1.1 General introduction

Sydnones are the most prominent members of the mesoionic class of non-benzenoid heteroaromatic compounds. Since their early discovery by Earl and Mackney in 1935,\textsuperscript{1} sydnones have received significant interest over the past century. Baker and Ollis (1949) introduced the concept of mesoionic molecules to an anhydro compound obtained from cyclodehydration of $N$-nitroso-$N$-phenylglycine.\textsuperscript{2} The generic name sydnone was suggested in the honour of University of Sydney, where it was discovered.

Sydnone (1.01) is the most widely studied among mesoionic compounds. According to the definition of mesoionic molecules, sydnones cannot be represented by any one covalent or polar structure, but can be represented by many polar and tetra polar canonical structures. In general, sydnones are represented by a positively charged aromatic ring with an enolate type exocyclic oxygen (Fig. 1).

![Figure 1](image-url)
The electronic distribution of sydnones can be gained from molecular orbital calculations as shown in Fig. 2. Depiction 1.02 shows the calculated bond orders, suggesting an enolate type bonding mode for the exocyclic oxygen which has been proved by the calculated net charges depicted in 1.03 and 1.04. Depiction 1.05 ascribes a large negative charge on the exocyclic oxygen atom which shows a scaled-dipole moment representation of a sydnone. The C4 carbon atom (α-carbon) has a $pK_a$ of ~18-20, which would stabilize the adjacent ketone type moiety. Moreover, the infrared spectra of number of sydnones show an absorbance at approximately 1730 cm$^{-1}$ which would suggest the presence of a carbonyl function.

Interestingly, representations 1.02-1.05 suggest that N3 is an iminium type nitrogen and is therefore acting as an electron withdrawing substituent on the attached phenyl ring. This concept has been proved by the work of Wang and co-workers as they conducted a series of physiochemical calculations and suggested that the sydnone π-electrons are unequally delocalised. They concluded that N2 and N3 were neutral, whereas C4, O1, O3 were negatively charged while C5 was positively charged. Moreover, they stated that there is little π-resonance interaction between the N3-phenyl ring and the sydnone ring. Consequently, these predicted results were found correct when compared with the synthetic studies and a general reactivity profile of a sydnone molecule can be drawn as shown in Fig. 3.

Sydnones have also gained interest through their promising biological properties including antibacterial, antineoplastic, anticancer and anti-inflammatory activity.
ON C₄ is nucleophilic and bears an acidic proton

N₃ is electron poor, the attached aromatic ring is reluctant to participate in electrophilic substitution

Figure 3

1.2 Methods of preparation

The classical method for the synthesis of sydnone involves two steps (Scheme 1).

**Step 1:** N-Nitrosation of N-substituted amino acid

**Step 2:** Cyclodehydration of N-nitroso-amino acid

Scheme 1

N-Nitrosation followed by cyclodehydration generally furnishes sydnones in good to excellent yields. Recently, several improvements have been introduced for the preparation of sydnones. Particularly, the employment of trifluoroacetic anhydride (TFA) has remarkably increased the rate of cyclodehydration (Scheme 2). ¹²
Turnbull et al\textsuperscript{13} have described nitrosation using isoamyl nitrite (IAN) for acid sensitive amino acids (Scheme 3).

\begin{center}
\includegraphics[width=\textwidth]{Scheme3}
\end{center}

**Scheme 3**

Azarifar et al\textsuperscript{14} have reported one-pot synthesis of sydnones directly from $N$-substituted amino acids (Scheme 4). The method employs dibromo-dimethylhydantoin (DBH) which avoids the isolation of the toxic $N$-nitrosoamine intermediate. Thoman and Voaden reported the use of charcoal to improve the purity of the isolated sydnone.\textsuperscript{15}

\begin{center}
\includegraphics[width=\textwidth]{Scheme4}
\end{center}

**Scheme 4**

A review by Stewart\textsuperscript{2b} lists about 117 reported sydnones and also describes several sydnones which cannot be synthesized, one such example is the sydnone with $R=H$. Nitrosation of such precursor would result in diazonium salt formation.

### 1.3 Sydnone stability

Sydnones are light brown crystalline solids, and can be stored at room temperature, although a few of them have been reported to decompose in the presence of light. Upon treatment with conc. acids, sydnones undergo ring cleavage with loss of CO\textsubscript{2} resulting in the formation of corresponding hydrazine derivatives and this chemistry has been proved to provide a route to synthesize various hydrazine derivatives (Scheme 5).\textsuperscript{16} Under alkaline conditions some of the sydnones are prone to undergo degradation to form foul
smelled isocyanides. Puranik and Suschitzky have reported the formation of corresponding glycyl amides when $N$-substituted-4-bromo-sydnone were reacted with piperdine (Scheme 6).\textsuperscript{17} Heat can also cause degradation of sydnones.\textsuperscript{18}

![Scheme 5](image)

**Scheme 5**

![Scheme 6](image)

**Scheme 6**

### 1.4 Functionalisation of sydnone at C4-position

The C4 position of sydnone ring is both acidic and nucleophilic which leads to undergo two possible modes of functionalisation;

1. Electrophilic aromatic substitution reaction
2. Deprotonation followed by electrophile addition

#### 1.4.1 Electrophilic aromatic substitution reaction

**a) Halogenation**

Several methods have been developed for the introduction of halogens at C4 position of sydnone. Dumitrascu et al\textsuperscript{19} synthesized a series of 4-halosydnones (1.15, 1.17) using acetic acid, sodium acetate and appropriate halogen source (Scheme 7). Turnbull et al\textsuperscript{20} employed dichloroiodobenzene and triethylamine to get 4-chlorosydnone (1.18) in good to excellent yields (Scheme 8).
4-Bromosydnone derivatives are the most studied halogenated sydnone. Kato et al.\textsuperscript{21} employed bromine and sodium bicarbonate to obtain \textit{N}-phenyl-4-bromosydnone (Scheme 9, 1.19). Taj et al.\textsuperscript{22} employed bromine in acetic acid and synthesized a series of 4-bromo-3-aryl-pyrazoline derivatives (Scheme 10, 1.20). \textit{N}-Halosuccinimides have also been used for the synthesis of 4-bromo and 4-chloro sydnones.\textsuperscript{20}
b) Direct acylation

Earlier, Friedel-Crafts reaction on sydnones has remained elusive as the treatment of sydnones with an acid chloride and aluminium chloride failed to form the desired 4-acylsydnone. Presumably, the Lewis acid was found to be coordinated with exocyclic oxygen atom of sydnone. Zhang et al reported intramolecular Friedel-Crafts acylation of \textbf{1.21} with BF$_3$.Et$_2$O and acetone (Scheme 11).\textsuperscript{23}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme11.png}
\caption{Scheme 11}
\end{figure}

However, recently Tien et al\textsuperscript{24} achieved direct acylation of sydnone by sonication with perchloric acid and acetic anhydride. A heterogenous clay catalyst protocol has been developed by Turnbull et al\textsuperscript{25} (Scheme 12).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme12.png}
\caption{Scheme 12}
\end{figure}

\subsection*{1.4.2 Lithiation}

This reaction provides a convenient means to introduce a variety of substituents mainly by lithiation of sydnone at C4 position followed by transmetallation. Lithiation of sydnone is facile and commonly carried out using \textit{n}-butyllithium.

Fuchigami and co-workers\textsuperscript{26} described the synthesis of alkylthio and arylthio sydnones (\textbf{1.25}) \textit{via} intermediacy of lithiated sydnone \textbf{1.24} which in turn is formed by deprotonation of C4 proton with \textit{n}-butyllithium followed by
addition of sulphide. The authors have also reported the synthesis of selenide- (1.26), phosphide- (1.27) and arsenide- (1.28) derived sydnones from similar route (Scheme 13).

Kalinin and co-workers\textsuperscript{27} reported transmetallation of lithiated sydnone to the corresponding organocopper compound which efficiently underwent palladium mediated coupling processes with aryl and alkenyl halides (Scheme 14).
1.30 \[ \text{PhI} \]
\[ \text{Pd(PPh}_3\text{)}_4 \] 5 mol%

\[ \text{1.31} \]

\[ \text{1.30} \]
\[ \text{Br} \]
\[ \text{Ph} \]
\[ \text{Pd(PPh}_3\text{)}_4 \] 5 mol%

\[ \text{1.32} \]

Scheme 14

1.4.3 Substitution of C4-bromine group

Kato and Ohta\textsuperscript{21} reported a method on removal of bromine atom from 4-bromo-N-phenylsydnone in presence of magnesium metal and subsequent quenching with water gave the unsubstituted parent sydnone presumably via Grignard reagent. Alternatively, sodium borohydride can be used for the removal of sydnonyl bromide.\textsuperscript{28} Tein\textsuperscript{24} developed an ultrasound zinc-mediated method for the removal of sydnonyl bromine.

Turnbull \textit{et al}\textsuperscript{29} developed palladium catalyzed Sonogashira coupling of 4-bromosydnones employing various alkynes (\textbf{Scheme 15}).

\[ \text{1.33} \]

Scheme 15

Recently, Browne \textit{et al}\textsuperscript{30} have reported the scope of Suzuki-Miyaura cross coupling of 4-bromo-N-phenylsydnone with a variety of boron containing substrates under the influence of various catalyst (\textbf{Scheme 16}). Moran \textit{et al}\textsuperscript{31} have described direct arylation, alkenylation and alklynylation protocol for the synthesis of 4-substituted-N-phenylsydnone from \textit{N}-phenylsydnone (\textbf{Scheme 17}).
1.4.4 Reactions of C4 carbonyl sydnones

Shih and co-workers\textsuperscript{32} synthesized imidazolyl substituted sydnone by reacting 4-formylsydnone with aromatic glyoxals in the presence of ammonium acetate and acetic acid (Scheme 18).

Tein\textsuperscript{33} has developed application of Schmidt reaction to C4 acylated sydnones for the synthesis of sydnonyl methylamides (Scheme 19).
Gireesh et al$^{10,34}$ constructed fused imidazo[2,1-b][1,3,4]-thiadiazole derived sydnones (1.40) by the sequential reactions of 4-formyl-N-phenylsydnone with thiosemicarbazide, citric acid and appropriate acyl bromides (Scheme 20).

The same authors have carried out Biginelli type reaction and obtained corresponding 1,2,3,4-tetrahydro-pyrimidine derived sydnones (Scheme 21).$^{35}$
1.5 Ring transformation reactions of sydnone

The most important synthetic application of sydnones is their [3+2] dipolar cycloaddition reaction with alkynes, alkenes and arynes to give several other heterocycles such as pyrazole, 1,3,4-oxadiazole, phenyl indazole, pyrazoline and tetrazine (Scheme 22).36-40

Reagents and reaction conditions – a: DMAD, toluene, 80 °C; b: acrylonitrile, toluene, 80 °C; c: bromine in acetic anhydride, 0-25 °C; d: arynes, TBAF, THF, rt; e: trimethyl-vinylsilane, toluene, 110 °C; f: nitrileimine (C₆H₅C≡NNC₆H₅)

Scheme 22
1.5.1 Alkyne cycloaddition

Sydnones undergo [3+2] cycloaddition with alkynes followed by loss of carbon dioxide resulting in the formation of pyrazoles. The reaction was first discovered by Huisgen\textsuperscript{41} in 1962 and showed the compatibility of cycloaddition reaction for a range of simple hydrocarbon-substituted alkynes as well as those bearing acyl, acetal, alcohol and ester groups.

Cycloaddition reactions of sydnones are mainly performed with electron-deficient alkynes. For example, sydnone readily reacts with dienophile dimethylacetylenedicarboxylate (DMAD) and yields functionalised pyrazole derivatives.\textsuperscript{36}

Unsymmetrical alkynyl esters always produce two regioisomers of pyrazole derivatives. Hence, the alkynyl esters are synthetically more useful as these substrates offer a chance to study the regioselectivity of sydnone cycloadditions (Scheme 23).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\textbf{\textit{O}}};
\node (b) at (0,-1) {\textbf{\textit{O}}};
\node (c) at (1,0) {\textbf{\textit{N}}};
\node (d) at (1,-1) {\textbf{\textit{N}}};
\node (e) at (0.5,0.5) {Ph};
\node (f) at (0.5,-0.5) {Ph};
\node (g) at (1.5,0.5) {MeOOC};
\node (h) at (1.5,-0.5) {COOMe};
\draw (a) -- (b) -- (c) -- (d) -- (e) -- (f);
\draw (b) -- (g);\draw (c) -- (h);
\end{tikzpicture}
\end{center}

\textbf{Scheme 23}

Specklin \textit{et al}\textsuperscript{42} developed a protocol for one-pot synthesis of 1,4-disubstituted pyrazoles from arylglycines via copper-catalyzed-alkyne cycloaddition reaction (Scheme 24).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {Ph\text{N}};
\node (b) at (0,-1) {COOH};
\node (c) at (1,0) {1.};
\node (d) at (1,-1) {BuONO};
\node (e) at (2,0) {\text{Ph}};
\node (f) at (2,-1) {2. TFAA};
\node (g) at (3,0) {25 °C};
\node (h) at (3,-1) {solvent free};
\node (i) at (4,0) {CuSO$_4$-BPDS, Na asc., TEA, 60 °C \text{\textquoteright}BuOH/H$_2$O};
\node (j) at (5,0) {1.50};
\draw (a) -- (b);
\draw (c) -- (d);
\draw (e) -- (f);\draw (e) -- (g);\draw (e) -- (h);\draw (e) -- (i);\draw (e) -- (j);
\end{tikzpicture}
\end{center}

\textbf{Scheme 24}
Decuypere and co-workers\textsuperscript{43} described copper (I)-catalyzed cycloaddition of 4-bromosydnones and alkynes for the synthesis of 1,4,5-trisubstituted pyrazoles (Scheme 25).

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme25.png}
\end{center}

**Scheme 25**

Foster \textit{et al}\textsuperscript{44} reported regioselective alkyne cycloaddition of 4-trifluoromethylsydnone with phenylacetylene to afford 5-trifluoromethylpyrazoles (Scheme 26).

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme26.png}
\end{center}

**Scheme 26**

### 1.5.2 Alkene cycloaddition

The 1,3-dipolar cycloaddition of sydnone with alkenes has been known for over 40 years. Huisgen\textsuperscript{45} reported that such cycloadditions would result in the formation of $\Delta^2$-pyrazolines which upon addition of an oxidant give rise to corresponding pyrazoles. Studies suggested that, the alkene cycloadditions proceeded analogously with that of alkynes. The reaction pathway of alkene dienophiles give rise to an azomethine imine intermediate (which decides the final product) accompanied by loss of carbon dioxide (Scheme 27).

Sasaki\textsuperscript{46} described the conversion of 7-azanorborenes (1.54) into linear polycycles by sequential cycloaddition reactions with \textit{N}-phenylsydnone (Scheme 28).
Kato\textsuperscript{47} reported ring-expanded product by the cycloaddition reaction of sydnone with cyclobutene. Heating N-phenylsydnone with benzocyclobutene afforded corresponding benzodiazepine (Scheme 29).

Nan’ya\textsuperscript{48} \textit{et al} have employed quinones as an alternative class of activated dienophiles to get indazole-4,7-diones (1.57). As outlined in Scheme 30, the cycloaddition of 2-methyl-\textit{p}-quinone with N-phenylsydnone generated 1:1 regioisomers.
Mais\textsuperscript{49} prepared diazepinones (1.58) from alkylidenecyclobutenones via [3+2] cycloaddition followed by \textit{in situ} ring opening initiated by the azomethine imine intermediate (Scheme 31).

![Scheme 31]

The cycloaddition of sydnones with vinylsilanes and vinylstannes has been demonstrated by Gonzalez-Nogal and co-workers.\textsuperscript{39} Vinylsilanes showed reluctant toward cycloaddition and the reaction was thought to be sensitive to steric hindrance. Interestingly, the authors obtained a mixture of pyrazolines and pyrazoles with excellent regiocontrol (Scheme 32).

However, the cycloadduct of corresponding vinylstannane did not undergo retrocycloaddition, instead eliminated a carboxylate group to give stannyl ester (Scheme 33).

![Scheme 32]

![Scheme 33]
In view of the importance of sydnones as useful synthons and in continuation of exploring synthetic utility of sydnones, this thesis involves five chapters concerning the synthesis of novel heterocycles and analyzed for their pharmacological properties.

References


