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Mesoionic sydnone derivatives: An overview

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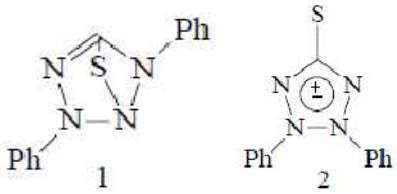
ABSTRACT

Mesoionic compounds are dipolar five or six membered heterocyclic compounds in which both the negative and the positive charge are delocalized, for which a totally covalent structure cannot be written, and which cannot be represented satisfactorily by any one polar structure. The most important member of the mesoionic category of compounds is the sydnone ring system. Sydnones are mesoionic compounds having the 1, 2, 3-oxadiazole skeleton bearing an oxygen atom attached to the 5 position. Sydnones are dipolar, pseudo-aromatic heterocycles with a unique variation in electron density around the ring. These characteristics have encouraged extensive study of the chemical, physical, and biological properties of sydnones, as well as their potential applications. A large number of sydnone derivatives have been synthesized with biological interest and reported to possess a wide spectrum of biological and pharmacological activities like antimicrobial, anti-inflammatory, analgesic, anti-pyretic, antitumour, antiarthritic and antioxidant properties. The research and development of new sydnone functionalisation methods in conjunction with the cycloaddition reactions will provide the focus of future research in the development of sydnone drugs. Thus there is wide scope for structurally modified sydnone derivatives to explore more potent biodynamic molecules.

Keywords: Sydnone, mesoionic compounds, 1, 2, 3-oxadiazolium-5-olates.

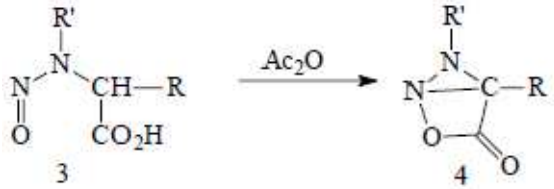
INTRODUCTION

Over 120 years ago, Emil Fischer oxidized dithizone; yielding an orange, crystalline compound he entitled dehydrodithizone. Fischer assigned the bicyclic structure **1** to this species, however, better understanding of the nature of such species was gained as time progressed and more advanced analytical techniques became available. In 1946, Baker, Ollis, and Poole coined the term mesoionic (mesomeric/ionic) to describe the monocyclic, dipolar nature of compounds such as dehydrodithizone. In 1955, these three authors published a paper in *Chemistry and Industry* which specifically defined the term mesoionic. Using their definition, dehydrodithizone is considered the first known mesoionic species and is assigned the dipolar, monocyclic structure **2**.



1 2

In 1935 the first sydnone was synthesized in Sydney, Australia. Earl and Mackney reported that treatment of N-nitroso-N-phenylglycine with acetic anhydride afforded a general, anhydro derivative to which the bicyclic structure was assigned. Due to the general utility of the reaction a variety of analogous compounds where prepared and given name “sydnone”(due to their preparation in Sydney, Australia)



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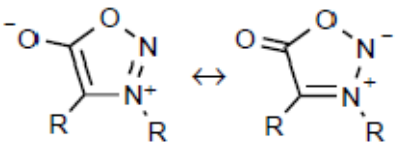
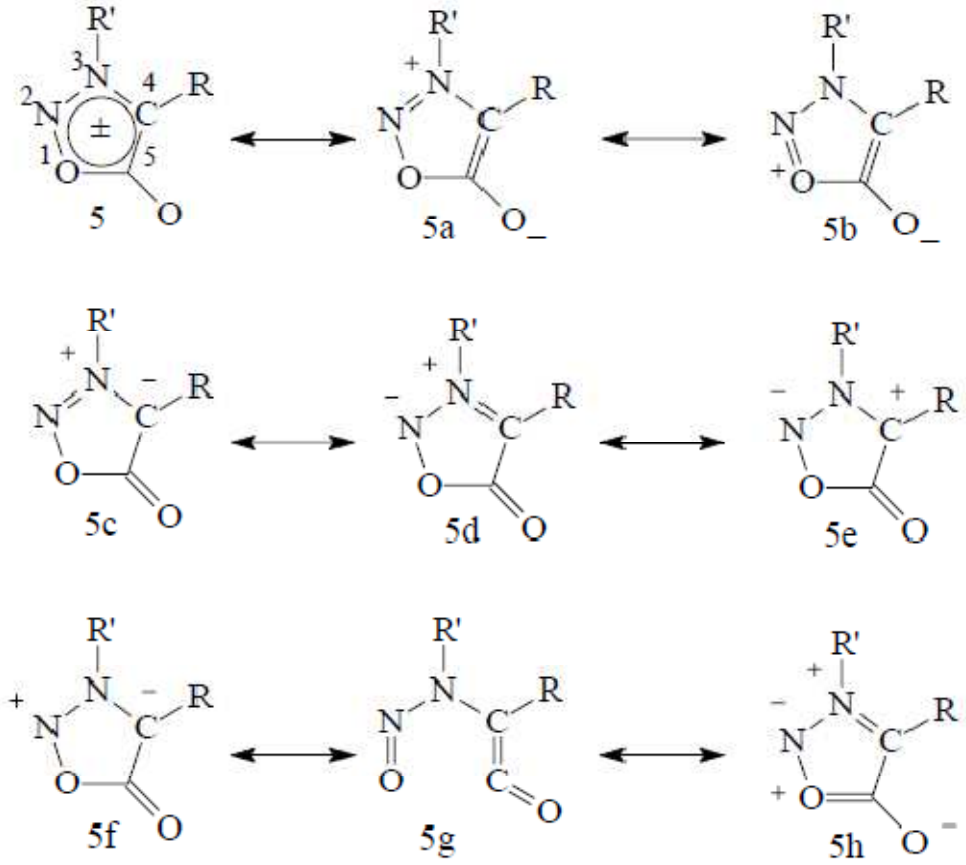
Sydnones show evidence of a greater degree of polarity, stability towards heating and lower reactivity towards acids and bases than would be predicted for the strained, bicyclic representation 4. Thus in the 1940’s Bakes, Ollis and Poole published a series of paper in which they concluded that synones were infact monocyclic, dipolar derivatives of oxadiazoles[1]. In 1946 Bakes, Ollis and Poole coined term mesoionic (mesomeric/ionic) to describe the monocyclic dipolar nature of compounds such as dehydrodithizone. In 1955 these three authors specifically defined the term mesoionic. Using their definition, dehydrodithizone is considered the first known mesoionic species and is assigned the dipolar, monocyclic structure.

The most important member of the mesoionic category of compounds is the sydnone ring system. Sydnones are dipolar, pseudo-aromatic heterocycles with a unique variation in electron density around the ring. These characteristics have encouraged extensive study of the chemical, physical, and biological properties of sydnones, as well as their potential applications. Mesoionic compounds are dipolar five or six membered heterocyclic compounds in which both the negative and the positive charge are delocalized, for which a totally covalent structure cannot be written, and which cannot be represented satisfactorily by any one polar structure. The formal positive charge is associated with the ring atoms, and the formal negative charge is associated with ring atoms or an exocyclic nitrogen or chalcogen atom. Mesoionic compounds are a subclass of betaines. Sydnones are mesoionic compounds having the 1,2,3-oxadiazole skeleton bearing an oxygen atom attached to the 5 position[2]. Imines of sydnone are compounds of sydnone having an imino group in place of the exocyclic oxygen atom[3].

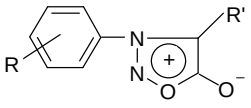


Baker, Ollis, and Poole also suggested that sydnones should be placed in a class by themselves called mesoionic (meaning mesomeric/ionic), because of the unique characteristics of the sydnone ring system. They proceeded to outline the general concepts governing their electronic structure until formal qualifications for a compound to be deemed mesoionic were set forth in 1953. It was then proposed that to be considered mesoionic, a compound should: (1) contain a fully delocalized positive and negative charge; (2) be planar and contain a five-membered heterocyclic ring with an exocyclic atom or group capable of bearing a considerable amount of negative charge density; and (3) possess a considerable resonance energy. These three characteristics allowed mesoionic systems to be clearly distinguished from formally related dipolar species such as ylides and zwitterions. In the latter species, there is a great deal of charge localization whereas in the mesoionic systems, charge distribution is delocalized and no single fitting resonance form can be drawn. Formally, sydnones are derivatives of 1, 2, 3-oxadiazoles; however, since 1, 2, 3-oxadiazoles are known to be open chain, alpha carbonyl diazo derivatives, it appears that sydnones are the only derivatives of this class that are cyclic in nature. Therefore, the name “sydnone” has become the most

common way to describe these compounds because of this unique distinction, and is used by Chemical Abstracts as a way of grouping these oxadiazole derivatives. Sydnones are generally represented by a positively charged aromatic ring with an enolate type exocyclic oxygen. Many possible resonance hybrids allow for multiple canonical representations for which structure **5** is preffered representation.

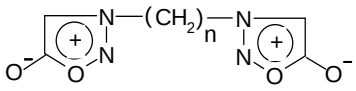


In structure 5, N3 is an iminium-type and is therefore acting as an electron withdrawing substituent attached on phenyl ring. This suggestion is refuted by the work of Wang and co-workers which agreed with the suggestion that the sydnone π-electrons are unequally delocalized[4]. Sydnones, being nitrogenous compounds, are chemically 1,2,3-oxadiazolium-5-olates **6** and are unique, dipolar, heteroatomic members of the general class of mesoionic compounds[5].



6

A large number of sydnone derivatives have been synthesized with biological interest[5-9] and reported to possess a wide spectrum of biological and pharmacological activities like antimicrobial, anti-inflammatory, analgesic, anti-pyretic, antitumour and antiarthritic. Many sydnone derivatives have also been reported for antioxidant properties[10-12]. A number of sydnones have been examined in search for antitumor agents. In this regard, a number of polymethylene-bis-sydnones **7** have been synthesized by Daeniker and Druey[13] and some antitumor activity for the ethylene homolog was reported by these workers.



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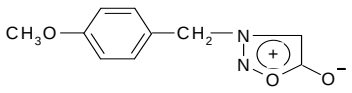
Greco *et al*. [14] have screened a series of sydnones for anticancer activity and it was found by these workers that, 3-(*p*-methoxybenzyl) sydnone **8** was effective against carcinoma-755 in mice and was inactive against sarcoma-180 and leukemia-1210 systems.



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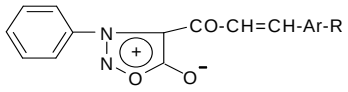
In a study, two series of compounds have been synthesized by Satyanarayana and Rao [15] belonging to 4-[1-oxo-(3-substituted aryl)-2-propenyl]-3-phenylsydnones **9** and 3-[4-[3-(substituted aryl)-1-oxo-2- propenyl] phenyl] sydnones **10**. Some of the compounds from both the series showed significant analgesic (acetic acid induced writhing in mice), anti-inflammatory (carrageenan induced paw edema in rats) and antiarthritic (adjuvant induced arthritis in rats) activities. The compounds of **9** series were also tested for tumor reducing effects *in vivo* and antioxidant effects *in vitro* by Anto et. al[16]. All of them were cytotoxic to tumor cells *in vitro*, while only methyl substituted derivative showed increased *in vivo* tumor reducing activity. Some of the compounds were found to inhibit lipid peroxidation and scavenged superoxides and hydroxyl radicals *in vitro*. The tumor reducing activity was found to be independent of their antioxidant activity. Satyanarayana *et al*.[17] tested three derivatives in the series **9** (**9a**, Ar = Ph, R = 4-CH_3; **9b**, Ar = Ph, R = 3-OCH_3 and 4-OH and **9c**, Ar = Ph, R = 4-CF_3) for *in vitro* cytotoxicity in 56 cell lines representing cancers of non-small cell lung, colon, CNS, melanoma, ovarian, prostate, breast and leukemia and all these compounds exhibited promising activity. Average growth inhibition of 50% was in the range of 1.7-3.5 μM. **9a** was highly selective against SNB-75 tumor cell line of CNS.



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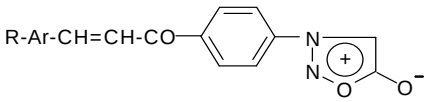
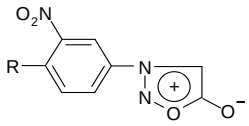


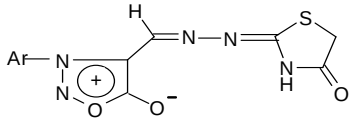
10

A series of compounds, N- (4'-substituted-3'-nitrophenyl) sydnones **11** with potential antitumor activity was prepared based on active analogues by Dunkley and Thoman[18]. Out of the six compounds, 4'-fluoro derivative (**6**, R=F) has an improved activity against all three cell lines namely, MCF7 (Breast), NCI-H460 (Lung) and SF-268 (CNS).



11

The heterocyclic substituted sydnone derivatives that possess 4-oxo-thiazolidine **12** and thiazoline **13** groups were prepared by Shih and Ke[19]. Among these compounds, 4-methyl-2- [(3-arylsydnon-4-yl-methylene) hydrazono]-2, 3-dihydro-thiazole-5-carboxylic acid ethyl ester 13**a** and 4-phenyl-2- [(3-arylsydnon-4-yl-methylene) hydrazono]-2, 3-dihydro-thiazoles 13**b** exhibited the potent DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging activity, comparable to that of vitamin E.



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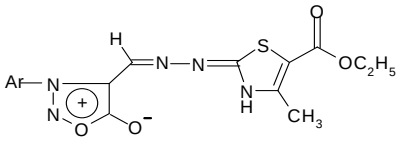
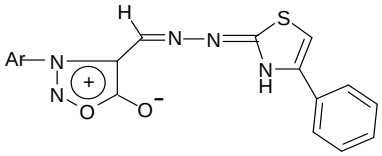
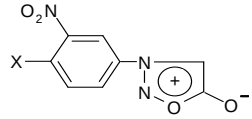


13a



13b

The effects of new aryl-sydnones, 3-[4-X-3-nitrophenyl]-1,2,3-oxadiazolium-5-olates 14, where X = Cl (SYD-1); pyrrolidino (SYD-2); piperidino (SYD-3) and morpholino (SYD-4) on the survival of mice bearing Sarcoma 180, Ehrlich carcinoma, B10MCII (Fibrous histiocytoma) and L1210 leukemia ascitic tumors, on proliferation of cultured tumor cells and on synthesis of DNA in L1210 leukemia were determined by Grynberg et al[20]. SYD-1 and SYD-2 *in vivo* significantly enhanced the survival of S180, Ehrlich and B10MCII tumor-bearing mice. Furthermore, SYD-2 showed significant activity against L1210. SYD-3 and SYD-4 did not show antitumor activity. SYD-1, *in vitro* was the most cytotoxic against all the above tumor cells. All of the drugs tested inhibited thymidine uptake by L1210 cells, SYD-4 being the least active.



14

The most attractive of the many potential applications of sydnones, is their biological properties, which include anti-fungal, anti-inflammatory, analgesic, antibacterial, and anti-tumor activities. 3-tertiary amino-4-tertiary amino methyl sydnone derivatives[21] and 3-hydrocarbon-4-tertiary amino methyl sydnones[22] showed analgesic activity. 3-arylthioalkyl-4-optionally substituted sydnones showed anti-inflammatory and antibacterial activity[23]. Sydnone imine compounds showed antihypertensive and antianginous activity[24]. 1,5-disubstituted alkyl sydnones showed anti-inflammatory activity[25]. 3-aminosydnoneimine compounds showed reducing pulmonary systemic blood pressure[26]. 3-[4-(Azidocarbonyl)] phenylsydnone obtained from 3-(4-hydrazinocarbonyl) phenylsydnone on curtius rearrangement with alcohols, water and amines afforded the corresponding carbamates, 4,4'-(sydnone-3-yl) diphenyl urea and 4-(heterocyclyl)phenyl ureas. Compounds on one-pot ring conversion yielded the 1,3,4-oxadiazolin-2-one derivatives, which on reaction with N_2H_4 gave the 4-amino-1,2,4-triazolin-3-ones. All these compounds exhibited moderate antimicrobial activity against *Escherichia coli* (Gram –ve) and *Micrococcus luteus* (Gram +ve) and two fungal strains, *Asperigillus niger* and *Penicillium* notatum[27]. The 3-aryl-(4-cinnamoyl)sydnones obtained from 4-acetyl-3-arylsydnones and arylaldehydes, used for synthesis of 3-arylpropenoic acids and 5-phenyl-2,4-pentadienoic acid. Many cinnamic acids are bioactive molecules and are also precursors for many pharmacologically active molecules. Esters and amide derivatives of cinnamic acids have been shown to exihibit antibacterial and antifungal activities while 4-methoxy cinnamic acid and its ethylesters have been classified as a new group of glycosidase inhibitors. Some oligomers of this acid have shown to possess inhibitory action of coagulation proteinases[28]. 5-Phenyl-2,4-pentadienoic acid and its derivatives have been considered as potential antimalarials.[28] Deaminatively produced carbonium ions are intermediates of high reactivity and they have been utilized for this reason in several methods for the inhibition monoamine oxidase enzyme by sydnones[29]. A simple and high yielding method for the integration of a 1,2,4-triazole ring with 1,2,4-triazine-5-one has been developed starting from 3-arylsydnones. The structures were proved by their spectral data and screened for antihaemostatic activity[30]. They have attained importance due, not only to their structural features and chemical

properties, but also to their biological properties. Sydnones are less toxic, but potent porphyrinogenic and anti-inflammatory compounds, and have the effect of scavenging free radicals[31]. Some azodyestuffs containing a sydnone ring were prepared by the diazonium coupling of 3-(p/m-aminophenyl)sydnones with phenol or 1-/2-naphthols possesses a significant response of cororiary dilation and inhibition of collagen induced platelet aggreation[32]. Sydnones are relatively non-toxic, but potent, porphyrinogenic and anti-inflammatory compounds. Coumarins (2H- 1-benzopyrans) possess a variety of biological activities such as antibacterial antifungal, antimicrobial anticancer, anti-ulcer and antifeedant 1990. It was also found that coumarins display a very strong anti-invasive activity in vitro against human mammary carcinoma cells , Further research In view of their importance, the 3-[(7-Acetoxy-4-methylcoumarin-8-yl)-methyl] sydnone derivatives may possess a variety of biological activities[33]. Sydnones and coumarins (2H-1-benzopyrans) possess a variety of biological activities such as antibacterial, antifungal, antimicrobial, anticancer, anti-ulcer, and antifeedant. It was also found that coumarins display a very strong anti-invasive activity in vitro against human mammary carcinoma cells. In view of their importance, further study of biological screening of synthesized compound 3-[(7-Acetoxy-4-methylcoumarin-8-yl)-methyl] sydnone may show related potent activities[34]. Molsidomine, N-(Ethoxycarbonyl)-3-(4-morpholinyl)-sydnone imine is mesoionic sydnone imine an orally active, long acting vasodilator drug[35].

Mesocarb is a mesoionic sydnone imine. It has been shown to act as dopamine reuptake inhibitor which is slower acting but longer lasting and less neurotoxic than dextroamphetamine. Mesocarb is still used for a variety of application; these include counteracting the sedative effects of benzodiazepine drugs, increasing workload capacity and cardiovascular function, treatment of hyperactivity in children as a nootropic, and as a drug to enhance resistance to extremely cold temperature. It is also listed as having antidepressant and anticovulsant properties. Some novel bismesoionic compounds, 3[4/3-(5*H*/substituted- 2-sulphido-1,3,4-thiadiazolium-4-carbonyl)phenyl]sydnones and 4-[4-(5*H*/substituted-2-sulphido-1,3,4-thiadiazolium)benzoyl]-5*H*/substituted-1,3,4-thiadiazolium- 2-thiolates have been synthesized from 3-[(hydrazinocarbonyl)phenyl] sydnones and these compounds exhibited *in vitro* antitubercular activity and also antimicrobial activity[36]. A series of novel 3-[4-(diethylamino)phenyl]-4-substituted-1-ylsulfonyl)sydnones have been synthesized.Compound 3-[4-(Diethylamino)phenyl]-4-(piperazin-1-ylsulfonyl)sydnone and 3-[4-(Diethylamino)phenyl]-4-[(4-methylpiperazin-1-yl)sulfonyl]sydnone exhibited highest activity against *micrococcus,Staphylococcus aureus, Bacillus subtilis, Escherichia coli, and Pseudomonas aeruginosa*[37]. 4-acetyl-3-(4-chlorophenyl)sydnone synthesized by acetylation of 3-(4-chlorophenyl) sydnone showed promising antibacterial and anti-inflammatory activities[38].

Cephanone, 3-(5-methyl-1,3,4 thiadiazol-2- ylthiomethyl)-7-[2-(3-sydnone)acetamido]-3-cephem- 4-carboxylic acid sodium salt , is a new semisynthetic cephalosporin derivative with a broad antibacterial spectrum similar to that of cephalothin . The compound was active in vitro against a variety of gram-positive and gram-negative bacteria. All strains of Staphylococcus aureus tested were inhibited by concentrations of 6.2 µg or less of cephanone per ml [39].

Stability of sydnone

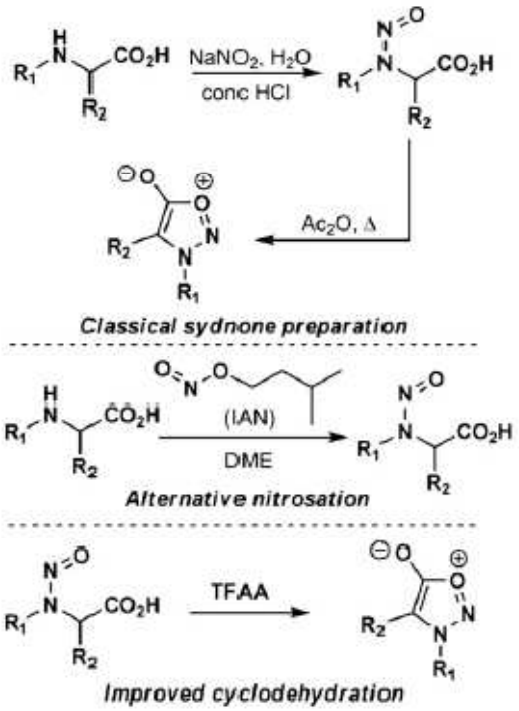
Many sydnones are isolated as crystalline solid and commonly purified by recrystallisation from ethanol. Sydnones can be stored at room temperature, although a few have been known to degrade in the presence of light and heat. Conc. HCl can also cause degradation of sydnones, yielding the hydrazine derivatives with loss of CO_2. Heat can also cause degradation of the mesoionic ring system to the formation of pyrrolidinehydrazine and CO_2 (Scheme 1) as follows.

Scheme 1.

Synthesis of sydnone derivatives

Sydnones can readily prepared by cyclodehydration of *N*-substituted-*N*-nitroso-amino acids with reagents such as acetic anhydride. The resulting compounds contain a mesoionic aromatic system which can be depicted with polar resonance structures. Classically sydnones are sythesized in just in two steps from N-substituted amino acid. N-nitrosation followed by cyclohydration generally furnishes the mesoionic products in good to excellent yields. Whilst this is this is the most common method. Several improvement or alternative have been introduced. The employment of trifluoroacetic anhydride (TFAA) has superseded the use of acetic anhydride largely due to an increased rate of cyclisation. The cyclisation of N-nitroso-N-phenyl-glycine by means of acetic anhydride seems to

proceed through the following mechanisms proposed by Bakers et al. Turnbull et al. have described nitrosation using isoamyl nitrite (IAN) for acid-sensitive starting materials (Scheme 2)



Scheme 2.

Similarly some other mesoionic compounds are formed by the loss of NH_4Cl. It has been found that dehydration can proceed through other reagents like trifluoroacetic anhydride (TFAA), thionyl chloride and carbonyl chloride. This reaction is found to be temperature dependent, as the rate of reaction speeds up when the reaction mixture is heated [40].

Functionalisation of synones at C4 position

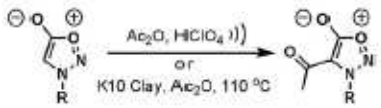
In figure 1, the C4 position of the sydnone ring is both acidic and nucleophilic. This gives rise to two possible modes of functionalisation;

1) Electophilic aromatic substitution or
2) Deprotonation followed by electrophile addition

Figure 1.

Direct acylation:

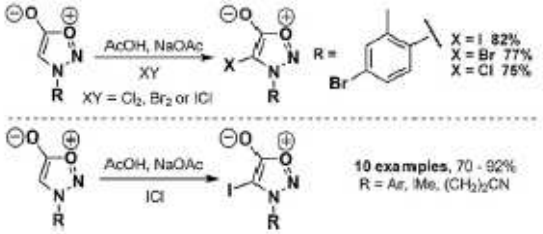
The classical friedal-craft reaction has remained elusive as a means for the electrophilic acylation of sydnones. Direct acylation has been achieved by sonication with perchloric acid and acetic anhydride, as reported by Tien (Scheme 3).



Scheme 3.

Halogenation

A range of halogenations method has been developed for the introduction of halogens into the C4 position of sydnone. To date chloro, bromo, and iodo analogues, have been synthesized employing a broad spectrum of typical electrophilic halogenating reagents. Dumitrasca et al synthesized a range of halo sydnones employing acetic acid, sodium acetate and appropriate halogen source (Scheme 4). Both N-alkyl and N-aryl–substituted sydnones can be transformed by this method in good to excellent yield with esters, nitriles, ethers carboxylic acids and halogens being tolerated on N- aryl substituents.



Scheme 4.

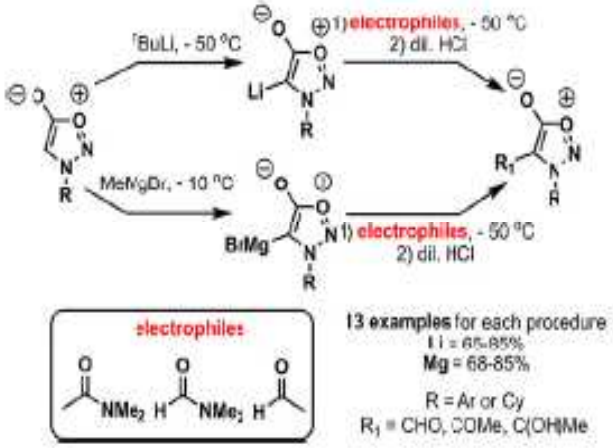
Lithiation

Lithiation of sydnones provides a convenient means for the introduction of a variety of a variety of substituents by two main processes.

1)Deprotonation followed by quench with an electrophile OR

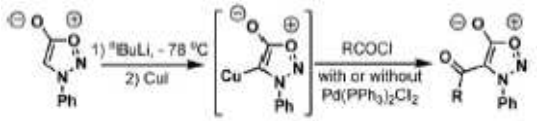
2)lithiation followed by transmetalation and subsequent chemistries.

Lithiation of the sydnone C4 proton is relatively facile and is commonly carried with n-butyllithium. Tien et al. reported the generation of the sydnone anion by treatment with methyl magnesium bromide (Scheme 5)



Scheme 5.

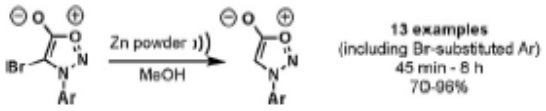
Kalinin and co-worker described the transmetalation of lithiated sydnone to the corresponding oganocopper reagents. The intermediate sydnonylcopper was then shown to efficiently undergo palladium-mediated coupling processes with aryl and alkenyl halides in good yields. This methodology was extended by Turnbull for the acylation and aroylation of sydnone C4 position. The reaction proceeds via the copper sydnone and, curiously some examples work better in the absence of palladium and some in its presence (Scheme 6).



Scheme 6.

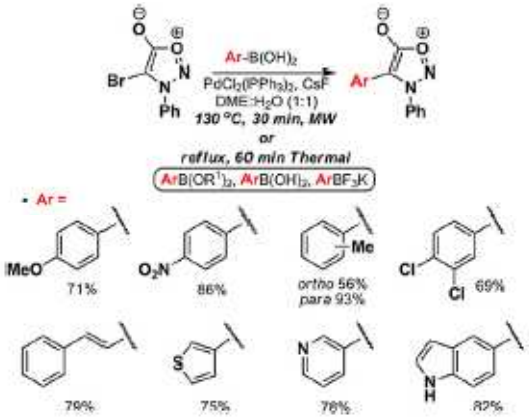
Modification of C-4 halogenated sydnones

Kato and Ohta conducted studies on the reactivity of C-4 –bromo-N-phenyl sydnone. They found that heating this compound in the presence of magnesium metal, and subsequently quenching with water, returned the unsubstituted parent sydnone presumably via the Grignard reagent. Alternatively sodium bromohydride can be used for the removal of a sydnonyl bromide. Tien developed an ultrasound accelerated zinc mediated method for the removal of bromine from a variety of sydnones (Scheme 7)



Scheme 7.

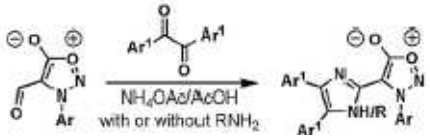
Both traditional and microwave-heating processes delivered the coupled products in good yields, within simple and practical protocol. Furthermore Moran et al have discovered a direct arylation, alkenylation and alkynylation protocol for the synthesis of C-4 substituted sydnones. A variety of aromatic iodides and bromides can be coupled in good yield. A selection of bromoalkenes were also successfully (Scheme 8)



Scheme 8.

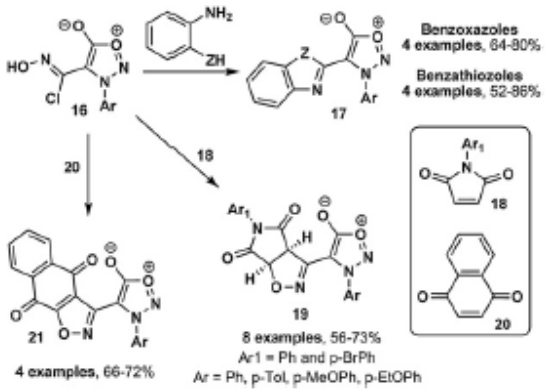
Modification of C-4 carbonyl sydnones

C-4 carbonylated sydnones have recently been used by Shin and co-workers for the synthesis of imidazolyl-substituted sydnones. Treatment of 4-formyl sydnones with aromatic glyoxals in the presence of ammonium acetate and acetic acid, delivers the imidazoles in good yields (Scheme 9). The introduction of a primary amine starting material results in its incorporation into the imidazole products.



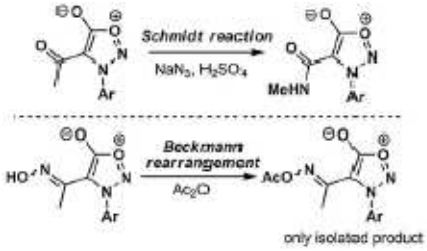
Scheme 9.

The some authors has also converted the C-4 aldehyde into a chlorooxime and the studied the reactivity in nitrile oxide cycloadditions and nucleophilic substitution reactions (Scheme 10).



Scheme 10.

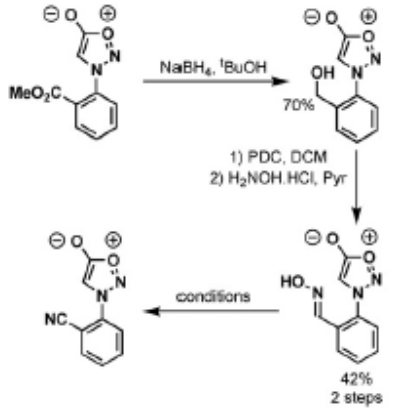
Tien has described the application of the Schmidt reaction to C-4 acylated sydnones for the synthesis of sydnonyl–methylamides. A range of sydnones were treated with sodium oxide and sulfuric acid to give the product deriving from methyl migration (Scheme 11).



Scheme 11.

Modification at N-3

On employment of sodium borohydride in tert-butyl alcohol, they obtained the desired product in 70% yield, and, presumably, the electron-withdrawing nature of the sydnone ring promoted the reduction of the ester in this case. With this in hand, oxidation with pyridinium dichromate (PDC) and oxime formation with hydroxylamine hydrochloride gave the aldoxime (Scheme 12).

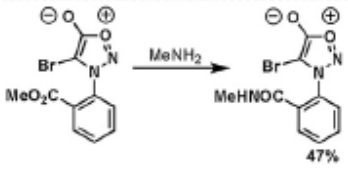


Scheme 12.

Modification at N-3 with C-4 protection with bromine

Kalinin et al found that treatment of N-methyl-4-phenylsydnone, with butylithium gives the N-lithiomethyl-4-phenylsydnone, which can be quenched with a variety of electrophiles. This discovery makes an important method for the rapid elaboration of the sydnone nitrogen substituent. The same authors then opted to assess the C4

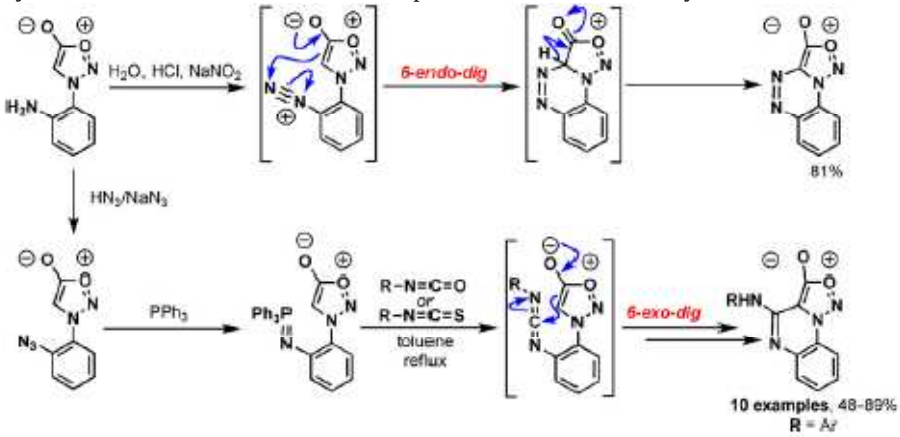
protection with bromine followed by subsequent N-phenyl substituent manipulation. Some interesting findings were made, which are attributable to the electron-withdrawing nature of the sydnone (Scheme 13).



Scheme 13.

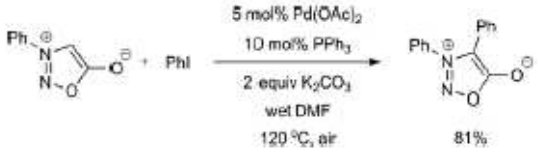
Synthesis of tricyclic sydnones with modification at C-4 and N-3

Treatment of N-(2-aminophenyl) sydnone with nitrous acid led toa diazonium intermediate, which underwent intramolecular addition by the sydnone at the C-4 position (Scheme 14). Alternatively, synthesis of the and conversion in to the phosphineimide followed by exposure to an isocynate or isothiocynate delivers sydnoquinoxalines in moderate-to-good yield. Both examples serve to highlight the stability of the sydnones to a range of relatively harsh reaction conditions and their potential for dual reactivity[40].

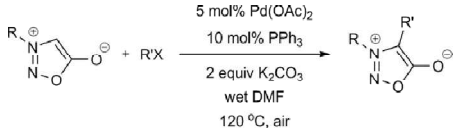


Scheme 14.

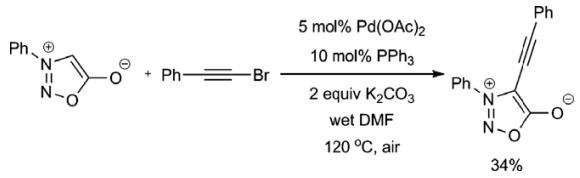
The palladium-catalysed direct cross-coupling reaction of electron- rich heteroaromatics with aryl halides and pseudohalides has emerged as an incredibly useful and general synthetic technique to access biaryl structures.1 These processes are superior to traditional cross-coupling techniques because a stoichiometric amount of an organometallic reagent is not required. This results in lower costs, less waste and, if the organometallic would need to be prepared, shorter syntheses. This concept has been applied successfully to the direct coupling of a range of heterocycles including furans, oxazoles, imidazoles, triazoles, purines, indoles and pyrroles. Examples of intramolecular direct couplings have also been reported (Scheme 15)[41].



An example of the direct arylation of N-phenyl sydnone with iodobenzene.



Direct alkenylation of sydnones

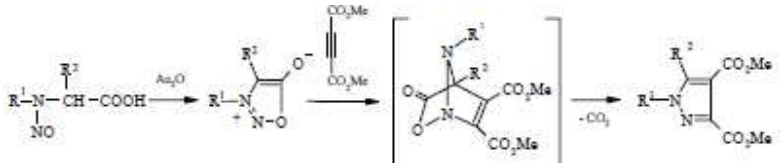


Direct alkynylation of N-phenyl sydnone.

Scheme 15

Cycloaddition of sydnone:

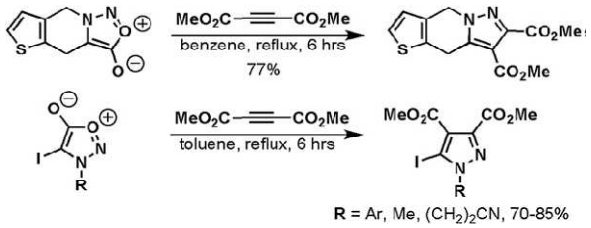
Sydnone rings possess not only a mesoionic character but also a labile nature. The charge distribution on the ring can be varied according to their resonance form depending on their aryl substituents at the positions N(3) and C(4).1 In general, N(3) behaves as an electron-withdrawing substituent and C(4) shows as an electron-donating character to form the so-called duality effect for the ring. Sydnones can be converted to dihydropyrazoles by reacting with cyclopentadiene. Dehydrogenation of dihydropyrazole to form a pyrazole is strongly dependent on the nature of aryl substituents[42]. Sydnones undergo smooth cycloaddition with acetylenes to give pyrazoles in high yield. The reaction involves a 1,3-dipolar cycloaddition of the sydnones, behaving like a cyclic azomethine imine, to the corresponding acetylene followed by carbon dioxide evolution and aromatization(Scheme 16)[43].



Scheme 16.

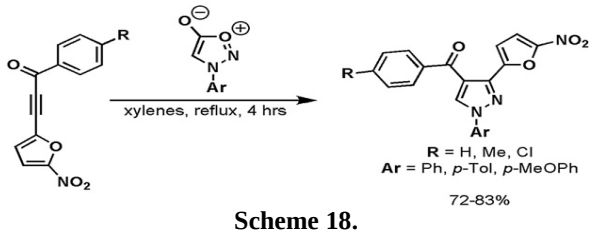
Alkyne cycloadditions

The most important synthetic application of sydnones is their cycloaddition reaction with alkynes. The cycloaddition was compatible with a range of simple hydrocarbon-substituted alkynes as well as those bearing, alcohol, acetal, acyl, and ester groups. Cycloaddition reactions of sydnones are most commonly carried out with electron-deficient alkynes. For example, the reactive dienophile, dimethyl acetylenedicarboxylate, reacts readily with C4-substituted sydnones, and this chemistry has been exploited to generate functionalised pyrazole products (Scheme 17).



Scheme 17.

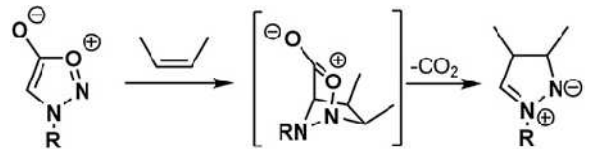
An interesting and highly functionalised class of α,β-acetylenic ketones has been employed in sydnone cycloadditions by Hegde et al. and was found to generate the corresponding pyrazoles in excellent yield and as single regioisomers . The authors also demonstrated that replacing the furan with a 5-nitrothiophene provided similar results (Scheme 18). These compounds were further tested for their antibacterial and antifungal activities



Scheme 18.

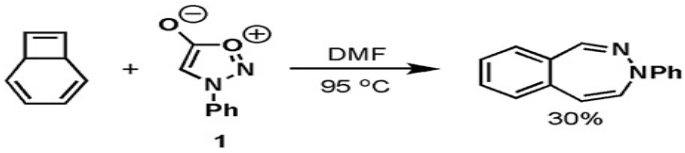
Alkene cycloadditions

The dipolar cycloaddition of sydnones to alkenes could give rise toΔ^2-pyrazolines, and that the addition of an oxidant to this mixture allowed the corresponding pyrazoles to be isolated. The general reaction pathway involves a cycloaddition/cycloreversion process with evolution of CO_2. In the case of alkene dienophiles, this gives rise to an azomethine imine and it is the subsequent chemistry of this intermediate that determines the ultimate product distribution (Scheme 19).



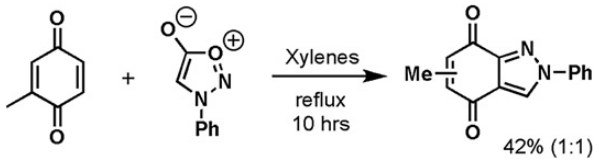
Scheme 19.

Kato confirmed the potential of sydnones to react with cyclobutenes to furnish ring-expanded products. Specifically, heating benzocyclobutene with sydnone 1 provided the corresponding benzodiazepine, albeit in low yield (Scheme 20).



Scheme 20.

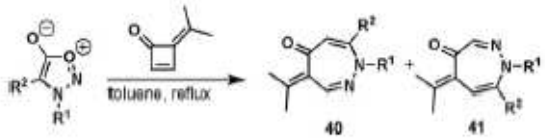
Quinones are an alternative class of activated dienophiles/ dipolarophiles and the group of Nan'ya has demonstrated that these can participate in sydnone cycloadditions to produce indazole-4,7-diones (Scheme 21).



Scheme 21.

Martin has shown that diazepinones can be prepared from alkylidenecyclobutenones, presumably via [3+2] cycloaddition followed by in situ ring opening initiated by the azomethine imine intermediate (Table 1).

Table 1



R^1	R^2	Yield (40:41) (%)
Ph	Me	56 (100:0)
Ph	H	93(100:0)
Ph	Cl	84(100:0)
Me	H	65(4:3)
Bn	H	58(4:3)
Me	Me	75 (100:0)
$(CH_2)_4$		57 (100:0)
$(CH_2)_3$43		(100:0)

Intramolecular reactions provide a powerful strategy for generating products with defined regiochemistry, particularly when the corresponding intermolecular processes are poorly selective. In the context of sydnone cycloadditions, this approach has been employed in the assembly of an antidepressant indazole, FS-32. Thermally induced 1, 3-dipolar cycloaddition reaction of N-methyl sydnone with methyl propionate gave 1-methyl-3-pyrazolecarboxylate with good regioselectivity and new pyrazolylimidazolinone has been synthesized using the cycloadduct as a key intermediate. There herbicidal activity evaluations are in progress[44].

Conclusions and future outlook

Sydnones are highly versatile and robust members of the mesoionic class of heteroaromatic compounds. They possess an array of interesting chemical and physicochemical properties, as well as a variety of biological activities. With respect to their functionalisation, modern techniques such as metal catalysed cross-coupling and direct arylation processes have been found to be as directly applicable to these unusual compounds as they are to the more common heteroaromatic substrates. The cycloaddition of alkynes consistently gives pyrazole products. These all have the potential to furnish some very interesting molecular moities. The research and development of new sydnone functionalisation methods in conjunction with the aforementioned cycloaddition reactions will provide the focus of future research in the development of sydnone drugs.

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