

## Synthesis of New Sulfa-Nitron Compounds

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### Abstract

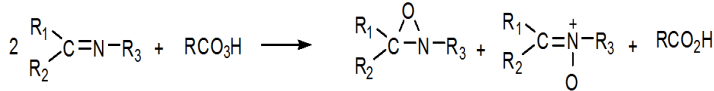
The Schiff bases were synthesized from sulfa drugs with some aldehyde and then converted to nitrones by oxidation of Schiff bases with peracetic acid which synthesized by using of hydrogen peroxide with acetic acid. The resulting products were identified by physical properties like melting point (m.p.), retardation factor (R<sub>f</sub>) and color. Also compounds showed the expected data in identification techniques like FTIR, <sup>1</sup>HNMR, mass spectroscopy and Elemental analysis (CHN). The results verified the chemical structures of synthesized compounds.

**Keywords:** Nitron, sulfa drugs, Schiff base, sulfa-nitron.

### Introduction

Nitrones have taken special interests due to their successful applications as building blocks in the synthesis of various natural and biologically active compounds<sup>1</sup>. They are commonly used precursors<sup>2</sup> in the synthesis of a variety of heterocycles, as spin trapping reagents, in the identification of transient radicals<sup>3,4</sup> and as therapeutic agents<sup>5</sup>.

Oxidation of imines by peroxide acids gives a mixture of nitron and oxaziridine<sup>6</sup>, as shown in scheme-1.

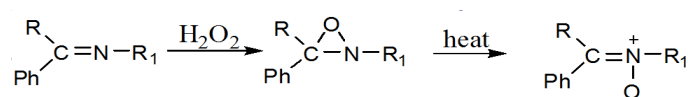


Scheme-1

There is a competition between the formation of nitron and oxaziridine compounds. Many factors affect the formation of the product ratio, such as less bulky substituents on the imino-

N-atom and non hydroxylic solvents<sup>7</sup>. Spontaneous rearrangement of oxaziridines into nitrones is observed, either upon heating or treatment with acids<sup>8</sup>.

The reaction between imines and hydroperoxides was also employed to the synthesis of a variety of 3-aryloxaziridine derivatives, which were rearranged by heating to corresponding nitrones, as shown in scheme-2<sup>9</sup>.



Scheme-2

R, R1=Alkyl or aryl group.

### Material and Methods

A series of Schiff bases were synthesized in order to study them and to synthesize the nitron compounds. The general structures of Schiff bases and nitrones are illustrated below in figure-1.

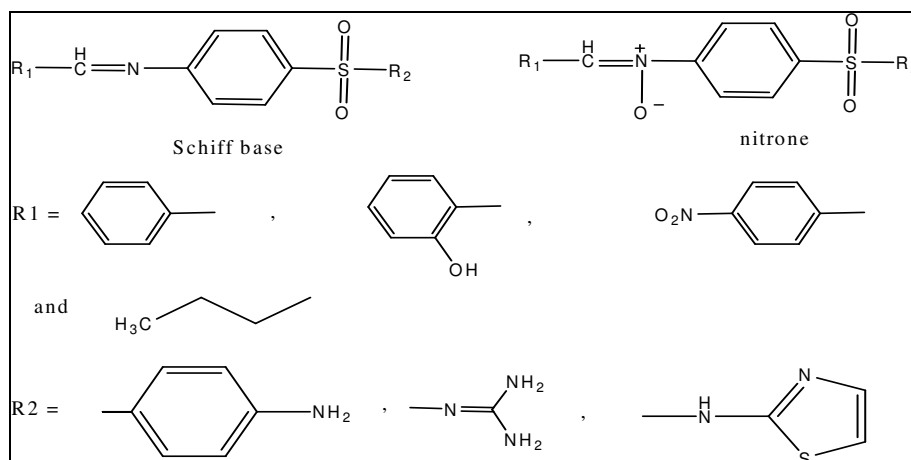
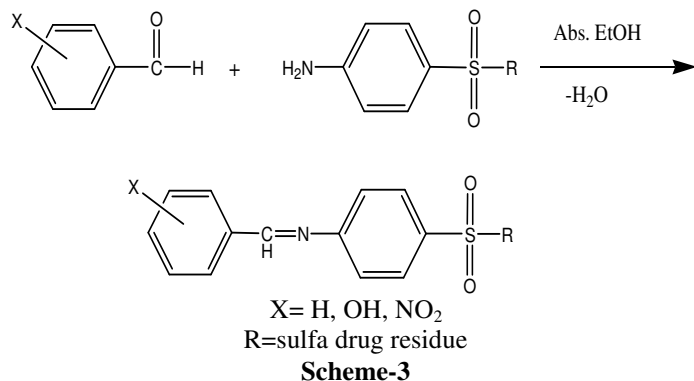


Figure-1

The general structures of Schiff bases and nitrones

**General method to synthesize Schiff bases:** The procedure of which is according to the following: To (0.028 mol) of sulfa drug (160 ml) of absolute ethanol was added (0.028 mol) of aldehyde were mixed in (250 ml) round bottom flask. To the reaction mixture 3 drops of glacial acetic acid were added as catalyst. The reaction mixture was refluxed for several hours according to the type of substrate as shown in Table-1 and then the mixture was cooled overnight. The precipitate was filtered and purified by recrystallization from absolute ethanol<sup>10</sup>.

The different Schiff bases were prepared and studied in this research. Schiff bases were formed by the condensation reaction of some aldehydes such as benzaldehyde, salicylaldehyde, p-nitro and p-hydroxy benzaldehyde with sulfa drug such as sulfadiazine, sulfamerazine, sulfamethoxazole, sulfaguanidine, sulfisoxazole and 4,4-diamino diphenylsulfone, in absolute ethanol with elimination of water at the end of the reaction, as shown in scheme-3.

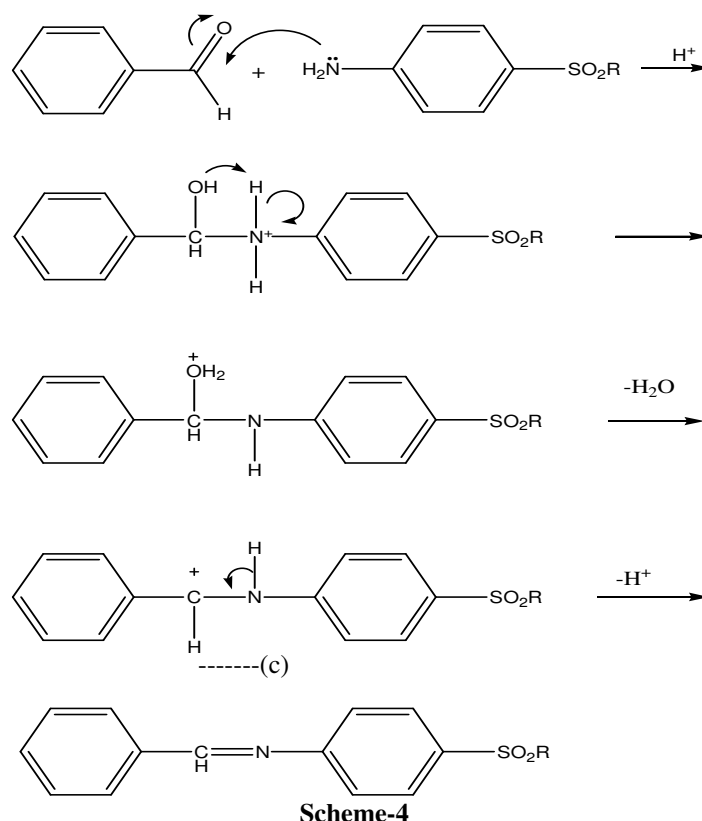


**Table-1**

**The symbol, time of reaction and structure of Schiff bases**

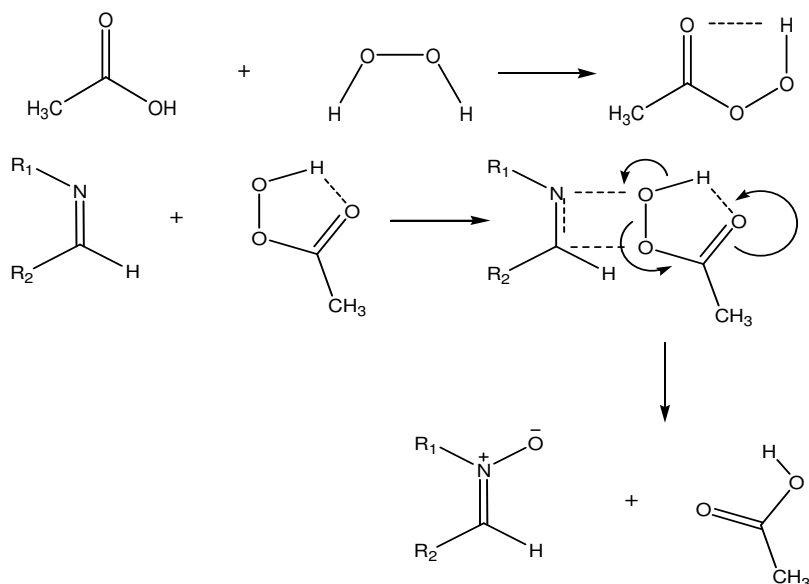
Symbol	Time of reaction hours	Structure
S1	8	
S2	30	
S3	15	
S4	11	
S5	12	

The mechanism of the reaction, as illustrated in scheme-4, included the nucleophilic attack of an amine at the carbon atom of carbonyl group.



**Synthesis of nitrone:** These compounds were prepared agreed literature<sup>11</sup>. In 50ml round bottom flask, 0.002 mole of an imine and peracetic acid prepared from mixture of 0.013 mol (1.2 ml) 36% H<sub>2</sub>O<sub>2</sub> with (2.5 ml) from glacial acetic acid were added, during this addition, the solution was cooled to -5°C. After the addition is complete, the reaction mixture was kept below 10°C with continuous stirring in dark over a period of 3 hours, and then left at 0°C for 24 hours. The solid was removed by filtration and washed with two portions of 5ml of acetone, ethanol, then tasted by KI-Starch paper to indicate removed any unreacted H<sub>2</sub>O<sub>2</sub>. The precipitate nitrone was recrystallized from absolute ethanol.

A series of nitrone compounds have been synthesized and studied in our research. All these compounds were synthesized by the oxidation reaction of Schiff base with peracetic acid, as shown in the mechanism below. Then the peracetic acid was added drop by drop to Schiff base that was placed in ice bath in temperature between -5 to -10 °C. The oxidation was carried out due to the suggested mechanism, as shown in scheme-5. All these reactions were monitored by thin layer chromatography TLC.



**Scheme-5**  
**The suggested mechanism of nitron formation**

From this mechanism we proved, with regard to the oxygen transfer to the C=N in Schiff base, that the observed lack of stereo retention in the oxidation of *cis*- and *trans*-acyclic substituted Schiff bases, which indicates a stepwise oxygen atom transfer process. However, there is insufficient evidence to fully elucidate whether oxygen transfer to the C=N Schiff base occurs via the peroxy species.

The purification of nitron compounds was tested first by thin layer chromatography TLC using different eluents. The best separation was obtained in mixture of (n-Hexane: Ethyl acetate) having a ratio (3:2), respectively as eluent. Accordingly, the compounds were purified by column chromatography using the above eluent.

## Results and Discussion

The resulting data were obtained for the synthesised compounds from analysis data as following:

*(Z)*-4-(4-aminophenylsulfonyl)-*N*-(2-hydroxybenzylidene) aniline oxide (N1) melting point (m.p.) 205-208°C, yellow needles yield 83%, TLC, DCM:CHCl<sub>3</sub> 2:3, retardation factor R<sub>f</sub>= 0.43, FTIR  $\bar{\nu}$  /cm<sup>-1</sup>: 1616 (C=N), 1135 (N-O), 3365 (OH), 3120 (NH). <sup>1</sup>HNMR (500 MHz, dimethyl sulfoxide (DMSO));  $\delta$ : 8.96 (s, CH=N→O), 7.59-8.06 (AA'BB' H<sub>arom</sub>), 6.99-7.70 (m, H<sub>arom</sub>), 12.39 (s, OH). Mass (m/z): 368 [M]<sup>+</sup>, 185, 142, 120, 92. For C<sub>19</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>S (found): 62.09 % C, 4.31 % H, and 6.82 % N.

*(Z)*-*N*-butylidene-4-(*N*-(diaminomethylene)sulfamoyl) aniline oxide (N2) m.p. 230-231°C, orange needles yield 87%, TLC, n-hexane: EtAc 3.5:1.5, R<sub>f</sub>= 0.73, FTIR  $\bar{\nu}$  /cm<sup>-1</sup>: 1622 (C=N), 1180 (N-O), 3220, 3344 (NH). <sup>1</sup>HNMR (500 MHz, DMSO);  $\delta$ :

9.73 (s, CH=N→O), 7.62-8.04 (AA'BB' H<sub>arom</sub>), 7.29 and 7.34 (t, d, H<sub>guanidine</sub>), 2.34 (m, 2H, CH<sub>2</sub>), 2.12 (q, 2H, CH<sub>2</sub>) 1.24 (t, 3H, CH<sub>3</sub>). Mass (m/z): 284 [M]<sup>+</sup>, 256, 213, 198, 185, 167, 71, 69. For C<sub>11</sub>H<sub>18</sub>N<sub>4</sub>O<sub>3</sub>S (found): 45.96 % C, 5.94 % H, and 19.49 % N.

*(Z)*-4-(*N*-(diaminomethylene) sulfamoyl)-*N*-(2-hydroxybenzylidene) aniline oxide (N3) m.p. 220-223 °C, yellow-brown fine needles yield 75%, TLC, benzene: CHCl<sub>3</sub> 3:7, R<sub>f</sub>= 0.55, FTIR  $\bar{\nu}$  /cm<sup>-1</sup>: 1618 (C=N), 1132 (N-O), 3444 (OH), 3224, 3353 (NH). <sup>1</sup>HNMR (500 MHz, DMSO);  $\delta$ : 8.98 (s, CH=N→O), 7.51-7.82 (AA'BB' H<sub>arom</sub>), 6.99-7.79 (m, H<sub>arom</sub>), 6.73 (m, br, H<sub>guanidine</sub>), 12.70 (s, OH). Mass (m/z): 334 [M]<sup>+</sup>, 318, 142, 121, 105, 94. For C<sub>14</sub>H<sub>14</sub>N<sub>4</sub>O<sub>4</sub>S (found) 50.32% C, 4.18 % H, and 16.90 % N.

*(Z)*-*N*-(2-hydroxybenzylidene)-4-(*N*-pyridin-2-ylsulfamoyl) aniline oxide (N4) m.p. 215-217°C, yellow-brown fine needles yield 80%, TLC, benzene: CHCl<sub>3</sub> 3:7, R<sub>f</sub>= 0.68, FTIR  $\bar{\nu}$  /cm<sup>-1</sup>: 1627 (C=N), 1138 (N-O), 3128 (NH). <sup>1</sup>HNMR (500 MHz, DMSO);  $\delta$ : 8.96 (s, CH=N→O), 7.52-7.94 (AA'BB' H<sub>arom</sub>), 6.96-7.69 (m, H<sub>arom</sub>), 6.73, 12.57 (s, OH). For C<sub>18</sub>H<sub>15</sub>N<sub>3</sub>O<sub>4</sub>S (found): 58.48 % C, 4.12 % H, and 11.51 % N.

*(Z)*-*N*-(2-hydroxybenzylidene)-4-(*N*-thiazol-5-ylsulfamoyl) aniline oxide (N5) m.p. 227-229 °C, red-brown needles yield 79%, TLC, n-hexane: EtAc 3:2, R<sub>f</sub>= 0.49, FTIR  $\bar{\nu}$  /cm<sup>-1</sup>: 1616 (C=N), 1182 (N-O), 3498 (OH), 3145 (NH). <sup>1</sup>HNMR (500 MHz, DMSO);  $\delta$ : 8.97 (s, CH=N→O), 7.52-7.87 (AA'BB' H<sub>arom</sub>), 6.99-7.69 (m, H<sub>arom</sub>), 6.86, 7.38 (d, d, H<sub>thiazole</sub>), 12.60 (s, OH). Mass (m/z): 375 [M]<sup>+</sup>, 213, 137, 121, 83. For C<sub>16</sub>H<sub>13</sub>N<sub>3</sub>O<sub>4</sub>S<sub>2</sub> (found) 52.06 % C, 2.95 % H, and 11.31 % N.

The relevant IR spectral bands that can provide from appear of band (N-O) in the range (1132-1182  $\text{cm}^{-1}$ )<sup>12</sup> that verify convert of Schiff bases to nitrones. In <sup>1</sup>HNMR spectra obtained bands in the range (8.96-9.73 ppm) which belongs to nitrone groups (s, CH=N→O)<sup>13</sup>. Mass spectrometry give the molecular ion and other fragments which indicated the structure of prepared nitrones. The elemental analysis found resemble to theoretical values.

The intermediate form throughout the reaction undergoes elimination of water to yield the appropriate Schiff base. The yield of products depends on the type of substituted groups. Therefore, the presence of electron donating groups in amine and electron withdrawing groups in an aldehyde increases the yield of products or vice-versa. As an example, the yield of S2 was 87% more than S1 75%, and also in N2 the yield was 87% while N1 the yield was 83%.

## Conclusion

New nitrone were obtained from oxidation of Schiff bases by peracetic acid. This method was easier than other methods to produce nitrone. The Schiff bases were synthesised of some sulfa drugs with different aldehyde compounds. The chemical structures of new sulfa-nitron compounds were characterized by identification methods.

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