

# Synthesis and Reactions of Sulphone Hydrazides

Mohamed E. Khalifa

**Abstract**—The chemistry of sulphone hydrazide has gained increase interest in both synthetic organic chemistry and biological fields and has considerable value. The therapeutic importance of these compounds is the attractive force to continue research in such a point. The present review covers the literature up to date for the synthesis, reactions and applications of such compounds.

**Keywords**—Sulphone hydrazide compounds, Reactions, Synthesis, Biological activities.

## I. INTRODUCTION

SULPHONE hydrazides exhibit a great interest due to their importance in synthesis a variety of valuable heterocyclic compounds which have pharmaceutical activities and chemotherapeutic value [1]–[4] against cognitive disorder, Alzheimer's disease [5], [6], hepatitis C virus [7]–[9],  $\beta$ -lactamase inhibitory properties against class A and C enzymes, antitumor [10], tuberculosis [11]–[16], antimycobacterial agents [14] and bacteriostatic activity with respect to the Koch bacillus [17]. They also produce ring-closed hydrazide-imide copolymers with novel properties used in manufacturing separating membranes [18], cross-linked tough foam copolymer which have good resistance to heat and chemicals [19]–[21] besides their industrial uses in various fields such as rubber [22], epoxy resins [23], leather [24], flame-resistant fibers [25]–[27], color developer [28], [29], stain bleaching and/or anti dye-transfer [30], decomposable blowing agents [31]–[36], flexible self-expandable and self-contained unit with pyrotechnic sheet [37] and their utility analytical field as a sensitive fluorescent labeling reagent for determination of aromatic and aliphatic aldehydes e.g. 4-(5,6-dimethoxy-2-phthalimidinyl)phenyl sulfonyl hydrazide (DPSH) [38].

## II. SYNTHESIS

The main objective of this section is to provide a comprehensive account for the synthesis of various sulphone hydrazide compounds. Usually, they are prepared by the reaction of sulphonyl chloride and hydrazines [39] or reduction of azo compounds [40]. However, these reactions were carried out in organic solvent such as pyridine and DMF [41]–[43].

### A. Diels-Alder Reactions with Cyclic Sulfoxones

Reactions of spiro[1-benzothiophene-4,5'-[1,3]dioxane]-

4',6'-dione **1** with various amines led to the formation of 4-carbamoylhexahydrobenzo[b]thiophene-4-carboxylic acid 1,1-dioxides **2** or their decarboxylation products, depending on the conditions. Hydrazinolysis of the spiro adducts in DMF gave the corresponding monohydrazides **3** [44].

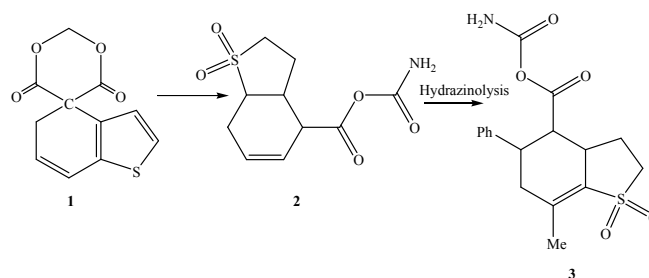


Fig. 1 Diels Alder reaction with cyclic sulfones

### B. From Hydrazines

Reaction of trifluoromethanesulfonyl chloride and trifluoromethanesulfonyl chloride with hydrazine, phenyl hydrazine and 1,1-dimethylhydrazine at low temperature gave the corresponding trifluoromethanesulfonyl hydrazides **4** [45].

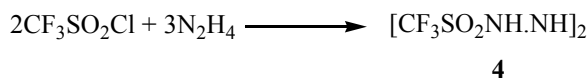


Fig. 2 Synthesis of trifluoromethanesulfonyl hydrazides **4**

Treating of *p*-MeC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>Na with alkyl bromide in EtOH to yield *p*-MeC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>R **5** [R, Me, Et, Pr, Bu, iso-Amyl, benzyl, which on heating with KMnO<sub>4</sub>, and water to yield *p*-HO<sub>2</sub>C.C<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>R **6**. The mixture of **6** in 20 cc. EtOH and 0.012 mol 60% N<sub>2</sub>H<sub>4</sub>.H<sub>2</sub>O was heated on a water bath for 1 h., and the residue recrystallized from EtOH to give a quantitative yield of 4-(alkylsulfonyl)benzohydrazide **7** having the same antituberculous activity as isonicotinyl hydrazide [46].

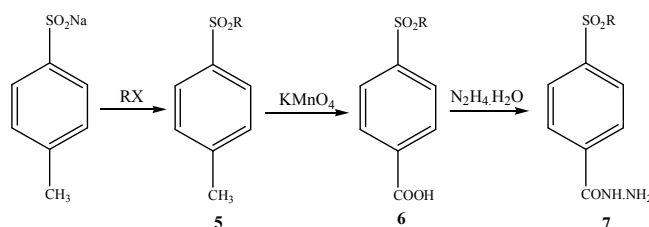


Fig. 3 Synthesis of 4-(alkylsulfonyl)benzohydrazide **7**

Treatment of hydrazine derivatives with sulfonyl chlorides in the presence of basic alumina, in a mortar with grinding by a pestle, afforded the corresponding sulphone hydrazide

Mohamed E. Khalifa is with the Faculty of Science, department of Chemistry, Taif University, Taif 21974, Saudi Arabia and with Higher Institute of Engineering and Technology, department of Chemical Engineering, New Damietta, Egypt (phone: +966569846966, e-mail: mohamedezzat200@hotmail.com)

derivatives **8**.

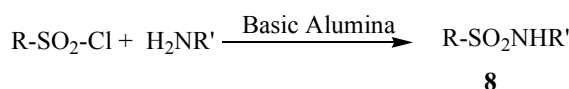


Fig. 4 Synthesis of sulphone hydrazide derivatives **8**

On the other hand, *t*-butyl carbazate can be used instead of hydrazine that reacted with sulphonyl chloride in the presence of basic alumina to produce intermediate **9**. Hydrolysis of the intermediate carbazate **9** gave directly in situ the sulphone hydrazide derivatives **10** under mild conditions [47].

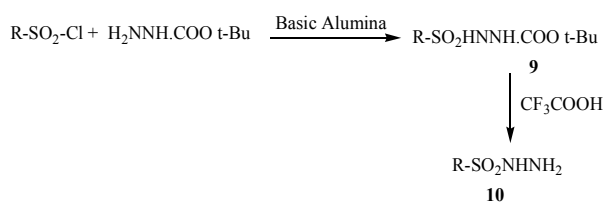


Fig. 5 Synthesis of sulphone hydrazide derivatives **10**

### C. By Microwave Irradiation

The chemical application of microwave irradiation has now become an area of interest for the synthesis of a wide variety of compounds and efficient functional group transformations under solvent-free conditions [48]–[53], where this method was initially introduced in 1986 [54]. The advantages of microwave-expedited chemical transformations are cleaner reactions, higher efficiency and selectivity, shorter reaction times, and the ease of manipulation.

A synthesis of 1-aryl-2-*p*-toluenesulphonyl hydrazides **12** under solvent-free conditions involved mixing the *p*-toluenesulphonyl chloride **11** and aryl hydrazine (1:2 ratio) followed by exposure to microwave irradiation (600W) under solvent-free conditions, where the reaction carefully monitored (by TLC) to regulate the ratio of the substrates, irradiation time and power level of the microwave oven to achieve the maximum yield [55].

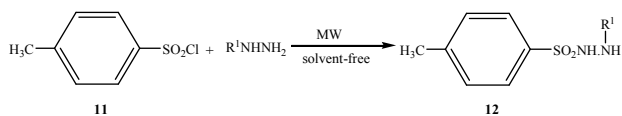


Fig. 6 Synthesis of 1-aryl-2-*p*-toluenesulphonyl hydrazides **12**

## III. REACTIONS

### A. Oxidation

Oxidation of *p*-RC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>NHNH<sub>2</sub> (**13**; R = H, Me, MeO, Cl, Br, AcNH) in AcOH with KMnO<sub>4</sub> and in several drops of 3% aq. H<sub>2</sub>O<sub>2</sub> gave the symmetric diaryl disulphide S,S,S',S'-tetraoxides **14** [56].

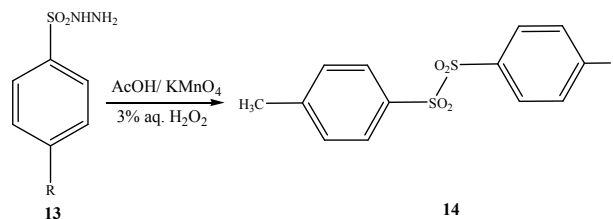


Fig. 7 Oxidation using acidic potassium permanganate

The oxidation of sulphonhydrazides with benzeneselenenic acid (PhSeO<sub>2</sub>H) produce the corresponding selenosulphonate derivatives, where phenyl areneselenosulphonates (**15**, R = aryl) were obtained. The method is also applicable to alkaneselenosulphonates, as illustrated by the methane derivative (**15**, R = Me) [57].

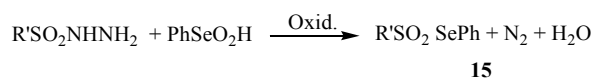


Fig. 8 Oxidation of sulphonhydrazides with benzeneselenenic acid

Phenyl areneselenosulphonates were reacted to the acetylinic derivatives to yield the adducts **16** [58]

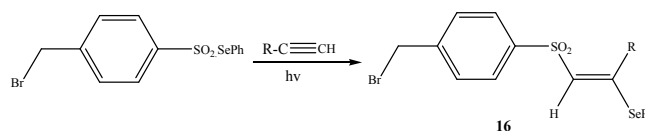


Fig. 9 Reaction with acetylinic derivatives

### B. Nucleophilic Reaction

Nucleophilic displacement reactions of *p*-MeC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>NHNH<sub>2</sub> on RX (X = Br, Cl; R = aryl, alkyl) gave sulphonates *p*-MeC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>R **17** in 80-95% yields [59].

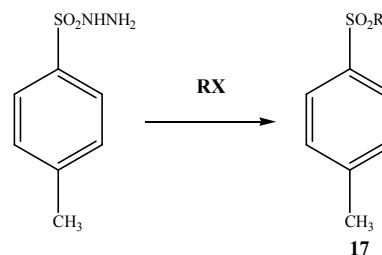


Fig. 10 Reaction with alkyl halides

### C. Reaction with Thiophenecarboxaldehydes

4,4'-Sulphonyl bis(benzohydrazide) was treated with thiophenecarboxaldehydes to yield condensation products **18** (R = H, Cl, Br) and **19**, which showed bactericidal activity [60]. Also, methionine sulphone hydrazide was coupled to 6-aldehydosugars and the reaction was catalytically enhanced by Mn<sup>2+</sup> under physiological condition. The reaction was applied to label surface glycoproteins of erythrocytes with I-35S after treating cells with galactose oxidase [61].

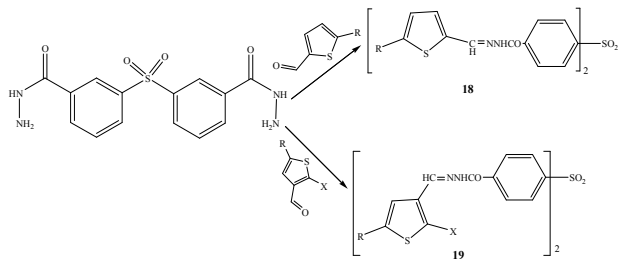


Fig. 11 Reaction with thiophenecarboxaldehydes

#### D. With Cyanogen Bromide and/or Acetyl Acetone

The synthetic potential of sulphonyl-/sulphonyl acetic acid hydrazide derivatives **20** has been utilized in two ways. In one case cyanogen bromide has been used as a source of single carbon and carbohydrazide acts as a source of four atoms reacting through its enol form generating the amino oxadiazole derivatives **21**. In the second case, double electrophilic character of acetyl acetone and the enhanced nucleophilicity of <sup>1</sup>N-nitrogen of the carbohydrazide have been used to synthesize 2,5-dimethyl pyrroles **22**. The synthesized compounds exhibited antimicrobial activity against gram -ve bacterium *Escherichia coli*, gram +ve bacterium *Bacillus staphylococci* and fungi *Penicillium* and *Aspergillus* [62].

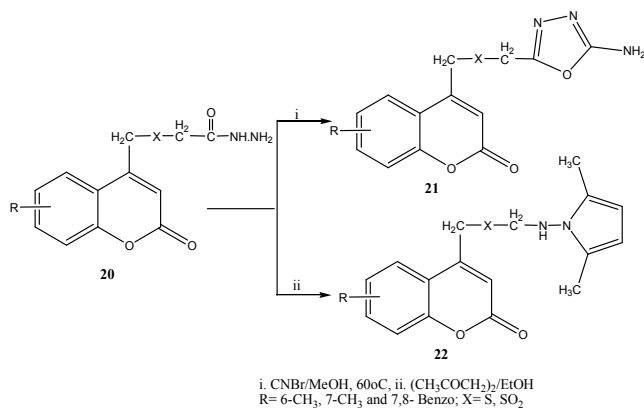


Fig. 12 Reaction with cyanogen bromide and/or acetyl acetone

#### E. With Acetylenic Ester

The reaction of the aryl sulphonyl hydrazide with the acetylenic ester in the presence of triphenyl phosphine led to the corresponding derivatives **23** in good yields [63].

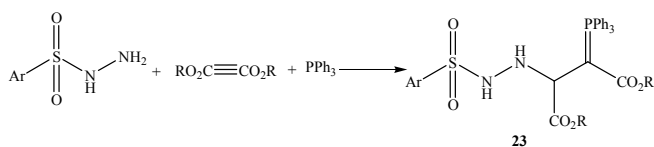


Fig. 13 Reaction with acetylenic esters

#### F. With 5-Aryl-2,3-Dihydrofuran-2,3-Diones

Decyclization of 5-aryl-2,3-dihydrofuran-2,3-diones under the action of *p*-toluenesulphonyl hydrazides in anhydrous dioxane afforded β-N-(4-methylphenylsulphonyl) hydrazides

of aroyl pyruvic acid **24** which exhibit antiinflammatory, and antimicrobial activities [64].

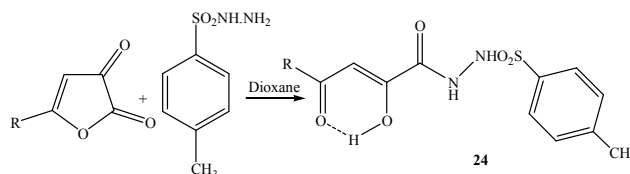


Fig. 14 Decyclization action of sulphone hydrazides

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