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REVIEW

THE STATE OF ART IN SYDNONES CHEMISTRY AND APPLICATIONS

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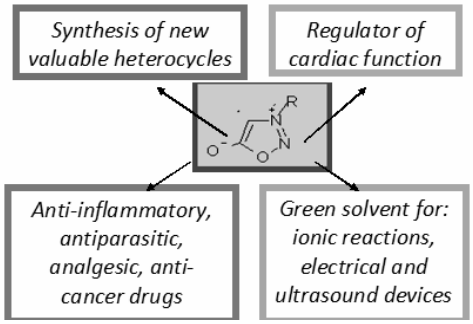
Sydnones are mesoionic stable compounds firstly synthesized more than 80 years ago. Their aromatic behavior as well as their property to give 1,3-cycloaddition reactions make these compounds a valuable tool for the synthesis of new heterocycles having complex structures. The bioactivity of numerous sydnones, or the heterocycles resulted from them, explains easily the interest for these compounds reflected also by numerous publications in this area. The present review analyzes the recent syntheses, reactions and applications of sydnones, since 2010. The subject was of interest for a number of researchers from the Centre of Organic Chemistry for a long time and it is still included in their research area.



INTRODUCTION

The sydnones are mesoionic compounds, firstly described by Earl and Mackney in 1935.[1] The interest for this class of compounds was generated by their value as synthons in building heterocyclic complex molecules[2], as well as their pharmaceutical applications. [3, 4]

Researchers from the Romanian Academy Centre of Organic Chemistry have published a first paper on this subject in 1965 [5] and since then numerous studies have been performed in the field of sydnone synthesis or their reactions. [6-11] It explains our contemporary interest to evaluate the state of art in sydnone synthesis, properties and applications. This review will present the new researches concerning sydnones depicted into papers published after the review of Browne and Harrity.[2]

SYDNONE STRUCTURE

Sydnones belong to the class of mesoionic heterocycles, being dipolar compounds with the positive and the negative charges delocalized. According IUPAC definition mesoionic compounds consist usually in five member ring heterocycles which cannot be correctly represented by a covalent or only one polar structure [12], consequently described by multiple canonical structures. Sydnones are planar conjugated entities, considered aromatic.[13] The sydnone aromaticity is supported by: their planar structure, the delocalized charges and the considerable resonance energy.[14]

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 (compounds **1-6** [15, 16]) evidenced mostly a planar structure for the

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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.

The UV-Vis spectra [17] bring more pertinent information concerning the conjugation of sydnone ring with external double bonds revealing the importance of steric factors.

Beside the planarity, the cyclic structure of sydnones enclosing six delocalized π electrons sustains the aromatic structure proposal. [18] Also ^{1}H-NMR studies confirm the conjugated cyclic structure ruling out any open tautomeric form. [19] Moreover spectral data (IR, ^{1}H- and ^{13}C-NMR) of substituted sydnones [20] correlate well with the Hammet constants, endorsing the aromatic properties.

Meanwhile the reactivity of sydnones does not agree entirely with an aromatic structure. In addition to the electrophilic substitution reactions [21] proper to aromatic compounds, the sydnones give Huisgen 3+2 cyclo-additions [22] with alkenes or alkynes, arynes, etc. Such reactions are an important asset for the synthesis of new interesting heterocyclic compounds with plentiful applications.

The quantum-calculations[18] promote the sydnone aromaticity, the aromatic stabilization energy (ASE) of the heterocyclic ring having a positive value. The application of Ramsden atom connectivity-matrix analysis [23] sustains also an aromatic conjugated structure for sydnones.

New hints concerning the resonance structures of sydnones have been given by the study of solvent polarity effect on the nitrogen shielding in the spectrum of 3-methylsydnone.[24] The small influence of the solvent polarity and its hydrogen donor capacity for the N-2 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 as represented in Figure 2.

The *ab initio* calculations confirm the distribution of charge in the sydnone molecule. The most probable resonance structure (see Fig. 2) has the highest negative charge at the external oxygen atom, the nitrogen N-2 having a very small negative charge. [24] The mesoionic structure of sydnones is also sustained by the high values of their dipole moments. [25]

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. [26]

SYNTHESIS OF NEW SYDNONES

Most of the lately synthesized sydnones has an aromatic substituent at N-3, which enhances the stability of the compound. Their preparation [27, 28] followed mostly the well known multi-steps method generally used for sydnone synthesis. It may start by preparing the aromatic amine [29-32] followed by the corresponding substituted glycocol. The resulted intermediate is transformed by nitrosation and cyclization, usually using acetic anhydride, into the *N*-substituted sydnone. An example is the synthesis of coumarinyl derivative **7**, described by Patel and Patel [29] (Scheme I).

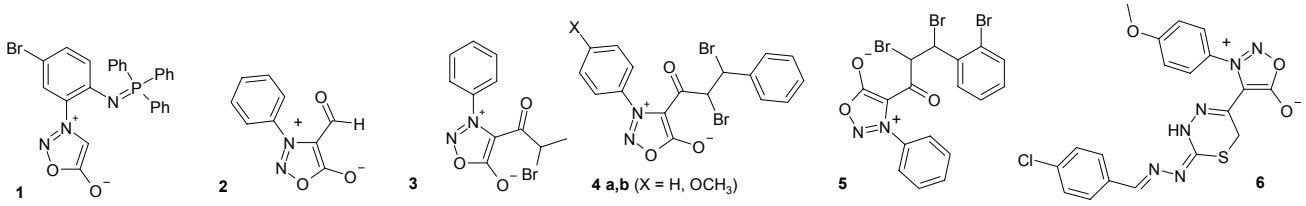


Fig. 1 – Different sydnones analyzed by X-ray spectroscopy.

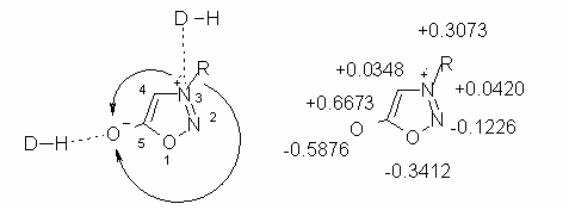


Fig. 2 – The electron charge migration and the charge distribution in 3-methyl-sydnone (R=CH_3).

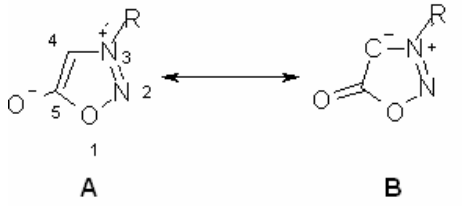
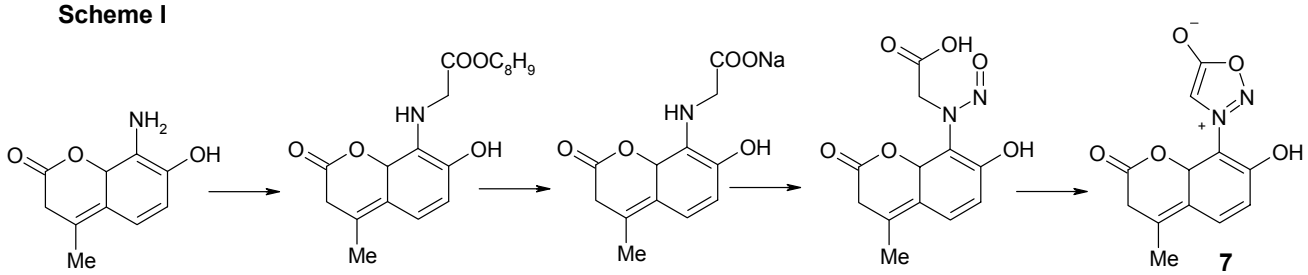
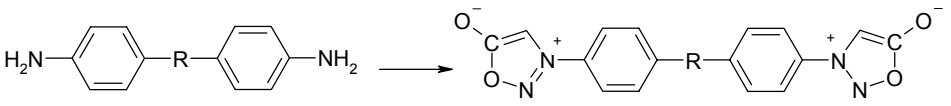


Fig. 3 – The resonance structures frequently accepted for sydnones.

Scheme I



Starting from the corresponding diamines, a number of bis-sydnones **8** [33] have been synthesized:



R = CH_2, O, SO_2

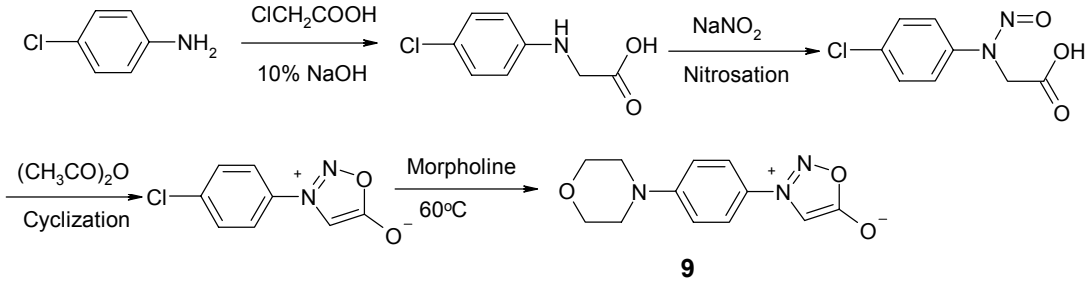
In some cases the N-3 substituent may be build after the sydnone ring synthesis. An example is the work of Patel and coworkers [34] for preparing compounds **9** (Scheme II).

Another example is the synthesis of some stilbene derivatives [35] such as compounds **10** (Scheme III).

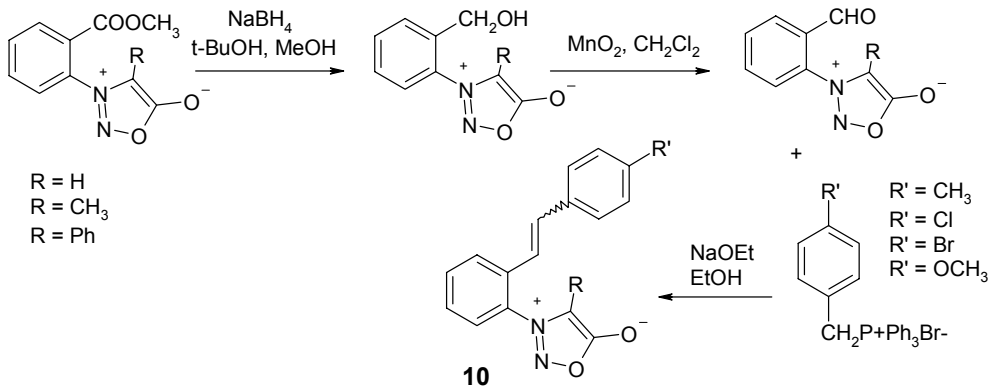
Or the more complex structures **11** and **12**,[36] shown in Scheme IV.

The recent interest concerning fluorinated aromatic and heteroaromatic compounds generates a new approach in the synthesis of sydnones containing fluorine. The preparation may start with the corresponding fluorinated pyruvic ester by a stepwise procedure [37] as presented in Scheme V.

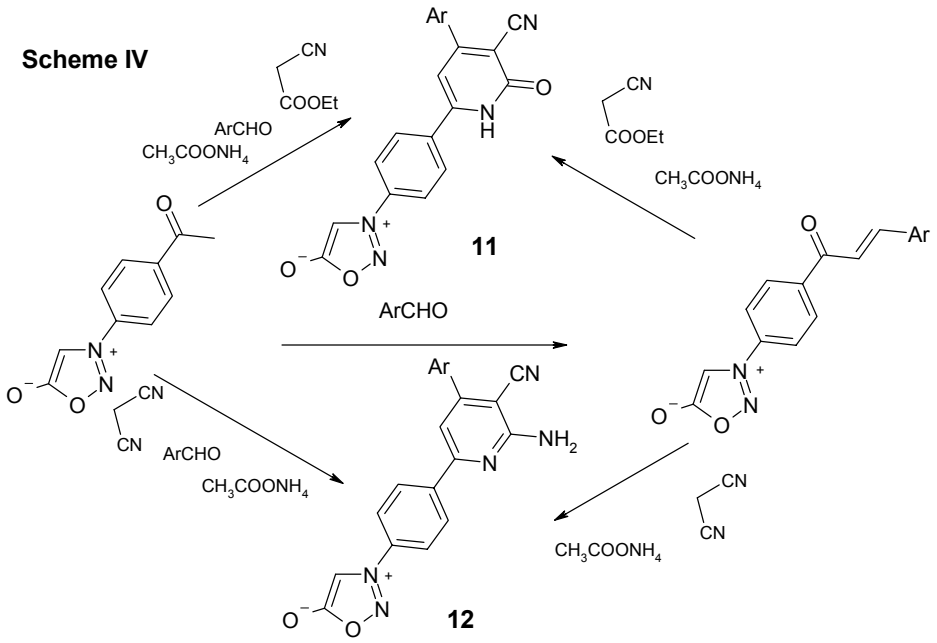
Scheme II



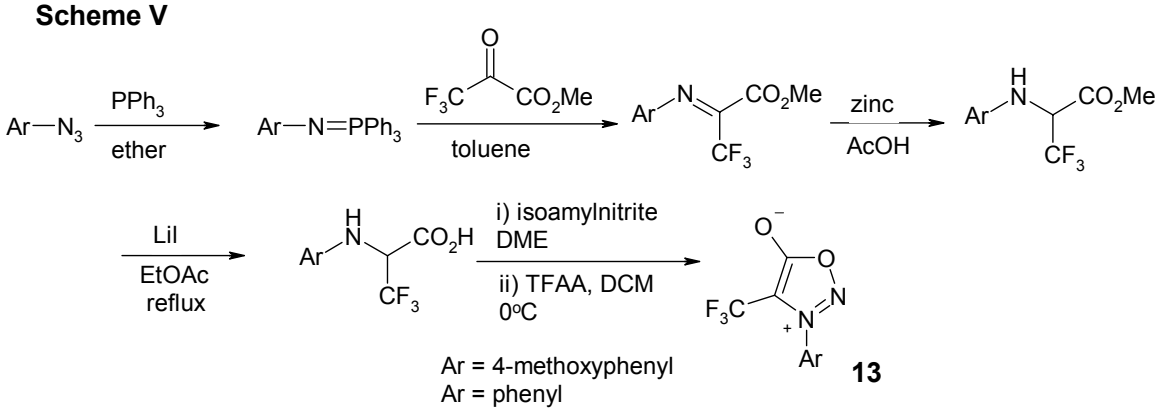
Scheme III



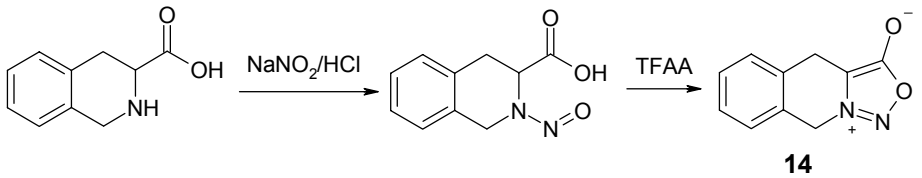
Scheme IV



Scheme V



A polycyclic compound **14** was synthesized starting from a cyclic compound as raw material, as was described by Mani and coworkers: [38]



Thus, the sydnone synthesis depends on the available raw materials as well as the structure design for the final product.

SYDNONE REACTIONS

The reactions performed starting from sydnones may be classified into two groups:

1. Reactions conserving the sydnone moiety;
2. Reactions leading to the loss of sydnone moiety.

Both types of reactions have been lately studied, generating a variety of products with numerous practical applications due to their bioactivity.

1. Reactions conserving the sydnone moiety

1.1. Reactions at C-4

The works considered in this chapter consist in substitution reactions performed at the C-4. These reactions are either electrophilic substitutions at the carbon atom of the sydnone ring bearing the

less positive charge (C-4), or oxidative coupling reactions.

Electrophilic substitution

By electrophilic substitution[39a-c] different halogen atoms or a nitro group dispatched the C-4 hydrogen atom. Depending of the reaction conditions different products may be obtained. Thus, if the halogen is taken in excess in reaction with 3-aryl-sydnones, it may also halogenate the phenyl ring. It is the case of 3-(3,5-dimethoxyphenyl)sydnone[39b] when beside the 4-halogeno-sydnone, compounds halogenated at the 3,5-dimethoxyphenyl ring have been isolated and characterized. Iodination at C-4 was performed with good yields by using *N*-iodosuccinimide in acetic acid.[39c]

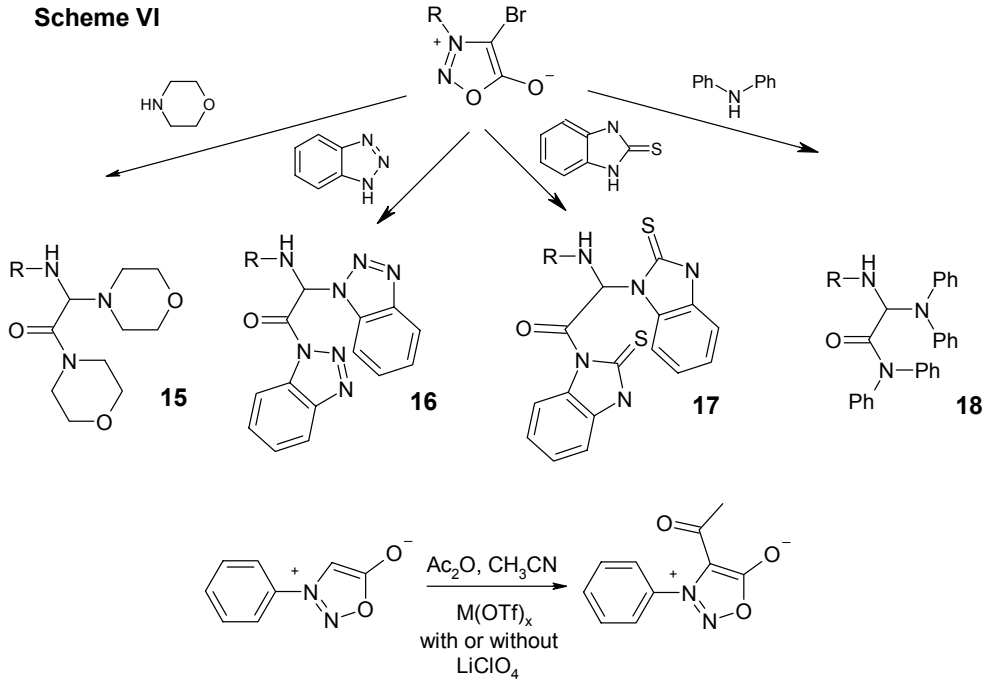
The 4-halogeno-sydnones are valuable raw materials for the synthesis of different biological active compounds [40] like **15-18**, as represented in Scheme VI.

There are other substitution reactions of sydnones. Based on the substituent introduced at C-4 acetylation, formylation and sulfonation have to be mentioned.

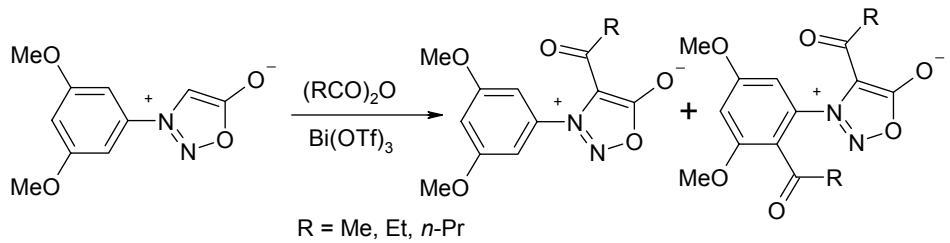
Acetylation

There are a great number of papers dealing with the synthesis of an acetyl derivative at C-4. Most of acetylations are performed by treatment with acetic acid and an acid catalyst like: P_2O_5, $HClO_4$ and BF_3. [41] Bismuth triflate or other metal triflates (M = La, Sc, Y, Hf, Gd, In) [42] may be also catalysts for this reaction. The reaction may be achieved in acetonitrile with microwave (MW) irradiation. The yields are better by the irradiation procedure compared with the classical procedures. The presence of a bulky radical in the *ortho* position of the phenyl ring (R) leads to lower yields.

Scheme VI



This green MW procedure may be used for preparing sydnone derivatives acylated also at the phenyl ring. [43] Thus, by the acylation of sydnone **19** two products **20** and **21** have been obtained:



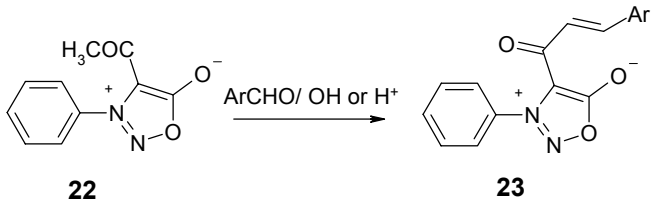
19 **20** **21**

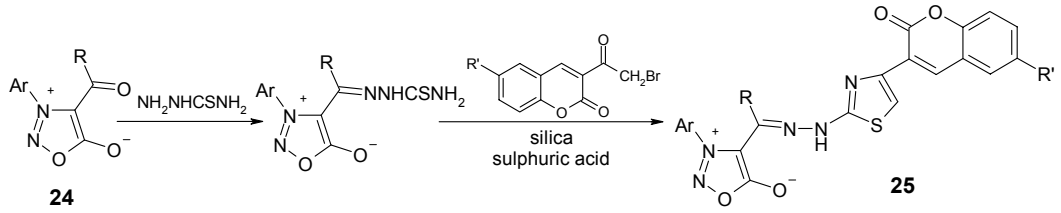
Mild conditions for preparing the 4-acetyl derivative have been proposed by Azarifar and coworkers,[44] the reaction being carried out with acetic anhydride in neutral conditions with 1,3-dibromo-5,5-dimethylhydantoin as promoter.

The sydnone acetyl derivative is a raw material for a large variety of compounds, most of them with potential biological activity. A great number of compounds **23** are prepared by crotonic condensation of the 4-acetyl-3-phenylsydnone (**22**) with a diversity of aromatic aldehydes. [45] Better yields are obtained by ultra sounds treatment which leads also to the decrease of reaction time. [46]

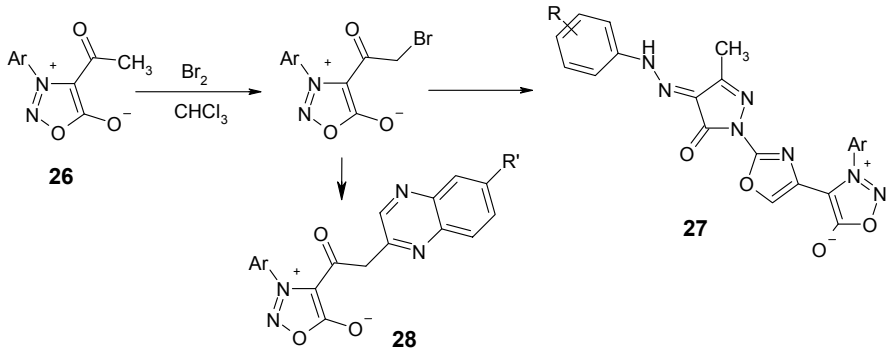
By condensation of the 3-aryl-4-acyl-sydnone **24** with thiosemicarbazide, the corresponding thiosemicarbazones are isolated and treated with a number of (6-substituted)-3-bromoacetylcoumarins resulting a diversity of substituted coumarins **25** with a sydnone moiety.[47]

Other way of valorization of 4-acetyl-sydnones such as **26** is by their bromination followed by condensation with nitrogen compounds, supplying therefore a variety of heterocycles with pharmaceutical activity like **27** or **28** [48,49] (See Scheme VII). One pot synthesis was also successful.



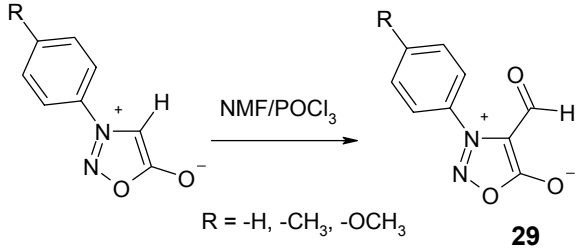


Scheme VII



Formylation

The formyl derivatives of sydnones **29** are precursors for a number of biologically active compounds. Their preparation is performed by treatment of sydnones with *N*-methyl-formanilide (NMF) and $POCl_3$:[50]



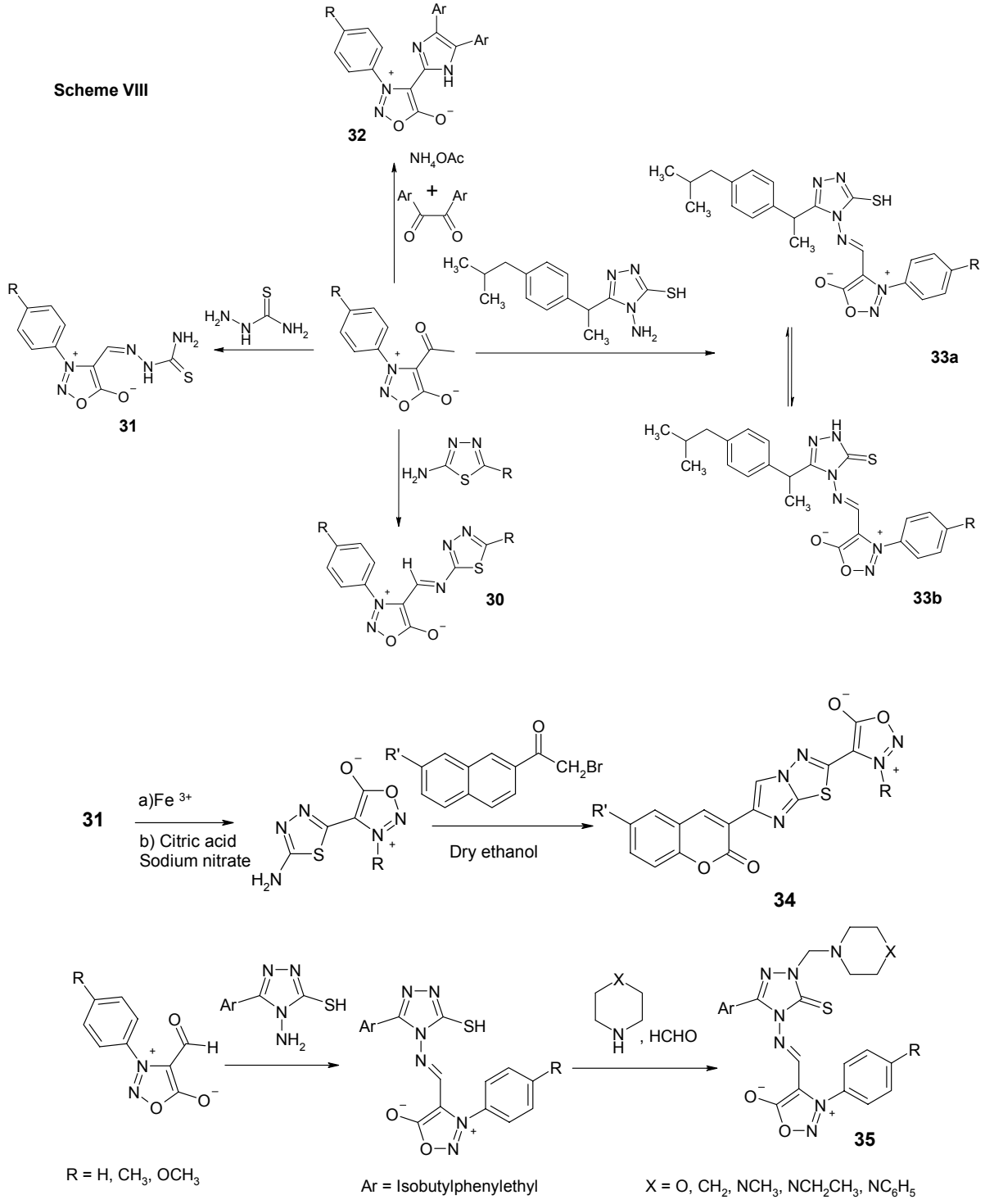
Vilsmeyer-Haack's formylation reaction is also used for preparing 4-formyl-sydnones. [51]

Starting from the 3-aryl-4-formyl-sydnones by condensation with the corresponding amino-derivatives a number of compounds resembling to different biologically active molecules (see Scheme VIII) have been synthesized. [52-54] For the synthesis of **32** the amino-derivative is formed during the reaction, from the 1,2-di-ketone and NH_4OAc.[52b]

The compound **31**, obtained by such condensation, may be transformed in a more complex heterocyclic compound **34**, [53] which is anti-cancerogenic.

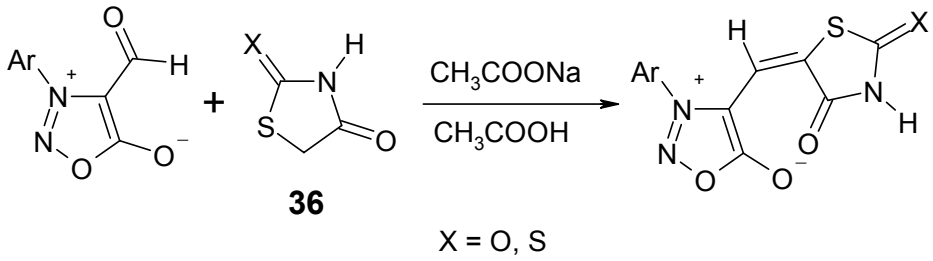
New Mannich bases **35**, with a sydnone moiety, have been prepared starting from a 3-ayl-4-formyl-sydnone (**29**) by a two step condensation. [50]

Scheme VIII



The compounds **35** with a piperidine or morpholine residues (X=CH_2, O) seem to have good analgesic and anti-inflammatory activity.

Methylene active compounds like **36** may be also a good condensation counterpart for 4-formyl-sydnones [55]:

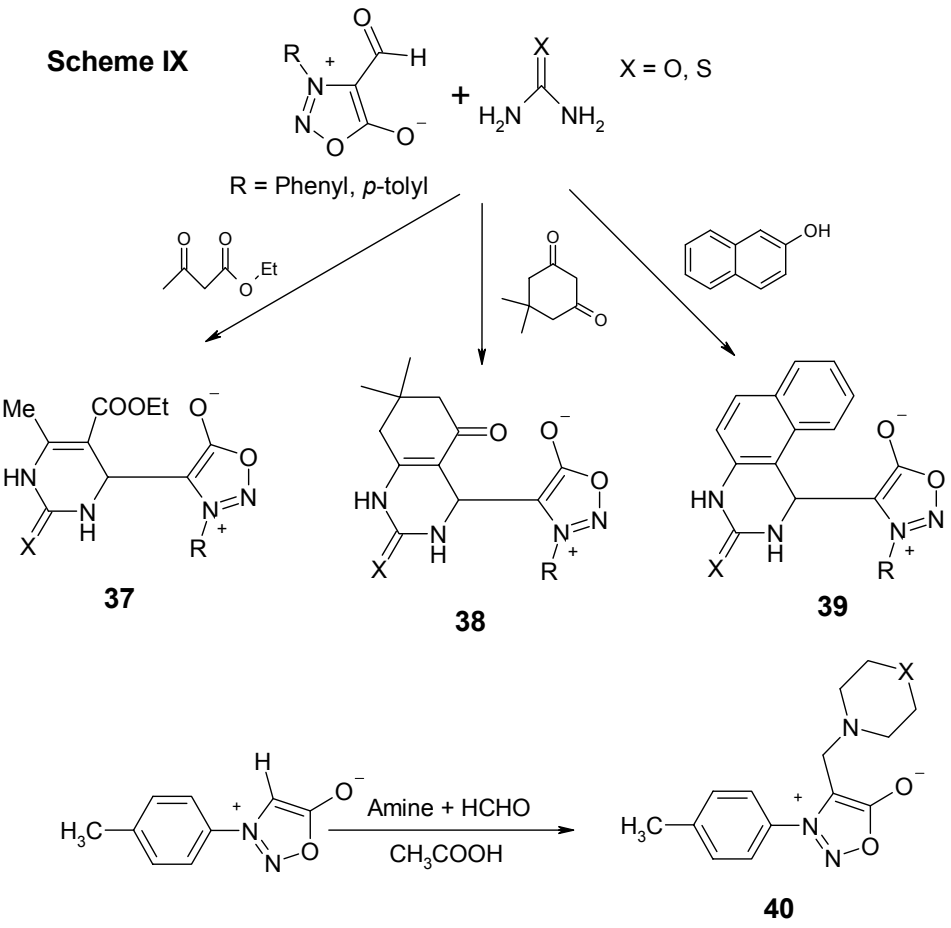


36

Complex heterocyclic structures such as **37-39** have been obtained by one pot reactions of 4-formylsydnone with urea or thiourea and a variety of organic compounds [56] (see Scheme IX).

Similarly, by treatment with paraformaldehyde and cyclic amino-derivatives a number of new compounds **40** [X = N-CH_3; NH; O; CH_2; N-CO-CH_3; N-C_6H_5; N-(dibenzo[*b*,*f*] [1,4]thiazepine); N-C_6H_4-3-Cl; N-C_6H_3-2,3-Cl; N-CH_3, 3-C_6H_5; N-$(CH_2)_2O(CH_2)_2OH$] have been prepared, and their antifungal, antibacterial, antiviral, and anticancer activities checked. [57]

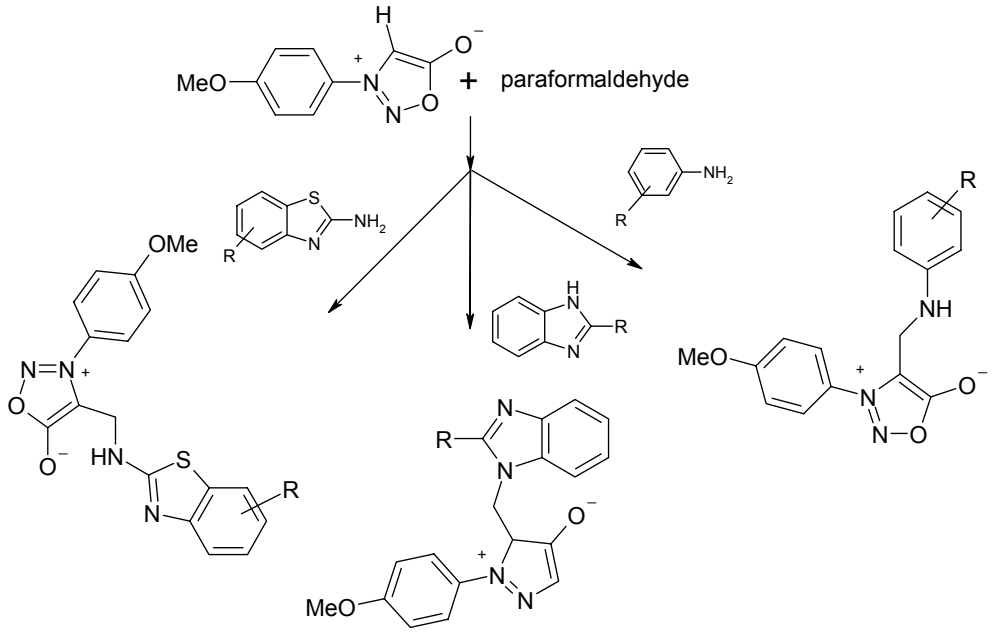
Scheme IX



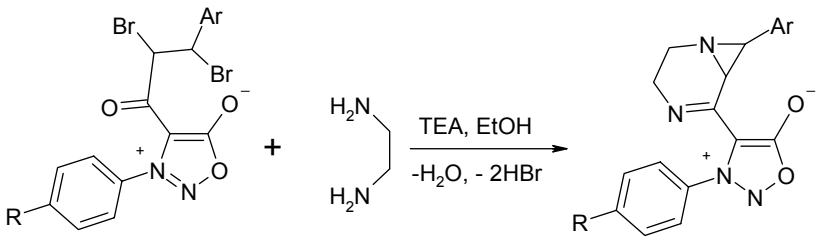
37 **38** **39**

40

By the same procedure [58a] the following substituted sydnones have been synthesized:

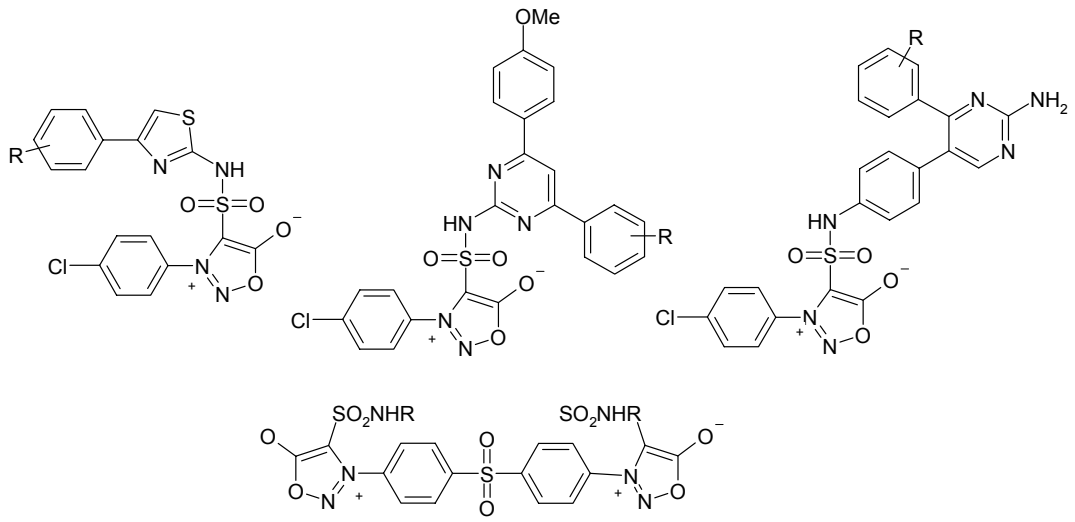


These compounds showed antifungal and antiviral activities.
Compounds with a carbonyl group at C-4 are the precursor for aziridines [58b] having sydnone moiety:



Sulfonation

Another electrophilic substitution was performed using chlorosulfonic acid. The 4-chlorosulfonylsydnones with different aromatic group at N-3 have been the raw material for preparing a variety of sulfonamides bearing a sydnone moiety, by their treatment with aromatic or heterocyclic amines. Examples of such compounds are given below: [59]



According the authors, some of the new synthesized compounds have antibacterial and antifungal activities.

Oxidative coupling

By oxidative coupling carbon-carbon bond are created leading to new sydnone derivatives. Based on the sydnone partner structure alkenylation and alkynation or arylation, etc. may be performed.

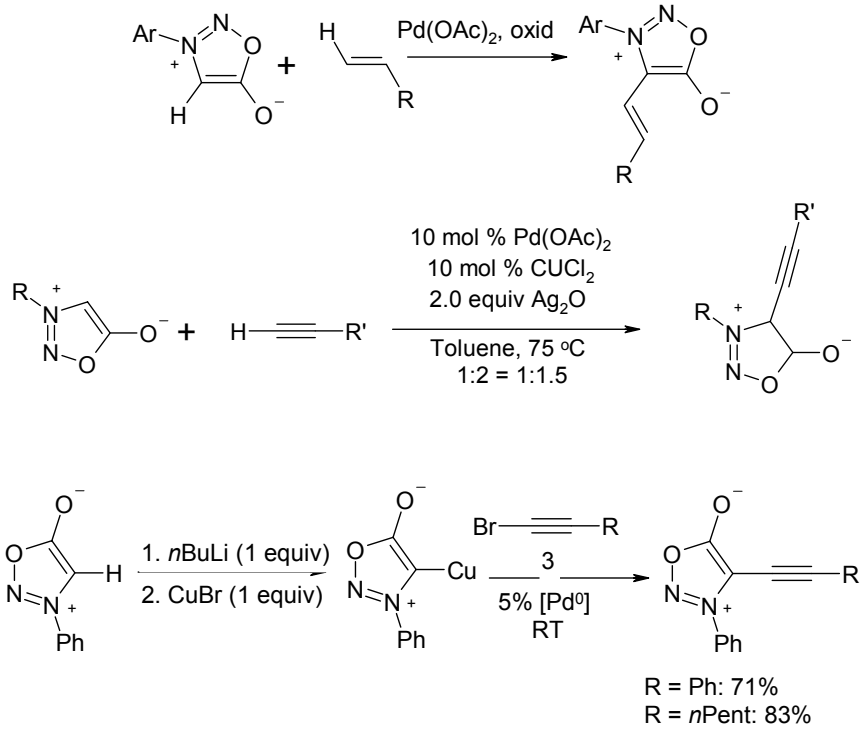
Alkenylation and alkynation

By treatment with alkene or alkyne a number of new 4-substituted sydnones have been obtained. A progress in the synthesis of new alkenylsydnones was accomplished by a direct reaction of 3-arylsydnones with alkenes under mild oxidation conditions.[60]

The oxidants may be: $K_2S_2O_8$, AgOAc and even O_2. The tandem $Pd(OAc)_2$ and AgOAc seems to give the best results (around 80%). A direct cross coupling catalyzed by Pd was performed also with alkenyl halides.[61]

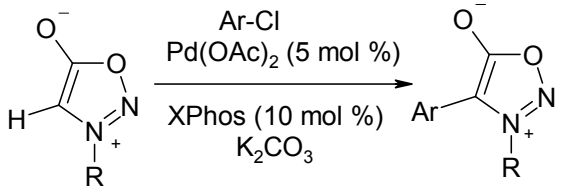
The alkene may be replaced by alkyne, the catalyst being a Pd-Cu salts mixture, in combination with Ag_2O [62] as oxidant.

The procedure goes straightforward [62] compared with the multi steps coupling of sydnone with halogeno-alkyne.[63]



Arylation and dimerization

By sydnone reaction with halogeno-arene, 4-arylsydnones [64] have been prepared. Pd salts are used as catalyst for the C-4 arylation reaction, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos) being the co-catalyst.



Bis-sydnones have been obtained in good yield through coupling reactions catalyzed by $Pd(OAc)_2$. An example is the dimerization of 3-(4-methoxyphenyl)sydnone.[65]

1.2. Reaction at the 3-aryl moiety of sydnones

The phenyl ring presents at N-3 is a good moiety for building complex compounds with potential pharmaceutical activity. Thus, a number of new barbituric acid derivatives **41** [66] has been synthesized starting from 3(4-acetyl-phenyl)sydnone and 3-aryl-4-formyl-sydnone by two successive crotonic condensations (see Scheme X).

Multidrug-resistant tuberculosis (TB) is a contemporary threat to human health worldwide. Synthesis of new efficient drugs is a target for many researchers. New compounds with sydnone moiety, such as **42**, have been synthesized [67] and their anti-tubercular activity checked.

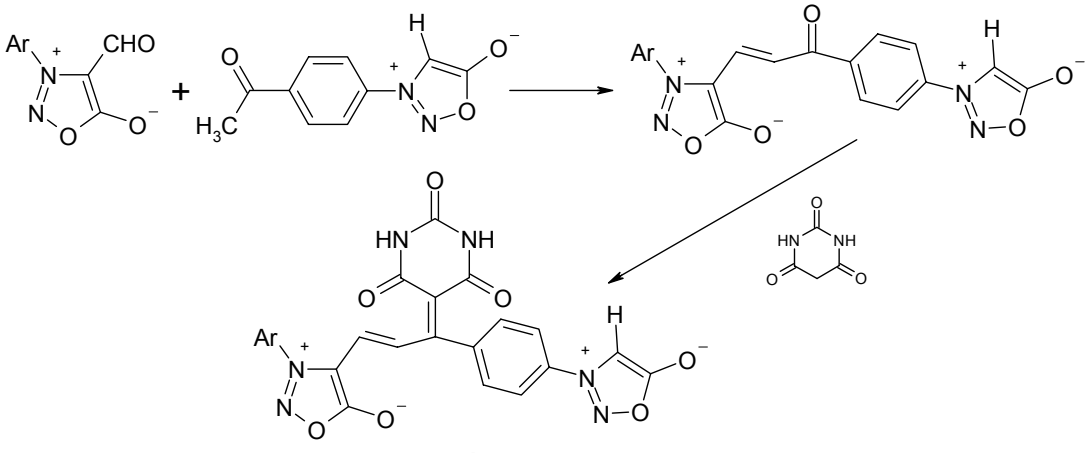
2. Reactions leading to the loss of sydnone moiety

Among these reactions, where the sydnone structure is not preserve, dipolar 1-3 cycloaddtion reaction, known as Huisgen cycloaddition, deserves a special place due to its synthetic value. Reduction or oxidation as well as rearrangements are also observed during such reactions.

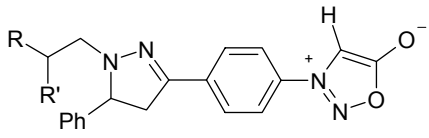
2.1. 1-3 Cycloaddition reactions

Described by Huisgen and coworkers [68] in 1960, the 1-3 polar cycloaddition reactions proved to still be a valuable tool for the preparation of a large variety of 5 member ring heterocyclic compounds.

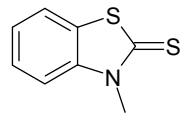
Scheme X



41



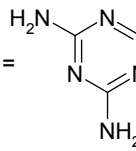
42

a R =  R' = H

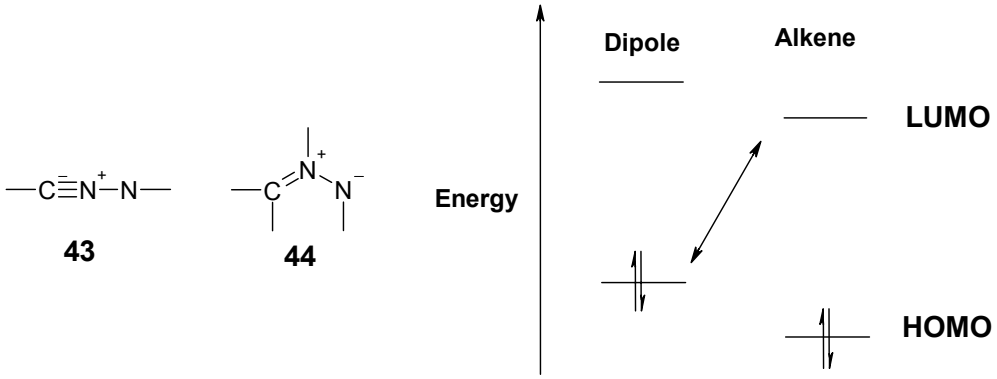
b R = R' = $HOCH_2CH_2$-

c R = *t*-butyl R' = H

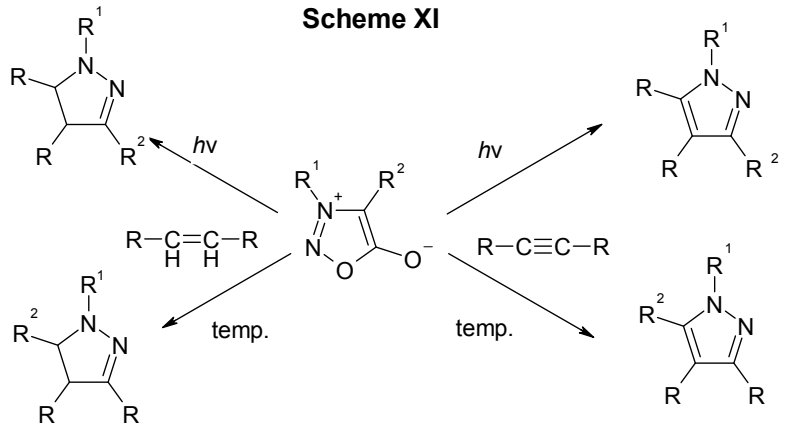
d R = $CH_3CH_2CH_2CH_2$ R' = H

e R =  R' = H

Due to their polar structure sydnones take part in such reactions having as partner alkenes or alkynes. Starting from a variety of sydnones or their partners, different compounds may be prepared by an easy way. Sydnones react as dipoles, giving as intermediate [69] different structures, depending on the reaction conditions. In photolytic conditions a linear nitrile imine **43**, and by a thermal reaction a bent azomethine imine **44** are formed. In both situations, the interaction of orbitals for such dipole-alkene cycloaddition is $HOMO_{dipole}$ - $LUMO_{alkene}$, as shown below:



Scheme XI

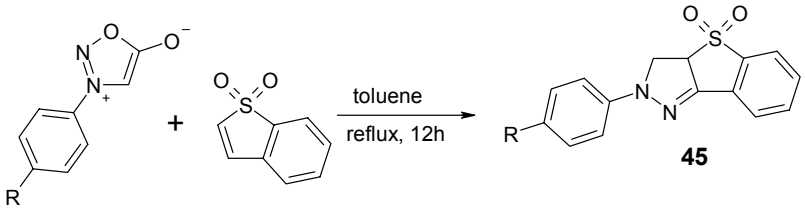


A general scheme (Scheme XI) depicted by Sindler-Kulyk and coworkers[70] display the compounds that may be synthesized from sydnone and alkenes or alkynes. It shows the product substituent position, which is controlled by the reaction conditions (thermal or photochemical). The resulted pyrazolines or pyrazoles are positional isomers.

The recent findings concerning the sydnone [3+2] cycloadditions to double or triple bonds are presented below.

Sydnones and alkenes

A recent example, of alkene cycloaddition to a double bond is the reaction of 3-*N*-aryl-sydnones with benzothiophene:[71]

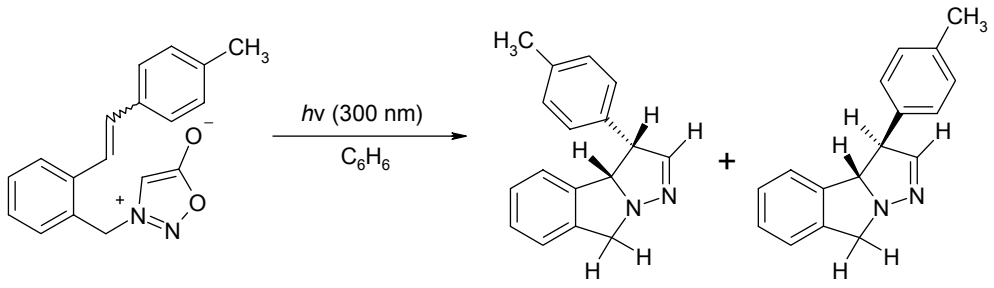


R	Yield (%)
H	35
4-Me	33
4-I	38
4-Cl	40

R	Yield (%)
4-OMe	35
4-F	45
3,4-OCH_2O	30

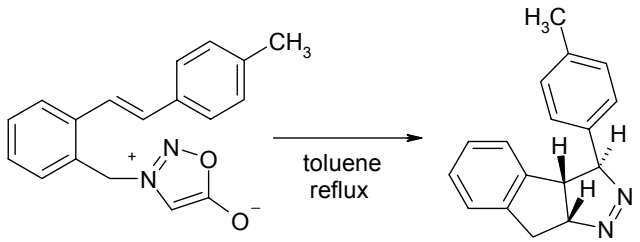
The structure proposed for the product **45** is supported by the ^{1}H-NMR spectrum.[71]

When the double bond belongs to the sydnone molecule, an intramolecular cyclization may occur, complex polycyclic compounds being obtained, such as **47** and **48**. By photochemical cyclization from both isomers *cis* and *trans* **46** the same mixture of compounds is obtained. The cycloaddtion reaction is regioselective but not stereoselective.[70]



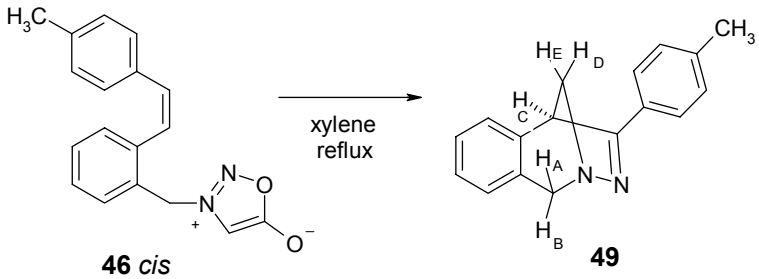
46 **47a** **47b**

From the *trans* isomer, in toluene at reflux, the pyrazoline **48**, another regio-isomer, was obtained,[70] the cyclization being in this case highly stereoselective.



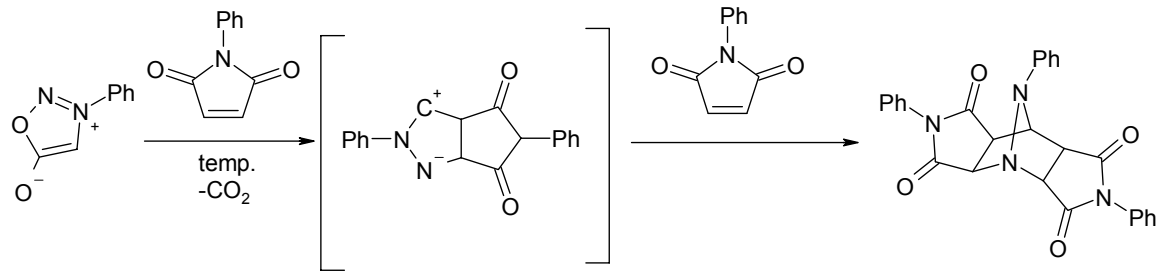
46 *trans* **48**

The thermal cycloaddition of **46** *cis* isomer generates a bridged structure **49**:[70]



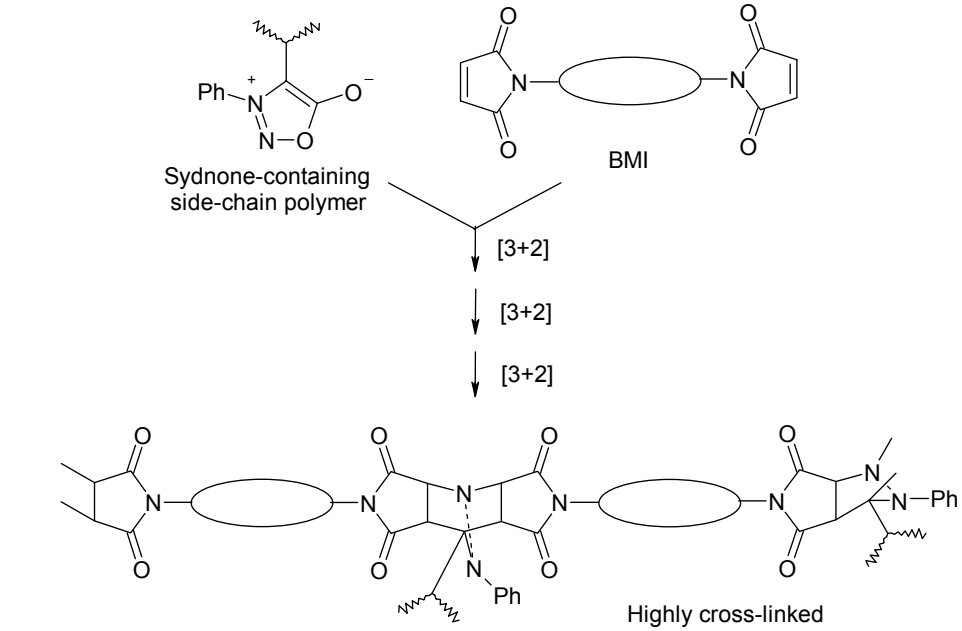
46 *cis* **49**

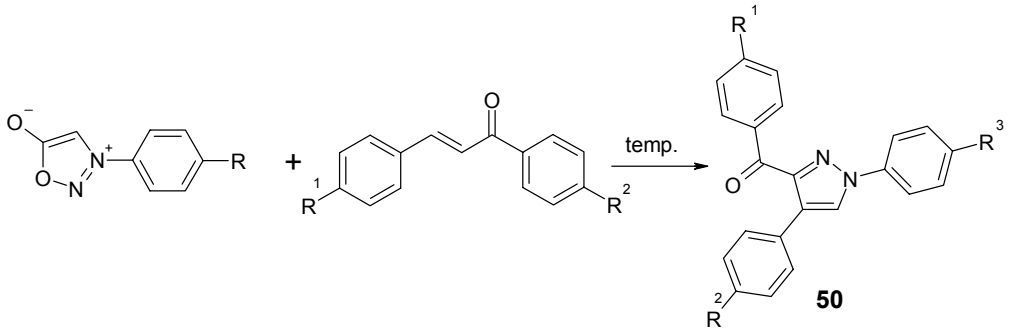
An interesting polycyclic product results by a double cycloaddition of phenyl-maleimide to 3-phenylsydnone: [72]



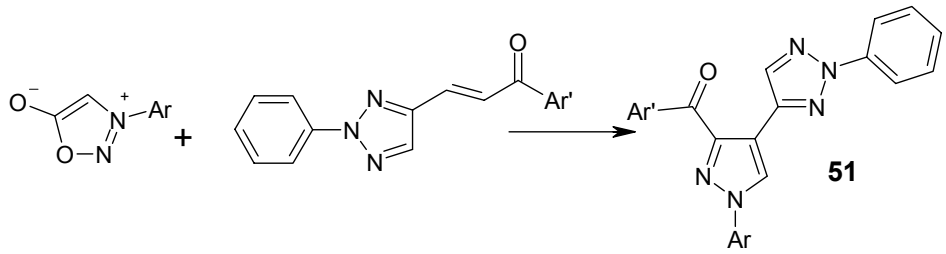
The reaction has been used for crosslinking polymers.[72]

In some cases the double bond addition lead to pyrazole, by the oxidation or elimination reactions of the intermediate pyrazoline. Such examples are presented further on. By thermal cycloaddition reaction of 3-arylsydnone and α,β-unsaturated ketones a number of pyrazoles (**50**, R_{1-3} = H or CH_3) [73] have been synthesized.



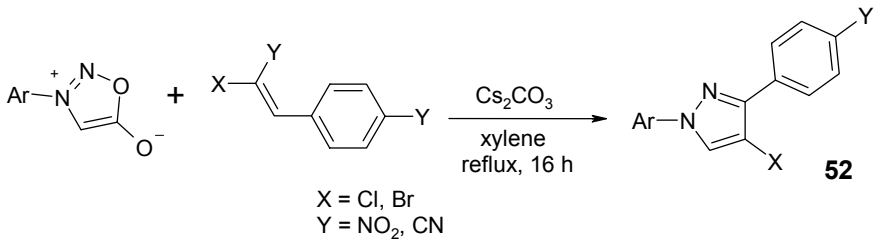


A similar cycloaddition was described by Zheng and Liu.[74]



The proposed structures for pyrazoles **50** and **51** were sustained by ^{1}H-NMR and X-ray crystal analysis.

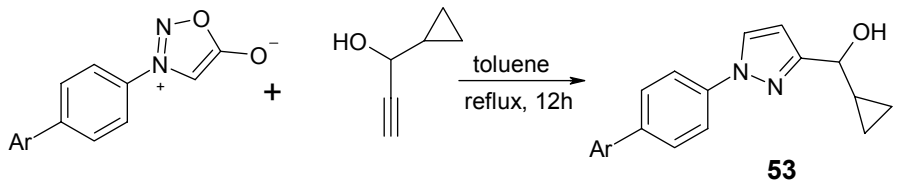
The cycloaddtion at high temperature of 1,2-dihaloalkene to 3-arylsydnone lead to halogenopyrazoles. An example is the work of a Chinese research team [75] recently published. Thermal cycloaddtion of 2-aryl-1,1-dihalo-1-alkenes to 3-arylsydnones leads to pyrazoles **52:**



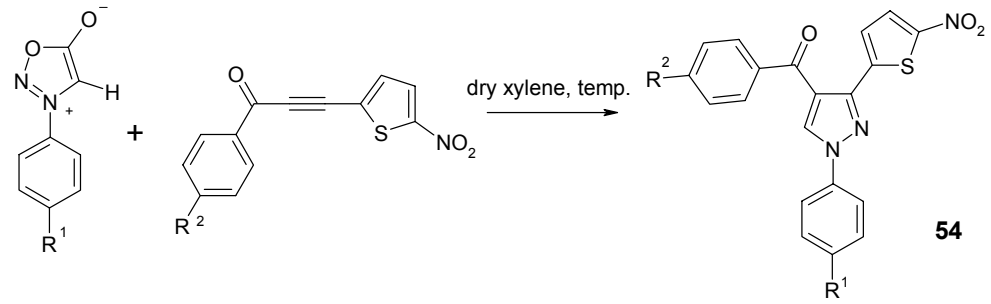
Sydnones and acetylenes

The triple bond addition to sydnones generates pyrazoles. Starting from different substituted sydnones and acetylenes a variety of pyrazoles has been synthesized. Most of the pyrazoles are bioactive compounds with activities such as: antiviral, antibacterial, antifungal, anticarcinogenic, insecticidal, antioxidant, etc.[76]

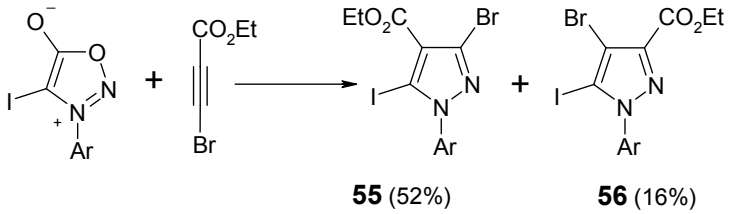
From 1-cyclopropylprop-2-yn-1-ol as dipolarophile and several arylsydnones, in toluene at reflux, pyrazoles **53** were synthesized with yields of 30-38%. [71]



Acetylenic ketones may be another dipolarophile[77] leading to pyrazoles **54** (R_1=H, CH_3, OCH_3; R_2=H, CH_3, OCH_3, Cl). Some of these compounds showed good antibacterial and antifungal activity.



Esters of acetylene mono- or di-carboxylic acids are also good dipolarophiles. From the ester of bromo-acetylene carboxylic acid and several 3-arylsydnones, in xylene at reflux, the pyrazoles **55** and **56** have been prepared. [78]

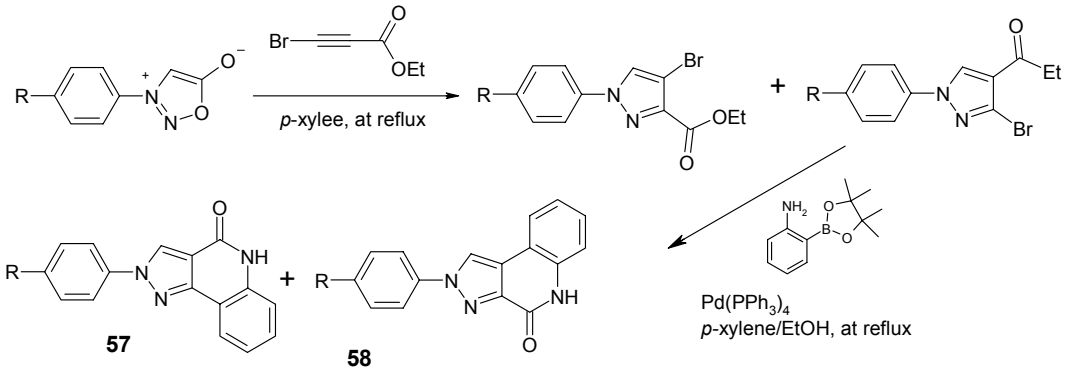


The 3,5-dihalogeno-pyrazole, such as **55**, is the major regio-isomer and may be easily separated.

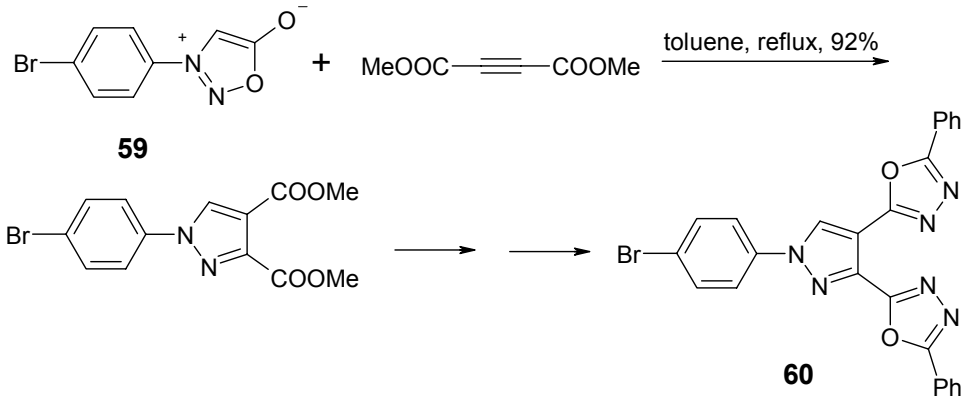
By decarboxilation and Pd-coupling reaction new substituted pyrazoles may be obtained. Starting from the bromo-acetylene carboxylic acid, in one-pot reactions, pyrazoloquinolinone derivatives **57** and **58** have been prepared. [79] The step by step transformations (1,3-dipolar cycloaddition, followed by a Suzuki reaction, and intramolecular cyclization) are presented in Scheme XII. As proven for

compounds with similar structures, the compounds **57** and **58** have biological activity as adenosine receptor antagonists.[80]

Scheme XII

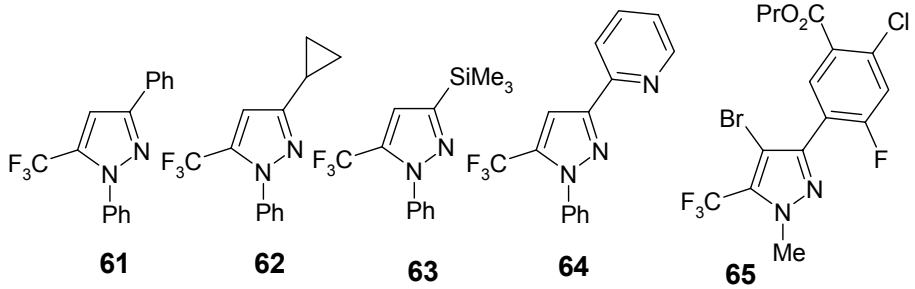


The cycloaddition of acetylene dicarboxylic ester to 3-(4-bromophenyl)sydnone (**59**) lead to an intermediate, that may generate by a multi step transformation new pyrazoles **60**.[81] The phenyl (Ph) may be replaced by substituted (*m*-CF3-C6H4, 2,6-di-CF3-C6H3, *p*-OMe-C6H4) aryl groups, but also by heteroaryl-groups like: 2- and 3-thienyl, 2-benzo[*b*]thienyl, dibenzo[*b*,*d*]thiophen-4-yl, and dibenzo[*b*,*d*]furan-4-yl. All these aromatic groups extend the conjugation in the resulting heterocycles. Thus, such compounds may be used for obtaining conducting polymers.



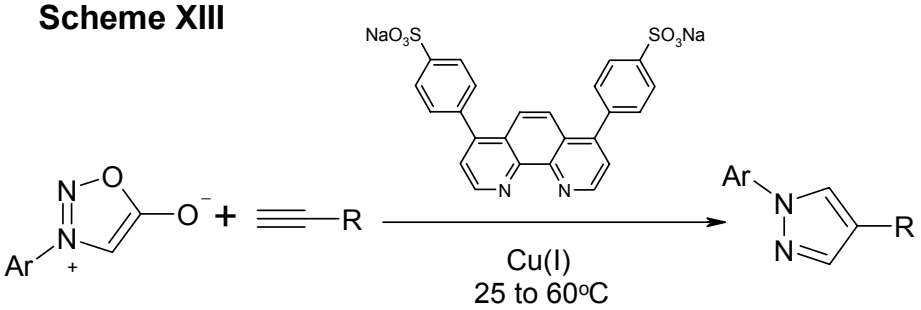
Similar pyrazoles have been prepared [82] starting from the sydnone **59** and phenyl- or diphenyl-acetylene as dipolarophiles.

Performing the cycloadditions with different sydnones and alkynes a variety of pyrazoles may be prepared. Harrity and coworkers [83] regioselectively synthesized a number of 3-substituted 5-trifluoromethylpyrazoles. Compounds **61-64** are examples from this work. The synthetic procedure may be used for preparing biological active compounds, like the herbicide *Fluazolate* (**65**).

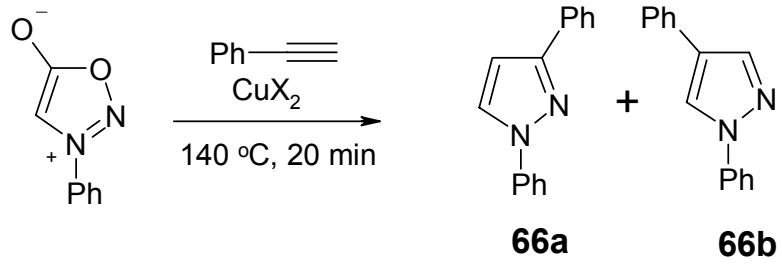


The regioselectivity goes to 100% when the cycloaddition is performed in the presence of a catalyst based on Cu (I) [84] obtained by the reduction of Cu(II) salt with sodium ascorbate. The complex of Cu (I) with a phenanthroline derivative seems to give the best results (see Scheme XIII).

Scheme XIII



As recently proven,[85] the copper catalyst influenced the regioselectivity. Thus, the use of $Cu(OTf)_2$ as catalyst in a Huisgen reaction of a sydnone with a terminal acetylene leads to 1,3-substituted pyrazoles, while $Cu(OAc)_2$ provides the 1,4-isomer. The cooper catalyst gives quickly a remarkable conversion, reducing the reaction time to less than 1h, compared with at least 4h for other catalysts like: ZnI_2, $Zn(OAc)_2$, $InBr_3$, $In(OTf)_3$, $MgBr_2$.[85] Depending on the cooper salt anion, phenylacetylene cycloaddtion to 3-phenylsydnone may provide as major product **66a** or **66b**.

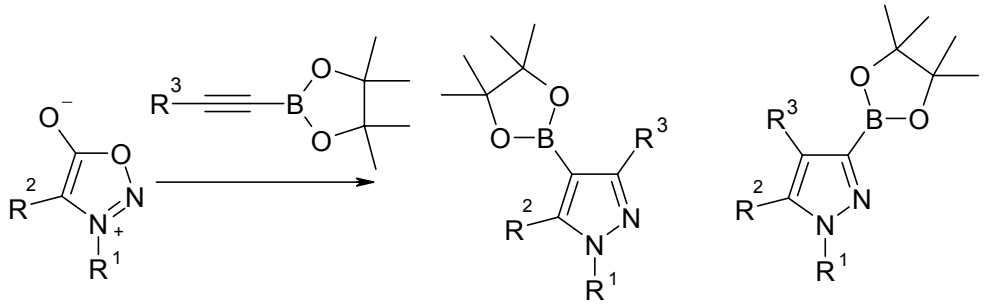


The highest conversion (~100%) was with $Cu(OTf)_2$ as catalyst, the ratio **66a/66b** being 9/1.[85] By using Cu(2-ethylhexanoate)$_2$ the pyrazole **66b** is the major product (ratio **66a/66b** = 8/92) [85] obtained with a conversion of 88%. According to the experimental results, it seems that $Cu(OTf)_2$ acts as a Lewis acid activating the sydnone, which gave by cycloaddtion with phenylacetylene the isomer **66a**. In $Cu(OAc)_2$ and Cu(2-ethylhexanoate)$_2$ cases, Cu(II) is reduced to Cu(I) forming the cuprous acetylide which undergoes cycloaddtion to sydnone providing mainly the regio-isomer **66b**.

The presence of a substituent at sydnone C-4 as well as the geometry of the dienophiles (e.g. azine substituted alkynes) influence the regioselectivity [86] of the cycloaddtion reactions.

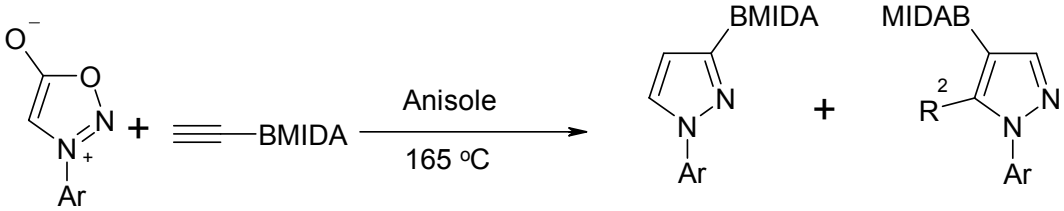
A study for discovering new reactions based on immunoassay technique was developed by Taran and coworkers.[87] Among the investigated reactions the addition of sydnones to terminal alkynes gave good yields in the chosen experimental conditions, namely: Cu-phenantroline complex (prepared in situ), triethanolamine and sodium ascorbate, in a mixture of water/t-butanol as solvent.

The interest for boron chemistry, determined by the various applications found not long ago, [88] has been noticed also in connection with sydnone cycloaddtions. A number of pyrazoles with boron comprising substituents have been synthesized starting from sydnones. Thus, from mono- or di-substituted sydnones and alkynylboronates, new pyrazoles **67** [R_1= C_6H_5, CH_3; R_2= H, CH_3, iC_3H_7, C_6H_5; R_3= H, $Si(CH_3)_3$, C_6H_5] have been obtained.[89] The reaction may be performed in conditions generating with high yield the isomer **67a**. The boron group could be replaced with aromatic rings through a Suzuki coupling reaction catalyzed by $PdCl_2$.[89]



67a **67b**

Another strategy for synthesizing new pyrazoles was based on the cycloaddition reaction of 3-arylsydnone to a terminal alkynyl boronate ester, namely ethynyl *N*-methyliminodiacetic acid boronate (BMIDA): [90]



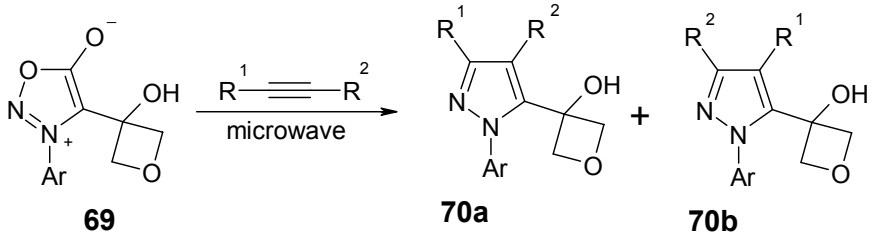
68a **68b**

Electron-withdrawing groups (F, NO_2) in the *para* position of the *N*-aromatic ring lead to better yields of the cycloaddition reaction. The ratio of **68a**/**68b** was around 7/3. [90]

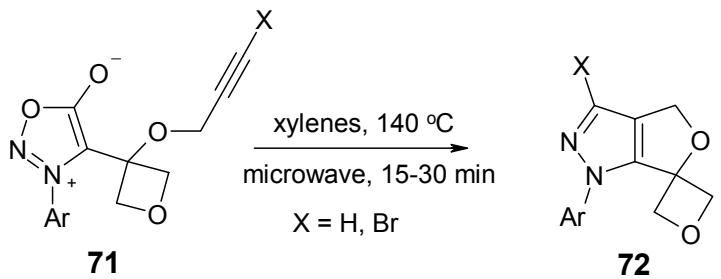
New pyrazoles with polycyclic skeleton have been prepared by inter- or intra-molecular cycloaddition. Intermolecular cycloadditions of oxetanyl-substituted sydnones **69** [91] to acetylene derivatives generate pyrazoles **70a** and **70b**. The reaction is regio-selective **70a** being the main product.

Sydnones **71** with a triple bond in the lateral chain gave as only product [91] the corresponding pyrazoles **72**.

The dienophile may also have a cyclic structure. Some examples are given below.

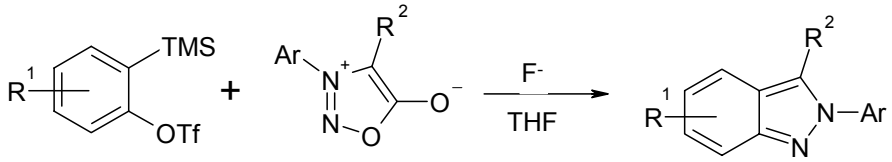


69 **70a** **70b**

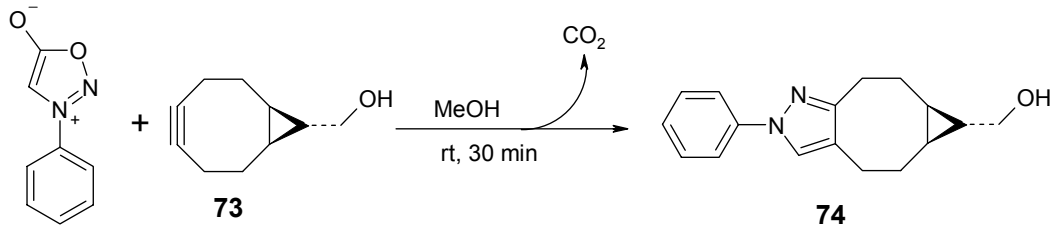


71 **72**

2*H*-Indazoles have been prepared by cycloaddition of sydnone to aryne. The aryne was generated *in situ* by treatment of the appropriate *ortho*-substituted benzene with fluorine compounds (CsF or TBAF). Using a variety of sydnones and aryne precursors, a number of indazoles has been prepared: [92]

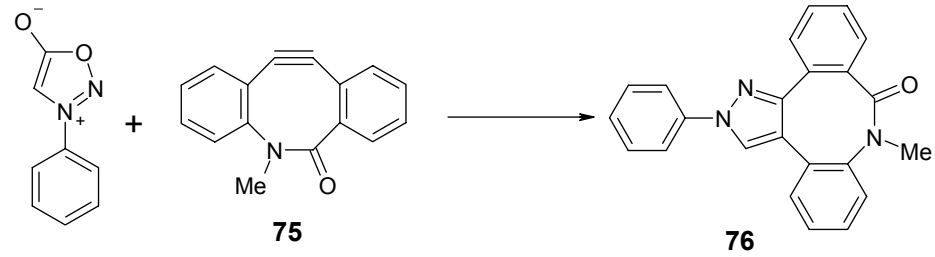


Bicyclo [6.1.0] nonyne derivative **73** was used for the synthesis of a new pyrazole **74.** [93] The reaction is strain promoted and proceeds with high yield (99%) without copper catalyst. It may be performed also in buffered water solution at the physiological pH. Thus, this reaction may be used for labeling protein.



Similar cycloadditions, leading to new pyrazoles with complex polycyclic structures, have been performed by Taran and coworkers [94] starting from various 3-arylsydnones and **73**.

More recently the alkyne **75** was used successfully [95] in cycloaddtion with 3-phenylsydnone:

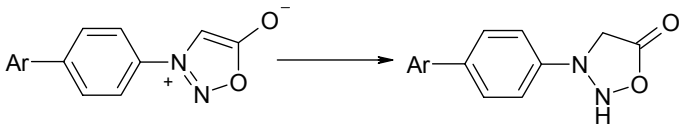


The reaction was performed at room temperature in CH_3CN/H_2O (volume ratio 1/1) giving regioselectively compounds **76**. The paper reports a DFT-free energy calculation for a number of cycloadditions between 3-phenylsydnone and strained alkenes and alkynes in view of protein labeling.

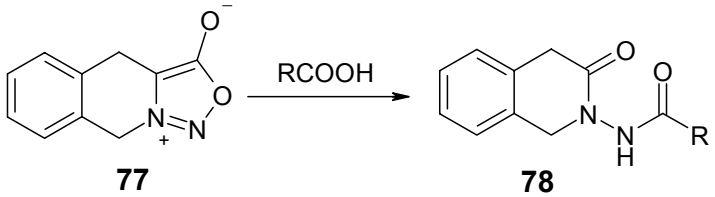
2.2. Miscellaneous reactions

There are other reactions beside cycloadditions leading to the transformation of sydnone ring.

The sydnone ring may be reduced electrochemically by controlled potential electrolysis, [96] leading to an oxadiazole derivative.



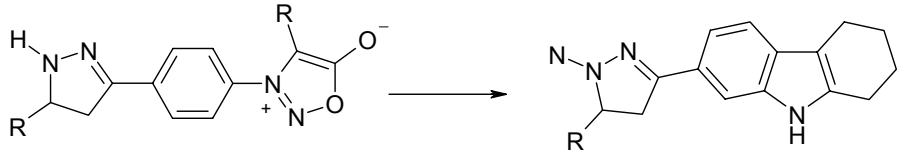
By an oxidative decarboxilation sydnone **77**, in the presence of an organic acid (RCOOH), may be turned into different hydrazides **78**. [96] The reaction was performed in xylene at reflux for 12-16 h.



77 **78**

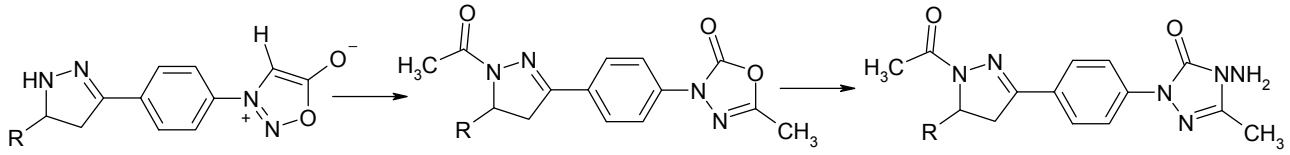
Starting from the 3-arylsydnones **79**, on treatment with cyclohexanone in conc. HCl, followed by rearrangement, carbazoles **80** were obtained.[98] The new carbazoles have been screened for antitubercular and anticarcinogenic activities. They proved to have antitubercular, antioxidant and DNA cleavage activities.

By treatment with acetic anhydride and bromine, then hydrazine, new heterocycles **81** with potential biological activity [99] have been synthesized.



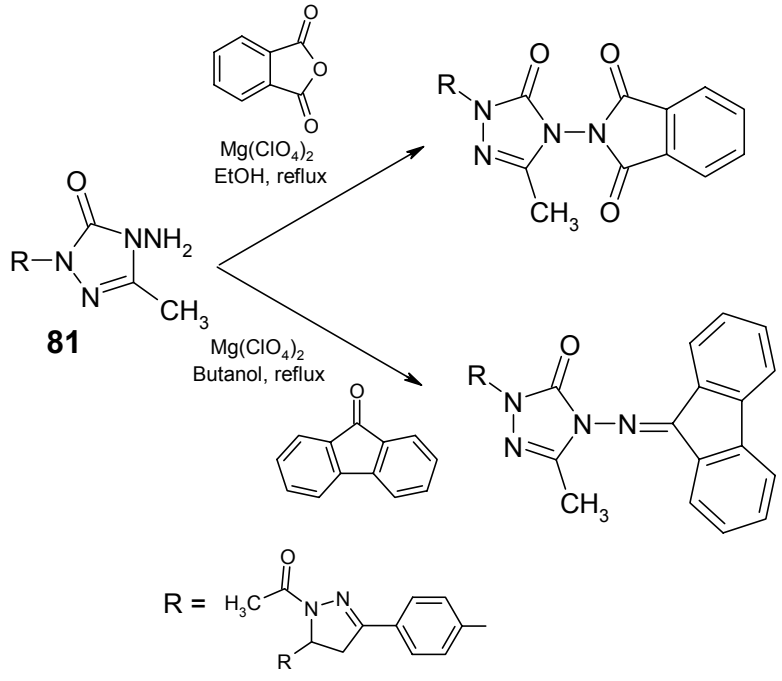
79 **80**

a: R = Phenyl, b: R = *o*-chlorophenyl, c: R = *m*-chlorophenyl, d: R = *p*-chlorophenyl, e: R = *p*-nitrophenyl, f: R = *o*-hydroxyphenyl, h: R = styryl, i: R = methyl, j: R = *p*-anisyl, k: R = *p*-tolyl



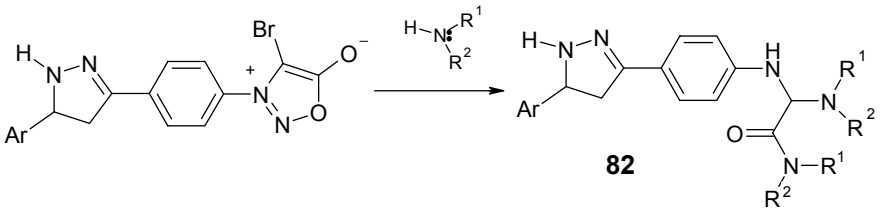
81

The heterocycles **81** may be precursor for new anti-tubercular agents. [100]



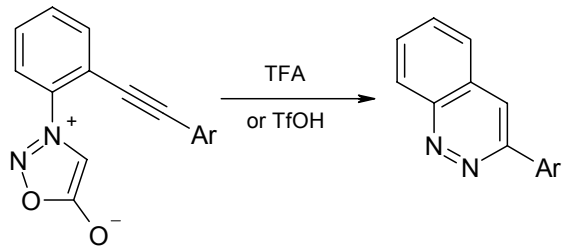
81

By treatment of sydnones similar to **79** with secondary amines, the sydnone ring opens with amides **82** [101] formation:



82

The presence of a triple bond in the *ortho* position of the aromatic ring from N-3 leads, on treatment with TFA or TfOH, to the synthesis of 3-arylcinnolines, with high yields (60-86%).[102]

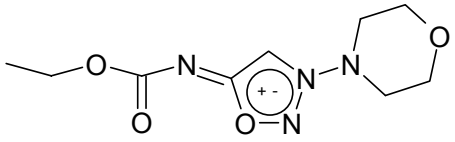


SYDNONES DERIVATIVES APPLICATIONS

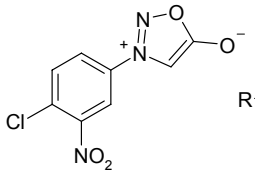
The new sydnones derivatives, synthesized since 2010, found a variety of practical applications. Most of the compounds have been tested as drugs for different diseases. Thus, many of the new compounds proved to have antibacterial and antifungal activity. [59, 103] Some sydnones may be used against parasites, like for instance: *Leishmania amazonensis* [104] or have general antihelmintic activity. [105] Many sydnone derivatives proved to have analgesic and anti-inflammatory effects.[106] Releasing NO, *Molsidomine* [*N*-(ethoxycarbonyl)-3-(4-morpholino)sydnone-imine, **83**] has been found efficient [107] for the cardiac function rescue in rats . The compound **83** may also remove films [108] made by bacteria like *Salmonella enterica* and *Escherichia coli*.

Other sydnones, like **84-86**, have been used for the treatment of cancer becoming promising agents for destroying cancer cells.[109] Studies related to the way of action against cancer of these compounds have been performed, demonstrating their metabolic interference.

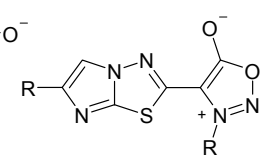
The insertion by coordination of a transition metal may enhance the biological activity of sydnone derivatives, as shown by palladium (II) [110] or lanthanide (III) [111] complexes. In these complexes sydnone ring is not involved in the coordination with the metal ion.



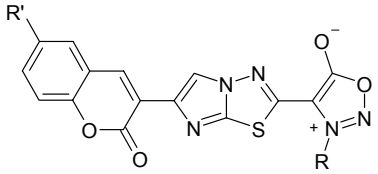
83



84



85



86

The meosoionic structure leads to other applications of sydnones, such as ionic liquids [112] which are considered green solvents. The advantage of sydnones as such solvents consist in their neutral state due to the equal electric charges of opposite sign, fact making possible their use in ionic reaction like electrochemical processes, etc. Sydnones may be also used as battery solvent[113] in a mixture with ethylene- and diethyl-carbonates (molar ratio: 0.05/1/1). The mixture with ethanol, 2-(p-methoxy phenylsulfonyl)-4-methylsydnone seems a good solvent for ultrasound transmission.[114]

CONCLUSIONS

The chemistry of sydnones has been very dynamic in the last years. New compounds have been obtained proving that sydnones are a versatile synthon for preparing a large variety of heterocycles. Most of the new compounds found applications as drugs with: anti-bacterial, anti-fungal, anti-helmintic activity and even proved to be efficient in fighting some types of cancer disease.

The mesoionic structures allowed applications as solvent for ionic reactions or for electrical devices.

All the applications evidenced make sydnones still of interest for organic chemists and not only them, despite so many years passed since their discovery.

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