Applications of N-Chlorosuccinimide in Organic Synthesis

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Abstract: N-Chlorosuccinimide (NCS) is a versatile reagent and its significance is not limited to chlorination and oxidation. It mediates or catalyzes many chemical reactions, including halocyclizations, formation of heterocyclic systems, formation of new carbon–carbon bonds, rearrangements, and functional group transformations.

1 Introduction

N-Chlorosuccinimide (1) (1-chloropyrrolidine-2,5-dione; NCS) was first synthesized in 1886 by the chlorination of succinimide (2) with chlorinated lime.1 In newer methods, potassium hypochlorite,2 tert-butylhypochlorite (Scheme 1)3 and chlorine in aqueous sodium hydroxide4 have been applied for this transformation.

Scheme 1

From the very beginning, NCS was used in chlorination and oxidation reactions. In the last 20 years, however, there has been an upsurge of interest in NCS, arising from the observation that it is a versatile reagent capable of mediating a plethora of different chemical transformations. In modern synthetic organic chemistry, the search continues for new methods excelling in selectivity, mildness, and efficiency.

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2 Chlorination

2.1 Chlorination of Benzene Derivatives

Aromatic chlorination reactions are usually carried out with elemental chlorine, sulfuryl chloride, chlorine(I) oxide, or hypochlorites. In the search for new and safer reagents, NCS has been examined.

The treatment of reactive aromatic compounds, such as N-alkylanilines, with NCS in hot benzene gave a mixture of o- and p-chloroanilines in a ratio exceeding 2:1 (Scheme 2). The results were interpreted as arising from a rearrangement of intermediate N-chloro isomers. Difficulties in obtaining monochlorinated products with acceptable yields in the reaction of deactivated anilines were obviated by the use of a dipolar aprotic solvent such as acetonitrile.

Ring chlorination of aromatic compounds with NCS proceeds by electrophilic substitution and involves a positive halonium species, the formation of which is facilitated by polar solvents and the presence of acidic catalysts. The required amount of the catalyst depends on the character of the substituents. Chlorination of polyalkylbenzenes required the use of catalysts such as p-toluenesulfonic acid or strong mineral acids. A good yield of 2-chloro-1,3,5-trimethylbenzene (7) was obtained from 6 by treatment with an equimolar amount of NCS and catalytic amount of p-toluenesulfonic acid in methanol at reflux temperature. A comparable result was obtained in a reaction performed at room temperature overnight with two equivalents of the catalyst (Scheme 3).

Electrophilic chlorination and bromination of activated aromatics was carried out efficiently in a biphasic solid-liquid system (NXS–hexane or NXS–CCl₄) using catalytic amounts of 70% perchloric acid. Both 1,3-dimethoxybenzene and 2,3-dimethylanisole (8; Scheme 4) were halogenated regiospecifically at the 4-position at room temperature.

Biographical Sketches

W. Marek Gołębiewski was born at Grądy (Poland) in 1945. He studied chemistry at the University of Warsaw and received his PhD in 1973 under direction of Prof. J. T. Wróbel achieving the first total synthesis of Lythraceae alkaloid decaline. After graduation he assumed the position of a research associate at the same university. He performed postdoctoral research at McMaster University (Ontario, Canada) with Prof. I. D. Spenser and at Purdue University (Indiana, USA) with Prof. M. S. Cushman. He obtained his Habilitation at the University of Warsaw in 1986. In 1994, he moved to the Institute of Industrial Organic Chemistry, where he was promoted to the position of Associate Professor in 1996. His current research interests are the stereoselective synthesis of biologically active compounds and the structure elucidation of natural products.

Mirosław Gucma was born in Zary (Poland) in 1972. He received his diploma from the Department of Chemistry at the Technical University of Warsaw. In 1999 he started work at the Institute of Industrial Organic Chemistry in Warsaw. Since 2001 he has been carrying out graduate research under supervision of Prof. W. M. Gołębiewski, where he is investigating the application of cycloaddition reaction in the synthesis of new plant-protection agents. His research interests include new synthetic methods and structure–activity relationships.
The chlorination of 9-bromoanthracene (10) with NCS and a catalytic amount of hydrochloric acid produced both 9,10-dichloroanthracene (11) (65% yield) and 9-bromo-10-chloroanthracene (12) (35% yield) as shown in Scheme 5. This result was explained by the better leaving-group ability of bromide compared to chloride. Recrystallized NCS did not react with dibenzo[a,c]anthracene without the presence of HCl, underlining the need for chlorine generation to initiate the reaction.

The treatment of 9-methylanthracene (13) with NCS and hydrochloric acid affords a nuclear chlorination product, 9-chloro-10-methylanthracene (14) (65% yield), and a benzylic radical chlorination product, 9-chloromethylanthracene (15) (35% yield) as shown in Scheme 6.

The participation of Lewis acids as catalysts in the chlorination of a wide range of substituted benzenes by NCS in acetonitrile was recently described. In the case of electron-donating substituents, catalytic amounts of iron(III) chloride were sufficient; for unsubstituted benzene, or in the case of electron-withdrawing substituents, an equimolar loading of iron(III) chloride was required. For strongly deactivated systems, such as nitrobenzene, increased temperatures (150 °C) and/or solvent-free conditions were indispensable. Various activated aromatic compounds were efficiently and selectively halogenated in dichloromethane with NCS, NBS and NIS in the presence of catalytic amounts of zirconium(IV) chloride.

To circumvent the harsh reaction conditions required for deactivated aromatics, new superacids catalysts were introduced. Boron trifluoride monohydrate was found to be an effective and inexpensive catalyst for several reactions, including halogenations with NXS (X = Cl, Br, I). The reaction temperatures and times were adjusted depending on the degree of substrate deactivation. For nitrobenzene, the reaction mixture was heated to 110 °C for 18 hours in a closed pressure tube. Reactions with hypochlorites and sodium chlorate–trimethylsilane complex were extremely sluggish. Quantum chemical density functional theory calculations suggested that the reaction of benzene chlorination proceeds via Cl⁺ transfer from the triply protonated destabilized NCS (16) to an aromatic substrate (Scheme 7). A driving force for the reaction is probably an electrostatic relief which accompanies the transfer of the positively charged chlorine cation to yield chlorobenzene (17).

The chlorination of heterocyclic systems with two heteroatoms and substituted at the 3- and 5-positions yields selectively ring-chlorinated products. The chlorination of 3,5-diarylisoxazoles 18 with NCS in refluxing acetic acid afforded the 4-chloro derivatives 19 (Scheme 8). In the cases of electron-withdrawing substituents or a methyl group on the Ar group, the addition of a catalytic amount of sulfuric acid was required for an efficient chlorination.

The chlorination of the bis(oxazole)indole 20 using NCS gave the dichloride 21 (86% yield) and the trichloride 22 (5% yield), where chloride was installed at both position 4 of the isoxazole and position 2 of the indole system (Scheme 9). The partial synthesis of the oxazole natural product diazonamide was thus completed.
The treatment of 3,5-dimethylpyrazoles 23 (N1-unsubstituted or N1-substituted with methyl or aryl groups) with NXS in ethyl acetate or acetone afforded 4-halo derivatives 24 in good yields and short times under ultrasound irradiation and in the absence of any catalysts (Scheme 10).\(^{25}\)

\[
\begin{array}{c}
\text{Me} \\
\text{N} \\
\text{Me} \\
\text{N} \\
\text{X} = \text{Cl, Br, I; } R = \text{H, Me, aryl}
\end{array}
\]

Scheme 10

The chlorination of heterocyclic systems that have just one heteroatom takes place mainly at the \(\alpha\)-position. Treatment of 1-methylpyrrole (25) with NCS in chloroform yielded a mixture of 2-chloro-1-methylpyrrole (26, \(X = \text{Cl}\)) and 1-methyl-2-succinimidopyrrole (27) (Scheme 11). The yield of 2-chloropyrrole depended on the solvent (was high in benzene, CCl\(_4\), THF), and on the presence of a base (NaHCO\(_3\)), which suppressed the acid-catalyzed \(\alpha\)-chlorination. Similar treatment of 1-methylpyrrole with NBS or NIS yielded only the 2-halo-1-methylpyrroles 26. \(^{26-28}\) 2H NMR spectroscopic studies showed that the imide-substituted pyrrole was formed by an addition–elimination process. Unsubstituted pyrrole gave only 2-chloropyrrole, as did pyrroles with extremely large N-substituents.\(^{26-28}\)

\[
\begin{array}{c}
\text{N} \\
\text{Me} \\
\text{X} = \text{Cl, Br, I}
\end{array}
\]

Scheme 11

The chlorination of (1’-methyl-1’H-pyrrol-2’-yl)-2,2-dimethylpropan-1-one (28) furnished the 5’-chloro derivative 29 (Scheme 12).\(^{29}\)

\[
\begin{array}{c}
\text{N} \\
\text{Me} \\
\text{Cl} \\
\text{Me}
\end{array}
\]

Scheme 12

Acid-sensitive substrates are effectively chlorinated by NCS in the presence of mildly acidic ammonium nitrate; in the specific case of thiophene (Scheme 13), a mixture of 2-chlorothiophene (31) (59% yield) and 2,5-dichlorothiophene (32) (10% yield) was obtained.\(^{20}\) In another approach, the halogenation took place in a two-phase system – solid NXS (1 equiv) in hexane or CCl\(_4\) – with catalytic amounts of 70% perchloric acid and afforded 2-chloro- or 2-bromothiophene. When two equivalents of NXS were used, 2,5-dihalothiophenes were obtained in high yield. 2-Methylthiophene and halo derivatives showed similar reactivity.

\[
\begin{array}{c}
\text{N} \\
\text{S} \\
\text{NH}_4\text{NO}_3 \\
\text{Cl}
\end{array}
\]

Scheme 13

The chlorination of disubstituted aziridines 33 with NCS in the presence of trifluoromethylcarbinols as chiral solvating agents gave the optically active \(N\)-chloroaziridines 34 in very good chemical yield (Scheme 14). The chlorination of 2-phenylaziridine under kinetic resolution conditions yielded optically active (\(E\))- and (\(Z\))-1-chloro-2-phenylaziridines along with unreacted optically active substrate.\(^{30}\)

\[
\begin{array}{c}
\text{R} \\
\text{R} = \text{Ph, Me, H; } R = \text{aryl, cyclohexyl}
\end{array}
\]

Scheme 14

The treatment of 2-methylsulfanyl-3\(H\)-pyrimidin-4-one (35a) and its 6-methyl derivative 35b with NCS afforded products 36 corresponding to chlorination at position 5 of the ring (Scheme 15). A similar result was obtained in the chlorination of 2,4(1\(H,3H\))-pyrimidine-2,4-dione.\(^{31}\)

\[
\begin{array}{c}
\text{R} \\
\text{R} = \text{H, Me}
\end{array}
\]

Scheme 15

The reaction of NCS and imidazo[1,2-a]pyridines 37, substituted at the 3-position with electron-withdrawing groups such as formyl, nitro or bromide, led to the \textit{ipso} reaction products 38 with chlorine installed at position 5 of the imidazole ring (Scheme 16). On the other hand, treatment of imidazo[1,2-a]pyridines substituted at the 3-position by an ester or chlorine group resulted in chlorination at the 5-methyl group to afford compounds 39. The intermediacy of 3-halogenoimidazo[1,2-a]pyridinium compounds was proposed in order to explain the results.\(^{32}\)
Electrophilic halogenation of 2H-cyclopenta[d]pyridazines 47 with NCS in dichloromethane readily afforded the 5- and 7-derivatives 48 and 49 as well as 6-chloro compounds in a much slower reaction (Scheme 19). On the other hand, reaction of the 5,6,7-trichloro derivative of 47a in refluxing carbon tetrachloride with one equivalent of NCS under a nitrogen atmosphere furnished the product of radical substitution at the methyl group (64%).

Scheme 19

The reaction of the 1-methylpyridazino[3,4-b]quinoxaline-4,4-dicarboxylates 50 with NCS or NBS in acetic acid afforded the 3-halogeno-1-methylpyridazino[3,4-b]quinoxaline-4,4-dicarboxylates 51. The reaction of these dicarboxylate compounds with hydrazine hydrate resulted in hydrolysis and decarboxylation to provide the monocarboxylates 52; treatment of these compounds with nitrous acid effected oxidation to furnish the respective 3-halogeno-4-hydroxy-1-methylpyridazino[3,4-b]quinoxaline-4-carboxylates 53. Further reaction of these products with hydrazine hydrate afforded the 3-halogeno-1-methylpyridazino[3,4-b]quinoxalin-4-ols 54, and subsequent oxidation with NCS or NBS in water or aqueous acetic acid provided the 3-halogeno-1-methylpyridazino[3,4-b]quinoxalin-4(1H)-ones 55 (Scheme 20). These final products demonstrated in vitro antifungal activity.

Scheme 20
2.3 Oximes

Base-induced dehydrohalogenation of hydroximoyl chlorides 57 generates nitrile oxides 58, which are versatile intermediates in heterocyclic chemistry (Scheme 21). The hydroximoyl chlorides can be obtained by a plethora of methods. Originally the most popular, though not safe, methods for their synthesis were chlorination of oximes 56 with chlorine gas 59 or nitrosyl chloride 60. In newer methods, tert-butyl hypochlorite, 39 sodium hypochlorite, 40 a hydrogen chloride–Oxone system, 41 benzyltrimethylammonium tetrachloroiodate 62 and N-tert-butyl-N-chlorocyanamide 43 are used. The most convenient and most frequently used method of selective hydroximoyl chloride preparation, without accompanying ring chlorination, utilizes NCS with N,N-dimethylformamide as solvent. 44 As the only exception to this rule, the authors described that the reaction of strongly activated 2,4-dimethoxybenzaldehyde oxime yielded a 2:1 mixture of ring-chlorinated product and hydroximoyl chloride. French chemists reported a clean synthesis of 4-tert-butyl hydroximoyl chloride by chlorination of 4-N,N-dimethylbenzaldehyde oxime in chloroform in the presence of pyridine. 45 However, in our hands, the repeated reaction still afforded a mixture of products. 46

![Scheme 21](image)

2.4 Amines, Imines, Enamines

N-Halogenation of amines have been performed with sodium hypochlorite or hypobromite. 47 NCS chlorination of volatile aliphatic amines using vacuum gas/solid reaction was shown to give primary and secondary N-chloramines and N,N-dichloroamines efficiently (Scheme 22). 48 The process was carried out at room temperature with solid NCS. In the case of primary amines, adipic acid was used as a co-reagent to trap small amounts of unreacted amine. The same technique, when applied to imines, resulted in N-chloroaldimines. 49

The chlorination of secondary amines of 7-azabenzonorbornadienes like 64 with NCS at low temperatures afforded mainly the anti-N-chloro products 65 (Scheme 23). Kinetic control of the reaction was governed by electronic factors. 50 The contribution of syn-derivatives 66 increased along with enhancement of the electronegativity of the aromatic substituents.

![Scheme 23](image)
double dehydrochlorination of the dichloroimines 79 with methanolic sodium methoxide afforded a new, efficient synthesis of pyridines 80 (Scheme 27).55a 1-Pyrrolines were similarly converted into 3-chloropyrroles.55b

A new regio-, stereo-, and chemoselective method has been elaborated for the synthesis of 2-dichloromethylimidazoline derivatives 83 by the reaction of enones 81 with p-toluenesulfonamide and NCS as nitrogen and chlorine sources, respectively (Scheme 28).56 A proposed mechanism for this electrophilic reaction involves the formation of aziridinium intermediates 82 from interaction of TsN–HCl with olefins and a new [2+3] cycloaddition via aziridinium ring opening. In this reaction, it was not possible to replace NCS by NBS. Acidic hydrolysis of the product imidazolines afforded vicinal diamines, important intermediates in the synthesis of pharmaceutically valuable compounds.

The treatment of tricyclic enamiones 84 with one equivalent of NCS in dichloromethane at room temperature gave α-chlorenaminones 85 in an efficient manner. When the reaction was repeated with two equivalents of NCS, the α,γ-dichloro compound 86 was obtained (Scheme 29). These results were rationalized in terms of an initial reaction at nitrogen atom. The isolated C8–C9 double bond turned out to be completely inert under these halogenation conditions.57

### 2.5 Alkynes and Alkenes

1-Chloroalkynes 88 are prepared in good yields by reaction of lithium acetyides 87 with NCS (Scheme 30) as an alternative to chlorination with chlorine gas or hypochlo-

**Scheme 25**

**Scheme 26**

**Scheme 27** Aromatization via imine dichlorination and double dehydrochlorination

**Scheme 28**

**Scheme 29**

**Scheme 30**
catalyzed the chlorination of olefins with NCS. Reaction of mono-, di- and trialkyl olefins yielded rearranged allylic chlorides as the major products, with vinyl chlorides as the minor components. The selectivity of the reaction was improved when electron-withdrawing groups were present, as in alkene 95; here, the reaction resulted in preferred elimination of the selenium compound leading towards the conjugated products 96 (Scheme 32).61 Similarly, a steric bias favors formation of allylic chlorides, since in syn-elimination, the conformation of the H and Se moiety that would lead to the vinyl chloride is disfavored.

On the other hand, NCS serves as a source of chlorine radicals when initiators are present. Allylic chlorination of (+)-3-carene (97) with NCS in the presence of either \( \alpha,\alpha' \)-azobisisobutyronitrile (AIBN), UV light, or silica gel resulted in a rearranged allylic chloride 98 as the major product, in addition to the non-rearranged allylic chloride 99 and 3,4-dichlorocarane (100) which was a result of formal addition of chlorine to the original double bond (Scheme 33).62 Since the reaction catalyzed by a typical free-radical initiator (in this case, AIBN) required a much longer time than the reaction catalyzed by a mildly acidic silica gel, it is likely that the latter chlorination is not a free-radical process. Reaction of (+)-2-carene with NCS under the same conditions as above afforded mainly aromatic products formed by cleavage of the cyclopropane ring.

Halofluorination of different aliphatic, alicyclic and aromatic alkenes was performed in a highly regio-, stereo-, and chemoselective way with halogen fluorides or with a combination of fluoride reagents and some halogen sources, such as \( N \)-haloamides or \( N \)-haloimides.64 Newer, more versatile, sources of fluoride include silicon tetrafluoride as well as ammonium and phosphonium compounds (Scheme 35).54 Yields decreased from NIS through NBS to NCS. The Markovnikov rule of selectivity was followed in all the reactions.
Chlorination of silyl enol ether 106 with NCS in acetonitrile gave the adduct of chlorosiloxycarbonyl cation with succinimide. In the presence of an azide nucleophile and a quaternary ammonium chloride, the chlorosiloxycarbonyl cations 107 underwent a Schmidt-type rearrangement to anilide derivatives 109 via chloroazides 108 when heated in boiling decalin (Scheme 36).65

Scheme 36

NCS also served as an electrophile in the electrophilic addition of various alcohols to the enol ethers 110. The reactions occurred readily in non-polar solvents, such as benzene. Polar solvents slowed the reaction down dramatically and lowered the yield of ethers 111 and 112 (Scheme 37).66

Scheme 37

The haloamidation of olefins was carried out by reaction with N-haloimides (X = Cl, Br) or bromoamides with nitriles in the presence of Lewis acids.67 It was presumed that the reaction involves nucleophilic attack of nitrile on the halonium ion 113 followed by hydrolysis to afford haloamides 114 (Scheme 38).

Scheme 38

2.6 Aralkyl and Alkylheterocyclic Systems

The chlorination of aralkyl and heteroaralkyl systems is generally a free-radical process, particularly in the presence of free-radical initiators as well as in nonpolar solvents, and products of benzylic chlorination are formed. The chlorination of 6-methylphenanthidine furnishes 6-chloromethylphenanthidine.68 Similarly, chlorination of 1-methylphthalic results in 1-chloromethylphthalic.69

In some alkyl heterocyclic compounds, an ionic mechanism is plausible. Chlorination of 2-aryl-4,5-dimethyl-1,3-oxazoles 115 with NCS in acetonitrile provided 4-chloromethyl derivatives 116 as the major products and 5-chloromethyl derivatives 117 as the minor components (Scheme 39). A proposed mechanism invokes addition to the C4–C5 double bond of the oxazole ring and regioselective opening of the halonium intermediate. No ‘benzylic’ chlorination was observed in the case of the reaction in refluxing acetic acid with NCS of 3,5-diarylisoxazoles with a p-methyl substituent on 5-phenyl ring.70 Similarly, 2-aryl-4,5-dimethyl-1,3-thiazoles undergo highly regioselective halogenation at the C4-methyl group.71

Scheme 39

2.7 Carbonyl and Carboxylic Compounds

Halogenation of methylene groups activated by carbonyl and carboxyl functions requires the presence of appropriate catalysts. An efficient α-halogenation of β-ketoesters and α-halogenation of cyclic ketones with NCS and acidic Amberlyst-15 was described.72 The reaction occurred at room temperature in ethyl acetate with high yields. Alternatively, methyl ketones were monochlorinated via their lithium enolates.73

The other catalyst that has been used for α-monochlorination of ketones and β-ketoesters is phenylselenyl chloride.61 The regioselectivity of the mesityl oxide (118) reaction was solvent-dependent (Scheme 40). In acetonitrile, a vinyl halogenation took place, whereas in methanol only methyl halogenation was observed and furnished 120.

Scheme 40

Enantioselective halogenation of β-keto esters with N-halo-succinimides catalyzed by Lewis acids has been elaborated. With 5 mol% of titanium–TADDOL complexes at room temperature, enantioselectivities of up to 88% ee could be obtained for the chlorination reaction. Under
comparable conditions, the bromination reactions with NBS are slower and less stereoselective.\textsuperscript{74}

The \(\alpha\)-fluoro- and \(\alpha\)-chloro-\(\beta\)-ketosteres \textbf{122} and \textbf{123} were prepared by electrophilic reaction of \(\beta\)-keto esters \textbf{121} with NCS or 1-chloromethyl-4-fluoro-1,4-diazaonobicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA) in the presence of titanium chlorides such as titanium tetra-chloride, (\(\eta^5\)-cyclopentadienyl)titanium trichloride, or the titanium–TADDOL complexes (Scheme 41).\textsuperscript{75} \(\text{CpTiCl}_3\) was the most effective catalyst used for the preparation of \(\alpha\)-fluoro- or \(\alpha\)-chloro-\(\beta\)-keto esters from \(\beta\)-keto esters; in most cases the ratio of mono- to difluorinated \(\beta\)-keto esters was greater than 9:1. Titanium–TADDOL complexes were shown to be effective catalysts for the one-pot enantioselective heterodihalogenation of \(\beta\)-ketoesters with F-TEDA and NCS, affording \(\alpha\)-chloro-\(\alpha\)-fluoro-\(\beta\)-keto esters in moderate to good yields. Either enantiomer of \(\alpha\)-chloro-\(\alpha\)-fluoro-\(\beta\)-ketoester \textbf{124} or \textbf{125} could be prepared, simply by reversing the order of reagent addition in the halogenation step.

An imidazolidine-type diamine with \(C_2\)-symmetry served as the organocatalyst in an asymmetrical \(\alpha\)-chlorination reaction of simple ketones. Optically active \(\alpha\)-chloro ketones were formed with excellent enantioselectivities using NCS as the chlorine source.\textsuperscript{76} These products have broad synthetic utility, in particular for pharmaceutical applications.

NCS was used as an acid scavenger in the chlorination of \(\alpha\),\(\beta\)-unsaturated ketones and esters by chlorine in methanol. Mixtures of Markovnikov and anti-Markovnikov methoxychlorides and dichlorides were obtained.\textsuperscript{77} NCS did not react in this process with hydrochloric acid to generate chlorine as was the case with NBS, but was presumed to chlorinate directly an intermediate methoxy enol to afford the anti-Markovnikov product.

Alternatively, the \(\alpha\)-monohalogenation of 1,3-diketones, \(\beta\)-keto esters, and cyclic ketones has been conducted at room temperature in ionic liquids with \(N\)-halosuccinimides in excellent yields in the absence of a catalyst.\textsuperscript{78} These recovered green recyclable reaction media were reused up to six times with consistent activity.

Enantioselective \(\alpha\)-chlorination of aldehydes by NCS catalyzed by L-proline amide and (2\(R\),5\(R\))-diphenylpyrrolidine was achieved (Scheme 42).\textsuperscript{79} The aldehydes were isolated with excellent yield (up to 99\%) and optical purity (up to 95\%). The proposed mechanism involves \(N\)-chlorination of initially formed enamine followed by a 1,3-sigmatropic shift of the chlorine atom and then hydrolysis. This mechanistic hypothesis was supported by studies of reaction kinetics, isotope effects and density functional theory calculations.\textsuperscript{80}

\begin{equation}
\text{R} = \text{alkyl, allyl, Bn}
\end{equation}

\textbf{Scheme 42}

An efficient and chemoselective \(\alpha\)-chlorination of acyl chlorides was accomplished with NCS in thionyl chloride as a solvent in the presence of catalytic amounts of hydrochloric acid (Scheme 43).\textsuperscript{81,82} This ionic reaction was slowed down considerably when \(\alpha\)-substituents were present. NBS reacted faster than NCS, while \(\alpha\)-iodination was achieved with molecular iodine. This method is superior to the Hell–Volhard–Zelinsky reaction that used chlorine and that lacked the selectivity observed with NCS.

\begin{equation}
\text{R} = \text{Ph, t-BuO; } X = \text{Cl, Br, I}
\end{equation}

\textbf{Scheme 43}

The halogenation of \(N\)-benzoyl- and \(N\)-Boc-protected azetidinones \textbf{128} with NXS in acetonitrile in the presence of sodium bicarbonate afforded the 3-halo azetidinones as a mixture of two diastereoisomers, \textbf{129} and \textbf{130}, with the \textit{trans} isomer prevailing under kinetic control (Scheme 44).\textsuperscript{83}

\begin{equation}
\text{R} = \text{Ph, t-BuO; } X = \text{Cl, Br, I}
\end{equation}

\textbf{Scheme 44}
The kinetics of chlorine transfer reactions between NCS and four conjugated bases – phenylidinitromethane, Mel- 
drum’s acid, phenylmalononitrile and phenylidinitromethane – in water were examined. A straight-line 
relation of log k for the S_N2 reactions and the pK_a of the first three conjugated acids of the nucleophiles was 
observed. The deviation of phenylidinitromethane was explained by proton-transfer reactions.

2.8 Chalcogen Compounds

The most widely used chemicals for chlorination of sul-
fides are sulfuryl chloride and NCS. NCS is particularly 
convenient because the extent of chlorination can be 
easily controlled and this reagent can be used with acid-sen-
sitive substrates, in contrast to sulfuryl chloride, where a 
side product is hydrochloric acid. The sulfide chlorination 
reaction follows an ionic mechanism that involves a trans-
fer of chlorine from sulfur to carbon. The treatment of di-
alkyl sulfides and alkyl aryl sulfides with NCS gave α-
chlorosulfides which were hydrolyzed without isolation 
to aldehydes (Scheme 45). On the other hand, the treat-
ment of diaryl or alkyl aryl selenides and diaryl or dialkyl 
tellurides with NCS followed by alkaline hydrolysis af-
forded the corresponding selenoxides or telluroxides. A 
suggested mechanism involves formation of chloroseleni-
um and chlorotellurium species that are stabilized in com-
parison to chlorosulfonyl compounds, which tend to 
rearrange to the α-sulfides. The procedure is compatible 
with several sensitive groups, including alkenes, alcohols, 
ketones and esters.

Scheme 45

NCS treatment of α-phenylselanylesters 135 in carbon tet-
rachloride was shown to be an efficient method for the 
preparation of α-chloro-α-phenylselanylesters 136 and α-
chloro-α,β-unsaturated esters 137 (Scheme 46). Treatment 
with 1.2 equivalents of NCS afforded mainly α-
chloro-α-phenylselanyl esters, whereas with 2 molar 
equivalents of NCS, α-chloro-α,β-unsaturated esters were 
obtained.

The chlorination of alkyl methyl sulfoxide 138 with NCS 
afforded mainly 1-chloroalkyl methyl sulfoxides 140. In 
the presence of a base, the regioselectivity was reversed 
and alkyl chloromethyl sulfoxides 139 were isolated as 
the major products; this was rationalized by assuming ab-
traction of a more acidic and less hindered proton by the 
base (Scheme 47).

Sulfones were shown to undergo α-chlorination by treat-
ment with n-butyllithium and inverse addition of the 
formed carbaniion to NCS, which was present in excess.
Sulfonate-stabilized carbanions were chlorinated by NCS 
in hexamethylphosphoramide (HMPA) in good yields. A 
one-pot procedure was developed for the conversion of 
phenols 141 into aryl trichloromethanesulfonates 142 
using NCS, p-methylsulfonylethyl chloromethane-
sulfonate (143) for transfer of chloromethylsulfonyl 
group, and a base (Scheme 48).

Scheme 46

Scheme 47

Scheme 48

3 Replacement of Other Groups by Chlorine

Using NCS, the replacement of several groups such as 
OH, COOH and NH_2 by chlorine was demonstrated. Site-
selective deoxyhalogenation at C-6 of the carbohydrate 
N-phthaloylchitosan (143) to halides 144 with an NXS– 
triphenylphosphine system was described. The reaction 
took place in polar aprotic solvents (N-methyl-2-pyrroli-
done or N,N-dimethylformamide) and proceeded most 
easily with NCS as compared to the other N-halosuccin-
imides (NCS > NBS > NIS), reflecting the order of halide 
on nucleophilicity in this type of solvent (Scheme 49).

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The reagent is useful also in the preparation of halides from other carbohydrates, nucleosides and other substituted alcohols.91

Scheme 49
Cyclic secondary alcohols undergo kinetic resolution by enantioselective SN2 displacement of hydroxyl groups with chlorides in the presence of chiral BINAP to afford inverted chlorides in 54–94% ee and unreacted alcohols in 69–98% ee and 82–98% yield. NCS was the optimal chlorinating agent for achieving good enantioselectivity, while tetrahydrofuran was the best solvent in this respect.92

Alkali metal acetates catalyze the Hunsdiecker reaction, in this case the halodecarboxylation of α,β-unsaturated carboxylic acids 145 with N-halosuccinimides that led to haloalkenes 146 (Scheme 50). The reactions, carried out in acetonitrile–water at room temperature, proceeded in good yields and good stereoselectivities through an ionic pathway.93

Scheme 50
A mild conversion of primary amines into the corresponding halides was achieved via a halodeamination reaction of N-substituted N-tosylhydrazines 147 with NCS (or NBS) in anhydrous tetrahydrofuran in the presence of light (Scheme 51). A suggested reaction mechanism involves a stabilized hydrazyl radical which undergoes halogenation. Elimination of p-toluenesulfonic acid and nitrogen then affords the alkyl halide.94

Scheme 51

4 Halocyclizations
α-Substituted γ,δ-unsaturated amides and thioamides 148 underwent halocyclization to γ-butyrolactones 149 and 150 with several electrophiles, including NCS and NBS (Scheme 52). 1,3-Asymmetric trans induction was most pronounced for NBS (>99:1); for NCS the ratio of 149 to 150 was reduced to 3:2.95

Scheme 52
Haloenol lactones 153 and 154 were prepared from cyclic anhydrides 151 via lactonization of the corresponding keto phosphoranes 152 in the presence of halosuccinimides. 1H NMR and 31P NMR studies of the reaction led to a proposed mechanism for the reaction (Scheme 53). The products of this reaction show biological activity and are useful intermediates in organic synthesis.96

Scheme 53
Chlorolactonization of unsaturated acids was performed with NCS and phenylselenyl chloride, or with NBS and diphenyl diselenide, in acetonitrile.61

N-Halosuccinimides were used to carry out the halocyclization of 4-allyl-1,2,3,4-tetrahydroisoquinoline (155) to azabicyclo[3.2.1]heptanes 156 via a 5-exo-trig route (Scheme 54).97

Scheme 54
5 Rearrangements and Functional Group Transformations

NCS can be used to mediate several types of rearrangements and functional group transformations.

Cyclic dithiane alcohols 157, with a fused aromatic ring, have been shown to undergo rearrangement to 1,3-diketones 158 with a one-carbon ring extension upon treatment with excess of NCS (Scheme 55). A key step in the proposed mechanism is conversion of the intermediate b into c with migration of bond ‘a’, a step which is favored by high electron density on the adjacent carbon atom.98

The treatment of 3-indolecarboxylate 159 with NCS and different primary and secondary alkenols afforded 3-allylated 2-indolones 161 in good yield (Scheme 56).99 This novel transformation involves α-chlorination, addition of alcohol to the imine bond, and [3,3]-sigmatropic rearrangement of the intermediate 160. This Claisen rearrangement is highly stereoselective for Z-alkenols.

Epoxides were regioselectively converted into vic-haloalcohols 163 with 1.2 equivalents of NXS and triphenylphosphine at reflux temperature. On the other hand, treatment with 2.5 equivalents of NXS and triphenylphosphine at reflux temperature afforded sym-
metrical vic-dihalides. When different N-halooimides were used successively, unsymmetrical vic-dihalides 165 were obtained in high yield (Scheme 59).102

Scheme 59

1,3-Oxathiolanes, 1,3-dithiolanes and 1,3-dithianes were efficiently converted into the corresponding acetals with NCS or NBS and various alcohols and diols. The transformations occurred rapidly at room temperature, preferentially in dichloromethane, without liberation of carbonyl compounds (Scheme 60).103

Scheme 60

A new method was elaborated for the synthesis of acetals 167 from carbohydrates and aldehydes. It involved the addition of triphenylphosphine to a solution of aldehyde and NCS (or NBS) in anhydrous N,N-dimethylformamide with formation of methanium salt 166, followed by addition of the carbohydrate (Scheme 61).104

Scheme 61

The oxidative hydrolysis of various vinyl halides with oxygen-containing groups to α-halomethyl ketones was described (Scheme 62). This reaction, affording products in good yield and purity, required catalytic amounts of the corresponding hydrohalic acid.105

Scheme 62

The treatment of α,α-diisopropylhomoallylic alcohols with tin(II) chloride and NCS in dichloromethane at –40 °C gave allylic trichlorotins, which subsequently underwent nucleophilic addition to N-tosylimines to afford the corresponding α-substituted homoallylic amines (Scheme 63).106

Scheme 63

The reaction of secondary amines with sodium nitrite and NXS under phase-transfer catalysis conditions afforded efficiently the corresponding N-nitrosoamines (Scheme 64). Without the catalyst present, N-chloroamines were the major products. The proposed mechanism involves initial formation of a nitril halide followed by a key intermediate, nitrogen dioxide.107

Scheme 64

α-Phenylthio secondary propanoamides were stereospecifically transformed to (Z)-α-phenylthio-β-chloroprop-enamides upon treatment with NCS (Scheme 65). The reaction of analogues with extended alkyl chains was less efficient and was not stereoselective.108

Scheme 65

6 Formation of New Carbon–Carbon Bonds

NCS has been shown to participate in several reactions wherein new carbon–carbon bonds are formed.
The aldol-type reaction of aldehydes with propen-2-yl acetate and primary alcohols in the presence of NCS and tin(II) chloride produced 4-substituted 4-alkoxybutan-2-ones 169 in good yield (Scheme 66). When methanol was used as an alcohol, but-3-en-2-one 170 was also obtained after elimination of a molecule of methanol. The reaction involved the formation of hemiacetal 171 from the aldehyde and alcohol with the participation of NCS·SnCl₂, followed by nucleophilic attack of propen-2-yl acetate.

Dimesitylboron-stabilized carbanions 172 react with aliphatic aldehydes in the presence of NCS (or trifluoroacetic acid anhydride) to afford, after an acidic workup, the corresponding ketones 173 in a type of boron-Wittig transformation (Scheme 67). This condensation–redox reaction proceeded in satisfactory yields for aldehydes with primary and secondary alkyl groups; as the only exception, anion substrates derived from dimesitylmethylborane underwent mainly an alternative reaction to afford the corresponding alkenes.

Nucleophilic displacement on sulfur of dimethylsuccinimidosulfonium fluorosulfate (174) by morpholine enamine 175 afforded sulfonium enamine 176 which, upon heating with sodium cyanide in acetonitrile, furnished isomeric cyanomorpholine bicyclo[n.1.0]alkanes 177 and/or 178 (Scheme 68).

The regioselective methylthiomethylation of various, mostly 2,6-disubstituted, phenols with excess succinimidosulfonium chloride (Corey–Kim reagent) was examined. The reaction, carried out in the presence of triethylamine, afforded several types of mono-, bis- and tris-substituted cyclohexa-2,4-dien-1-ones in good yields via rearrangement of the oxasulfonium salts 179 (Scheme 69).

Alternatively, reaction of the Corey–Kim reagent with excess monosubstituted phenols furnished the o-methylthiomethylated phenols. This reagent induced the cyclization of tryptamine derivatives with concomitant introduction of the methylthiomethyl group at C-3.

An oxidative homo-coupling of arylzinc compounds was achieved in the presence of a catalytic amount of Pd²⁺ or Pd⁰ through the use of NCS as an oxidant. This reaction revealed a new and facile synthetic method for the preparation of biaryls from aryl halides or arenes via arylzinc intermediates (Scheme 70).
7 Formation of Heterocyclic Systems

_N-Halosuccinimides have been used to enable new syntheses of heterocyclic systems. The treatment of phenyl isocyanide with NXS and sodium azide under phase-transfer catalysis conditions afforded 5-halo-1-phenyltetrazoles 180 in good yields (Scheme 71). The active species are probably halogen azides which add to the phenyl isocyanide._116

Scheme 71

The reaction of some cyclopentenes and indenes with disulfur dichloride in tetrahydrofuran in the presence of NCS and a base (DABCO or DIPEA) enabled an effective conversion into several unsaturated and chlorinated fused heterocyclic and carbocyclic compounds (Scheme 72). Cyclopent-1-en-1-ylacetic acid (181) afforded the trichlorocyclopenta[1,2]dithiole ester 182 via the corresponding acid as a result of tetrahydrofuran cleavage by disulfur dichloride. Inden-3-ylacetic acid (183) furnished methyleneindenes 184 and 185, 1,2-dithiolone 186, and thiophene derivative 187, a new liquid crystalline material._117

Scheme 72

3-Amino-1_H-indene-2-carbonitrile (188) reacted with sulfur dichloride, triisobutylamine and NCS to give the corresponding indeno[1,2,6]thiadiazine 189 in a reaction that involved dehydrogenation and chlorination of the cyclopentathiazine moiety (Scheme 73).

Scheme 73

Under similar conditions, 2-aminocyclopent-1-enecarbonitrile (190) afforded the cyclopenta[1,2,6]thiadiazine 191, and 2-aminocyclohept-1-enecarbonitrile yielded a formally antiaromatic cyclohepta[1,2,3]dithiazole._118
Some of the product compounds showed useful features as new liquid crystals and near-IR dyes.

The application of the Pummerer reaction methodology to N-acylamino-2-thiophenyl derivatives with NCS and tin(IV) chloride provided a direct synthesis of 5-thiophenoxazoles (Scheme 74).\textsuperscript{119}

Scheme 74

The treatment of triphenylformazanes \textsuperscript{192} with NCS (or NBS) resulted in cyclodehydration and formation of 2,3,5-triphenylterazolium halides \textsuperscript{193}. Similarly, syn-phenylhydrazones of 2-pyridinealdehyde \textsuperscript{194} afforded 8-azaindazolium salts \textsuperscript{195} (Scheme 75).\textsuperscript{120}

Scheme 75

8 Oxidations

The oxidation of alcohols by NCS requires the presence of appropriate catalysts.

Primary alcohols are chemoselectively oxidized by NCS to aldehydes in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) catalyst. A broad range of aliphatic, benzylic and allylic alcohols were oxidized, without any over-oxidation (Scheme 76). The reactions were carried out in dichloromethane–aqueous buffer system (pH 8.6) at room temperature in the presence of tetrabutylammonium chloride (TBACl) as a phase-transfer agent. The oxidation of secondary alcohols proceeds with a much lower efficiency and at a rate that is at least one order of magnitude lower than that observed for primary alcohols.\textsuperscript{121}

Scheme 76

Japanese chemists examined the use of N-\textit{tert}-butylbenzenesulfenamide as a catalyst in the oxidation of various primary and secondary alcohols to the corresponding carbonyl compounds.\textsuperscript{122} The reaction was performed in the presence of potassium carbonate and molecular sieves. Selective oxidation of primary hydroxy groups took place when diols were subjected to the reaction, albeit in moderate yields (Scheme 77). A mechanistic investigation suggested that a key species in the chlorination was N-\textit{tert}-butylbenzenesulfinimido chloride (formed from N-\textit{tert}-butylbenzenesulfenamide and NCS), which oxidized the alcohols to the carbonyl products while regenerating the catalyst.

Scheme 77

In another variant of this approach, polymer-supported sulfinimidoyl chlorides were used either as catalysts with NCS or in stoichiometric amounts.\textsuperscript{123} In the first case, longer reaction times were required than in the case of monomeric sulfonamide.

The frequently applied oxidation of alcohols by the Corey–Kim reagent (NCS·SMe\textsubscript{2} complex) is related to the oxidation that is mediated by activated dimethyl sulfoxide and has been reviewed.\textsuperscript{124} A newer example of this reaction is shown in Scheme 78.\textsuperscript{125} The oxidation of β-hydroxy ketones (prepared from isoxazolines by reductive hydrogenation) with NCS·SMe\textsubscript{2} and triethylamine afforded the stabilized sulfonium ylides \textsuperscript{196} which were desulfurized with zinc in acetic acid. In the search for a more user-friendly variant of this reagent, an odorless complex of NCS and dodecyl methyl sulfide was introduced.\textsuperscript{126}

Scheme 78

The kinetics and mechanism of the palladium(II)-catalyzed oxidation of allyl alcohol by NCS in aqueous alkaline medium was studied by an Indian research group.\textsuperscript{127} A mechanism involving the hypochlorite ion as the reactive species of the oxidant was proposed.
The oxidation of aryl and alkyl thioacetates, as well as several thiols and disulfides, by a combination of NCS and dilute hydrochloric acid afforded the corresponding sulfonyl chlorides in good yield. A smooth reaction course was envisaged to involve the rapid generation of reactive molecular chlorine.

The oxidation of dialkyl, diaryl and benzylphenyl sulfides by an equimolar amount of NCS gave sulfoxides. In aqueous solution containing chloride ion, the first step is chlorination by chlorine, formed in the reaction, followed by hydrolysis to afford the corresponding sulfoxides (Scheme 79). In alcoholic solutions, alkoxysulfonium salts were postulated as intermediates. Diphenyl sulfoxides afforded the corresponding sulfones in the presence of excess NCS, while dialkyl sulfides gave only cleavage products.

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\text{Scheme 79}
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The kinetics and mechanism of the oxidation to sulfoxides of aromatic sulfides and arylmercaptaoacetic acids by NCS was examined. The measurements, carried out in an acetonitrile–water mixture, showed that protonated NCS and NCS are the active oxidizing species in the oxidation of aromatic sulfides, and NCS is the active species in the case of phenylmercaptaoacetic acids. Structure–reactivity correlations for the oxidation of the sulfides and arylmercaptaoacetic acids indicated that chlorosulphonium ion was an intermediate.

A similar mechanism was proposed for the oxidation with N-halosuccinimides of diaryl or alkylaryl selenides and diaryl or dialkyl tellurides. NCS was found to be a much better oxidant than NBS. The reactions with a positive halogen source required a subsequent alkaline hydrolysis to afford the corresponding selenoxides or telluroxides (or hydrates) (see Scheme 45).

The oxidation of the amino acid cysteine and its derivatives into cystine was performed with NCS. The oxidation of the amino acid cysteine and its derivatives into cystine was performed with NCS. The oxidation of cystine by NCS was performed with NCS.

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\text{Scheme 79}
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9 Deprotections

Both NCS and NBS have been shown to be effective deoximating agents. The parent ketones were obtained in excellent yields by stirring oximes and NCS (or NBS) at room temperature in carbon tetrachloride. A novel method was invented for the chemoselective deprotection of S,S- and S,O-acetals and ketals, in the presence of their O,O-analogues, to the carbonyl compounds. The reactions were carried out efficiently in a chloroform solution at room temperature with catalytic amounts of NCS, NBS, or similar sources of electrophilic halogens, in the presence of dimethyl sulfoxide as the source of oxygen. The suggested mechanism involves halogenation on the sulfur atom and nucleophilic attack of the dimethyl sulfoxide oxygen at the central carbon atom.

10 Transformations of NCS

NCS has been used as a convenient source of NIS. This electrophilic iodination reagent was prepared by treatment of NCS with sodium iodide in acetone and subsequent filtration of the precipitated sodium iodide. Similarly, NBS was obtained from NCS by reaction with tetraethylammonium bromide.

The chlorine atom in NCS can be substituted by sulfur nucleophiles, such as tetrahydrothiophene, 3H-benzothiazole-2-thione or dialkylsulfides, to result in the formation of succinimidosulfonium chloride. The reaction of NCS with an equimolar amount of sulfur in dichloroethane in the presence of tetramethylammonium iodide afforded N-chlorothiosuccinimide. A similar reaction occurred upon heating of NCS with excess sulfur dichloride. Subsequent heating of the resulting N-chlorothiosuccinimide in inert solvents was accompanied by loss of sulfur dichloride and formation of disuccinimidosulfide (Scheme 80).

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\text{Scheme 80}
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11 Miscellaneous Reactions

Early investigations into the halogenation of saturated hydrocarbons with NCS were moderately successful in the alicyclic series, where cyclohexyl chloride was prepared in 42% yield from cyclohexane after heating at reflux for 12 hours. NBS proved to be less convenient because some decomposition was observed upon prolonged heating. The treatment of N,N-dialkylsulfenamides with NCS in solution with dichloromethane yielded dialkylamino succinimidosulfonium chlorides. These products underwent
nucleophilic displacement on sulfur by carbanions, formed from active methylene compounds, to afford the novel stabilized sulfur ylides 197 (Scheme 81). 144

Scheme 81

NCS was found to be a more satisfactory reagent than sulfonyl chloride in the conversion of hydrogen phosphates into phosphorochloridates 198, since the reaction medium remains neutral (Scheme 82). 145

Scheme 82

N-Halosuccinimides (NCS and NBS) were also shown to mediate the alkoxylation at C-7 of pyrazino[2,3-c][1,2,6]thiadiazine-2,2-dioxides 199 with lower alcohols (Scheme 83). Some evidence indicates that the reaction does not involve the 7-halointermediates and may instead be mediated by free radicals, since it can be catalyzed by typical free-radical initiators such as tert-butylhydroperoxide. 146

Scheme 83

The N,N-dimethylformamide-induced reaction of [(Z)-1-bromo-1-alkenyl]dialkylboranes 200 with NXS afforded the 1,2-disubstituted (E)-vinyl bromides in a stereoselective manner (Scheme 84). The envisaged reaction mechanism includes the formation of a halonium ion and the 1,2-migration of the alkylaminoboryl and halogeno groups. 147

Scheme 84

The stereoselective synthesis of β-alkyl-α-halocarboxylic acids 202 was achieved by a reaction cascade comprising the 1,4-addition of dialkyl aluminum chlorides to α,β-unsaturated N-acyloxazolidinones substituted with chiral auxiliaries 201, followed by the reaction of aluminum enolates with N-halosuccinimides and, finally, basic hydrolysis (Scheme 85). 148 Oxazolidinones derived from glucosamine showed the highest stereocontrol.

Scheme 85

12 Biological Activity of NCS

NCS exhibits bacteriostatic and bactericidal activity resulting from its strong oxidative action. 149 Studies of cellular mechanisms in Escherichia coli and Staphylococcus epidermis showed that this chloramine inhibited the action of enzymes containing sulphydryl groups that interfere with the synthesis of bacterial DNA, RNA and proteins.

13 Conclusions

This review has demonstrated the broad synthetic utility of NCS. The versatility and selectivity of this reagent can be further enhanced and modified by the formation of complexes with Lewis bases (PPh3, sulfides), and compounds with Lewis acids. The reactivity of NCS can be altered within a wide range – from nucleophilic properties (in the presence of Lewis bases), through free-radical reactivity, to electrophilic character – depending on the substrate, solvent, reaction conditions and the presence of catalysts and additives. NCS possesses general acid–base properties and is thermally and photochemically the most stable of the three N-halosuccinimides.

Further applications of NCS and its derivatives can be expected. One of the possible new avenues could be the application of chiral complexes with participation of NCS.

References

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REVIEW

Applications of N-Chlorosuccinimide in Organic Synthesis

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