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A REVIEW ON SYDNONES

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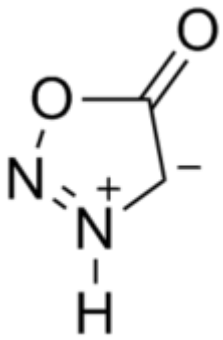
Abstract: 1,2,3-oxadiazolium-5-olate (sydnone) is used as a versatile synthon in heterocyclic synthesis. A large number of sydnone derivatives have been synthesized with biological interest and reported to possess a wide spectrum of biological and pharmacological activities like antimicrobial, anti-inflammatory, analgesic, antipyretic, antitumor, antiarthritic and antioxidant properties. Among all the mesoionic compounds, sydnone ring is the most widely studied because of each of its synthesis from primary amines and it is the only mesoionic ring which undergoes a wide variety of chemical reactions of synthetic utility. Syndones form a subclass of mesoionic compound which again form subclass of mesomeric betaines. These characterstic of five membered heterocyclic mesoionic compounds have encouraged concentration on the study of chemical, physical and biological properties of sydnones, as well as their potential applications. Thus there is wide scope to explore more novel sydnones as a potent biodynamic molecules.

Index Terms - Antioxidant , Pharmacological ,Spectroscopy ,Physical and Chemical properties. Sydnone, Antimicrobial, Anti-inflammatory, Analgesic, Anti-pyretic, Antitumor, Antiarthritic.

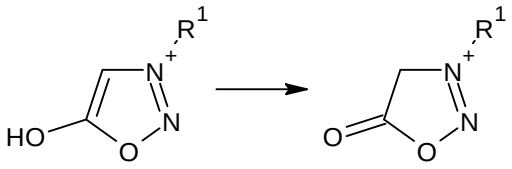
I. INTRODUCTION

Mesoionic compound are distinct type of heterocycles (five and six membered) which belong to the class of nonbenzenoid aromatic. Mesoionics are compounds having both delocalized negative and positive charges,for which a totally covalent structure cannot be drawn and which can exclusively be represented by dipolar canonical formulas . Mesoionic heterocycle contain, two or more heteroatoms with an exocyclic heteroatom (oxygen, nitrogen and sulphur). The formal positive charge is associated with the ring atoms and the formal negative charge is associated with ring atoms or an exocyclic heteroatom (oxygen, nitrogen and sulphur). The most important member of the mesoionic category of compound is the sydnone ring system. These characteristic of five membered heterocyclic mesoionic compound have encouraged highlighting their potential biological activities. Sydnones are mesoionic compounds having the 1,2,3-oxadiazole skeleton bearing an oxygen atom attached to the fifth position .[2,3] Sydnoneimines are compounds of sydnone having imino group in place of the exocyclic oxygen atom[2].

Sydnone (1,2,3 oxadiozolium - 5 - olate)



The most important member of the mesoionic category of compounds is the sydnone ring system. Sydnones are dipolar, pseudo-aromatic heterocyclic 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 compound having the 1,2,3-oxadiazole skeleton bearing an oxygen atom attached to a position [3] . Imines of sydnone are compounds of sydnone having an imino group in place of the exocyclic oxygen atom [4].



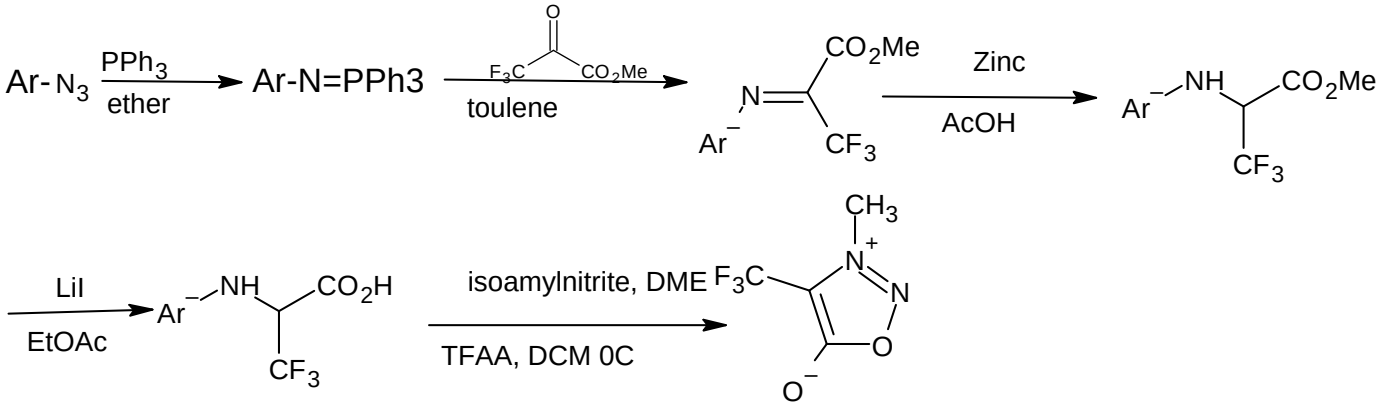
A B

Synthesis:

1. The recent interest concerning fluorinated aromatic and heteroaromatic compounds generates a new approch in the synthesis of sydnones containing fluorine. The preparation may start with the corresponding fluorinated pyruvic ester by a stepwise procedure as presented in Scheme 3

Schemes

1. A polycylic compound 4 was synthesized starting from a cyclic compound as raw material, as was described by Mani and coworkers[6] .



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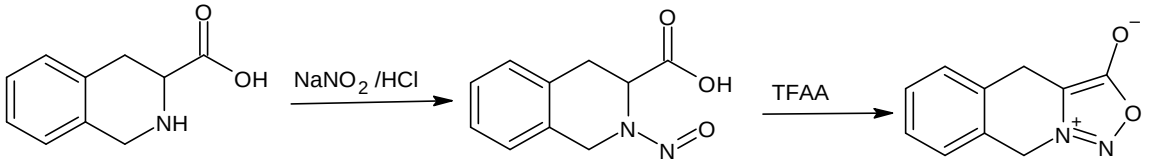
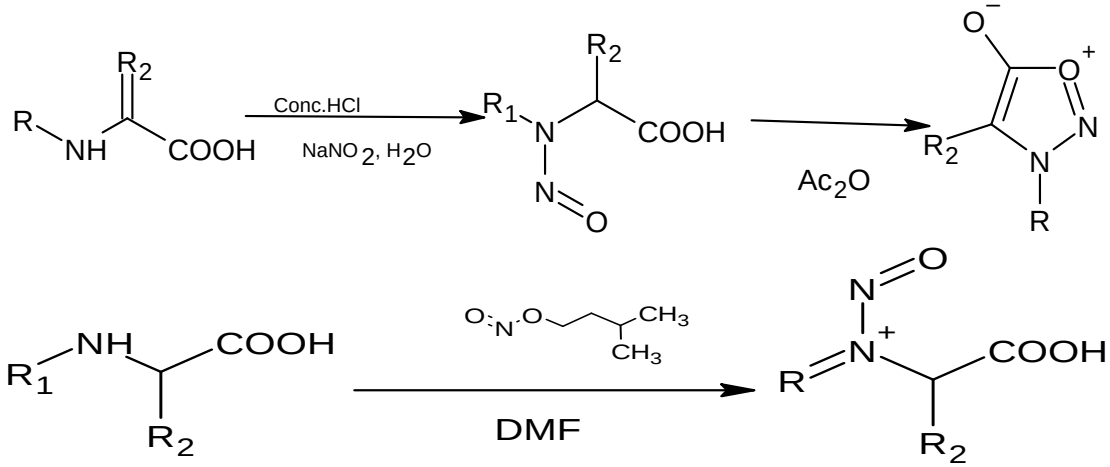
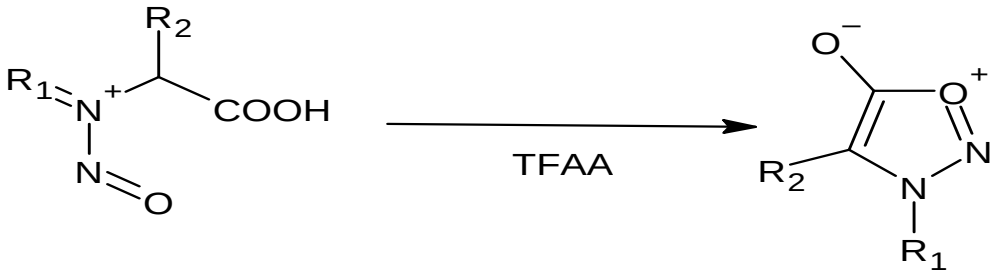


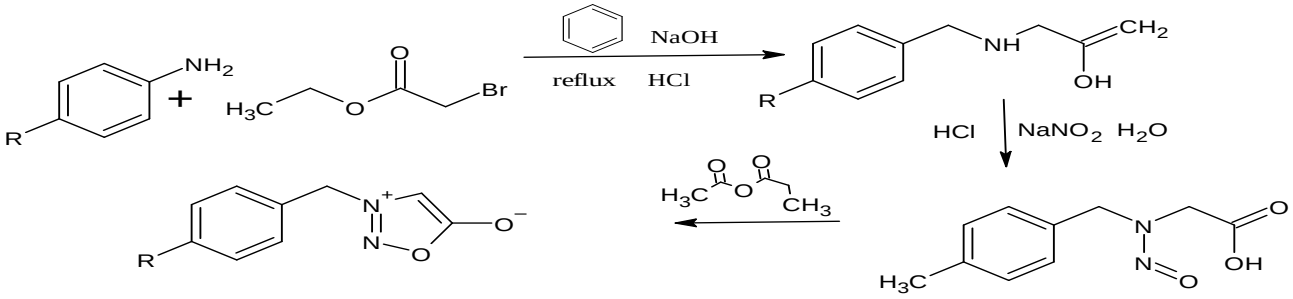
2. Sydnones can readily prepared by cyclodehydration of N-substituted-N-nitroso-amino acids with reagents such as acetic anhydride. The resulting compounds contain a mesoionic aromatic system which can be depicted with polar resonance structures. Classically sydnones are sythesized in just in two steps from N-substituted amino acid. Nnitrosation 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 toproceed through the following mechanisms proposed by Bakers et al. Turnbull et al. have described nitrosation using isoamyl nitrite (IAN) for acid-sensitive starting materials (scheme2).

Similarly some other mesoionic compounds are formed by the loss of NH4Cl. 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 [7].





In order to determine how the parameters affect the behavior of the sydnone ring toward to the electrophile, a series of arylalkyl groups at N(3) substituted sydnones were prepared. A typical preparation procedure, as shown in Scheme 6, was used to prepare 3-arylsydnone, 3-arylmethylsydnones and 3-phenyl- ethylsydnone [8].



Stability of sydnone

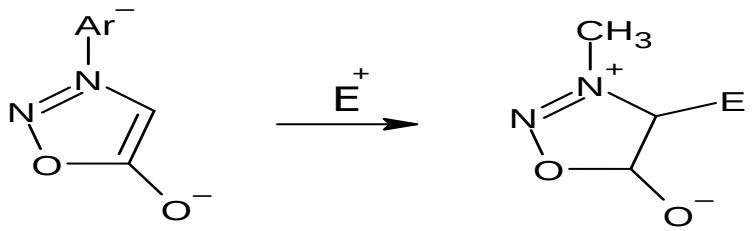
Many sydnones are isolated as crystalline solid and commonly purified by recrystallisation from ethanol. Sydnones can be stored at room temperature, although a few have been known to degrade in the presence of light and heat. Conc. HCl can also cause degradation of sydnones, yielding the hydrazine derivatives with loss of CO2. Heat can also cause degradation of the the mesoionic ring system to the formation of pyrrolidinehydrazine and CO2.

Reaction of Sydnone.

Notable reaction sydnone include 21,3-dipolar cycloadditions with alkenes and alkynes wherein reactions occur across the sydnone N-2 and C-4 positions, resulting in extrusion of carbon dioxide and the formation of pyrozoles. Alternatively, heating sydnones in the presence of acid has been reported as a synthetic route to monosubstituted hydrazine salts.

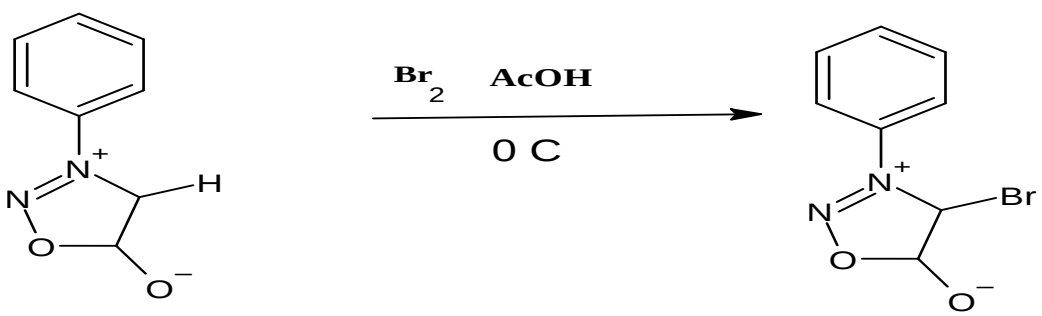
If the sydnone ring is unsubstitued at the C-4 position (H present) it is prone to electrophilic aromatic substitution (EAS), and to metallations.

1. Electophilic aromatic substitution apportunities for sydnone unsubstituted at the C-4 position.



As mentioned above EAS is the most studied area of sydnone reactions and,accordingly,will be discussed in more detail.Previously reported EAS reactions include acylation, halogenation,nitration, and sulfonation. The most studied type EAS reaction in sydnone chemistry is halogenation at C-4 position and the most studied halogenation reaction of sydnone involve bromination and chlorination. Bromination was first accomplished in1946 by Kenner and Mackay using bromine in actic acid and subsequently, other reagents such as NBS and KBrO3 / HBR were used successfully.

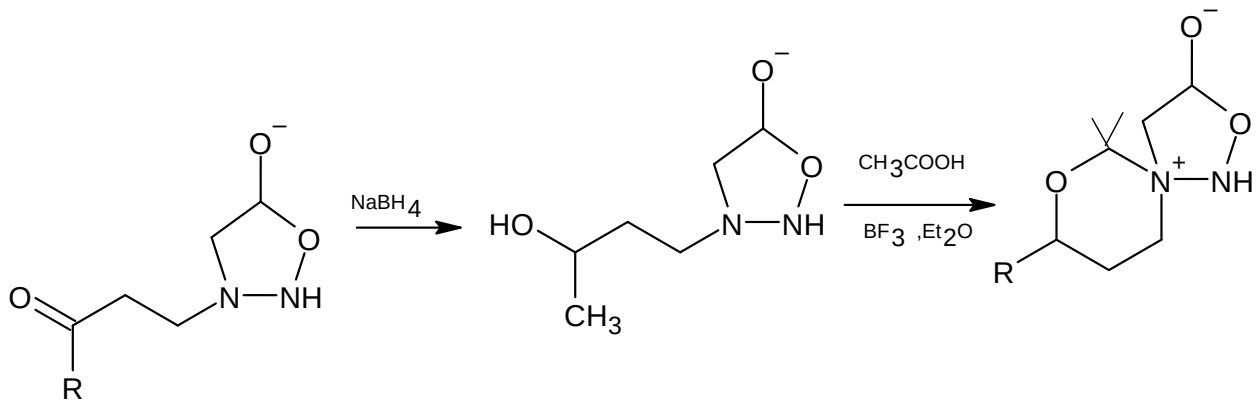
2. First reported bromination of 3-phenylsydnone.



Chlorination of sydnone has also been accomplished by a variety of methods including, Cl2, NCS/DMF, KClO3/HCl and PhlCl2.In contrast until recently, iodination of sydnones had proven to be much more difficult, however, two efficient methods are now available,viz,ICl2/AcOH and NIS/AcOH[9].

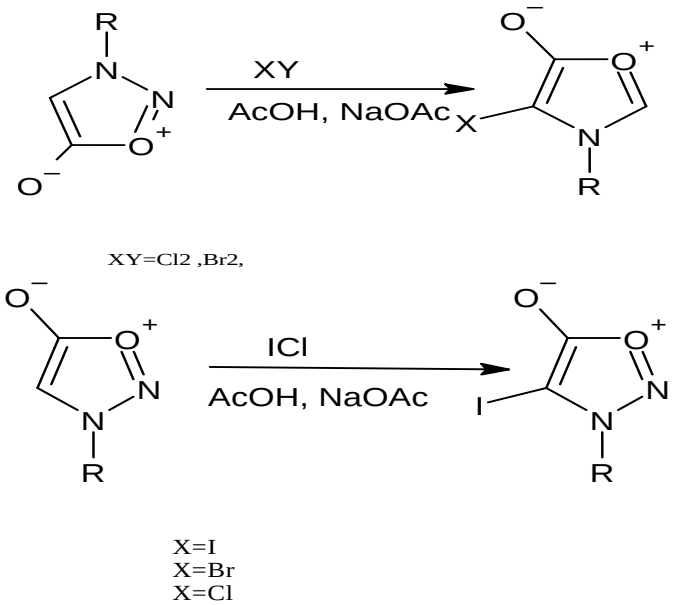
Acylation and Formalyation of sydnone ring

Greco and his co-workers reported unsuccessful attempts to acylate the sydnone ring in the conventional Friedel-Crafts reaction using many catalysts such as aluminum chloride, stannic chloride, and phosphoric acid. However, they successfully prepared a variety of 4-acylsydnone deravatives when phosphorous pentoxide was refluxed with one molar equivalent of carboxylic acid and sydnone. Later, other chemists spectulated that the failure of Friedal-Crafts acylation was due to the coordination between Lewis acid and the exocyclic oxygen of the sydnone which eventually yielded a sydnone containing fused ring compounds rather than the desired acylated product[10].



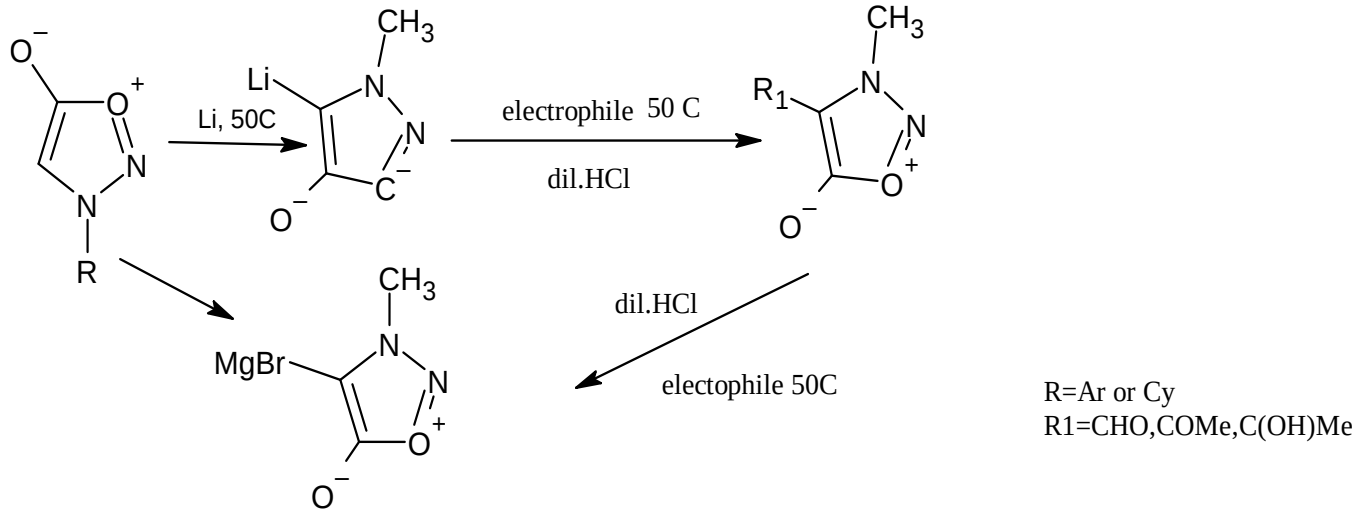
Halogenation

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 . 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.

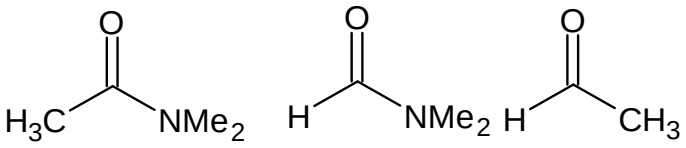


Lithiation

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[11]



electrophile



Properties of Sydnone

The relatively unusual positions of these peaks can be very helpful in determining the Since sydnones are pseudo-aromatic compounds, this makes the sydnone ring reactive toward electrophilic substrates.3 Accordingly, as mentioned previously, it is common to represent the ring as resonance form 3a in Scheme 2. However, spectrometric techniques such as IR, 1H NMR and 13C NMR may or may not concur with this supposition. For example, IR and 13C NMR spectra both indicate the presence of a "pseudo-carbonyl" which appears often as a sharp, well-resolved signal.

Thus, sydnones can be characterized by a C=O stretch (~1744 cm-1) at the C-5 position and, if a hydrogen is present, the C-H absorption at the C-4 position (~3150 cm-1).1 Further characterization involves 1H NMR and 13C NMR spectroscopy. In the 1H NMR spectrum of a sydnone, there is a unique signal at ~6.8-7.0 ppm for the hydrogen attached to C-4, if present. The 13C NMR spectrum contains two signals corresponding to the C-4 and C-5 positions onthe sydnone ring at ~95 ppm and ~165 ppm, respectivelypresence or otherwise of the sydnone moiety[12].

Physicochemical properties of sydnone

The electronic structure of sydnone ring Using a new method of molecular orbital calculation modified from Hückel framework, Kier and Roche calculated reasonable values of charge densities and bond orders for 3-methylsydone and 3-phenylsydone. The calculated bond order value of C5-O6 bond in structure XXV and XXVI along with the X-ray structure of 3-(*p*-bromophenyl) sydnone, 3-(*p*-ethoxyphenyl) sydnone and 3-(*p*-tolyl)sydnone pointed out a carbonyl-like double bond characters of the C5-O6 bond of the sydnone ring. Moreover, it can be noticed that the exocyclic oxygen O6 is highly negative charged (-0.53) even stronger than the carbonyl oxygen of butyrolactone (-0.38) indicating a very polarizable carbonyl group [13].

The delocalized positive charge of the ring which has been previously proved to be unevenly distributed is mainly borne on the number three nitrogen especially when an electron withdrawing group is attached to the nitrogen such as a phenyl ring. This suggests an iminium-type nature of this nitrogen and therefore has an electron withdrawing impact which will deactivate the attached aryl substituents towards all electrophilic reagents. Even though, the calculated bond order of the N-O was 1.22 Å which was close to 1.14 Å of the double bond N=O, the X-ray confirmed its single bond nature. Interestingly, the high electron density of C4 was later supported by the finding of Greco and O'Reilly who reported a strong acidity of 3-phenylsydnone with pK_a value of 18-20. Consequently, sydnone is an electron donating reagent and the electrophilic substitution at this position is possible [14].

II APPLICATION

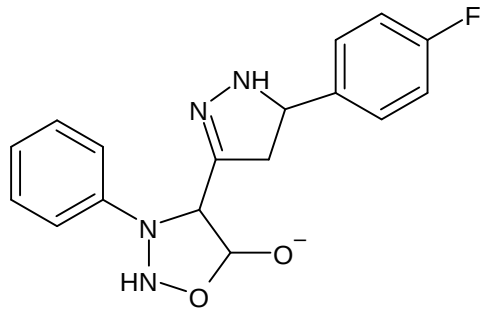
Biological activity of sydnone

The distinguished structure of sydnone having positive and negative charges along with its aromaticity and high lipophilicity enables it to react with biomolecules like DNA and enzymes. Consequently, sydnones exert a wide array of biological activities like anti-inflammatory, analgesic, anti-arthritis, cytotoxicity, anti-parasite (malaria and leishmaniasis), antidiabetic, antioxidant, antimicrobial and nitric oxide donation. In our present review, we will focus on the most studied and investigated biological activities.

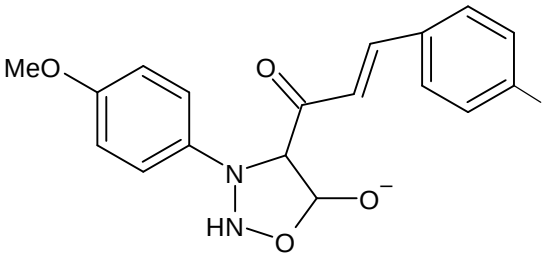
Anti-inflammatory activity

The first report on the anti-inflammatory activity of sydnone-containing compounds was in 1974 by Wagner and Hill who reported that sydnones bearing 2-arylthioethyl or 2-arylsulfoxyethyl at the position N3 were promising scaffolds for designing new anti- methyl or hydrogen atom at C4 was essential for the activity. Aromatic ring attached to the sulfur increased the potency with a maximum activity when both *ortho* positions were substituted with an electronegative atom. They found that the inhibition of arthritic swelling by 4-methyl-3-[2-(phenylthio) ethyl] sydnone was equal to *hydrocortisone* and *phenylbutazone* while 4-methyl-3-[2-(2,4-dichlorophenylthio)ethyl] sydnone was six times stronger than *hydrocortisone* [16].

Studies on the anti-inflammatory activity of more sydnone analogues were continued later by combining sydnone with other pharmacophores such as thiazole, pyrazoleand styryl ketone. It was found that 3-substituted-4-(thiazol-4-yl) sydnone had a weak to moderate activity . On the other hand, the presence of 5-arylpyrazole at C4 of the sydnone ring resulted in a favourable anti-inflammatory activity as an anti-arthritis, anti-edema, and analgesic with less ulcerogenic side effects. For example, compound XXXV was found to be more effective than *aspirin*; ED_{50} 28.3 *vs.* 81.4 mg/Kg, respectively [17]. Sydnones containing substituted styrylketone were also investigated for their anti-inflammatory activity. Deshpande and his co-workers stated that some sydnonylstyrylketone XXXVI showed significant analgesic activity especially when there was an electron withdrawing group attached to the styryl moiety such as furyl, 4-nitrophenyl, and 4-chlorophenyl. However, replacing the 4-methoxyphenyl group in XXXVI by 3-chloro-4-flurophenyl enhanced the biological activity and decreased the ulcerogenicity compared to ibuprofen. Styryl-substituted sydnone exhibited a considerable analgesic activity in acetic acid-induced writhing but failed to show any significant activity in hot plate test suggesting that they act through peripheral rather than central effect [18].



XXXV



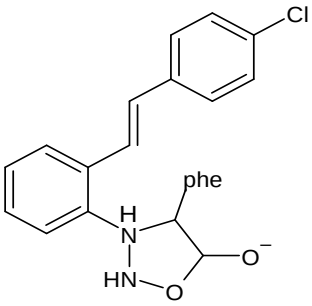
XXXVI

Cytotoxic and anticancer activity

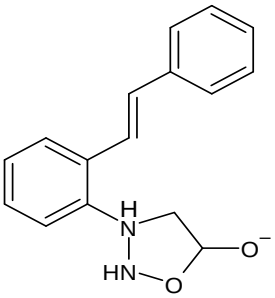
The 3-(4-chloro-3-nitrophenyl) sydnone and 3-(4-pyrrolidono-3-nitrophenyl) sydnone exhibited a significant cytotoxic activity against sarcoma 180, Ehrlich carcinoma and *B10MCII* fibrous histiocytoma. Remarkably, only the first one showed a growth inhibitory activity against *L1210* leukaemia ascites tumors. They argued that the cytotoxic effect of sydnones might be due to inhibition of thymidine uptake by the cancerous cells [19].

Furthermore, sydnones were also linked to other pharmacologically active molecules to produce more potent cytotoxic agents. In this stream, sydnone-substituted chalcones were successfully synthesized and significantly inhibited the growth of Ehrlich ascites cells and Dalton's lymphoma ascites cells. Noteworthy, the existence of a methyl group on the chalcone moiety enhanced the survival of the experimental tumour-bearing animals while chloride atom produced a toxic compound . A few years later, other 3-(halogen-substituted phenyl) sydnones were synthesized and tested against many cancer cell lines *in vitro*. It was found that a fluoride atom at the *para* position of the phenyl ring resulted in a sound antiproliferative activity against breast cancer *MCF7*, lung cancer *NCI-H460* and central nervous system cancer *SF-268*. In contrast, replacing the halogen atom by other heterocyclic rings such as indole and isoindole was detrimental to the cytotoxic activity [20].

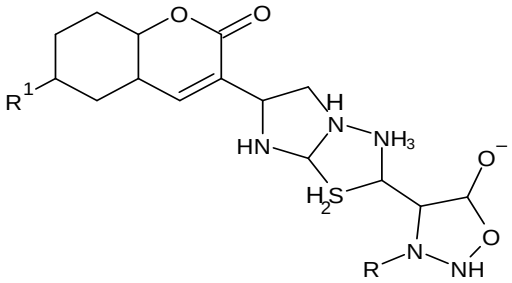
In addition, new stilbene-sydnone hybrids were prepared and found to decrease the viability and proliferation of cervical carcinoma (*Hela*), breast carcinoma (*MCF7*), colon carcinoma (*SW620*), pancreatic carcinoma (*MiaPaCa2*) and lung carcinoma (*H460*) cell lines *in vitro*. The most potent agents were found to have a chloride or methyl substituent on the stilbene moiety with a phenyl or methyl group at C4 of the sydnone ring like in structures XXXVIII and XXXIX . Others reported a significant anticancer activity for new sydnones derivatized with imidazo [2,1-b][1,3,4] thiadiazole and coumarin at C4 of the sydnone ring (XL) against *HT-29* human colorectal adenocarcinoma cell line. They found that the hydrophobicity of R was crucial for the cytotoxic activity and the existence of a chlorine atom on the coumarin ring (R^1) sharply raised the activity to be comparable to that of *cisplatin* [21].



XXXVIII



XXXIX



XL

Antimicrobial activity

It has been demonstrated by numerous studies that sydnone derivatives have antibacterial and antifungal activities. Penicillin 3-arylsydnone hybrids were prepared by Naito and his colleagues from 3-arylsydnone-4-carboxylic acid and 6-aminopenicillanic acid. They were found to be active against penicillinase-producing bacteria strains. On the other hand, penicillin 3-alkylsydnones were inactive against the same resistant strains. It was postulated that the existence of a phenyl group at N3 of the sydnone ring resulted in sterical hindrance which protects the β-lactam carbonyl in a manner similar to that of *oxacillin*[22]. Sydnone-chalcone hybrids were also prepared and showed high antibacterial activity against gram-positive bacteria (*Staphylococcus aureus)* and weak activity against gram-negative bacteria (*E. coli)*. However, they did not exert antifungal activity. The existence of nitro group at the chalcone moiety enhanced the antibacterial activity. Remarkably, bromination of the α, β-unsaturated ketone of the chalcone and the position C4 in the sydnone ring resulted in good bactericide molecules [23].

Antioxidant activity

Sydnone and its related compounds have been reported as antioxidant agents in various literature sources. In 1994, it was found that sydnone ring can enhance the antioxidant activity of chalcone by inhibiting lipid peroxidation and scavenging free radicals. Of interest, sydnone-substituted chalcones suppressed superoxide production by peritoneal macrophages *in vivo* in the presence of phorbol myristate acetate ester (PMA) which was linked to tumour generation. Recently, 3-(halogen-substituted phenyl) sydnones combined with chalcone were reported as strong 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavengers. The existence of fluorine and chlorine atoms at the phenyl ring of the sydnonyl moiety increased the antioxidant activity by nine folds compared to the commonly used antioxidant agent butyl hydroxy anisole (BHA) [24].

Additionally, sydnones substituted at C4 with thiazolidinone and thiazoline rings exhibited a moderate to potent DPPH free radical scavenging activity *in vitro*. Apparently, 2,3-dihydrothiazole ring linked to 3-phenylsydnone yielded powerful and rapid antioxidant compounds whose scavenging activities The absence of N-H group rendered the latter to be a weak scavenger [25].

Antimalarial activity

In 1965, sydnone-based derivatives emerged as a new class of antimalarial agents. It was reported that 3-piperonylsydnone and 3-phenylsydnone showed activity against *Plasmodium berghei;* the main parasite that causes malaria in mice. Nyber and Chen stated that 3-piperonylsydnone exhibited antimalarial activity when administered orally or subcutaneously at a dose of 10 mg/Kg with no toxic side effects even at a dose up to 500 mg/Kg. Since 3-phenylsydnone showed less activity and higher toxicity, it was of interest for other researchers to conduct a structure-activity analysis on the antimalarial activity of sydnone and piperonyl compounds. It was found that the N-N bond is essential for the antiplasmodial activity either in the sydnone or in the piperonyl moiety. However, 3-piperonylsydnone was still the most active molecule among all tested compounds. On the other hand, 4,4-bis (acetamidophenyl) sulfone derivatives were very potent antimalarial agents, while sydnone rendered it less active or inactive when they were combined in one structure . Unfortunately, studies on sydnone-containing antimalarial agents were discontinued [26].

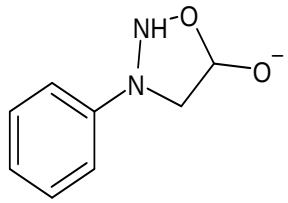
III CHARACTERIZATION

Sydnones spectral studies

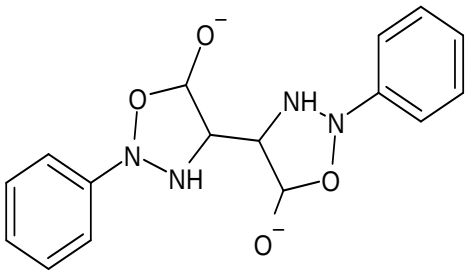
Ultraviolet (UV) spectroscopy

The properties of the ultraviolet spectra of sydnones were well reviewed by Stewart and Kier and Roche. Briefly, absorption maxima in the range 290-340 nm was considered as a proof of the presence of the aromatic ring of sydnone. Alkyl sydnone absorbs at the lower wavelength (<300 nm). For example, 3-methylsydnone, 3-*n*-butyl sydnone and 3-cyclohexylsydnone showed their UV absorption maxima at 290, 289.5 and 292 nm, respectively. A bathochromic shift was observed for 3-arylsydnone due to conjugation as in 3-phenylsydnone and 3-(1-naphthyl) sydnone which absorb at 310 and 315, respectively. Many factors can remarkably affect the UV spectra of sydnones:

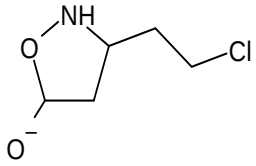
1. Conjugation: An aromatic system substituted at C4 of the sydnone ring has a stronger bathochromic effect such as 3-methyl-4-phenylsydnone whose UV maxima was at 317 nm. Similarly, 4-acetylated sydnone absorbs at a longer wavelength such as 4-acetyl-3-phenylsydnone and 3-phenylsydone absorb at 324 and 310 nm.
2. Steric factors can retard the conjugation due to the disturbance of the planarity of the molecule. The UV maxima of 3-(2, 6-methylphenyl) sydnone was found to be at 255 nm even shorter than that of 3-alkyl sydnone which lacks conjugation.
3. Electrostatic interaction in *bis*-sydnone system makes the co-planarity system more rigid and therefore the UV absorption wavelength is unusually high like in XXVII ,XXVIII, XXIX and XXXI whose maximum absorptions were at 292, 350, 292 and 303, respectively[27,28].



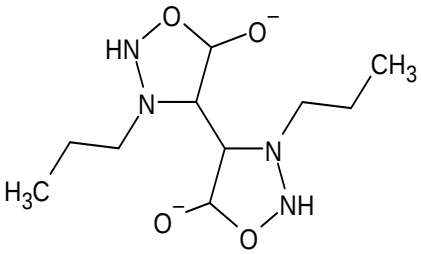
XXVII



XXVIII



XXIX



XXXI

Infrared (IR) spectroscopy

A survey of the literature since their early preparation until today revealed two characteristic IR bands for sydnones. The stretch of sydnone carbonyl (C5-O) ranges from 1740 to 1770 cm^{-1} while the absorption band of carbon-hydrogen (C4-H) was more than 3000 cm^{-1}. However, electrophilic substitution at C4 led to the loss of the carbon-hydrogen band and an increase in the wavenumber of the carbonyl up to 1780-1830 cm^{-1}. For example, acetylation of 3-(4-chlorophenyl) sydnone resulted in upshifting the CO band from 1750 cm^{-1}[25] to 1786 cm^{-1}[3]

CONCLUSIONS

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

REFERENCES

[1] McNaught AD;Wilkinson A,IUPAC compendium of chemical terminology.1997,67,1371
[2] Sachin K.Bhosale, Shreenivas R. Deshpande and Rajendra D.Wagh.,2012. Mesoionic sydnone derivatives.
[3] IUPAC compendium of Chemical Terminology 2nd Edition1995,67,1371
[4] W.Baker;WD Oills; VD Poole, J.Chem.so.1949.307.
[5] Florin ALBOTA and Michaela Dina STANESCU.,2017.The state of art in sydnone chemistry and application.
[6] DL Browne; JP Harrity,Tetrahedron 2010,(66),553-58.
[7] 8.Mei-Fang Ding,Kai-Fang Cheng,Ying-Nan Chen,Shaw-Tao Lin.,2013.The electrophilic substitution of sydnone: the reaction with 3-aryl-4-phenylsydnone, 3-arylmethylsydnones and 3-phenylethylsydnone.
[8] Jonathan Michael Tumey.,2015. Synthesis and reactivity of sydnone derived 1,3,4-oxadiazole-2(3H)-ones.

[9] Abdualrahaman Mohamad Abdualkadar, Muhammad Thher, Nik Idris Nik Yusoff.,2017. Mesoionic sydnone a review in their chemical and biological properties .
[10] DL Browne; JP Harrity,Tetrahedron 2010,(66),553-58.
[11] Jonathan Michael Tumey.,2015. Synthesis and reactivity of sydnone derived 1,3,4-oxadiazole-2(3H)-ones.
[12] Wang Y, Lee PL, Yeh MH.,1984. Structure of 3-(p-ethoxyphenyl)sydnone, and 3-(p-tolyl) sydnone. Acta cryst Sect C: Cryst str comm.
[13] Greco CV, O'Reilly BP.,1970.Mesoionic compounds vi metallation of sydnone.An estimation of acidity..
[14] Wagner H, Hill JB, Ray RE, Aspinall RL.,1974-1975.Antiflamatory sydnone 1 and 2.
[15] Satyabarayana K, Rao MNA.,1995. Synthesis of 4-[5-(substituted aryl)-4,5-dihydro-1H-pyrazol-3yl]-3-phenyl-sydnone as anti-inflammatory,antiarthritic and analgesic agents.
[16] Deshpande SR,Pai KV, Pai RS.,2011-2012.Design and synthesis of certain mesoionic sydnonyl styrylketones as potential nonsteroidal anti-inflammatory agents.
[17] Grynberg N, Gomes GR, Echevarria A, Miller J.,1992 Some new aryl-sydnones: effect on murine tumomurs anticancer.
[18] Butkovic K, Marinic Z, Sindler-Kulyka M.,2011. Synthesis of 3-(o-stilbenyl)-sydnone and 3-(o-stilbenyl)-4-substituted-sydnone derivatives and their antitumor evaluation.
[19] Tegginamath G,Kamble RR, Taj T, Kattimani PP, Meti GY.,2013. Synthesis of novel imidazole[2,1-B][1,3,4]thiadiazole appended to sydnone as anticancer agents.
[20] Naito T, Nakagawa S,Takahashi K, Masuko K, Fujisawa K.,1968.Synthesis of 6-aminopenicilanic acid derivatives 3.6-(3-substituted-sydnone-4-corboxamido)-pencillanates.
[21] Moustafa MAA, Eisa HM.,1992. Synthesis and antimicrobial activity of 3-(substituted-phenyl)-sydnones.
[22] Bhosale SK, Deshpande SR,Wagh RD.,2015.Ultrasound assisted one pot synthesis, spectral, antimicrobial and antioxidant studies of novel 4-[1-oxo-3-(substituted phenyl)-2propenyl]-3-substituted phenyl sydnones.
[23] Shih Amh, Su YS, Wu C L.,2007.Synthesis and evalution of antioxidant activity of sydnonyl substituted thiazolidinone and thiazoline deravatives.
[24] Popoff IC, Singhal GH, Engle AR.,1971.Antimalarial agents 7. Compounds related to 4,4-Bis(aminophenyl)sulfone.
[25] Stewart FHC.,1964.The chemistry of the sydnones
[26] Kier LB, Roche EB.,1967. Medicinal chemistry of the mesoionic compound.
[27] Lawson KD, Brey WS, Kier LB.,1964. Hydrogen chemical shift of 3-alkyl and 3-phenyl sydnones.