Preparation of Poly [N- Aryl Sulfonamide Maleimide Derivatives]

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ABSTRACT

In this work N- arylsulfonylamides maleimides and their corresponding polymers were prepared from reaction of maleimide as N-sodium salt with chlorosulfonic acid, then reacted with aryl amines, the new N- sulfonamide maleimides were polymerized by free radical using Azobisisobuteronitrile at 70 ºC with dioxane as a solvent. The physical properties of all prepared polymers were studied and characterized by FTIR and UV. spectroscopy. These new- sulfonamide polymers were exhibit drugs properties as antibiotics after treating bacterial infections due to containing the (-SO₂NH) and imide groups. Thermogravimetric analyses of the prepared polymers were measured, and swelling % was studied, and controlled release of ampicillin drug polymer was studied in {PH=7.4} at 37 ºC. some of the prepared polymers are antibacterial agents to overcome shortcomings which is critically important.
INTRODUCTION

In organic chemistry, an imide is a function group consisting of two carbonyl groups bound to nitrogen. These compounds are structurally related to acid anhydrides. The relationship between esters and amide and between imides and anhydrides are analogous, the amine-derived groups are less reactive. In terms of commercial application, imides are best known as components of high strength polymers (1).

![Imide structure](image)

A general linear imide functional group (Imide) refers to derivation of imide itself (NH) or organic derivation (RN). The organic functional group called an imide contains two acyl groups are attached to NH or NR.

Most imides are derived from dicarboxylic acids and their names reflect the parent acid. Examples are succinimide derived from succinic acid and phthalimide derived from phthalic acid. For imide derived from amines (vs. ammonia), the N-substituent is indicated by a prefix, e.g. N-ethylsuccinimide is derived from succinic acid and ethylamine (1).

Carbodiimides have the formula RN=C=NR, they are unrelated to imides.

The ligand in coordination chemistry known as imide has the formula NH. An imide is an intermediate in nitrogen fixation (2).

Being highly polar, imides exhibit good solubility in polar media. The N-H center for imides derived from ammonia is acidic and can participate in hydrogen bonding. Unlike the structurally related acid anhydrides, they resist hydrolysis and some can even be recrystallized from boiling water (3).

Many high strength or electrically conductive polymers contain imide subunits, i.e. the polyimides. One example is Kapton where the repeat unit consists of two imide groups derived from aromatic (4).
Tetracarboxylic acids are another example of poly imides. Polyglutarimide typically made from polymethyl methacrylate (PMMA) and ammonia or a primary amine by aminolysis and cyclization of the PMMA at high temperature and pressure, typically in an extruder. This technique is called reactive extrusion. A commercial polyglutarimide product based on the methylamine derivative of PMMA, called kamax (TM), was produced by the Rohm and Haas company. The toughness of these materials reflects the rigidity of the imide functional group.

Interest in the bioactivity of imide-containing compounds was sparked by the early discovery of the high bioactivity of the Cycloheximide as an inhibitor of protein biosynthesis in certain organisms (4-5). Thalidomide is one unfortunate result of this research. A number of fungicides and herbicides contain the imide functionality. Examples include captan, which has been phased out because of its carcinogenic properties, and procymidone (5, 6).

Illustrative imides, from left: N-ethylmaleimide, a biochemical reagent, phthalimide, and industrial chemical intermediate, Captan, a controversial herbicide, thalidomide, a drug that once caused many birth defects, a subunit of kaptan, a high strength polymer used to make "space suits" (5).

Most common imide are prepared by heating dicarboxylic acids or their anhydrides and ammonia or primary amines. The result is a condensation reaction:

\[(RCO)_2O + R'NH_2 \rightarrow (RCO)_2N R' + H_2O\]

These reactions proceed via the intermediacy of amides. The intramolecular reactions of carboxylic acids with amides are far faster than the intramolecular reaction, which is rarely observed.
Certain imides can also be prepared in the isoimide-to-imide Mumm rearrangement (5).
For imides derived from ammonia, the N–H center is acidic. Thus, alkali metal salts are well known, a well-known example being potassium pthalimide. These salts can be alkylated to give N–alkylimides, which in turn can be degraded to release the primary amine. Strong nucleophiles, such as potassium hydroxide or hydrazine are used in the release step.

The nitrogen in imides is not very basic, which allows it to form stable compounds with halogens.

Treatment of imides with halogens and base gives the N-halide derivatives. Examples that are useful in organic synthesis are N-chlorosuccinimide and N-bromosuccinimide (6).

It is the responsibility of anyone who administers drugs to show animals to do so in accordance with the regulations on the drug’s label. That means giving a drug to an approved animal species, for an approved indication, by one approved route of administration, and at an approved dosage as well as observing the approved withdrawal times, unless specifically directed by a veterinarian within a valid veterinarian-client-patient relationship (7).

Owners of show animals would be wise to remember that some drugs, such as sulfonamides, may be detectable in the urine longer than the withdrawal time on the product label. It is prudent and many other imides were prepared (8-10).

**MATERIALS AND METHODS**

**Instruments:**
- Gallen-Kamp MFB-600 melting point apparatus.
- Electronic spectra measurements using Cintra-5 UV-Visible spectrophotometer.
- Infrared spectrophotometer measurements using SP3-100 Pye-Unicam (600-400 cm⁻¹).
- Viscosity measurements using capillary viscometer type Ostward viscometer, at 30 ºC.
- Thermogravimetric analysis using NETSCH GeratebauGmbtt Model STA-409.

All chemical materials were purchased from Fluka and BDH.
**Preparation of N-sodium maleimide (C1)**

In a (100 ml) round bottom flask provided with a magnetic bar was placed (5 g) of maleimide which was dissolved in (10 ml) of dioxane, the 50% of sodium hydroxide was added with vigorous stirring the precipitate was filtered, then washed with ethanol several time, the sodium maleimide was obtained with high product.

**Preparation of N-sulfonyl maleimide (C2)**

A sample (5 g) of the prepared sodium salt C1 was reacted with chlorosulfonic acid (2.5 ml, 0.01 mol) at 0 °C the mixture was stirred (1 hr). The product was cooled, and the product was washed by ether for several times.

The physical properties were measured with High yield which equal to (90%) was obtained.

**Synthesis of N-Substituted maleimides (C3-C8)**

In a (100 ml) round bottom flask was added (2 g. -0.1 mol) of N-Sulfonyl maleimide, dissolved in (10 ml) of dry dioxane.

The stochiometric amount of primary amine such as (4-amino pyridine, 2-amino pyrimidine, 2-naphthyl amine, 2,2,6,6 tetra methyl pipridine, para amino benzoic acid, ampicillin). The mixture was refluxed for (1 hr.) the clear solution was cooled to room temperature. The precipitate of N-Sulfonyamide maleimide monomers were characterized, table (1) shows the physical properties of C3-C8.

**Table- 1: Physical properties of prepared monomers C3-C8**

<table>
<thead>
<tr>
<th>No.</th>
<th>-Ar</th>
<th>Color</th>
<th>Yield %</th>
<th>U.V absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3</td>
<td>= R1</td>
<td>Brown dark</td>
<td>80</td>
<td>-</td>
</tr>
<tr>
<td>C4</td>
<td>= R2</td>
<td>Brown dark</td>
<td>90</td>
<td>-</td>
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</table>
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<table>
<thead>
<tr>
<th>No.</th>
<th>Structure</th>
<th>Color</th>
<th>CONVERSION %</th>
<th>$\eta$</th>
<th>Softening point</th>
</tr>
</thead>
<tbody>
<tr>
<td>C5</td>
<td><img src="image" alt="Structure" /></td>
<td>Violet</td>
<td>85</td>
<td></td>
<td>$n^* 330$</td>
</tr>
<tr>
<td>C6</td>
<td><img src="image" alt="Structure" /></td>
<td>Brown</td>
<td>75</td>
<td></td>
<td>$n^* 487n$-</td>
</tr>
<tr>
<td>C7</td>
<td><img src="image" alt="Structure" /></td>
<td>White</td>
<td>87</td>
<td>353</td>
<td></td>
</tr>
<tr>
<td>C8</td>
<td>Ampicillin = <img src="image" alt="Structure" /></td>
<td>White</td>
<td>80</td>
<td>269</td>
<td></td>
</tr>
</tbody>
</table>

**Free radical Polymerization of prepared monomers to C9-C14.**

To a screw capped polymerization bottle containing (3g) of N-Sulfonamide maleimide (C3-C8) were added (0.05g) (0.25%) by weight of the monomer concentration of AIBN and 20ml of freshly distilled of dioxane. The clear solution was flashed with pure nitrogen, followed by stream nitrogen gas. The bottle was closed and incubated in water bath at $(70^\circ\text{C})$ for (2 hrs.). The mixture was cooled and the contents were poured in to a beaker. The Polymer was formed, the coagulated polymer was washed with ethanol and dried in vacuum oven, The physical properties were studied.

**Table -2 : Physical properties of prepared sulfonamide maleimide polymers (C9-C14)**

<table>
<thead>
<tr>
<th>No.</th>
<th>-Ar</th>
<th>Color</th>
<th>CONVERSION %</th>
<th>$\eta$</th>
<th>Softening point</th>
</tr>
</thead>
<tbody>
<tr>
<td>C9</td>
<td>-R₁</td>
<td>brown</td>
<td>80</td>
<td>0.41</td>
<td>350&gt;</td>
</tr>
<tr>
<td>C₁₀</td>
<td>- R₂</td>
<td>brown</td>
<td>78</td>
<td>0.48</td>
<td>350&gt;</td>
</tr>
</tbody>
</table>
RESULTS AND DISCUSSION

In this work, sodium maleimide salt was prepared, then converted to N-Sulfonylmaleimide according to the following reaction:

\[
\text{NH} + \text{NaOH} \rightarrow \text{N-Na} + \text{HSO}_2\text{Cl} \rightarrow \text{N-SO}_2\text{H} \]

\[
\text{ArNH}_2 \rightarrow \text{AIBN} \quad 70^\circ \text{C} \quad \text{C9-C14}
\]

**Scheme (I)**

The N-Sulfonyamidmaleimide monomers (C3-C8) were polymerized free radically using AIBN as initiator gave different substituted sulfonoamidemaleimidopolymers (C9-C14), these sulfonoamide polymers contain the radical SO₂NHAr, which exhibit as antibiotics to treat bacteria infections by interfering with a bacteriums production.

These new monomers were characterized and physical properties were listed in table (1) and their corresponding polymers were listed in table (2).
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FTIR spectrum of N-Sulfonylmaleimide as shown in (Fig 1) indicated the absorption of υSO₂ which appeared characteristic absorption at (1388 cm⁻¹) asymmetric SO₂ and at (1122 cm⁻¹) symmetric SO₂ and the broad absorption at (3404) due to OH of Sulfonic acid.

Figs.(2-5) showed the FTIR spectrum of prepared N-Substituted Sulfonamide Maleimide monomer which showed the characteristic absorption of υ–NH Sulfonamide at (3292,3335,3263m₃390cm⁻¹) and υ-C=O at (1716-1666,1714-1626,1720-1766,1707cm⁻¹) for maleimide monomers, υSo₂Asym.(1354,1398,1392,1394), υ-So₂sym at (1192,1120,1101,1150) and their corresponding polymers which is the same absorptions with disappering of vinyl υ C=C absorption of maleimide. These prepared sulfonamide maleimide derivatives polymers exhibit outstanding thermal stability, Which are evaluated by thermogravimetric analysis (TGA) which recorder a function of temperature with loss of weight of polymer samples such as C10,C12 as shown in (Fig.8, Fig.9).

Table 3 shows thermal decomposition for typical N-Substituted Sulfonamidemaleimide degradation temperature appeared at (141-339 °C) and (279-450°C) this was because high polarity of Sulfonamide group and aromatic groups which exist in polymer, that restrict the mobility of chain, therfore polymer degraded before melting stage.

**Table -3: Weight Loss Decomposition temperature for C10 and C12 poly sulfon amide maleimide.**

<table>
<thead>
<tr>
<th>No.</th>
<th>Temp. ⁰C</th>
<th>Weight Loss%</th>
<th>Temp. ⁰C</th>
<th>Weight Loss%</th>
<th>Temp. ⁰C</th>
<th>Weight Loss%</th>
</tr>
</thead>
<tbody>
<tr>
<td>C10</td>
<td>279</td>
<td>9.3</td>
<td>347</td>
<td>14.9</td>
<td>450</td>
<td>24.6</td>
</tr>
<tr>
<td>C12</td>
<td>141.1</td>
<td>17.3</td>
<td>277.8</td>
<td>-9.5</td>
<td>339</td>
<td>40.7</td>
</tr>
</tbody>
</table>

The elemental analysis values agreed quite well with the calculated values for the proposed polymer structures.

The hydrolysis of the prepared polymers in basic medium in pH 10 was illustrated as in scheme2.
Fig. (6) Swelling curve of (C₉-C₁₄) of N-substituted sulfonamide polymers at pH7 at 37 °C shows the Swelling % through 4 days, we performed dynamic swelling studies. The S% is calculated according to the following relation ship:

\[ S\% = \frac{M_1 - M_0}{M_0} \times 100 \]

Where: \( M_0 \) is the mass of dry polymer at time 0.
\( M_1 \) is the mass of swollen polymer at time t.

The S% for all polymers (C₉-C₁₄) were ranged between 7-15.8% .
Fig. -2: FT-IR Spectrum of N-2-pyrimidyl sulfonamide maleimide
Fig. 3: FT-IR Spectrum of N-Naphthal sulfonamide maleimide
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Fig. 4: FT-IR Spectrum of N-2,2,6,6 tetra methylpipyridine sulfonamide maleimide
Fig. -5 : FT-IR Spectrum of N-Benzonic sulfonamide maleimide

Fig. -6 : Swelling of C9-C14 at pH7 at 37 °C
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Fig. -7: Controlled Release Ampicillin Sulfonamide polymer C\textsubscript{14} in pH 7.4 at 37 °C

Fig. -8: Thermal analysis of C12
Fig. -9 : Thermal analysis of C10

REFERENCES


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