

SYNTHESIS OF SYDNONES AND NEW SYDNONES

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ABSTRACT

Sydnone is a mesoionic molecule with a five-membered aromatic heterocyclic ring, mostly 1,2,3-oxadiazole, or a six-membered ring in some situations. The molecule is neutral, with a positive charge shared by the annular atoms that is counterbalanced by a negative charge on an exocyclic atom (s); despite the fact that sydnone has no single polar or covalent structure, the structure XIV is utilized as a representation of current work.

The small influence of the solvent polarity and its hydrogen donor capacity for the N2 shielding, exclude a resonance structure with a negative charge at this atom. The shielding of N-3 seems to be in agreement with a solvent (D-H)-sydnone interaction (the donor part D with N-3 atom and H with the O of conjugated carbonyl) leading to an electron charge migration.

KEYWORDS:

Sydnone, molecule, compound

INTRODUCTION

The word sydnone was started from the expression "College of Sydney" where this class of compounds was first arranged by Earl and Mackney in 1935. They proposed the development of intertwined three and four-membered ring item (I) from the activity of acidic anhydride on N-nitrosophenylglycine which was later viewed as offbase by different scientists. Initially, a melded ring framework is probably not going to be shaped by a straightforward intramolecular reworking and would be a profoundly stressed unsteady structure because of the presence of a β -propiolactone gathering. Hence, Baker and his associate excluded the scaffold bond and suggested an in part fragrant five-membered ring (II and III) which was a cross breed of numerous zwitterionic structures.

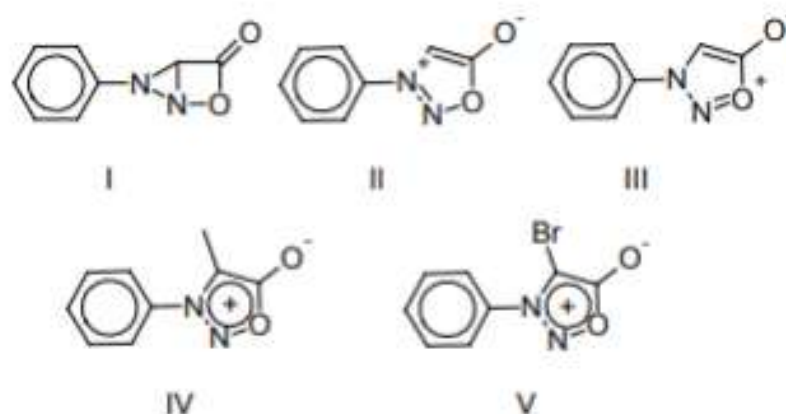


Figure 1.1: Sydnone Structure

Besides, corrosive hydrolysis decays sydnone into hydrazine, carboxylic acids and carbon dioxide while hot fluid sodium hydroxide can return the sydnone into the beginning N-nitroso compound. These two realities demonstrate that the bicyclic framework proposed by Earl is implausible. Thirdly, different scientists demonstrated that acidic anhydride can change over the dextro-rotating N-nitroso-N-phenylalanine into the optically idle N-phenyl-C-methylsydnone (IV). The loss of optical movement infers either racemization or an adjustment in the hybridization of C4 from a chiral sp^3 state into an achiral sp^2 . The oxygen atom connected to C5 was end up being in an enolate structure because of the fast development of a monobromo subordinate (V) in chilly acidic corrosive and bromine.

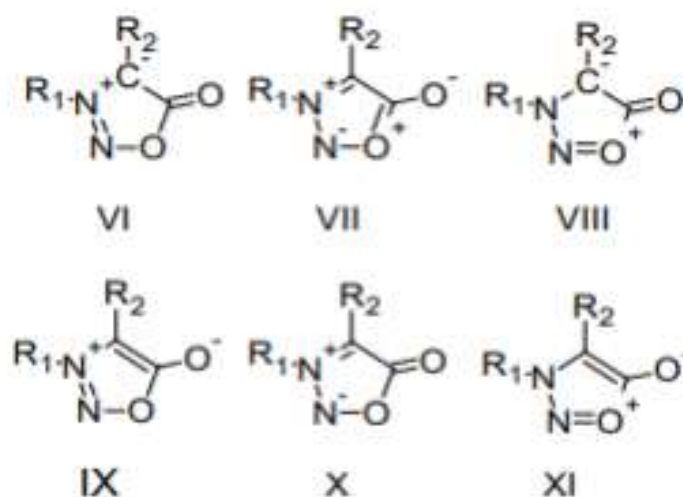


Figure 1.2: Sydnone molecule considered as a hybrid of bipolar and tetrapolar forms (VI-XI)

To put an end to the prior dispute, Baker and Ollis thoroughly analysed all potential sydnone structures and presented the following more precise description:

1. Sydnone is not well described by a single covalent structure from the prior options. To put it another way, the sydnone molecule should be viewed as a hybrid of bipolar and tetrapolar forms (VIXI), each of

which contributes differently to the hybrid ring. As a result, sydnones are known as mesoionic compounds.

The sydnone ring, in comparison to the cyclopentadienyl anion (XIIa, XIIb), tropylium cation (XIIIa, XIIIb), furan, pyrrole, and pyridine, meets all of the prerequisites for developing aromatic characteristics. The ring receives one electron from the exocyclic oxygen atom, completing the sextet of electrons. They came up with the formula XIV to describe the sydnone structure, which they were rather happy with.

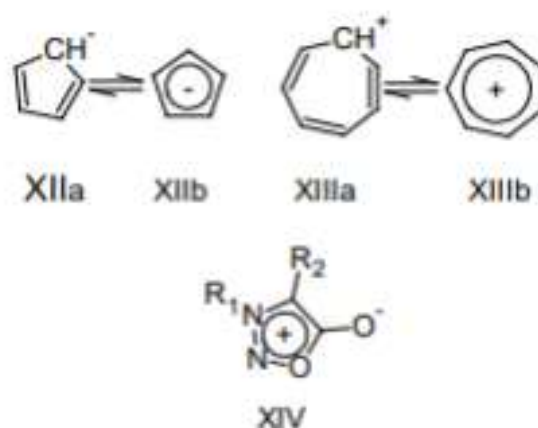


Figure 1.3: cyclopentadienyl anion (XIIa, XIIb) and tropylium cation (XIIIa, XIIIb)

The ab initio calculations confirm the distribution of charge in the sydnone molecule. The most probable resonance structure has the highest negative charge at the external oxygen atom, the nitrogen N-2 having a very small negative charge. The mesoionic structure of sydnones is also sustained by the high values of their dipole moments. The resonance structure A is mentioned as the most accurate for describing the sydnones, but another representation in agreement with sydnones spectral data seems to be B. The resonance structure B is in accord with the values of the carbonyl IR stretching bands of a number of substituted sydnones.

SYNTHESIS OF SYDNONE

Earl and his colleague first made sydnone by using the cyclodehydration action of acetic anhydride on N-nitroso derivatives of amino acids. They discovered that dissolving N-nitroso-N-arylglycine in excess acetic anhydride at room temperature produced a nitroso-free, crystalline, and stable heterocyclic compound known as sydnone after 24 hours. The N-nitroso intermediate was made by nitrosating the amino group of N-phenylglycine with nitrous acid produced by the reaction of sodium nitrite with hydrochloric acid. Applegate and Turnbull later detailed the N-nitrosation of N-phenylglycine under neutral circumstances using isoamyl nitrite (IAN) in dimethoxyethane (DME) at ambient temperature.

They stated that when IAN was employed to make the N-nitroso derivative of N-(2-acetylphenyl) glycine with a high yield, it produced C-nitroso glycine instead of the N-nitroso derivative.

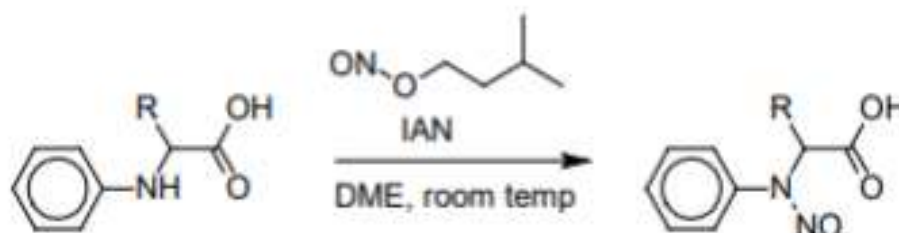


Figure 1.4: Preparation of N-nitroso analogues in neutral conditions

Baker later inferred a four-step method for cyclization of the Nnitroso starting material by losing a water molecule, as shown in Figure. To begin, the impact of acetic anhydride on the free nitroso acid will produce a mixed anhydride intermediate XV, whose carbonyl group will develop strong cationic characteristics. It was discovered that utilizing a potassium salt of the N-nitroso-N-phenylglycine slows down the production of the intermediate significantly. Second, ring closure is caused by the nitroso oxygen's nucleophilic assault on the acid carbonyl group (XVI). Finally, an acetate group is removed, resulting in the formation of a double bond between the two nitrogen atoms (XVII). Finally, proton loss and enolic oxygen production yield the ultimate sydnone product XVIII.

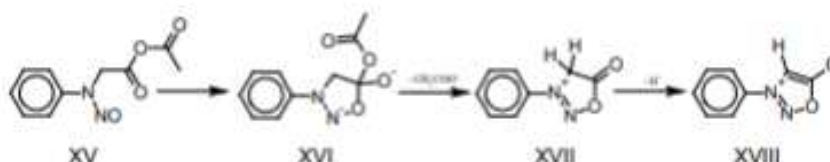


Figure 1.5: Mechanism of ring closure and sydnone formation

However, Eade and Earl discovered that some sydnone analogues, such as nitrocontaining sydnone, took a long time to prepare at room temperature, taking up to 7- 30 days with low to moderate yields. They stated that heating expedited the production of the sydnone ring, despite the fact that it lowered yield due to the product's quick hydrolysis by the hot acidic reaction media. When Baker and his colleagues utilised trifluoroacetic anhydride (TFAA) as a dehydrating agent, they reported for the first time an immediate and complete separation of Narylsydnone in 90% yield. The latter synthesis approach had previously been used to successfully create several complex sydnones, such as N,N-polyaliphatic bis-sydnone, with yields of 70-80%.

Furthermore, employing TFAA in dichloromethane at 5 °C, heat-labile sydnone such as 3-(2-methoxycarbonylphenyl) sydnone were produced in a significant yield of 75% in one hour. The sydnone system was also prepared using a variety of different reagents. Baker utilized thionyl chloride in 1950. They stated that employing thionyl chloride in dry ether at room temperature, they were able to convert N-nitroso amino acids to sydnone in a matter of minutes, with a poor yield of 28%. Using thionyl chloride in a combination of cold dioxane and pyridine, on the other hand, resulted in a 75 percent increase in yield after just 25 minutes.

As a result of the cyclodehydration of the N-nitroso derivatives of iminodicarboxylic acids, certain unusual sydnone structures have been discovered. For example, the impact of acetic anhydride on the diastereoisomeric combination of -di-(N-2- cyanoethylN-nitrosoamino) glutaric acid XX yielded 4, 4'-methylene bis [3-(2- cyanoethyl) sydnone] XIX. Individual and forms, on the other hand, produced largely the cyclic anhydride N-2-cyanoethyl-N-nitroso-Lglutamic anhydride XXI. Similarly, hydrolysis of the later cyclic anhydride in water at room temperature resulted in a 35 percent yield of 3-(2-cyanoethyl)-4-(2- carboxyethyl) sydnone XXII.

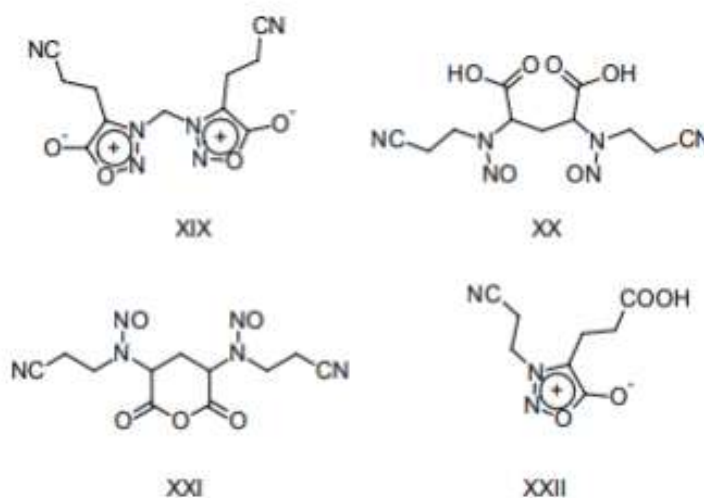


Figure 1.6: -di-(N-2-cyanoethylN-nitrosoamino) glutaric acid XX yielded 4, 4'-methylene bis [3-(2-cyanoethyl) sydnone] XIX, N-2-cyanoethyl-N-nitrosoLglutamic anhydride XXI, 3-(2-cyanoethyl)-4-(2-carboxyethyl) sydnone XXII

Recently, 1,3-dibromo-5,5-dimethylhydantoin XXIV (DBH) and N,N,N',N'-tetrabromobenzene-1,3-disulfonamide XXIII (TBBDS) were used as catalysts for the one-pot conversion of N-arylglycines into the corresponding sydnone in a neutral medium. Within 5-8 hours of stirring Narylglycine, TBBDS, sodium nitrite, and acetic anhydride in dichloromethane (DCM) at 5 °C, the sydnone ring was formed in

a very good yield. DBH, on the other hand, effectively enhanced cyclization within 10- 16 hours. It's worth noting that the preceding reagents produced sydnones with nitrophenyl groups in a yield of 80-88 percent, compared to 5-30 percent using Earl's approach.



Figure 1.7: 1, 3-dibromo-5, 5-dimethylhydantoin XXIV (DBH), tetrabromobenzene-1, 3-disulfonamide XXIII (TBBDS)

SYNTHESIS OF NEW SYDNONES

The vast majority of the of late incorporated sydnones has a fragrant substituent at N3, which upgrades the soundness of the compound. Their readiness 27, 28 followed for the most part the notable multi-steps technique by and large utilized for sydnone synthesis. It might begin by setting up the sweet-smelling amine 29-32 followed by the comparing subbed glyocol. The came about middle of the road is changed by nitrosation and cyclization, as a rule utilizing acidic anhydride, into the N-subbed sydnone. A model is the synthesis of coumarinyl subsidiary 7, portrayed by Patel and Patel 29 (Scheme I).

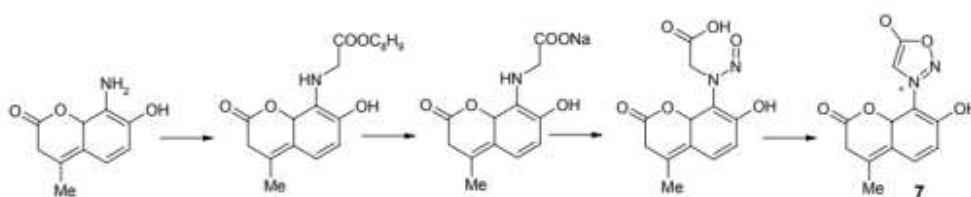


Figure1.8: Synthesis of New Sydnone-scheme I

Beginning from the relating diamines, various bis-sydnones 8 33 have been integrated:

Now and again the N-3 substituent might be work after the sydnone ring synthesis. A model is crafted by Patel and colleagues 34 for preparing compounds 9 (Scheme II).

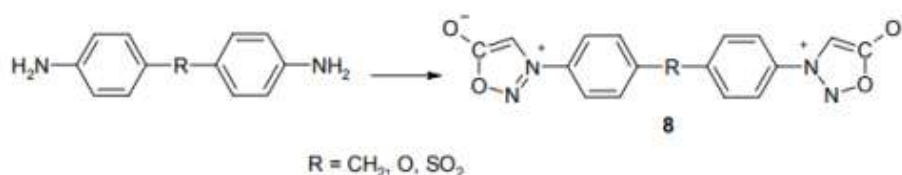


Figure 1.9: Synthesis of New Sydnones-scheme –II

Accordingly, the sydnone synthesis relies upon the accessible crude materials just as the structure plan for the last item.

Sydnone Reactions

The reactions performed beginning from sydnones might be arranged into two gatherings:

- i. Reactions rationing the sydnone moiety;
- ii. Reactions prompting the loss of sydnone moiety.

The two sorts of reactions have been of late contemplated, creating an assortment of items with various down to earth applications because of their bioactivity.

1. Reactions conserving the Sydnone moiety

1(A): Reactions at C-4

The studies discussed in this chapter are substitution reactions carried out at the C-4 level. Electrophilic replacements at the carbon atom of the sydnone ring with the least positive charge (C-4) or oxidative coupling reactions are the two types of reactions.

Electrophilic Substitution

The C-4 hydrogen atom was despatched by electrophilic substitution^{39a-c} of various halogen atoms or a nitro group. Various products can be produced depending on the reaction parameters. If the halogen is used in excess in a reaction involving 3-arylsydnones, the phenyl ring may be halogenated as well. In the instance of 3-(3,5- dimethoxyphenyl)sydnone^{39b}, molecules halogenated at the 3,5-dimethoxyphenyl ring have been isolated and described in addition to the 4-halogeno-sydnone. Using N-iodosuccinimide in acetic acid, excellent yields of iodination at C-4 were obtained. ^{39c}. the 4-halogeno-sydnones are useful starting materials for the production of a variety of biologically active compounds. There are more sydnone substitution reactions. Formylation and sulfonation must be noted because of the substituent added during C-4 acetylation.

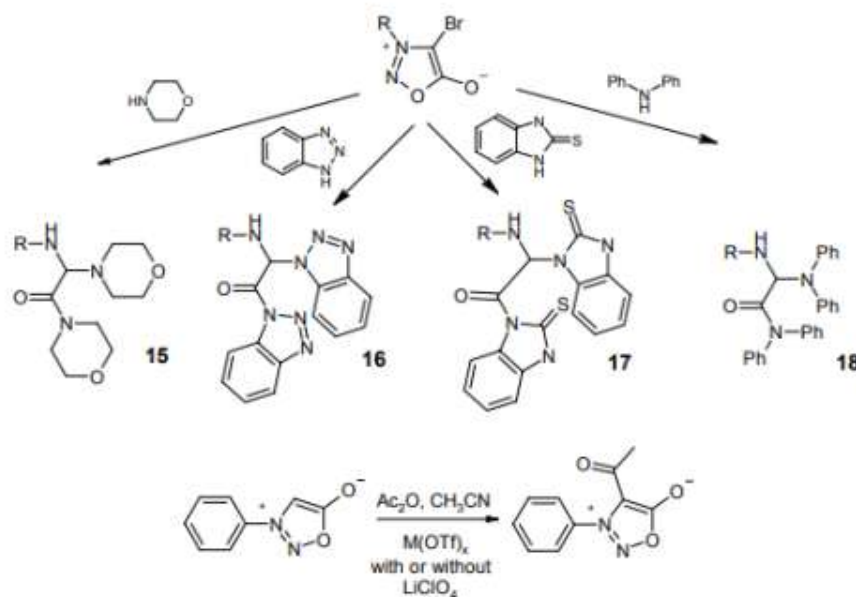


Figure 1.10: Electrophilic Substitution

Acetylation

A large number of studies have been published on the synthesis of an acetyl derivative at C-4. The majority of acetylations are carried out using acetic acid and an acid catalyst such as P₂O₅, HClO₄, or BF₃.⁴¹ This reaction might also be catalysed by bismuth triflate or other metal triflates (M = La, Sc, Y, Hf, Gd, In). In acetonitrile, microwave (MW) irradiation can be used to produce the reaction. When compared to traditional methods, the irradiation approach produces higher yields. Lower yields are caused by the presence of a bulky radical in the ortho position of the phenyl ring (R).

This green MW technique may also be utilised to make acylated sydnone derivatives at the phenyl ring. As a result of the acylation of sydnone 19, two products 20 and 21 were produced:

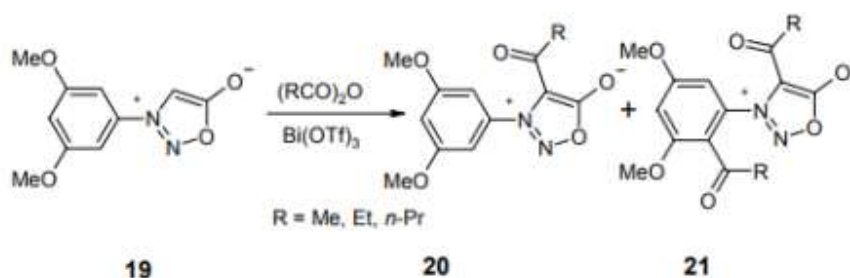


Figure 1.11: acylation of sydnone

1(B): Reaction at the 3-aryl moiety of sydnones

The phenyl ring located at N-3 is an excellent moiety for constructing complex compounds with medicinal promise. By two consecutive crotonic condensations, a variety of novel barbituric acid

derivatives 41-66 have been synthesised beginning from 3-(4-acetyl-phenyl) sydnone and 3-aryl-4-formyl-sydnone. Multidrug-resistant tuberculosis (MDR-TB) is a current global health problem. Many researchers are attempting to develop new, more effective medications. New compounds containing the sydnone moiety have been synthesized and their anti-tubercular action assessed.

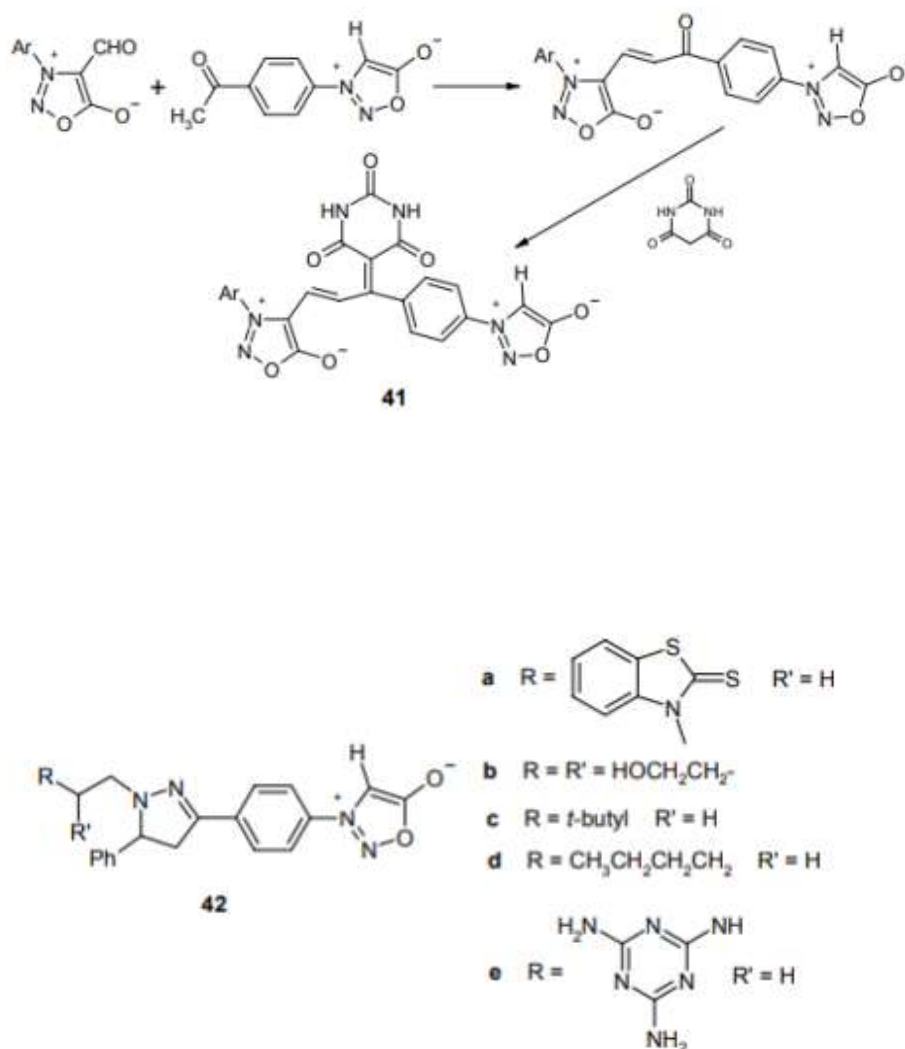


Figure 1.12: Reaction at the 3-aryl moiety of sydnones

Sydnones participate in reactions with alkenes or alkynes as partners because of their polar structure. Different compounds can be easily created by starting with a variety of sydnones or their partners. Sydnones react as dipoles, resulting in distinct structures as intermediates, depending on the reaction circumstances. A linear nitrile imine is generated under photolytic conditions, and a bent azomethine imine is created by a heat reaction. The orbital interaction for such dipole-alkene cycloaddition is HOMOdipole - LUMOalkene in both cases, as illustrated below:

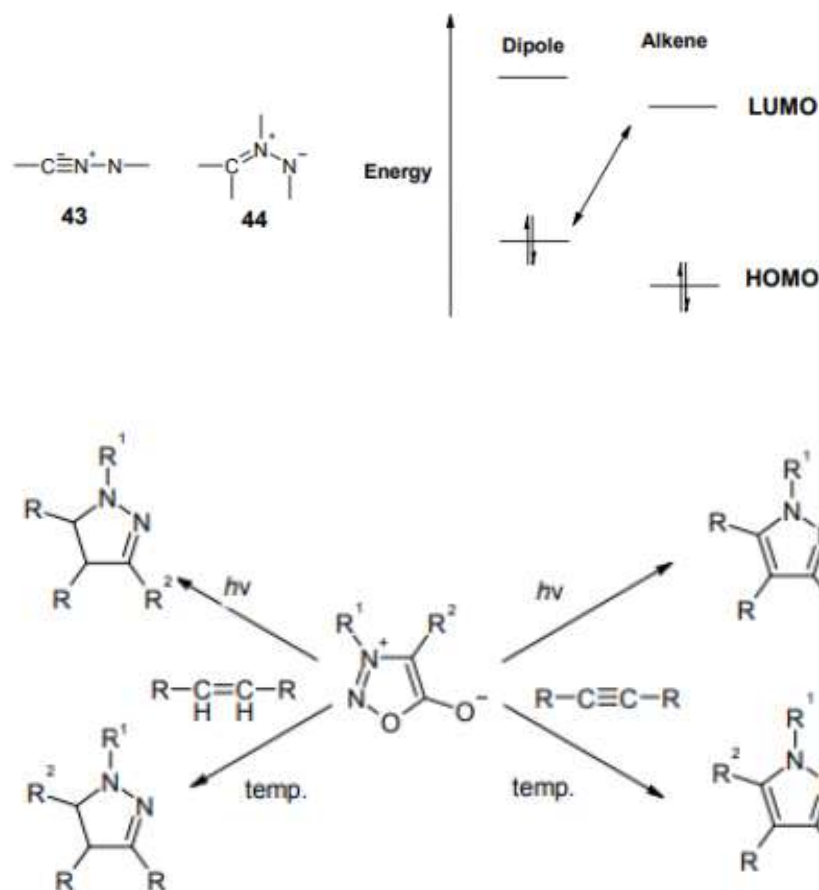


Figure 1.13: compounds synthesized from sydnone and alkenes or alkynes

Sindler-Kulyk and coworkers provided a generic scheme that shows the compounds that can be produced from sydnone and alkenes or alkynes. It depicts the location of the product substituent, which is determined by the reaction circumstances (thermal or photochemical). The pyrazolines or pyrazoles that arise are positional isomers.

CONCLUSION

Sydnone belongs to the class of mesoionic heterocycles, being dipolar compounds with the positive and the negative charges delocalized. According to IUPAC definition, mesoionic compounds consist usually in five-membered ring heterocycles which cannot be correctly represented by a covalent or only one polar structure, consequently described by multiple canonical structures. Sydnone is a planar conjugated entity, considered aromatic. The sydnone aromaticity is supported by: their planar structure, the delocalized charges and the considerable resonance energy.

The planarity of the sydnone ring has been proven by the X-ray analysis of numerous representatives. The crystal X-ray analysis of a diversity of sydnones evidenced mostly a planar structure for the

heterocyclic ring. The carbonyl substituent in compounds 2, 4-6 has a small deviation (less than 0.1 Å) but shows conjugation with the sydnone ring.

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