CHAPTER II

4-Amino-1-aryl-3-methyl-5-oxo-Δ²1,2,4-triazoles
Sydnones as synthons in heterocyclic synthesis

Purpose of the work:

Heterocyclic compounds are considered as the most promising molecules in drug designing. Many drugs are heterocycles which are of synthetic origin and this has resulted in the diversity of synthetic procedures for the heterocyclic rings. The search for useful precursors and the development of simple and concise procedures has become an important goal for organic synthetic chemists.

Surveying the literature on sydnones in the previous part of the thesis, it is apparent that the importance of the sydnone ring is due to its ability to undergo ring transformation to a variety of heterocyclic systems\(^1\). These conversions take place by 1,3-dipolar cycloaddition reactions and many such conversions have been reported from our laboratory\(^2\).

In continuation of the ongoing studies of this laboratory on heterocyclic construction mediated by sydnones, we thought of utilizing the sydnone ring for the synthesis of some more heterocyclic systems, which are accessible with difficulty by routine methods or even inaccessible.

One such reaction we focused our attention is the synthesis of 3-aryl-5-methyl-2-oxo-\(\Delta^4\)-1,3,4-oxadiazolines by facile, one pot conversion of 3-arylsydnones\(^1\). The synthesis of only very few of these compounds has been carried out with difficulty starting from phenylhydrazine\(^3,4\). This procedure resulted in the formation of isomers and with considerable low yield (<30%). However, the synthesis of such 1, 3, 4-oxadiazolinones, which were obtained in excellent yield (80-85%) from 3-arylsydnones have been reported from our laboratory by Badami and Mallur\(^5\). These compounds have not been studied for their reactions so far and this observation
encouraged us to extend our work with emphasis on the study of reactivity of the oxadiazolinone ring.

**Present Work:**

Since the 1,3,4-oxadiazolin-2-ones would show a strong affinity towards nucleophilic reagents, due to the presence of a lactone group, we initially treated these compounds with hydrazine hydrate as a nucleophile, with the hope that the ring fission would lead to hydrazides of the following type. These would serve as very good intermediates for synthetic work.

However, the oxadiazolinones underwent further ring transformation to the so far unknown 4-amino-1-aryl-3-methyl-5-oxo-$\Delta^2$-1,2,4-triazolo-$\Delta^2$-1,2,4-triazoles, which would be otherwise difficult to synthesize or even inaccessible by other methods. The mechanism may be proposed as following. The initial step is the attack of the nucleophile on the carbonyl carbon leading to ring fission resulting in the formation of the intermediate N-acetamido-N-aryl-N-carbomydrazide.
The acetamido carbonyl carbon is then attacked by the -CONH and not the free amino group, , resulting in the formation of a five membered ring rather than a six membered ring (IV).

Prolonged heating also did not give the tetrazine derivative. The reaction was traced by TLC and there was no indication of the formation (existence) of the intermediate suggesting that the ring fission and
the recyclisation by the attack of \(-\text{CONH}\) are simultaneous processes. The \text{N-amino triazolinones} were of great interest as they contained a free amino group, which is an important functional group to be utilized for variety of reactions. Making use of this functional group, some reactions are carried out during the present work and they are discussed in the Chapter 3.

The 3-aryl-5-methyl-2-oxo-\(\Delta^4\)-1,3,4-oxadiazoles have been prepared starting from 3-arylsydnones by the literature method\(^5\). The 4-amino-1-aryl-3-methyl-5-oxo-\(\Delta^2\)-1,2,4-triazolines were obtained by the reaction of 3-aryl-5-methyl-2-oxo-\(\Delta^4\)-1,3,4-oxadiazolines with hydrazine hydrate in ethanol (75 \% yield). These compounds were obtained in improved yield (80-85\%) in the absence of ethanol (Scheme).

**SCHEME**
Spectral Characterization:

The IR spectra (No. 1) of these compounds showed two $\nu_{\text{NH}}$ bands at 3333-3215 cm$^{-1}$ typical of a $-\text{NH}_2$ group. The $\nu_{\text{C}=\text{O}}$ appeared at 1709 cm$^{-1}$, lower than in the oxadiazolinones. This lower shift indicates the conversion of the lactone carbonyl into the amide carbonyl confirming the ring transformation. Further evidence for these compounds was obtained by $^1$H-NMR (300 MHz) spectra which exhibited a singlet at $\delta$ 4.3 (2H) (D$_2$O exchanged) (spectrum No.3) due to NH$_2$ protons (Spectrum No.2). The other two singlets at $\delta$ 2.35 and 2.37 were assigned to C$_4^\prime$ methyl and C$_3$ methyl protons respectively. The aromatic protons resonated as two doublets in the aromatic region $\delta$ 7.69 – 7.81 with identical J values (7.1 Hz) AA’BB’ pattern.

The 13C-NMR spectrum (No.5) of the compound showed weak singlets for four quaternary carbons at $\delta$119(C$_4^\prime$-Aromatic), $\delta$128(C1’Aromatic),$\delta$136(C3) and $\delta$154(C=O). The methyl carbon is observed as an intense singlet at $\delta$11.0. The aromatic 3’&5’ and 2’&6’ carbons appeared as intense signals at $\delta$117&$\delta$130 respectively.

The structure of this compound was further confirmed by its mass spectrum (Spectrum No.4). The molecular ion M$^+$ at m/e 204 agrees with the molecular weight of the compound and the presence of even number of nitrogens confirms the addition of two more nitrogens (even mass number according to the nitrogen rule). The molecular ion is the base peak. The formation of the stable ions at m/e 105, 91 and 57 is explained by the following fragmentation pattern.
**SPECTRAL DATA**

\[ \text{l-/>-Tolyl-4-amino-3-methyl-5-oxo-A2-1,2,4-triazole} \]

**IR Spectrum**

Spectrum No. 1

- $3333 \text{ cm}^{-1}$ and $3215 \text{ cm}^{-1}$: $\nu_{\text{NH}_2}$
- $1709 \text{ cm}^{-1}$: $\nu_{\text{C}=\text{O}}$
- $1641 \text{ cm}^{-1}$: $\nu_{\text{C}=\text{N}}$

**$^1\text{H}-\text{NMR Spectrum}$**

Spectrum No.2

- $\delta 2.35 \text{ (s, 3H)}$ : $\text{C}_4$-methyl
- $\delta 2.37 \text{ 9s, 3H)}$ : $\text{C}_3$-methyl
- $\delta 4.3 \text{ (s, 2H)}$ : $\text{NH}_2$ protons (D$_2$O exchanged)
- $\delta 7.69$-$7.71 \text{ (d, 2H, J 7.1 Hz)}$ : Aromatic protons AA 'BB' pattern
- $\delta 7.78$-$7.81 \text{ (d, 2H, J 7.1 Hz)}$ :
Spectra No. 4

Mass Spectrum

![Mass Spectrum Diagram]

- Molecular Formula: $\text{C}_7\text{H}_7\text{N}_2\text{O}$
- Molar Mass: 134 g/mol
- Significant Masses: 105, 91, 80, 57, 51, 40, 39, 29, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 g/mol
- Major Peak at 190
Where, \( X = \text{halogen} \) and \( Y = \text{alkylhalogen} \)

Snehata et. al., synthesized 3-(3',4',5'-trimethoxyphenyl)-5-mercapto-4H-1,2,4-triazole and screened for antifungal and antibacterial activities (2).

Antibacterial, antifungal, oxytoxic and catatonic activities (3) of 4-(2'-phenylindol-3'-yl)-5-phenoxyethyl-1,2,4-triazole-3-thiones (C) have been studied.

Messina, Botta, Corelli, Paladino (4) synthesized enantiomerically pure 1-[a-(benzofuran-2-yl)arylmethyl]-1H-1,2,4-triazoles (D) as antifungal and antiaromatase agents.

Hamada, Tashimasa, Takeyamma, Toshiaki (5) prepared triazoles (E) as intermediates for agrochemical fungicides.
\[
\text{Cl-SO}_2N\text{SO}_2-N'R''}
\]

(E)

\[Y = H, \text{halo, C1-8 alkyl etc.}\]

\[R', R'' = \text{C1-4, alkyl etc.}\]

Saha, Ashiskumar; End, David William (6) and others prepared triazoles (F) as farnesyl transferase inhibitors.

![Triazole Structure]

(F)

Sato, Jun; Shirai, Yauo; Homodo and coworkers (7) prepared 3-(2-substituted-indole-1-yl)sulfonyl-1,2,4-triazole derivatives (G) for bactericides.

![Triazole Structure]

(G)
Geslin, Michel; et.al., (8) studied 3-amino-1-phenyl-1H-[1,2,4]triazoles (H) as antagonists of corticotrophic hormone releasing factor.

\[
\begin{align*}
& \text{H} \\
\end{align*}
\]

\[
\begin{align*}
& R^1, R^2 = \text{Cl} \\
& R^3 = \text{H} \\
& R^4 = \text{Me} \\
& R^5 = \text{CHPrPh}, \quad R^6 = \text{Pr}
\end{align*}
\]

Moustafa, H. N. (9) synthesised and studied the reactions of new fused heterocycles derived from 3-(o-aminophenyl)-4-amino-5-mercapto-1,2,4-triazole (I) used for heterocyclic systems and spiro compounds.

\[
\begin{align*}
& \text{I} \\
\end{align*}
\]

Sato, Junji Shirai and other (7) prepared 3-chlorosulfonyl,1,2,4-triazole derivatives (J) as bactericides.

\[
\begin{align*}
& \text{J} \\
\end{align*}
\]
Katritzky, AlanR; Rogerey, Boris V and others (10) synthesized N, N-disubstituted 3-amino-1,2,4-triazoles (K) as antifungal agents.

\[
\begin{align*}
&\text{R}_1 \quad \text{N} \quad \text{N} \\
&\text{Z} \quad \text{H}, \; \text{Y} \quad \text{H}
\end{align*}
\]

(K)

Abdel-Fattah, M. E; El-Din Salam, Ezz; Mahomood M. A (11) synthesized and studied the antimicrobial activity of some 3-p-chlorophenoxy methyl-4-phenyl-1,2,4-triazol-5-yl-thio-acetylhydrazine derivatives (L).

\[
\begin{align*}
&\text{Cl} \\
&\text{OCH}_2 \\
&\text{CH}_2 \quad \text{CO} \quad \text{N} \quad \text{N} \\
&\text{S} \quad \text{CH}_2 \\
&\text{Ph} \\
&\text{N} \quad \text{N} \quad \text{S} \quad \text{CH}_2 \quad \text{CO} \quad \text{N} \quad \text{N} \quad \text{H} \\
&\text{N} \quad \text{N} \quad \text{S} \quad \text{CH}_2 \\
&\text{Ph} \\
&\text{N} \quad \text{N} \quad \text{S} \quad \text{CH}_2 \quad \text{CO} \\
&\text{N} \quad \text{N} \quad \text{H} \\
&\text{N} \quad \text{N} \quad \text{S} \quad \text{CH}_2 \\
&\text{Ph} \\
&\text{N} \quad \text{N} \quad \text{S} \quad \text{CH}_2 \quad \text{CO} \\
&\text{N} \quad \text{N} \quad \text{H}
\end{align*}
\]

(L)

Muller; K-helmt;kluth, J; Gesig, E. R. F (12) prepared sulfonylamino (thio) carbonyl-1,2,4-triazole-5-mes(H) as herbicides.

\[
\begin{align*}
&\text{R}_3 \quad \text{SO}_2 \quad \text{HN} \\
&\text{Q}_1, \; \text{Q}_2 = \text{O}, \; \text{S} \\
&\text{R}_1 = \text{alkyl}, \; \text{cycloalkyl}, \; \text{alkyl}, \; \text{amino etc} \\
&\text{R}_2 = \text{alkyl}, \; \text{alkoxy}, \; \text{halo etc} \\
&\text{R}_1, \; \text{R}_2 = \text{alkylene}
\end{align*}
\]

(M)
Brenner, Michael; Weinrich, Marion; Weiser, Thomas et. al (13) studied triazolones (N) with neuroprotective effect.

![Chemical Structure of Triazolone](image)

\[
\begin{align*}
R^1 &= \text{(un) substituted aryl, aralkyl, alkyl} \\
R^2 &= \text{(un) substituted aryl, aralkyl, alkyl, heterocyclic} \\
R^3 &= \text{H, (un) substituted alkyl alkenyl, alkenyl}
\end{align*}
\]

Kucukgugel, Ilkay; Kucukguzel.s.Guniz and others(14) synthesized N-alkyl/aryl-N'-[4-(3-aralkylthio-4-alkyl/aryl-4H-1,2,4-triazole-5-yl)phenyl] thioureas(O) and tested for antimycobacterial activity against Mycobacterium tuberculosis H37 Rv as well as Mycobacterium fortuitum ATCC 6841, which is a rapid growing opportunistic pathogen.

![Chemical Structure of Thiourea](image)

Sikorski, James.A. (G.D.Searle & Co., USA) (15) studied substituted 1,2,4-triazoles(P) which are useful for inhibiting the activity of cholesteryl ester transfer protein.
R\(^1\) = higher alkyl, higher alkenyl etc.
R\(^2\) = (un) substituted aryl, heteroaryl etc.
R\(^3\) = H, SH, halo.
R\(^1\) = tridecyl
R\(^2\) = 3-Meo-C\(_6\)H\(_{14}\)
R\(^3\) = SH

This compound had an IC\(_{50}\) for inhibition of CETP in human serum of 50 mM.

Ikizler, Aykut A.; Ikizler, and co-workers (16) synthesized and studied antitumor activity of some 4,5- dihydro-1H-1,2,4-triazol-5-ones(Q).

\[
\text{\text{(Q)}}
\]

Yamada, Naotakai; Kusamo, Daisuke; etal.,(17) studied the bleaching activity of 4-alkyl-3-propargyl-1,2,4-H-triazoles(R).

\[
\text{\text{(R)}}
\]

Cesar, Jozko; Sollner, Marija (18) used 3,5,-disubstituted 1,2,4- triazoles (S) for the synthesis of peptidomimetics.
Demirayak, Seref; Benkli and others (19) synthesized and studied the antimicrobial activities of some 3-arylamino-5-[2-(sub-1-imidazolylethyl]-1,2,4-triazole derivatives (T).

Udupi, R. H; Purushottamachar, P; Bhat, A. R. (20) synthesized and were screened antimicrobial activities of 1,2,4-triazole derivatives containing triazolo-thiadiazole and triazolo-thiadiazolidine ring systems. (U & V)

R = (un) substituted ph, (aryloxy) methyl, etc.
**EXPERIMENTAL:**

Preparation of 4-amino-1-aryl-3-methyl-5-oxo-Δ₂-1,2,4-Triazoles.

(General procedure)

a) 3—[p-Tolyl]-5-methyl-2-oxo-Δ₄-1,3,4-oxadiazole (1.9 g., 0.01 moles) was dissolved in 15 ml of dry alcohol. To this solution was added hydrazine hydrate (1.5 ml, 0.01 moles) and refluxed on a water bath for 8 hrs. The reaction mixture was cooled and poured into ice cold water, the solid separated was filtered, washed with water and recrystallised from ethanol.

b) A mixture of oxadiazolinone (1.9g, 0.01 moles) and hydrazine hydrate (1.5 ml, 0.01 moles) was heated on a water bath for 6 hrs. The reaction mixture cooled and poured into ice water. The solid separated was isolated as above.

The other derivatives prepared by the same procedure are listed in Table No.9
### CHARACTERISATION DATA OF COMPOUND

4-Amino-1-aryl-3-methyl-5-oxo-Δ^2-1,2,4-triazoles

Table No. 9

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>Yield%</th>
<th>M.P °C</th>
<th>Molecular formula</th>
<th>Elemental Analysis Found (Calcd)</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>60</td>
<td>162-63</td>
<td>C_9H_{10}N_4O</td>
<td>C% 56.51 (56.76) H% 5.18 (5.25) N% 29.35 (29.44)</td>
<td></td>
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<tr>
<td>H</td>
<td>4-CH₃</td>
<td>75</td>
<td>171-73</td>
<td>C_{10}H_{12}N_4O</td>
<td>58.00 (58.84) 5.65 (5.87) 27.30 (27.44)</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>4-Cl</td>
<td>78</td>
<td>162-65</td>
<td>C_{9}H_{9}N_4OCl</td>
<td>48.02 (48.11) 4.05 (4.00) 25.02 (24.95)</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>3-Cl</td>
<td>55</td>
<td>133-35</td>
<td>C_{9}H_{9}N_4OCl</td>
<td>48.00 (48.11) 3.90 (4.00) 24.82 (24.95)</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>4-Br</td>
<td>71</td>
<td>185-87</td>
<td>C_{9}H_{9}N_4OBr</td>
<td>40.18 (40.16) 3.36 (3.34) 21.10 (21.19)</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>2-OCH₃</td>
<td>76</td>
<td>170-72</td>
<td>C_{10}H_{12}N_4O_2</td>
<td>58.75 (58.84) 5.88 (5.87) 27.41 (27.44)</td>
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<tr>
<td>H</td>
<td>4-OCH₃</td>
<td>65</td>
<td>174-76</td>
<td>C_{10}H_{12}N_4O_2</td>
<td>58.90 (58.84) 5.88 (5.87) 27.36 (27.44)</td>
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<tr>
<td>H</td>
<td>4-COOH</td>
<td>50</td>
<td>180-82</td>
<td>C_{10}H_{10}N_4O_3</td>
<td>51.32 (51.30) 4.25 (4.27) 23.92 (23.96)</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>2-CH₃</td>
<td>62</td>
<td>175-77</td>
<td>C_{10}H_{12}N_4O</td>
<td>58.80 (58.84) 5.85 (5.85) 27.48 (27.44)</td>
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</tr>
<tr>
<td>3-Cl</td>
<td>4-CH₃</td>
<td>70</td>
<td>176-78</td>
<td>C_{10}H_{11}N_4OCl</td>
<td>58.86 (47.20) 5.80 (5.87) 27.41 (27.44)</td>
<td></td>
</tr>
<tr>
<td>2-Cl</td>
<td>5-OCH₃</td>
<td>74</td>
<td>162-65</td>
<td>C_{10}H_{11}N_4O_2Cl</td>
<td>47.20 (65.40) 4.30 (4.32) 22.01 (22.00)</td>
<td></td>
</tr>
<tr>
<td>2-OCH₃</td>
<td>5-OCH₃</td>
<td>68</td>
<td>148-50</td>
<td>C_{11}H_{14}N_4O_3</td>
<td>65.40 (41.62) 6.90 (6.92) 27.70 (27.71)</td>
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</tr>
<tr>
<td>3-NO₂</td>
<td>4-Cl</td>
<td>69</td>
<td>162-65</td>
<td>C_{9}H_{9}N_4O_3Cl</td>
<td>41.62 (41.64) 3.10 (3.08) 26.99 (26.98)</td>
<td></td>
</tr>
<tr>
<td>2-Cl</td>
<td>5-Cl</td>
<td>71</td>
<td>150-53</td>
<td>C_{9}H_{9}N_4OCl_2</td>
<td>41.78 (41.73) 3.10 (3.08) 21.61 (21.63)</td>
<td></td>
</tr>
</tbody>
</table>
RESULTS OF ANTIMICROBIAL SCREENING

The invitro antimicrobial screening of all these compounds showed that they are more active against the fungii. All these compounds exhibited moderate to weak activity against E. coli while none of them were active against C. bacillus when compared to the reference drug-norfloxacin.

However, most of them exhibited enhanced activity against the fungal cultures used. The m-Cl (No. 4), 2 & 4- methoxy (No. 6 & 7) the dimethoxy (compound No. 12), the o-methyl ( No. 9) and the NO and Cl (No. 13) substituted compounds exhibited antifungal activity higher than compared to Griseofulvin, against penicillium. In particular, the o-methyl (No 9) and the dimethoxy (No. 12) showed significant enhanced activity. The combination of chloro and methyl substituents (No 10) exhibited the highest activity amongst all these compounds. But these compounds were moderately active against A. candida. Enhanced fungal inhibition was observed for the 4-carboxy (No. 8) and 2-Chloro-5-methoxy (No. 11) derivatives against A. candida and the rest of the compounds showed activity equal to that of the reference drug. (Table No. 10)
ANTIMICROBIAL ACTIVITY OF 4-amino-1-aryl-3-methyl-5-oxo-Δ^2-1,2,4-Triazoles

Table No. 10

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>R</th>
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<th>Antibacterial</th>
<th>Antifungal</th>
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</tr>
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<td>1</td>
<td>H</td>
<td>H</td>
<td>11</td>
<td>_</td>
</tr>
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<td>_</td>
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<td>5</td>
<td>H</td>
<td>4-Br</td>
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<td>_</td>
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<td>H</td>
<td>2-CH₃</td>
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<td>_</td>
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<td>5-OCH₃</td>
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<td>_</td>
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<td>3-NO₂</td>
<td>4-Cl</td>
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Reference

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<tr>
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<th>C. bacillus mm</th>
<th>Penicillium mm</th>
<th>A. candida mm</th>
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<td>Norfloxacin</td>
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<td>34</td>
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<tr>
<td>Griseofulvin</td>
<td>_</td>
<td>_</td>
<td>17</td>
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</table>
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