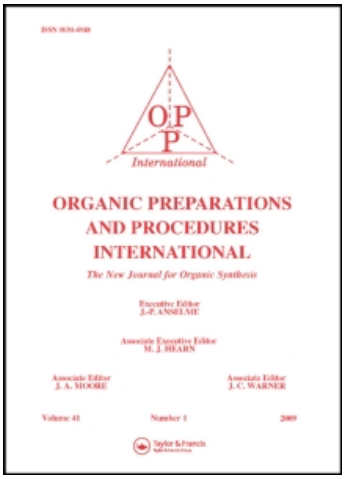

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SYNTHESIS AND REACTIONS OF SULFAMIDES. A REVIEW

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EXPERIMENTAL PROCEDURES

SYNTHESIS AND REACTIONS OF SULFAMIDES. A REVIEW

Séan D. McDermott and William J. Spillane*
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INTRODUCTION

The preparation, physical and chemical properties and chemical reactions of sulfamide were first reviewed by Audrieth, Sveda, Sisler and Butler.[1] In 1958, Dorlars[2] published what could be considered a collection of syntheses of various sulfamides. However little is mentioned in these reviews on the reactions of the sulfamides. Scott and Spillane in a series of reviews[3-5] on sulfamic acid and its derivatives include substantial sections on the chemistry of sulfamides. These reviews however are mostly mechanistically orientated and the synthetic uses of sulfamides are not emphasised. Appel and Kohnke[6] in 1978 presented a review on acyclic sulfur-nitrogen compounds of which a small portion deals with sulfamides (sulfuric acid diamides). A comprehensive review of sulfamide chemistry appeared[7] in 1977 and a few years later sulfamide was surveyed as part of a review on sulfamic acid chemistry.[8] In the latter review the section on sulfamide contains 121 references and is organised into three parts i.e. synthesis, physical properties and reactions. The arrangement of the present review follows broadly that of Benson and Spillane (excluding physical studies). However some of the more important syntheses will be given in detail and the mechanistic aspect (strongly emphasised in previous

reviews) will not be highlighted. This review contains 33 references which have been published since the last review. Many of these deal with important synthetic aspects of sulfamide chemistry.

I. SYNTHESIS

1. Preparation of Monosulfamides from Sulfamide

One of the earliest known reactions of sulfamide was its ability to produce substituted sulfamides with aliphatic amines. This reaction was reported by Paquin[9] and subsequently patented by Hamann.[10] A typical procedure is as follows. Preparation of N-Cyclohexylsulfamide.[9] - Cyclohexylamine (4.95 g, 0.05 mole) and sulfamide (4.8 g, 0.05 mole) were heated together for 1 hr at 90° and then for 4 hrs at 120°. Ammonia was evolved and the solution was then allowed to cool and a paste formed. Dilute hydrochloric acid (5 ml) was stirred in. The light brown solid which formed was filtered and washed with cold water to give crude cyclohexylsulfamide (7.16 g, 80%). This was recrystallised from H_2O to give plates, mp. 87-89°.

In the above procedure no diluting solvent is used; however the reaction may also be conducted in water under reflux for 5 hrs, and on cooling the product crystallises out. Using a 1:2 ratio of sulfamide:amine, the symmetrical disubstituted sulfamide is obtained.

The unsymmetrically disubstituted sulfamide N-butyl-N'-cyclohexylsulfamide was synthesised by Paquin by reacting N-butylsulfamide with cyclohexylamine in a 1:1 ratio at 145° for 5 hrs and the product was formed in 77% yield.[9] Although these "amide exchange" reactions were not pursued by

Paquin, several series of unsymmetrical disulfamides have recently been synthesised by modified versions of this method[11] (Eg. 1).

$$\underset{\underline{1}}{RNHSO_2NH_2} + \underset{\underline{2}}{R'NH_2} \longrightarrow \underset{\underline{3}}{RNHSO_2NHR'} \qquad (1)$$

R = cyc-C_6H_{11}, n-Bu, $PhCH_2$, n-C_6H_{13}

R' = cyc-C_6H_{11}, n-Bu, n-C_6H_{13}, n-C_8H_{17}, cyc-C_7H_{13}

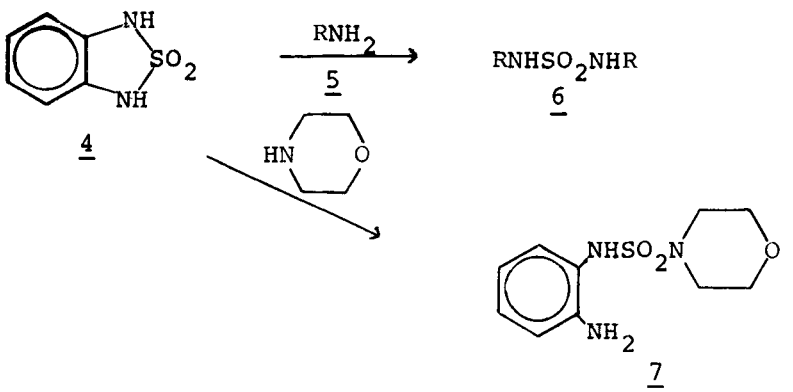
Preparation of N-n-Butyl-N'-n-hexylsulfamide (Method A).[11] - N-n-Butylsulfamide (0.2g, 1.3 mmole) and n-hexylamine (2ml, 17 mmoles) were heated together for 12 hrs at 80° and the solution allowed to cool. Dilute hydrochloric acid (5 ml) was then added and a white material (0.030 g) separated out. This was recrystallised from aqueous ethanol to give N-n-butyl-N'-hexylsulfamide, mp. 112-114° in 20% yield.

Preparation of N-n-Butyl-N'-cyclohexylsulfamide (Method B).[11]- N-n-Butylsulfamide (0.2 g, 1.315 mmole) and cyclohexylamine (0.130 g, 1.31 mmole) were heated in a tightly stoppered flask in an oil bath at 130° for 2 hrs. Dilute hydrochloric acid was added and the crude product collected. Recrystallisation from aqueous ethanol and drying in vacuo over P_2O_5 gave N-n-butyl-N'-cyclohexylsulfamide (0.23 g, 74%), mp. 96-99°, lit.[9] 99-101°.

Generally the yields obtained by method A were not as good as those from method B. Method B conditions consist of a) 1:1 molar ratio of sulfamide to amine and b) 130° for 2 hrs. Synthesised by this method was R'$NHSO_2$NHR'' where R' = cyc-C_6H_{11}, n-Bu, $PhCH_2$, n-C_6H_{13}, R'' = n-Bu, n-C_5H_{11}, n-C_6H_{13}, $PhCH_2$, cyc-C_6H_{11}, cyc-C_7H_{13}.

The cyclic sulfamide (1,3-dihydro-2,1,3 benzothiadiazole 2,2-dioxide) (4) which may be synthesised from sulfamide and o-phenylenediamine[12] (recently synthesised by an alternative

route[13]), was reacted[14] with a number of amines (Eq. 2) and with the primary amines (5) R = cyc-C_6H_{11}, R = n-Bu, R = $PhCH_2$. The fully exchanged product (6) is formed in high yield. However, in one instance, with the secondary amine morpholine, the half-exchanged product (7) was formed in 59% yield.[14]



(2)

The synthesis of aromatic sulfamides may be achieved from the aromatic amine and sulfamide;[15] however, the products invariably consist of both the monoarylsulfamide and diarylsulfamide and optimum yields of the monoarylsulfamides from the reaction are less than 40%. There has been one report of an exchange reaction between an aromatic sulfamide and an aromatic amine namely the reaction of o-nitrophenylsulfamide with aniline yielding phenylsulfamide and o-nitroaniline.[16]

2. Reaction of Amines with Sulfamyl Chlorides

The most widely used route to substituted sulfamides and the conventional method of synthesis involves the direct reaction of the sulfamyl chloride with the appropriate amine.[17] Mixed aliphatic-heterocyclic, aliphatic-aromatic and

$$RR'NSO_2Cl + R''R''' NH \longrightarrow RR'NSO_2NR'' R''' \qquad (3)$$

heterocyclic-aromatic sulfamides have been synthesised by

this method.

Preparation of Unsymmetrical Sulfamides. General Procedure.[17]- For the reaction of liquid amines, amine (2 moles) was treated with sulfamyl chloride (1 mole) without a solvent. The reaction is exothermic and after stirring for some time the mixture sets to a crystalline mass which after cooling is dissolved in ethanol. The substituted sulfamide is then precipitated by slowly pouring the alcoholic solution into crushed ice and water which is slightly acidified with hydrochloric acid. The filtered and dried crude product may be recrystallised generally from aqueous ethanol solutions. For solid amines the amine/chloride mixture is dissolved in an appropriate amount of an inert solvent e.g. chloroform or benzene and refluxed overnight. The solution is then cooled and the solvent removed under reduced pressure and the residue treated as with the liquid amine case.

Another route to substituted sulfamides was proposed by Atkins and Burgess[18] who utilised a species of type RN = SO_2 (a N-sulfonylamine) by the dehydrohalogenation of the appropriate sulfamyl chloride. Reaction of the sulfonylamine (generated in situ) with an amine yielded the substituted sulfamide (Eq. 4).

$$\underset{\underline{8}}{C_2H_5\overset{H}{N}SO_2Cl} \xrightarrow[-78^{o}]{Et_3N} \left[C_2H_5N{=}{=}SO_2\right] \xrightarrow{C_6H_5NH_2} \underset{\underline{9}}{C_2H_5NHSO_2NHC_6H_5} \quad (4)$$

Thus ethylsulfamyl chloride in toluene was added dropwise to triethylamine in toluene at -78° and the triethylamine hydrochloride removed at this temperature. The filtrate was added to aniline at -78° and after work up N-ethyl-N'-phenylsulfamide (54%) was produced. Catt and Matier[19] have used this method for the synthesis of N-t-butylsulfamides.

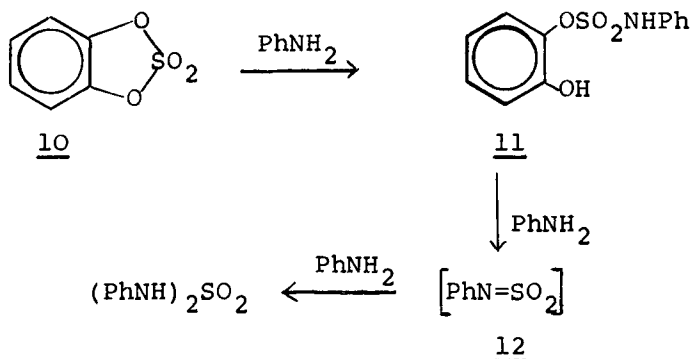
$$\underline{t}\text{-}C_4H_9NHSO_2Cl \xrightarrow{Et_3N} [\underline{t}\text{-}C_4H_9N{=}SO_2] \xrightarrow{RNH_2} \underline{t}\text{-}C_4H_9NHSO_2NHR \quad (5)$$

R = substituted C_6H_5

These sulfamides may be used as a route to primary sulfamides *via* a trifluoroacetic acid cleavage of the t-butyl group to leave the free $-NH_2$ group.

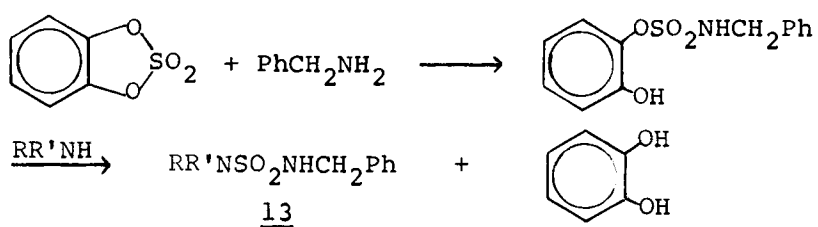
$$(CH_3)_3\overset{+}{C}\overset{H}{N}H\text{-}SO_2NHR \longrightarrow H_2NSO_2NHR + [(CH_3)_3C^+] \quad (6)$$

When Du Bois and Stephenson[20] investigated the reaction of catechol sulfate (10) with aromatic amines (Scheme 1), an interesting side-product N,N'-diphenylsulfamide resulted.



Scheme 1

Du Bois[21] further reacted intermediates of type 11 with amines in an effort to synthesise unsymmetrical sulfamides (Scheme 2).



Scheme 2

Thus when cathecol sulfate was reacted with benzylamine in DMF in the presence of triethylamine at 0^{o} the product 2-hydroxyphenyl-N-benzylsulfamate was produced in 98% yield. Isolation and subsequent reaction in refluxing dioxan with (a) benzylamine (b) cyclohexylamine (c) dimethylamine and (d) aniline resulted in the formation of the unsymmetrical sulfamide 13 in 91, 90, 96 and 60% yields respectively. Quast and Kees[22] reported a modified synthesis of sulfamyl chlorides using antimony pentachloride as a catalyst in the preparation of methylsulfamyl chloride, tert-butylsulfamyl chloride and 1-adamantyl sulfamyl chloride. Archibald et al.[23] have synthesised various sulfamides of 2-aminobenzoquinolizine from sulfamyl halides and have examined their pharmacological properties in detail.

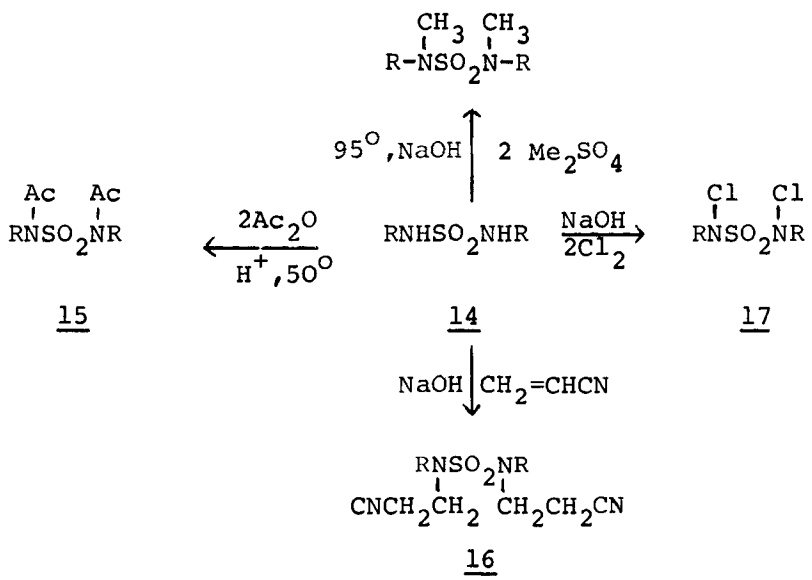
3. Reaction of Amines with Sulfuryl Chloride

The following is typical of the synthesis of a symmetrical N,N'-disubstituted sulfamide from sulfuryl chloride and the amine.[24]

Preparation of N,N'-Dicyclohexylsulfamide.[24] - Cyclohexylamine (99 g, 1M), pyridine (64 ml) and pet-ether (bp. 40-60^{o}) (300 ml) were maintained at -20^{o} with constant stirring. Sulfuryl chloride (32 ml, 0.4M) in pet-ether (bp. 40-60^{o}) (100 ml) was added dropwise with stirring. The temperature of the reaction was raised to room temperature and stirring was continued for a further hour. The solvent was stripped and the residue was dissolved in a solution made up of conc. hydrochloric acid (90 ml) and water (500 ml). The mixture was stirred for 30 mins and the crude product was obtained on filtration. This product was refluxed with ethanol (30 ml), conc. hydrochloric acid (150 ml) and water (150 ml) for 1.5 hrs (to hydrolyse any imidosulfamide formed). The hot solution

was filtered into cold water (600 ml) to yield N,N'-dicyclohexylsulfamide (55 g, 53%). Recrystallisation from 50% aqueous ethanol gave the pure product, mp. 153-154°.

Sowada employed this method for the synthesis of many N,N'-disubstituted sulfamides. These sulfamides were further substituted by the same author to produce various tetrasubstituted sulfamides (Scheme 3).



Scheme 3

Acid-catalysed acetylation,[25] and base-catalysed alkylation,[26] chlorination[27] and cyanoethylation[28] leads to the tetra substituted products in high yields.

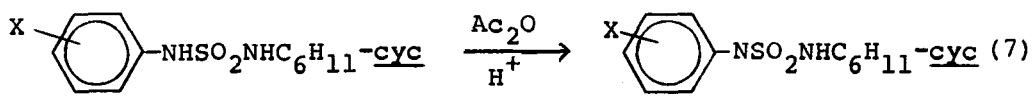
Parnell[29] synthesised the N,N'-diarylsulfamides quite conveniently in dry pyridine at 0°. The following presents a typical procedure.

Preparation of N,N'-di-p-Nitrophenylsulfamide.[29] - Sulfuryl chloride (40 ml, 0.51 mole) was added dropwise during 1 hr to a vigorously stirred solution of p-nitroaniline (100 g, 0.72 mole) in dry pyridine (300 ml) maintained between -5° and 0°.

After being kept at room temperature overnight, the solution was added gradually to a rapidly stirred solution of concentrated hydrochloric acid (300 ml) and water (1.5 L). The resulting gummy solid was collected and extracted with cold 1 M NaOH (500 ml). The alkaline extract was added to 1M acetic acid (300 ml) in water (700 ml) to yield the product and a granulated solid which was purified similarly to give N,N'-di-p-nitrophenylsulfamide (69 g, 56%), mp. 195-197°(dec.). Yields for other amines varied from 34-95%. The sulfamides were further substituted by reaction with methyl sulfate and dilute NaOH.

From the substitution reactions of the dialkylsulfamide (above) it is evident that the reaction depends on the lability of the amine hydrogen and thus an investigation of the acidity (pKa) of these sulfamides could have some synthetic importance. Such an investigation was recently undertaken[30] and the difference in acidity between dialkyl and diarylsulfamides indicates the possibility of selective substitution (on the nitrogen containing the aromatic moiety) in a sulfamide of type $RNHSO_2NHR'$ where R = aromatic and R' = aliphatic.

A recent study[31] has shown that selective acetylation occurs on the aromatic nitrogen in a series of N-cyclohexy-N'-aryl-sulfamides (18) (Eq. 7).



(7)

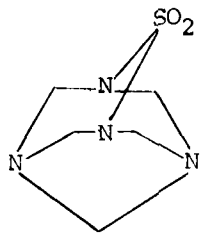
18

Unterhalt and Seebach[32] have reported pKa values for the ionization of a series of tri-alkylsulfamides, $RNHSO_2Me_2$. These authors[33] have also reported on the alkylation of trialkylsulfamides under conditions of phase transfer catalysis.

II. HETEROCYCLIC SYNTHESIS

1. Condensation of Sulfamides with Aldehydes

The use of sulfamide and N-substituted sulfamides to form heterocycles had been studied to a certain extent by Paquin[9]. Ethylenediamine, formaldehyde and sulfamide were condensed to produce a homopentamethylenetetramine (19). Gilbert et al.[34] formed the novel heterocycle 20 from paraformaldehyde and sulfamide.



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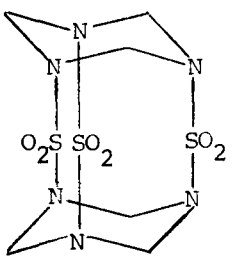
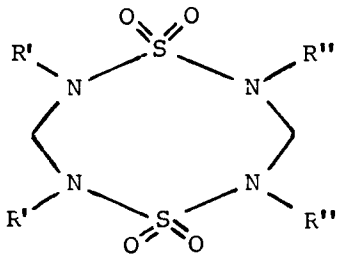


20

Preparation of Tetracyclic Sulfamide (20).[34] - Paraformaldehyde (3g) and sulfamide (3.75 g) were stirred with sulfuric acid (30 ml) for 1 hr at room temperature. During the reaction a white solid formed, was filtered off, dried and crystallised from dimethylacetamide and water. Product 20 was isolated in quantitative yield. This tetracyclo compound may also be prepared by acid-catalysed rearrangement of 19.

Dusemund[35] further extended the scope of this reaction by condensation of sulfamide (and N-substituted sulfamides) with formaldehyde, acetaldehyde, chromono-3-carbaldehyde, succinaldehyde and phthaldehyde. N-n-Butylsulfamide reacted with formaldehyde to yield 2,4-di-butyl-perhydro-1,5,2,4,6,8 dithiatetrazocin in 1,1,5,5-tetroxide (21).



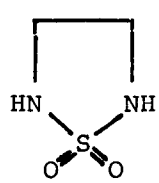
21

Preparation of 2,4-Dibutyl-perhydro-1,5,2,4,6,8 dithiatetrazocin 1,1,5,5 tetroxide (21).[35] - N-n-Butylsulfamide (0.01 mole), formaldehyde (3 ml, 30% solution) and concentrated hydrochloric acid (10 drops) were heated together with stirring for 1 hr at 40°. Water (100 ml) was then added and the product crystallised out as needles. These were collected and recrystallised from ethanol/water to give compound 21 (R'' = n-Bu, R' = H) mp. 177° in 40% yield.

Similarly prepared was 21 (R'' = $PhCH_2$, R' = H) mp. 198-200° in 20% yield. These were further substituted by methylation with methyl iodide to give 21, R' = CH_3, R'' = n-Bu, R'' = $PhCH_2$.

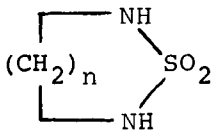
2. Condensation of Sulfamide with Diamino and Dibromo Compounds

Ciaperoni et al.[36] reported the reaction of sulfamide with ethylene-diamine to produce 1,2,5-thiadiazolidine 1,1-dioxide (22).

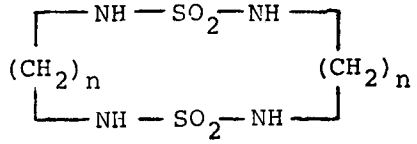


22

Larger rings were synthesised by reacting diamines of type $NH_2CH_2 — (CH_2)_n — CH_2NH_2$ with sulfamide.[37] For n = 2-6 the cyclic product (23) was formed however for n = 7,8,10 the macrocyclic (24) was formed.



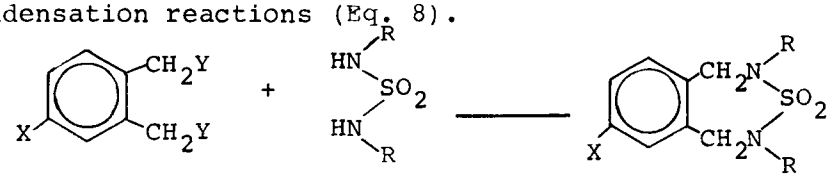
23



24

Preparation of 2,3,4,5,6,7-Hexahydro-1,2,7 thiadiazepine-1,1-dioxide.[36] - A solution of 1,4-diaminobutane (8.8 g, 0.1 mole) in anhydrous pyridine (50 ml) was added dropwise to a solution of sulfamide (9.6 g, 0.1 mole) in anhydrous pyridine (100 ml) at room temperature. The reaction mixture was boiled under reflux for 30 hrs. The crystalline precipitate formed was filtered, washed with ether and recrystallised from dimethyl-sulfoxide-isopropanol - ether to give 23 (n = 2) 14 g, 93% mp. 261°. The same procedure was followed for n>6 but on work up the macrocyclic products 24 were obtained in 60-90% yield.

Knollmuller[38] has also synthesised heterocycles by condensation reactions (Eq. 8).



(8)

25

26

Y = Br, NH_2

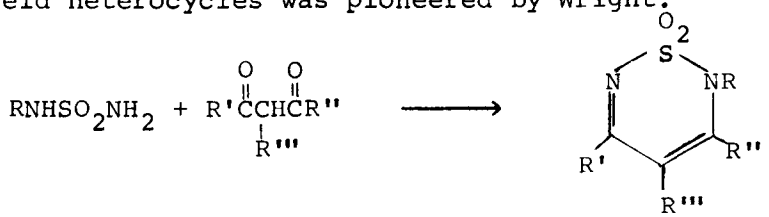
X = H, Cl

R = H, $PhCH_2$, $CH_2C_6H_4NO_2$-p

cyc-C_6H_{11}, C_6H_5

3. Reaction of Sulfamides with the Carbonyl Group

The reaction of sulfamides with α- and β-diketones (Eq.9) to yield heterocycles was pioneered by Wright.[39]

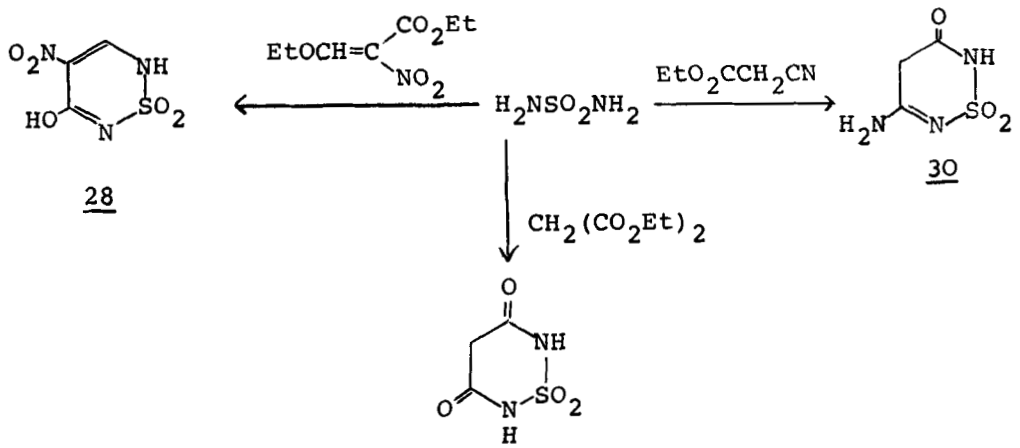


(9)

27

Preparation of 3,5-Diphenyl (2H)-1,2,6-thiadiazine-1,1-Dioxide.[39] - Into a stirred mixture of 1,3 diphenyl-propane dione 1,3 (R'=R" =Ph, R'"= H) (4.66 g, 0.03 mole) and n-butylsulfamide in dry ethanol (30 ml) was passed dry hydrogen chloride gas until the temperature reached 50°. The solution was then heated under reflux for 5 hrs and concentrated in vacuo, the residue taken up in ether and water. The ether layer was separated, dried over anhydrous magnesium sulfate and the ether removed. The residue was recrystallised from ethanol to give 27, R = n-Bu, R'=R" =Ph, R'"= H in 39% yield mp. 99-100°.

A considerable amount of work has been done by Stud and his coworkers[40] on these and related reactions of sulfamides



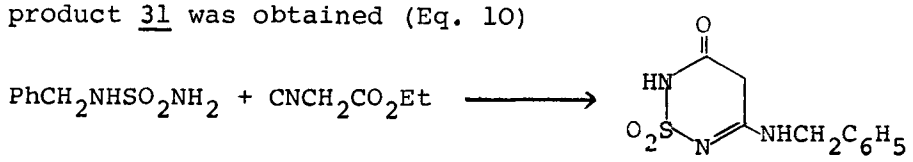
28 30 29

Scheme 4

and some of these are represented in Scheme 4.

Some of these compounds may be viewed as analogs of pyrimidine and purine. A recent study investigated the methylation and glycosidation products of these compounds.[41] A separate group[42] has also studied the synthesis and X-ray structure of new nucleosides of the 1,2,6-thiadiazin-1,1-dioxides.

When N-benzysulfamide was reacted with ethylcyanoacetate,[43] product 31 was obtained (Eq. 10)

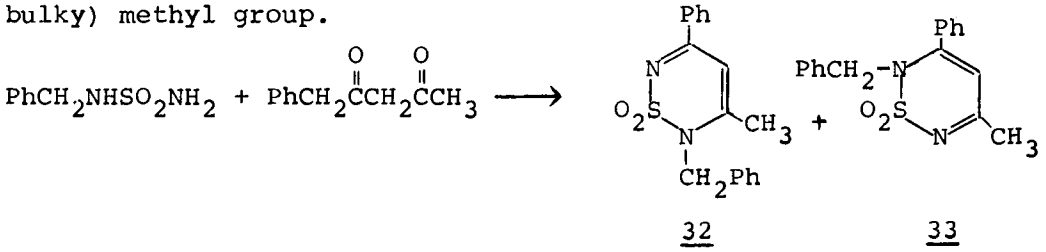


(10)

31

contained the benzyl group resting on the exocyclic amino group and the occurrence of this may be due to a Dimroth rearrangement.

When substituted sulfamides are reacted with unsymmetrical 1,3-dicarboxyl compounds (or their acetal derivatives) two isomers of the resulting thiadiazine 1,1-dioxide can exist.[44] (Eqn. 11). Thus, for example, in the reaction of benzylsulfamide and benzoylacetone two isomers were formed (32) and (33) in the ratio of 9:1 respectively. The steric factor is evident here where it is seen that the nitrogen containing the benzyl group attacks the carbonyl containing the (less bulky) methyl group.



32 33

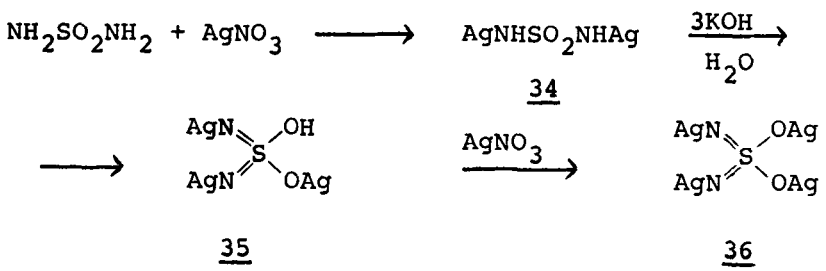
(11)

III. REACTION WITH INORGANIC REAGENTS

1. Reaction of Sulfamide with Silver Nitrate, Thionyl Chloride and Chloramine

The amino hydrogens in sulfamide may be replaced stepwise by silver atoms as described by Traube[45] and extended

by Popitsch and Nachbaur[46] and the overall sequence may be represented as follows (Scheme 5).



Scheme 5

Popitsch has solved the structures of trisilver(1)-sulfamide-ammonia-water[47] (35) and tetrasilver(1) sulfamide[48] (36) and has recently[49] correlated the colour of these compounds with their crystal structures. Disilversulfamide crystals are colourless, trisilversulfamide crystals are deep red. The colour cannot be explained on the basis of the covalent nature of the Ag-N bond length above as they are similar in all three and the authors conclude that the colour phenomenon is attributable to the number of Ag(I) atoms bonded to the donor atoms (N, O). Diffuse reflectance[50] and infrared[51] spectra of these silver (1) sulfamides have recently been measured as have the infrared and Raman spectra of sulfamide single crystals.[52]

Treatment of N,N'-disubstituted sulfamides bearing active hydrogens at α-carbons with thionyl chloride and triethylamine gave sulfenamines which were postulated to arise from N-sulfinylamine and N-sulfonylamine intermediates.[53]

$$(R'R''CHNH)_2SO_2 \xrightarrow{SOCl_2\text{-}NEt_3} (R'R''C{=}N)_2S_{1\text{-}4} \qquad (12)$$

$R' = Ph, Me; R'' = CO_2Me, CO_2Et$

The pentaamine cobalt(III) complex of sulfamide has recently[54] been synthesised and the kinetics of its hydrolysis measured. Two sites of co-ordination are present, N and O, however the properties of the complex are most consistent with N-coordination.

When sulfamide is reacted with ammonia-free chloramine, ammonium chloride and hydrazodisulfamide result.[55] The reaction of chloramine with sulfur dioxide is a complex

$$2\ NH_2SO_2NH_2 + NH_2Cl \longrightarrow H_2NSO_2NHNHSO_2NH_2 + NH_4Cl \qquad (13)$$

process but the products also include hydrazodisulphamide

$$NH_2Cl + SO_2 \longrightarrow H_2NSO_2NHNHSO_2NH_2 \qquad (14)$$

2. Reaction of Sulfamides with Inorganic Halides

The condensation of chloral with N,N'-dimethylsulfamide in the presence of PCl_5 afforded a high yield of N-1,2,2,2 tetrachloroethyl-N', N'-dimethylsulfamide containing an extremely reactive chlorine atom, which very readily exchanges with isocyanate, azide, isothiocyanate and diethoxyphosphinyl groups[56] (Scheme 6).

$$Me_2NSO_2NH_2 + Cl_3CCH(OH)_2 \longrightarrow Cl_3CCH(OH)NHSO_2NMe_2 \xrightarrow{PCl_5}$$

37

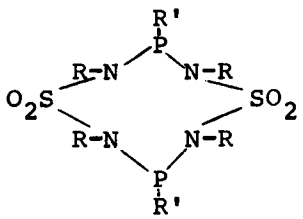
$$Cl_3CCHClNHSO_2NMe_2 \xrightarrow{\text{Reagent}} Cl_3CCNHSO_2NMe_2$$

38 (X) **39**

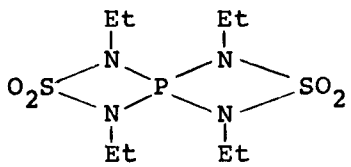
Reagent	
AgNCO	X = -N=C=O
NaN_3	= $-N_3$
KSCN	= -N=C=S
$(C_2H_5O)_2PR$	= $-P(=O)(OC_2H_5)R$

Scheme 6

With $R'PCl_2$, (R' = Et,Ph) sulfamides $(RNH)_2SO_2$ (R = Me, Et) lead to the formation of 8-membered rings (40).[57] Treatment of 40 (R = Et, R' = Ph) with PCl_5 gave a 93% yield of 41.



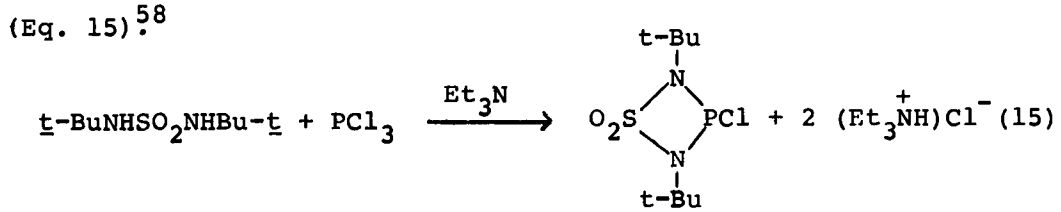
40



41

The reaction of N,N'-dimethyl or N,N'-diethylsulfamide with PCl_3 in the presence of tertiary amines lead to apparently polymeric materials of composition $\left[O_2S(NMe)_2PCl\right]_n$ and ring-opened respectively.

Treatment of $(t\text{-BuNH})_2SO_2$ with PCl_3 in the presence of triethylamine yielded the phosphetidine 1,1 dioxide (42) (Eq. 15).[58]



$$t\text{-BuNHSO}_2\text{NHBu-}t + PCl_3 \xrightarrow{Et_3N} O_2S(t\text{-BuN})_2PCl + 2\,(Et_3\overset{+}{N}H)Cl^- \quad (15)$$

42

The significance of 42 is that it represents the first example of a four membered nitrogen-sulfur-phosphorous (III) ring. The heterocycle 42 may be further derivatized by reaction with SbF_3 or Me_3SiNMe_2. The successful synthesis of 42 can be attributed to the steric demands of the t-butyl groups since the attempted synthesis of the methyl or ethyl

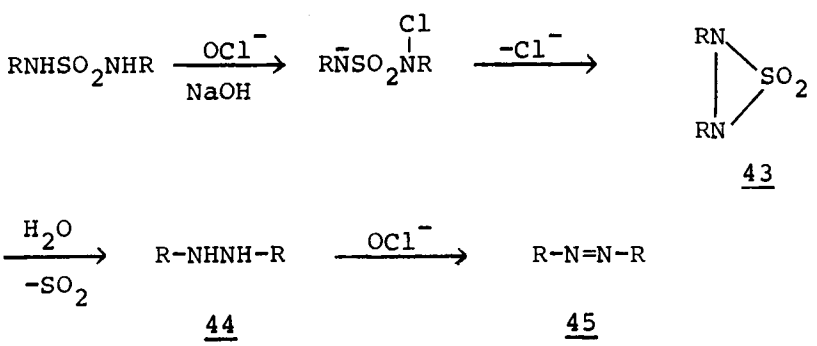
analogs of 42 resulted in polymeric or open-chain compounds.[57] New five- and six-membered saturated heterocycles containing $N-SO_2-N$ bonds were prepared by reaction of $(RNH)_2SO_2$, (R = Me, Et) with ClCOCOCl, ClCSCl and $(ClSiMe_2)_2O$ in the presence of Et_3N.[59]

The structural rigidity which was invoked to explain the tendency of $(t\text{-Bu-NH})_2SO_2$ to form heterocycles has recently been confirmed when a X-ray crystal structure of $(t\text{-BuNH})_2SO_2$ was reported.[60] The authors show that the compound is held in a C_2 conformation and propose that as the steric bulk of the alkyl moiety diminishes the energy difference between the two possible conformations (C_2 and C_S) will decrease giving rise to a less rigid sulfamide. These less rigid sulfamides when treated with active halides tend to form polymers rather than discrete heterocycles.

IV. OTHER REACTIONS

1. Oxidation with Hypochlorite to Yield Azoalkanes

Ohme and Schmitz[61] have reported that the reaction of N,N'-dialkylsulfamides with hypochlorite and base leads to the formation of azoalkanes in accordance with Scheme 7.



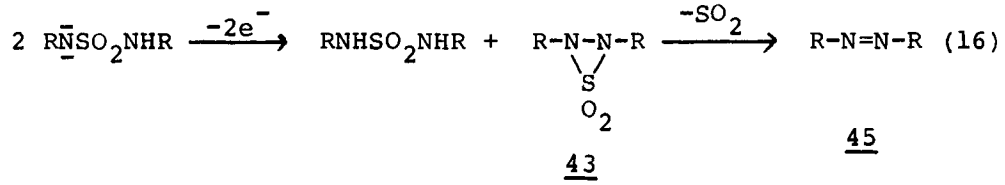
Scheme 7

The intramolecular nature of the reaction was shown by the fact that when N,N'-dipropylsulfamide and N,N'-dibutylsulfamide were submitted to the reaction no mixed azoalkane (45), n-Pr-N=N-Bu-n was obtained. The isolation of di-n-propylhydrazine in 50% yield when insufficient hypochlorite was used supports the involvement of the N,N'-dialkylhydrazines (44) as intermediates. The intermediacy of the thiadiaziridine 1,1-dioxide (43) was demonstrated by Timberlake[62] who isolated 2,3-di-t-butylthiadiaziridine-1,1-dioxide (43, R = t-Bu) when $(t\text{-BuNH})_2SO_2$ was subjected to the reaction. The synthesis and reactions of a series of thiadiaziridine 1,1-dioxides (43) have recently been reported by Timberlake[63] where the compounds are treated with various reagents leading to ring-opened products, including the sulfamide. The original mechanism has recently revised by the same authors.[64]

2. Anodic Oxidation of the Monoanion to Yield Azoalkanes

Bauer and Wendt[65] have shown that anodic oxidation of the anions of N,N'-dialkylsulfamides leads to N-N coupling with the formation of azoalkanes in high yields.

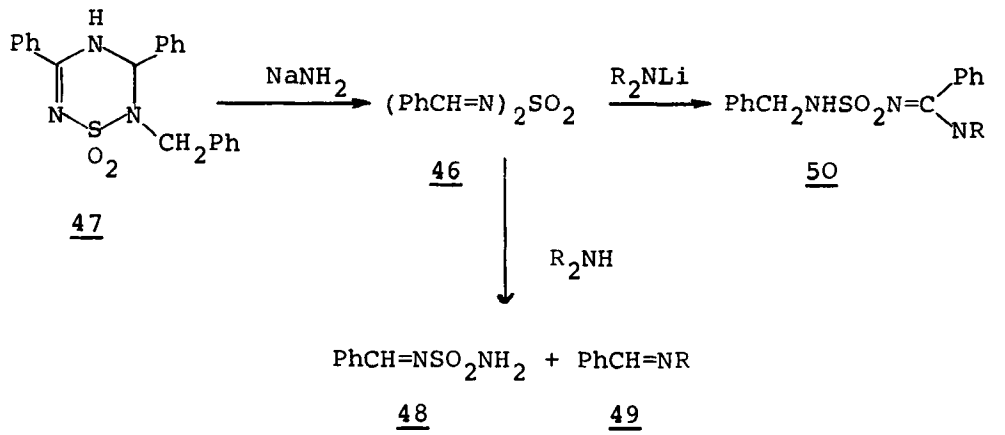
Preparation of Azocyclohexane.[65] - Procedure: N,N'-Dicyclohexylsulfamide (5.2 g, 0.02 mole) is dissolved in dry methanol (100 ml) and converted into the lithium salt by addition of an equimolar amount of lithium methoxide. The solution is oxidised at controlled potential at a carbon electrode in a divided cell at 0° under an N_2 atmosphere. After consumption of 0.04F the solvent is removed and the residue extracted with n-pentane (2 x 50 ml). Subsequent drying of the combined extract over anhydrous Na_2SO_4 and removal of the solvent by evaporation afforded azocyclohexane (2.73 g, 90% mass yield and 74% current yield) mp. 34°.



Similarly prepared were azoalkanes 45 where R = n-butyl (88%), R = t-butyl (81%) and R = adamantyl (78%).

3. Reaction with Various Amines

When dibenzylidenesulfamide (46)[66] was treated with sodamide, the thiatriazine dioxide 47 resulted. Reaction of (46) with various amines yielded monobenzylidinesulfamide (48) and the corresponding Schiff base (49) while reaction with lithium amides yielded the N'-substituted-N^2-benzylsulfamyl benzamidines (50) (Scheme 8).

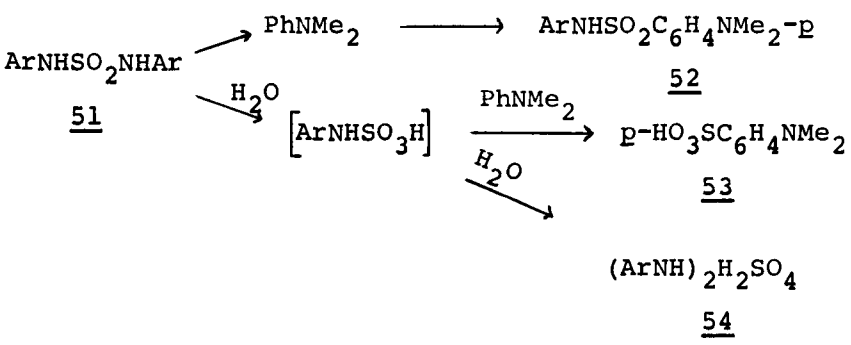


Scheme 8

Timberlake[67] has reported that the reaction of propynylsulfamides with sodium hydride and acetic anhydride yields cyclization and rearrangement products depending on reaction conditions. A number of ethylenediamine (sulphamide) nickel (II) and copper (II) complexes have been prepared

recently from reactions of ethylenediamine and sulphamide.[68]

The reaction of sulfamide with aromatic amines yields not only diarylsulfamides but also gives rise to rearranged sulfanilanilides.[69] Together with this amine exchange process, it was shown that in the presence of traces of water an intermolecular transfer of a sulfonic acid group can occur from the intermediate sulfonic acid.[70] These processes may be seen as competitive nucleophilic reactions for the sulfur (VI) centre of the sulfamides. This competition was studied[71] (Scheme 9) for diarylsulfamides using dimethylaniline as the aromatic amine in the absence and presence of water.



Scheme 9

Preparation of p-Dimethylaminobenzenesulfonanilide (Anhydrous Conditions).[71] - Diphenylsulfamide (51, Ar = Ph) (2 g, 0.008 mole) and dimethylaniline (10 ml, 0.078 mol) were heated together for 2 hrs at 196°. When the mixture was left at room temperature overnight, compound 52 (Ar = Ph) (1.62 g, 73%), mp. 175-176° (from ethanol) separated out. The dimethylaniline mother liquor was treated with ether (ca. 100 ml) and extracted with 0.5 M NaOH (2 x 30 ml). Acidification of the combined extracts afforded the starting material (51, Ar = Ph) 23% yield.

Preparation of p-dimethylaminobenzene sulfonic acid (In the presence of water).[71] - Diphenylsulfamide 51 (Ar = Ph) (2 g, 0.008 mol), water (0.144 g, 1.008 mol) and dimethylaniline (10 ml, 0.078 mole) were heated together at 196° for 2 hrs. The mixture was cooled to 0° and maintained at this temperature overnight, whereupon p-dimethylaminobenzenesulfonic acid(53),(1.56 g, 97%) separated out. It is evident that where water is present (even though the amine is in large excess) it will compete better for the sulfur(VI) centre to give rise to sulfonated products. When p-nitrophenylsulfamide is used in the second procedure above both the anilide (11%) and the sulfonic acid (87%) are formed due to the more electrophilic (and consequently less selective) nature of this sulfamide. The use of anhydrous conditions makes this reaction a valuable route to sulfonanilides.

The products of the reaction of monosulfamides with aromatic amines have recently been studied.[72] Trans-sulfonation, trans-sulfamylation and hydrolysis products were isolated. Under certain conditions mixed aromatic/aliphatic unsymmetrical sulfamides may be obtained in reasonable yield.

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