

## NITRILE OXIDES: A KEY INTERMEDIATE IN ORGANIC SYNTHESIS

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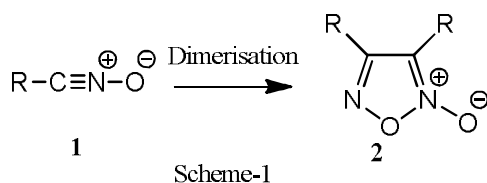
### ABSTRACT

Nitrile oxides have an illustrious history, some even known back in the nineteenth century, fruitful development of the generation and their utility in synthetic principle has been achieved only in recent years. The nitrile oxides were considered as a versatile key intermediates and acts as efficient 1,3-dipole in 1,3-dipolar cycloaddition reactions. The cycloaddition of nitrile oxides with various dipolarophiles leads to the formation of wide range of five membered heterocyclic compounds such as isoxazoles, isoxazolines, oxadiazoles, oxadiazolines, dioxazolidines etc. An up to date information about the methodologies adopted for the generation of nitrile oxides, their utility in organic synthesis, stereochemistry of the products have been presented in this review article.

**Keywords:** Cycloaddition, photolysis, dipolar, INOC, oxadiazoles, isoxazoles.

### INTRODUCTION

Nitrile oxides,  $R-C\equiv N^+-O^-$  are organic compounds which contain a monovalent functional group  $-CNO$ , which bound directly to a carbon atom of the organic moiety of a molecule. Most nitrile oxides<sup>1</sup> are highly reactive and in the absence of trapping agents they undergo rapid dipolar cycloaddition with themselves to give furoxans<sup>2</sup> (Scheme-1).



The dimerization is faster in the case of lower aliphatic nitrile oxides than in the case of aromatic nitrile oxides. Steric bulk increases the stability of nitrile oxide, for example tertiary butyl nitrile oxide is readily generated and examined in solutions, whereas mesityl nitrile oxide is a stable crystalline solid. Similarly, the presence of both electron donor and

accepter substituent in aromatic nitrile oxides in the *para* position stabilize the nitrile oxide, whereas the electron withdrawing group at the *ortho* position makes the nitrile oxide unstable<sup>1,2</sup>. Huisgen categorized the nitrile oxide as being member of a broader class of 1,3-dipoles that were capable of undergoing (3+2) cycloaddition reactions<sup>3</sup>.

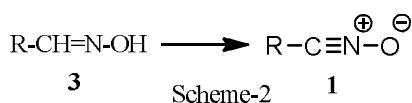
### Generation of Nitrile Oxides

All known methods for the synthesis of nitrile oxides start with organic system already containing  $-C-N-O$  sequence of the nitrile oxide structure. Many methods are reported to generate nitrile oxide. The usual synthetic methods of nitrile oxides involve the oxidative dehydrogenation of aldoximes, dehydration of primary nitro compounds and the dehydrohalogenation of hydroxyiminoyl halides.

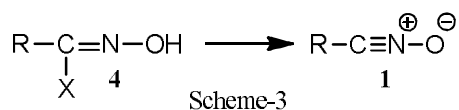
An oxidative dehydrogenation methods of aldoximes<sup>3</sup> to nitrile oxides<sup>1</sup> (Scheme-2) using oxidants such as lead tetraacetate<sup>4</sup>, alkali hypohalite<sup>5</sup>, *N*-bromosuccinimide in dimethyl formamide followed by base

treatment<sup>6</sup>, 1-chlorobenzotriazole<sup>7</sup> are reported. Literature reveals that t-butyl hypiodite (t-BuOI) was found to be a powerful reagent for the *in situ* generation of nitrile oxides under mild conditions<sup>8</sup>. Rai et al<sup>9</sup> used chloramine-T as an oxidant for generating nitrile oxide *in situ* from aldoximes in presence of a dipolarophile and were successful in getting isoxazoline in good yield. Moreya et al<sup>10</sup>, reported the *in situ* generation of nitrile oxides by the reaction of aldoximes with tertiary butyl hypochlorite and bis(tributyl tin) oxide. The reaction proceeded efficiently under mild condition in which *O*-stannylated aldoximes are thought to be the intermediate.

Rai and Co-workers<sup>11</sup> have successfully reported the *in situ* generation of nitrile oxides by the reaction of aldoximes with mercuric acetate as mild oxidising agent, while Kiegiel et al<sup>12</sup> reported the use of Mn(IV) oxide (MnO<sub>2</sub>) for the same reaction. Iodobenzene diacetate in MeOH containing a catalytic amount of TFA efficiently oxidizes aldoximes to nitrile oxides at room temperature<sup>13</sup>. Treatment of aldoximes with Magtreive (CrO<sub>2</sub>) in acetonitrile at 80°C generates nitrile oxides which were trapped *in situ* by the dipolarophile to furnish a variety of isoxazolines and isoxazoles as 1,3-dipolar cycloaddition products<sup>14</sup>.

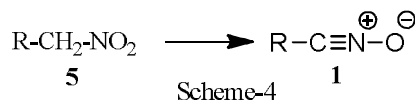


Hydroxyiminoyl halides<sup>4</sup> are second most commonly used precursors for the preparation of nitrile oxides<sup>1</sup> (Scheme-3). For instance, Tokunaga et al<sup>15</sup> utilized silver acetate for the generation of nitrile oxide starting from hydroxyiminoyl halides. The dehydrohalogenation of hydroxyiminoyl halides leads to the formation of nitrile oxides<sup>16</sup>.

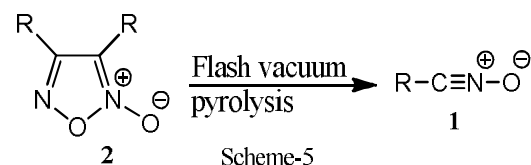


The primary nitro alkanes<sup>5</sup> are found to be next common starting material for the preparation of nitrile oxides<sup>1</sup> (Scheme-4).

For instance, the dehydration of primary nitro compounds with aryl isocyanate leads to the formation of nitrile oxides<sup>17</sup>. Di-tert-butyl dicarbonate [(BOC)<sub>2</sub>O] in presence of 4-dimethyl amino pyridine (DMAP) was also used for an *in situ* generation of nitrile oxide from nitro alkanes<sup>18</sup>.



It was reported that; flash vacuum pyrolysis of furoxans generates nitrile oxides (Scheme-5); which were trapped *in situ* with alkenes to yield 2-isoxazolines<sup>19</sup>.



Nitrile oxides may be trapped *in situ* with olefins in a bimolecular or an intramolecular mode. Tandem oxidative dearomatization of phenols/intramolecular nitrile oxide cycloaddition sequences lead to useful synthetic intermediates.

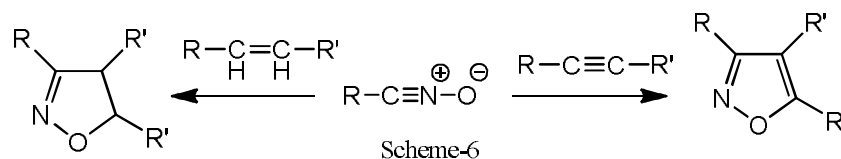
All the methods discussed above generate nitrile oxides *in situ* and in the presence of a dipolarophile. So far, only two isolable nitrile oxides are reported in the literature and the stability of these nitrile oxides is due to steric interaction<sup>20,21</sup>. Rai and et al<sup>9</sup> method not only allows *in situ* generation but also allows the isolation of nitrile oxides. By employing this method they have isolated and characterized the nitrile oxide, of which some are liquids and some are solids. The unstable compound identified by NMR spectrometry slowly dimerizes on standing it alone or in presence of added vinyl sulfone, undergo cycloaddition to yield isoxazoline in good yield<sup>22</sup>.

### Reactions of Nitrile Oxides

1,3-Dipolar cycloaddition of nitrile oxide to C=C bond of dipolarophile is of considerable importance in organic synthesis, since this reaction yields 2-isoxazolines. Isoxazole and isoxazolines act as versatile building blocks in the construction of new molecular systems for several reasons. First of all, they

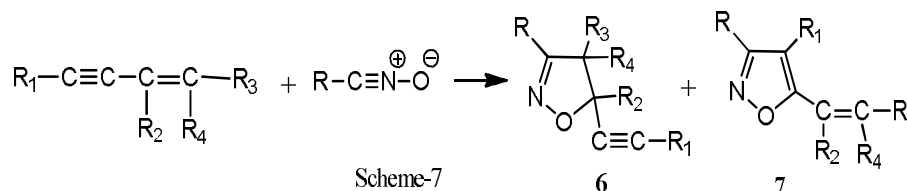
can be very efficiently prepared from readily available precursors; secondly, they can be conveniently modified, thus allowing transformation of molecule with simple structure to functionally complex derivatives; thirdly, a suitable pattern of substituents makes the isoxazoline ring survive under a variety of chemical reaction conditions, thus allowing manipulation in other parts of the molecule; and finally the liability of the nitrogen-oxygen bond to catalytic or chemical reduction under mild conditions unravels a vast array of different functionalities.

Nitrile oxides undergo 1,3-dipolar cycloaddition reactions with various dipolarophiles. There are exhaustive review articles on this topic, available in the literature<sup>3,20,21,23,24</sup>. Therefore, only the important reactions of nitrile oxides are outlined here. Alkenes and alkynes serve as an excellent dipolarophiles. Cycloaddition of nitrile oxides to olefins yield isoxazolines while addition of nitrile oxides to alkyne yields isoxazole directly (Scheme-6).



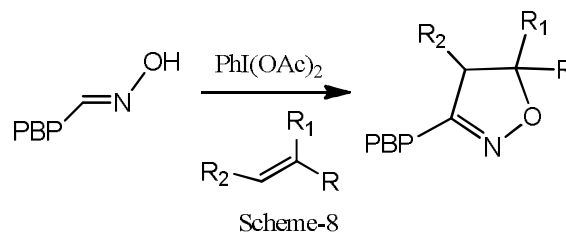
If the dipolarophile possesses more than one set of unsaturation in an en-yne, addition to either (or both) site(s) may occur. Indeed with nitrile oxides as dipole and 1,3-en-yne

as substrate, the chemoselectivity is very sensitive to the substitution pattern of the en-yne, either product (6) or (7) may predominate (Scheme-7).



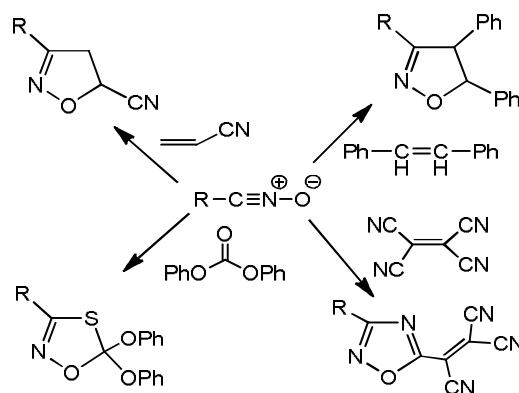
Unlike the frequently unselective reaction of 1,3-en-yne with 1,3-dipole, nitrile oxides add chemo, regio and stereoselectively to the free double bond of (1,3-en-yne)Co(CO)<sub>6</sub> complexes to provide 5-alkenyl-2-oxazoline derivatives in moderate yield<sup>25</sup>. The ability to add nitrile oxides is not restricted to C-C multiple bonds, they

also add to C=O group to produce 1,3,4-dioxazoles. However C=O is less reactive as a dipolarophile and is clearly shown by the reaction of BNO with *p*-benzoquinone<sup>26</sup>. Similarly acetylacetone prefers to react as an enol (80%) rather than as a ketone (Scheme-8)<sup>27</sup>.



Though C=S group is not a good dipolarophile in Diel's-Alder reaction, but is a very reactive dipolarophile in 1,3-dipolar cycloaddition of nitrile oxides. For instance; Cycloaddition of nitrile oxides to C=S group yields 1,4,2-oxathiazolines. Similarly, nitrile oxide addition to C=N is known to yield 1,2,4-oxadiazoline, however it is comparatively less reactive as a dipolarophile than C=S. The C-N group normally does not undergo 1,3-dipolar cycloaddition reaction because of its poorer

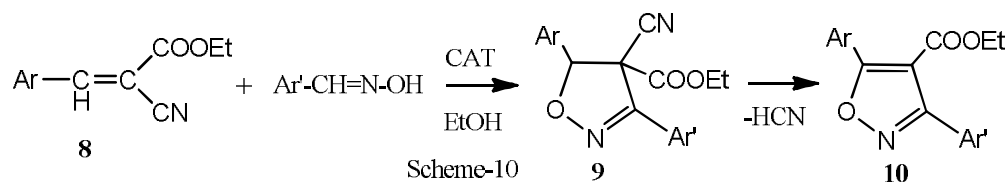
dipolarophile nature compared to C=C group. Thus, in the case of acrylonitrile, nitrile oxide reacts with alkene to form cyano substituted 2-isoxazoline. However, if the C=C bond is deactivated by multiple substitution, the C-N group may become a better dipolarophile. Thus, tetracyano ethylene adds nitrile oxide yielding 1,2,4-oxadiazole derivative as one of the product. All these reactions were summarized (Scheme-9).



Scheme-9

Nitrile oxides generated *in situ* by the oxidative dehydrogenation of aldoximes with chloramine-T reacted with  $\alpha,\beta$ -unsaturated compounds to afford ethyl 3,5-diarylisoaxazole-4-carboxylates<sup>10</sup> which exhibited remarkable antimicrobial activity. In a typical reaction an equimolar mixture of aldoxime,  $\alpha,\beta$ -unsaturated compounds<sup>8</sup> and chloramine-T tr

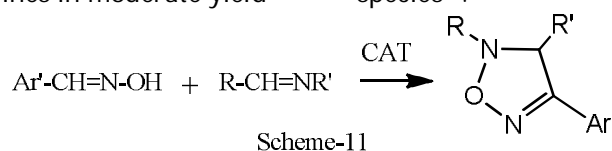
hydrate in ethanol was refluxed on a water bath for 3 hours. After the completion of the reaction, the products<sup>10</sup> were obtained in good yield. Here, the usual expected cycloadducts<sup>9</sup> underwent elimination reaction to give of HCN under reaction conditions to give the more stable products<sup>10</sup> (Scheme-10)<sup>28</sup>.



Scheme-10

A series of 1,2,4-oxadiazolines have been synthesized by the intermolecular 1,3-dipolar cycloaddition of *in situ* generated nitrile oxides with imines in moderate yield

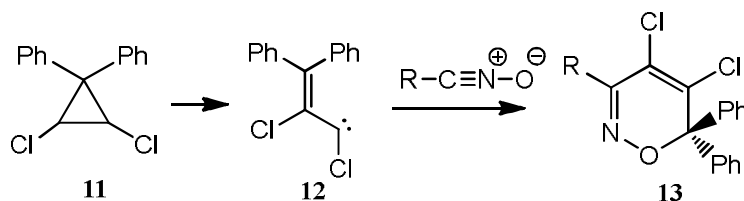
(Scheme-11). The products have been evaluated for their antimicrobial activity against different bacteria and fungi species<sup>29</sup>.



Scheme-11

The unusual formal [3+3] cycloaddition of nitrile oxide with vinyl carbene (12) derived by the ring opening of the cyclopropane (11) yield 1,2-oxazines (13)

in moderate to good yield but it is not clear whether 1,2-oxazine is directly formed by concerted cycloaddition or by a stepwise process (Scheme-12)<sup>30</sup>.

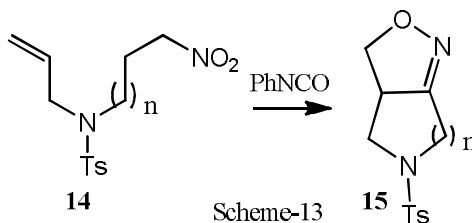


Scheme-12

### Application of Nitrile Oxide Cycloaddition Reactions

1,3-Dipolar cycloaddition of nitrile oxide to different dipolarophiles has been extensively used as a powerful tool in the synthesis of five membered heterocycles. For instance; Rai et al<sup>31</sup> used intramolecular 1,3-dipolar cycloaddition reaction for synthesizing functionalized pyrrolidine, piperidine, hydroazepine, hydroazocine and tricyclic quinolinoisoxazoline starting from corresponding nitro alkenes. The starting

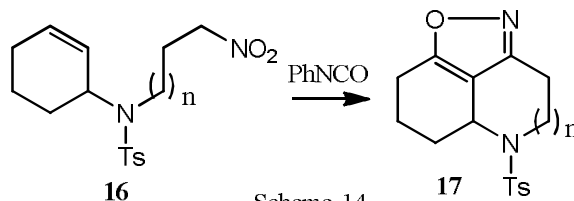
nitro alkenes were prepared by the alkylation of *N*-tosyl allylamine with dibromoalkane followed by treating with silver nitrite. *In situ* transformation of (14) into a nitrile oxide was carried out by means of phenyl isocyanate and led to spontaneous cycloaddition with the formation of isoxazolines (15) fused to 5,6 and 7 membered heterocycles. Under very high dilution,<sup>14</sup> formed an isoxazoline<sup>15</sup> fused to 8- membered azocines in 10 % yield (Scheme-13).



Scheme-13

Using the same procedure, tricyclic quinolinoisoxazoline (17) was formed on intramolecular cycloaddition of starting

amino cyclohexene derivative (16) (Scheme-14)<sup>31</sup>.

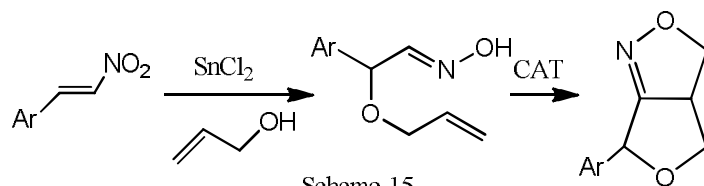


Scheme-14

Later they were succeeded in getting functionalized tetrahydrofuran and

tetrahydropyran by the INOC of 2-allyloxy aldoxime formed by the reduction of β-

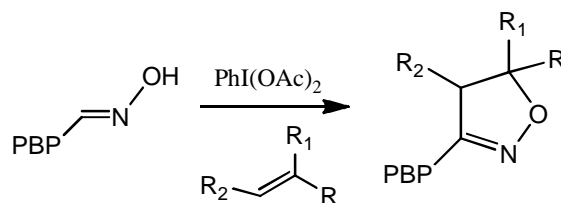
nitrostyrene with  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  in the presence of an unsaturated alcohol (Scheme-15)<sup>32</sup>.



Scheme-15

An aryl substrate with dual functionality consisting of a nitrile oxide and a pinacolyl boronate ester was prepared by mild hypervalent iodine oxidation (diacetoxyiodobenzene) of the corresponding aldoxime, without

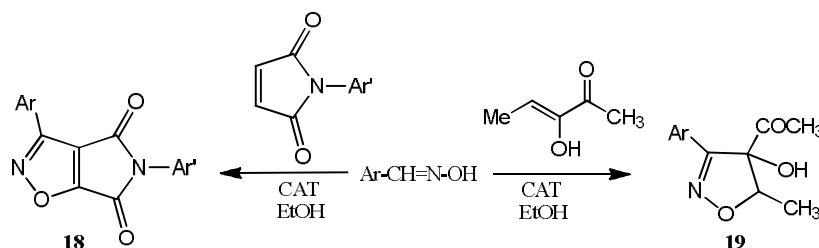
decomposition of the boronate functionality. The nitrile oxide was trapped *in situ* with a variety of dipolarophiles to yield aryl isoxazolines with the boronate ester function intact and available for subsequent reaction (Scheme-16)<sup>33</sup>.



Scheme-16

Ajay kumar et al<sup>34</sup> reported the synthesis of a series of thirteen cycloadducts 3-Aryl-5-N-aryl-4,6-dioxo-pyrrolo[3,4-d]-7,8-dihydroisoxazolines<sup>18</sup> by the reaction of *in situ* generated nitrile oxides obtained from the catalytic dehydrogenation of aldoximes with chloramine-T on *N*-aryl maleimides

(Scheme-17). Later they demonstrated the use of nitrile oxide as a dipolarophile in 1,3-dipolar cycloaddition with acetyl acetone and obtained the substituted isoxazolines<sup>19</sup> in good yield. Here the nitrile oxide gets added to enolic double bond of acetyl acetone (Scheme-17)<sup>35</sup>.



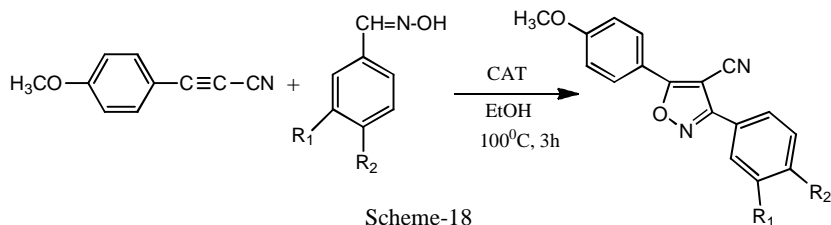
Scheme-17

Alkylidenepyrrolidines undergo reactions with nitrile oxides generated *in situ* from hydroximoyl chlorides and nitrilimines to give a range of novel heterocyclic compounds. With hydroximoyl chlorides give isoxazoles, presumably by

cycloaddition/elimination<sup>36</sup>. A series of 3-aryl-5-(4-methoxyphenyl)-isoxazole-4-carbonitriles have been synthesized by the *in situ* generated nitrile oxides obtained by the catalytic oxidation of aldoximes with chloramine-T in alcohol and 3-(4-

methoxyphenyl)propionitrile in moderate yield (Scheme-18). The products tested for

their antibacterial and antifungal activity against different organism<sup>37</sup>.

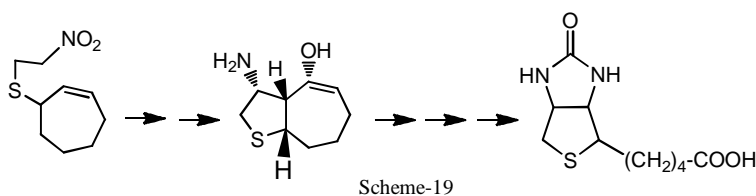


### SYNTHESIS OF NATURAL PRODUCTS VIA CYCLOADDITION OF NITRILE OXIDES

The application of intramolecular nitrile oxide cycloaddition (INOC) reaction to the synthesis of complex natural products has recognized as powerful synthetic tool, one equally akin to the intramolecular Diel's-Alder reaction in its potential scope of application. This is particularly the case with nitrile oxide and the INOC reaction has been extensively utilized in total synthesis. The INOC reaction generally displays

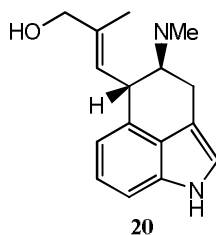
exceptional regio- and stereochemical control, which undoubtedly accounts for the popularity of this reaction. Internal cycloaddition of nitrile oxides has been found to offer a powerful solution to many problems in complex natural product synthesis.

Confalone and coworkers have utilized the INOC reaction for the stereospecific synthesis of the key amino alcohol, which was converted to ( $\pm$ ) biotin through several steps (Scheme-19)<sup>38</sup>.



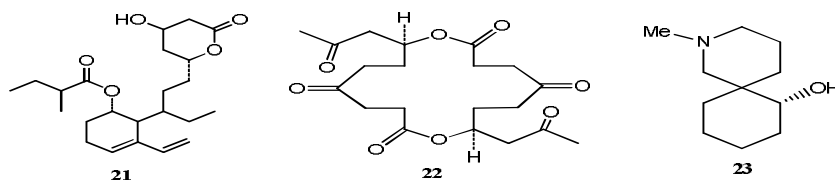
Mukayama et al<sup>17</sup> synthesized chanoclavine (20), a member of ergot alkaloids via

intramolecular nitrile oxide-olefin cycloaddition.

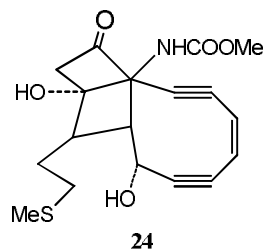


The key step for the synthesis of hexahydronaphthalene portion of the hypocholesterolemic agent, compactin (21)<sup>39</sup> antibiotic vermiculene (22)<sup>40</sup>, the spirocyclic alkaloid sibirine (23)<sup>41</sup>, lignans

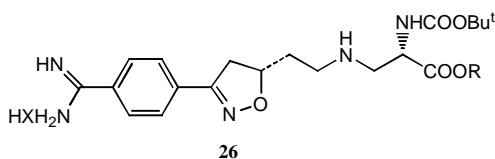
such as Burseren, Brassilignan, Dehydroxycubebin etc.<sup>42</sup> and the prostaglandin<sup>43</sup> involves the INOC reaction of the corresponding cycloalkenyl oximes.



Stereoselective 1,3-dipolar addition of bromonitrile oxide S (+)-isopropylidene-3-butene-1,2-diol represent the key step in the preparation of potent muscarinic receptor<sup>44</sup>. A new approach to the synthesis of the aglycon portion (24) of calicheamicin, an anticancer antibiotic possessing phenomenal anticancer properties is based upon an intramolecular alkenyl nitrile oxide



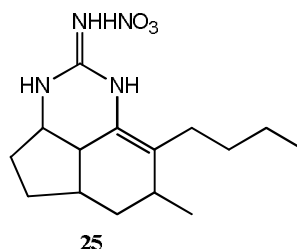
An effective and chiral specific synthesis of DMP 754 (26), a novel peptide, orally active and extremely potent platelet GP 11b 1111a antagonist involves 1,3-dipolar cycloaddition of nitrile oxide to isobutyl vinyl acetate as key step<sup>47</sup>. 5-



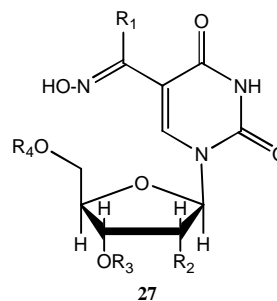
## SUMMARY

In summary, it seems that nitrile oxide cycloaddition chemistry can be seen as a powerful strategic tool for crafting the diverse molecules of nature. Not only can one build a variety of carbocyclic and heterocyclic ring system through its agency, but additionally, one can to exploit diastereofacial selective cycloaddition reaction in a rational way so as to achieve a satisfactory solution to the problem of acyclic stereo control. The nitrile oxide thus seems a reasonably mild reagent in affording C-C double bond forming reactions with the simultaneous incorporation of manipulable heteroatom functionality. Much focus was given in this report about methodologies that have been used to generate nitrile oxides and thereby their transformation in to useful molecules.

dipolar cycloaddition reaction which leads directly to the incorporation of the full functionality of the aglycon<sup>45</sup>. The same strategy was utilized for the stereoselective synthesis of the ptilocaulin (25), an antileukemic and antimicrobial agent isolated from marine sponges involving formation of the  $\beta$ -ring by intramolecular nitrile oxide cycloaddition<sup>46</sup>.



Aroylpyrimidine nucleoside oximes (27) were prepared by the reaction of corresponding pyrimidine nucleosides with stable nitrile oxides. The nitrile oxides are generated *in situ* from the corresponding hydroxymoyl chlorides<sup>48</sup>.



It also comprises the stereochemistry of the products. The review may become useful tool for the researchers to devise new molecules and study their biological studies.

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