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REVIEW

N-Halo Reagents. *N*-Halosuccinimides in Organic Synthesis and in Chemistry of Natural Compounds

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Abstract—The review summarizes published data on the application of *N*-halocuccinimides in organic synthesis and in natural compounds chemistry. Halogenation, imidation, oxidation, and other reactions are discussed.

I. INTRODUCTION

A large group of substances generically called *N*-halo reagents is widely used in fine organic synthesis and in the chemistry of natural compounds. These include *N*-halo amines, *N*-halo amides, *N*-halo carbamates, *N*-halo ureas, etc. The scope of application of such compounds is so wide and syntheses therewith are so vast that all *N*-halo reagents cannot be considered within the framework of a single review article. Therefore, the present review is limited to the application of *N*-halosuccinimides in organic synthesis and natural compounds chemistry.

Some specific features of *N*-halosuccinimides determine their wide aplication in organic synthesis. First of all, this is high lability of the N–Hlg bond and various modes of its splitting. Depending on the conditions, a number of highly reactive intermediates can be formed: halogen radicals, halogen cations, halogen anions, N-radicals, N-cations, N-anions, etc. [1]. As a result, *N*-halosuccinimides promote very important reactions, such as halogenation, solvolytic halogenation, imidation, oxidation, as well as other processes resulting in formation of compounds with C–Hlg, C–O, C=O, S–Hlg, P–Hlg, C–N, P–N, S–N, S=N bond, etc.

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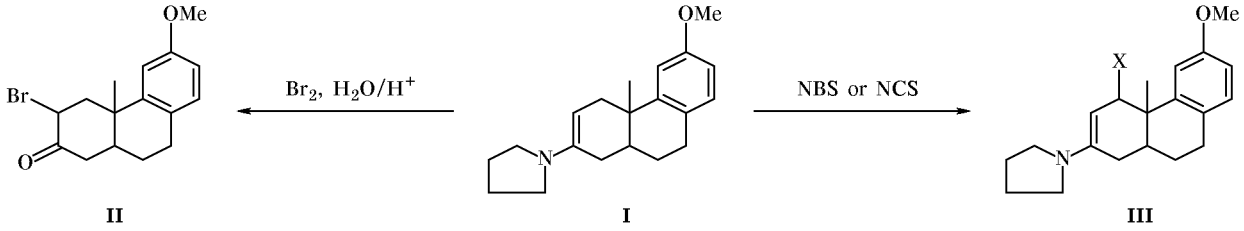
Scheme 1.



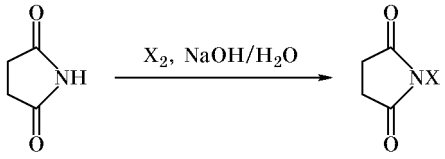
X = Br, Cl.

N-Halosuccinimides play an especially important role in the chemistry of natural compounds, where they are widely used as halogenating, hydroxyhalogenating, oxidizing, and condensing agents.

The second specific feature of *N*-halosuccinimides, responsible for their wide application, is high selectivity of processes with participation of these compounds, which cannot be achieved through the use of other reagents. For example, the bromination of enamine **I** with bromine leads to formation of monobromoenamine whose hydrolysis yields α-bromoketone **II** (Scheme 1) [2]. Direct bromination of the synthetic precursor of enamine **I** (the corresponding ketone) results in replacement of hydrogen by bromine both in the α-position with respect to the carbonyl group and in the aromatic ring. Treatment of **I** with *N*-bromo- and *N*-chlorosuccinimides affords the corresponding β-haloamines **III** (Scheme 1).

Finally, *N*-halosuccinimides are accessible and relatively stable compounds, as compared to the other *N*-halo reagents. *N*-Halosuccinimides are usually prepared from succinimide by the action of molecular halogens or of hypohalite ion in aqueous–alkaline medium [1–3] (Scheme 2).

Scheme 2.



X = Cl (NCS), Br (NBS).

N-Iodosuccinimide (NIS) is obtained by reaction of elemental iodine with succinimide silver salt in acetone [3]. *N*-Halosuccinimides are crystalline substances with a specific odor. They decompose on heating (sometimes with explosion). Some aspects of the chemistry of *N*-halosuccinimides were reviewed in [4]. However, since that time many new data have been published, which require generalization. On the other hand, there are no reviews on the application of *N*-halosuccinimides in organic synthesis and chemistry of natural compounds. The present article should fill this gap to some extent.

II. HALOGENATION REACTIONS

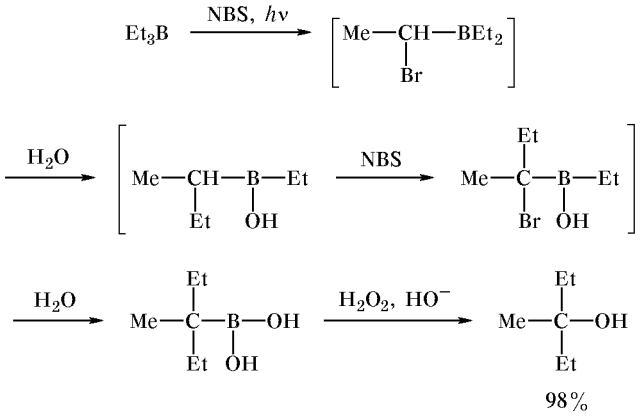
II.1. C-Halogenation

II.1.1. Replacement of hydrogen by halogen at a saturated carbon atom. Homolytic replacement of hydrogen by halogen at a saturated carbon atom occurs either under UV irradiation or in the presence of radical initiators, such as benzoyl peroxide or azobis(isobutyronitrile) (AIBN). However, this procedure have found almost no application for halogenation of saturated hydrocarbons, since both *N*-halosuccinimides and halogens as halogenating agent provide the same results, namely formation of mixtures of monohalogen derivatives with various isomer ratios. The chlorination of octane with chlorine (UV irradiation, 20°C) and *N*-chlorosuccinimide (benzoyl peroxide, 98°C) yields a mixture of 1-chloro- (14 and 15%), 2-chloro- (30 and 31%), 3-chloro- (28 and 29%), and 4-chlorooctanes (27 and 25%), in the two cases the isomer ratios being almost similar [5].

Photochemical halogenation of the alkyl groups in trialkylboranes is characterized by greater selectivity, and this process is used to prepare strongly branched alcohols [6] (Scheme 3). Likewise, 5-butylnonan-5-ol is synthesized from tributylborane, and 1-cyclohexylcyclohexanol, from dicyclohexylboronic acid [6].

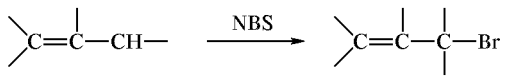
Radical halogenation of various naturally occurring compounds has been reported in [7–17]. Praly *et al.* [7] studied radical bromination with *N*-bromosuccinimide of a series of acetylated glucopyranose derivatives and obtained mixtures of different brominated products. The bromination of friedelin with *N*-bromosuccinimide in a mixture of DMSO with chloroform

Scheme 3.



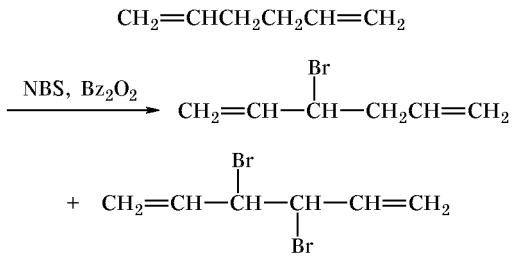
(5 : 1, 30 days) gave 1β,23-dibromofriedelin, 2α,23-dibromofriedelin, 2,2-dibromofriedelin, and other dibromo derivatives which were isolated and identified [8]. By bromination of a mixture of α- and β-ergocryptines with *N*-bromosuccinimide in dioxane at 60°C (70 min) a mixture of α- and β-2-bromoergocryptines was obtained in an overall yield of 55% [9]. The reaction of *N*-bromosuccinimide with guaiazulene in benzene gave a mixture of lactarozulene, 7-[(*Z*)-2-bromo-1-methylethenyl]-1,4-dimethylazulene, 7-(2-bromo-1-methylethyl)-1,4-dimethylazulene, 7-(bromomethyl-2-bromoethyl)-1,4-dimethylazulene, and other compounds [10]. The bromination of lupenyl acetate to 30-bromolupenyl acetate with *N*-bromosuccinimide was effected in a 2.5 : 1 DMSO–chloroform mixture [11]. Treatment of 4-chloroestra-3,5-diene-3,17-diol diacetate with *N*-bromosuccinimide in DMF gave 80% of the corresponding 6-bromo derivative [12]. Radical bromination of cyclosporin A acetate with *N*-bromosuccinimide in boiling CCl_4 in the presence of AIBN led to formation of acetyl-η-bromocyclosporin A in 40% yield [13]. The chlorination with *N*-chlorosuccinimide of isopulegol [14] and 3-methoxysampangine [15] was reported. As a result, 10-chloroisopulegol (50%) and 4-chloro-3-methoxysampangine (53%), respectively, were isolated.

Halogenation with *N*-halosuccinimides of an activated C–H bond is much more facile and selective. An example is so-called allylic halogenation, i.e., hydrogen replacement at an allylic carbon atom. For this purpose, *N*-bromosuccinimide is used most widely. Its steric structure and almost nonpolar N–Br bond make it most appropriate for radical allylic bromination [3]:



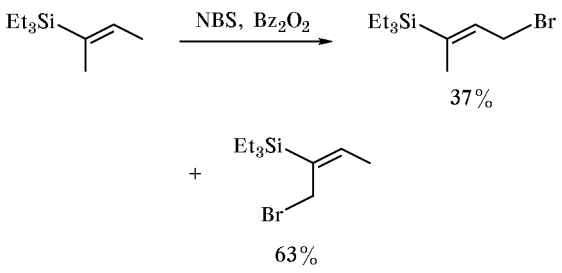
Allylic bromination with *N*-bromosuccinimide can be initiated by heating, UV irradiation, addition of chemical initiators (such as benzoyl peroxide, AIBN, etc.), or by applying *N*-bromosuccinimide onto SiO_2. In the absence of initiator methylene groups are brominated more readily than methyl groups, and the latter undergo bromination much more readily than CH groups. Olefins possessing normal and branched chains are brominated with *N*-bromosuccinimide via replacement of only one hydrogen atom in each allylic position. For example, 1,5-hexadiene reacts with *N*-bromosuccinimide in the presence of benzoyl peroxide, yielding a mixture of 3-bromo- and 3,4-dibromo-1,5-hexadiene [5] (Scheme 4).

Scheme 4.



Two products are also formed when the substrate contains two allyl groups per C=C bond, e.g., in the allylic bromination of 2-triethylsilyl-2-butene [16] (Scheme 5).

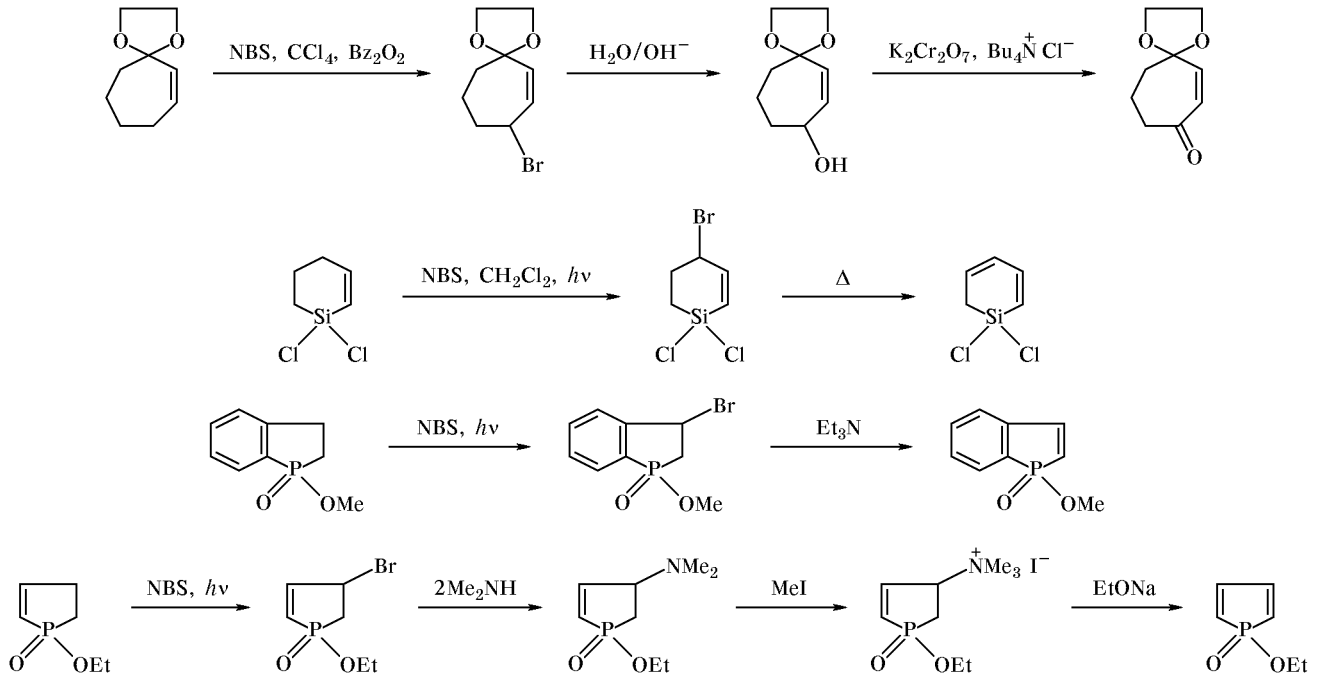
Scheme 5.



When four allyl groups per C=C bond are present, as in the tetramethylethylene molecule [3], fourfold bromination is possible.

Not only olefins but also unsaturated ketones [17, 18], nitriles [3], esters [19], unsaturated lactones [3], unsturated amino acid esters [20], cyclic olefins [13, 4, 21–23], and some heterocyclic compounds [24–27] undergo allylic bromination with *N*-bromosuccinimide. Cyclohexene reacts with N-bromosuccinimide in boiling CCl_4 in the presence of benzoyl peroxide to give 3-bromocyclopentene in 63% yield [1]. The bromination of 1,4-cyclohexadiene with

Scheme 6.

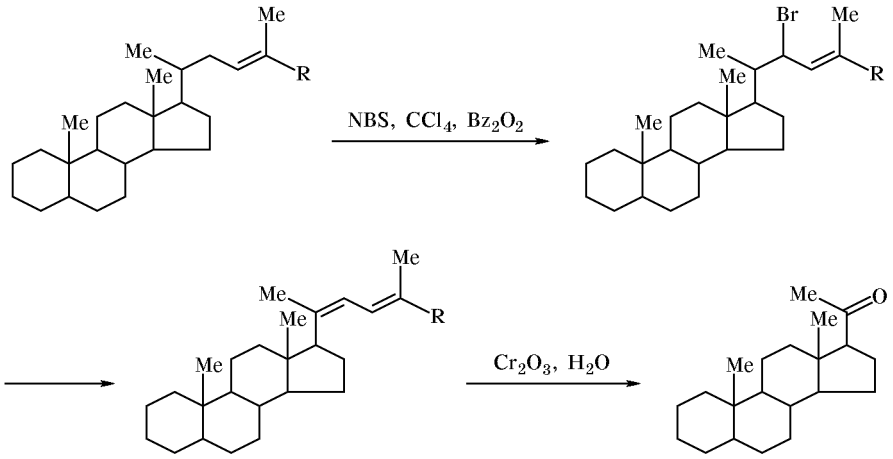


N-bromosuccinimide leads to formation of either 3-bromo-1,4-cyclohexadiene or 3,6-dibromo-1,4-cyclohexadiene, depending on the conditions [3]. According to [3], double bromination at each allylic position in cyclic olefins is possible; however, such products undergo further transformations including allyl rearrangments and elimination of HBr.

Allylic bromination of alicyclic compounds with *N*-bromosuccinimide sometimes results in formation of carbonyl functionality, e.g., in the synthesis of 2-cycloheptenone derivatives [21]. Allylic bromination often provides a synthetic route to building up of the second double bond in various heterocyclic compounds [28–31] (Scheme 6).

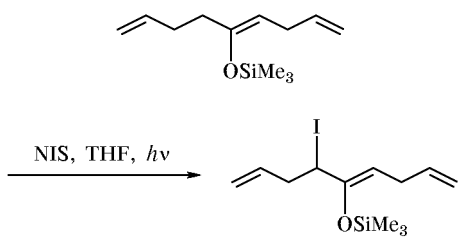
A preparative procedure was developed [3] for shortening of the side chain in bile acids according to Wieland. A bile acid ester is initially converted into olefin by reaction with Grignard compound and subsequent elimination of water, and the olefin is then treated with *N*-bromosuccinimide. Allylic bromination affords derivative which loses hydrogen bromide to give the corresponding diene. Oxidation of the latter gives carbonyl compound which is used in the synthesis of steroid hormones (Scheme 7).

Scheme 7.



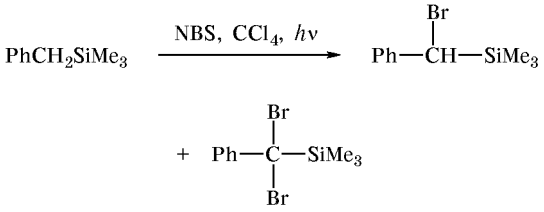
Only a few cases of allylic halogenation with *N*-chlorosuccinimide have been reported, e.g., in the synthesis of 5-chloromethyluracil or 6-chloromethyl-2-methylthiouracil from 5-methyluracil or 2,6-dimethylthiouracil [3]. These reactions were carried out in boiling chloroform in the presence of benzoyl peroxide. Examples of allylic iodination with *N*-iodosuccinimide are also known. One stage of the total synthesis of (±)-velloziolone is allylic iodination of trimethylsilyl ether derived from the enol form of 1,8-nonadien-5-one; as a result, the corresponding 4-iodo derivative was obtained [32] (Scheme 8).

Scheme 8.



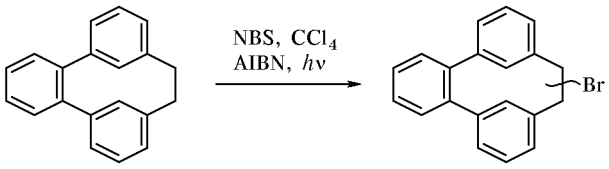
Substitution of hydrogen by halogen at a benzyl carbon atom can also be regarded as an example of halogenation of an activated C–H bond with *N*-halosuccinimides. Such reactions usually occur under UV irradiation in the presence of radical initiators. The bromination of benzyl(trimethyl)silane [33] and some phenylalanine derivatives [34] has been reported (Scheme 9).

Scheme 9.



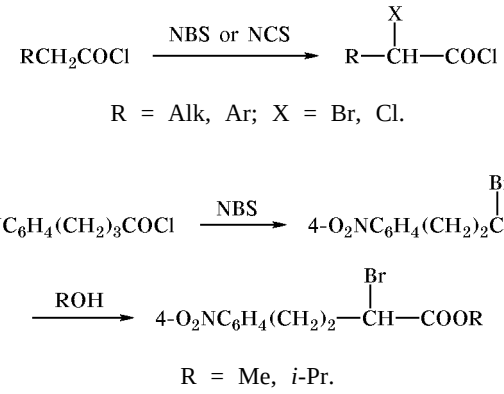
Presumably, bromination with *N*-bromosuccinimide of some metaparacyclophane derivatives [35] may also be regarded as a particular case of allylic halogenation (Scheme 10).

Scheme 10.



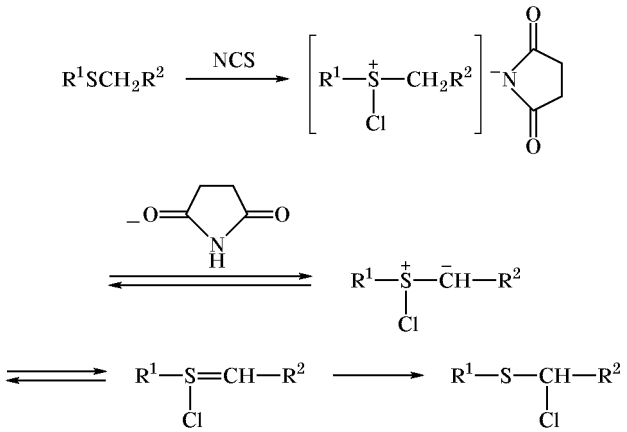
Halogenation of C–H bonds activated by various electron-acceptor groups [COOH, COCl, COOR, $(RO)_2PO$, etc.] and heteroatoms was well documented. Easton *et al.* [36] described radical α-bromination of *N*-benzyl- and *N*-phthaloylalanine methyl esters, as well as of glycine methyl ester. The reactions were carried out in CCl_4 under UV irradiation. Carboxylic acid chlorides relatively readily undergo halogenation by the action of *N*-halosuccinimides. This reaction is sometimes used as a preparative method for synthesizing acyl chlorides [37] and α-halo esters [38] (Scheme 11).

Scheme 11.



Hydrogen substitution by halogen in alkyl sulfides [39–43] and dithianes [44, 45] by the action of *N*-halosuccinimides provides an example of halogenation of C–H bonds activated by the presence of heteroatoms. The process is believed [44] to follow electrophilic mechanism involving intermediate formation of halosulfonium salts (Scheme 12).

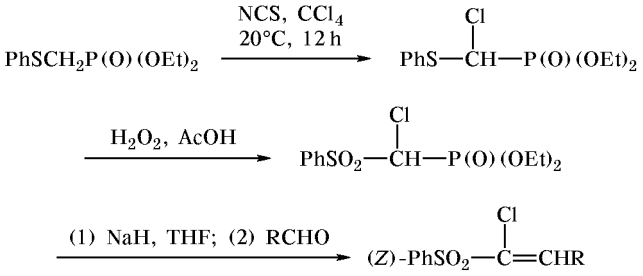
Scheme 12.



α-Halogenation of alkyl sulfides with *N*-halosuccinimides is often a step in multistep syntheses

of unsaturated sulfides and sulfones. Yamamoto *et al.* [39] described the synthesis of substituted chlorovinyl sulfones, one stage of which is chlorination of diethyl phenylthiomethylphosphonate with *N*-chlorosuccinimide (Scheme 13).

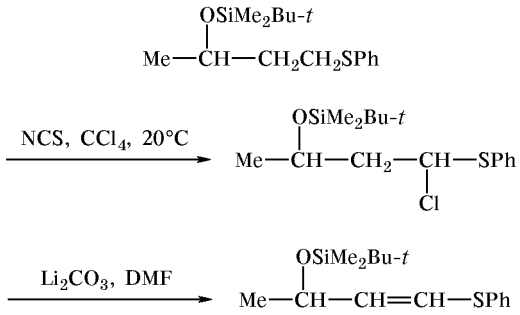
Scheme 13.



R = Ph, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-ClC_6H_4, 4-$Me_2NC_6H_4$.

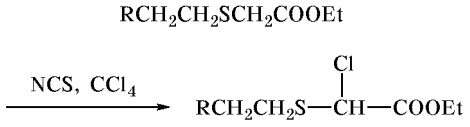
Tanaka *et al.* [43] synthesized 3-(*tert*-butyldimethylsiloxy)-1-butenyl phenyl sulfide via a multistep procedure including chlorination of 3-(*tert*-butyldimethylsiloxy)butyl phenyl sulfide with *N*-chlorosuccinimide as a key stage (Scheme 14).

Scheme 14.



It should be noted that halogenation of the same alkyl sulfide with different *N*-halosuccinimides could give different results. For example, the chlorination of ethyl (2-perfluoroalkylethylthio)acetates with *N*-chlorosuccinimide yields ethyl α-chloro-(2-perfluoroalkylethylthio)acetates, whereas with *N*-bromosuccinimide a mixture of mono- and dibromo derivatives is formed [41] (Scheme 15).

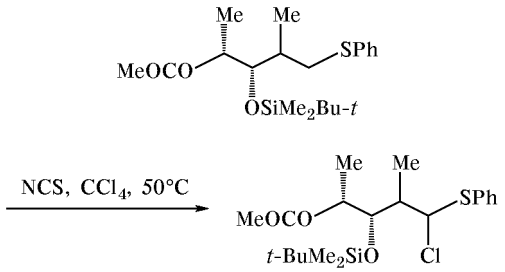
Scheme 15.



R = C_4F_9, C_6F_{13}, C_8F_{17}.

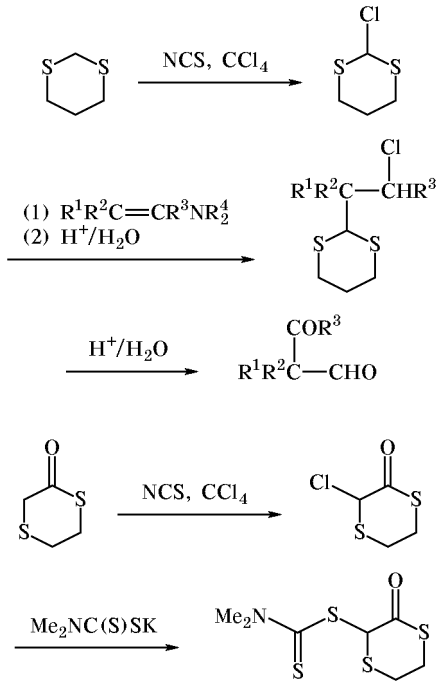
Chlorination of methyl 3-(*tert*-butyldimethylsiloxy)-2,4-dimethyl-5-phenylthiopentanoate with *N*-chlorosuccinimide gave methyl 3-(*tert*-butyldimethylsiloxy)-5-chloro-2,4-dimethyl-5-phenilthiopentanoate which was used in the 20-step synthesis of (+)-(9*S*)-dihydroerythronolide [40] (Scheme 16).

Scheme 16.



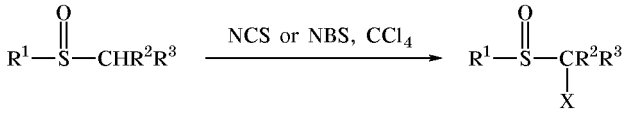
Multistep syntheses of various carbonyl compounds often include halogenation of 1,3- [44] and 1,4-dithianes [45] with *N*-halosuccinimides (Scheme 17).

Scheme 17.



Halogenation with *N*-halosuccinimides of α-C–H bond activated by the presence of sulfur(IV) atom provides a preparative procedure for synthesizing α-halo sulfoxides [46] (Scheme 18). However, this procedure cannot be used to prepare α-halo *tert*-butyl sulfoxides, for in this case cleavage of the carbon–sulfur bond in intermediate halosulfonium ion occurs.

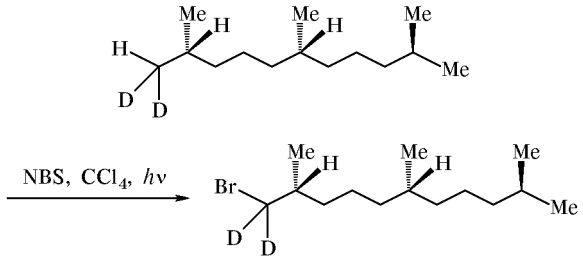
Scheme 18.



R^1 = Alk, Ar; R^2, R^3 = H, Alk, Ar; X = Cl, Br.

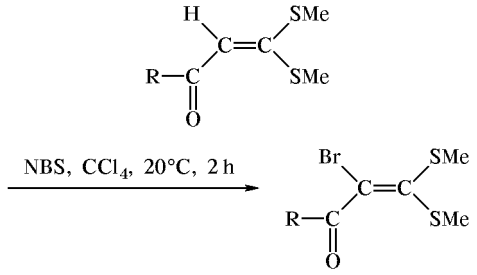
Halogenation of CH bond activated by deuterium atom has been reported. 1-Bromo-1,1-dideutero-2,6,10-trimethylundecane was synthesized by selective bromination of 1,1-dideutero-2,6,10-trimethylundecane with *N*-bromosuccinimide and was then used in the synthesis of labeled α- and γ-tocopherols [47] (Scheme 19).

Scheme 19.



II.1.2. Replacement of hydrogen by halogen at an unsaturated carbon atom. Examples of substitution of hydrogen at an unsaturated carbon atom by halogen under the action of *N*-halosuccinimides are considerably fewer in number. As a rule, such reactions occur relatively readily at carbon atom in polar conjugated double bond system of unsaturated ketones [48] and esters [49], e.g., as shown in Scheme 20.

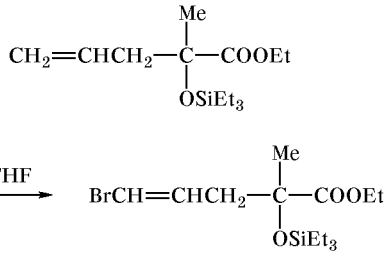
Scheme 20.



R = CH_2=CH$(CH_2)_2$, PhCH=CH$(CH_2)_2$, MeCH=CH$(CH_2)_2$, $(Me)_2$C=CHCH_2CH_2, CH_2=CHCH_2OCH_2CH=CHCH_2O.

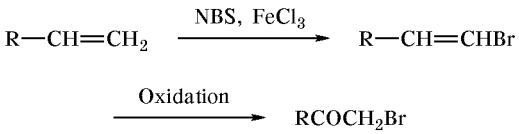
As noted in [50], ethyl 2-methyl-2-(triethylsiloxy)-4-pentenoate reacts with *N*-bromosuccinimide in tetrahydrofuran to give 90% of the corresponding 5-bromo derivative (Scheme 21).

Scheme 21.



Kumaravel *et al.* [51] described the synthesis of bromomethyl alkyl ketones by bromination of the corresponding terminal olefins with *N*-bromosuccinimide in the presence of $FeCl_3$ and subsequent oxidation of the bromination products (Scheme 22).

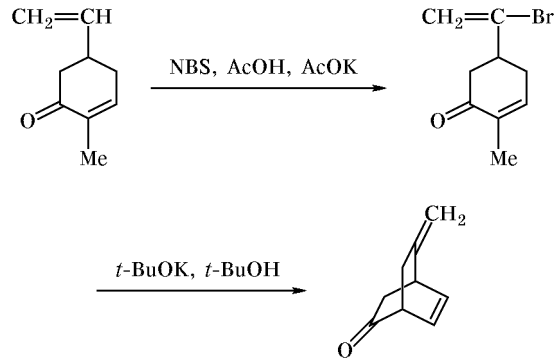
Scheme 22.



R = C_nH_{2n+1} (n = 10, 12–18).

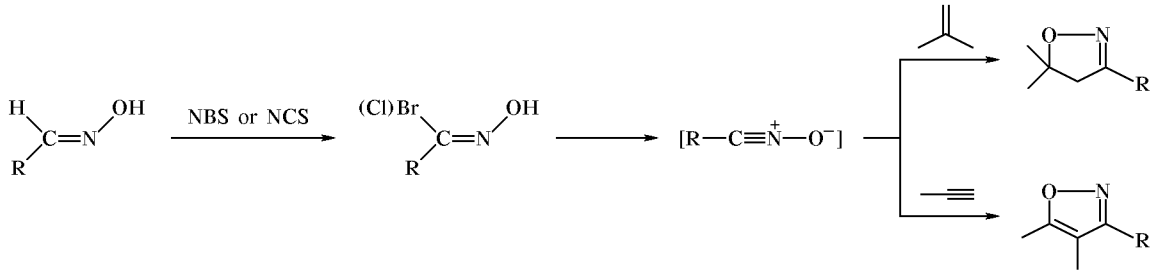
The transformation of (*S*)-carvone into bicyclo[2.2.2]oct-5-en-2-one was reported in [52]. Its reaction with *N*-bromosuccinimide gave bromo derivative which underwent cyclization by the action of potassium *tert*-butoxide in *tert*-butyl alcohol.

Scheme 23.

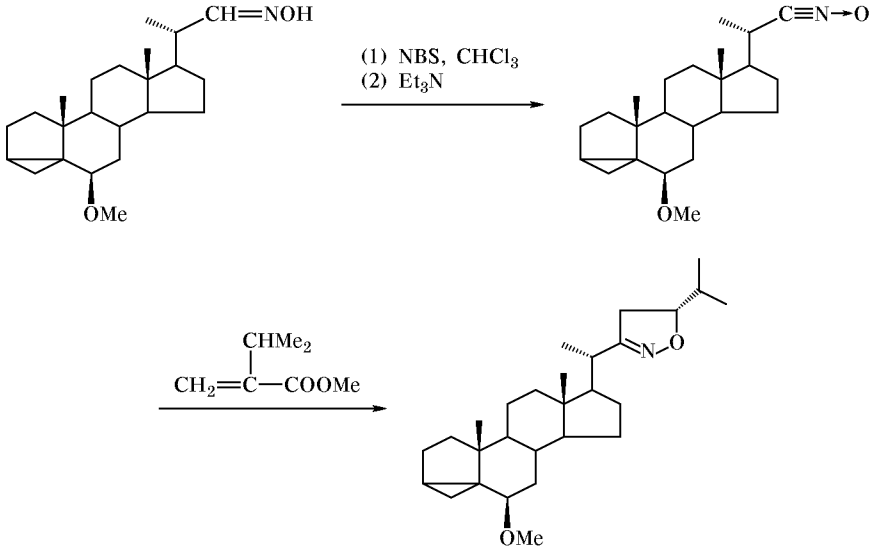


Halogenation of *syn*- and *anti*-aldehyde oximes with *N*-halosuccinimides yields hydroximoyl halides which are converted into nitrile oxides by the action of organic bases. Nitrile oxides are used in the synthesis of isoxazoles and dihydroisoxazoles [53, 54] (Scheme 24). These reactions have found application in the synthesis of isoxazole derivatives of steroids. Khripach *et al.* [55] described bromination of steroid

Scheme 24.

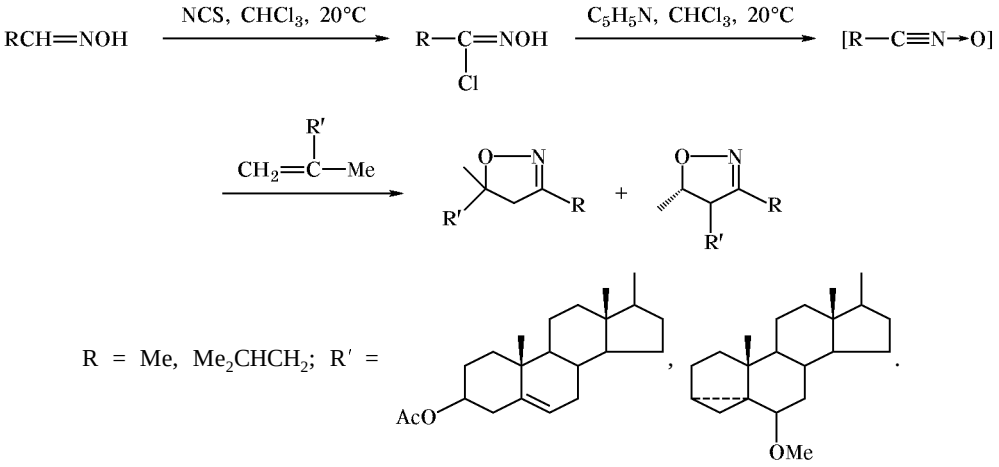


Scheme 25.



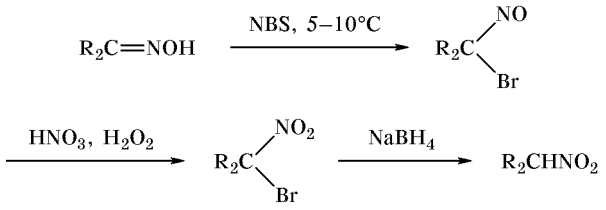
aldehyde oxime with *N*-bromosuccinimide. The subsequent dehydrobromination gave steroid nitrile oxide which reacted with C_5–C_7-dipolarophiles to give dihydroisoxazole derivatives (Scheme 25). Structurally related isoxazoles were synthesized in a similar way [56]. A number of dihydroisoxazolyl steroids were obtained from steroid olefins and nitrile oxides which were generated by the action of *N*-chlorosuccinimide on aldehyde oximes [57] (Scheme 26). *N*-Bromosuccinimide reacts with ketone oximes to give bromo

Scheme 26.



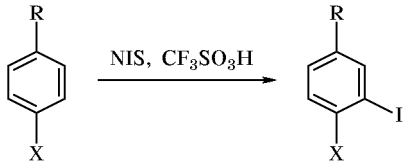
nitroso derivatives which undergo oxidation and debromination to afford nitro compounds [58] (Scheme 27).

Scheme 27.



II.1.3. Halogenation of aromatic compounds. Replacement of hydrogen in an aromatic ring by halogen under the action of *N*-halosuccinimides follows electrophilic substitution pattern. General relations holding in this process are the same as in the halogenation of aromatic compounds by halogens. Benzene reacts with *N*-bromosuccinimide only in the presence of catalysts, such as aluminum, iron, and zinc chlorides; the reaction leads to formation of 40–70% of bromobenzene. The presence of catalysts is also necessary in the halogenation with *N*-halosuccinimides of sterically hindered aromatic compounds. Olah *et al*. [59] reported on the iodination with *N*-iodosuccinimide in the presence of trifluoromethanesulfonic acid of a series of aromatic hydrocarbons deactivated by strong electron-acceptor groups (Scheme 28).

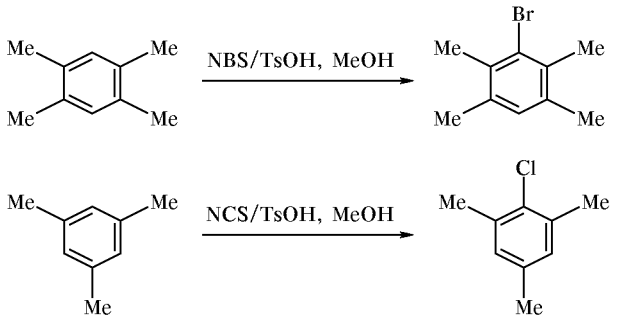
Scheme 28.



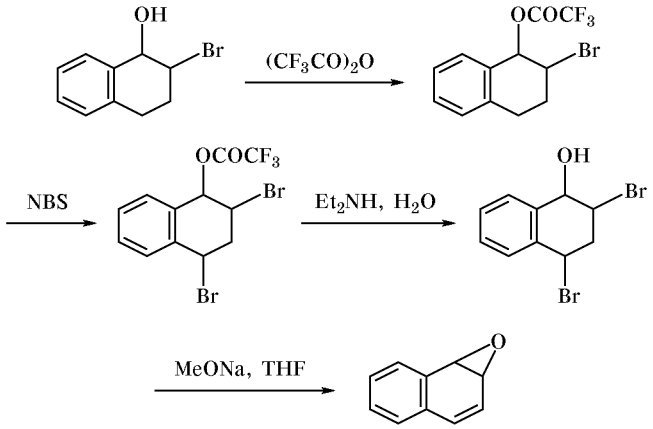
R = NO_2, CF_3; X = Cl, Br, F.

It was presumed [59] that the reactive species is either protonated *N*-iodosuccinimide or the system iodine–trifluoromethanesulfonate ion. Halogenation with *N*-halosuccinimides of sterically hindered aromatic hydrocarbons, such as durene and mesitylene, was effected in methanol in the presence of *p*-toluenesulfonic acid [60] (Scheme 29). *N*-Bromosuccinimide relatively readily reacts with naphthalene and its derivatives in the absence of a catalyst, yielding the corresponding α-bromo substituted compounds [61]. The reactions with anthracene and phenanthrene are even more facile; here, bromine replaces hydrogen in position *9* [4]. Tetrahydronaphthalene derivatives react with *N*-bromosuccinimide, resulting in hydrogen replacement in the saturated ring [62]. This reaction is used in the synthesis of 1,2-epoxynaphthalene, as shown in Scheme 30.

Scheme 29.



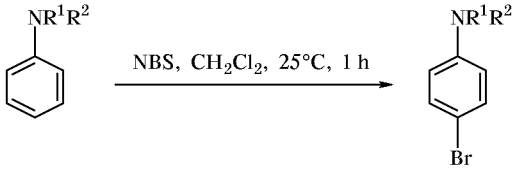
Scheme 30.



1,2-Epoxynaphthalene can also be synthesized by direct bromination of epoxytetrahydronaphthalene with *N*-bromosuccinimide and subsequent dehydrobromination [63]. The bromination of phenol with *N*-bromosuccinimide yields mainly *p*-bromophenol [64], while 3,5-disubstituted phenols give rise to 2-bromo or 6-bromo derivatives [65].

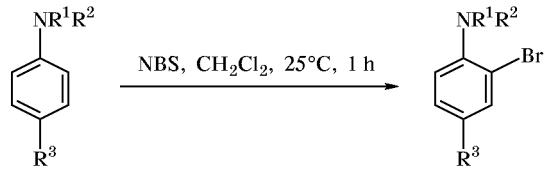
2-Bromo-4-methylaniline was obtained in 91% yield by reaction of *N*-bromosuccinimide with 4-methylaniline in dimethylformamide [66]. *N*-Substituted anilines are brominated with the same reagent at the *para* position [67] (Scheme 31).

Scheme 31.



If the *para* position is occupied, bromine atom enters the *ortho* position [67] (Scheme 32).

Scheme 32.



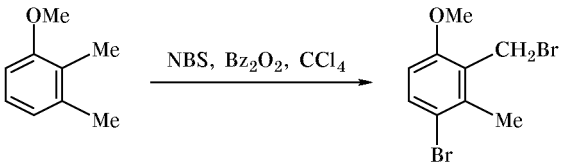
R^1 = 2-$O_2NC_6H_4S$, R^2 = Me, R^3 = OMe.

If the *meta* position is occupied by an electron-acceptor group, *p*-bromo derivatives are formed; when an electron-donor group is present in the *meta* position, 2,4-dibromo derivatives are obtained [67].

Bromination of methyl 3,5-dimethoxybenzoate with *N*-bromosuccinimide in acetonitrile gave methyl 2-bromo-3,5-dimethoxybenzoate which was then used in the total synthesis of calicheamicinone (calicheamicin aglycon) [68].

Some examples of radical bromination of aromatic ring with *N*-halosuccinimides have been reported. Heating of a mixture of 2,3-dimethylanisole, *N*-bromosuccinimide, and benzoyl peroxide in boiling carbon tetrachloride for 28 h resulted in formation of 4-bromo-2-bromomethyl-3-methylanisole in 90% yield [69] (Scheme 33). When the same reagents were heated in CCl_4 for 34 h under reflux, a mixture of 4-bromo-2,3-dimethylanisole (81%) and 2-bromomethyl-4-methylanisole (10%) was obtained [69].

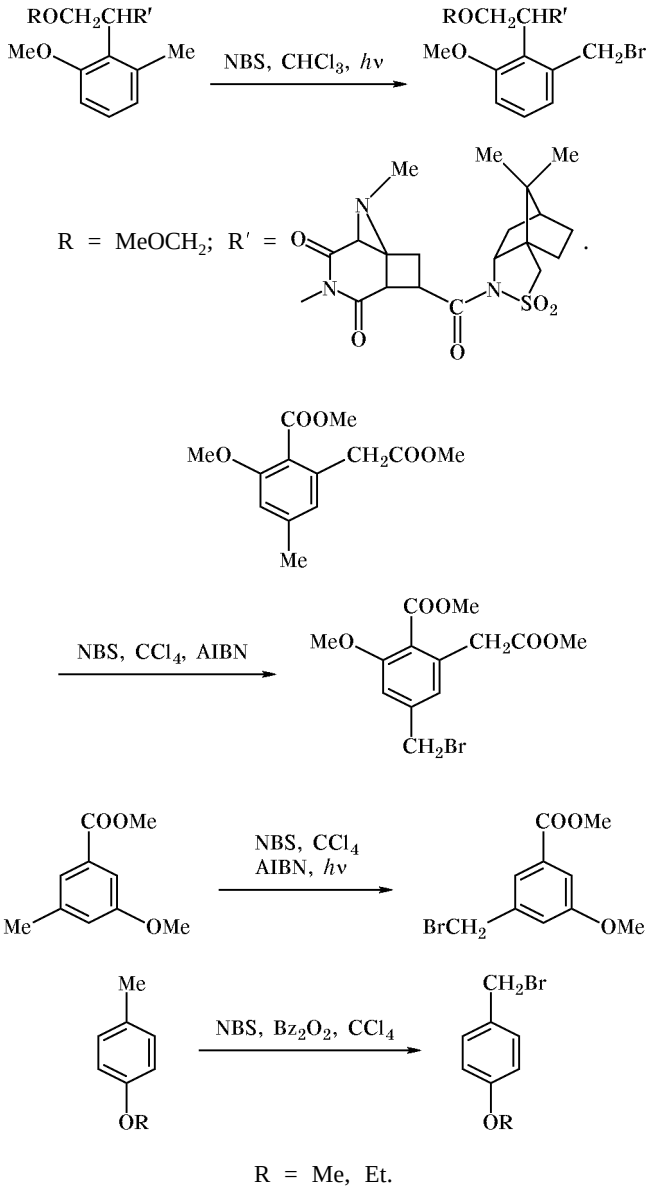
Scheme 33.



Radical bromination of 4-deoxy-9-epipodophyllotoxin with *N*-bromosuccinimide in the presence of benzoyl peroxide occurs at positions *2* and *6* of the aromatic ring to form the corresponding dibromo derivative in 25% yield [70].

Halogenation with *N*-halosuccinimides at the side chain of aromatic compounds is a radical reaction promoted by UV irradiation or radical initiators (benzoyl peroxide, AIBN, etc.). The most widespread reaction is halogenation of methyl group directly attached to an aromatic ring. This process is characterized by high selectivity; some examples are shown in Scheme 34 [71–74].

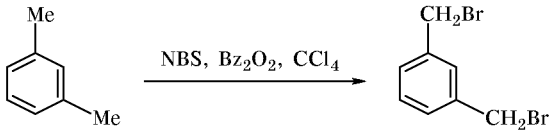
Scheme 34.



R = Me, Et.

Provided that the substrate contains two methyl groups attached to aromatic ring, formation of bis(halomethyl) derivatives is possible in the presence of excess *N*-halosuccinimide [75–78] (Scheme 35).

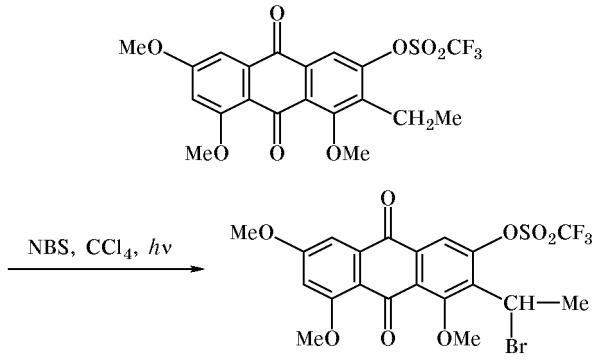
Scheme 35.



Other alkyl groups at an aromatic ring can also undergo halogenation. Kelly *et al.* described radical

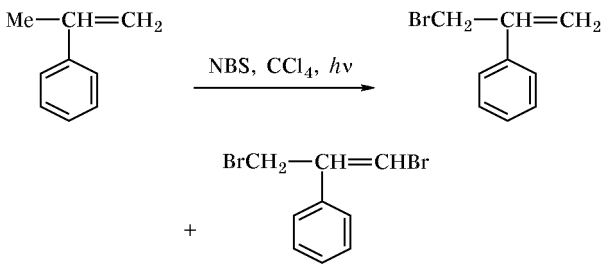
halogenation with *N*-bromosuccinimide at the ethyl group of 3-ethyl-4,5,7-trimethoxy-2-trifluoromethylsulfonyloxy-9,10-anthraquinone [79] (Scheme 36).

Scheme 36.



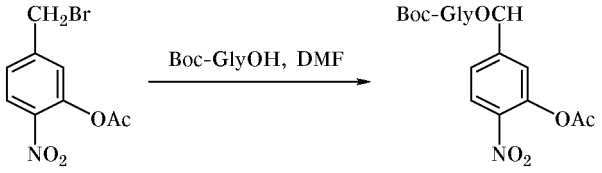
Side-chain bromination of α-methylstyrene with *N*-bromosuccinimide gives a mixture of mono- and dibromo derivatives [80] (Scheme 37).

Scheme 37.



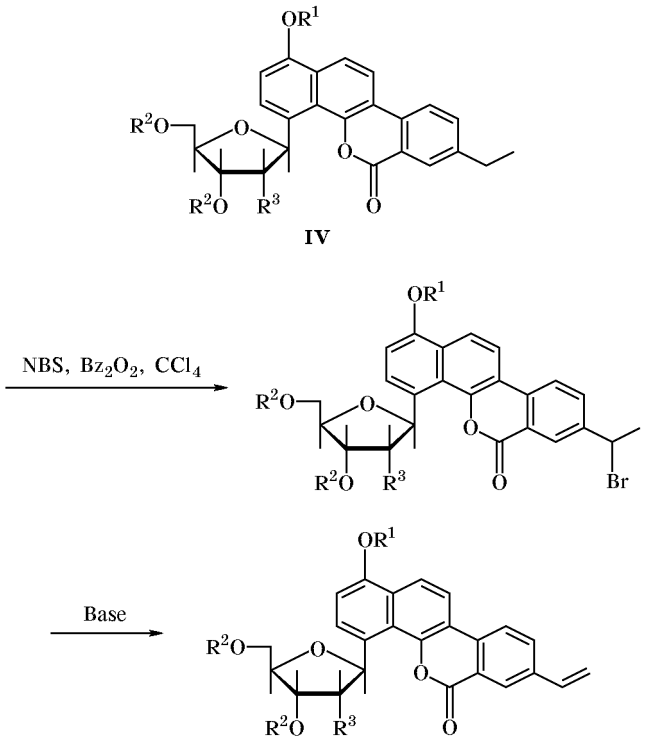
Likewise, two products (α-bromoisopropylbenzene and α,β-dibromoisopropylbenzene) are formed in the bromination of isopropylbenzene with *N*-bromosuccinimide [81]; with excess *N*-bromosuccinimide, the dibromo derivative becomes the major product. Selivanov *et al.* [82] reported on modification of Boc-glycine with 5-bromomethyl-2-nitrophenyl acetate which was synthesized by bromination of 5-methyl-2-nitrophenyl acetate with *N*-bromosuccinimide (Scheme 38).

Scheme 38.



During multistep synthesis of C-glycosides [83], vinyl group was built up via side-chain bromination of compound **IV** with *N*-bromosuccinimide and subsequent dehydrobromination.

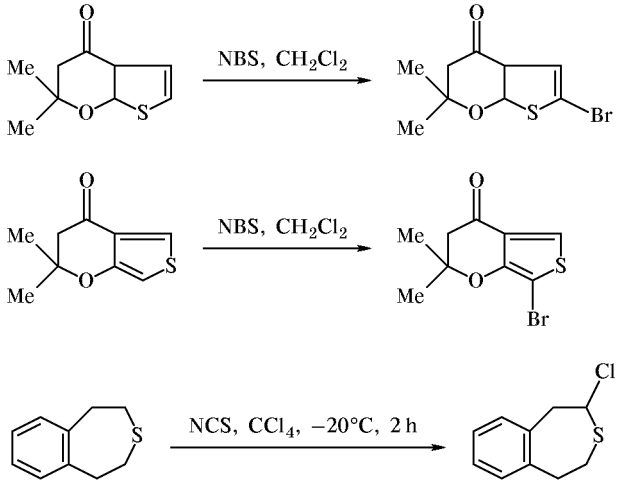
Scheme 39.



$R^1 = R^2 = Ac$; $R^3 = OAc$.

II.1.4. Halogenation of heterocyclic compounds. Halogenation of heterocyclic compounds with *N*-halosuccinimides is not selective. Depending on the reaction conditions and substrate nature, different products are formed. Thiophene readily reacts with *N*-bromo-

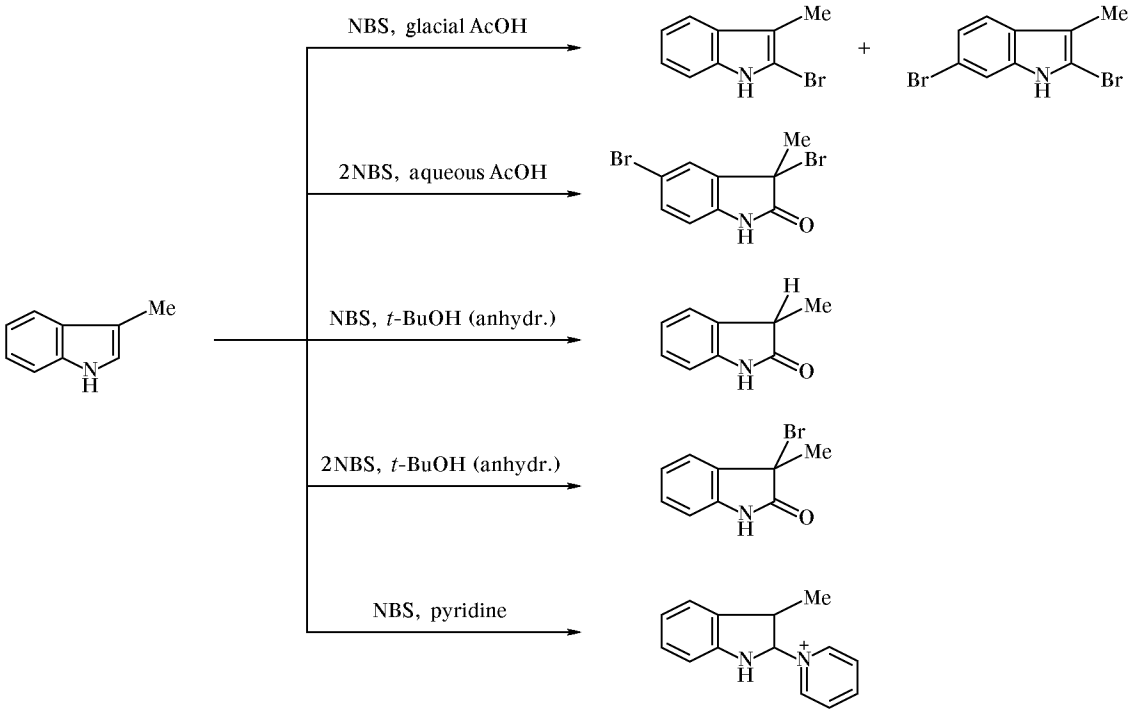
Scheme 40.



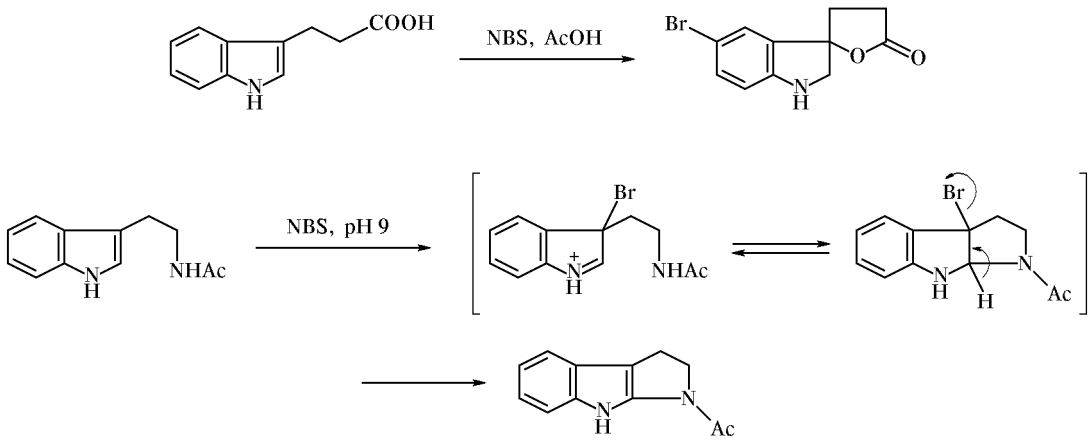
succinimide in organic solvents (CH_2Cl_2, AcOH, etc.) to give 2-bromothiophene, but the yield is poor (~30%) [3]. Such thiophene analogs as thieno[2,3-*b*]- and thieno[3,4-*b*]pyrans also undergo relatively ready bromination with *N*-bromosuccinimide [84]. Chlorination of 3-thiabenzocycloheptane with *N*-chlorosuccinimide occurs at the 2-position [85] (Scheme 40).

Indole and *N*-benzoylindole react with *N*-bromosuccinimide at the 3-position [86]. 3-Substituted indoles react in a more complicated manner, with formation of mixtures of different products, depending on the conditions and reactant ratio. Scheme 41 shows possible ways of the reaction of 3-methylindole with *N*-bromosuccinimide [87]. It was presumed that *N*-bromosuccinimide reacts with 3-substituted indoles at the β-position of the latter. β-Haloindolium intermediates thus formed tend to undergo various solvolytic transformations. Intramolecular trapping of such intermediates was observed in the reactions of *N*-bromosuccinimide with 3-indolylpropionic acid and *N*-acetyltryptamine [87] (Scheme 42). In the latter case nucleophilic addition of nitrogen followed by elimination of hydrogen bromide leads to formation of pyrrolo[2,3-*b*]indole. Radical bromination of indole

Scheme 41.



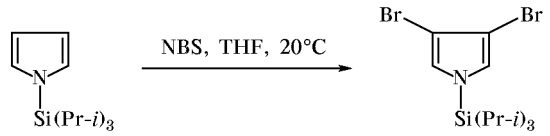
Scheme 42.



derivatives with *N*-bromosuccinimide under UV irradiation [88] or in the presence of benzoyl peroxide [89] was reported to afford 2-bromoindoles in fairly high yields (78–100%).

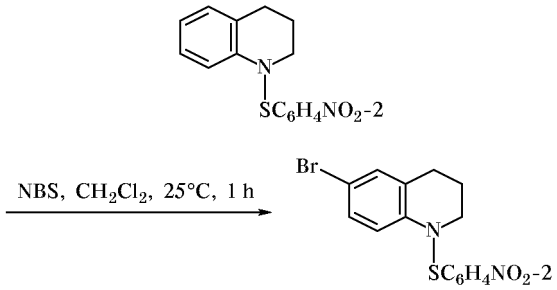
Halogenation with *N*-halosuccinimides of other nitrogen-containing heterocycles is also known. Shum and Kozikowski [90] described bromination of 1-triisopropylsilyl-1*H*-pyrrole with *N*-bromosuccinimide. As a result, 3,4-dibromo-1-triisopropylsilyl-1*H*-pyrrole was obtained in 78% yield (Scheme 43).

Scheme 43.



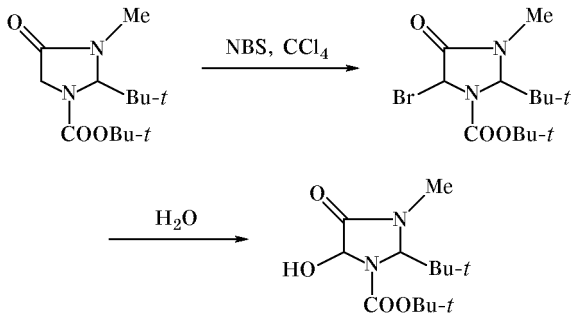
Michida *et al*. [67] studied bromination with *N*-bromosuccinimide of *N*-(2-nitrophenylthio)-1,2,3,4-tetrahydroquinoline. The reaction was carried out in methylene chloride, and the corresponding 6-bromo derivative was obtained (Scheme 44).

Scheme 44.



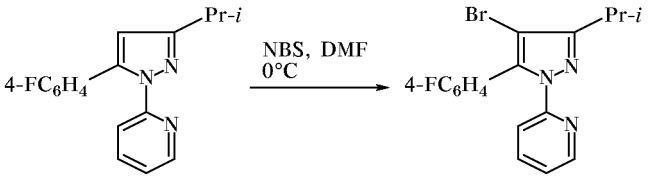
Oxidative bromination of 5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*,*d*]quinolizin-8-one to 1,3-dibromo-5,6-dihydro-8*H*-dibenzo[*a*,*d*]quinolizin-8-one by the action of *N*-bromosuccinimide in CCl_4 was reported in [91]. The reaction of *tert*-butyl 2-*tert*-butyl-3-methyl-4-oxoimidazole-1-carboxylate with *N*-bromosuccinimide in CCl_4 in the presence of azobis(isobutyronitrile) gave 90% of unstable *tert*-butyl 5-bromo-2-*tert*-butyl-3-methyl-4-oxoimidazol-1-carboxylate which was readily hydrolyzed to the corresponding 5-hydroxy derivative [92] (Scheme 45).

Scheme 45.



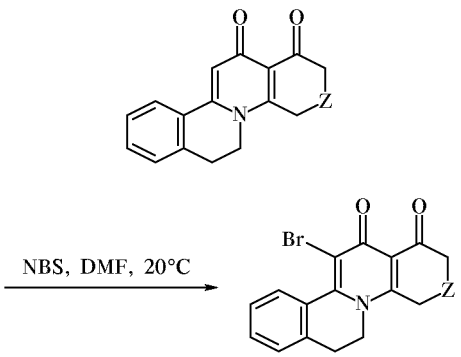
2-[5-(4-Fluorophenyl)-3-isopropyl-1*H*-pyrazol-1-yl]pyridine reacts with *N*-bromosuccinimide in DMF at 0°C. The bromination occurs at the 4-position of the pyrazole ring [93] (Scheme 46).

Scheme 46.



Gulyakevich *et al.* [94, 95] showed that 8-aza-D-homogonanes are brominated with *N*-bromosuccinimide exclusively at the C^{11} atom of the heteroaromatic ring (Scheme 47).

Scheme 47.



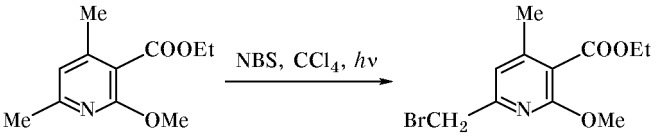
Z = CH_2, CMe_2.

5,15-Diphenylporphine was found [96] to react with *N*-bromosuccinimide in chloroform at 0°C in the presence of pyridine to afford 5,15-dibromo-10,20-diphenylporphine in 85% yield. Halogenation of other porphyrin derivatives with *N*-halosuccinimides was also reported [97–99].

As concerns oxygen-containing heterocycles, reactions of *N*-halosuccinimides with 2-substituted 2,3-dihydrobenzofurans [100], 2-substituted octahydrobenzofurans [101], and some 3,4-dihydrobenzopyran derivatives [102] were reported. In the first two cases the halogenation involves position *3*, and in the latter case, 6-halo derivatives are formed.

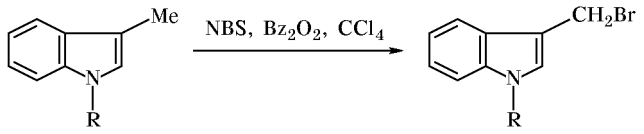
A large number of publications deal with bromination at side chains of heterocyclic compounds with *N*-bromosuccinimide. Bromomethyl derivatives thus obtained are important products widely used in fine organic synthesis. As a rule, the bromination process follows a radical mechanism and is characterized by high selectivity. For example, photochemical bromination of ethyl 2-methoxy-4,6-dimethylpyridine-3-carboxylate with *N*-bromosuccinimide yields ethyl 6-bromomethyl-2-methoxy-4-methylpyridine-3-carboxylate [103] (Scheme 48).

Scheme 48.



Likewise, 2,3-dimethylindole [104] and 4-chloro-2,6-dimethylquinoline [105] react with *N*-bromosuccinimide at only one methyl group, as a rule in the 2-position. Reactions of N-substituted 3-methylindoles with *N*-bromosuccinimide give rise to the corresponding 3-bromomethyl derivatives [106] (Scheme 49).

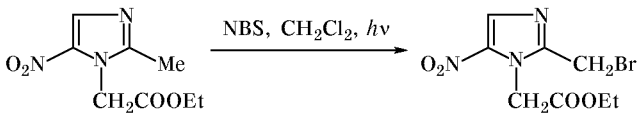
Scheme 49.



R = Bz, $PhSO_2$.

Bromomethyl derivatives are formed in relatively high yields in the bromination with *N*-bromosuccinimide of N-substituted 2- and 3-methylcarbazoles [107]. Ethyl 2-bromomethyl-5-nitroimidazole-1-carboxylate was obtained by photochemical bromination of ethyl 2-methyl-5-nitroimidazole-1-carboxylate [108] (Scheme 50).

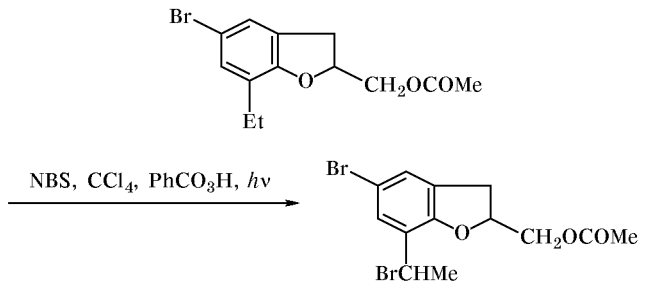
Scheme 50.



Bloomer *et al.* [109] studied bromination with *N*-bromosuccinimide of oxygen-containing heterocycles having a methyl group in the ring, namely of substituted α- and γ-pyranones. These reactions were performed in the presence of benzoyl peroxide, and the corresponding monobromomethyl derivatives were obtained. Analogous product was synthesized by reaction of 7,8-dimethoxy-5-methylcoumarin with *N*-bromosuccinimide [110].

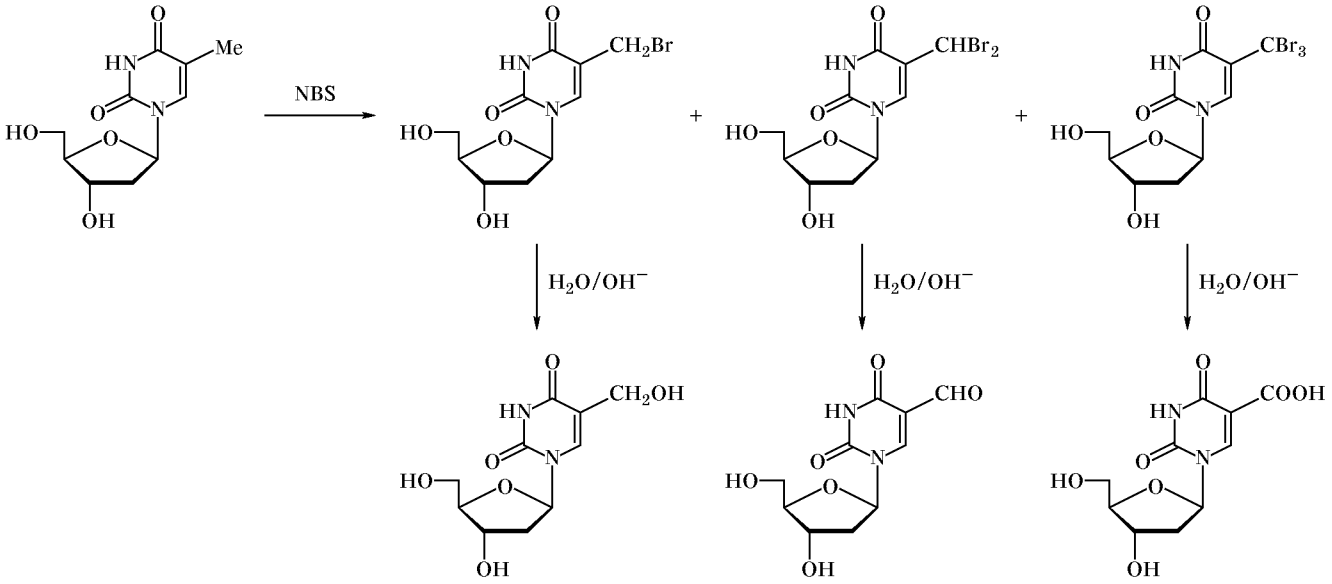
Halogenation of other side-chain alkyl groups in heterocyclic compounds is a much rarer case. Weerawarna *et al.* [111] showed that the reaction of 2-acetoxymethyl-5-bromo-7-ethyl-2,3-dihydrobenzofuran with *N*-bromosuccinimide involves both the 7-ethyl group and the dihydrofuran ring which undergoes aromatization to give 2-acetoxymethyl-5-bromo-7-(1-bromoethyl)benzofuran (Scheme 51).

Scheme 51.

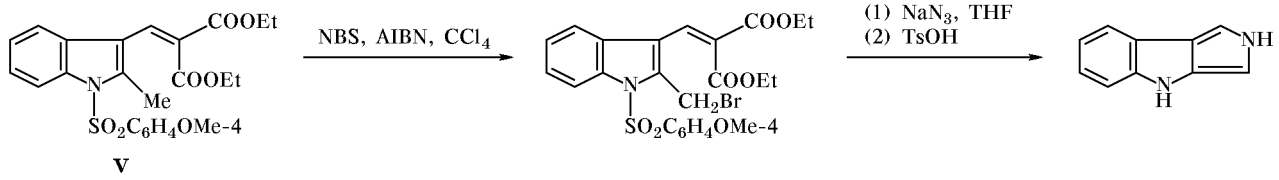


Sato *et al.* described the synthesis of optically active pyrrolidine systems [112], where one of the key stages is chlorination with *N*-chlorosuccinimide of the phenylthioacetyl fragment in 2-ethynyl-1-[(phenylthio)acetyl]pyrrolidine. The chlorination was accomplished in CCl_4 at 0–20°C (5 h). Halogenation with *N*-halosuccinimides of methyl groups in heterocyclic fragments of various natural compounds often precedes halogen replacement by functional groups. Scheme 52 illustrates such a process which includes bromination of the methyl group in thymidine with *N*-bromosuccinimide and further transformations of the resulting mono-, di-, and tribromomethyl derivatives into 5-hydroxymethyl-, 5-formyl-, and 5-carboxy-2-deoxyuridines [113]. She *et al.* [114] described a preparative procedure for synthesizing pyrrolo[3,4-*b*]indoles via bromination of the methyl group in compound **V**, replacement of bromine by azido group, and subsequent cyclization (Scheme 53). In the synthesis of 5-(1-azido-2-haloethyl)-2-deoxyuridines [115] the azido group was introduced in a similar way. Halogenation with *N*-bromosuccinimide, followed by bromine replacement by acetoxy group, was a part of of the multistep transformation of deacetoxycephalosporins into cephalosporins [116] (Scheme 54). A key step of the synthesis of eremantolide A is bromination with *N*-bromosuccinimide of the ethyl group in the

Scheme 52.

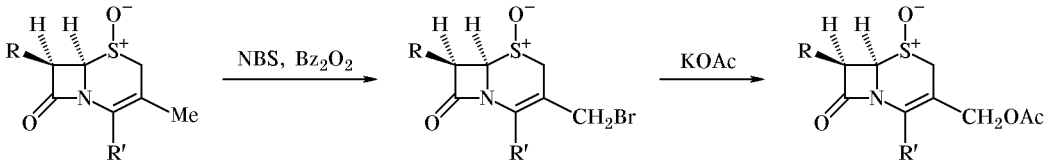


Scheme 53.



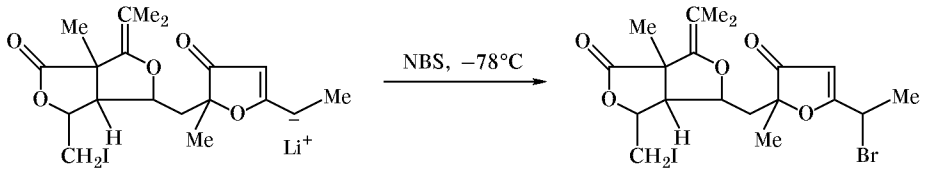
V

Scheme 54.



R = $PhOCH_2CONH$, R′ = CCl_3CH_2OCO.

Scheme 55.



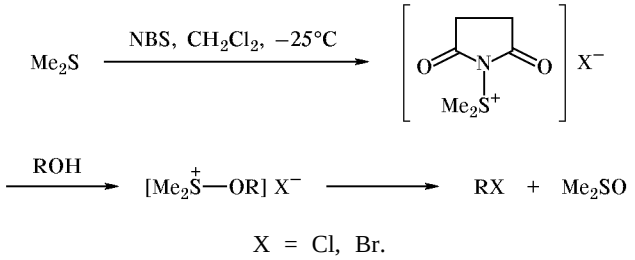
VI

dihydrofuran fragment of lithium derivative **VI** [117] (Scheme 55). 5-Ethyl-2′-deoxyuridine was converted into 2′-deoxy-5-vinyluridine via bromination of the ethyl group with *N*-bromosuccinimide [113].

II.1.5. Replacement of functional groups by halogen. Halogen derivatives are often synthesized by replacement of various functional groups by halogen using *N*-halosuccinimides as reagents. The most frequent reactions are those in which an alcoholic hydroxy group is replaced by chlorine or bromine. For this purpose, two procedures are suitable. The first of these consists of treatment of alcohol with *N*-halo-

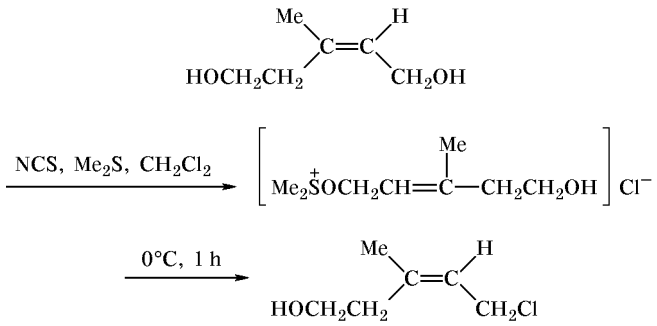
succinimide in the presence of dimethyl sulfide in an inert organic solvent (e.g., CH_2Cl_2) at low temperature [118]. In the first stage *N*-halosuccinimide reacts with dimethyl sulfide to give succinimidosulfonium salt which is converted into alkoxysulfonium salt by the action of alcohol. Decomposition of alkoxysulfonium salt yields halogen derivatives (Scheme 56).

Scheme 56.



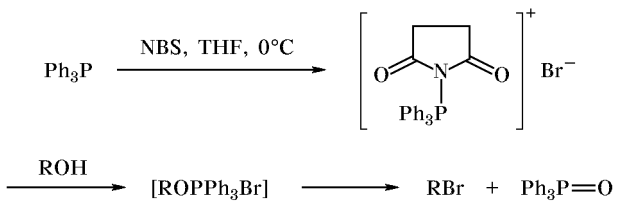
This procedure was successfully applied to convert allyl and benzyl alcohols into the corresponding chlorides and bromides in 80–90% yield [118]. Under analogous conditions, diphenylmethanol is quantitatively converted into diphenylmethyl chloride [119], 2-cyclohexenol is converted into 3-chlorocyclohexene [119], and geraniol, into geranyl bromide [120]. Substitution of hydroxy group by chlorine or bromine in some unsaturated aliphatic alcohols [121–126], furfuryl alcohol [127, 128], and 1-3*H*-farnesol [129] was reported. Saturated primary and secondary aliphatic and alicyclic alcohols do not react with *N*-halosuccinimides. The selectivity of the above reaction is illustrated by Scheme 57 which shows the transformation of (*Z*)-3-methyl-2-pentene-1,5-diol into allyl chloride [119].

Scheme 57.



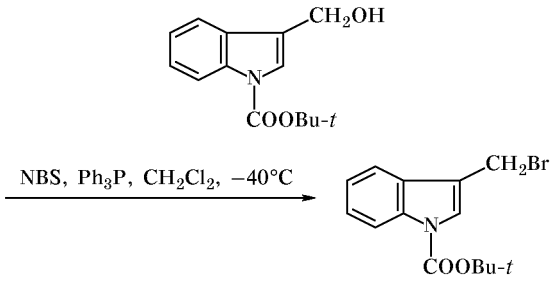
According to the second procedure, an alcohol is treated with *N*-halosuccinimide in the presence of triphenylphosphine [130]. The reaction is carried out at reduced temperature in an anhydrous organic solvent (CH_2Cl_2, THF, DMF, etc.). Replacement of one hydroxy group requires 2 equiv of *N*-halosuccinimide and triphenylphosphine. Primary hydroxy group can be replaced by halogen in the presence of secondary hydroxy group. Presumably, the first reaction stage is formation of triphenyl(succinimido)phosphonium salt which gives rise to five-coordinate phosphorus compound in the presence of alcohol. Thermal decomposition of the latter intermediate yields halogen derivative (Scheme 58).

Scheme 58.



Five-coordinate phosphorus compounds were isolated in reactions of *N*-bromosuccinimide with alcohols in the presence of triphenylphosphine in dimethylformamide [131]. The procedure was successfully applied to replace by bromine the hydroxy group in a number of unsaturated aliphatic [132–134] and aromatic [135, 136] alcohols. The hydroxy group in isopulegol [137] and 2-(3-hydroxypropyl)-5-(3,4-dimethoxyphenyl)-2,3-dihydropyridin-4-one [138] was replaced by chlorine, and that in *tert*-butyl 3-hydroxymethylindole-1-carboxylate was replaced by bromine [139] by the same method (Scheme 59).

Scheme 59.

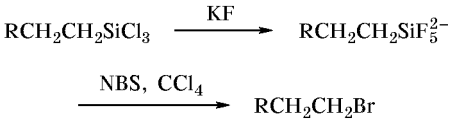


Furuhata *et al.* [140] examined the chlorination of finely crystalline cellulose with the system *N*-chlorosuccinimide–triphenylphosphine. Initially, only the 6-hydroxy group was replaced. Further chlorination resulted in replacement of the 3-OH group with inversion of configuration, and the maximal degree of substitution attained 1.86.

Other functional groups can also be replaced by halogens. Trichlorosilanes react with fluoride ion to form pentafluorosilyl dianions **VII**. Reaction of the

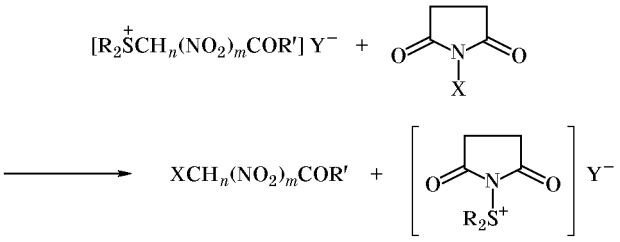
latter with *N*-bromosuccinimide is accompanied by cleavage of the Si–C bond with formation of alkyl halides [141] (Scheme 60).

Scheme 60.



Sulfonium salts having a nitro group in the α-position react with *N*-halosuccinimides under relatively mild conditions; the reaction involves cleavage of the C–S bond with formation of halogen derivatives [142] (Scheme 61).

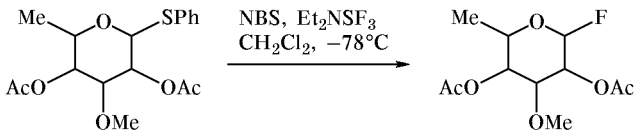
Scheme 61.



R = Me, Et; R′ = Me, Ph; Y = Cl, Br; X = Cl, Br; *n* = 1, 2; *m* = 1, 2.

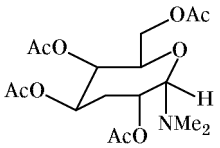
Nicolaou *et al*. described replacement of the phenylthio group in 3,5-diacetoxy-4-methoxy-2-methyl-6-phenylthiotetrahydropyran by fluorine in the reaction with *N*-bromosuccinimide in the presence of Et_2NSF_3 [143] (Scheme 62).

Scheme 62.

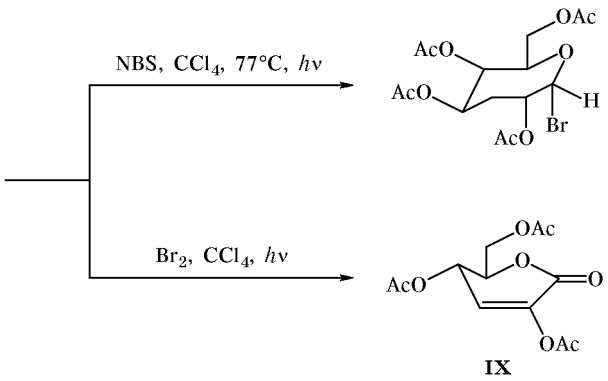


The dimethylamino group in amino glycoside **VIII** was replaced by bromine via reaction with *N*-bromosuccinimide in CCl_4 under UV irradiation [144] (Scheme 63). In the reaction with molecular bromine lactone **IX** was obtained. Substitution of *O*-acyl [145–147], *O*-benzyl [148–151], and *O*-benzylidene [152] moieties by halogen via treatment with *N*-halosuccinimides is widely used in carbohydrate chemistry for removal of the above protective groups. For example, the 6-*O*-benzoyl group in carbohydrate **X** was replaced by bromine by the action of *N*-bromosuccinimide in CCl_4 in the presence of $BaCO_3$ [147] (Scheme 64). The replacement of *O*-benzyl group in **XI** was accomplished with the aid of *N*-bromosuccinimide under UV irradiation [148] (Scheme 65).

Scheme 63.

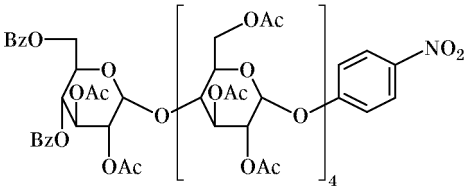


VIII

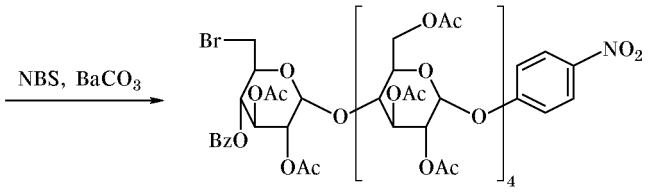


IX

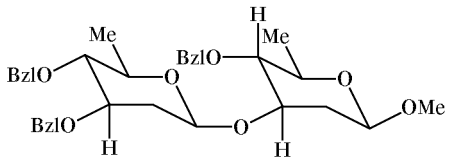
Scheme 64.



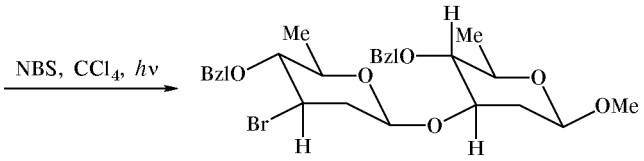
X



Scheme 65.

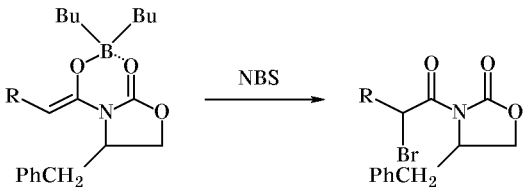


XI



Three-component system *N*-bromosuccinimide–hydrogen fluoride–pyridine was used to replace the 1-*O*-benzyl group in β-D-pentabenzylglucose by fluorine [151]. In the reaction of compound **XII** with *N*-bromosuccinimide removal of the dibutylboryl group is accompanied by bromine addition to carbon atom of the conjugated bond system rather than to oxygen [153] (Scheme 66).

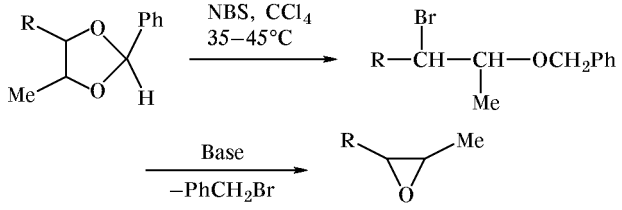
Scheme 66.



XII

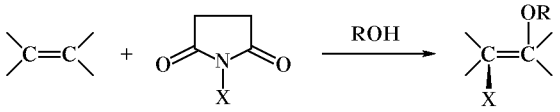
Nerinckx *et al.* [154] reported on the replacement of *tert*-butyldimethylsilyl group by bromine with the aid of *N*-bromosuccinimide. Regioselective ring opening in 1,3-dioxolane derivatives by the action of *N*-bromosuccinimide yields β-bromo benzyl ethers which readily undergo cyclization to oxiranes in the presence of bases [155, 156] (Scheme 67).

Scheme 67.



II.1.6. Solvolytic halogenation of olefins and cyclic olefins. *N*-Halosuccinimides are capable of reacting with olefins in hydroxy-containing solvents (e.g., water, alcohols, carboxylic acids, etc.) to give addition products of halogen and solvent anion at the C=C bond (Scheme 68).

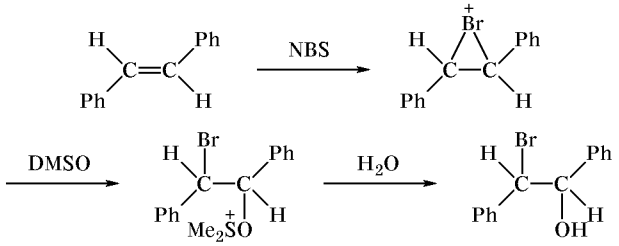
Scheme 68.



X = Cl, Br, I; R = H, Alk, Ar.

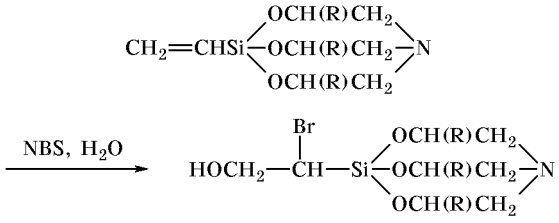
Such reactions are generally called solvolytic halogenation or solvohalogenation. Reactions of olefins with *N*-bromosuccinimide in aqueous medium (hydroxybromination) were studied to the greatest extent. The process follows electrophilic mechanism and yields α-bromo hydroxy derivatives (bromohydrins). As a rule such reactions are carried out in mixtures of water with organic solvents (dimethyl sulfoxide [157], acetone [158], acetonitrile [159], etc.) in order to make the reaction mixture homogeneous and hence to ensure a smoother process. The organic solvent can participate in the reaction. Using ^{18}O label, Dalton and Jones [160] found that in the reaction of *trans*-stilbene with *N*-bromosuccinimide in moist DMSO the oxygen atom in the final product is taken from the solvent and that the first reaction stage is formation of bromonium intermediate (Scheme 69).

Scheme 69.



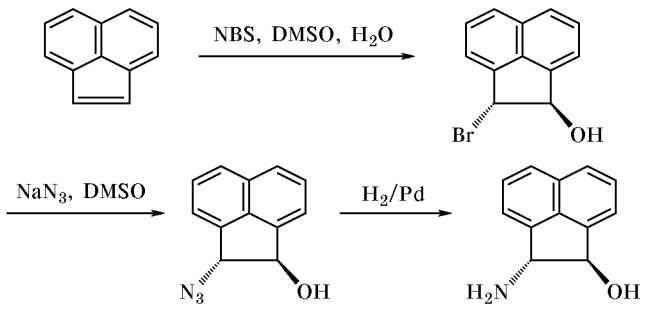
Nasim *et al.* [161] described hydroxybromination of 1-vinylsilatranes, which resulted in formation of the corresponding bromohydrins (Scheme 70).

Scheme 70.

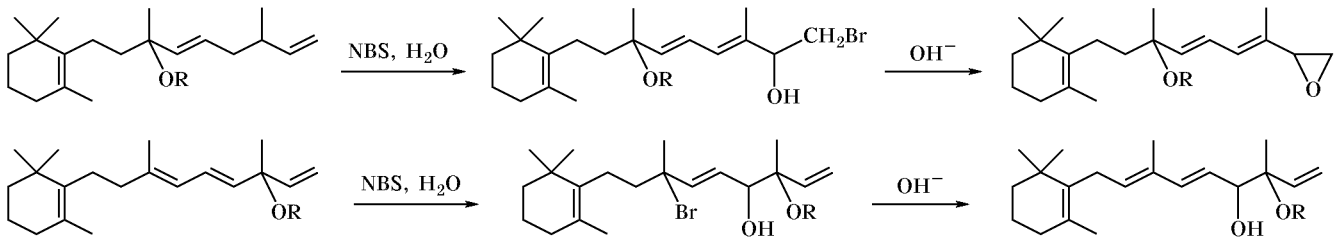


cis-2-Aminoacenaphthen-1-ol was synthesized by a multistep procedure including hydroxybromination of acenaphthylene with *N*-bromosuccinimide in moist DMSO [162] (Scheme 71).

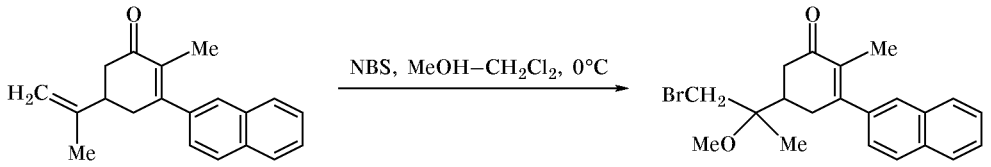
Scheme 71.



Scheme 72.



Scheme 73.

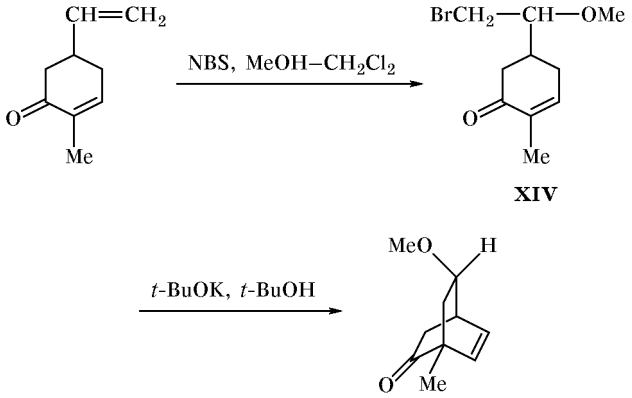


XIII

The hydroxyhalogenation process is especially important in the chemistry of natural compounds [163–165]. The resulting halohydrins are then brought into further transformations with the goal of building up a new double bond or oxirane ring. Scheme 72 shows examples of regioselective hydroxybromination of isoprenoid alcohols and their acetates by the action of *N*-bromosuccinimide in aqueous medium [166]. Depending on mutual arrangement of double bonds in the initial compound, two kinds of bromohydrins were obtained, which reacted with bases to give different products. A procedure was developed for selective epoxidation of natural compounds having terminal multiple bonds. It is based on hydroxybromination of a natural substrate with *N*-bromosuccinimide in an aqueous polar solvent and subsequent treatment of bromohydrins thus formed with potassium carbonate in methanol. The procedure was used to convert farnesyl acetate into 10,11-epoxyfarnesyl acetate in an overall yield of 60% [167]. The selective epoxidation technique was also applied in the synthesis of 2,3-epoxysqualene containing carbon isotopes in positions *10* and *15* [168]. 2,3-Epoxy-29-hydroxysqualene [169], 2,3-epoxy-29-methylenesqualene [170], and 14α,15-epoxy-5α-cholestan-3-yl benzoate [171] were obtained under analogous conditions.

Reactions of olefins with *N*-bromsuccinimide in alcohols lead to formation of β-bromo ethers [172]. The reaction follows the Markownikoff pattern and is characterized by high regioselectivity. As an example, Scheme 73 shows methoxybromination of compound **XIII** in MeOH–CH_2Cl_2 (2:3) to afford 1:1 epimeric mixture of β-bromo ethers in an overall yield of 83% [173]. (*S*)-Carvone reacts with *N*-bromosuccinimide in MeOH–CH_2Cl_2 to give bromo methoxy derivative **XIV** which undergoes cyclization in the presence of potassium *tert*-butoxide [52] (Scheme 74).

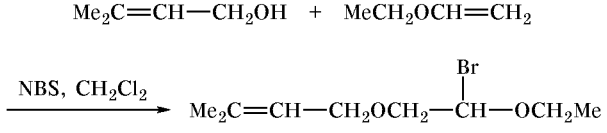
Scheme 74.



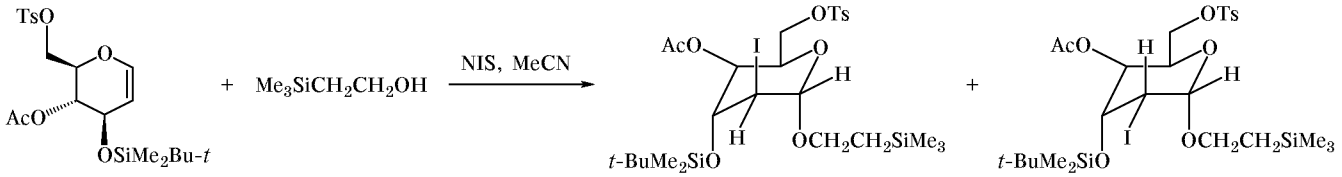
XIV

Boldwin *et al.* [174] developed a preparative method for synthesizing α-halo acetals. A mixture of an alcohol and ethyl vinyl ether was treated with *N*-halosuccinimide in methylene chloride. Following this procedure, 1-(2-bromo-2-ethoxyethoxy)-3-methyl-2-butene was prepared from 3-methyl-2-buten-1-ol (Scheme 75). Likewise, (*E*)-1-(2-bromo-1-ethoxyethoxy)-3,7-dimethyl-2,6-octadiene was synthesized

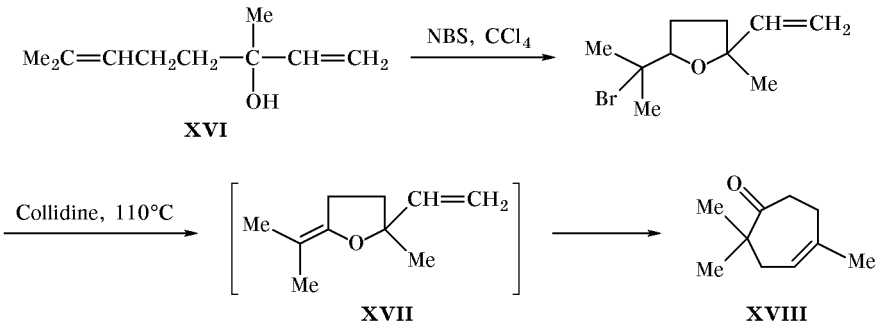
Scheme 75.



Scheme 76.



Scheme 77.

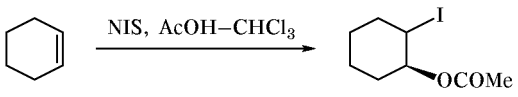


from geraniol, and (*Z*)-1-(2-bromo-1-ethoxyethoxy)-3,7-dimethyl-2,6-octadiene, from nerol [174].

2-Trimethylsilylethanol adds at the double C=C bond of dihydroxydihydropyran derivatives **XV** in the presence of *N*-iodosuccinimide to afford a mixture of α-*manno*- and β-*gluco*-2-deoxy-2-iodoglycosides (Scheme 76). Tertiary alcohols having a double bond in the γ-position react with *N*-bromosuccinimide to give α-bromoalkyltetrahydrofurans [81]. This reaction underlies the transformation of linalool into karahanaenone [81]. The reaction of linalool (**XVI**) with *N*-bromosuccinimide gives 85% of 5-(1-bromo-1-methylethyl)-2-methyl-2-vinyltetragidrofuran which undergoes dehydrohalogenation by the action of collidine at 100°C. [3,3]-Sigmatropic rearrangement of the resulting allyl vinyl ether **XVII** yields karahanaenone (**XVIII**) (Scheme 77). Likewise, intramolecular addition of hydroxy group at C=C bond in the presence of *N*-iodosuccinimide is used in the synthesis of *C*-aryl glycosides [176].

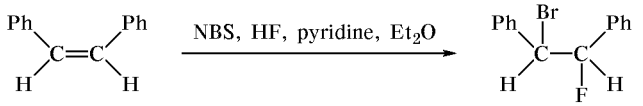
Reactions of olefins with *N*-halosuccinimides in the presence of acids could give rise to β-halo esters. An example is the reaction of cyclohexene with *N*-iodosuccinimide in chloroform in the presence of acetic acid, which results in formation of 2-iodocyclohexyl acetate [177] (Scheme 78).

Scheme 78.



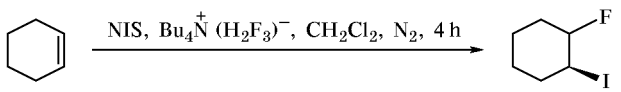
Two procedures for fluorohalogenation of olefins have been developed. The first of these is based on the reaction of olefins with *N*-halosuccinimides in a mixture of pyridine with diethyl ether in the presence of hydrogen fluoride. Under these conditions, *cis*-stilbene reacts with *N*-bromosuccinimide to afford a mixture of *erythro*- and *threo*-1-bromo-2-fluoro-1,2-diphenylethanes (43% and 18%, respectively) [178] (Scheme 79).

Scheme 79.



Following the second procedure, an olefin reacts with *N*-halosuccinimide in the presence of tetrabutylammonium dihydrogen trifluoride. For example, the reaction of cyclohexene with *N*-iodosuccinimide and tetrabutylammonium dihydrogen trifluoride gives *trans*-1-fluoro-2-iodocyclohexane in 86% yield [179] (Scheme 80).

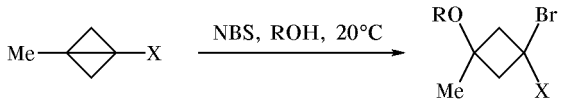
Scheme 80.



A relatively large number of publications deal with solvolytic halogenation of various unsaturated alicyclic compounds. Razin and Zadonskaya [180]

described a fairly ready reaction of methyl 3-methylbicyclobutane-1-carboxylate (or 3-methylbicyclobutane-1-carbonitrile) with *N*-bromosuccinimide in water or methanol, which resulted in formation of substituted 1-bromo-3-hydroxy(or methoxy)cyclobutanes having *cis* configuration (Scheme 81).

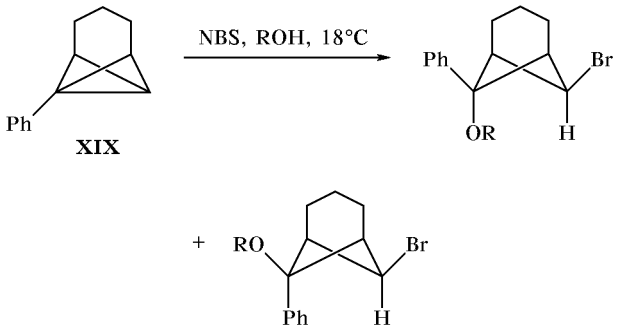
Scheme 81.



X = COOMe, CN; R = H, Me.

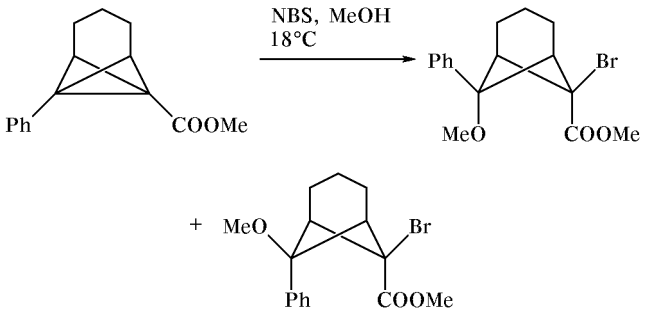
On the other hand, the reaction of 3-phenylbicyclobutane-1-carbonitrile with *N*-bromosuccinimide in methanol is not stereoselective; it gives both possible stereoisomeric cyclobutane adducts at a ratio of 3:2 [180]. Solvolytic bromination of 1-phenyltricyclo-[4.1.0.0^{2,7}]heptane (**XIX**) in methanol or aqueous tetrahydrofuran at room temperature is also nonselective. The reaction is accompanied by cleavage of the central C^1–C^7 bond with formation of *exo* and *endo* isomers of 7-bromo-6-methoxy(or hydroxy)-6-phenylbicyclo[3.1.1]heptane at a ratio of 15(or 13):1 [181] (Scheme 82).

Scheme 82.



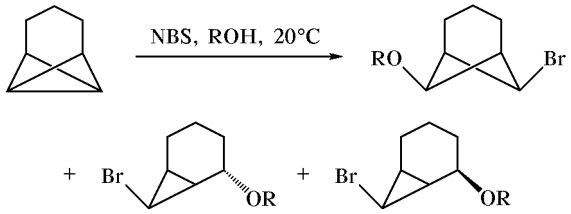
Razin *et al.* [182] studied the reaction of methyl 3-phenylbicyclobutane-1-carboxylate and its tricyclic analog, methyl 7-phenyltricyclo[4.1.0.0^{2,7}]heptane-1-carboxylate, with *N*-bromosuccinimide in methanol at room temperature. According to the authors, the bicyclobutane derivative exhibits *syn*-stereoselectivity, giving rise to a 2.2:1 mixture of *cis*- and *trans*-bromomethoxycyclobutanes (overall yield 75%). However, its tricyclic analog reacts in a nonstereoselective fashion, yielding a mixture of *endo*,*endo*- and *endo*,*exo*-bromomethoxynorpinanes at a ratio of 1:7 (overall yield 82%) [182] (Scheme 83).

Scheme 83.



Solvolytic bromination of tricyclo[4.1.0.0^{2,7}]-heptane with *N*-bromosuccinimide in water or methyl alcohol gives a mixture of three products, the major of which is that possessing a norcarane structure. The products are formed via cleavage of the C^1–C^2 bond in the initial compound [183] (Scheme 84).

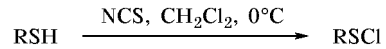
Scheme 84.



II.2. S-Halogenation

Chlorinolysis of the S–H bond in thiols by the action of *N*-chlorosuccinimide is used as a preparative method of synthesis of sulfenyl chlorides [184–188]. The reaction is carried out in anhydrous inert solvents (CH_2Cl_2, $CHCl_3$, etc.) at reduced temperature (0–2°C) (Scheme 85).

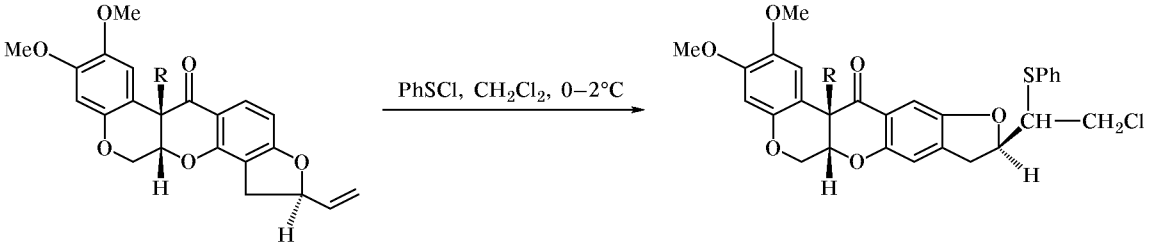
Scheme 85.



R = $HOCOCH_2$, $EtOCOCH_2$, $PhCH_2$, Ph, 4-ClC_6H_4, etc.

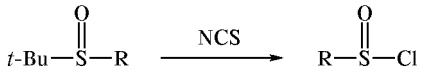
N-Chlorosuccinimide as chlorinating agent ensures high selectivity of the process which is not accompanied by such side reactions as chlorination of α-CH bonds and other functional groups present in the substrate. After separation of liberated succimimide, sulfenyl chlorides can be brought into further syntheses without isolation from the solution, which is very important in sulfenylation of natural compounds. Tupper *et al.* described the synthesis of sulfide analogs of ergoline alkaloids, utilizing a solution of

Scheme 86.



4-chlorobenzenesulfenyl chloride which was prepared by chlorination of 4-chlorobenzenethiol with *N*-chlorosuccinimide in methylene chloride [188]. A solution of benzenesulfenyl chloride in methylene chloride, prepared from benzenethiol and *N*-chlorosuccinimide, was used in the synthesis of specifically labeled (*Z*)- and (*E*)-[7′-^{2}H] rotenol analogs [187] (Scheme 86). Sulfinic acid chlorides were obtained by chlorinolysis of the C–S bond in *tert*-butyl sulfoxides by the action of *N*-chlorosuccinimide [189] (Scheme 87).

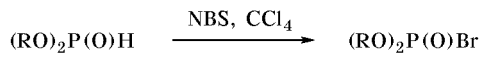
Scheme 87.



II.3. P-Halogenation

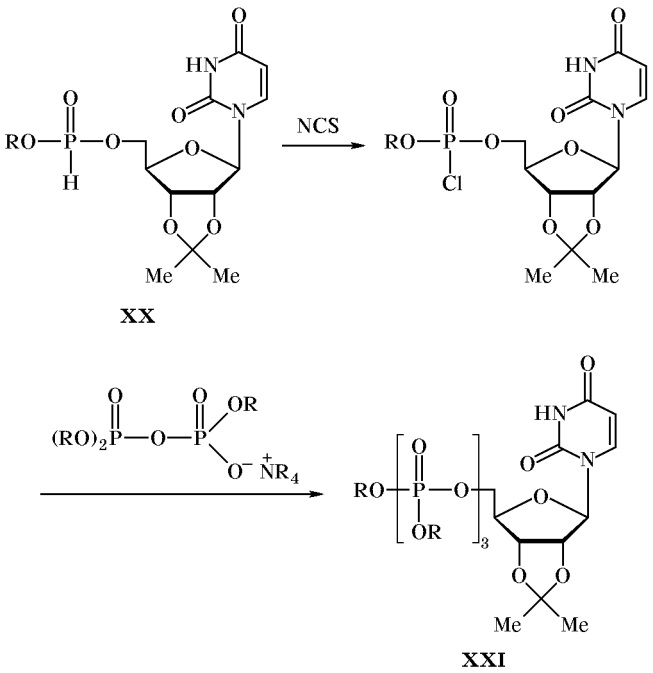
Unlike molecular bromine which reacts with dialkyl hydrogen phosphites to form mixtures of several products, *N*-bromosuccinimide with the same substrates gives rise to dialkylbromophosphates which are obtained in relatively high yields (Scheme 88). These products are used in the synthesis of glucose 1-phosphates [133, 190].

Scheme 88.



Syntheses of various natural compounds often utilize unstable phosphorylating agents which are prepared with the aid of *N*-chlorosuccinimide as chlorinating agent. For example, the chlorophosphate procedure for preparation of nucleoside triphosphate **XXI** [113] includes chlorination of phosphonate **XX** with *N*-chlorosuccinimide (Scheme 89).

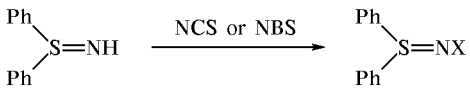
Scheme 89.



II.4. N-Halogenation

N-Halosuccinimides are mild N-halogenating agents ensuring formation of unstable *N*-halogen derivatives while other halogenating agents promote various side processes. *N*-Chlorosuccinimide is frequently used in the N-chlorination of unstable and difficultly accessible amines of the steroid series [3], azasteroid lactams [191], and aliphatic [3], aromatic [192], and some heterocyclic amines [193]. N-Halogenation of *S,S*-diphenylsulfimide with *N*-chloro- and

Scheme 90.

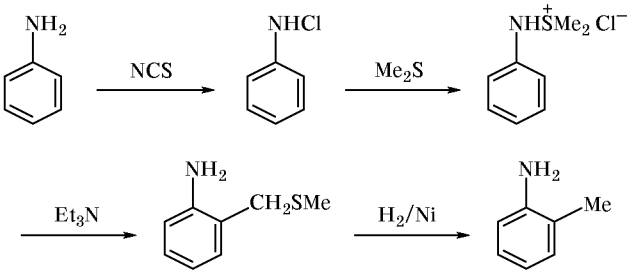


N-bromosuccinimides was reported in [194, 195] (Scheme 90).

Some processes have been developed which include the stage of N-halogenation of various nitrogen-containing compounds to obtain *N*-halogen derivatives; the latter were brought into further syntheses without isolation. Rosini [196] proposed a convenient method for regeneration of aldehydes and ketones from the corresponding *p*-tolylsulfonylhydrazones which were treated with *N*-bromosuccinimide in acetone in the presence of methanol at room temperature. The author presumed that the reaction begins with bromination of the NH group to give *N*-bromo derivative which then reacts with methanol to form carbonyl compound.

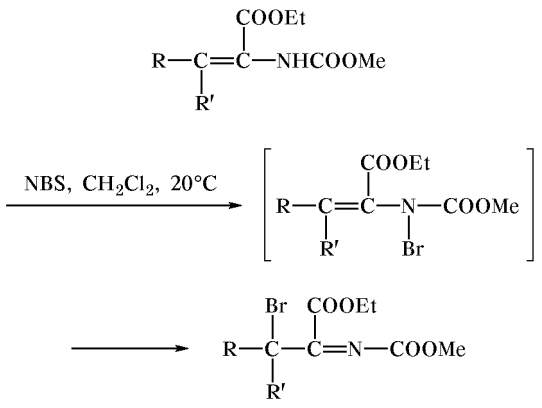
A multistep procedure for *ortho*-alkylation of aromatic amines includes chlorination with *N*-chlorosuccinimide as intermediate stage [197] (Scheme 91).

Scheme 91.



Presumably, the formation of β-bromo-α-amino acid esters in reactions of unsaturated α-amino acid esters with *N*-bromosuccinimide also includes the *N*-bromination stage [198] (Scheme 92).

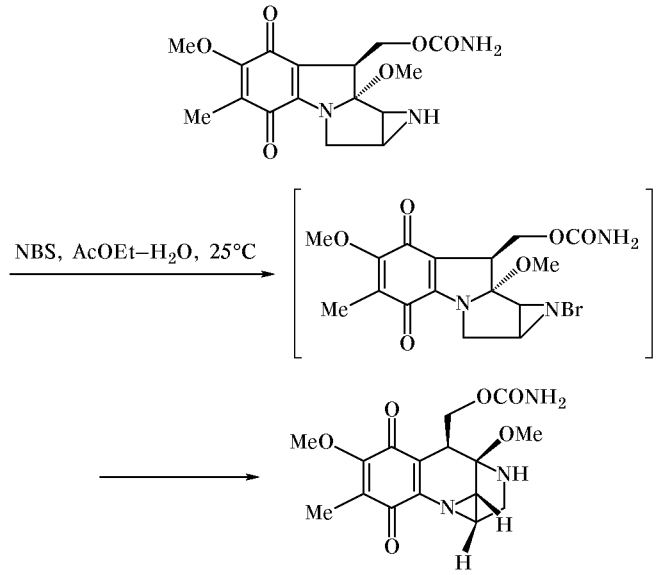
Scheme 92.



R = Ph, Me; R′ = H, Me.

According to Kasai *et al.* [199], the transformation of mitomycin A into isomitomycin A by the action of *N*-bromosuccinimide proceeds through N-bromination (Scheme 93).

Scheme 93.



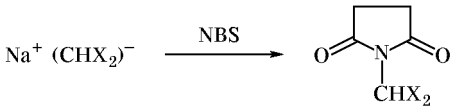
Reactions of azides with *N*-bromosuccinimide in the presence of benzoyl peroxide are often used in carbohydrate chemistry to convert the azido group into *N*-bromoimino moiety [200].

III. IMIDATION REACTIONS

III.1. C-Imidation

N-Halosuccinimides are capable of exchanging the halogen atom for organic fragments via reactions with compounds having labile hydrogen atoms. *N*-Bromosuccinimide is known [4] to react with CH acid sodium salts to give the corresponding N-derivatives (Scheme 94).

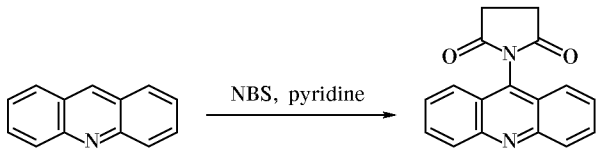
Scheme 94.



X = CN, PhCO, MeCO, EtOCO.

Unlike anthracene which reacts with *N*-bromosuccinimide to give 9-bromo derivative, the reaction of acridine with *N*-bromosuccinimide yields 6-succinimidoacridine [4, 201] (Scheme 95). Imidation with *N*-chlorosuccinimide of pyrrole and its N-substituted derivatives was reported [202]. These reactions result in formation of α-substituted products.

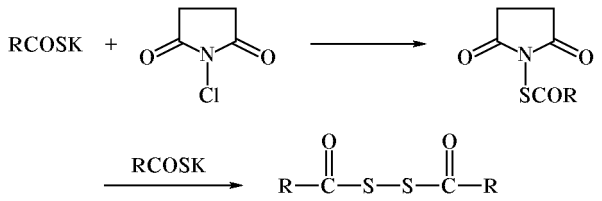
Scheme 95.



III.2. S-Imidation

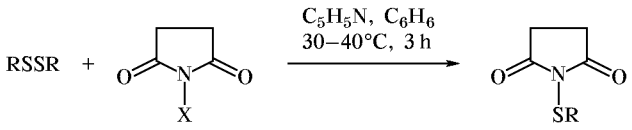
Thiocarboxylic acid potassium salts relatively readily react with *N*-chlorosuccinimide to form sulfenamides; reaction of the latter with excess thiocarboxylic acid potassium salt is accompanied by cleavage of the S–N bond to form disulfides. Both symmetrical and unsymmetrical disulfides can be obtained in this way [203] (Scheme 96).

Scheme 96.



Homolytic dissociation of the S–S bond in disulfides in reactions with *N*-halosuccinimides yields sulfenamides [204] (Scheme 97).

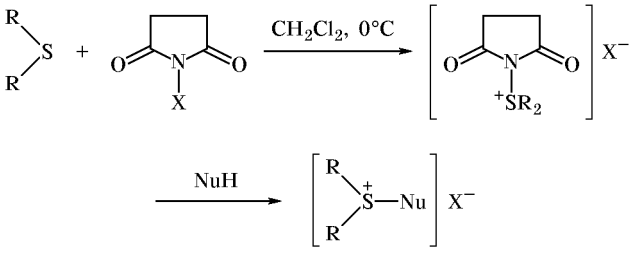
Scheme 97.



R = Ph, 4-ClC_6H_4, 2-MeC_6H_4, 4-MeC_6H_4, 2-$MeOC_6H_4$, 4-FC_{6H_4}, $C_6H_5CH_2$; X = Cl, Br.

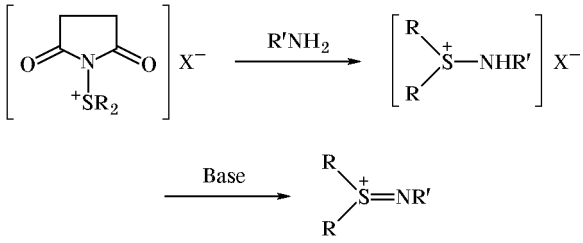
Reactions of *N*-halosuccinimides with sulfides are used for generation of succinimidosulfonium salts which are convenient reagents for sulfonium group transfer to nucleophiles [205, 206] (Scheme 98).

Scheme 98.



Succinimidosulfonium salts react with amines to give sulfimides, and this reaction serves as a preparative method for synthesis of sulfimides [207–210] (Scheme 99).

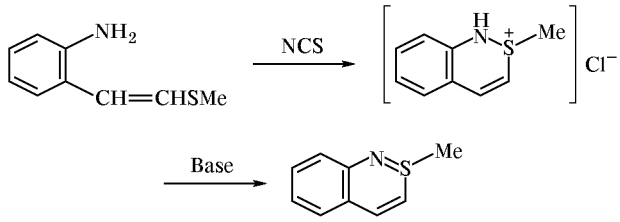
Scheme 99.



R = Me, Et, RR = $(CH_2)_4$, $(CH_2)_5$; R′ = Alk, Ar, Het; X = Cl, Br.

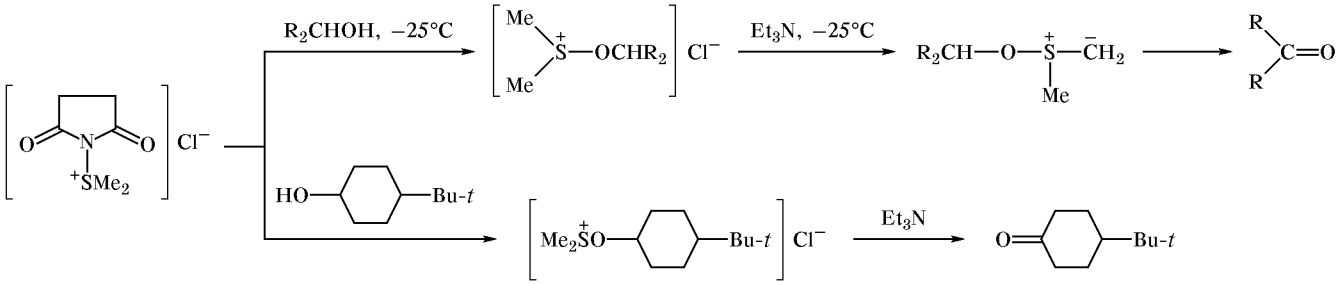
Aromatic amines having an alkylthio group in the *ortho* position react with *N*-chlorosuccinimide to give cyclic aminosulfonium salts which are converted into cyclic sulfimides in the presence of bases [211] (Scheme 100).

Scheme 100.

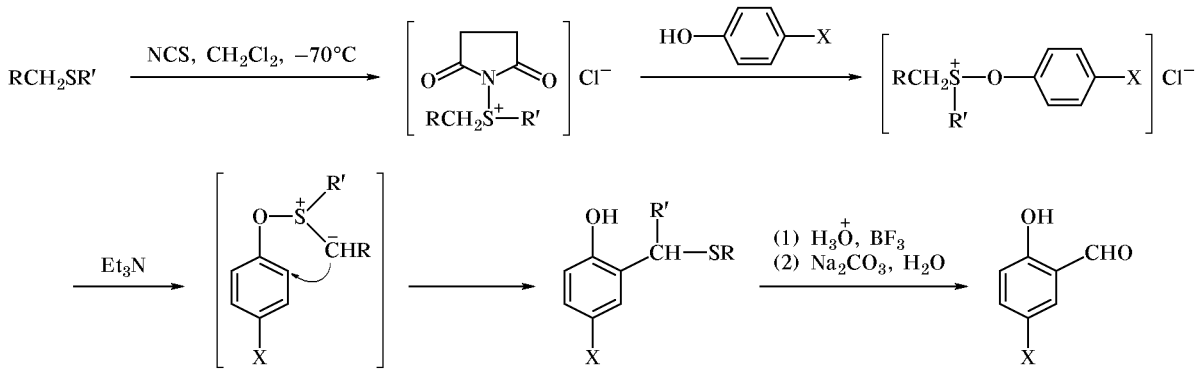


Succinimidosulfonium salts readily react with hydroxy-containing compounds to afford alkoxy- or aroxysulfonium salts, whose further transformations are determined by the nature of the hydroxy compound. Alkoxysulfonium salts derived from saturated primary and secondary alcohols are converted (on treatment with bases) into carbonyl compounds through intermediate ylides [212, 213] (Scheme 101). Under similar conditions, alkoxysulfonium salts formed from allyl and benzyl alcohols are converted into the corresponding chloro derivatives (see above). Treatment with bases of alkoxysulfonium salts derived from phenols also gives rise to ylides which undergo [2,3]-shift to afford *ortho*-alkylthio phenols. This procedure was proposed for *ortho*-formylation of phenols [214] (Scheme 102). Decomposition of succinimidosulfonium salts by the action of inorganic bases also leads to formation of carbonyl compounds, and this process frequently constitutes a part of multistep synthetic transformations [215] (Scheme 103).

Scheme 101.

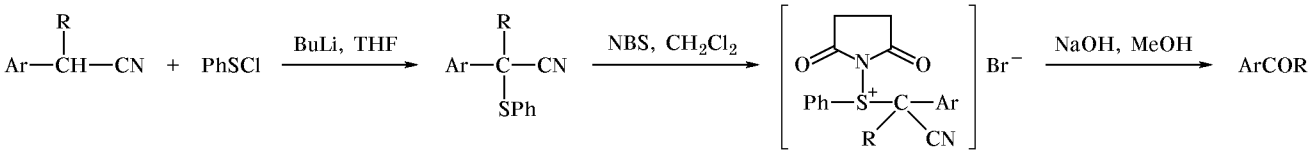


Scheme 102.



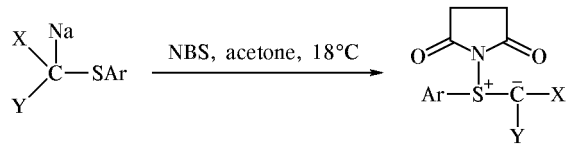
R = H, Alk; R′ = Alk; X = H, Me, OMe.

Scheme 103.



Succinimidosulfonium salts derived from dimethyl sulfide and *N*-chlorosuccinimide react with CH acids in the presence of triethylamine to form relatively stable sulfur ylides [216]. Sulfur ylides were also formed in reactions of *N*-bromosuccinimide with sodium salts derived from sulfides having a labile α-hydrogen atom [217] (Scheme 104).

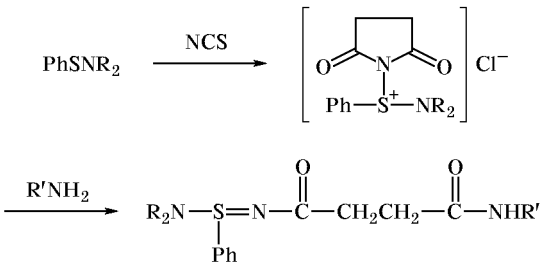
Scheme 104.



X = MeCO, Y = EtOCO, Ar = 2-$NO_2C_6H_4$; X = $PhSO_2$, Y = Ph, Ar = 4-$NO_2C_6H_4$.

Reactions of *N*-chlorosuccinimide with *N*,*N*-dialkylarenesulfenamides lead to formation of azasulfonium salts which react with amines, yielding *N*,*N*-disubstituted sulfinamidines [218] (Scheme 105).

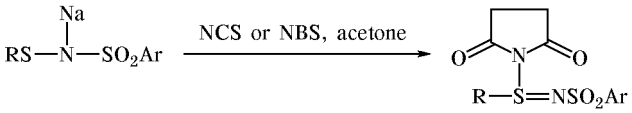
Scheme 105.



R = Me; R′ = Alk, Ar.

N,*N*-Disubstituted sulfinamidines are also formed by reactions of *N*-chloro- or *N*-bromosuccinimide with *N*-arylsulfonylarenesulfenamide sodium salts [219, 220] (Scheme 106).

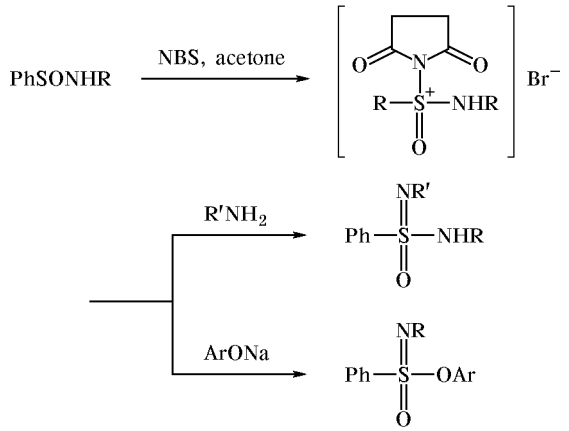
Scheme 106.



R = 2-$NO_2C_6H_4$, 4-$NO_2C_6H_4$; Ar = Ph, 4-MeC_6H_4; X = Cl, Br.

Reactions of *N*-bromosuccinimide with *N*-substituted sulfinamides in the presence of amines or phenoxides yield, respectively, sulfonimidamides or aryl sulfonimidates [221] (Scheme 107).

Scheme 107.

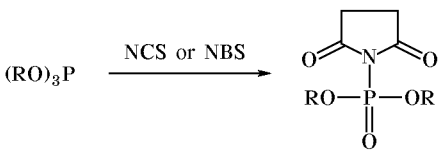


R = PhC_6H_{11}, R′ = C_6H_{11}, Ar = 4-$NO_2C_6H_4$.

III.3. P-Imidation and N-Imidation

N-Chloro- and *N*-bromosuccinimides react with trialkyl phosphites, following the Arbuzov reaction pattern; the products are the corresponding dialkyl amidophosphates [222] (Scheme 108).

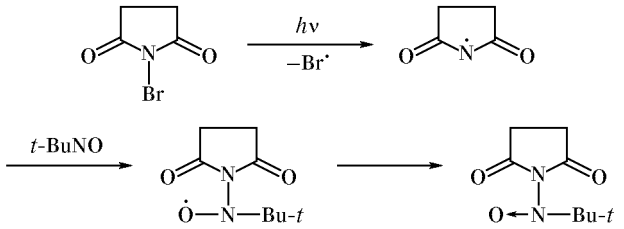
Scheme 108.



R = Bu, Me_3CCH_2.

This reaction is used in organic synthesis as a method for building up P^V-N bond. Janzen [223] described capture of succinimidyl radical, generated by photolysis of *N*-bromosuccinimide, by aliphatic nitroso compounds. As a result, azoxy compounds having a succinimide fragment were obtained [223] (Scheme 109).

Scheme 109.

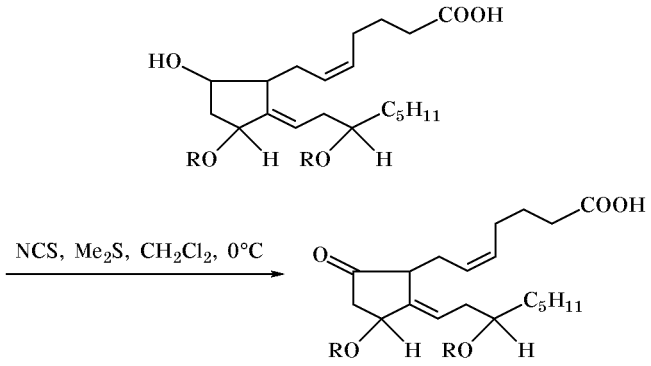


IV. OXIDATION REACTIONS

IV.1. Oxidation of Alcohols

N-Bromosuccinimide oxidizes primary alcohols to aldehydes which are converted into esters through acetals in alcoholic medium [3]. To obtain pure aldehyde, a mixture of alcohol and *N*-bromosuccinimide in an organic solvent (benzene, toluene, etc.) is refluxed for a short time. This procedure was used to oxidize 4,5-dimethoxyphthalyl [3] and furfuryl alcohols [224]. Secondary alcohols are oxidized with *N*-bromosuccinimide to ketones in relatively high yields [3]. In some cases oxidation of secondary alcohols is effected with the *N*-chlorosuccinimide–dimethyl sulfide complex in an organic solvent (toluene, methylene chloride, etc.). An improved procedure for preparation of prostaglandins [118] involves *N*-chlorosuccinimide in the presence of dimethyl sulfide as oxidant instead of Johnson's reagent; as a result, the yield of keto acid is increased by 20% (Scheme 110).

Scheme 110.

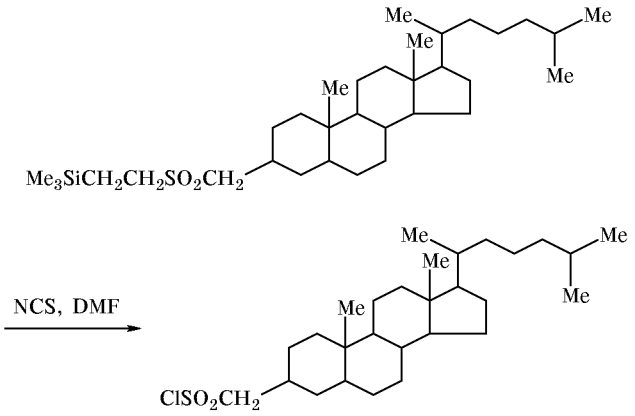


Takayanagi *et al.* [225] reported on the oxidation of 1-chloro-6-methyl-5-hepten-2-ol to the corresponding ketone with the aid of *N*-chlorosuccinimide in the presence of dimethyl sulfide.

IV.2. Oxidation of Sulfur-Containing Compounds

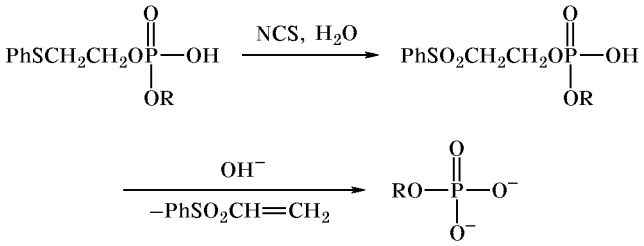
Thiols and thioureas are oxidized with *N*-halosuccinimides in aqueous medium to the corresponding disulfides [3, 226]. Diaryl sulfides and aryl benzyl sulfides react with *N*-bromosuccinimide in aqueous medium to give the corresponding sulfoxides [227]. No sulfone formation is observed in these reactions. *N*-Halosuccinimides are often used as oxidants in syntheses and transformations of sulfur-containing natural compounds. *N*-Chlorosuccinimide was used to oxidize thiol groups to obtain disulfide bridges in the synthesis of cystine-containing peptides [226]. While preparing steroid sulfonates, Henriques *et al.* [228] used *N*-chlorosuccinimide as oxidant and chlorinating agent to create a sulfonyl chloride functionality (Scheme 111).

Scheme 111.



The oxidizing ability of *N*-chlorosuccinimide with respect to sulfides was also utilized in the synthesis of polynucleotides on a polyamide support [113]. In the initial stage nucleotide was bound to a polymeric matrix via esterification of the corresponding 5′-phosphate with the 2-ethanethiol group. After a series of consecutive transformations extending the polynucleotide chain, oxidation of S(II) to S(VI) was performed using *N*-chlorosuccinimide with the goal of separating the completed polynucleotide from polyamide support (as a result of β-elimination in the sulfone in alkaline medium). Oxidation of sulfides to sulfones with *N*-chlorosuccinimide underlies a procedure for deprotection of the phosphate fragment of nucleotides (removal of protective groups on the basis of S-substituted 2-mercaptoethanol) [229]. For this purpose, the sulfide moiety is oxidized with *N*-chlorosuccinimide, followed by β-elimination of the resulting sulfone in alkaline medium (Scheme 112).

Scheme 112.

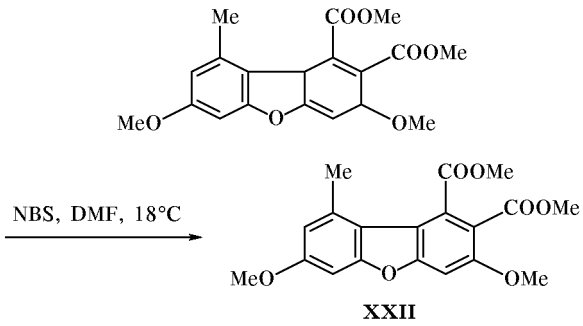


R is a nucleoside.

IV.3. Oxidation of Unsaturated Compounds

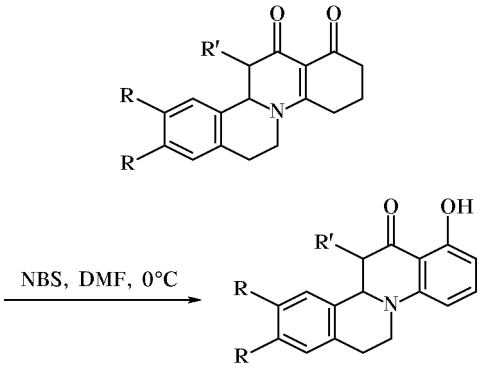
Unsaturated compounds can also be oxidized with *N*-halosuccinimides. Diphenylacetylene reacts with 2 equiv of *N*-bromosuccinimide to give 98% of benzil [230]. Oxidation of purines with *N*-bromosuccinimide in acetate buffer was reported to produce a mixture of several products [231]. Some natural compounds undergo aromatization under the action of *N*-bromosuccinimide. An example is the transformation of cyclohexadiene ring into benzene in the multistep synthesis of strepsilin derivative **XXII** [232], shown in Scheme 113. Mikhal'chuk *et al.* [233] were the first

Scheme 113.



XXII

Scheme 114.



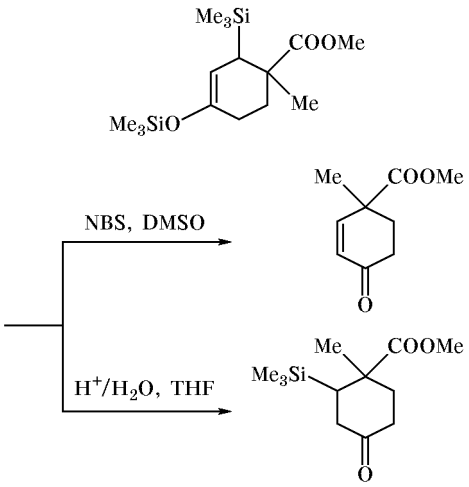
R = H, OMe; R′ = H, Me.

to obtain 17a-hydroxy-8-aza-D-homogona-1,3,5,13,-15,17-hexaen-12-ones by selective aromatization of 8-aza-D-homogonanes with *N*-bromosuccinimide (Scheme 114).

V. REACTIONS INVOLVING CLEAVAGE OF CARBON–HETEROELEMENT BOND

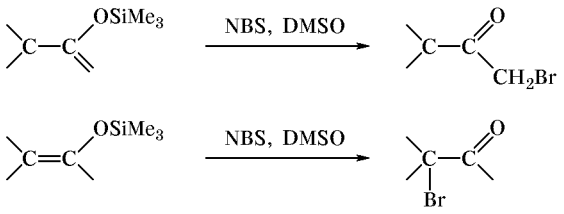
Reactions of *N*-halosuccinimides with some substrates are accompanied by cleavage of carbon–heteroelement bond. For example, *N*-bromosuccinimide reacts with cyclohexenecarboxylates having trimethylsilyl and trimethylsiloxy groups, yielding oxocyclohexenecarboxylates as a result of cleavage of the C–Si and Si–O bonds. Acid hydrolysis of the same substrates leads to formation of oxocyclohexanecarboxylates [234] (Scheme 115).

Scheme 115.



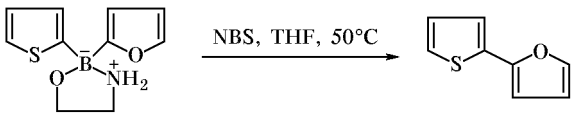
Reactions of *N*-bromosuccinimide with silyl enol ethers yield α-bromo ketones [235] (Scheme 116).

Scheme 116.



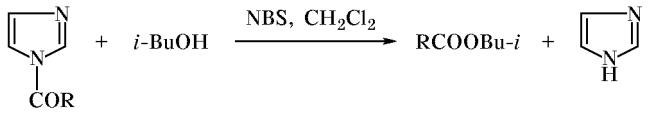
Cragg *et al.* [236] believe that reactions of organoboron compounds having furan and thiophene rings with *N*-bromosuccinimide, which involve cleavage of the C–B bond, open a new way of regioselective coupling of heteroaromatic groups under mild conditions (Scheme 117).

Scheme 117.



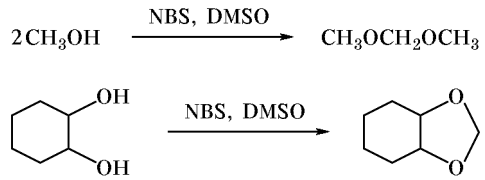
The acylating power of *N*-acylimidazoles with respect to alcohols considerably increases in the presence of *N*-bromosuccinimide which favors cleavage of the C–N bond [237] (Scheme 118).

Scheme 118.



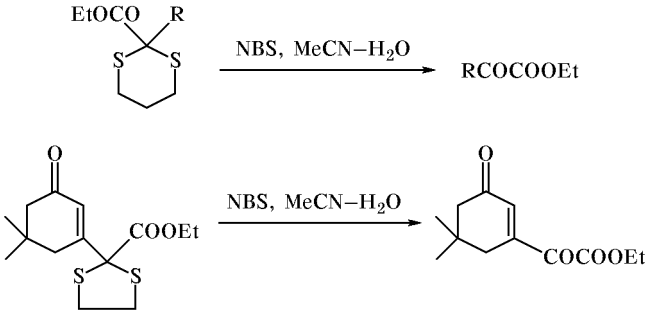
A preparative procedure for synthesizing formaldehyde acetals was reported. It is based on the reaction of alcohols and diols with DMSO in the presence of *N*-chloro- or *N*-bromosuccinimide. The methylene group in the final product originates from dimethyl sulfoxide as a result of cleavage of the C–S bond. The mechanism of this process was proved by studying the reaction with DMSO labeled with hydrogen isotopes [238] (Scheme 119).

Scheme 119.

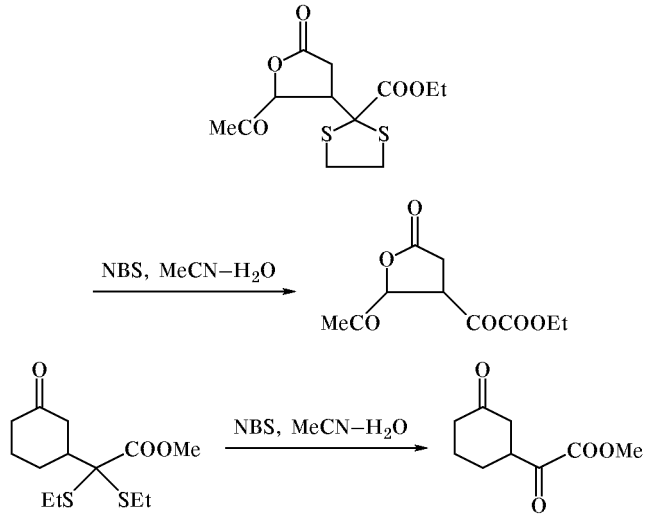


Of great importance is hydrolytic cleavage of the C–S bond in thioacetals, 1,3-dithiolanes, and 1,3-dithianes. Their reactions with *N*-halosuccinimides give rise to carbonyl functionality and are often used in multistep syntheses of various carbonyl compounds [239–244] (Schemes 120, 121).

Scheme 120.

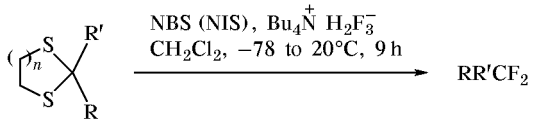


Scheme 121.



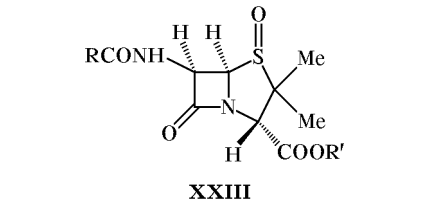
A nontrivial method for synthesizing difluoromethylene compounds is based on the oxidative fluorodesulfurization of dithioacetals with the aid of *N*-bromo- or *N*-iodosuccinimide [245] (Scheme 122).

Scheme 122.

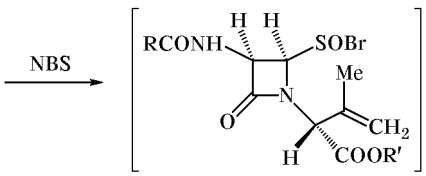


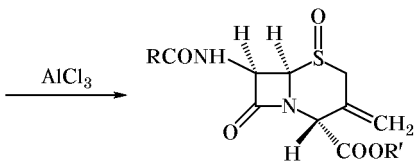
R = H, Et, $BuCH_2CH_2CH(Me)$, $CH_3CH_2CH(OH)$; R′ = Ph, 4-PrC_6H_4, 4-$MeOC_6H_4$; *n* = 1, 2.

Scheme 123.



XXIII

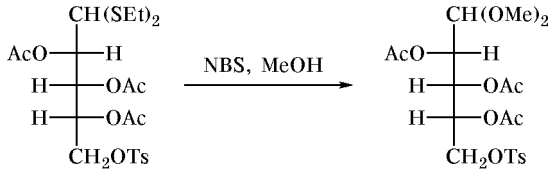




XXIV

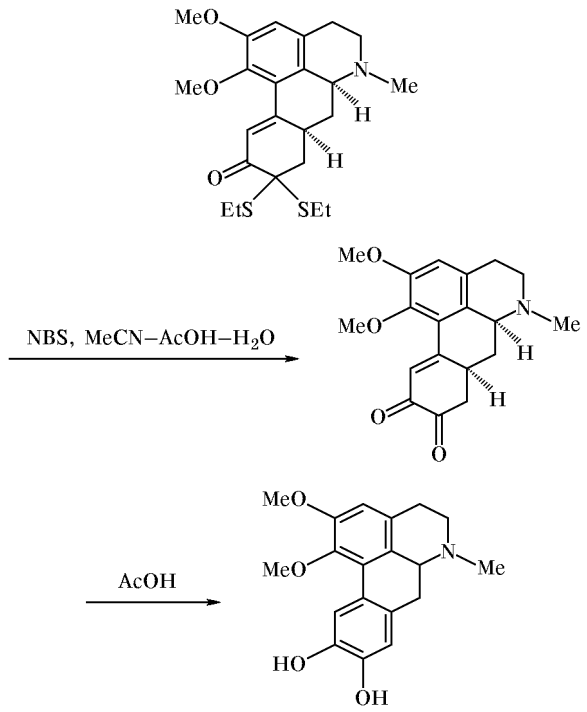
Some tranformations of natural compounds also involve cleavage of C–S bonds by the action of *N*-halosuccinimides. In particular, cleavage of the C–S bond in the five-membered ring of sulfoxide penicillin derivative **XXIII** constitutes one of the key stages in the synthesis of 3-methylenecepham (**XXIV**) which is used in turn for preparation of 3-halo- and 3-methoxycephams [246] (Scheme 123). Treatment of acylated derivatives of D-arabinose and D-glucose diethyl dithioacetals with *N*-bromosuccinimide in methanol leads to formation of the corresponding dimethyl acetals [247] (Scheme 124).

Scheme 124.



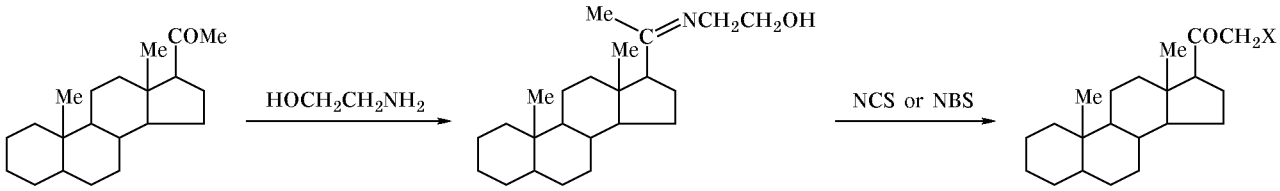
Ozaki and Kim [248] reported a new synthesis of aporphine alkaloids, which includes deacetalization of the corresponding diethyl dithioacetal by the action of *N*-bromosuccinimide and subsequent isomerization of diketone into diol [248] (Scheme 125).

Scheme 125.



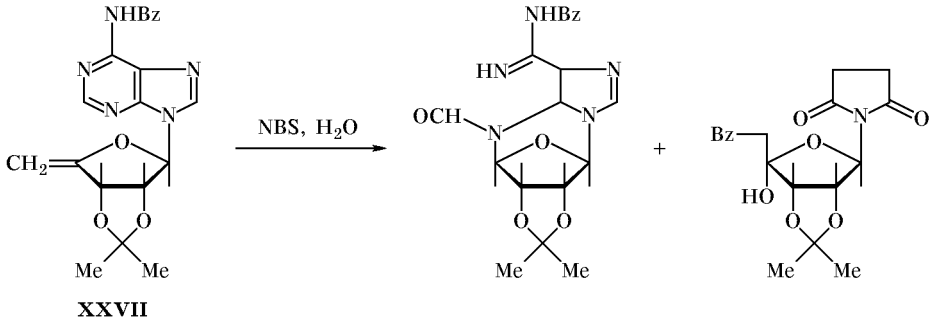
A new procedure was proposed for selective halogenation of the acetyl group in steroid **XXV**. The

Scheme 126.



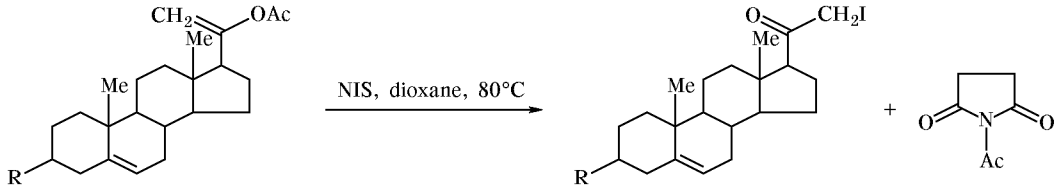
X = Cl, Br.

Scheme 127.



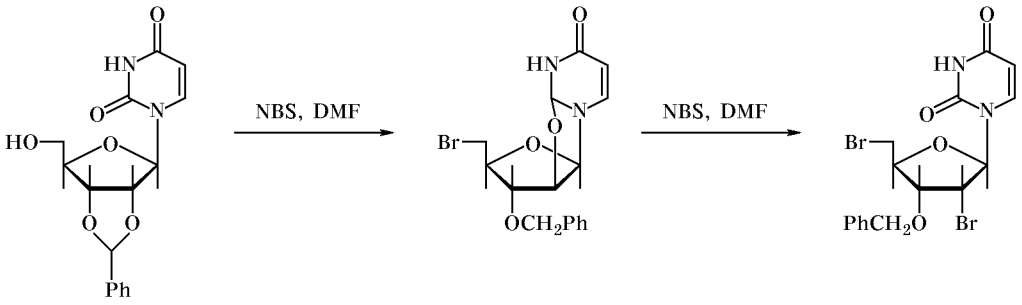
XXVII

Scheme 128.



R = AcO.

Scheme 129.



latter was converted into Schiff base **XXVI** by treatment with 2-aminoethanol. The subsequent reaction of **XXVI** with *N*-chloro- or *N*-bromosuccinimide resulted in halogentation of the methyl group and simultaneous cleavage of the C=N bond [249] (Scheme 126). The reaction of purine nucleoside **XXVII** with *N*-bromosuccinimide is accompanied by opening of the pyrimidine ring via cleavage of the C–N bond [250] (Scheme 127). Some transformations of natural compounds involve cleavage of C–O bond by the action of *N*-halosuccinimides. For example, halogenation of keto steroids at position *21* can be accomplished by reaction of the corresponding enol acetate with halogenating agents which do not affect the double C=C bond. Such a reagent may be *N*-iodosuccinimide: It promotes elimination of the acetyl group and iodine

addition to the methylene group [3] (Scheme 128). Cleavage of the C–O bond also occurs in the transformation of 2′,3′-*O*-benzylideneuridine into 3′-*O*-benzyl-2′,5-dibromo-2′-deoxyuridine by the action of *N*-bromosuccinimide [251] (Scheme 129).

Thus, published data indicate a wide synthetic potential of *N*-halosuccinimides and a great interest of researchers in these compounds. Being accessible reagents, *N*-halosuccinimides are extensively used in many fields of fine organic synthesis and of natural compounds chemistry as well. Original procedures for synthesizing various classes of organic compounds, including natural products, have been developed on the basis of *N*-halosuccinimides.

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