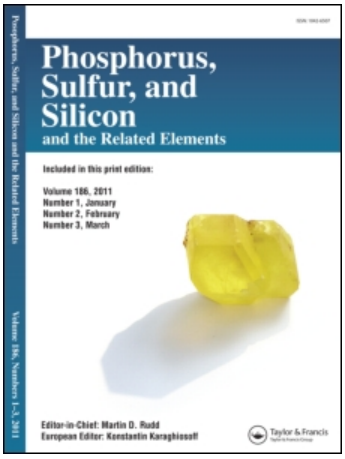


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# REVIEW ON THE CHEMISTRY OF SULFONOHYDRAZIDES AND SULFONOAZIDES

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# REVIEW ON THE CHEMISTRY OF SULFONOHYDRAZIDES AND SULFONOAZIDES

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Sulfonohydrazides recently have achieved considerable importance as organic reagents. They can, for instance, be used in the synthesis of olefins, aldehydes, and diazo compounds, the characterization of sugars; dechlorination of certain chlorinated heterocycles; and the conversion of a keto into a methylene group.

By heating, sulfonoazides are transformed into sulfonylnitrenes. These are very reactive chemical intermediates; they will, for example, insert into carbon-hydrogen bonds. Accordingly, sulfonoazides are chiefly important as precursors of sulfonylnitrenes.

Sulfonohydrazides and sulfonoazides are used industrially as "blowing" and cross-linking agents in the manufacture of foam rubbers and plastics.

## PREPARATION

### Sulfonohydrazide Preparation

Organic sulfonohydrazides, **1**, are generally easily prepared in high yield and purity by reaction of the appropriate sulfonyl chloride with two molar equivalents of hydrazine hydrate in a suitable solvent, e.g., dioxan, tetrahydrofuran, benzene, ether, or ethanol at fairly low temperatures (0–25°)[1,2]

$$RSO_2 \cdot Cl + 2N_2H_4H_2O \rightarrow RSO_2 \cdot NH - NH_2 + NH_2 \cdot NH_2 \cdot HCl$$

**1**

Vigorous stirring is required with water-immiscible solvents like benzene and ether; with ethanol the reaction mixture is kept cold to avoid

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possible reaction between the solvent and the sulfonyl chloride, though this does not generally occur appreciably in the presence of an excess of hydrazine.[3–5] Also to avoid the partial formation of the *N*,*N*′-disulfonohydrazide, the sulfonyl chloride gradually is added to the solution of hydrazine hydrate.

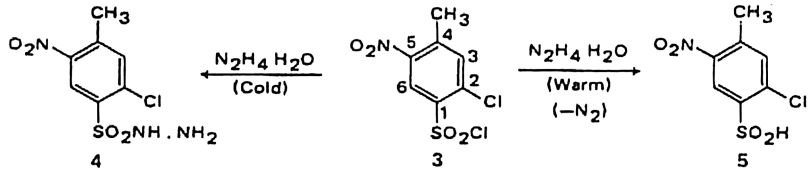
Alternatively, one molar equivalent of hydrazine hydrate or hydrazine hydrochloride may be used in the presence of a suitable base (for instance, lithium hydroxide,[6] sodium hydroxide,[7] ammonia,[8] triethylamine,[9] or pyridine.[10]

For the successful preparation of arylsulfonohydrazides containing electron-withdrawing substituents in the *ortho* or *para* positions of the aromatic nucleus, the condensation with hydrazine must be carried out at low temperatures.[11–14] Thus, *o*-nitrobenzenesulfonohydrazide is obtainable[11] at 10°, but at 35–40° the only product is the sulfinic acid (**2**).[1,12]

$$o\text{-}O_2N\cdot C_6H_4SO_2Cl \xrightarrow[35\text{–}40^\circ]{2N_2H_4\cdot H_2O} o\text{-}O_2N\cdot C_6H_4\cdot SO_2H + H_2 + N_2$$

**2**

The relative stabilities of the nitrobenzenesulfonohydrazides are $m > p > o$.[12] The differences can be applied to separate a mixture of isomeric nitrosulfonyl chlorides; by reaction with hydrazine at such a temperature one isomer gives the sulfonohydrazide, while the other yields the sulfinic acid. With ethanolic hydrazine hydrate at 35°, a mixture of *o*- and *p*-nitrobenzene sulfonyl chlorides gave *o*-nitrobenzenesulfinic acid and *p*-nitrobenzenesulfonohydrazide. After separation, these two-compounds can be reconverted to the sulfonyl chlorides by treatment with chlorine.[12] When 2-chloro-5-nitro-*p*-toluenesulfonyl chloride (**3**) was treated with hydrazine *in the cold*, the corresponding sulfonohydrazide (**4**) was obtained, but on warming the mixture gave the sulfinic acid (90%) (**5**) and the calculated quantity of nitrogen:[13]

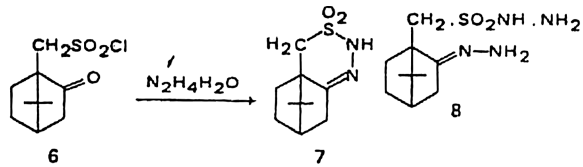



When a mixture of the sulfonyl chloride (**3**) and its 6-nitroisomeride was heated with hydrazine hydrate at 60°, a mixture of the sulfinic acid (**5**, 74%) and 2-chloro-6-nitro-*p*-toluenesulfonohydrazide (55%) was obtained.[12] This result seems surprising in view of the relative stability of the nitrobenzenesulfonohydrazides; it would be expected

that the products should be reversed–namely 2-chloro-6-nitrobenzenesulfinic acid (nitro group *ortho* to the sulfonyl group) and 2-chloro-5-nitrobenzenesulfonohydrazide (nitro group *meta* to the sulfonyl group).

The preparation of certain halogenobenzenesulfonohydrazides, like 2,4-dichlorobenzenesulfonohydrazide, requires the use of not more than two molar equivalents of hydrazine hydrate at 0° or below. With a large excess of hydrazine at room temperature the main products were 2,4-dichlorobenzenesulfonic acid and 2,2′,4,4′-tetrachlorodiphenyl sulfone.[14] The formation of 2,4,6-trichlorobenzenesulfonohydrazide requires even milder conditions, and here the bissulfonohydrazide was formed as a by-product.[14] Farrar[15] discovered that 2,4,5-trichlorobenzenesulfonyl chloride—though it gave the hydrazide in the usual way—reacted abnormally with other nitrogeneous bases: Ammonia gave mainly the ammonium salt of the disulfonimide, and phenylhydrazine acted simply as a reducing agent giving 2,4,5-trichlorobenzenesulfinate (90%) and evolution of nitrogen.

*p*-Azobenzenesulfonohydrazide is best obtained by reaction of the sulfonyl chloride with hydrazine in pyridine-dioxan.[16] Condensation of camphor-10-sulfonyl chloride (**6**) with hydrazine hydrate (1 molar equivalent) does not afford the sulfonohydrazide, but only the hexahydrobenzothiadiazine 3,3-dioxide (**7**). Use of a large excess of hydrazine did not give the dihydrazide (**8**) but an unidentified product (m.p. 137–138°):[17]




6 7 8

*N*-Substituted sulfonohydrazides can be synthezised[18,19] using *N*-substituted hydrazines, including *N*-acyl hydrazines:

$$R'CONH \cdot NH_2 + R^2SO_2Cl \xrightarrow[(1\ mole)]{C_5H_5N} R'CONH{-}NHSO_2R^2$$

$$R \cdot NH \cdot NH_2 + R'SO_2Cl \xrightarrow[in\ CHCl_3\ or\ EtOH]{Base\ (1\ mole)} R \cdot N(SO_2R') \cdot NH_2$$

$$R' \cdot SO_2NH \cdot NH_2 + R \cdot C_6H_4CH_2Cl \xrightarrow{Base} R'SO_2NH \cdot NH \cdot CH_2C_6H_4 \cdot R$$

**9**

$$+R'SO_2 \cdot N(CH_2C_6H_4R) \cdot NH_2$$

**10**

The mixture of the 1,2-(9) and 1,1-(**10**) sulfonohydrazides can be separated by making use of the solubility of **9** in aqueous alkali.[19] *N*-Arylsulfonyl-*N*′-phenylhydrazones **11** may be obtained as follows:[20]

$$C_6H_5SO_2Cl + Ar \cdot NH{-}N{=}CR_2 \xrightarrow[\text{Pyridine}]{\text{Tetrahydrofuran}} Ar \cdot N(SO_2C_6H_5) \cdot N{=}CR_2$$

**11**

*N*,*N*′-Diarylsulfonohydrazides of oxalic, malonic, succinic, and glutaric acids (**12**; $n = 0$, 1, 2, or 3 respectively) are obtainable[21] by condensation of the corresponding dicarboxylic acid dihydrazides with an

$$RSO_2NH \cdot NH \cdot CO[CH_2]_n \cdot CONH \cdot NHSO_2R$$

**12**

arylsulfonyl chloride in warm pyridine. The yields from malonohydrazide were very low, probably due to the strongly acidic hydrogen atoms of the methylene group leading to the main reaction, the formation of the chlorohydrazide as shown below:

$$Ar \cdot SO_2Cl + CH_2(CO \cdot NH \cdot NH_2)_2 \rightarrow ClCH(CO \cdot NH \cdot NH_2)_2 + Ar \cdot SO_2H$$

This method has been extended[22] to the synthesis of poly(sulfonohydrazides) by condensation of dicarboxylic acid dihydrazides with aromatic disulfonyl chlorides. Organic disulfonohydrazides also are synthesized by the reaction of the disulfonyl chlorides with hydrazine or phenylhydrazine.[23,24]

## Sulfonoazide Preparation

Organic sulfonoazides, **13**, can be conveniently prepared by reaction of the appropriate sulfonyl chloride with sodium azide (the Forster-Fierz method):[25]

$$RSO_2 \cdot Cl + NaN_3 \rightarrow RSO_2N_3 + NaCl$$

**13**

The sulfonyl chloride is generally dissolved in ethanol, dioxan,[17] or acetone,[4] then added to a concentrated aqueous solution of sodium azide. The reaction is slightly exothermic, and Dermer and Edmison[26] recommend cooling the mixture during the addition; the condensation is rapid and dilution with ice-water precipitates the sulfonoazide.

Cremlyn[27] prefers to use aqueous acetone to avoid the possibility of ethylsulfonate formation, and this now appears to be the favored solvent.

Kobayashi and Yamamoto[28] found that the reaction of a sulfinyl chloride, **14**, with sodium azide did not give the expected sulfinyl azide, but instead the sulfonyl azide, **13**:

$$\underset{\mathbf{14}}{\mathrm{ArSOCl}} + \mathrm{NaN_3} \rightarrow \underset{\mathbf{15}}{\mathrm{ArSO_2N_3}} + \mathrm{ArSO_2 \cdot SAr} + \mathrm{ArSSAr}.$$

The other main method of synthesis of organic sulfonoazides is by the action of nitrous acid on the sulfonohydrazide,[25] the nitrosation is carried out at 0° by sodium nitrite/concentrated hydrochloric acid:

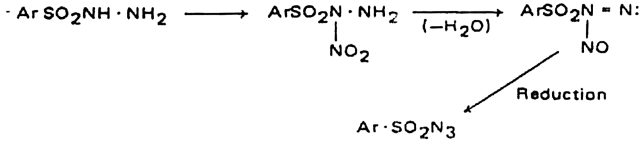
$$\mathrm{RSO_2NH \cdot NH_2} + \mathrm{HNO_2} \rightarrow \mathrm{RSO_2N_3} + 2\mathrm{H_2O}.$$

Both methods give good yields; the sodium azide route is generally preferred as it is shorter, although Cremlyn[29] claimed that nitrosation appeared to give a cleaner sample of $N^4$-acetylsulfanilyl azide.

Surprisingly, treatment of $N^4$-acetylsulfanilyl hydrazide (**15**) with nitric acid also gave the azide (**16**, 33% yield):

$$\underset{\mathbf{15}}{p\text{-}\mathrm{CH_3CONH \cdot C_6H_4 \cdot SO_2NH\ NH_2}} \xrightarrow[0^\circ]{\mathrm{HNO_3—H_2SO_4}} \underset{\mathbf{16}}{p\text{-}\mathrm{CH_3CO \cdot NHC_6H_4 \cdot SO_2N_3}}$$

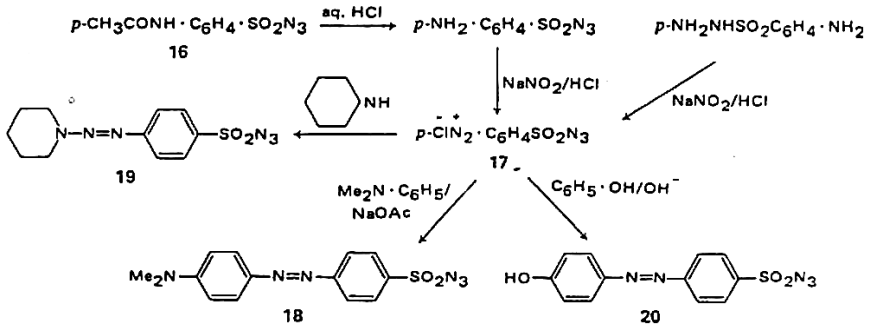
This reaction may possibly involve initial nitration:




However, Breslow[25] suggested that, since the final stage involves reduction and rearrangement to the linear azide group, a more reasonable mechanism may be initial reduction of the nitric acid to $N_2O_3$ (or a precursor) followed by normal nitrosation. The low yield

of azide, **16**, is presumably due to oxidative decomposition of the sulfonohydrazide.

Arenesulfonoazides containing various functional groups have been obtained indirectly[16,30,31] by coupling *p*-azidosulfonylphenyldiazonium chloride (**17**) with dimethylaniline,[31] piperidine,[30] or phenols[16] leading to azides (**18, 19**, **20** respectively):




Danhaeuser and Pelz[32] prepared *p*-azidosulfonylphenylisocyanate (**21**) via the Curtius rearrangement of the corresponding carbonyl azide (**22**):

$$p\text{-ClCO}\cdot C_6H_4SO_2Cl \xrightarrow{NaN} [p\text{-}N_3CO\cdot C_6H_4\cdot SO_2N_3] \xrightarrow[4\text{ hr}]{80^\circ} O{=}C{=}N\cdot C_6H_4SO_2N_3$$

**22** **21**

Various *N*,*N*′-dialkylsulfamoyl azides, **23**, are obtainable[33] by reaction of the appropriate sulfamoyl chloride **24** with sodium azide. Later[34,35] this was extended to a variety of sulfamoyl chlorides; and it was shown that the same azides were obtained from the amine and chlorosulfonyl azide:

$$RR'N\cdot SO_2Cl + NaN_3 \xrightarrow{CH_3CN} RR'N\cdot SO_2N_3 + NaCl$$

(**24**) **23**

$$2RR'NH + Cl\cdot SO_2N_3 \longrightarrow RR'N\cdot SO_2N_3 + RR'NH\cdot HCl$$

**23**

Griffiths[36] recently found that chlorosulfonyl azide can be prepared safely and efficiently by reaction of a sulfuryl chloride or fluoride

(X = Cl or F) with an equimolar quantity of sodium azide:

$$X \cdot SO_2Cl + NaN_3 \xrightarrow{CH_3CN} Cl \cdot SO_2N_3 + NaX$$

Chlorosulfonyl azide can be successfully used for the synthesis of a number of arylsulfamoyl azides by condensation with the appropriate aromatic amine:

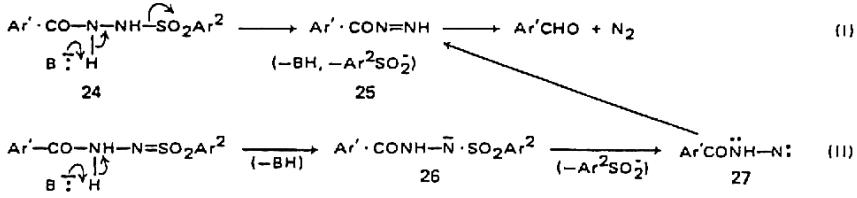
$$2Ar \cdot NH_2 + Cl \cdot SO_2N_3 \xrightarrow{CH_3CN} ArNH \cdot SO_2N_3 + Ar\overset{+}{N}H_3\overset{-}{Cl}$$
$$(\simeq 50\%)$$

## CHEMICAL REACTIVITY

### Sulfonohydrazides

#### *Elimination Reactions*

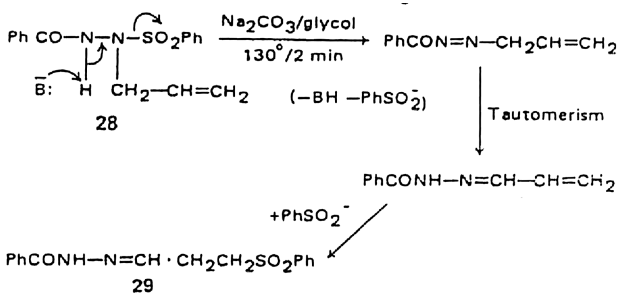
The chemistry of sulfonohydrazides is dominated by the facility with which the elements of sulfinic acid are eliminated, especially in basic media. This forms the basis of the role of sulfonohydrazides in the McFadyen-Stevens aldehyde synthesis.[18,37] This is the base-induced elimination of sulfinic acid from carboxylic acid-*N'*-sulfonohydrazides, **24**, to yield the aldehyde with evolution of nitrogen via the acyldiimide **25**; by a bimolecular mechanism (Route I) the reaction may lead directly to the diimide **25**:




Alternatively, deprotonation to the anion, **26**, has been proposed[38] as the first step, followed by loss of a sulfinic acid anion to give the fragment, **27**, which might subsequently rearrange to **25** (Route II).

The McFadyen-Stevens reaction generally goes well with the benzenesulfonyl hydrazide of an aromatic or heterocyclic acid and is very fast in a heterogeneous medium, e.g., glass powder. In such cases, the aldehydes are formed in approximately 80% yields by heating the hydrazide with sodium carbonate in aqueous or

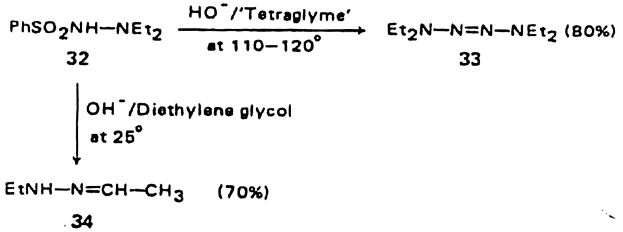
ethylene glycol solution.[18,39] An unusual example is *N*′-allyl-*N*′-benzenesulfonylbenzhydrazide (**28**) which undergoes the usual loss of the benzenesulfinic acid anion, followed by tautomerism and addition of the eliminated anion, to give **29**:[39]




Elimination also occurs with *N,N*′-disubstituted sulfonohydrazides provided there is a hydrogen atom attached to the nitrogen atom bearing the sulfonyl group. The products depend on the nature of the *N*′-substituents and their environment;[40,41] *N,N*′-dibenzylbenzenesulfonohydrazide (**30**) gives dibenzyl (**31**):

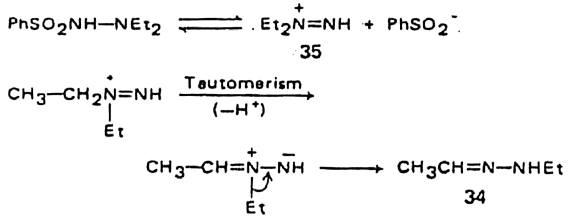
$$\underset{\mathbf{30}}{PhSO_2NH{-}N(CH_2ph)_2} \xrightarrow[(-PhSO_2^-)]{OH^-} \underset{}{\overset{-}{N}{=}\overset{+}{N}(CH_2Ph_2)} \xrightarrow[(-N_2)]{} \underset{\mathbf{31}}{PhCH_2CH_2Ph}$$

Other *N,N*′-disubstituted sulfonohydrazides may decompose to tetrazenes, a route favored by the use of aprotic solvents, or rearrange to hydrazones; for instance, *N,N*′-diethylbenzenesulfonohydrazide (**32**) gives the tetrazene (**33**) or the hydrazone (**34**):




The tetrazenes probably arise from attack by the intermediate azamine on the unreacted hydrazide; while the rearrangement to the hydrazone (**34**) is intramolecular and probably occurs via the

azaminium cation (**35**):[42,43]



Unsubstituted sulfonohydrazides apparently decompose similarly via the unstable diimide (**36**), detectable by its reducing action on olefins:[44]

$$\mathrm{Ts \cdot NH \cdot NH_2} \xrightarrow[\mathrm{OH^-}]{\mathrm{Hot}} \underset{\mathbf{36}}{[\mathrm{NH{=}NH}]} \xrightarrow[(-\mathrm{N_2})]{\mathrm{CH_2{=}CH \cdot CH_2OH}} \mathrm{CH_3CH_2CH_2OH} \quad (99\%)$$

(Where Ts = *p*-Me $\cdot \mathrm{C_6H_4SO_2}$)

*N′*-Monosubstituted sulfonohydrazides decompose with substitution of the hydrazide moiety by hydrogen, the reaction again probably proceeds via an unstable diimide intermediate:

$$\mathrm{Ts \cdot NH{-}NHC(Me)Et} \xrightarrow[\mathrm{Bu^tOH}]{\mathrm{OH^-/hot}} \mathrm{Ph{-}\underset{|}{\overset{\mathrm{Et}}{\overset{|}{C}}}H \cdot Me}$$

(80%) retention of configuration

The high degree of stereospecificity observed in *t*-butanol has been interpreted[45] as indicating an electrophilic displacement of nitrogen as a result of a frontal attack by $H^+$. The decomposition of sulfonohydrazides has also been observed[46] in acid solution, and the products are in agreement with the initial formation of an azaminium salt.

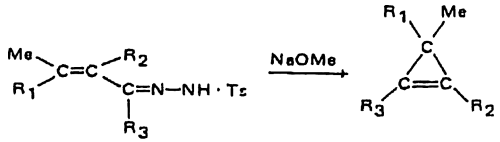
The decomposition of *p*-toluenesulfonohydrazones by alkali, known as the Bamford-Stevens reaction,[47] achieves the same result as the oxidation of unsubstituted hydrazides and provides a useful preparative route to diazoalkanes, e.g.:

$$\mathrm{PhCH{=}N{-}NH \cdot Ts} \xrightarrow[55\text{–}80^\circ]{\mathrm{NaOMe/C_5H_5N}} \mathrm{Ph \cdot CHN_2 + ArSO_2Na}$$

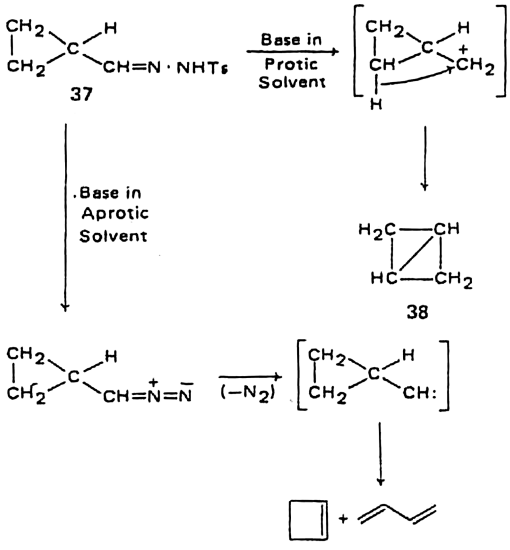
Generally, aromatic aldehyde or ketone sulfonohydrazones undergo such base-induced 1,1-elimination of sulfinic acid at sufficiently low

temperature to permit isolation of the diazoalkanes in moderate yields.[48]

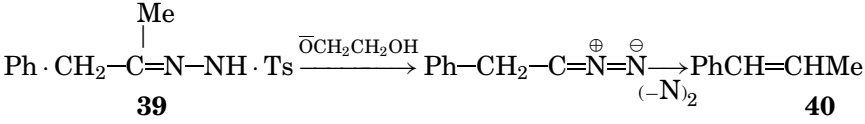
On the other hand, the derivatives of aliphatic aldehydes and ketones usually require high temperatures (130–150°) for their decomposition so that the diazoalkanes decompose, as fast as they are produced, yielding azines and other compounds derived from the corresponding carbenes; this can be applied in the synthesis of cyclopropenes:[49]




Carbene-derived products also may be obtainable[50] by photolysis of salts of *p*-toluenesulfonohydrazones. An alternative reaction path, competing more or less effectively with the Bamford-Stevens reaction, involves the carbonium ion which is thought to arise by proton transfer from a protonic solvent (whereas carbenes are presumably formed by direct thermal fragmentation of the diazoalkane with loss of nitrogen). The reaction involving the carbonium ion can be the major process with sodium methoxide in hydroxylic solvents (e.g., alcohols).[51] An illustration is afforded by the decomposition of cyclopropanecarboxaldehyde *p*-toluenesulfonohydrazone (**37**) to either cyclobutene and butadiene (aprotic solvent),[52] or to bicyclobutane (**38**) (protic solvent):[53]

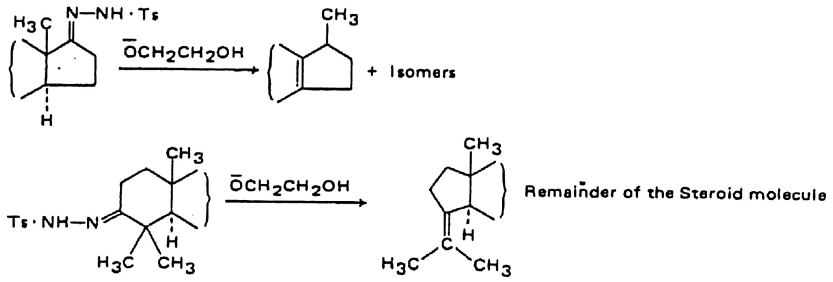


Sometimes, the diazo compounds decompose to give high yields of olefins,[51,54] for instance benzyl methyl ketone *p*-toluenesulfonohydrazone (**39**) on warming with sodium in ethylene glycol gives methyl phenyl ethylene[55] (**40**):

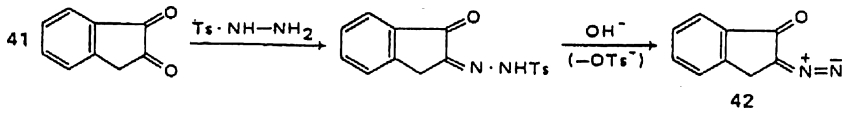



**39** **40**

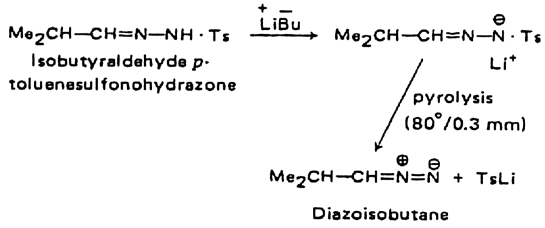
This has been applied to the formation of several steroid olefins, by heating the appropriate *p*-toluenesulfonohydrazone with sodium in ethylene glycol,[56] although it often results in rearrangement of the carbon skeleton:



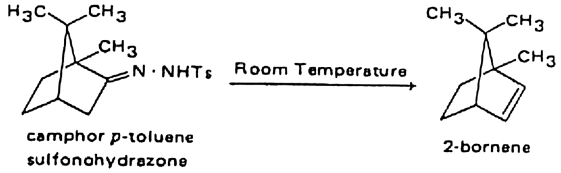

The Bamford-Stevens reaction also is useful[57,58] for the conversion of an $\alpha$-diketone into the corresponding $\alpha$-diazoketone; thus, 1,2-indanedione (**41**) gives a high yield of 2-diazo-1-indanone (**42**):



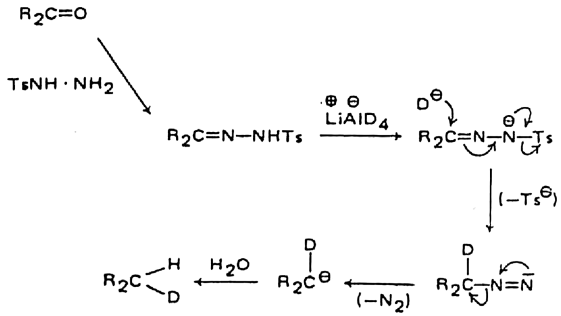

Lithium salts of *p*-toluenesulfonohydrazones decompose, by pyrolysis under reduced pressure,[59] to yield diazo compounds:



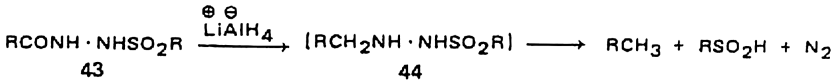
Aliphatic *p*-toluenesulfonohydrazones, containing an $\alpha$-hydrogen atom, react with alkyl lithium reagents to give olefins.[60,61] This provides a useful route to obtain several olefins which would be difficult to prepare by other means; for instance camphor *p*-toluenesulfonohydrazone gives a quantitative yield of 2-bornene:[61]




The reduction of *p*-toluenesulfonohydrazones with lithium aluminium hydride or sodium borohydride can be used for the conversion of a keto into a methylene group.[56,62] When the reduction was carried out with deuterated complex halides only one of the introduced hydrogen atoms was found[56] to come from the reducing agent; the other arises from the water added at the end of the reaction, which suggested the following mechanism:




A variant is the reductive cleavage of 2-acyl-1-sulfonohydrazides, **43**, with lithium aluminium hydride to yield a hydrocarbon via an intermediate sulfonoalkylhydrazino compound, **44**:




In this reaction good results are usually obtained[18,63] with aliphatic sulfonohydrazides, but only very poor yields with aromatic hydrazides.

Arylsulfonohydrazides also can be reduced[64] by Raney Nickel in boiling aqueous methanol to afford excellent yields of amines and arylsulfonamides by nitrogen-nitrogen bond scission:

$$p\text{-AcNHC}_6\text{H}_4 \cdot \text{SO}_2\text{NH—NH}_2 \xrightarrow{\text{Raney Ni}} p\text{-Ac} \cdot \text{NHC}_6\text{H}_4\text{SO}_2\text{NH}_2 + \text{NH}_3$$

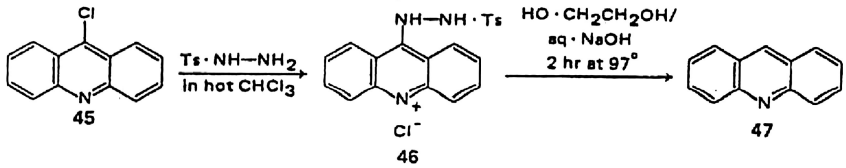
$$\text{PhSO}_2\text{NH—N=CHPh} \rightarrow \text{PhSO}_2\text{NH}_2 + \text{PhCH}_2\text{NH}_2$$

$$\text{PhSO}_2\text{NH—N=CMe}_2 \rightarrow \text{PhSO}_2\text{NH}_2 + \text{Me}_2\text{CH} \cdot \text{NH}_2$$

$$p\text{-NH}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{SO}_2\text{NH} \cdot \text{NHCO} \cdot \text{C}_9\text{H}_{19} \rightarrow p\text{-}NH_2C_6H_4SO_2NH_2 + \text{C}_9\text{H}_{19}\text{CONH}_2$$

## *Dechlorination*

*p*-Toluenesulfonohydrazine reacts with 5-chloroacridine (**45**) to give a salt, **46**, which on heating decomposes to acridine (**47**);




This is a useful method[65] for the dechlorination of 5-chloroacridines containing reducible groups, like nitro or cyano.

The reverse type of process occurs with bromine, which readily oxidized sulfonohydrazides to the corresponding sulfonyl bromides.[29,66]

$$\text{ArSO}_2\text{Cl} \xrightarrow{2\text{N}_2\text{H}_4} \text{ArSO}_2\text{NH} \cdot \text{NH}_2 \xrightarrow{\text{Br}_2} \text{Ar} \cdot \text{SO}_2\text{Br}$$

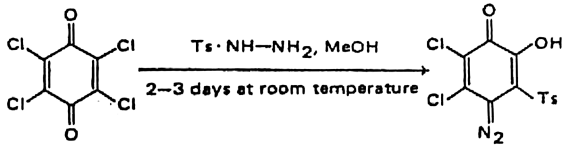
This provides a useful synthetic route for the conversion of a sulfonyl chloride into a sulfonyl bromide.[66] In the final step, the sulfonohydrazide may be treated with bromine in an inert solvent like chloroform or carbon tetrachloride at 10–15°, or with a mixture of bromate-bromide in 10% hydrochloric acid at room temperature:

$$3\text{Ar} \cdot \text{SO}_2\text{NH} \cdot \text{NH}_2 + 2\text{NaBrO}_3 + \text{NaBr} + 3\text{HCl} \xrightarrow{10\%\text{HCl}} 3\text{Ar} \cdot \text{SO}_2\text{Br} + 3\text{NaCl} + 6\text{H}_2\text{O} + 3\text{N}_2$$

## *Hydrazone Formation and Acylation*

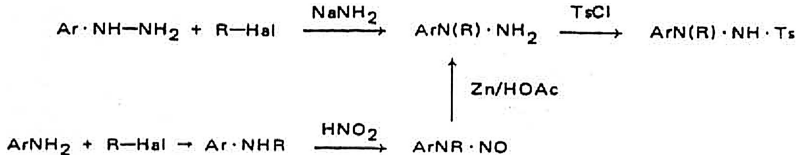
Aromatic sulfonohydrazides readily form hydrazones by heating with the appropriate aldehyde or ketone in alcoholic solution,[67–69] although the aromatic carbonyl derivatives are usually formed in higher yields. Condensation of *p*-toluenesulfonohydrazide with a 3-, 7-, 17-, or 20-keto steroid gave well-defined crystalline hydrazones, and their subsequent reduction (sodium borohydride) provides a useful method of converting a keto to a methylene group.[70] This has been extended[71] to the carbohydrate field where crystalline D-glucose *p*-toluenesulfonohydrazone has been reduced (potassium borohydride) to 1-deoxy-D-glucital. *p*-Toluenesulfonohydrazide[72,73] and other sulfonohydrazides[74] (e.g., *p*-nitrophenyl, *p*-azobenzene, and *p*-nitrobiphenyl) give crystalline hydrazones with sugars which can be used for their characterization.

Treatment of higher halogenated p-benzoquinones with *p*-toluenesulfonohydrazide gave[75] hydroxy-*p*-toluenesulfonyl-*p*-benzoquinone diazides. The reaction involves exchange of two halogen atoms *ortho* to each other; thus, chloranil (**48**) gives 2,3-dichloro-*p*-benzoquinone diazide (**49**):




**48** **49**

Some methods for preparation of *N*-alkyl or acyl-sulfonohydrazides have been discussed; other routes are illustrated[43] by the following sequences:




The last stage proved quite difficult and was best accomplished by boiling with *p*-toluenesulfonyl chloride in benzene. Attempts[76] to obtain *N*-arylsulfonohydrazides (**50**) by treatment of a phosphoro-diamidic hydrazide (**51**) with an arylsulfonyl chloride in pyridine failed to give pure

products, though these

$$\underset{\mathbf{50}}{RNH(R'NH)P(:O)\cdot NHNHSO_2Ar} \qquad \underset{\mathbf{51}}{RNH(R'NH)P(:O)NH\cdot NH_2}$$

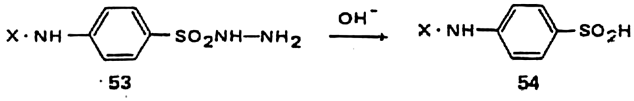
can be obtained by reaction of the arylsulfonohydrazide with the *N*,*N*′-disubstituted phosphorodiamidic chloride.

Reaction of arylsulfonohydrazides with various isothiocyanates yields 1,4-disubstituted thiosemicarbazides,[69,77] **52** (cf. ref 78):

$$p\text{-}X\,C_6H_4SO_2NHNH_2 \xrightarrow{RN{=}C{=}S} \underset{\mathbf{52}}{p\text{-}X\,C_6H_4SO_2NHNHCSNHR}$$

Various arylsulfonohydrazides will undergo[79] papain or ficin-catalyzed condensations with *N*-acylamino-acids to form the corresponding 1-acyl-2-arylsulfonohydrazides.

The *p*-aminobenzenesulfonohydrazides (**53**; X = $MeO_2C$ or AcNH), by heating with 5% aqueous sodium hydroxide, were hydrolyzed to the corresponding *p*-aminobenzenesulfinic acids (**54**).[80]

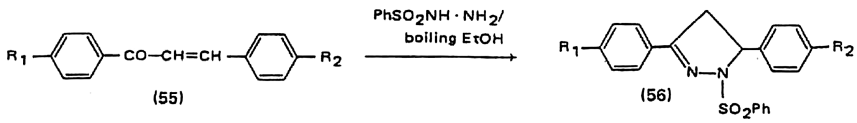



**53** **54**

In contrast, hydrolysis of various arylsulfonohydrazides, without the amine substituent on the benzene ring, normally gave the corresponding arylsulfonic acids.

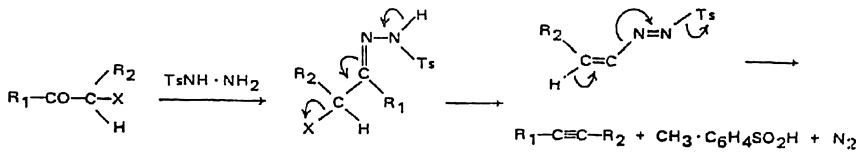
## *Miscellaneous Reactions*

Sammour and Elkasaby[81] report that the action of benzenesulfonohydrazide on benzalacetophenone does not give the corresponding hydrazone as previously claimed,[82] but this compound, and a number of other chalcones, **55**, gave the corresponding 1-benzenesulfonyl-3,5-diarylpyrazolines (**56**):

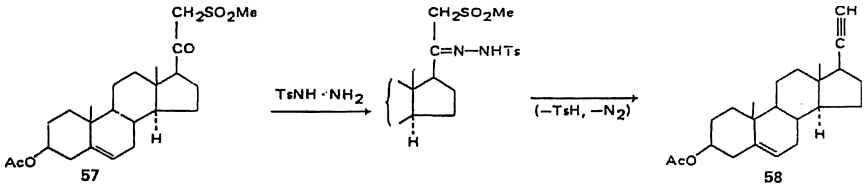



(55) (56)

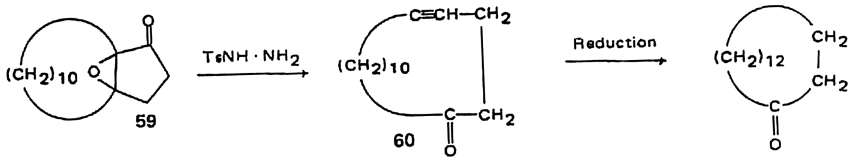
Wieland[83] has discovered a new synthesis of acetylenes by reacting $\alpha$-halogeno- or $\alpha$-sulfonyloxyketones with *p*-toluenesulfonohydrazide:



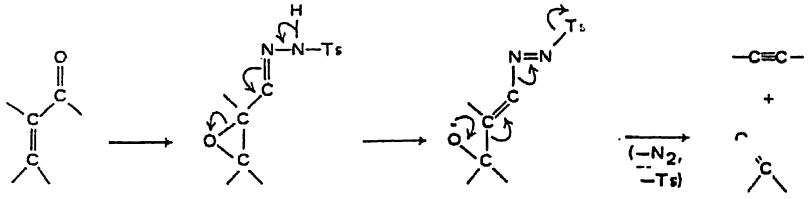
In this manner, 3-$\beta$-acetoxy-20-oxo-21-methylsulfonyl-oxy-5-pregnene (**57**) can be converted into 3-$\beta$-acetoxy-5-pregnene-20-yne (**58**):



An example of a new fragmentation reaction[84] is provided by the conversion of bicyclo [10,3,0]-1,12-epoxy-13-pentadecanone (**59**) into 4-cyclopentadecyne-1-one (**60**) by *p*-toluenesulfonohydrizide; the alkyne (**60**) can then be reduced to cyclopentadecanone, known commercially as Exaltone—an important perfume base:



The transformation goes in high yield under mild conditions and provides a useful route for the synthesis of large ring ketones from bicyclic $\alpha,\beta$-unsaturated ketones; the postulated mechanism[84] is as follows:



### *Thermolysis*

There have been a number of reviews[85–87] dealing with sulfonoazides, including a recent extensive article on sulfononitrenes.[25] The most important chemical reaction of sulfonoazides is *thermolysis* to sulfononitrenes, **61**, since the latter are useful reactive intermediates.

On heating sulfonoazides evolve nitrogen; the actual decomposition temperature depends on the structure of the compound, the aliphatic azides are generally more stable than the aromatic analogues.[88,89] In the thermolysis of 1-pentanesulfonoazide in a mineral oil, there appeared[88] to be two main reactions:

$$R \cdot SO_2N_3 \rightarrow R \cdot SO_2\ddot{N}: + N_2 (1st\ order\ reaction)$$

**61**

and the radical-chain decomposition:

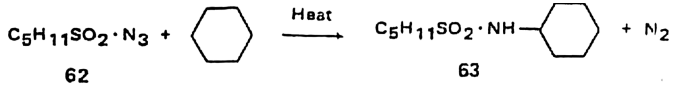
$$R' \cdot + RSO_2N_3 \rightarrow RSO_2^{\cdot} + R'N_3$$

$$RSO_2^{\cdot} \rightarrow R' + SO_2$$

$$R \cdot + R'H \rightarrow RH + R'.$$

An investigation of the evolution of sulfur dioxide showed that as the temperature was increased there was a small rise in the quantity of sulfur dioxide. Generally, aliphatic sulfonoazides decomposed in hydrocarbon solvents by these two mechanisms, and therefore the decomposition did not obey first order kinetics; though in the presence of radical inhibitors the free-radical chain reaction was suppressed and a first order graph was obtained. In contrast, kinetic studies of the thermolysis of *p*-toluenesulfonoazide shows that it is a first-order reaction in which loss of nitrogen and formation of the electron deficient nitrene is the rate-determining step. Other aromatic sulfonoazides behaved similarly, and so did aliphatic sulfonoazides *in diphenyl ether, but not in hydrocarbon solvents*. In the decomposition of aliphatic sulfonoazides in hydrocarbon solvents the source of the initiators of the free-radical chain reaction is obscure, possibly they arise from traces of hydro-peroxides in the solvent, since Leffler and Tsuno[90] have shown that *t*-butyl hydroperoxide accelerates the decomposition of benzenesulfonoazide, and conclude that formation of the nitrene was induced by free radicals. An aromatic sulfonoazide will undergo free-radical thermolysis in the presence of a source of free radicals *but not in its absence*. The absence of free-radical reactions in the thermolysis of aliphatic sulfonoazides in *an aromatic solvent* or of aromatic sulfonoazides may be due to the formation of the corresponding sulfonoanilide which would probably function as an effective radical trap.[25]

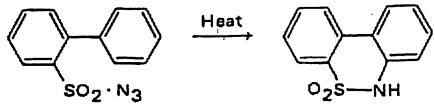
Both aliphatic and aromatic sulfonoazides will insert into the carbon-hydrogen bonds of saturated hydrocarbons, thus thermolysis of 1-pentanesulfonoazide (**62**) in cyclohexane gave a 54% yield of the sulfonamide (**63**):



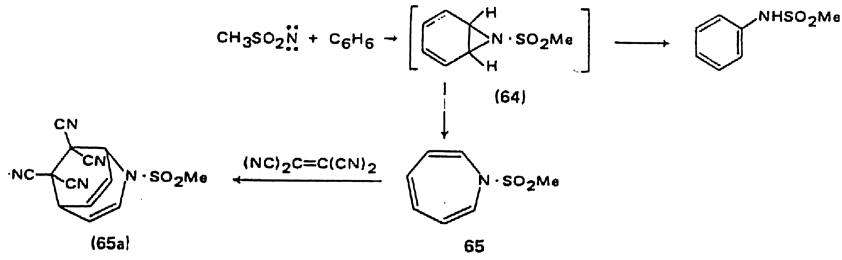

62 63

Attempts[25,91] have been made to determine the relative reactivity of primary, secondary and tertiary carbon-hydrogen bonds by reaction of *p*-toluenesulfonozide with 2-methylbutane.

In reactions of sulfonoazides with aromatic compounds, recent studies[92,93] indicate that only small amounts of *m*-isomers are formed, and with compounds containing *o*/*p*-directing substituents the *o*/*p*-isomers are the main products; in these reactions the sulfonyl-nitrene behaves as a highly reactive electrophilic reagent. In the thermal decomposition of a sulfonoazide, the spin conservation rule suggests that the nitrene should be initially formed as a singlet; the evidence[25,94] favors aromatic substitution being a singlet reaction. Several intramolecular cyclizations with aromatic sulfonoazides have been reported,[95] for instance:




Formylnitrenes react with aromatic compounds to give azepines, but sulfonylnitrenes give sulfonamides although both reactions are supposed to proceed via aziridine intermediates, **64**. However, Abramovitch and Uma[96] have demonstrated that azepine (**65**) was formed in the reaction of methanesulfonoazide with benzene:




(65a) 65

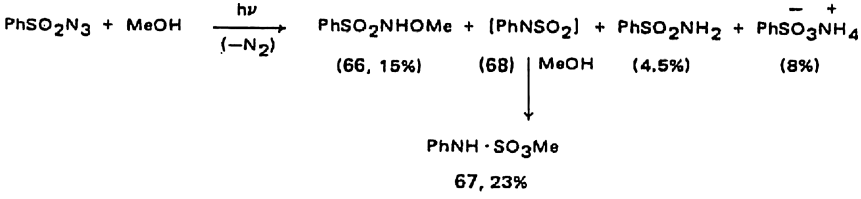
The transient existence of **65** was proved by performing the reaction in presence of tetracyanoethylene which trapped the azepine (**65**) as the Diels-Alder adduct (**65a**) which was isolated.

One puzzling feature in the decomposition of the majority of aromatic sulfonoazides with aromatic compounds is the formation of some unsubstituted sulfonamide:

$$\mathrm{Ar \cdot H + RSO_2N_3 \xrightarrow{Heat} Ar \cdot NHSO_2R + RSO_2NH_2}$$

In no case has the source of the hydrogen atoms been identified.[25]

The work of Smolinsky, Wasserman, and Yager[97] shows that the low temperature photolysis of sulfonoazides can give sulfonylnitrenes; however there is still some doubt regarding the actual existence of nitrenes in many photochemical reactions:[25] in the photolysis of benzenesulfonoazide in methanol the major products were the O—H insertion product (**66**) and methyl-*N*-phenylsulfamate (**67**) arising from reaction of the Curtius rearrangement product, **68**, with methanol.[98]

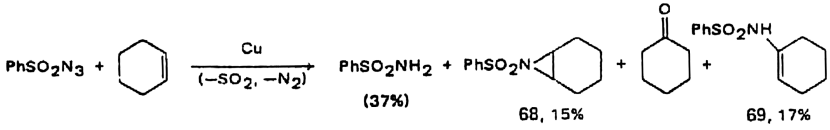



The O—H insertion product (**66**) may be derived from the nitrene, but it is also possible[98] that it might arise from a protonated species. In contrast, photolysis of sulfonoazides in isopropanol solution[99] gave the corresponding sulfonamide, acetone, and nitrogen:

$$\mathrm{CH_3SO_2N_3 + CH_3{-}\underset{\displaystyle OH}{\underset{|}{CH}}{-}CH_3 \xrightarrow{h\nu} CH_3SO_2NH_2 + (CH_3)_2CO + N_2}$$

This photolysis probably proceeds via a radical-chain mechanism[99] with two propagation sequences. The decomposition of sulfonoazides can also be catalyzed by metals. Copper catalyzes the thermolysis of benzene sulfonoazide in boiling methanol to benzene sulfonamide[100] (80%), and the copper-catalyzed decomposition of benzenesulfonoazide in cyclohexene also was studied.[101] The products included benzenesulfonomide, benzenesulfonylaziridine (**68**), the enamine (**69**), and

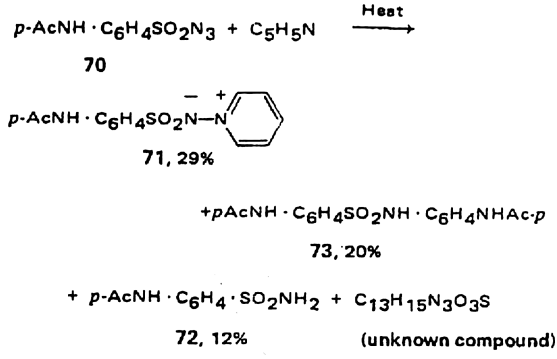
cyclohexanone:




The reactions may involve a copper-azide complex,[101] however it would be just as reasonable to propose a copper-catalyzed radical decomposition mechanism.[25]

## *Reactions of Sulfonylnitrenes with Functional Groups*

When *N*-acetylsulphanilyl azide (**70**) is heated with pyridine, the products were[102] *N*-(*p*-acetamidobenzenesulphimido) pyridine (**71**), *N*-acetylsulfanilamide (**72**), the bis-sulfonyl compound (**73**), and an unknown compound:




The Zwitterionic structure of the major product (**71**) has been proved by Datta,[103] and several similar 1-aminopyridinium derivatives have been obtained from reactions of other aromatic sulfonoazides with pyridine. Attempts to prepare the corresponding 1-aminoquinolinium derivatives filed, though Cremlyn[28] reported the isolation of *N*-(*p*-acetamidobenzenesulfonimido) dimethylaniline (**74**) from the reaction of the azide (**70**) with dimethylaniline:

$$p\text{-AcNHC}_6\text{H}_4 \cdot \text{SO}_2\text{N}_3 + \text{Ph} \cdot \text{NMe}_2 \rightarrow$$
(**70**)

$$p\text{-AcNH} \cdot \text{C}_6\text{H}_4\text{SO}_2\,\bar{\text{N}} \rightarrow \text{N}\overset{+}{\text{M}}\text{e}_2\text{Ph}$$
(**74**, 7%)

The thermal decomposition of sulfonoazides in dimethyl sulfoxide yields *N*-sulfonylsulfoximines (**75**):[104]

$$p\text{-MeO}\cdot C_6H_4\cdot SO_2N_3 \xrightarrow[(-N_2)]{\text{Heat}} p\text{-MeO}\cdot C_6H_4SO_2\ddot{\underset{\cdot\cdot}{N}} \xrightarrow{Me_2SO}$$

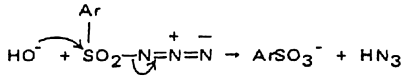
$$p\text{-MeO}\cdot C_6H_4SO_2N{=}S(O){=}Me_2$$

(**75**, 31%)

The product presumably arises through the trapping of the intermediate sulfonyl nitrene by the dimethyl sulfoxide.

## *Reactions of Sulfonoazides not Involving Intermediate Nitrenes*

Aromatic sulfonoazides show pseudo-halogen activity and the azido group can be displaced by direct attack of a nucleophile (e.g., sodium hydroxide, ammonia, or piperidine) on the electrophilic sulfur atom of the intact azide molecule with loss of hydrazoic acid:[29]

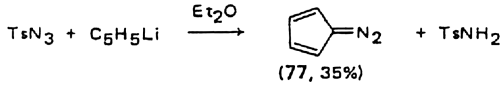


A useful synthesis of diazo compounds involves reaction of sulfonoazides with reactive hydrogen compounds; thus malonic ester gives an almost quantitive yield of diethyl diazomalonate (76):[25]

$$Ts-N_3 + CH_2(CO_2Et)_2 \xrightarrow{NEt_3/CH_3CN} (EtO_2C)_2C{=}\overset{+}{N}{=}\overset{-}{N} + TsNH_2$$

**76**

This diazo-transfer reaction can be applied to a variety of active hydrogen compounds.[105] Doering and De Puy[106] applied it to the synthesis of diazocyclopentadiene (77):




Ito[107] obtained phenyl azide by reaction of phenylmagnesium bromide with benzenesulfonyl azide:

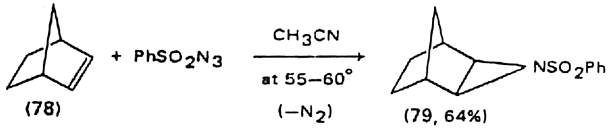
$$PhMgBr + PhSO_2N_3 \xrightarrow[-15^\circ]{Et_2O} PhN{=}N{-}SO_2Ph \xrightarrow[120\text{–}130^\circ]{\text{Heat}} PhN_3 + PhSO_2MgBr$$

$$\underset{\displaystyle MgBr}{|}$$

(82%)

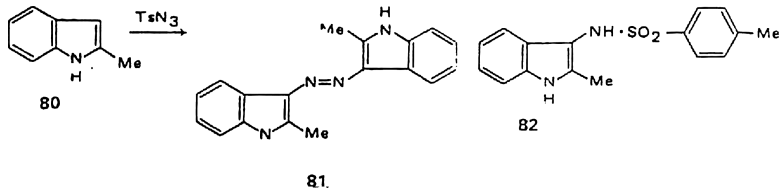
Grignard reagents react with *p*-toluenesulfonoazide to give salts of tosyltriazines;[108] these can be fragmented in aqueous sodium pyrophosphate to form alkyl or aryl azides, or reduced by Raney Nickel/aqueous alkali to amines.

Sulfonoazides react with unsaturated compounds; thus benzenesulfonoazide reacts with norbomene (**78**),[109,110] at such low temperatures that a nitrene cannot be involved, to give the *exo*-aziridine (**79**):



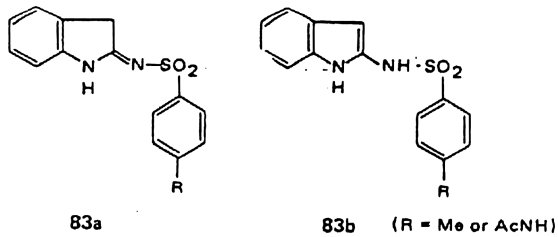

The reaction was postulated[109] to be analogous to epoxidation, though it is just as likely to occur via an intermediate triazoline which with other azides can sometimes be isolated.[25] The reaction of organic azides with olefins has been examined extensively,[25] with azides, such as cyanogen azide, *p*-toluenesulfonoazide, and picryl azide, the intermediate triazolines decompose into aziridines and imines.[111]

2-Methylindole (**80**) with *p*-toluenesulfonoazide gave a mixture of the 3,3'-azobis(2-methylindole) (**81**) and the sulfonoamidoindole (**82**):

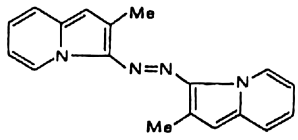



Other 2-substituted indoles behaved similarly with *p*-toluenesulfonoazide; with an excess of the azide and increasing temperature the sulfonoamide (**82**) became the major product.

Indole reacts smoothly with both *p*-toluenesulfonoazide and $N^4$-acetylsulfanilohydrazide at 50° to give a tautomeric mixture of 50% each of (**83a**) and (**83b**):[112]

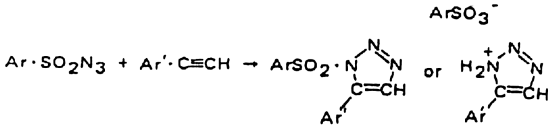


With alkylpyrrocolines, *p*-toluenesulfonoazide gave an excellent yield of the azo compound (**84**) within 2 minutes (cf., 24 hr required for a similar reaction with 2-methylindole):



**84**

Finzi[113] claimed that arylacetylenes and sulfonoazides yield either the sulfonamide, **85**, or the triazolinium salt, **86**, depending on the nature of the substituents:



**85** **86**

The reaction between ethoxyacetylene and *p*-toluene-sulfonoazide, after several days at room temperature, gave a high yield of the diazo iminoester (**87**):[114]

$$\mathrm{EtO{-}C{\equiv}CH + TsN_3 \rightarrow \underset{\displaystyle \underset{\displaystyle \mathrm{OEt}}{|}}{\mathrm{TsN{=}C{-}CHN_2}}}$$

**87**

These represent a new class of aliphatic diazo compounds which can be used in the synthesis of heterocycles.[115]

Sulfonoazides react with trialkyl phosphites:[116]

$$\mathrm{RSO_2N_3 + (R'O)_3P \rightarrow RSO_2N{=}P(OR')_3 + N_2}$$

Leffler and Tsuno[90] showed that this reaction could be applied to the analytical determination of sulfonoazides, though it does depend on the solvent. In benzene at fairly low temperatures, the intermediate triazene **88** can be isolated and on warming decomposes to the phosphinimine **89**:

$$\underset{\displaystyle \mathbf{88}}{\mathrm{PhSO_2N{=}N{-}N{=}PPh_3}} \xrightarrow{\text{Warm}} \underset{\displaystyle \mathbf{89}}{\mathrm{PhSO_2N{=}PPh_3}} + \mathrm{N_2}$$

$$\mathrm{PhSO_2N_3 + Ph_3P \rightarrow}$$

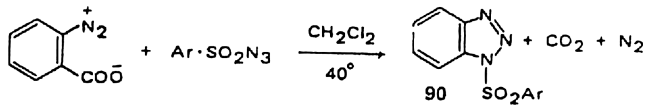
In chloroform and other solvents the reaction can be much more complex.

Fischer and Anselme[117] found that diazo compounds are formed by treatment of hydrazone anions with *p*-toluenesulfonazide:

$$R_2C{=}N{-}\bar{N}H + p\text{-}MeC_6H_4SO_2N_3 \xrightarrow[(-N_2)]{} R_2C{=}N_2 + p\text{-}MeC_6H_4SO_2\bar{N}H$$

(50%)

Arylsulfonoazides can be used as benzyne traps, since they react with benzyne to yield benzotriazoles, **90**:[118]



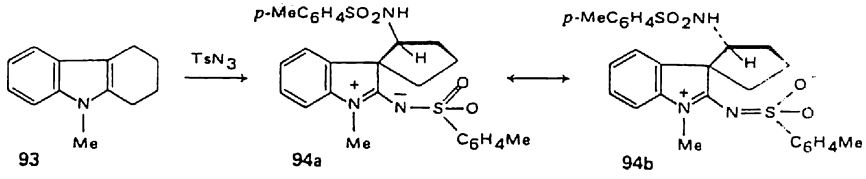

1,3-Dicarbonyl compounds containing reactive methylene groups, on treatment with 2 mmol of *p*-toluenesulfonoazide, gave intermediate diazo compounds, **91**, which by thermolysis were converted into diacyl acetylenes, **92**:

$$ArCOCH_2COCH_2Ar' \xrightarrow{2TsN_3} \underset{\underset{N_2}{\|}}{ArCOC}\cdot CO\cdot \underset{\underset{N_2}{|}}{CAr'} \xrightarrow{Heat} \underset{\mathbf{92}}{ArCO\cdot C{\equiv}CC\cdot OAr'}$$

**91**

The ring closure of the intermediate diazo compound (**91**) was largely prevented by carefully selected reaction conditions, and it was suggested[119] that thermolysis involves a cyclopropenone intermediate.

When *p*-toluenesulfonoazide reacts with *N*-methyl-tetrahydrocarbazole (**93**) several products are formed;[120] one compound is the indoline-3-spirocyclopentane whose electronic structure, as determined by x-ray crystallography,[121] has (**94a** and **94b**) as the major contributors:




Aromatic sulfonoazides can be quantitatively determined[122] within ±1% by boiling (0.15–0.35 g) with 2 *N*-sodium hydroxide (5 ml),

standing for 1 h, neutralizing with nitric acid, and titration with 0.1 *N* silver nitrate using potassium chromate as indicator: The end point is the development of a red-brown color.

## PHYSICAL PROPERTIES

The majority of organic sulfonohydrazides are crystalline solids which often melt with decomposition so that the observed melting points often vary considerably with the rate of heating.[67] Aliphatic sulfonoazides are usually oils, while the aromatic derivatives are low melting solids; disulfonoazides are generally solids.[25] Small amounts of the lower members can be distilled in vacuo provided adequate shielding is used. Sulfonohydrazides and sulfonoazides are quite polar and can be often crystallized from ethanol, aqueous acetone is also a useful crystallization solvent for the azides. Aromatic sulfonoazides are usually stable below the melting point, though inorganic derivatives, like chlorosulfonoazide, are dangerously explosive.[36]



The ultraviolet spectra of aromatic sulfonohydrazides and hydrazones show[123] two main absorption bands; for instance benzenesulfonohydrazide and the acetone hydrazone has major bands at 219, 263, and at 223, 263 nm respectively. The bathochromic shifts due to various substituents in the aromatic nucleus have been discussed.[123] Benzene sulfonoazide shows the main bands at 225, 269 nm.[123]

The infrared spectra of sulfonohydrazones showed[124] a single N—H stretching vibration in the range 3205–3310 $cm^{-1}$. The sulfonohydrazides, which contain an additional $NH_2$ group, consequently show more bands in the N—H stretching region; the asymmetric mode of the $NH_2$ group is readily identified as the highest frequency band observed in the spectra (above 3350 $cm^{-1}$).[124] The asymmetric and symmetric vibrations of the $-SO_2-$ group appear as strong bands close to 1325 and 1160 $cm^{-1}$ respectively; in the hydrazones these bands are at a slightly higher frequency than for the corresponding sulfonohydrazide. All the sulfonoazides have a strong, sharp band at 2130 $cm^{-1}$ associated with the $-N_3$ group, which appears to be fairly insensitive to the nature of the substituents in *p*-substituted arylsulfonoazides.[125]

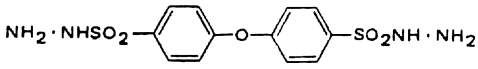
The dipole moments of arylsulfonohydrazides and their *N*-acyl derivatives capable of forming electrets can be calculated[126,127] by means of the molecular refractions derived from the measured dielectric constants.

In paper chromatography sulfonohydrazides can be located[67] as orange spots by spraying the paper with *p*-dimethylaminobenzaldehyde.

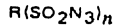
## USES

Dansyl (1-dimethylamino-5-sulfonyl) hydrazide has been reported[128] as a useful fluorimetric reagent for the qualitative and quantitative estimation of carbonyl compounds; for instance, it has been used[128] in the estimation of several conjugated steroid ketones.

Sulfonohydrazides with decomposition temperatures within the range 80–250° are claimed[129,130] to be effective "blowing" agents for the manufacture of cellular rubber and plastics. Two of the best compounds were the bis-sulfonohydrazide (95)[131] (cf. ref 23), and the thio analog.[132]




95




96

The corresponding bis-sulfonoazide and other sulfonoazides are also valuable cross-linking and "blowing" agents for plastics.[33,133] The ability of sulfonoazides to insert into carbon-hydrogen bonds enables them to be used for cross-linking hydrocarbon polymers.[25] The discovery that both polypropylene and polyisobutylene could be effectively cross-linked by treatment with bis-sulfonoazides led to the conclusion that C—H bond insertion involves the singlet nitrene, since these polymers are known[25] to be degraded by free-radicals rather than become cross-linked.

An elastic stereoregular polypropylene film can be obtained with a polysulfonoazide (**96**);[134] the polymer may also be treated with a mixture of a blowing agent (e.g., benzene-1,3-bis-sulfonohydrazide) and an azido cross-linking agent of general type **96** ($n = 2$–100) to give cellular polypropylene foam.[135]

Aromatic sulfonohydrazides have also been used[136] for the stabilization of soap during storage.

Some sulfonohydrazides are strongly fungicidal; examples include certain halogenobenzenesulfono-hydrazides,[137] and $N_4$-acetylsulphanilyl hydrazide and several of its derivatives.[23,29,67] The latter group of compounds show systemic fungicidal activity against several important pathogenic fungi, including wheat rust. A number of sulfonohydrazides are claimed to be therepeutically active.[138] several *p*-aminobenzenesulfonohydrazones[68] show antibacterial activity. Other sulfonohydrazides are reported[19] to inhibit the enzyme monoamine oxidase. Some arylsulfonoazides, particularly those

compounds containing halogeno or nitro groups, are nematicidal.[23] Some sulfonohydrazides and sulfonozide of different amino and dipeptides derivatives ware prepared.[139–158]

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