p*-sulfonamido-*N*-toluene-*p*-sulfonylsulfimide (**17**). The intermediacy of ethanethiol or benzenethiol was postulated (see section II.C.2 for the reactions of thiols with chloramine T).



16 **17**

b. Selenides

It is pertinent at this point to summarize the reactions of chloramine T with selenides, leading to selenimides **18**[52] presumably via intermediate chloroselenonium species. For example, selenide **19** gave the selenimide **20** with anhydrous chloramine T. (Interestingly, the sulfide corresponding to **19** did not give a sulfimide under similar conditions.) In a closely related synthesis, which formally represents a chloramine T reaction,



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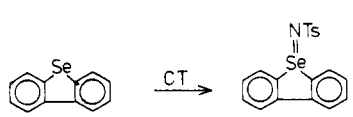


19 **20**

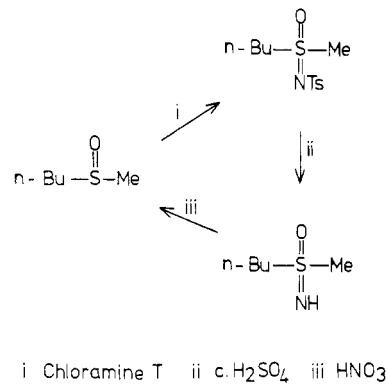
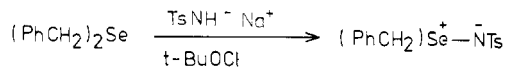


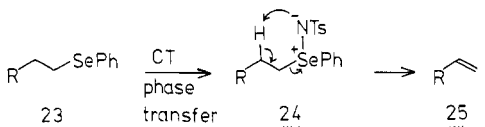
Figure 3.

dibenzyl selenide **21** was treated with *tert*-butyl hypochlorite and sodium toluene-*p*-sulfonamidate to give the selenimide **22**[53]



21 **22**

which was readily hydrolyzed by water to the sulfoxide. Similarly formed were selenimides from methyl phenyl selenide and tetramethylene selenide. No mention was made in this paper of a discrete chloramine T reaction. Possibly chloramine T trihydrate would have given the selenoxide by hydrolysis of the selenimide, but anhydrous chloramine T, as shown elsewhere,[52] may have given the desired product. An interesting recent aspect of selenimide chemistry emerged from the reaction of chloramine T with alkyl phenyl selenides, where the alkyl group is primary.[54] Chloramine T under phase-transfer conditions reacted with the selenide **23** giving the selenimide **24** which underwent facile β-elimination to give the terminal olefin **25**.



23 **24** **25**

c. Sulfoxides

Reagents **1** react with sulfoxides under neutral conditions.[31,56-58] When chloramine B or T was heated with dimethyl sulfoxide and copper powder[56] or with soluble cupric salts,[57] the sulfoximide **26** was obtained. Since absence of catalyst caused a substantial drop in yield, and a high yield insertion reaction to give **27** was observed when dioxan replaced dimethyl

26 **27**

sulfoxide, a mechanism involving a copper sulfonylnitrene was proposed.[56] A similar reaction was utilized in the preparation of several optically active sulfoximides (Figure 3).[58] certain chloramine T–sulfoxide reactions tended, however, to be low-yield processes.[57,58] Under acidic conditions sulfoxides were oxidized by chloramine T to the sulfones.[50]

d. Sulfimides

The sulfimide **28** reacted readily with chloramine T in methanol,[59] giving the sulfone diimide **29**, together with a low yield of the sulfoximide **30**. The yield of **29** could be greatly increased by addition of a large excess of *N*-sodiotoluene-*p*-sulfonamide.

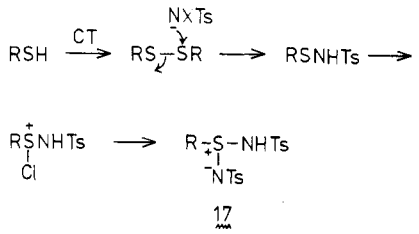
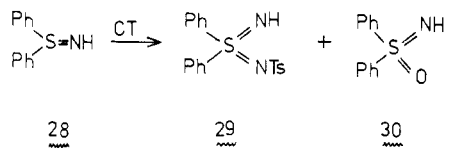
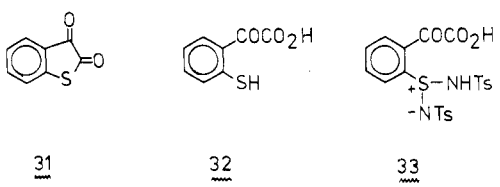


Figure 4.



2. Thiols and Disulfides

Ethanethiol and benzenethiol reacted with 2 molar equiv of chloramine T in alkaline solution to give products of structure **17** (R = Et or Ph).[26] Compounds of related structure (**33**) were also formed when thianaphthenequinone **31** was treated with chloramine T in alcohol.[60] The quinone undergoes alcohydrolysis to the thiol **32** which is oxidized to the disulfide and reacts again

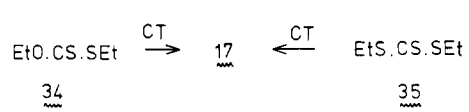


with chlorine T, giving **33.** Other related reactions of disulfides have been described.[37,61-64] Since disulfides give products of type **17** the mechanism for the thiol reactions presumably involves oxidation to disulfides (Figure 4). By analogy with current thoughts on sulfimide formation, further reaction with 1 mol of chloramine T to give a sulfenamide and thence the *S*-alkyl-*S*-tosylamido-*N*-tosylsulfimides **17** can be invoked.

The use of chloramine T in strongly acid media for the analytical estimations of thiols, disulfides, and trisulfides has been investigated.[50] Aryl thiols require 6 molar equiv of chloramine T to give the arylsulfonic acids. Alkanethiols generally require more oxidant, possibly because of further reactions of the alkyl side chain. For example, benzylthiol probably chlorinates at the α-methylene group, apart from the oxidative reactions of the thiol group. Disulfides require 10 molar equiv of oxidant, irrespective of the substituents. Oxidation of other compounds of type R_2S_2 (where R is more electronegative than S) also requires 10 molar equiv of chloramine T, as in MeOSSOMe,[65] $Et_2NSSNEt_2$,[65] $C_5H_{10}NSSNC_5H_{10}$,[66,67] and BrSSBr.[67,68] Dimethyl trisulfide and dipiperidinotrisulfide required 16 molar equiv.[66]

3. Xanthates, Dithiocarbonates, and Thioacid Esters

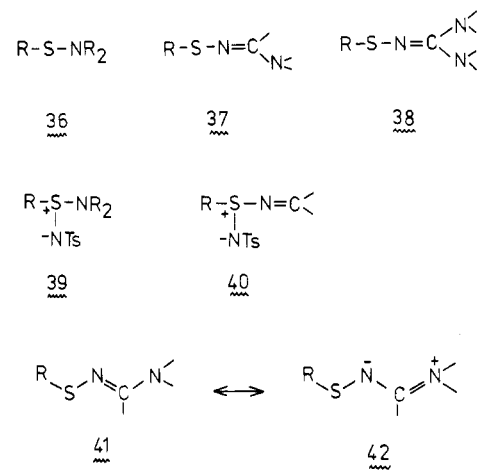
Both *O*-ethyl-*S*-ethyl xanthate **34** and *S,S'*-diethyl dithiocarbonate **35** reacted with aqueous chloramine T to give 1 molar



equiv of the *S*-tosylamido-*S*-tosylsulfimide **17** (R = Et).[62] It was suggested that in each case hydrolysis occurred to give the thiol and thence the product. Similar compounds have been isolated more recently from chloramine B reactions of the S esters of thioacetic, thiobenzoic, and thiosulfonic acids.[69]

4. Sulfenamides, Sulfenylamidines, and Sulfenylguanidines

Chloramine T reacts with sulfenamides **36,** sulfenylamidines **37,** and sulfenylguanidines **38** in aqueous acetone, giving tosyl sulfimide adducts such as **39** and **40.**[70] The variation in reactivity was in the order **38** > **37** > **36,** the differences being attributed to variations in electron density about sulfur, being greater for sulfenylamidines than sulfenamides, since canonical forms **41** and **42** are possible for the former but not for the latter. Sulfenamides derived from primary aromatic amines did not give similar products, but gave uncharacterized red oils. In a closely related reaction[71] a range of reagents **1** gave adducts with *N*-acyl-*S*-trichloroethylsulfenamides.



A postulated cyclic sulfenamide intermediate in a reaction of chloramine T with penicillanates has been trapped as an *S*-tosylamido-*S*-tosylsulfimide adduct (section II.C.9).

5. Sulfenyl Chlorides

Bromamine T reacted with sulfenyl chlorides[55] to give products **17.** The sulfenyl chlorides thus react in a similar manner to disulfides.

6. Sulfinyl Chlorides

The reaction of reagents **1** with arylsulfinyl chlorides **43** (Figure 5) gave a series of *S*-chloro-*S*-arylsulfoximides **44** which were then converted into the disulfonamides **45.**[72] A mechanistic study[73] using ^{36}Cl-enriched toluene-*p*-sulfinyl chloride and chloramine T suggested the reaction pathway depicted in Figure

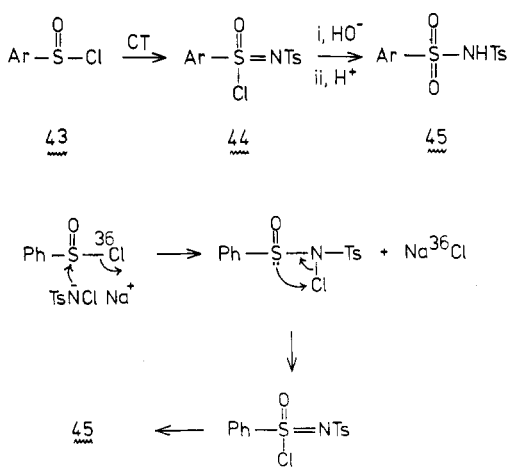


Figure 5.

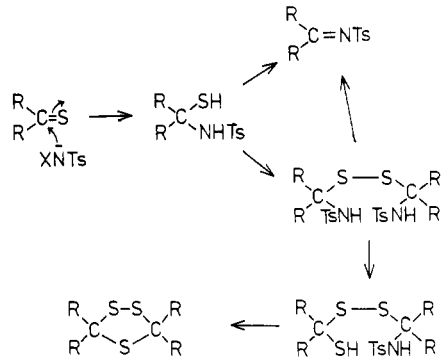
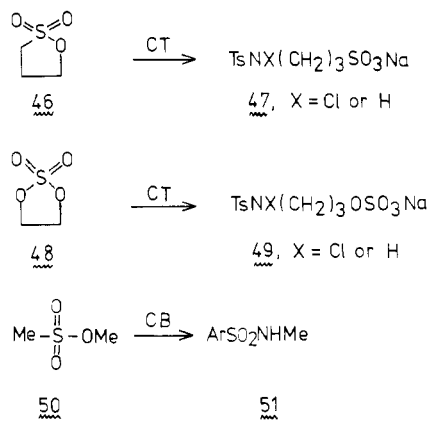


Figure 6.

5. This reaction exemplified the ability of chloramine T to act as a nucleophile.

7. Sultones, Ethylene Sulfates, and Sulfonates

Propane sultone (**46**) was hydrolyzed by aqueous chloramine T at 60–70 °C to the sulfonate **47**, but *N*-bromo-*N*-sodiosulfonamidates gave less stable products.[74] Ethylene sulfate (**48**) was similarly transformed (under anhydrous conditions) into the sulfate **49**.[74] The *N*-chlorobenzenesulfonamidate anion also reacted readily with methyl methanesulfonate (**50**) with displacement of methanesulfonate anion and formation of **51**.[21]

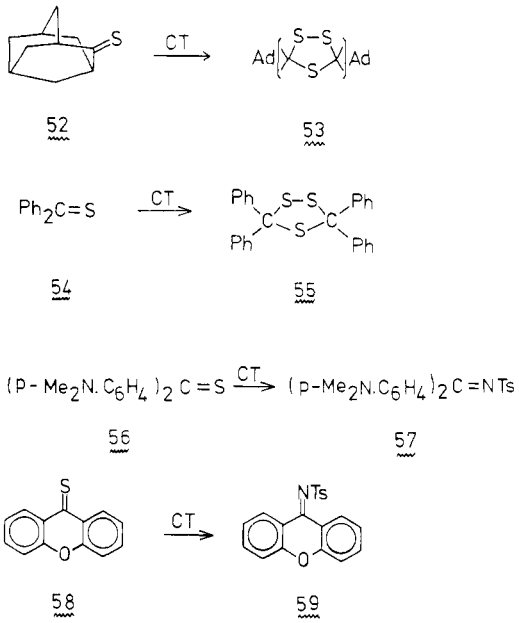


A second-order rate constant was determined, and observed to be five times that observed for the corresponding *N*-methylsulfonamidate anion, illustrating the "supernucleophilicity" (or "α-effect") of *N*-chloro anions. Each of these reactions illustrates nucleophilic attack at carbon, compared with the nucleophilic attack at sulfur in sulfinyl chlorides.

A relevant study which remains to be done is to investigate the reaction of chloramine T with a sulfinate ester in which there is possible nucleophilic attack at either the sulfinyl sulfur or the carbon adjacent to the oxygen group.

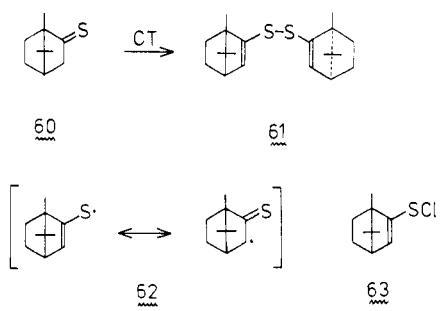
8. Thioketones and Selenoketones

Chloramine T was reacted with the non-thioenolizable thioketones, thioadamantanone (**52**), thiobenzophenone (**54**), Micheler's thione (**56**) and xanthenethione (**58**), in an investigation of the possible modes of attack.[75] Thioketones **52** and **54** gave in low yields as the major reaction products the thiozonides (1,2,5-trithiolanes) **53** and **55** in a reaction which exemplified the ability of chloramine T to act as a source of chloronium ion (and thus effect oxidative coupling of thiols) and of sulfonamidate anion. One of the possible mechanistic explanations is depicted in Figure 6. The *N*-tosylimine products obtained from **56** and **58** possibly arise from an intermediate

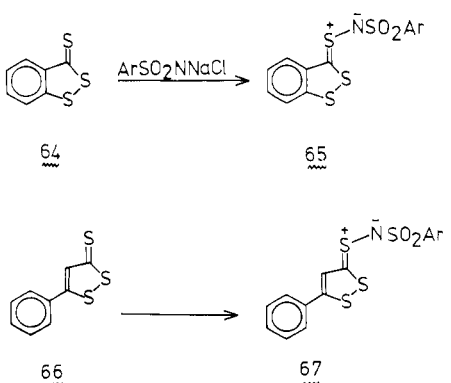


gem-sulfonamidothiol. *N*-Tosylimines **57** and **59** could also arise from an intermediate thiaziridine.

When thiocamphor (**60**), which is thioenolizable, was treated with chloramine T, the diene disulfide **61** was obtained.[75] This product may have arisen from dimerization of a vinyl sulfide radical **62** (evidence was obtained that photochemically generated halogen radicals also gave **61**), but the possibility of *ionic* oxidation via a vinyl sulfenyl chloride **63** was not precluded.



A related and important new reaction mode of thioketones emerged when 1,2-dithiole-3-thiones **64** and **66** were treated with *N*-chloro-*N*-sodioarylsulfonamides in methanol, affording the first thiocarbonyl sulfimides **65** and **67**.[76,77] A chlorosulfonium intermediate may be formed, chloride ion then being displaced by a sulfonamidate species. It was of interest that thermolysis of **65** and **67** resulted in sulfur extrusion, and formation of tosylimine, possibly by way of an intermediate thiaziridine (as suggested for the formation of **57** and **59**[75]).



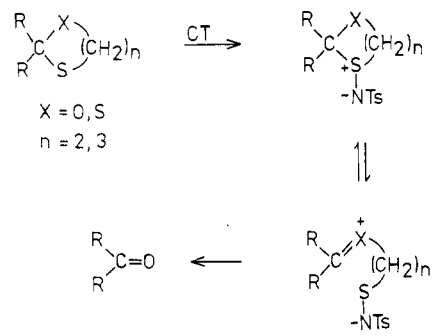
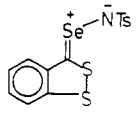


Figure 7.

The synthesis of selenocarbonyl sulfimides **68,** analogous to the thiocarbonyl sulfimides, has also been described.[78]



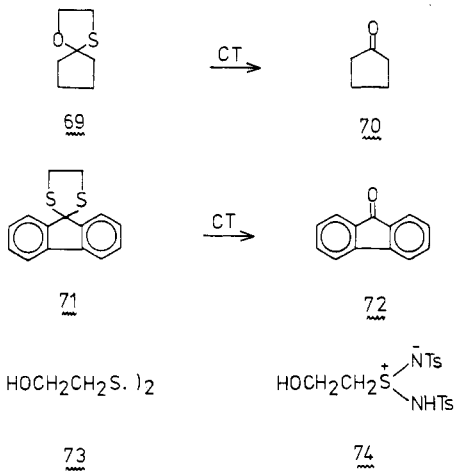
68

Interesting reactions may be anticipated from the hitherto undescribed reactions of reagents **1** with sulfines ($R_2C{=}S{=}O$), possibly leading to isoelectronic analogues of the sulfenes.

9. Sulfur Heterocycles

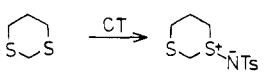
Although the reactions of sulfides with *N*-halo-*N*-metallosulfonamidates have been discussed (vide supra), and the formation of sulfimides from cyclic sulfides has been described, the reactions with saturated sulfur heterocycles warrant separate mention because of their intrinsic synthetic importance.

A new method has been described for the mild cleavage of the 1,3-oxathiolane- and 1,3-dithiolane-protected carbonyl group.[79-81] The oxathiolane **69** and the dithiolane **71** were converted in high yield by aqueous or alcoholic chloramine T into the deprotected ketones **70** and **72.** Interesting by-products in certain of the reactions were **74** and its precursor **73.** The



69 70 71 72 73 74

probable mechanism is depicted in Figure 7. Credence for the intermediacy of a sulfimide was given by the isolation of **76** from the reaction of chloramine T with **75.**[81]



75 76

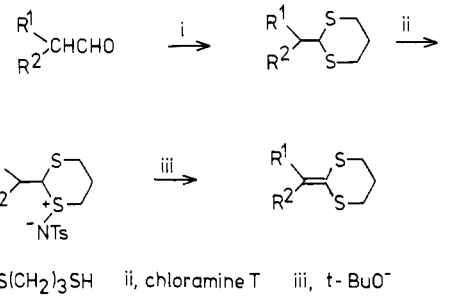
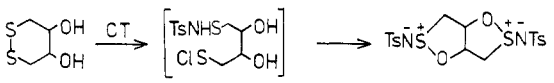


Figure 8.

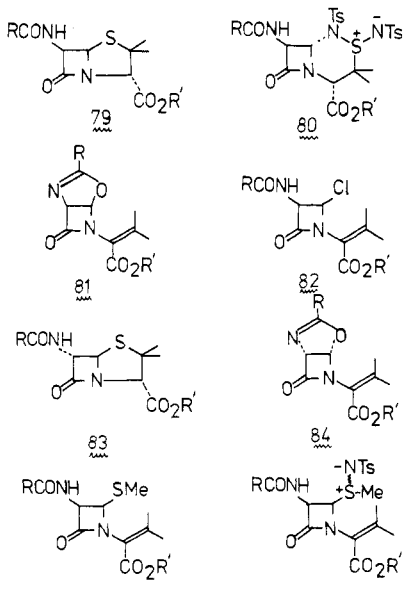
Further synthetic exploitation of chloramine T reactions with cyclic sulfides was very recently illustrated[82] by the transformation of aldehydes (Figure 8) into thioketene acetals. This is a particularly useful synthesis of a compound type which is of considerable current interest.

The cyclic disulfide **77** was converted into the novel 1,2-oxathiolane **78** by chloramine T, illustrating the intramolecular trapping of an intermediate sulfenamide.[83]



77 78

Chloramine T was observed to react with the thiazolidine ring of a range of penicillanates,[84] producing new analogues of these important antibiotics. Thus, treatment of **79** gave the β-lactam-fused thiadiazine sulfimide **80** possibly involving one or more of the reaction pathways depicted in Figure 9. Some evidence emerged that the initial step in the reaction may have been N-chlorination of the amide, followed by intramolecular transfer of chlorine to the sulfur of the thiazolidine ring. When an activated ester (**79,** R′ = CH_2CCl_3) was allowed to react with chloramine T, oxazolinoazetidinones **81** were formed, together with the *cis*-chloroazetidinone **82.** Interesting differences in reactivity were observed when the *epi*-penicillanate **83** was allowed to react with chloramine T to give an oxazolinoazetidinone **84,** enantiomeric with **81.** Other differences in reactivity were illustrated by the reaction of *seco*-penicillanates **85** with chloramine T leading to the sulfimides **86** and the corresponding sulfoxides.[85]



79 80 81 82 83 84 85 86

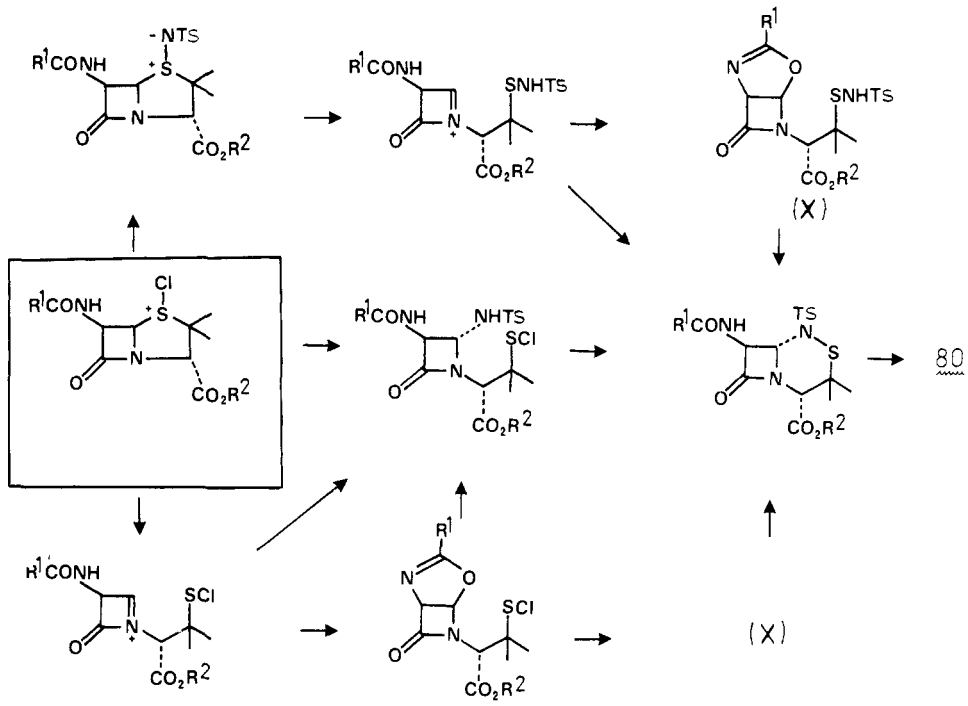


Figure 9.

These penicillanate studies therefore provided a range of new β-lactam products, arising from initial *S*-chlorosulfonium species. It is noteworthy that minor changes in substituents and in stereochemistry of the penicillanate molecules led to completely different reaction pathways from the *S*-chlorosulfonium precursors.

Considerable scope exists for the further exploitation of *N*-halogeno-*N*-metallo reagents in effecting modifications of sulfur heterocycles. Possible reaction modes include (a) nitrenoid insertion reactions in the presence of copper and its salts, (b) ring-opening reactions with bond cleavage adjacent to the sulfur atom, (c) sulfoxide formation, (d) sulfimide formation, (e) Pummerer rearrangements, (f) Stevens rearrangements leading to ring expansion, and (g), base-induced 1,2-elimination from sulfimides to give intermediate cyclic sulfonium species amenable to nucleophilic attack.

10. *Inorganic Group 6 Compounds: Oxidative and Analytical Uses*

Analytical uses of chloramine T and chloramine B in the estimation of sulfur-containing compounds involve oxidation to sulfuric acid in acid media.[67,86-90] Thus, hydrogen sulfide, thiosulfate, carbon disulfide, thiocyanate, sulfites, bisulfites, sulfurous acid, esters and amides of thiosulfurous acid, and polythionites have been quantitatively analyzed. At neutral pH partial reaction was usually observed and in basic solution little or none occurred.

Metallic ions (Zn, Cd, Hg, and Cn) have been estimated as their thiourea complexes which were oxidized by alkaline chloramine T (8 equiv) to sulfate.[91]

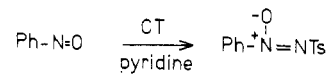
Semimicroanalytical determination of selenium and tellurium was achieved by acidic chloramine T oxidation to selenic and orthotelluric acids (6 equiv of chloramine T).[92]

D. Reaction with Group 5 Compounds

1. *Nitrogen Compounds*

a. Nitroso, Nitro, and Azo Groups

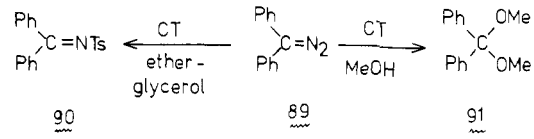
Chloramines T and B react with a large number of aromatic nitroso compounds to give azoxysulfones.[93] Thus, nitrosobenzene (**87**) condensed with chloramine T in pyridine to give **88.** Nitrosophenols and nitrosoanilines did not react in this manner, giving intractable products, whereas *N*-nitroso compounds and azobenzene failed to react.



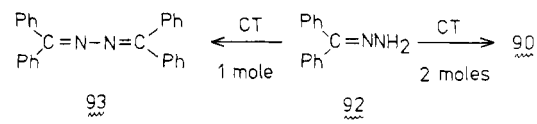
In a brief study of the reaction of chloramine T with nitrobenzene at 140 °C it was reported[94] that a brown gas, possibly nitrogen dioxide, was evolved. The reaction products were not characterized.

b. Diaryldiazomethanes and Diarylhydrazones

Chloramine T and related reagents react with diaryldiazomethanes[31,95,96] affording imines in what may formally be regarded as a nitrene–carbene combination reaction. Diphenyldiazomethane (**89**), for example, reacted with chloramine T in ether–glycol to give the *N*-tosylimine **90,** whereas in methanol the dimethyl ketal **91** was obtained. Ketone hydrazones, e.g.,



92, reacted with 1 molar equiv of chloramine T[96] to give the azine **93,** whereas 2 molar equiv of reagent gave *N*-tosylimines such as **90.**



c. α-Amino Acids

Oxidative reactions of chloramine T with α-amino acids were noted[4,97,98] at an early stage, and the production of highly toxic

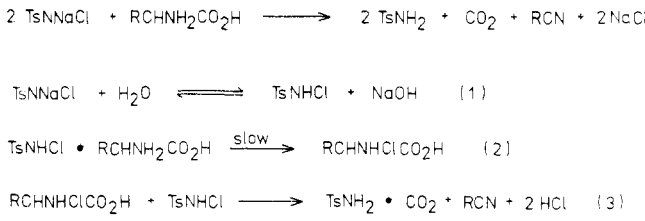


Figure 10.

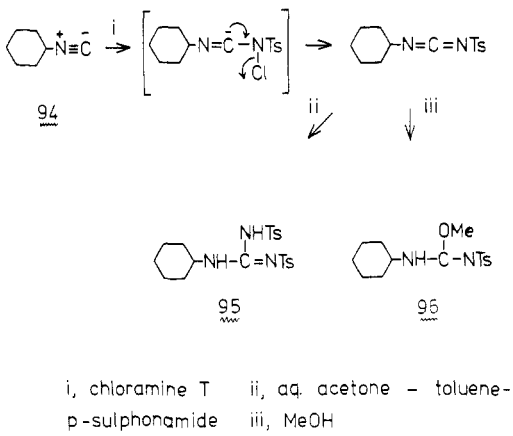


Figure 11.

products including cyanogen chloride has been reported (possibly explaining chloramine T poisoning).[99,100] In the oxidation[100] of the β-hydroxy amino acids threonine and serine using chloramine T periodate, aldehydes corresponding to α,β-cleavage, together with cyanogen chloride and carbon dioxide, were obtained.

Extensive kinetic and mechanistic studies of the oxidation in alkaline medium of amino acids such as glycine, alanine, valine, and leucine have been performed.[101-103] The stoichiometry of the reaction and the suggested reaction pathways are shown in Figure 10. In a typical study there was first-order dependence on chloramine T and leucine, and near inverse dependence on hydroxide ion. Oxidation was suggested to occur by two pathways involving (a) *N*-chlorotoluene-*p*-sulfonamide and (b) hypochlorite ion, as the main oxidizing species. Each interacted with a further mole of oxidant. Precise mechanistic details of the final step, involving decarboxylation and nitrile formation, are not available.

d. Isonitriles

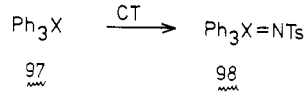
In a typical reaction[104] cyclohexyl isocyanide (**94**) was heated with chloramine T and calcium carbonate giving 1,2-bis(toluene-*p*-sulfonyl)-3-cyclohexylguanidine (**95**) (Figure 11). This product, also obtained from an aqueous acetone reaction of chloramine T, toluene-*p*-sulfonamide, and **94,** probably arises from a carbodiimide intermediate which is subjected to nucleophilic attack by a toluene-*p*-sulfonamidate (or *N*-chloro) anion. Chloramine T also reacted readily with **94** in methanol or ethanol to give the isourea ether **96.** An alternative initial step involving electrophilic attack by the isonitrile on an *N*-chloro species, giving an intermediate isonitrilo chloride, may possibly be envisaged.

2. Other Group 5 Compounds

The reactions of reagents **1** with compounds of group 5 may be broadly divided into the areas of synthetic and analytical chemistry.

a. Organophosphorus, Arsenic, and Antimony

It has been demonstrated that certain trialkyl and triaryl phosphines, arsines, and stibines react with chloramine T type reagents to give the corresponding imides.[25,31,105-110] For example, triphenylphosphine (**97,** X = P),[107] triphenylarsine (**97,** X = As),[110] and triphenylstibine (**97,** X = Sb)[109,110] gave the phosphinimide (**98,** X = P), arsinimide (**98,** X = As), and the stibinimide (**98,** X = Sb), respectively. In earlier reports,[106,107]



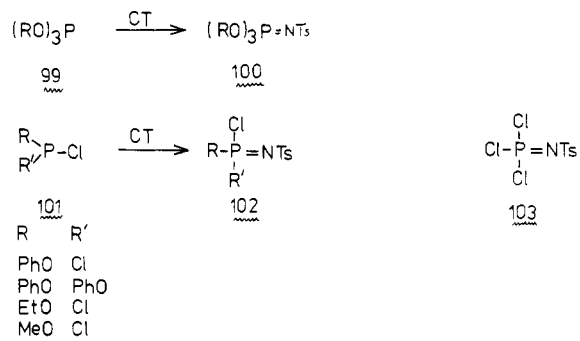
however, it had been stated that some reactions of chloramine T trihydrate with phosphines and arsines led to pentacoordinated derivatives of structure $R_3P(OH)NHTs$ or $R_3As(OH)NHTs$. A reassessment[111] showed that these "hydroxysulfonamides" which had been formed in the presence of water were more probably cyclic, six-membered, strongly hydrogen-bonded complexes of the phosphine oxide and toluene-*p*-sulfonamide. Mann et al.[111] suggested that hydrolysis of an initially formed arsenimide led to the hydroxysulfonamides, but Cadogan et al. have since shown[108] that the arsinimide is highly stable to hydrolysis, and that chloramine T, in fact, gives a triarylarsenic oxide which condenses with toluene-*p*-sulfonamide to give the observed product.

It has been shown[111] that chloramine T in acid media will react with group 5 triaryl derivatives, giving the series of products depicted in Table I.

TABLE I

Substrate	Product from chloramine T - acid
Ph_3P	Ph_3PO
Ph_3As	$Ph_3AsO \cdot HCl$
Ph_3Sb	Ph_3SbCl_2
Ph_3N	polychlorinated resin
Ph_3Bi	cleavage products
$Ar_3P(X)$, X = lone pair, S or Se	Ar_3PO + inorganic sulfate/selenate

Triaryl phosphites (**99,** R = aryl) and trialkyl phosphites (**99,** R = alkyl) reacted with anhydrous chloramine B giving the *N*-arylsulfonylphosphorimidates **100.**[113] Triethyl phosphite with anhydrous chloramine T in dry carbon tetrachloride gave the corresponding imide, but in boiling aqueous ethanol gave triethyl phosphate via the intermediate $(RO)_3PCl^+$.[112] Dialkyl hydrogen phosphites with aqueous chloramine T also gave phosphates.[112] The aryloxy and alkoxy phosphorus chlorides **101** reacted with anhydrous *N*-chloro-*N*-sodioarylsulfonamidates **1** in dry solution to give the imides **102.**[114] Phosphorus pentachloride also underwent reaction, giving **103.**[115] Phosphorus tribromide gave adducts similar to **103** with reagents **1.**[96,115]



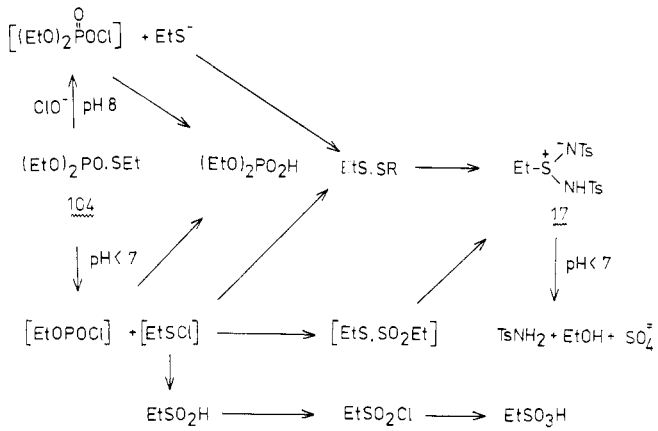


Figure 12.

TABLE II

Structural unit (with formal oxidation nos.)	Equivs. of chloramine T consumed
$\equiv\overset{+5}{P}=\overset{-2}{S}$	8
$\equiv\overset{+4}{P}-\overset{+4}{P}\equiv$	2
$\equiv\overset{+5}{P}-\overset{-2}{O}-\overset{+5}{P}\equiv$	0
$\equiv\overset{+5}{P}-\overset{-2}{S}-\overset{+5}{P}\equiv$	8
$\equiv\overset{+5}{P}-\overset{-2}{S}-\overset{+1}{H}$	8
$\equiv\overset{+5}{P}-\overset{-2}{S}-\overset{+1}{R}$	6
$\equiv\overset{+5}{P}-\overset{-2}{O}-\overset{+1}{R}$	0
$\equiv\overset{+3}{P}:$	2

In a paper which is comprehensive in its investigation, and which summarizes many relevant aspects of chloramine T chemistry, the reactions of triethyl phosphothiolate (**104**) (Figure 12) giving the *S*-ethyl-*S*-toluene-*p*-sulfonamido-*N*-toluene-*p*-sulfonylsulfimide (**17**) are described.[117] Reaction by-products included inorganic sulfate, toluene-*p*-sulfonamide, and diethyl hydrogen phosphate.

b. Oxidation and Analytical Procedures

Chloramine T and related reagents have been widely used in the oxidation and analysis of group 5 compounds, and aspects will be summarized in this section. Significant applications involve the analysis of the insecticides Parathion[118] and Malathion.[119]

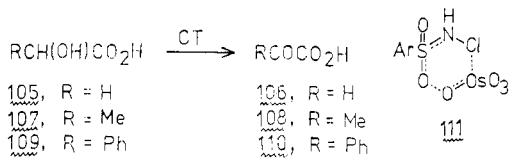
The oxidative properties were utilized in the preparation of arsenic acids.[120] Tertiary chloroarsines were refluxed in aqueous acetone with chloramine T to give arsenic acids, free from coloring matter and more easily isolable than by previous procedures. Phosphine and arsine were also oxidized to phosphoric and arsinic acids.[87,120] A possible intermediate in these reactions could be the reactive species H_3XO (X = As or P). Dialkyl hydrogen phosphites were oxidized by aqueous chloramine T[116] to give in good yield the dialkyl hydrogen phosphates. Triethyl and triphenyl phosphites similarly gave the phosphates.

Phosphorus–sulfur compounds have also been oxidized by aqueous chloramine T.[118,119,121–123] In basic solution[123] sulfates and phosphates are obtained. In an extension of these studies in acid solution,[124] a useful analytical method for discriminating between closely related structural groups was obtained. Units such as ≡P—S—R, ≡P═S, ≡P—SH, and many others could be estimated analytically, the oxidation products again being phosphates and sulfates. Analytical data are presented in Table II. Other studies of oxidations of triarylphosphine sulfides and selenides to triarylphosphine oxides, sulfates, and selenates have been reported.[125]

E. Reactions with Oxygen Functional Groups

1. Alcohols

Extensive studies of the kinetics and mechanism of the chloramine T oxidation of alcohols to aldehydes in alkaline, neutral, and acidic conditions have appeared.[126–132] In sodium hydroxide, for example, certain alcohol oxidations were catalyzed by Os(VIII),[128] including those of the α-hydroxy acids, glycollic (**105**), lactic (**107**), and mandelic acids (**109**), which gave the α-keto acids **106, 108** and **110,** respectively. An intermediate osmium–*N*-chlorotoluene-*p*-sulfonamide complex (**111**), whose



formation was the rate-determining step, was suggested as the oxidant. The noncatalyzed alkaline oxidation of a range of carbohydrates is discussed within the following section on the oxidation of aldehydes (section II.E.2).

In acid media, primary alcohols are oxidized to the aldehydes by chloramine T via initial protonation to give *N*-chlorotoluene-*p*-sulfonamide, followed by a rate-determining hydrolysis to give hypochlorous acid which was suggested[133] as the oxidant. This study showed first-order acid and zero-order alcohol dependence. An investigation of the oxidation of allylic alcohols[129,131] suggested that protonated hypochlorous acid (Figure 13) was, in fact, the active oxidant, and that 1,2-elimination of HCl from the alcohol hypochlorite occurred. A kinetic study of this reaction[134] showed first-order dependence on alcohol, although in stronger acid media there was second-order acid dependence and independence with respect to alcohol concentration. Kinetic and thermodynamic parameters were reported. The kinetics of chloramine T oxidation of secondary alcohols has recently been studied,[135] and in strong aqueous mineral acid the rate expression

$$-d[CT]/dt = k[CT][\text{alcohol}][H^+]^2$$

was empirically derived. The rate law, low kinetic isotope effect, and effect of solvent polarity on the rate agreed with a mechanism involving rate-determining reaction of either protonated chloramine T (*N*-chlorotoluene-*p*-sulfonamide) or protonated hypochlorous acid with the alcohol, giving the alcohol hypochlorite, followed by fast decomposition to ketone. The observed

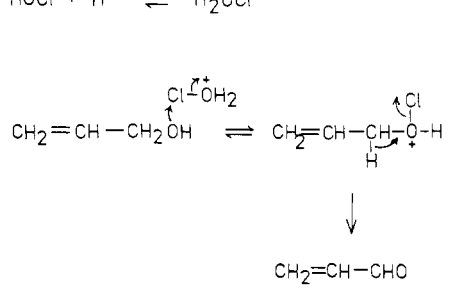


Figure 13.

order of 1.5 in hydrochloric acid was interpreted by simultaneous oxidation by Cl^+ or hypochlorous acid and protonated chloramine T. In a low-percentage acetic acid medium the oxidation was second order in chloramine T and first order in alcohol, *N,N*-dichlorotoluene-*p*-sulfonamide being suggested as the active oxidant.

2. Aldehydes

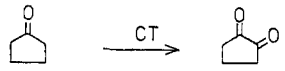
The oxidation of aldehydes to acids by alkaline chloramine T has been effected both with[136] and without[137-138] Os(VIII) catalysis. The uncatalyzed oxidation is achieved only when the aldehyde is capable of enolization as in, for example, acetaldehyde, propionaldehyde, *n*- and isobutyraldehyde, and may be similar in mechanism to the oxidation of aldehydes by bromine.[139] (Formaldehyde was not oxidized and benzaldehyde reacted slowly.) The addition of Os(VIII) catalyzed alkaline oxidation of both enolizable and nonenolizable aldehydes. It was again suggested[133] that an "activated complex" **111** facilitated the ability of chloramine T to abstract a hydride ion from the hydrated form of the aldehyde. Aspects of the mechanism remain to be resolved, and the nature of the chloramine T–osmium (VIII) complex in alkali is intriguing, particularly in the light of recent studies by the Sharpless group (vide infra) in other areas. A range of carbohydrates **112** including xylose, arabinose, mannose, and ribose has been oxidized in sodium hydroxide by chloramine T[140] to the corresponding aldonic acids **113,** the

112 113

oxidizing species being hypochlorite. A recent and detailed analysis of the oxidation of D(+)-sorbose[141] showed that in a highly alkaline medium there was a brief induction period, and then a first-order dependence on chloramine T and substrate. The order with respect to hydroxide was fractional (1.3), and activation energy and other thermodynamic parameters were ascertained.

3. Ketones

The chloramine T oxidation of ketones (e.g., **114**) to α-diketones **115** in alkaline media has been performed with[142] and

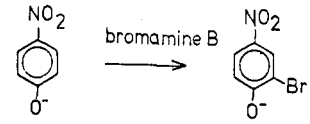


114 115

without[143,144] Os(VIII) catalysis. Kinetic studies show[144] for aliphatic ketones that there is first-order dependence on ketone and hydroxide concentration and suggest a mechanism in which there is slow reaction of the ketone enolate wit 1 mol of chloramine T, followed by fast reaction of the product with a second mole. In a similar study of the oxidation of cycloheptanone[145] the same steps were proposed, and it was shown that the rate-determining step was first order in chloramine T, ketone, and hydroxide.

4. Phenols

The use of chloramine T as a positive halogen source has been employed in the chlorination of phenols, and several kinetic and mechanistic studies of reagents **1** have been performed.[146-149] In the chlorination of *p*-cresol by chloramine T there is zero-order dependence on the concentration of the phenol. This had previously been attributed to hypochlorite formation from chloramine T as being the rate-determining step. It has been suggested that, in fact, the reaction goes through *N,N*-dichlorotoluene-*p*-sulfonamide,[146] formation of which is the limiting step. In the bromamine B (**1,** R = H, X = Br, M = Na) reaction with *p*-nitrophenoxide ion (**116**) to give 2-bromo-4-nitrophenol (**117**)[147] the suggested mechanism involved rapid

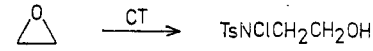


116 117

protonation of bromamine B, followed by rate-determining bromination of the substrate. The intermediacy of hypobromite ion was disproved. A later study of cresol chlorination by chloramine T between pH 6.82 and 2.10[148] showed second-order kinetics, with rate constants in the order *p*-chlorophenol < *p*-cresol < *o*-cresol < phenol < *m*-cresol. A mechanism involving *N,N*-dichlorotoluene-*p*-sulfonamide as the chlorinating agent was discussed, and activation energy and related parameters were calculated. A very recent[149] kinetic study of the chloramine T reaction of substituted phenols in the presence of mineral acids, and also in aqueous acetic acid, discusses the effects of added salts, pH, structural variations, and solvent dependence and implicates protonated chloramine T, protonated hypochlorous acid, and dichloramine T, depending on the reaction media.

5. Epoxides

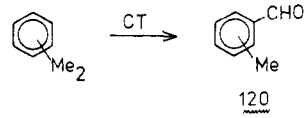
N-Halo-*N*-sodioarylsulfonamidates **1** react readily as nucleophiles with epoxide **118** giving *N*-halo-*N*-(2-hydroxyethyl)-sulfonamides (**119**). The nucleophilicity of the *N*-chlorotoluene-*p*-sulfonamidate anion was noted as being comparable with that of azide anion.[74] This nucleophilic reaction paralleled those of sultones, ethylene sulfates, and sulfonates (which see).



118 119

F. Reactions with Activated Methyl and Methine Groups

The observation that heating an aqueous solution of chloramine T produced, by autoxidation, benzaldehyde-*p*-sulfonamide[9] prompted an investigation of the oxidation of other aromatic methyl groups.[9,150] Thus, a range of compounds including the xylenes were oxidized by chloramine T and chloramine B in acetic acid, giving low to moderate yields of the corresponding aldehydes **120.** *N*-Chloro-*N*-sodiotoluene-*o*-sulfonamidate (**121**) gives the insertion product **122.** The mechanism and scope of



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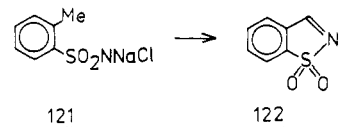
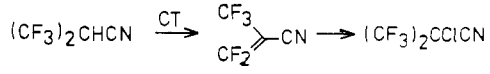


121 122

this type of reaction have apparently not been further investigated.

Bis(trifluoromethyl)acetonitrile (**123**) reacted with hydrated chloramine B to give the α-chloro compound **124** in high yield,[151] apparently via a perfluoro-α-methylacrylonitrile. Further studies of this unusual reaction mode will be of interest.

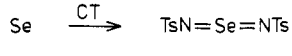


123 124

G. Reactions of Chloramine T-Based Reagents with Olefins

1. Allylic Amination Reaction

In an important new reaction Sharpless[152] showed that 2 molar equiv of anhydrous chloramine T reacted with selenium metal in methylene chloride to give a superior preparation of the imido selenium compound **125.** Many mono-, di-, tri-, and te-



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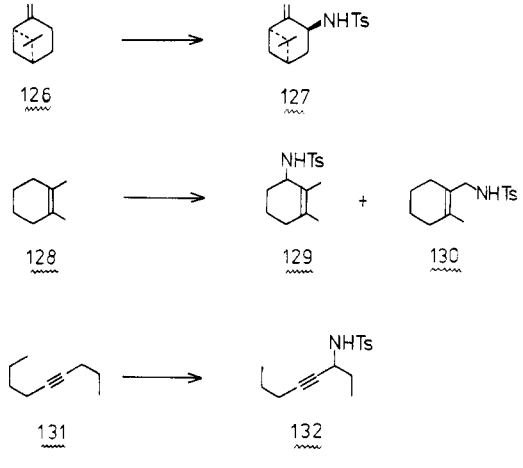
trasubstituted olefins reacted with **125** affording allylic amination products in good yield. For example, β-pinene **126** gave an 82% yield of the allylic amine derivative **127,** whereas the tetrasub-

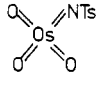


126 127 128 129 130 131 132

stituted olefin **128** gave each of the possible allylic amination products **129** and **130** in 50 and 10% yields, respectively. Acetylenes were similarly aminated, **131** giving **132** in 51% yield. Mechanistically these aminations may be envisaged as hetero-ene and [2,3]-sigmatropic processes, having much in common with the allylic insertion of oxygen by selenium dioxide. This new reaction provides the first instance of direct allylic amination of olefins. The allylic sulfonamides thus formed are readily cleaved by sodium naphthalide to the primary amines. (A similar allylic amination process was effected by the sulfodiimide analogue of **125,** but this reagent was prepared by a different route.[153])

2. Vicinal Oxyamination Reaction

In another unique reaction the Sharpless group[14] developed a new vicinal hydroxyamination process. The reaction of chloramine T trihydrate with olefins in the presence of a catalytic trace of osmium tetroxide produced cis-vicinal hydroxy tolu-



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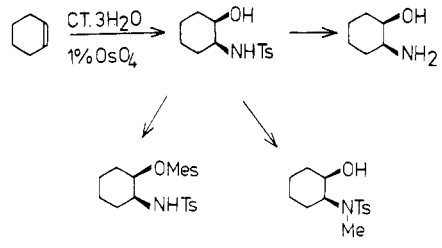
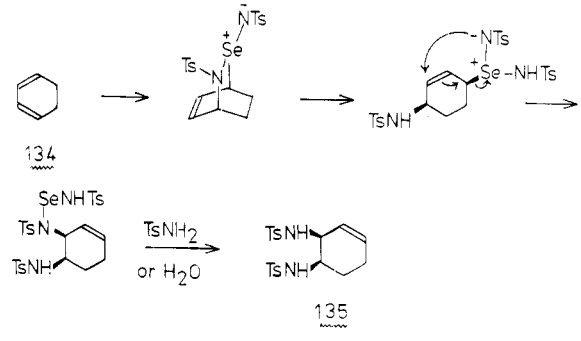


Figure 14.



134 135

Figure 15.

ene-*p*-sulfonamides, providing synthetic entries to otherwise difficultly accessible products (Figure 14). (This process represented an improvement on a related hydroxyamination procedure which gave vicinal *tert*-alkylamino alcohols.[154]) The continuously regenerated sulfonylimido osmium intermediate **133** was suggested as the effective reagent. Because of sometimes beneficial, and occasionally deleterious, effects of added silver ion, two procedures were described with and without added silver nitrate. The reactions of a large range of olefins provided good yields, although certain compounds including cholesteryl acetate and dimethyl fumarate failed to react or gave low yields.

3. Vicinal Diamination Reaction

Chloramine T based reagents continue to be exploited in effecting functionalization that would be otherwise difficult, as shown by the very recent reaction of **125** with a large range of 1,3-dienes to give 1,2-disulfonamides.[155] Generation of the reagent **125** in situ from chloramine T and selenium followed by reaction with the diene (e.g., **134**) gives the cis-vicinal disulfonamide **135.** The probable mechanism is depicted in Figure 15.

H. Chemiluminescence and Photochemistry

Chloramine T has been shown to give chemiluminescence in its reaction with neutral hydrogen peroxide[156] and 3-aminophthalhydrazide.[157] The emission process in the former reaction was interpreted as being indicative of a heterolytic fission process from a cyclic transition state involving chloramine T–hydrogen peroxide, with formation of singlet oxygen.

The stability of aqueous solutions of chloramine T in daylight has long been known. However, photochemical decomposition can be effected by irradiation with light in the blue region of the spectrum.[158] A study of the aqueous photochemistry (300 nm) of chloramine T indicated possible similarities to hypochlorite photochemistry.[159] A systematic study of the photochemistry of reagents **1** in alcohol, water, and other solvents would be of interest.

I. Reagent Biochemical and Biological Aspects

Since the early recognition and use of the antiseptic and disinfectant powers of chloramine T and chloramine B, the re-

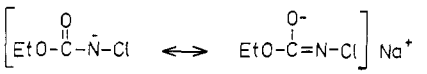
agents have been used in toothpastes, mouth washes, and soap and in the treatment of infected wounds. Hundreds of reports of related uses have since appeared and would require a separate review. Recently, however, the use of chloramine B as an oxidizing agent in the detection of hydroxyproline has been reported.[160] Chloramine B has also been successfully used in 1–2% aqueous solution as an in vitro bactericide in preventing bacteriosis of mulberry leaves.[161] The silkworm eggs were disinfected without reduction in the yield of larvae. Chloramine T has been used as a fungicide and showed in vitro effectiveness equivalent to that of sodium o-phenylphenate against *Geotrichum candida* arthrospores, the cause of sour rot of citrus fruit.[162] (Sodium hypochlorite was less effective.)

Chloramine T has also been shown to have an effect on the immunoreactivity of glucagen.[163] The change in immunoreactivity toward the specific antibody of glucagen exposed to chloramine T was due mainly to oxidation of the methionine residue at position 27 in the molecule. Chloramine T has also been shown to cause loss of precipitability in antibody preparations when labeling rabbit γ-globulin and anti-horse serum albumin antibodies with ^{131}I.[164] An apparently important report describes the use of chloramine T in the specific iodination of the surface proteins of intact enveloped viruses.[165] With low iodide concentrations chloramine T mediated iodination specifically on the external proteins of Rous-associated virus-61. With higher concentrations, both internal and external proteins were iodinated. The lipid envelope of the virus apparently provides an effective barrier to the iodinating complex generated at low iodide concentration, but not at higher concentration. The chloramine T procedure has previously unrecognized potential for such surface-specific labeling.

III. N-Halogeno-N-metallocarbamidates

A. Preparation

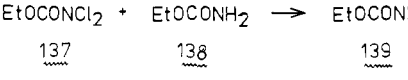
Most literature preparations have been of *N*-chloro-*N*-metallo derivatives, although an example of a bromo derivative has been described.[166] Compounds such as ethyl *N*-chloro-*N*-sodiocarbamate (**136**, sometimes termed *N*-chloro-*N*-sodiourethane)



136

have been isolated in anhydrous or in hydrated form from the reaction of alkali metal[167] or hydroxide[166–169] with *N*-chlorocarbamates which in turn are made by one of two general methods.

(*a*) *Disproportionation of N,N-Dichlorocarbamates.* *N,N*-Dichlorocarbamates **137**, prepared by the action of excess chlorine[166,170–173] or hypochlorous acid[167,174] on carbamates, disproportionate when stirred with an equimolar quantity of carbamate **138** to give the *N*-monochlorocarbamate **139**.[30,167,168,175–177]



137 **138** **139**

(*b*) *Direct Preparation.* Treatment of carbamate with a molar quantity of chlorine[166,169,170,176] or hypochlorite[178] gives *N*-monochlorocarbamates. An extensive series of *N*-monochloro- and *N*-monobromocarbamates has been prepared.[178]

In a recent modification[179] of these standard methods of preparation, an ice-cold, dry methanolic solution of carbamate was treated with equimolar quantities of *tert*-butyl hypochlorite, followed by sodium hydroxide in dry methanol. Evaporation of solvent, filtration, and washing with ether gave solid, anhydrous methyl- (caution: this product spontaneously and violently decomposed on several occasions during attempted storage at low temperature), ethyl-, trichloroethyl-, *tert*-butyl- and phenyl-substituted *N*-chloro-*N*-sodiocarbamates. Formamide thus treated did not give the desired derivative. This procedure, which has been further exploited,[180] is rapid and efficient.

The silver salts have also been prepared[166,168,169,180] as white crystalline solids which darken on exposure to light.

The *N*-halogeno-*N*-metallocarbamates appear to be moderately stable to storage at low temperature either in the anhydrous or hydrated forms (with the exception of methyl *N*-chloro-*N*-sodiocarbamate). It is of interest that they cannot undergo the Hofmann rearrangement to which the corresponding amide analogues are prone. (Aspects of the chemistry of *N*-haloamide salts are discussed within ref 177, together with the chemistry of *N,N*-dihaloamides and *N,N*-dihalocarbamates.)

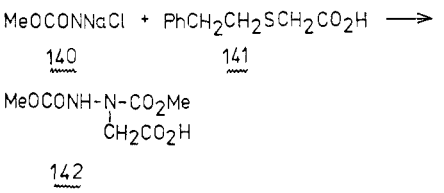
B. Properties

The structure of the reagents may be depicted as **136**, and, as for the related sulfonamidates, comparative bond length data are not available. All of the derivatives are crystalline solids which may be obtained in the anhydrous form, but which are hygroscopic. Compared with the sulfonamidates **1** there is a paucity of physical data in the literature. It would be of immediate interest to investigate the possible existence of *N*-chloro and *N,N*-dichloro species in equilibrium in solution, and to measure the basicity and nucleophilicity of the anionic species.

C. Reactions

1. Sulfides

An example has been reported[181] of the reaction of methyl *N*-chloro-*N*-sodiocarbamate (**140**) with phenylethylthioacetic acid (**141**). A vigorous reaction ensued, giving **142** via a possible



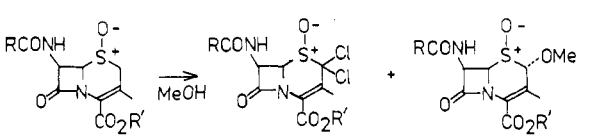
140 **141**

142

sulfone diimide intermediate. However, unlike the facile reactions of *N*-chloro-*N*-sodiosulfonamidates with sulfides, the *N*-chloro-*N*-sodiocarbamidates do not appear to react readily to give *N*-acylsulfimides. (These may, however, be prepared by reacting the sulfide with an *N*-chlorocarbamate to give an azasulfonium chloride which is deprotonated to give the sulfimide.[182] Alternatively, *N*-chlorocarbamidates generated in situ from *N,N*-dichloroamides and hypochlorite, or from amides and hypochlorite, react with sulfides to give *N*-acyl sulfimides.[182]) This lack of reactivity with sulfides was also noted for the penicillin derivative **85**, which had previously been shown to react with chloramine T.

2. Sulfoxides

N-Chloro-*N*-sodiocarbamidates have not been reported to give sulfoximides with sulfoxides. In a reaction in methanol with cephalosporanate sulfoxides **143**, products **144** and **145** which were obtained resulted from reaction of the sulfoxide α-anion

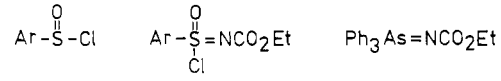


143 **144** **145**

with *N*-chloro species probably present in equilibrium in the reaction mixture.[183] This reaction mode exemplifies the behavior of the reagent as a "chloronium" ion source and as a base.

3. Sulfinyl Chlorides

Ethyl *N*-chloro-*N*-sodiocarbamate reacted in benzene with arenesulfinyl chlorides **146** to give the *N*-carbethoxyareneimidosulfonyl chlorides **147** which could be hydrolyzed to *N*-carboethoxyarenesulfonamides in hot dilute alkali.[184] This reaction paralleled that of chloramine T (section II.C.6).



146 147 148

4. Group 5 Triaryls

In a reaction with a group 5 derivative,[168] methyl *N*-chloro-*N*-sodiocarbamate in benzene gave the arsinimide **148,** paralleling the reactions of the *N*-halo sulfonamidates. The arsinimide was readily hydrolyzed to give triphenylphosphine oxide and methyl carbamate. Triphenylphosphine gave the corresponding triphenylphosphazocarboxylate.[185]

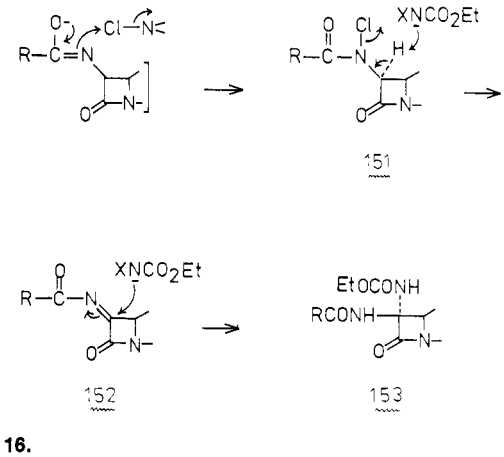
5. Primary Amides

N-Chloro-*N*-sodiocarbamates undergo a general reaction[167] with primary amides **149** to give allophanates **150.** In this reaction the primary amide is probably converted into the *N*-chloro-*N*-sodio salt, which undergoes the Hofmann rearrangement. This leads to an isocyanate which is trapped by the carbamidate anion, or by the *N*-chlorocarbamidate anion which is probably more powerfully nucleophilic. The resultant allophanates are readily hydrolyzed to give substituted ureas, or react with ammonia to give biurets. This reaction sequence thus affords a versatile route into a wide range of these latter products.

149 150

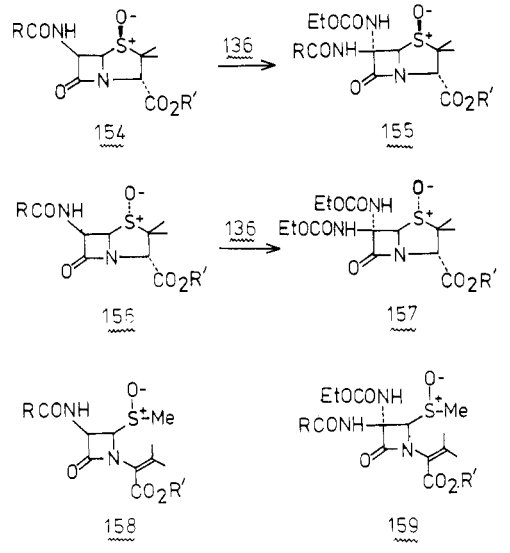
6. Secondary Amides

The penicillanates **79** in a unique reaction[186] gave the 6α-substituted product **153** (Figure 16). In this reaction of a secondary amide it is probable that initial *N*-chlorination to give **151** (reagent acting as source of "chloronium" ion) is followed by elimination of HCl to form **152** (reagent acting as base). Imine **152** is then trapped by a carbamidate or *N*-chlorocarbamidate anion to give **153** (reagent acting as nucleophile). Similarly, the (*S*)-sulfoxide **154** gave **155,** but the (*R*)-sulfoxide **156** was converted into a 6,6-dicarbamate derivative **157** in which the initial 6β-amido group had been totally replaced.[187] Mechanistic interpretations were postulated. An insertion reaction was also effected when **158** was converted into **159,** although sulfides **85** were unreactive. These reactions of compounds **79, 154, 156,** and **158** illustrate the lack of reactivity at sulfur of sulfides and sulfoxides, and the reactivity of suitably activated methine protons adjacent to the amido group. The extension of the reaction to other amides remains to be explored.



151 152 153

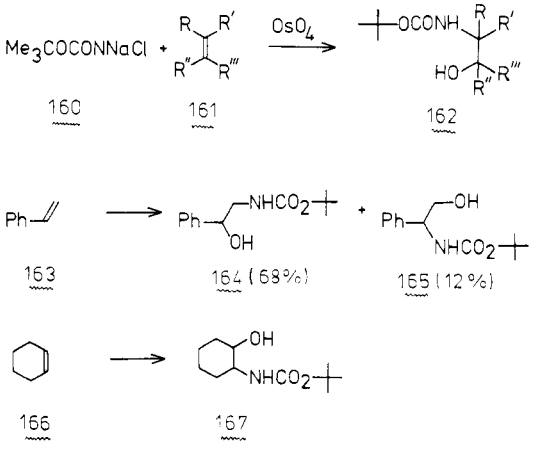
Figure 16.



154 155 156 157 158 159

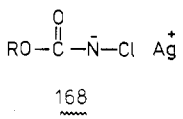
7. Vicinal Oxyamination of Olefins

The Sharpless group[180] has extended its studies on chloramine T–osmium tetroxide hydroxyamination of olefins, and has demonstrated that *N*-chloro-*N*-sodiocarbamates, particularly the *tert*-butyl derivative **160,** will effect good-yield cis-derivatization of olefins **161** to give products **162.** Typical examples include monosubstituted olefins such as **163** which gave the isomers **164** and **165** and disubstituted olefins (e.g., **166** giving **167**). In cases where stereoisomers were possible, only one was formed, assumed to be that arising from cis addition. Stilbene and dimethyl fumarate which were unreactive toward **133** gave good yields of products with **160.**



160 161 162 163 164 (68%) 165 (12%) 166 167

In a parallel study[180] *N*-chloro-*N*-argentocarbamates **168** have been employed and found to be of more general use than the



168

chloramine T based reagents. For example, the usefulness of ethyl *N*-chloro-*N*-sodiocarbamate was enhanced by converting it to its silver salt, and dimethyl fumarate and stilbene were thus converted into *cis*-hydroxyamino derivatives.

8. Attempted Reactions as Nitrene Precursors

Investigations into the use of *N*-chloro-*N*-metallocarbamates as sources of nitrenes have not yet proved successful, although low yields of aziridine were obtained from a reaction with cyclohexene.[169]

IV. Summary and Perspectives

Chloramine T and the related *N*-halogeno-*N*-metallo reagents exhibit a unique duality of behavior in that they react as sources of both "halonium" cations and nitrogen anions. The *N*-halogeno-*N*-metallo sulfonamidates, in particular, have been extensively exploited in effecting molecular modifications and transformations. The potential of the *N*-halogeno-*N*-metallo carbamidates remains largely unrealized although recently they have been increasingly evident in the literature.

Although there are structural similarities between the two groups of reagents, the modes of reaction as described in this review are in many ways strikingly different. The reasons for this remain to be explained in detail, but it can be anticipated that differences in the equilibria in which each of these groups of reagents exist in solution will be quantified; differences in their abilities to donate chlorine (i.e., to react as electrophiles) and differences in the basicity and nucleophilicity of the sulfonamidate and carbamidate anion species will be described.

Related reagents which may open new areas of reactivity will no doubt be developed. For example, the *N*-lithio analogues should exhibit significant differences in solubility and reactivity, possibly acting as nitrenoids (*N*-chloro-*N*-lithioaniline reacts thus[189]). *N*-Halogeno-*N*-metallophosphoramides are feasible, as are a range of hypothetical reagents derived from an amino group attached to an electron-withdrawing or charge-stabilizing system. A nitrene insertion reaction involving *N,N*-dichlorotoluene-*p*-sulfonamide and zinc possibly involved[190] an intermediate *N*-chloro-*N*-zinc species, suggesting the possible existence of a class of derivatives of **1** based on the transition metals.

V. References and Notes

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