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Recent progress in the application of *N*-halo reagents in the synthesis of heterocyclic compounds

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Contents

1. Introduction

Of the more than 20 million chemical compounds currently registered, about one half contain heterocyclic systems. Heterocycles are important, not only because of their abundance, but above all because of their chemical, biological and technical significance. Heterocycles count among their number many natural products, such as vitamins, hormones, antibiotics, alkaloids, as well as pharmaceuticals, herbicides, dyes, and other products of technical importance (corrosion inhibitors, anti-aging drugs, sensitizers, stabilizing agents, etc.).

The exploitation of reagents for developing new synthetic methods is an art and constitutes a challenging process in organic chemistry. Consequentially, considerable efforts have been made over the years to find newer reagents, which can minimize the drawbacks of those presently in use. For this purpose, a large number of compounds entitled *N*-halo reagents have been extensively used in organic synthesis. These include *N*-halo amines, *N*-halo amides, *N*-halo imides, *N*-halo ureas, *N*-halo saccharins, *N*-halo sulfonamides, *N*-halo sulfonimides etc.[1–6]

N-Halo compounds are versatile reagents and have been employed as potentially reactive intermediates that are widely used in organic synthesis. Although the scope of the application of such compounds is so wide that all *N*-halo reagents cannot be considered within the framework of a single review article, we have decided to introduce them briefly and believe that this may be useful to achieve new ideas and applications. It should be noted that the chemistry of *N*-halo reagents has been the subject of several review articles.[1–9] Numerous new data have subsequently been reported in the literature and these are summarized in the present review. Some specific features of *N*-halo reagents such as the high activity of the N–X bond and the various modes of splitting of this bond determine their wide application in organic synthesis.[7–14]

N-halo reagents are easy to handle with all of the halogen being consumed, and not half, as in the case of elemental halogens. 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. Consequently, *N*-halo reagents have the potential to promote important reactions such as halogenations, oxidations, and protection and deprotection as well as the formation of C–X, C–O, C=O bonds.[15–20]

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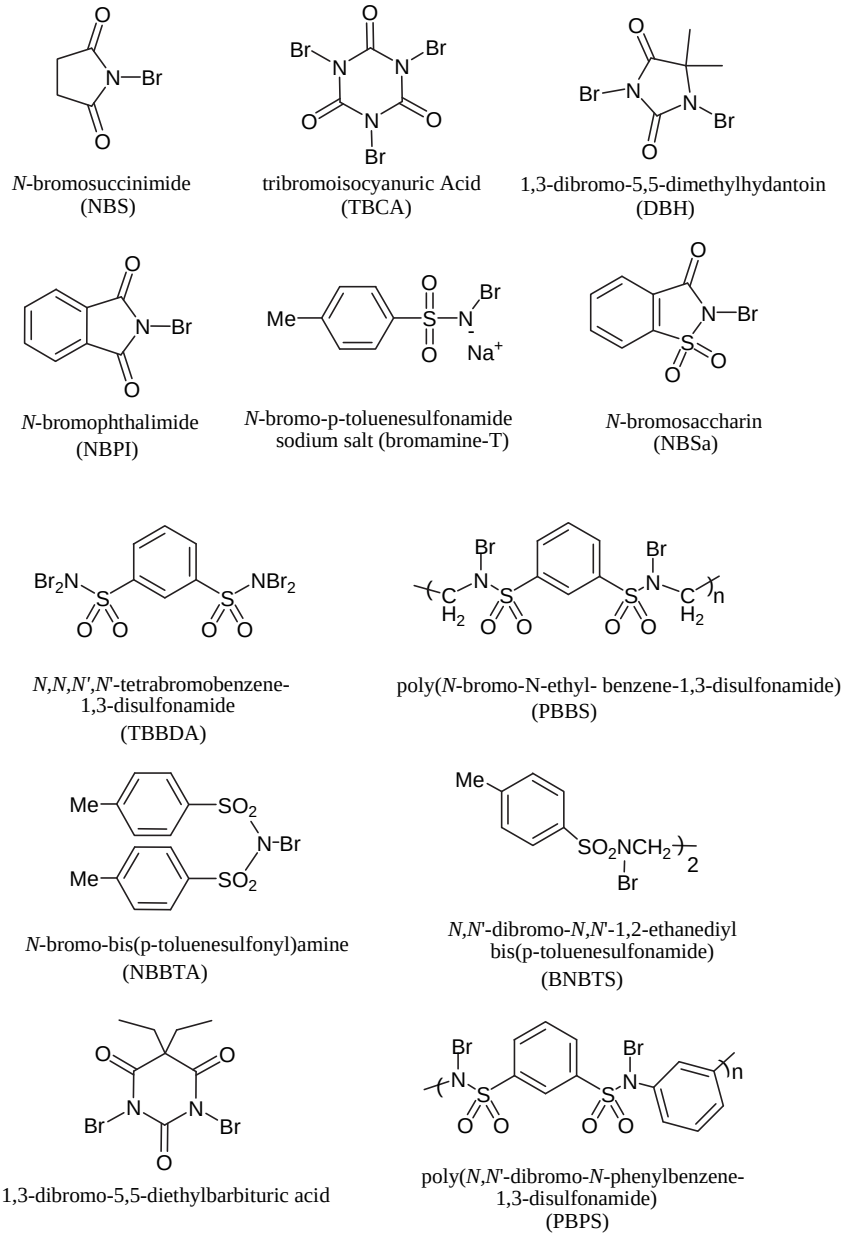
In addition to the numerous organic and inorganic halogenating agents, *N*-halo reagents play an especially important role as Lewis acid catalysts in the chemistry of heterocyclic compounds. Some of the *N*-halo reagents, which are presented in Schemes 1–4 are reviewed in this article. The rest of this review will focus on the variations found in the literature in the application of these useful reagents in the synthesis of heterocyclic compounds.



Scheme 1. *N*-Bromo reagents.

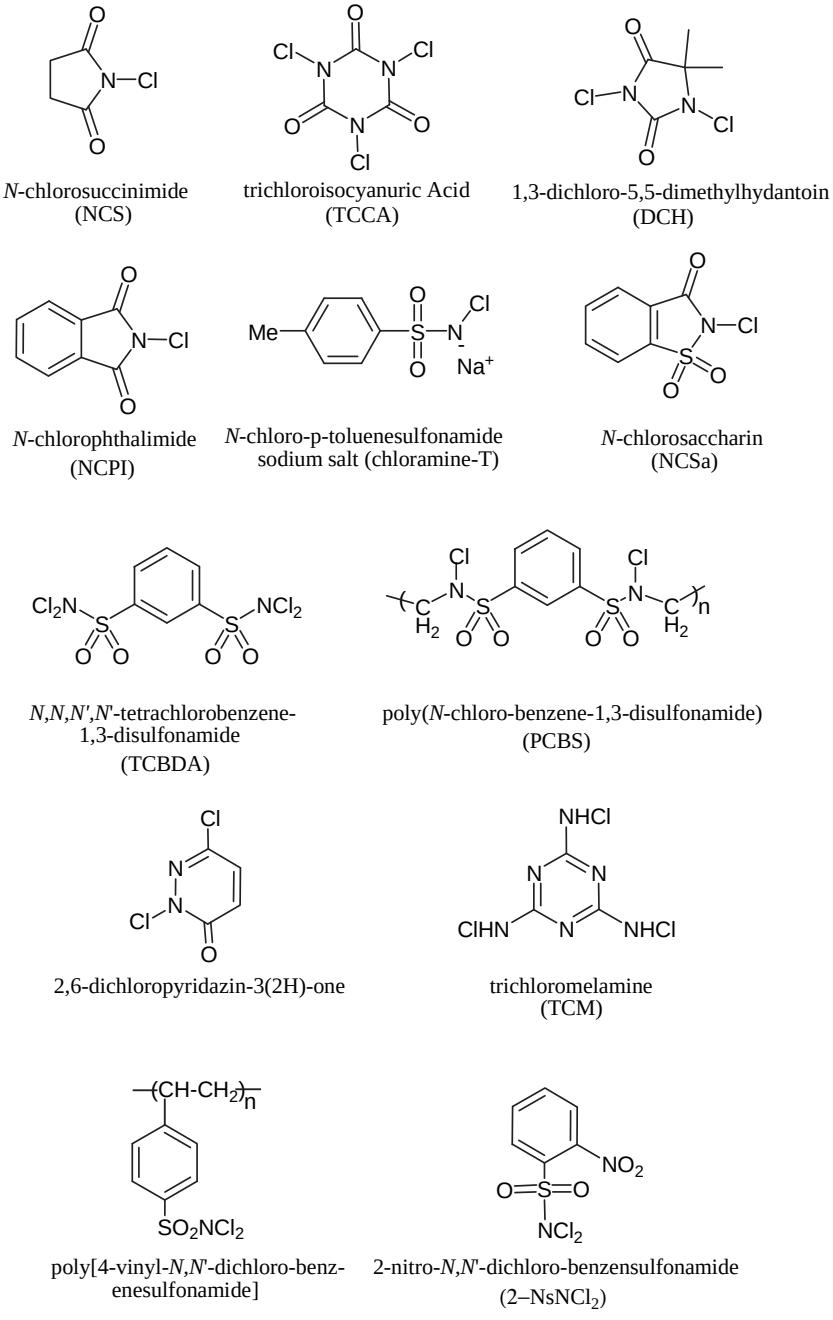
2. Three-membered heterocycles

The properties of three- and four-membered heterocycles are mostly a result of the great bond angle strain (BAEYER strain). The resultant ring strain imparts on the compounds high chemical reactivity. Ring opening leading to acyclic products is typical. Aziridine, an important three-membered heterocyclic ring system, is a useful precursor for the synthesis of several biologically important compounds, such as amino acids, amino sugars, and alkaloids. For this purpose, chloramine-T has been used in the presence of various catalysts to synthesis aziridine derivatives **2** from alkenes **1** (Scheme 5).[21–27]

Although the mechanistic aspects of the aziridation are not yet clear, Sudalai et al. have suggested an interesting mechanism for aziridation by NBS as catalyst (Scheme 6).[22]

In 2001,[28] the first aziridination of olefins under US and microwave irradiation was reported. Styrene **3** underwent aziridination under US irradiation in the presence of bromamine-T and $CuCl_2$ (Scheme 7). A good yield of aziridine **4** was obtained in 20 min at room temperature.

Both Fe(II)- and Mn-porphyrin complexes are effective catalysts for the aziridination of alkenes **5** using Bromamine-T, the reaction proceeding to form **6** with moderate-to-low stereospecificity (Scheme 8).[29,30]



Scheme 2. *N*-Chloro reagents.

N-Chlorosaccharin has been shown to undergo an electrophilic Ritter-type reaction with alkenes **7** in acetonitrile, and two different products have been obtained (imidazoline **8** or aziridine **9**). These reactions have been carried out at −42 °C up to room temperature (Scheme 9).[31]

The enantioselective epoxidation of chalcones **10** was carried out using TCCA as an oxidant in the presence of a chiral quaternary ammonium salt as a phase-transfer catalyst in good yields with moderate enantiomeric excesses of **11** (Scheme 10).[32]

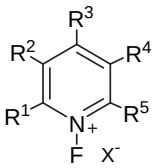
TCCA was used in the presence of base as an efficient oxidant for the epoxidation of enones **12** to form **13** and tandem oxidation–epoxidation of allylic alcohols in a water suspension system in the presence of a surfactant (Scheme 11).[33]

In addition, the preparation of epoxides **16** was efficiently achieved by the reaction of alkenes **14** with TCCA in aqueous acetone followed by treatment of the resulting chlorohydrins **15** with aqueous KOH in ether/pentane (Scheme 12).[33]

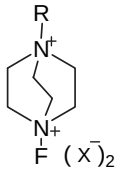
Nerinckx et al.[34] reported on the replacement of a *tert*-butyldimethylsilyl group by bromine with the aid of *N*-bromosuccinimide. Regioselective ring opening in 1,3-dioxolane derivatives **17** by the action of *N*-bromosuccinimide yields β-bromo benzyl ethers **18**, which readily undergo cyclization to oxiranes **19** in the presence of bases[35,36] (Scheme 13).

3. Five-membered heterocycles

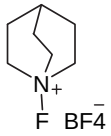
Since *N*-halo reagents contain halogen atoms, which are attached to nitrogen atoms, it is possible that they release X^+ in situ, which can act as a Lewis acid catalyst in the reaction medium. *N*-Halosuccinimides have been used to enable a new synthesis of



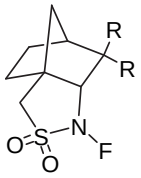
N-fluoropyridinium salts



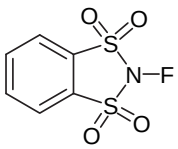
1-alkyl-4-fluoro-1,4-diaza bicyclo[2,2,2] octane



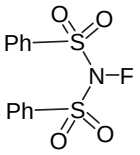
N-fluoroquinuclidinium tetrafluoroborate



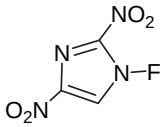
N-fluorocamphorsultam



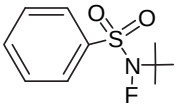
N-fluoro-o-benzene disulfonimide



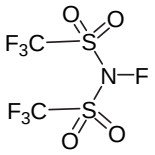
N-fluorobenzenseulfinimide



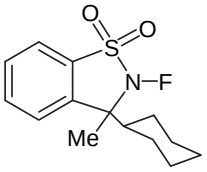
N-fluoro-2,4-dinitro-imidazole



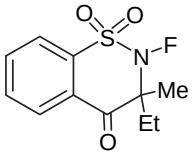
N-t-butyl-*N*-fluorobenzene sulfonamide



N-fluorobis[(trifluoromethyl) sulfonyl]imide

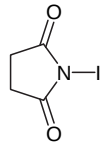


N-fluoro-3-cyclohexyl-3-methyl-2,3-dihydro-benzo[1,2-d]isothiazole-1,1-dioxide

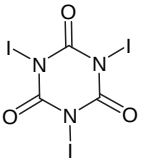


N-fluoro-3-ethyl-3-methyl-1,1-dioxo-2,3-dihydro-1λ^6-benzo[e]1,2-thiazin-4-one

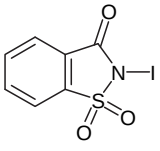
Scheme 3. *N*-Fluoro reagents.



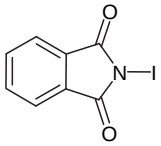
N-iodosuccinimide (NIS)



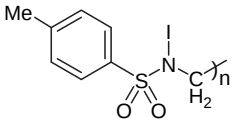
triiodoisocyanuric Acid (TICA)



N-iodosaccharin (NISa)



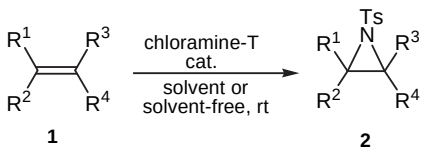
N-iodophthalimide (NIPI)



N,*N*′-diiodo-*N*,*N*′-1,2-ethanediyl bis(p-toluenesulfonamide) (NIBTS)

Scheme 4. *N*-Iodo reagents.

heterocyclic systems. The treatment of phenyl isocyanide **20** with NXS and sodium azide under phase-transfer catalysis conditions afforded 5-halo-1-phenyltetrazoles **21** in good yields (Scheme 14). The active species are probably halogen azides, which add to phenyl isocyanide.[37]



1 **2**

R^1, R^2, R^3 or R^4 = Alkyl or Aryl
Solvent: MeCN or H_2O
Catalyst:HPA/CTAB/MS 5ºA, Py/HBr_3, I_2/BTEAC, CuI/Ptc, MPHT or NBS
Ts: $MeC_6H_4SO_2$

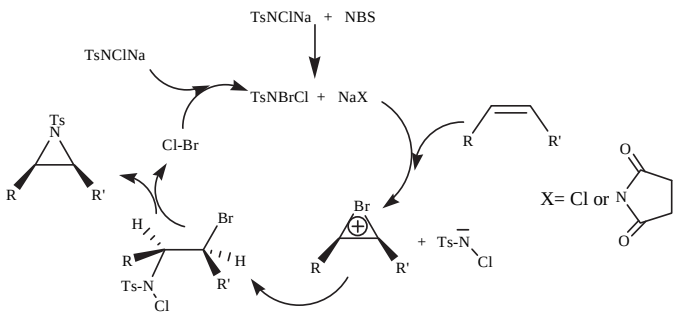
Scheme 5.

The application of the Pummerer reaction methodology to *N*-acylamino-2-thiophenyl derivatives **22** with NCS and tin(IV) chloride provided a direct synthesis of 5-thiophenyloxazoles **23** (Scheme 15).[38]

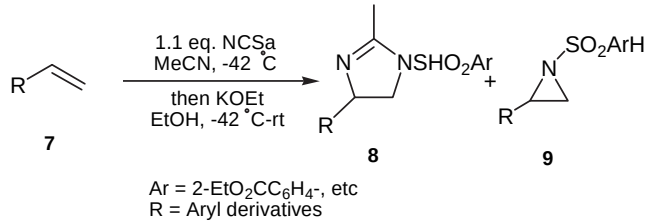
In 2006, Azarifar et al. reported an efficient method for the conversion of various *N*-arylglycines into sydnones **24** using 1,3-dibromo-5,5-dimethylhydantoin in the presence of $NaNO_2/Ac_2O$ under mild and neutral conditions (Scheme 16).[39]

The mechanism proposed for these transformations is shown in Scheme 17.

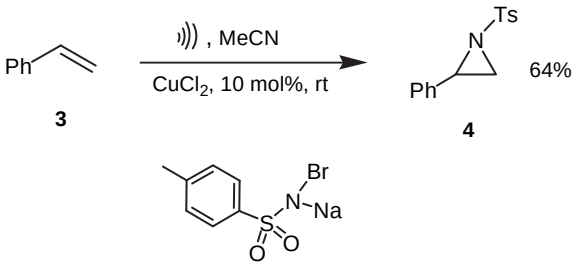
Koshima et al. have synthesised bis(indolyl)methanes **25** from the reaction of indoles with aldehydes and ketones in the presence of *N*-bromosuccinimide (NBS) as a mild and efficient catalyst under



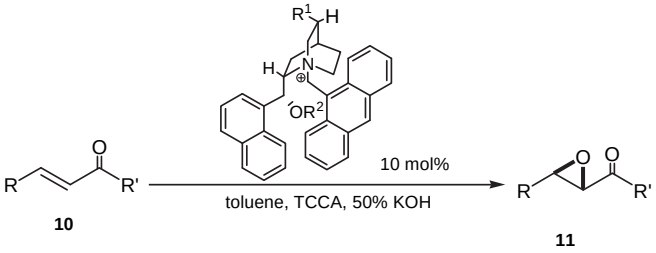
Scheme 6.



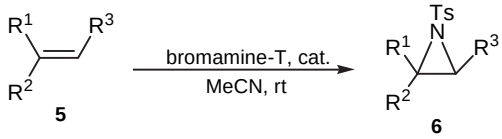
Scheme 9.



Scheme 7.

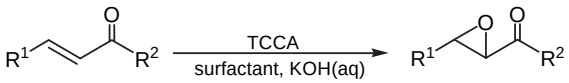


Scheme 10.

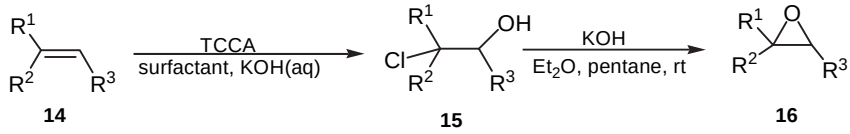


Catalyst = Fe(Por)Cl or Mn Complex
R^1, R^2, R^3 = Alkyl or Aryl

Scheme 8.



Scheme 11.

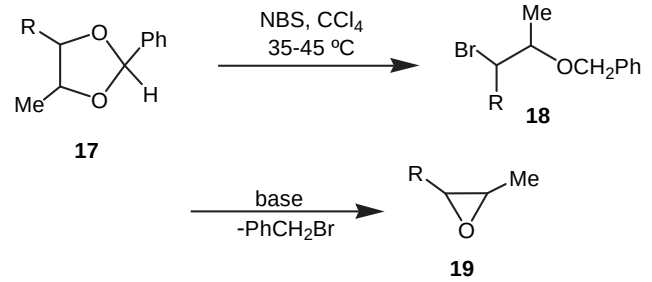


Scheme 12.

solvent-free conditions (Scheme 18). NBS might act as a source for Br^+, which activates the carbonyl group, or with probably generate small quantities of HBr or Br_2, which may be the actual catalysts for the reaction.[40]

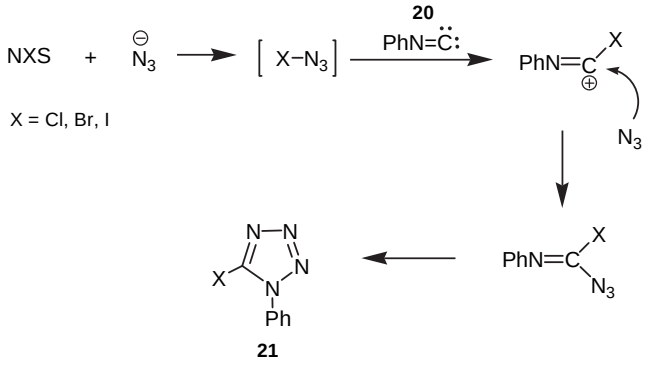
Ghorbani-Vaghei and Veisi have introduced the novel catalytic reagents poly(*N*,*N*′-dichloro-*N*-ethyl-benzene-1,3-disulfonamide) [PCBS] and *N*,*N*,*N*′,*N*′-tetrachlorobenzene-1,3-disulfonamide [TCBDA], for the efficient preparation of bis-indolyl, tris-indolyl, di(bis-indolyl), tri(bis-indolyl), and tetra(bis-indolyl) methanes from indole with various aldehydes and ketones in ethanol, water and in solid-state conditions at room temperature with excellent yields. This method is applicable to a wide range of aldehydes, including aromatic, aliphatic, α,β-unsaturated, heterocyclic substrates, and ketones. In addition, the efficiency, mild reaction conditions, easy work up, simplicity and chemoselectivity of this protocol provide a fast, green, and low-cost procedure for the synthesis of these compounds (Scheme 19).[41]

The benzimidazole ring is an important pharmacophore in modern drug discovery.[42] Benzimidazole derivatives exhibit significant activity against several viruses, such as HIV,[43] influenza,[44] and human cytomegalovirus (HCMV).[45] In addition, benzimidazoles are

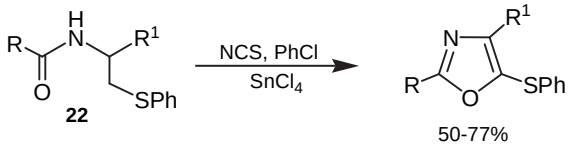


Scheme 13.

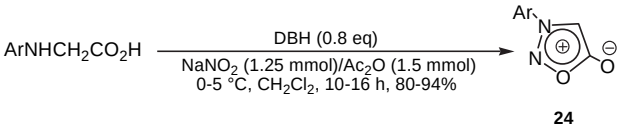
very important intermediates in organic reactions. Therefore, the preparation of benzimidazoles has gained considerable attention in recent years.[46] Medicinal chemists classify them as 'privileged sub-structures' for drug design. Very recently, *N*,*N*,*N*′,*N*′-tetrabromobenzene-1,3-disulfonamide (TBBDA) and poly(*N*-bromo-*N*-ethyl-benzene-1,3-disulfonamide) (PBBS) were found to be mild and effective catalysts for the synthesis of 2-aryl-1-



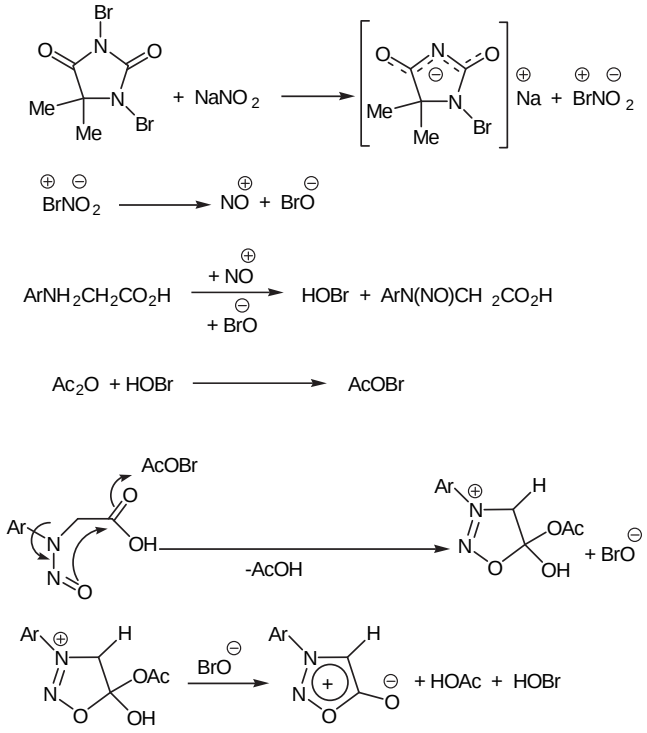
Scheme 14.



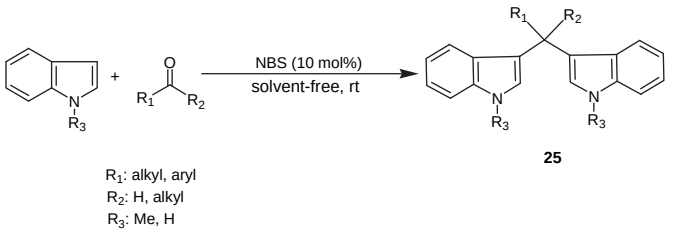
Scheme 15.



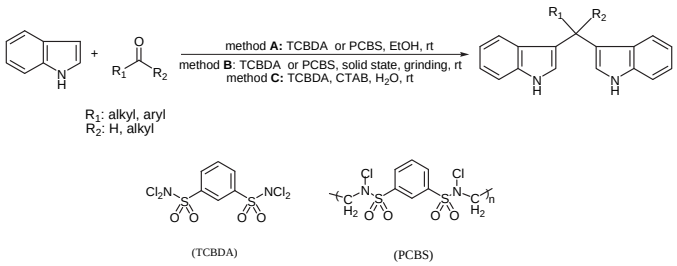
Scheme 16.



Scheme 17.

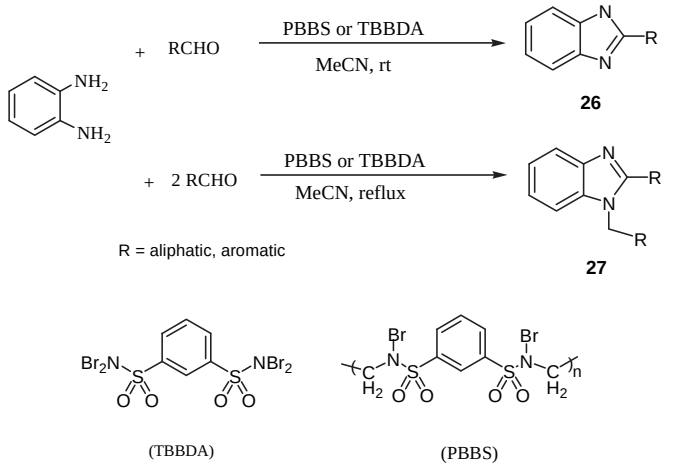


Scheme 18.



Scheme 19.

arylmethyl-1*H*-1,3-benzimidazoles **27** and new reagents for the synthesis of 2-arylbenzimidazoles**26** under mild conditions by the rapid condensation of various aryl aldehydes with *o*-phenylenediamine (OPDA). Moreover, the method has advantages in terms of product yields, selectivity, operational simplicity (easy work up of reactions) and environmental friendliness (non-corrosive reagents) (Scheme 20).[47]

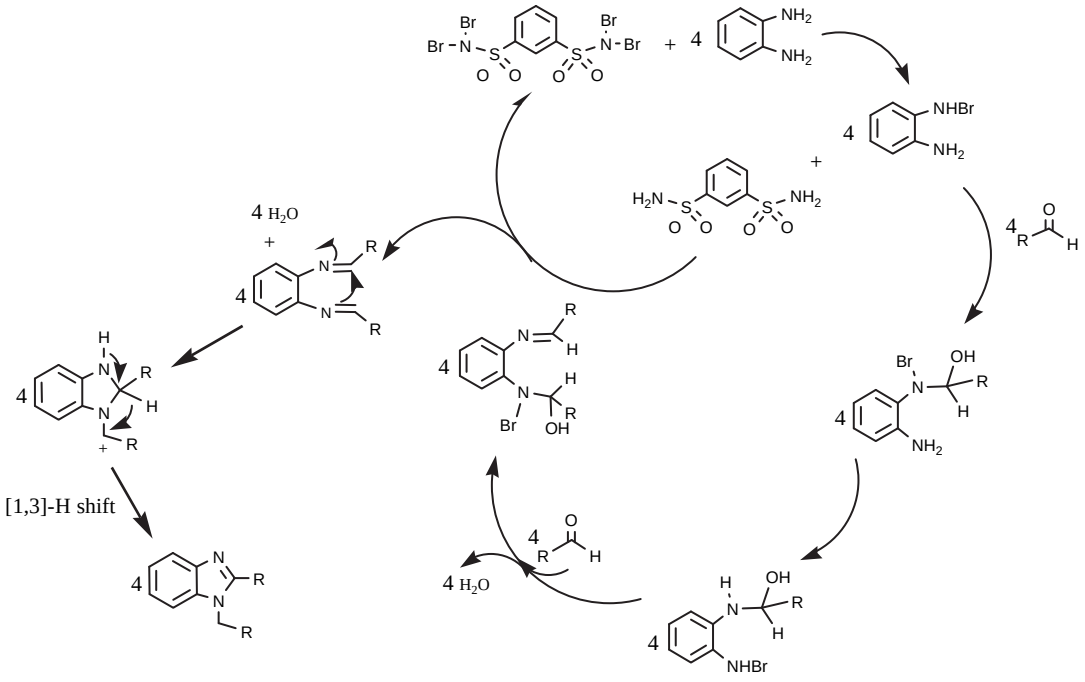


Scheme 20.

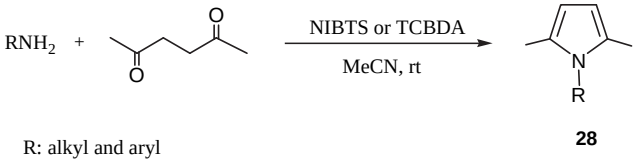
The proposed mechanism for the synthesis of the 1,2-disubstituted benzimidazoles may involve the iminium-catalyzed formation of *N*,*N*′-dibenzylidene-*o*-phenylenediamine, bromination, and ring closure to give a five-member ring, either in a sequential or a concerted manner (Scheme 21).

We have also introduced the novel catalytic reagent, *N*,*N*,*N*′,*N*′-tetrachlorobenzene-1,3-disulfonamide (TCBDA) and the new catalytic reagent, *N*,*N*′-diiodo-*N*,*N*′-1,2-ethandiylbis(*p*-toluenesulfonamide) (NIBTS), for the synthesis of various substituted pyrroles **28** by the Pall–Knorr reaction. The availability, easy synthesis, and reusability of the catalytic reagents, clean workup, and high yield make this method attractive for large-scale operations (Scheme 22).[48]

The reaction conditions were also applicable to the di- or triamino substrates, in giving bipyrrole or tripyrrole compounds **29** (Scheme 23) in excellent yields.



Scheme 21.



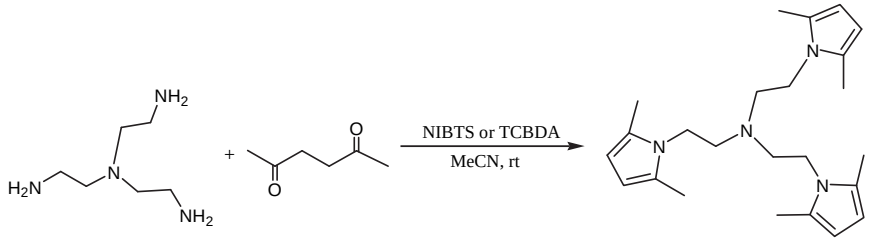
R: alkyl and aryl

28

Scheme 22.

The same workers have also reported an efficient oxathioacetalization, thioacetalization and transthioacetalization of carbonyl compounds in high yields employing NBS as catalyst (Scheme 25).[50]

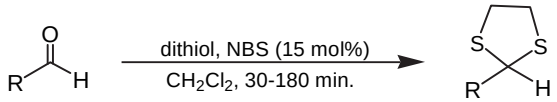
Ding et al. have shown the applicability of trichloroisocyanuric acid (TCCA) as a mild and efficient catalyst for the synthesis of 2-arylbenzothiazoles **31**. 2-Substituted benzothiazoles are conveniently synthesized using a new catalytic protocol that avoids the use of hazardous solvents or toxic metallic catalysts and features a simple workup and easy product isolation (Scheme 26).[51]



29

Scheme 23.

Kamal et al. have described a mild and highly chemoselective procedure for the conversion of aldehydes in the presence of ketones into 1,3-dithiolanes **30** using a catalytic amount of *N*-bromosuccinimide (NBS) under almost neutral reaction conditions (Scheme 24).[49]

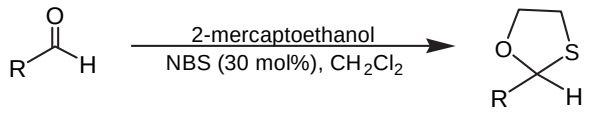


R: aryl, alkyl, alkenyl

30

Scheme 24.

The role of NBS is not clear, but a plausible explanation is that it reacts first with the dithiol to generate HBr, which may activate the carbonyl group for further reaction with dithiol to generate the corresponding product.

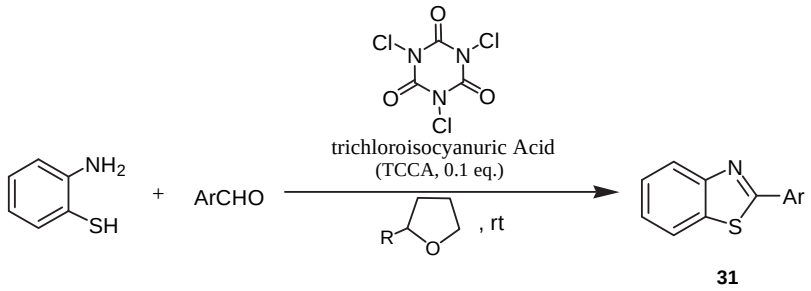


R: aryl, alkyl, alkenyl

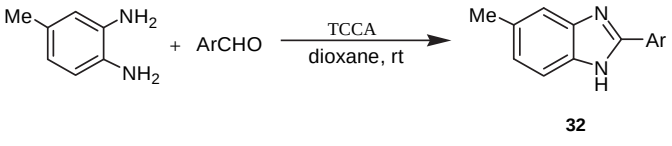
Scheme 25.

Recently, a simple and efficient procedure for the synthesis of benzimidazoles **32** using trichloroisocyanuric acid (TCCA) as the oxidant has been reported by Bigdeli et al. (Scheme 27).[52]

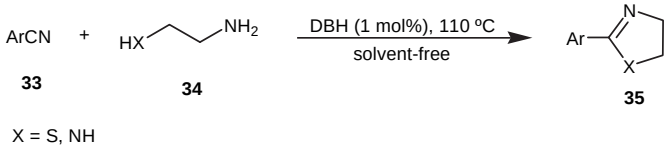
2-Substituted 2-imidazolines have attracted considerable attention in recent years in the development of compounds with pharmacologically useful properties. With such a wide range of potential uses, 2-substituted 2-imidazolines are an important class



Scheme 26.



Scheme 27.



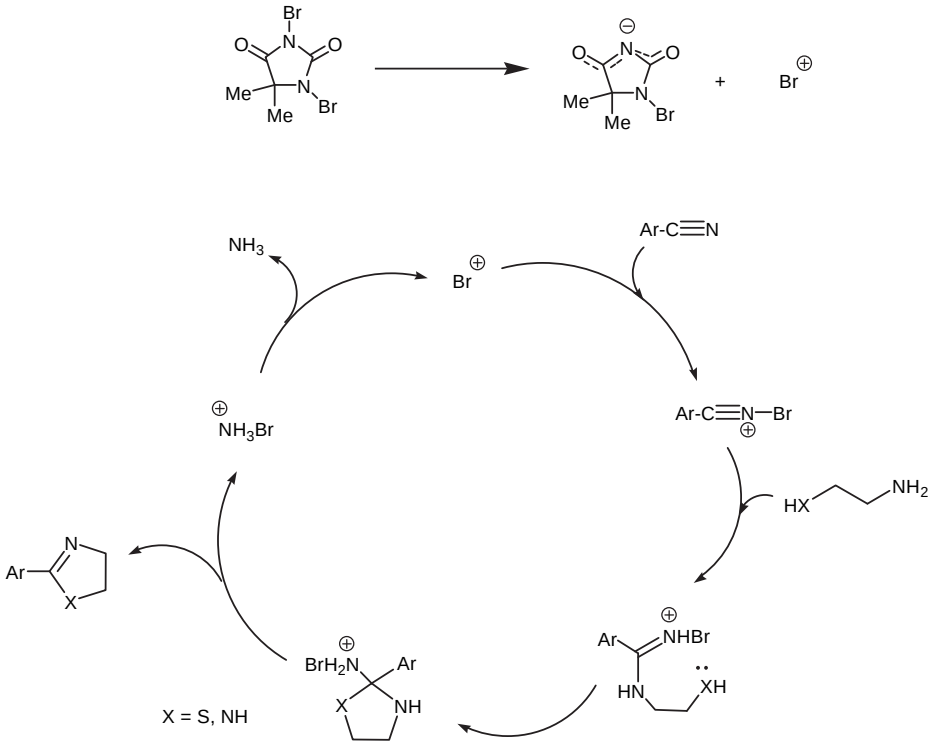
Scheme 28.

of compounds that have attracted increased synthetic interest.[53–58] 1,3-Dibromo-5,5-dimethylhydantoin (DBH) has been used to catalyze the formation of 2-arylimidazolines and 2-arylthiazolines **35** from the condensation of nitriles **33** with ethylenediamine and 2-aminoethanethiol **34** under solvent-free conditions (Scheme 28).[59]

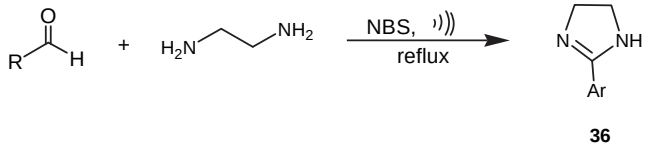
A catalytic cycle has been proposed to explain this reaction, with DBH serving to brominate the nitrile, allowing attack of the amine and subsequent ring closure (Scheme 29).

Marcos et al. have reported the preparation of 2-imidazolines **36** using a highly efficient and environmentally benign synthetic protocol to obtain novel compounds from the reaction of substituted aldehydes and ethylenediamine by ultrasound irradiation with NBS in an aqueous medium in high yields (80–99%) (Scheme 30).[60]

1,3,4-Oxadiazoles are an important class of heterocyclic compounds that have received attention in medicinal chemistry[61] as surrogates of carboxylic acids, esters, and carboxamides. The interest in their synthesis stems from their antimicrobial,[62] antifungal,[63] anti-inflammatory,[64] and antihypertensive[65] activities. They have proved to be useful in materials science as probes utilizing their fluorescence and scintillation properties.[66] In addition, oxadiazole

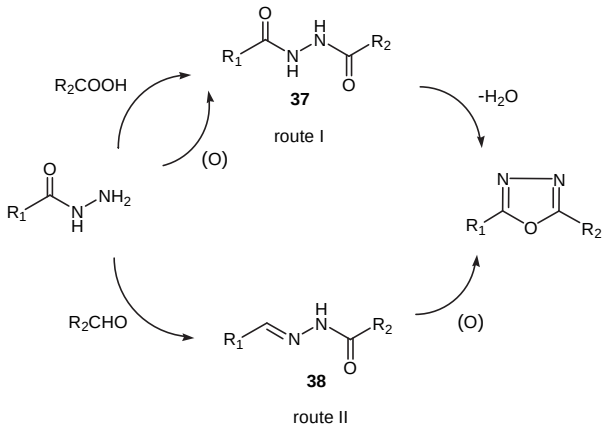


Scheme 29.



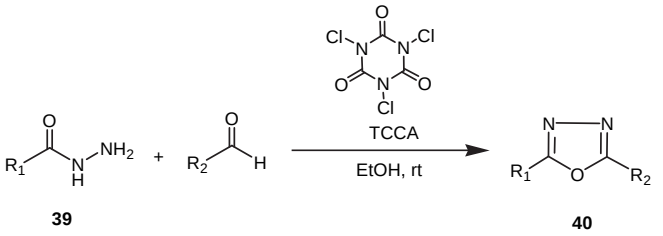
Scheme 30.

derivatives have been widely used as electron-conducting and hole-blocking materials in molecule-based as well as polymeric light-emitting devices (LEDs).[67] Among several multistep approaches reported so far for the synthesis of 1,3,4-oxadiazoles, the cyclodehydration of diacylhydrazines **37** and the oxidative cyclization of acylhydrazones **38** are the most popular (Scheme 31, routes I and II).



Scheme 31.

In 2008, Pore et al. reported an efficient method for the one-pot synthesis of unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles **40** using trichloroisocyanuric acid (TCCA) at ambient temperature (Scheme 32). A wide variety of aromatic as well as heterocyclic aldehydes exhibit condensation with a variety of acylhydrazines **39** followed by oxidative cyclization to yield the corresponding unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles. Moreover, it is



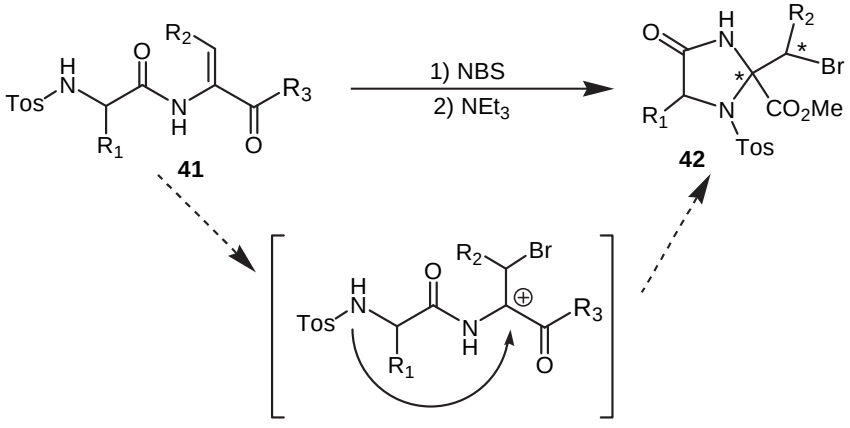
Scheme 32.

worthy of note that variation in the electronic nature of the substituent on the aromatic ring from acylhydrazines has also been successfully used for the synthesis of unsymmetrical 1,3,4-oxadiazoles. The mild nature of the synthesis and the short reaction times are notable advantages of the developed protocol.[68]

Ferreira and his group, in 2007, reported an efficient method for the synthesis of 4-imidazolidinone derivatives in good-to-high yields under mild conditions. When the N-protecting group was 4-tolylsulfonyl **41** the reaction of dehydrodipeptides with NBS afforded the 2,2-disubstituted 1-(4-tolylsulfonyl)imidazolidin-4-ones **42** in good-to-high yields (Scheme 33, compounds **42a**–**f**).[69] These workers believe that the initial step in the formation of these compounds is the bromination of the dehydroamino acid residue by NBS. This is followed by cyclization, which occurs by nucleophilic attack of the nitrogen atom of the sulfonamide moiety on the α-carbon atom of the second amino acid residue. The results show that the presence of the 4-tolylsulfonyl group is essential for the intramolecular cyclization.

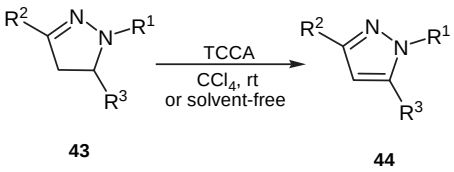
N-Halo reagents have also been applied for the aromatization of cyclic compounds. TCCA was used for the oxidation of 1,3,5-trisubstituted pyrazolines **43** to their corresponding pyrazoles **44** under either heterogeneous or solvent-free conditions in good yields at room temperature (Scheme 34).[70]

Dehydrogenation of a variety 2-imidazolines **45** to the corresponding imidazoles **46** was achieved by TCCA in the presence of DBU (Scheme 35).[71] Chemoselective oxidation of these compounds was successfully carried out in the presence of sulfides and alcohols.



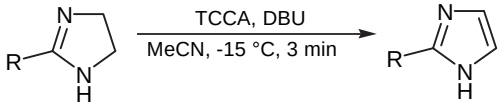
R_1	R_2	Reagent	Product	Yield (%)
H	H	**41a**	**42a**	92
Me	H	**41b**	**42b**	88
H	Me	**41c**	**42c**	94
Me	Me	**41d**	**42d**	74
H	Ph	**41e**	**42e**	86
Me	Ph	**41f**	**42f**	91

Scheme 33.



43 **44**

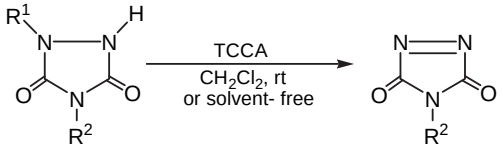
Scheme 34.



45 **46**

Scheme 35.

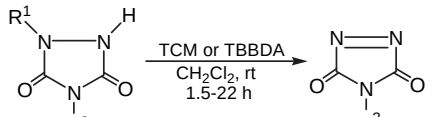
TCCA was used for the oxidation of urazoles **47** and bis-urazoles to their triazolinediones **48** under both heterogeneous and solvent-free conditions with excellent yields at room temperature (Scheme 36).[72]

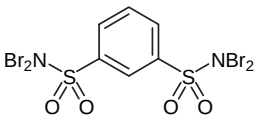


47 **48**

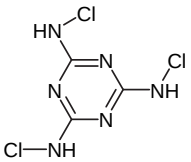
Scheme 36.

TBBDA and TCM were used as effective oxidizing agents for the conversion of urazoles and bis-urazoles into the corresponding triazolinediones under mild and heterogeneous conditions at room temperature with good-to-excellent yields (Scheme 37).[73]





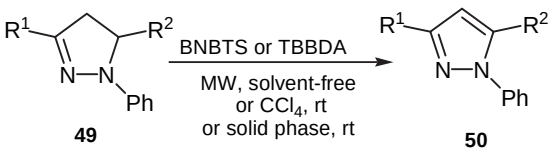
N,N′,N,N′-tetrabromobenzene-1,3-disulfonamide (TBBDA)



trichloromelamine (TCM)

Scheme 37.

N,N,N′,N′-Tetrabromobenzene-1,3-disulfonamide (TBBDA), BNBTS, and PBBS were used as efficient reagents for the oxidation of 1,3,5-trisubstituted pyrazolines **49** to their corresponding pyrazoles **50** in solvent-free conditions under microwave irradiation or room temperature (Scheme 38).[74–77]

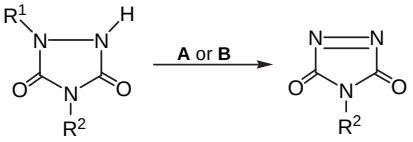


49 **50**

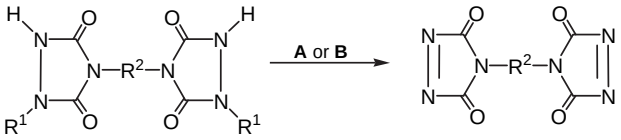
R^1, R^2 = Aryl

Scheme 38.

DBH has also been used for the efficient oxidation of uraazoles and bis-urazoles to their corresponding triazolinediones in solution and under solvent-free conditions (Scheme 39).[78]



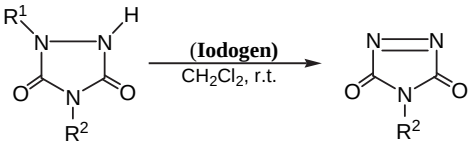
A: DBH (1 mmol), 2 h, 96-100%, CH_2Cl_2, rt
B: DBH (1 mmol), 2 h, 7-100%, solvent-free, rt

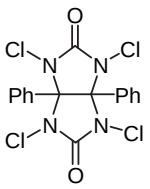


A: DBH (2 mmol), 4 h, 99-100%, CH_2Cl_2, rt
B: DBH (2 mmol), 4 h, 33%, solvent-free, rt

Scheme 39.

Khoramabadi-Zad et al. have described iodogen as a novel reagent for the efficient and practical oxidation of urazoles and bis-urazoles under heterogeneous conditions. This system could be used for the oxidation of a range of urazoles under mild and safe conditions (Scheme 40).[79]

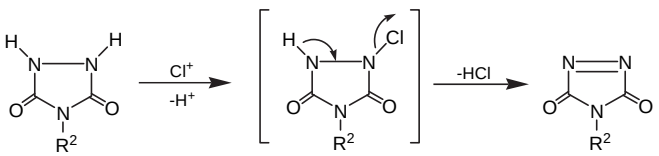




1,3,4,6-Tetrachloro-3a,6a-diphenylglycoluril (**iodogen**)

Scheme 40.

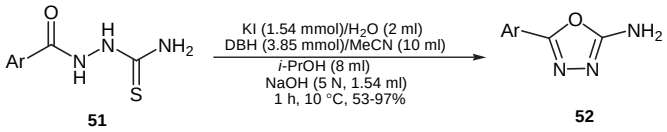
A plausible mechanism for this reaction involves in situ-generated chlorine cations acting as the oxidizing species. Subsequent elimination of hydrogen chloride then yields the 1,2,4-triazole-3,5-dione (Scheme 41).



Scheme 41.

Rivera et al. reported a suitable method for the synthesis of 5-substituted-2-amino-1,3,4-oxadiazoles **52**, as biologically active important molecules, via oxidative cyclization of thiosemicarbazides **51** using DBH in the presence of potassium iodide (Scheme 42).[80] The main advantage of this method is its applicability for the large-scale synthesis of the hydroxyl oxadiazoles.

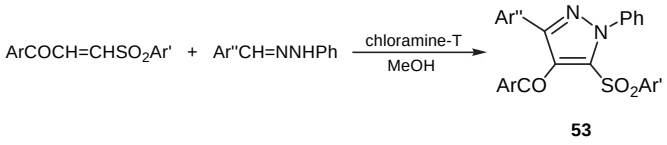
2-Pyrazolines **53** and 2-isoxazolines have been prepared by the reaction of araldehyde hydrazones and aldoximes with bifunctional



51 52

Scheme 42.

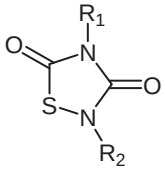
olefins in the presence of chloramine-T. The generated 2-pyrazolines were also oxidized to the corresponding pyrazoles in the course of the reaction (Scheme 43).[81]



53

Scheme 43.

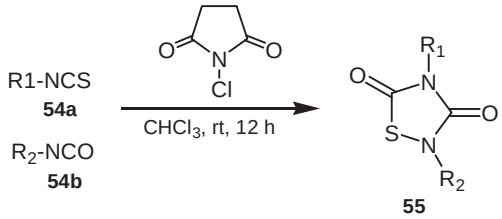
The thiadiazolidinone (TDZD) ring system (Fig. 1) possesses several interesting pharmacological properties.[82–86] In particular, 2,4-disubstituted TDZD derivatives inhibit the enzyme, glycogen synthase kinase 3β (GSK3β).[83,84] GSK-3β has been shown to be involved in several important cellular functions, and inhibitors of this enzyme are believed to have therapeutic potential in the treatment of disorders such as type-II diabetes and manic depression. Recently, it has also been reported that such derivatives possess potent antileukemic properties.[86] In spite of the therapeutic potential of the TDZD analogs, however the chemistry of this heterocycle remains relatively underexplored.



Thiadiazolidinone (**TDZD**) ring system

Figure 1.

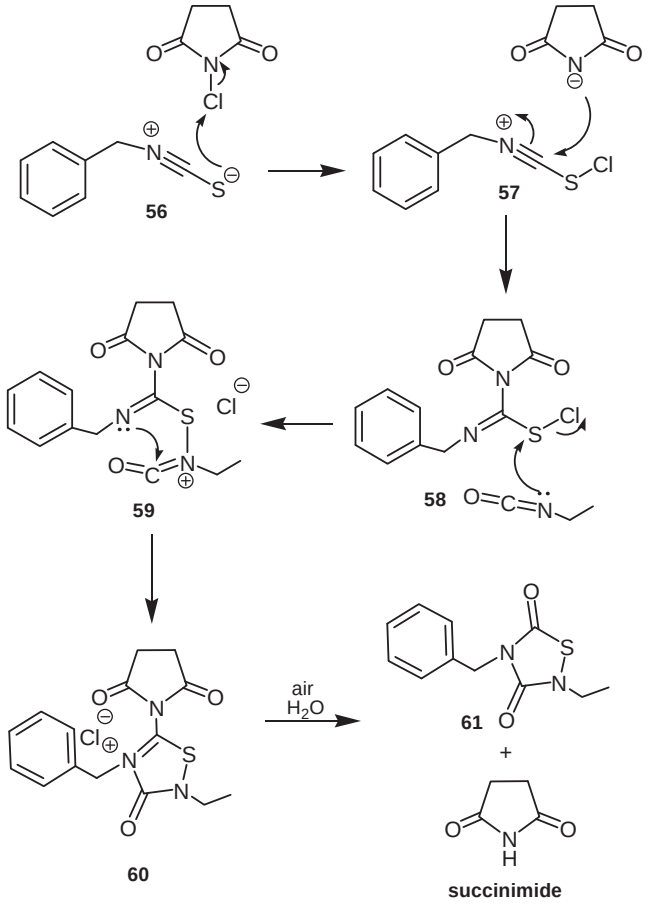
Recently, Crooks et al. have shown that, out of a variety of halogen equivalents examined, NCS was found to be the only halogenating agent that initiates the reaction pathway for the oxidative condensation of isothiocyanates **54a** with isocyanates **54b** to yield 1,2,4-thiadiazolidine-3,5-diones **55**. Compared to the classically used reagents for this transformation (i.e., chlorine gas or SO_2Cl_2), NCS is a safer and a more convenient alternative reagent for the preparation of 1,2,4-thiadiazolidine-3,5-diones (Scheme 44).[87]



55

Scheme 44.

The experiments suggested that NCS oxidizes the isothiocyanate functional group in a classical ionic manner, involving an initial oxidative reaction of NCS with isothiocyanate, as shown in Scheme 45, which illustrates a postulated mechanism for the reaction of NCS with benzyl isothiocyanate **56** and ethyl isocyanate. The initial electrophilic attack of the sulfur of **56** on the chlorine of NCS affords **57**, which is immediately converted into **58**. Sulfenyl chloride **58**

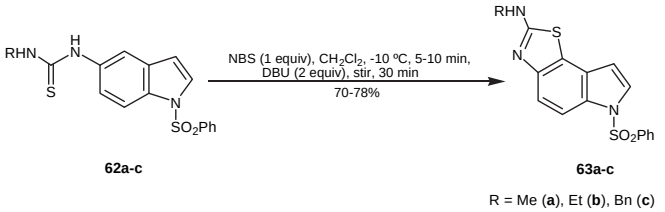


56 57 58 59 60 61

Scheme 45.

would then be capable of undergoing an electrophilic attack by the nitrogen of ethyl isocyanate, forming the highly electrophilic species **59**, followed by cyclization to **60**. Iminium chloride **60** would then undergo hydrolysis when exposed to air, yielding **61** and succinimide.

Thiazoles are important heterocycles and continue to be synthetic targets, because thiazolyl-(hetero)arenes and several classes of annulated thiazoles display a diverse array of biological activities.[88] NBS has been used for the cyclisation of thioureido-(hetero) arenes **62** to thiazolo(hetero)arenes **63** (Scheme 46). Accordingly, each of **62a–c** was separately treated with NBS in dichloromethane at −10 °C and then with DBU, and the substrates cyclised rapidly and regioselectively to 6-benzenesulfonyl-2-alkylamino-thiazolo [5,4-*e*]indoles **63a–c** in good yields.[89]

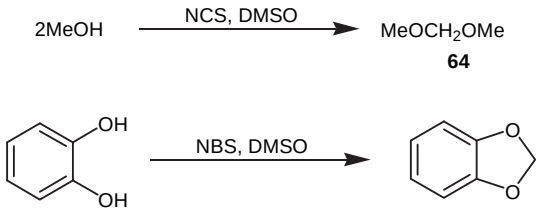


62a-c 63a-c

R = Me (**a**), Et (**b**), Bn (**c**)

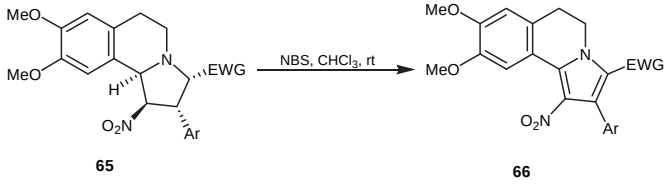
Scheme 46.

A preparative procedure for synthesizing formaldehyde acetals, such as **64** has been 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 (Scheme 47).[90]



Scheme 47.

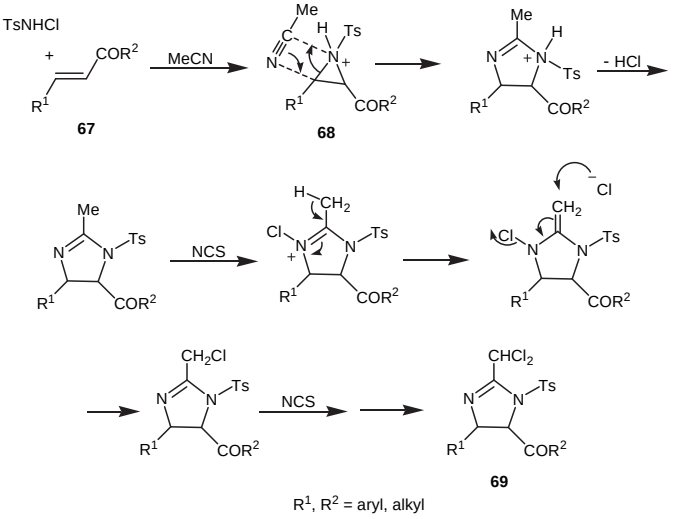
Considerable interest has been shown in substituted pyrrolo[2,1-*a*]isoquinolines, due to their diverse biological activities.[91,92] Nyerges et al. have discovered a new method for converting 1,2,3,5,6,10*b*-hexahydropyrrolo[2,1-*a*]isoquinolines **65** into 5,6-dihydropyrrolo[2,1-*a*]isoquinolines **66** using *N*-bromosuccinimide as an oxidant (Scheme 48).[93]



65 66

Scheme 48.

A new regio-, stereo-, and chemoselective method has been elaborated for the synthesis of 2-dichloromethylimidazoline derivatives **69** by the reaction of enones **67** with *p*-toluenesulfonamide and NCS as nitrogen and chlorine sources, respectively (Scheme 49).[94] A proposed mechanism for this electrophilic reaction involves the formation of aziridinium intermediates **68** from the interaction of TsNHCl with olefins and a new [2+3] cycloaddition via aziridinium ring opening. In this reaction, it was not possible to replace NCS by NBS. Acidic hydrolysis of the product imidazolines afforded vicinal diamines, important intermediates in the synthesis of pharmaceutically valuable compounds.

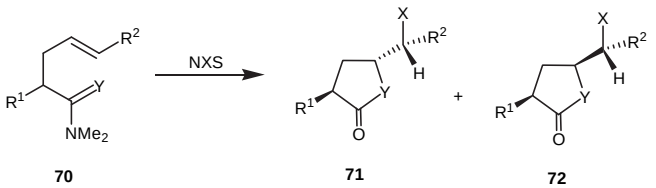


67 68 69

R1, R2 = aryl, alkyl

Scheme 49.

α-Substituted γ,σ-unsaturated amides and thioamides **70** underwent halocyclization to γ-butyrolactones **71** and **72** with several electrophiles, including NCS and NBS (Scheme 50).[95] 1,3-Asymmetric trans induction was most pronounced for NBS (>99:1); for NCS, the ratio of **71** to **72** was reduced to 3:2.95.

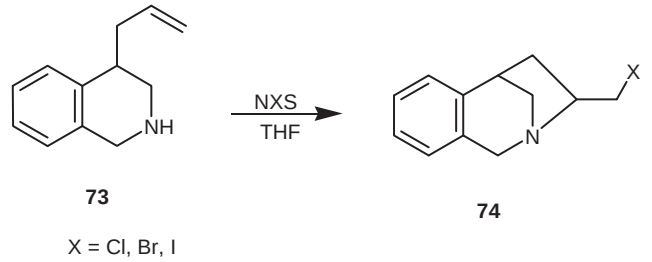


70 71 72

R1 = Me, Bn; R2 = Me, H; Y = O, S; X = Cl, Br

Scheme 50.

N-Halosuccinimides were used to carry out the halocyclization of 4-allyl-1,2,3,4-tetrahydroisoquinoline **73** to azabicyclo[3.2.1]heptanes **74** via a 5-*exo*-*trig* route (Scheme 51).[96]

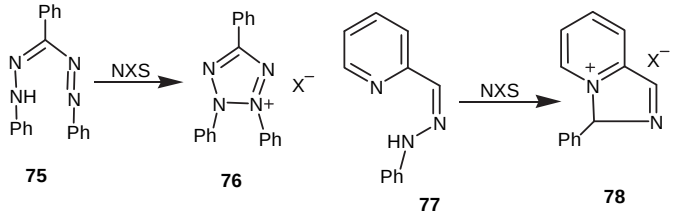


73 74

X = Cl, Br, I

Scheme 51.

Treatment of triphenylformazanes **75** with NCS (or NBS) resulted in cyclodehydration and the formation of 2,3,5-triphenyltetrazolium halides **76**. Similarly, *syn* phenylhydrazones of 2-pyridinealdehyde **77** afforded 8-azaindazolium salts **78** (Scheme 52).[97]



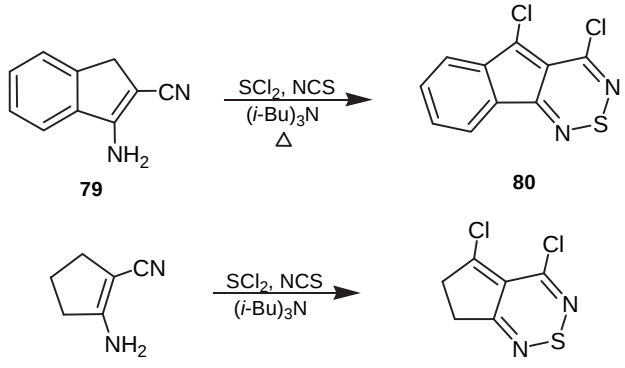
75 76 77 78

X = Cl, Br

Scheme 52.

4. Six-membered heterocycles

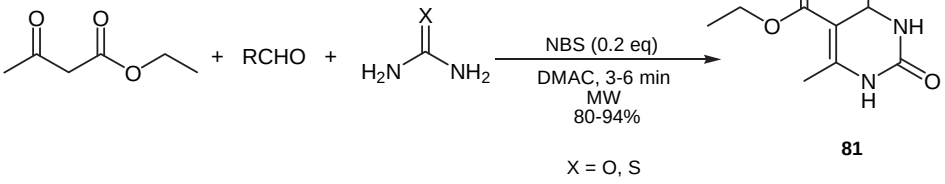
3-Amino-1*H*-indene-2-carbonitrile **79** reacted with sulfur dichloride in triisobutylamine and NCS to give the corresponding indeno[1,2,6]thiadiazine **80** in a reaction that involved dehydrogenation and chlorination of the cyclopentathiazine moiety (Scheme 53).[98]



79 80

Scheme 53.

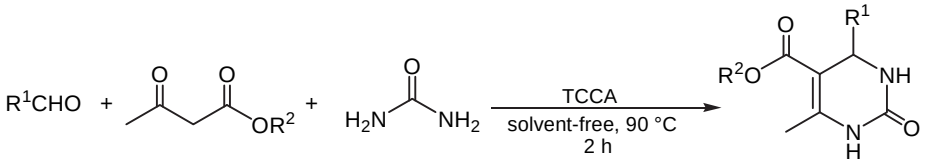
Dihydropyrimidinones (DHPMs) have attracted considerable attention, because of their wide spectrum of biological and therapeutic activities. Functionalized dihydropyrimidinones have been used as potent calcium channel blockers,[99] antihypertensive agents,[100] and neuropeptide Y antagonists.[101] Some marine natural products containing the dihydropyrimidinone-5-carboxylate unit such as batzelladine alkaloids have been found to be potent HIV (gp-120-CD4) inhibitors.[102] Thus, the synthesis of these heterocyclic compounds is of much current importance. The first protocol to prepare the compounds of this type was presented by Biginelli in 1893 and involved a three-component, one-pot condensation.[103,104] NBS has been reported as a mild, efficient and natural catalyst for the preparation of dihydropyrimidinones **81** under microwave irradiation (Scheme 54).[105]



81

Scheme 54.

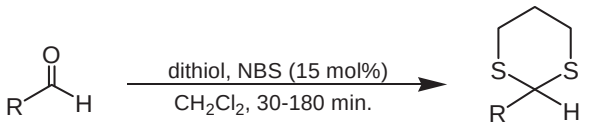
TCCA was used efficiently for the synthesis of 3,4-dihydropyridin-2(1*H*)-ones **82** through the three-component Biginelli reaction of a β-ketoester, an aldehyde and urea (Scheme 55).[106]



82

Scheme 55.

Kamal et al. have described a mild and highly chemoselective procedure for the conversion of aldehydes in the presence of ketones into 1,3-dithianes **83** using a catalytic amount of *N*-bromosuccinimide (NBS) under almost neutral reaction conditions (Scheme 56).[49]

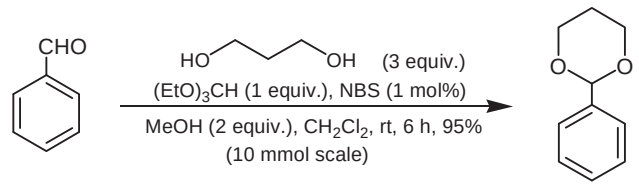


83

R: aryl, alkyl, alkenyl

Scheme 56.

Various types of carbonyl compounds were converted into the corresponding 1,3-dioxanes, such as **84** in the presence of ethyl orthoformate, 1,3-propanediol, and a catalytic amount of NBS via an in situ acetal exchange process (Scheme 57).[107]

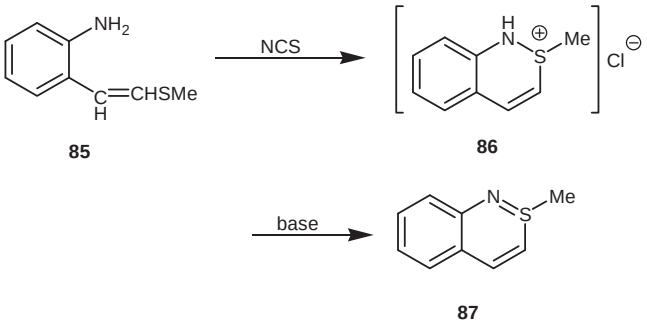


84

Scheme 57.

Aromatic amines having an alkylthio group in the *ortho* position, e.g., **85**, react with *N*-chlorosuccinimide to give cyclic aminosulfonium salts **86**, which are converted into cyclic sulfimides **87** in the presence of bases (Scheme 58).[108]

Indole and its myriad of derivatives continue to capture the attention of organic chemists. Several new indole-ring syntheses have been developed over the years and this trend is still ongoing.[109]

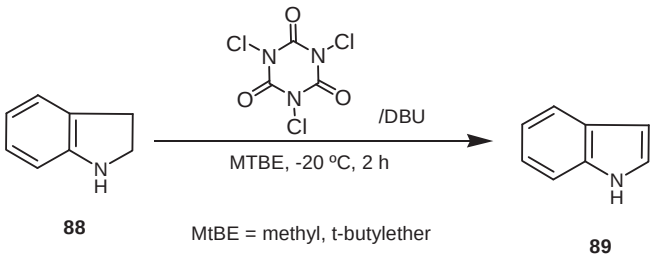


85 **86** **87**

Scheme 58.

Indoles bearing various substituents on the benzene ring often have potent physiological activities and can be useful intermediates for the synthesis of indole alkaloids. Synthetic interconversion of substituted indoles and the corresponding dihydro derivatives (indolines) is an important process, giving access to uncommonly substituted indoles.[110] The conversion of the indole ring into an indoline ring can easily be accomplished by catalytic hydrogenation or reduction with sodium cyanoborohydride in acetic acid. For the dehydrogenation of indolines to indoles, although studied extensively, there has, up to now, never been an efficient general method.

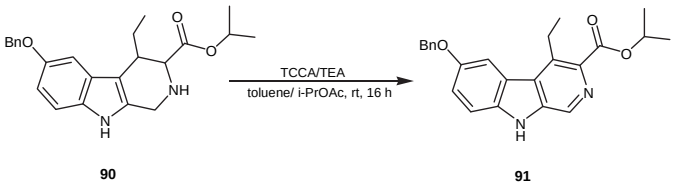
Tilstam et al. have reported a new mild and efficient dehydrogenation of indolines **88** to indoles **89**. For the dehydrogenation, trichloroisocyanuric acid is used in combination with DBU. After workup with sodium hydrogen sulfite, it was possible to obtain the indole in almost quantitative yield. The new method is also suitable for indolines bearing electron-withdrawing or -donating groups. Under these reaction conditions, no ring chlorination was observed (Schemes 59 and 60).[111]



88 89

Scheme 60.

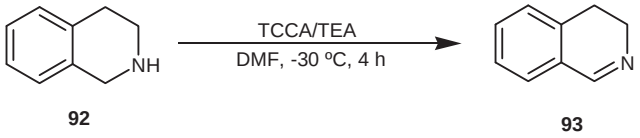
In another development project, the aromatization of a tetrahydro-β-carboline **90** with TCCA and TEA was successfully used for a scaleup to 15 kg in a pilot plant to produce **91** (Scheme 61).[112]



90 91

Scheme 61.

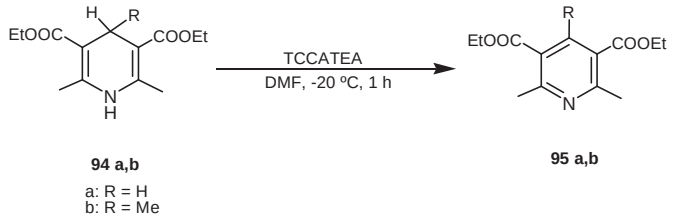
3,4-Dihydroisoquinoline **93** is a useful precursor for the synthesis of isoquinoline alkaloids. Using TCCA/TEA, 3,4-dihydroisoquinoline **92** could easily be obtained in high yield under mild conditions without being contaminated with larger amounts of the corresponding isoquinoline or the 1,2,3,4-tetrahydroisoquinolin-1-one normally seen in oxidations of tetrahydroisoquinoline (Scheme 62).[113] 3,4-Dihydroisoquinoline **93** was obtained in 88% yield.



92 93

Scheme 62.

1,4-Dihydropyridines are intermediates in the Hantzsch pyridine synthesis, one of the most useful pyridine-ring synthesis, and there is a demand for a general and convenient method for their oxidation to the corresponding pyridines. A variety of oxidizing agents, viz. HNO_3, PCC, $KMnO_4$, CAN, and *tert*-butyl hydroperoxide, at elevated temperature have been reported.[114] The use of TCCA/TEA was found to be very efficient for the dehydrogenation of 1,4-dihydropyridines.[115] Two cases, **94a** and **b**, were studied. In both cases, an almost quantitative yield of the pyridine derivatives **95a** (92%) and **95b** (95%) was obtained. In the case of **95b**, no demethylation was observed, a major obstacle reported with other methods (Scheme 63).

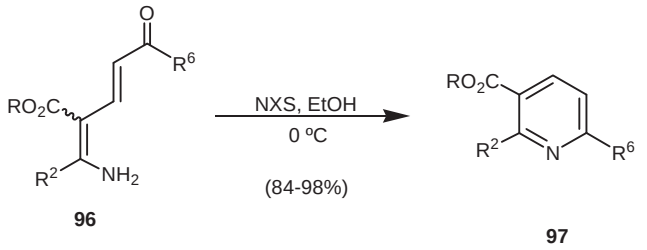


94 a,b
a: R = H
b: R = Me

95 a,b

Scheme 63.

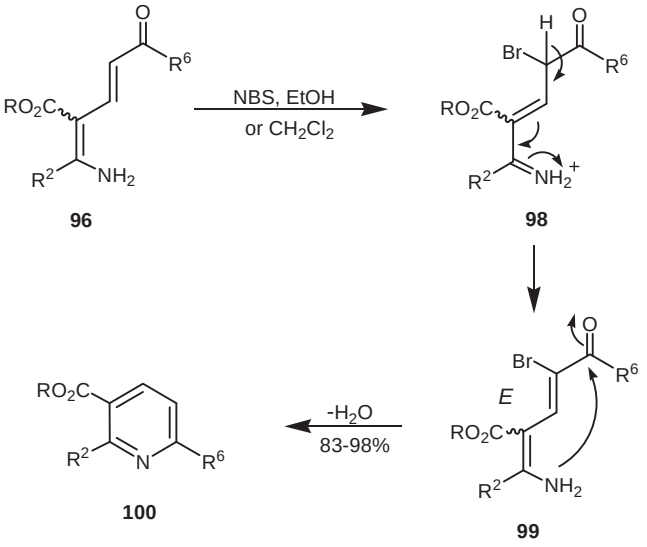
N-Halosuccinimide-mediated processes provide complementary and efficient routes to either 2,3,5,6-tetrasubstituted or 2,3,6-trisubstituted pyridines **97** under mild conditions. The reaction of Bohlmann–Rahtz intermediates, generated by Michael addition of an enaminoester and ethynyl ketones **96**, with *N*-bromosuccinimide provides facile access to 5-bromopyridines, whereas treatment of the same aminodienone intermediates with *N*-iodosuccinimide facilitates the rapid cyclodehydration of these substrates at a comparatively low temperature (Scheme 64).



96 97

Scheme 64.

The course of the reaction was rationalized by considering an initial regioselective addition to give *s-cis* bromide **98**, in equilibrium with the *s-trans* conformer (Scheme 65).[116] Facile deprotonation, rather than intramolecular nucleophilic substitution, prevents the formation of the pyrrole and gives instead the (4*E*)-hexadienone intermediate **99**, avoiding the need for double bond isomerization. This will undergo spontaneous cyclodehydration under mild reaction conditions to give the pyridine **100**. This method provides 5-substituted pyridines possessing latent functionality suitable for subsequent elaboration, a substitution pattern hitherto unavailable by the traditional Bohlmann–Rahtz methodology.



96 98 99 100

Scheme 65.

4-Chloroisocoumarins **101** are effective irreversible inhibitors of serine proteases[117] and potent inhibitors of amyloid peptide production.[118] Since there is a remarkable similarity in bioactivities between the carbon species and their phosphorus counterparts,[119] it would be anticipated that phosphorus 4-chloroisocoumarin analogs **102**–**104** might have potential bioactivities similar to those of the 4-chloroisocoumarins (Fig. 2).

A series of 4-halophosphaisocoumarins **103** and **104** were prepared with high regioselectivity in good-to-excellent yields under mild conditions by the reaction of 2-(1-alkynyl)phenylphosphonic acid monoesters **105** with NBS or NCS in DMF (Scheme 66).[120] Halocyclization reactions have been strongly affected by the substituents of the substrates, reaction solvents and electrophiles, which could be rationalized by the proposed mechanisms in Scheme 67.

Electrophilic addition of NBS or NCS to the C–C triple bond might form the corresponding intermediates **106**, **107** or **108**; their

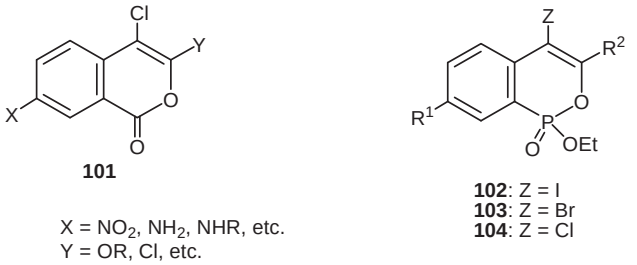
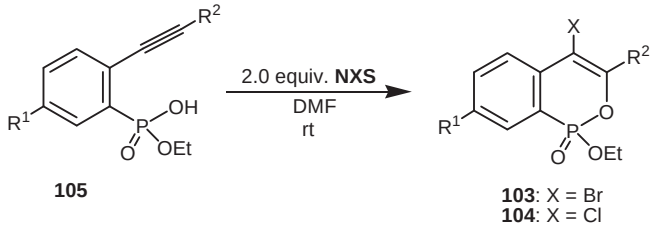


Figure 2.

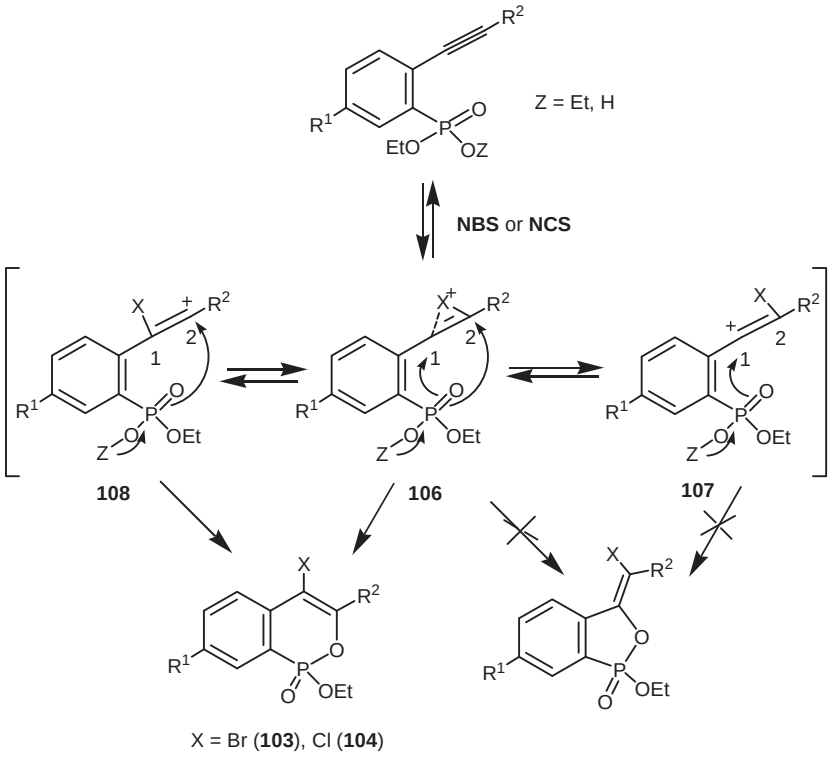


Scheme 66.

103 or **104**. Alternatively, the phosphonyl oxygen might also attack on position 1 of **106** or **107** to give the five-membered ring products. All the examined substrates, however, showed high regioselectivity for six-membered ring products, indicating that the 5-*exo*-dig process was very disadvantageous for 2-(1-alkynyl)phenylphosphonates. The observed regioselectivity might be caused by the following factors: (1) the longer bond lengths of C–P and P–O would make the phosphonyl oxygen much closer to the farther position of the triple bonds; and (2) the tetrahedral phosphonates might further increase the ring strain and lower the stabililty of the corresponding five-membered ring products.

In 2005, Hajra and his group have developed a Lewis acid-catalyzed intramolecular halo-arylation of alkenes **109** to **110** using inexpensive and easily available *N*-halosuccinimides (NXS) as the halogen source (Scheme 68).[121] This catalytic process is a region- and stereoselective method and is utilized to synthesize a diverse range of structural motifs, e.g., chromanones, chromans, quinolones, tetrahydroquinolines, and tetralins with halo-functionality **111**.

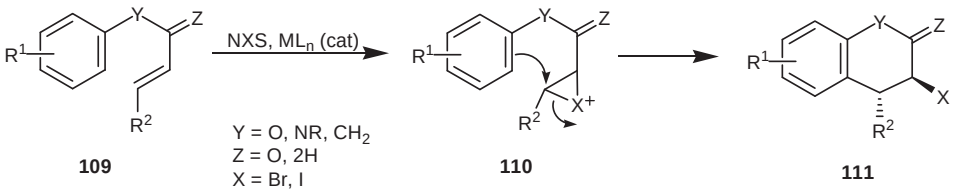
Quinolines are an important group of heterocyclic compounds. Several derivatives have been found to possess useful biological properties, such as antimalarial, antibacterial, anti-asthmatic,



Scheme 67.

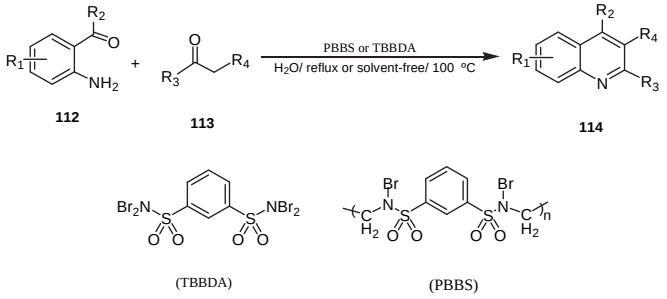
stabilities and the nucleophilicity of the phosphonyl oxygen play crucial roles in determining whether the alkynylphosphonates will cyclize. Intramolecular nucleophilic attack by the phosphonyl oxygen on position 2 of **106** or **108** would give the desired products

antihypertensive, and anti-inflammatory activities.[122–126] In addition, quinolines are valuable synthons for the preparation of nano and *meso* structures with enhanced electronic and photonic functions.[127–130] As a result of their importance as substructures in



Scheme 68.

a broad range of natural and designed products, a significant effort continues to be directed toward the development of new quinoline-based structures and new methods for their construction.[131] Thus, the synthesis of quinolines is an important and useful task in organic chemistry. Friedländer annulation is a straightforward method for the synthesis of these compounds[132,133] involving a condensation followed by a cyclodehydration between 2-aminoaryl ketones and α-methylene ketones, and is catalyzed by both acids and bases. Poly(*N*-bromo-*N*-ethyl-benzene-1,3-disulfonamide) [PBBS] and *N*,*N*,*N*′,*N*′-tetrabromobenzene-1,3-disulfonamide [TBBDA] were used as efficient reagents for the synthesis of quinolines **114** in excellent yields from 2-aminoaryl ketones **112** and carbonyl compounds **113** under aqueous and solvent-free conditions (Scheme 69).[134]



Scheme 69.

Cyclic sulfonamides (sultams) are a very important class of compounds, because they possess anti-inflammatory,[135] antimalarial,[136] and anti-HIV activities.[137] In particular, *anti*-dihydro-2,1-benzothiazine 2,2-dioxides (benzosultams) have potent lipoxygenase inhibitory activities and IL-8 receptor antagonist activities and are used as drugs for heart diseases (Fig. 3).[138,139] Therefore, intensive studies of the preparation of benzothiazine derivatives have been carried out.

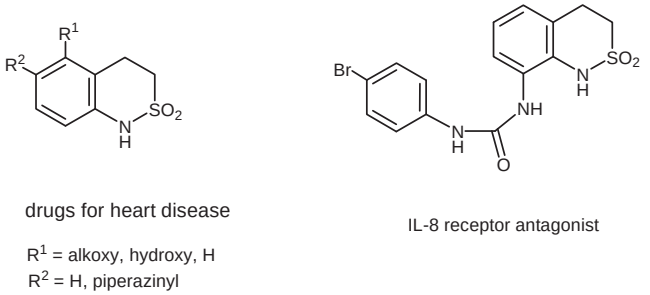
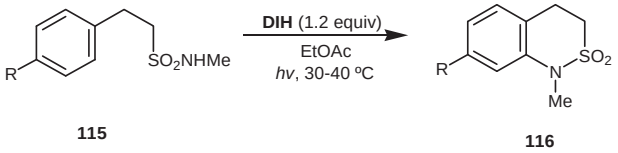


Figure 3.

1,3-Diiodo-5,5-dimethylhydantoin (DIH) is suitable for the preparation of the 3,4-dihydro-2,1-benzothiazine 2,2-dioxide skeleton **116** from *N*-methyl or *N*-benzyl 2-arylethanesulfonamides **115**, and the 1,2,3,4-tetrahydroquinoline skeleton from *N*-3-arylpropyltrifluoromethanesulfonamides under irradiation with a tungsten lamp. All these reaction proceed through the formation of an N–I bond in sulfonamides with DIH, the formation of a sulfonamidyl radical via hemolytic *N*–I bond cleavage, and the subsequent cyclization into the aromatic ring, followed by the oxidation of the aromatic rings with DIH, as shown in Scheme 70.[140]

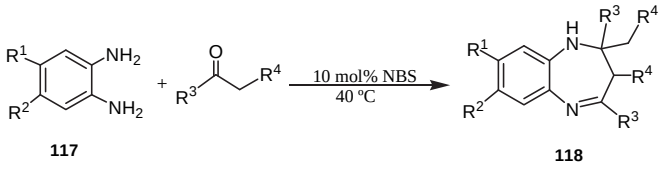


Scheme 70.

5. Seven-membered heterocycles

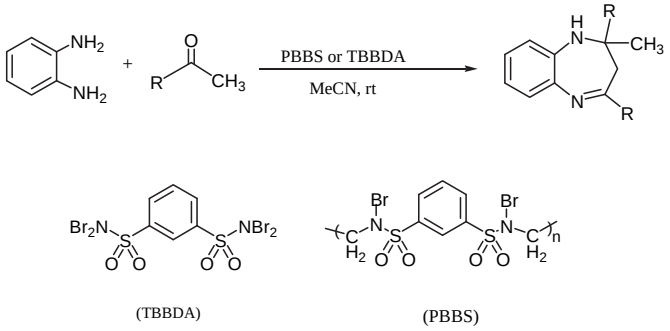
1,5-Benzodiazepines are important heterocyclic compounds from the point of view of biological activities.[141–144] General methods for preparing these compounds include the condensation of 1,2-phenylenediamine with α,β-unsaturated carbonyl compounds or β-haloketones.[145] As the condensation partners, ketones have also been used;[146] in this case, 1,2-phenylenediamine and 2 equiv of ketone were condensed through an intramolecular imine–enamine cyclization. Instead of 1,2-phenylenediamine, *o*-nitrophenyl azide, and *o*-nitroaniline have been used in the presence of a reducing reagent such as SmI_2 and $TiCl_4$/Sm.[147–150] In addition, the condensation of aldehydes with enamines prepared from 1,2-phenylenediamine was also reported.[151] Although these methods were useful and the products from each method were not similar, it is desirable to develop the reaction to readily provide divergent 1,5-benzodiazepine derivatives.

Various biologically important 1,5-benzodiazepines derivatives **118** were efficiently synthesized in excellent yields using catalytic amounts of NBS (10 mol %). This inexpensive, nontoxic, and readily available catalyst efficiently catalyzes the condensation of several aromatic, as well as aliphatic, ketones with substituted *o*-phenylenediamines **117** (Scheme 71).[152]



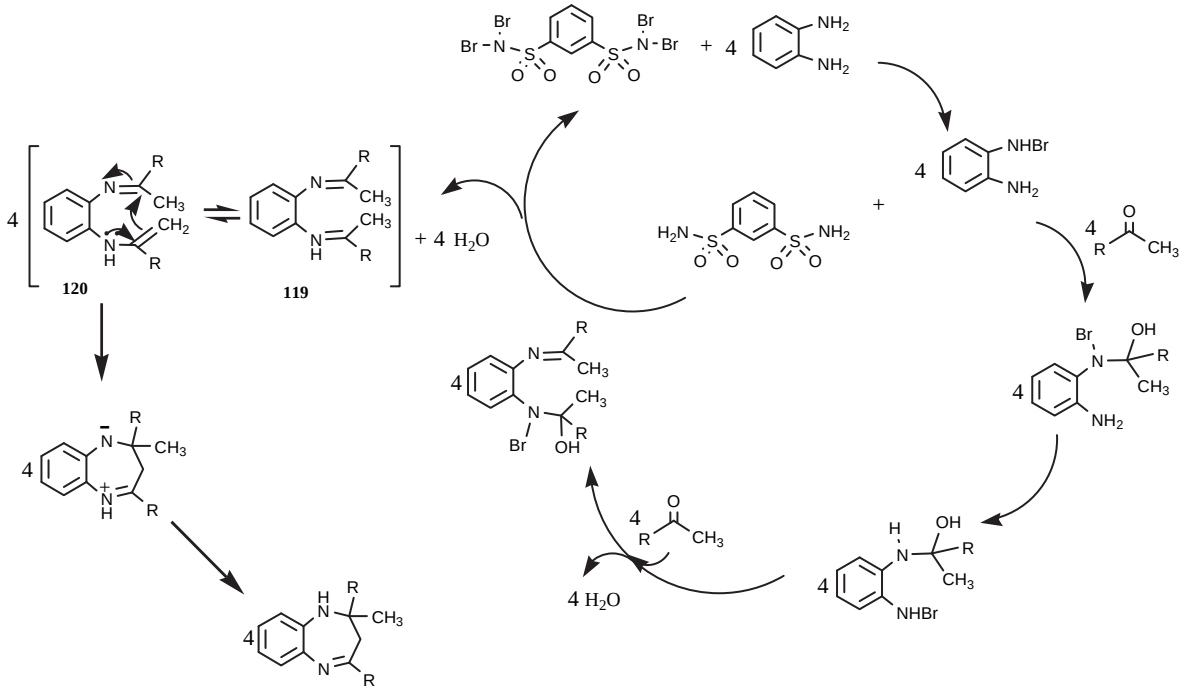
Scheme 71.

In 2009, we reported that *N*,*N*,*N*′,*N*′-tetrabromobenzene-1,3-disulfonamide (TBBDA) and poly(*N*-bromo-*N*-ethyl-benzene-1,3-disulfonamide) (PBBS) can be used as catalytic reagents for the synthesis of 1,5-benzodiazepines under mild conditions by the rapid condensation of various ketones with *o*-phenylenediamine (OPDA). Moreover, the method has advantages in terms of product yields, selectivity, operational simplicity (easy work up of reactions), and environmental friendliness (non-corrosive reagents) (Scheme 72).[153]



Scheme 72.

The mechanism of the condensation reaction could involve an intramolecular imine–enamine cyclization promoted by TBBDA or PBBS, as shown in Scheme 73. The amine of *o*-phenylenediamine is first activated by TBBDA or PBBS and then attacks the carbonyl group of the ketone, giving the intermediate diimine **119**. A 1,3-shift of the hydrogen attached to the methyl group then occurs to form an isomeric enamine **120**, which cyclizes to afford a seven-membered ring.



Scheme 73.

6. Conclusions

It should be noted that a correct and updated citation and literature survey is very important for researchers to find relevant information, to pioneer ideas, and to determine the progress of any subject. On the other hand, the published data using *N*-halo reagents indicate a wide synthetic potential of these reagents and a great interest of researchers in these compounds. A wide range of original procedures for synthesizing various classes of heterocyclic compounds have been developed on the basis of the *N*-halo reagents. We think that the present review article with advance the information on this very important subject and encourage active researchers in this field to synthesis new *N*-halo reagents and find applications for these new *N*-halo reagents in organic reactions or find more and more applications of the existing *N*-halo reagents in organic synthesis.

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