Russian Chemical Reviews **69** (3) 221 – 230 (2000) © 2000 Russian Academy of Sciences and Turpion Ltd

DOI 10.1070/RC2000v069n03ABEH000562

Sulfamides in the synthesis of heterocyclic compounds

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Abstract. A comparative analysis of the structures and physicochemical properties of sulfamides and ureas has been performed. New procedures for the synthesis of heterocyclic compounds containing the sulfamide fragment are surveyed and the properties of the resulting compounds are described. The bibliography includes 112 references.

I. Introduction

The chemistry of sulfamides has received sufficient attention in the literature. The synthesis, physicochemical properties and reactions of these compounds have been considered many times in reviews which were partially or completely devoted to sulfamides.[1–13] However, the latest review[13] was published more than 10 years ago. During the last decade, abundant experimental data have accumulated, which call for further generalisation.

Sulfamides attract permanent interest because acyclic and cyclic products containing sulfamide fragments exhibit a broad spectrum of physiological activities. Thus sulfamoylamidines possess antiulcerous[14] and diuretic[15] activities, 4-phenyl-1,2,5-thiadiazolidin-3-one 1,1-dioxide exhibits antispasmodic activity,[16] 5-alkyl-2-phosphinyloxymethyl-1,2,5-thiadiazolidin-3-one 1,1-dioxides are proposed for the treatment of rheumatoid arthritis,[17] and 1,2,5-thiadiazolidine 1,1-dioxides containing an indole substituent at position 2 are used for the treatment of migraine.[18,19] 5-Alkyl-2-fluoromethyl-1,2,5-thiadiazolidin-3-one 1,1-dioxides inhibit enzymes, *viz*., human leucocyte elastase and cathepsin G.[20] 6,7-Dihydro-5*H*-cyclopenta[*c*]- and 5,6,7,8-tetrahydrobenzo[*c*]-2,1,3-thiadiazine 2,2-dioxides act as myorelaxants,[21] and 3,5-dioxo-1,2,6-thiadiazine 1,1-dioxides are used as antiinflammatory agents.[22] Aryl-substituted seven- and eight-membered cyclic sulfamides inhibit HIV-1 protease.[23,24] Many sulfamides possess antibacterial properties.[25,26]

Sulfamides are also used in photography,[27] they are components of fungicide[28] and insecticide[29] mixtures and are employed as detergents.[30] 3,5-Dioxo- and 3,5-diimino-1,2,6-thiadiazine 1,1-dioxides are used for the preparation of azo dyes.[31] 3-Amino-1,2,6-thiadiazine 1,1-dioxides exhibit fungistatic activities.[32] *S*,*S*-Dioxides of benzothiadiazine, thiadiazine, and thiatriazine as well as some acyclic sulfamides can serve as herbicides.[33–35]

In the 1980s, a new class of chiral oxidising agents based on sulfamides was found. These are 2-sulfamoyloxaziridines which exhibit high enantioselectivity (40% – 91%) in asymmetric oxidation of sulfides to sulfoxides.[36–38]

It is believed[1,7,14,39–42] that the increased interest in sulfamide derivatives stems from the fact that these compounds are structurally similar to ureas. In this connection, we thought that it was worthwhile performing a comparative analysis of the structures and physicochemical properties of sulfamide and urea. However, the major aim of the present review is to systematise procedures for the synthesis of heterocyclic compounds based on sulfamide. Wherever possible, a comparative analysis of the properties of cyclic sulfamides and of the corresponding cyclic ureas was carried out.

II. Structure and physicochemical properties of sulfamide

Whereas the electronic structure of the carbonyl group has been studied comprehensively and described in detail, the data on the electronic structure of the sulfonyl group are ambiguous. The character of the S–O bond remains unclear, and the question of whether this bond is purely polar, semipolar, covalent or 'intermediate' is still open.

The question about the nature of the sulfonyl groups is closely related to the question about the participation of the *d* orbitals of the sulfur atom in bonding with other elements and to the question of whether the sulfur atom can exhibit 'hypervalence' thus violating the Lewis octet rule.[43]

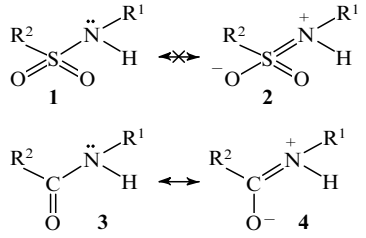
Quantum-chemical calculations with the 3-21G* and 6-31G* basis sets (*i.e*., taking into account the contribution of the *d* orbitals) for a series of model compounds containing the SO and SO_2 groups demonstrated that the contribution of the *d* orbitals to the formation of the S–O bond is insignificant.[44,45] Thus Reed and von Ragué Schleyer[44] concluded that the character of the S–O bond is determined primarily by the partially ionic σ bond and the $\pi-\sigma^*$ 'negative hyperconjugation'. However, studies of the electronic structures of sulfamides and heterocyclic compounds containing the SO_2 group by calculation methods demonstrated that $p_\pi-d_\pi$ interaction with the participation of the *d* orbitals of the sulfur atom contributes to the formation of the multiple S–O bond.[45–50] According to these calculations, the S–O bond has two components of the σ and π types, *viz*., the σ bond between the corresponding atomic orbitals of the oxygen and sulfur atoms and the π bond between, on the one hand, three lone electron pairs of the oxygen atom polarised toward the sulfur

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Received 25 November 1999
Uspekhi Khimii **69** (3) 239 – 248 (2000); translated by T N Safonova

atom, and, on the other hand, the *p* and *d* orbitals of the sulfur atom. However, the S–O bond is not, strictly speaking, a double bond because the π type of interaction is $p_\pi - d_\pi$ bonding with the participation of all three electron pairs of the oxygen atom. Nevertheless, as in Ref. 43, we shall arbitrarily denote these bonds as O=S=O. It should be remembered that these 'double' bonds differ substantially from true double bonds formed by elements of the second row (for example, from C=O bonds) and are characterised by a substantial contribution of the ionic state.[43–50]

The specificity of the structure of the sulfo group is reflected in the spatial configuration of the atoms in the sulfamide molecule as well as in the electron density distribution. Recently, the crystal structure of sulfamide has been studied by X-ray and neutron diffraction analysis (Table 1).[49, 51, 52] According to the results of these studies, the S and N atoms in the sulfamide molecule have tetrahedral and pyramidal bond configurations, respectively, whereas the nitrogen atom in amides and urea is characterised by sp^2 hybridisation and a planar bond configuration.[52] The urea molecule is planar and symmetrical. The bond angles in this molecule differ little from 120°.[53] This structure is consistent with the notion of conjugation between the π electrons of the C=O double bond and the lone electron pairs of the nitrogen atoms. This conjugation cannot occur in the sulfamide molecule because the sulfur atom does not possess unoccupied orbitals for participation in electron delocalisation. It has been demonstrated[45, 47] that the *d* orbitals of the sulfur atom are not involved in bonding with the S and N atoms in sulfamides. It was also found that sulfonamides cannot adopt the limiting resonance structure **2** analogous to the structure **4** for carboxamides.[57]



The electron-withdrawing effect of the SO_2 group is stronger than that of the carbonyl group, and hence the acidity of the amino groups in sulfamide is higher than that in urea. Thus the amino groups in urea exhibit a weakly basic character, whereas these groups in sulfamide are weakly acidic. Urea forms salts with acids[58] and sulfamide gives salts with heavy metals (for example, $AgNHSO_2NHAg$) and alkali metals.[1, 12, 59] These data agree with the Taft induction constants σ_1 for the electron-withdrawing substituents in dioxane (σ_1') and in weakly acidic solvents (σ_1'').[60]

Group	σ_1'	σ_1''
$CONH_2$	0.11	0.21 ± 0.02
SO_2NH_2	0.38	0.46 ± 0.03

Table 1. Comparative characteristics of the sulfamide and urea molecules.

Parameter	Sulfamide		Urea	
Bond lengths /Å	S–O	1.434	C–O	1.276
	S–N	1.614	C–N	1.356
	N–H	1.034	N–H	1.046
	N–H′	1.038	N–H′	1.070
Bond angles /deg	O–S–O′	118.0	O–C–N	120.9
	O–S–N	106.2	N–C–N′	118.2
	O′–S–N	107.0	C–N–H	122.5
	N–S–N′	111.7	C–N–H′	120.5
	H–N–H′	112.5	H–N–H′	117.0
Dihedral angle /deg	OSO/NSN	89.39		
Stretching vibrations /cm^{-1}	N–H	3210–3372	N–H	3342–3449
	SO_2	1315–1369, 1145–1155	C=O	1681
	SN_2	870–955	CN	1004, 1466

Note. The geometric parameters for the sulfamide molecule were taken from Refs 51 and 52, the parameters for the urea molecule were taken from Ref. 53, and the stretching vibration frequencies were published in Refs 53–56.

Therefore, sulfamide can be considered as an analogue of carbamide only bearing in mind that the N–SO_2 conjugation is actually not realised in sulfamide by virtue of electronic and steric factors and that, in addition, the NH bond in sulfamide is substantially more acidic, and, correspondingly, the nitrogen atom is less basic than those in urea.

The results of *ab initio* calculations[45–50] of the geometry, dipole moments, atomic charges and bond orders in sulfamides and heterocyclic compounds containing the NSO_2N fragment agree well with the experimental data.

In the crystal, the sulfamide molecules, like the urea molecules, are linked together through strong hydrogen bonds,[51, 52, 54, 58] which may be responsible for the rather high melting points of these compounds. In solutions of sulfamides, these hydrogen bonds are substantially weaker and are observed only in water, which is confirmed by the data from IR and Raman spectroscopy.[55]

The ^{15}N, ^{14}N and ^{33}S NMR spectra of sulfamide have also been reported.[61, 62]

III. Synthesis of heterocyclic compounds containing the sulfamide fragment

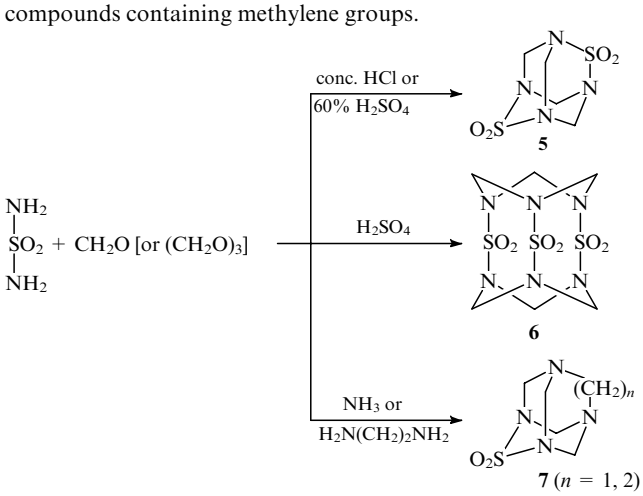
Since heterocyclic systems containing the NSO_2N fragment are highly diversified, we believe that it is more convenient to classify procedures for their synthesis according to the initial compounds, as in Ref. 12, rather than according to the resulting products, as in Ref. 13.

Sulfamide and urea are not as strong nucleophiles as ammonia or amines; nevertheless, they can also react with electrophilic reagents. Reactions of sulfamides with carbonyl compounds, diamines, dinitriles and other bifunctional reagents are considered in this Section.

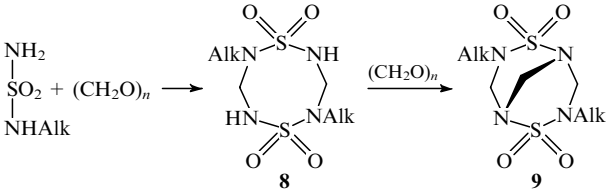
1. Reactions of sulfamides with carbonyl compounds

One of the most general procedures for the synthesis of heterocyclic compounds based on sulfamides involves their condensation with carbonyl compounds[39, 63–72] or with their acetals.[41, 42, 73]

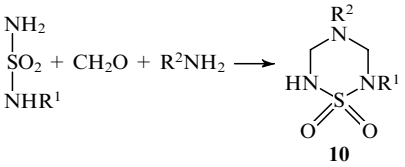
Formaldehyde,[7, 12, 13, 63, 65] paraformaldehyde[64] and trioxane[63] are most commonly used in the synthesis of heterocyclic compounds containing methylene groups.



Reactions of alkylsulfamides with paraformaldehyde in trifluoroacetic acid occur through the intermediate formation of 1,5-dithia-2,4,6,8-tetraazocine 1,1,5,5-tetroxides **8** to yield 2,6-dithia-1,3,5,7-tetraazabicylco[3.3.1]nonane 2,2,6,6-tetroxides **9**.[64]



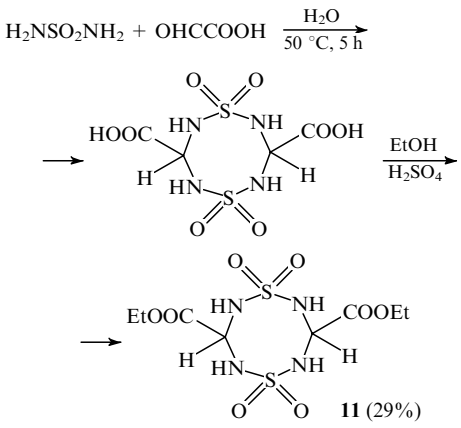
Condensation of sulfamides with formaldehyde and primary amines afforded tetrahydro-1,2,4,6-thiatriazine 1,1-dioxides **10** in 60% – 86% yields.[65]



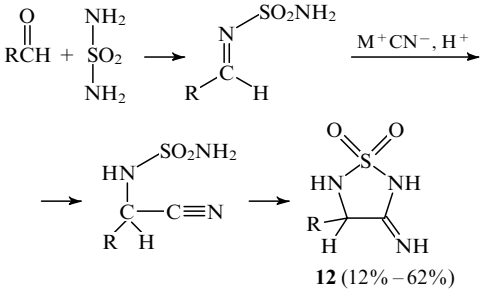
R^1 = H, OAlk, OAr; R^2 = Alk, Ar.

Ureas also react with formaldehyde to form a wide variety of products (both polymeric and heterocyclic) including compounds analogous to compounds **8** and **10**.[7, 74, 75]

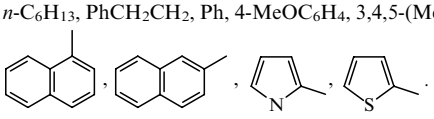
3,7-Bis(ethoxycarbonyl)perhydro-1,5-dithia-2,4,6,8-tetraazocine 1,1,5,5-tetroxide (**11**) was prepared from sulfamide and glyoxylic acid followed by esterification.[66]



3-Imino-4-substituted 1,2,5-thiadiazolidine 1,1-dioxides (**12**) were formed upon boiling of solutions of aldehydes, sodium (or potassium) cyanide and sulfamide in aqueous ethanol.[39] Presumably, the reaction proceeds as follows:

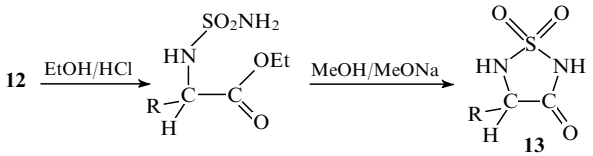


R = n-C_6H_{13}, $PhCH_2CH_2$, Ph, 4-$MeOC_6H_4$, 3,4,5-$(MeO)_3C_6H_2$,

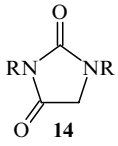


This reaction did not take place with paraformaldehyde, trioxane, acetone and acetophenone.

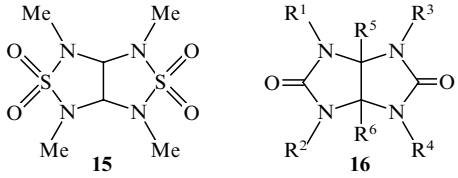
3-Oxo derivatives **13** are prepared from the corresponding 3-imino-1,2,5-thiadiazolidine 1,1-dioxides.



Unlike sulfamide derivatives **13**, 2,4-dioxoimidazolidines **14** are readily formed from ureas and α-dicarbonyl compounds in an acidic medium.[7, 76]

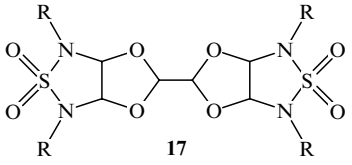


Over many years, the reactions of sulfamides with α- and β-dicarbonyl compounds have also been widely used in the synthesis of heterocyclic compounds.[5, 12, 13, 67 – 71] Thus the reaction of *N*,*N*′-dimethylsulfamide with glyoxal in an acidic medium (pH 3 – 4) afforded the first representative of bis(sulfamides) of the bicyclooctane series, *viz*., 2,4,6,8-tetramethyl-3,7-dithia-2,4,6,8-tetraazabicylco[3.3.0]octane 3,3,7,7-tetroxide (**15**), (the yield was 23%).[67]



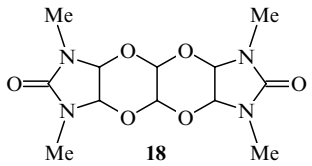
It should be noted that analogous bicyclic bisureas **16** have been prepared long ago from ureas and α-dicarbonyl compounds in 91% yield. Over the past century, tens of representatives of this class of compounds have been synthesised,[7, 77] whereas sulfamide analogues have been previously unknown.

With the aim of increasing the yield of compound **15**, we performed the reactions of *N*,*N*′-dialkylsulfamides with glyoxal monohydrate in 36.7% hydrochloric acid. However, new heterocyclic compounds, *viz*., 3,3′-bis(6,8-dialkyl-2,4-dioxa-7-thia-6,8-diazabicyclo[3.3.0]octane 7,7-dioxides) (**17**, the yields were 54% – 85%), were obtained instead of the expected products **15**. The structures of the products **17** were confirmed by X-ray diffraction analysis.

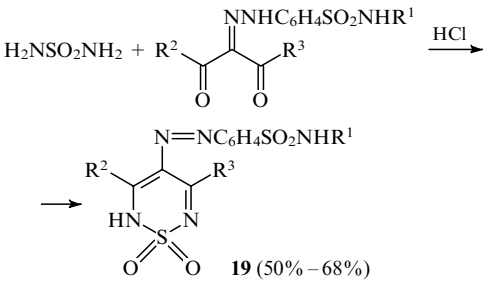


R = Me, Et, Pr, Bu.

The reaction of *N*,*N*′-dimethylurea with glyoxal afforded another product, *viz*., 4,6,12,14-tetramethyl-2,8,10,16-tetraoxa-4,6,12,14-tetraazatetracyclo-[7.7.0.0^{3,7}0^{11,15}]hexadecane-5,13-dione (**18**).[78]

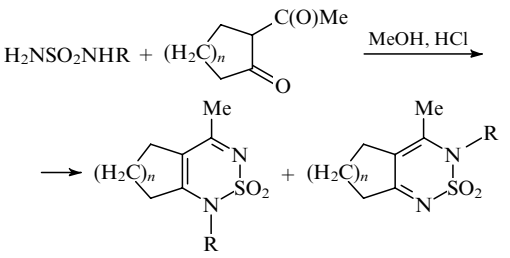


Reactions of sulfamide with β-diketones yielded various 1,2,6-thiadiazine 1,1-dioxide derivatives.[70, 71]



19 (50%–68%)

R^1 = H, CH_2CONH_2, $C(NH_2)$=NH, Ar; R^2 = Me, Ph; R^3 = Me, Ph.



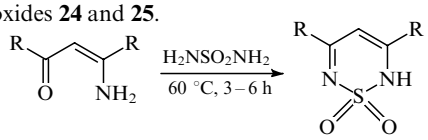
20 (7%), **21** (15%–43%), **22** (41%–74%), **23** (47%)

R = H, Me; n = 1 (**20**, **21**), 2 (**22**, **23**).

Reactions of sulfamide with symmetrical β-diketones afforded one type of products (**19**, $R^2 = R^3$); however, the reactions with unsymmetrically substituted β-diketones gave mixtures of tautomers (**20**–**23**, R = H). Moreover, the reactions of unsymmetrically substituted β-diketones with monosubstituted sulfamides afforded mixtures of regioisomers (**20**–**23**, R = Me).[70–72]

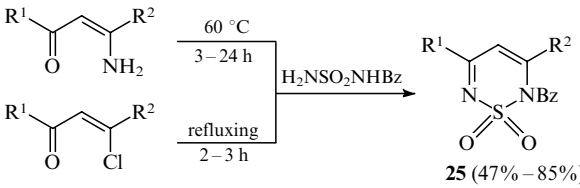
The reactivity of β-diketones with respect to sulfamide depends on both the electronic and steric characteristics of the substituents in the diketones. Thus 3,5-diphenyl-2*H*-1,2,6-thiadiazine 1,1-dioxide and its 2-butyl derivative were prepared in 45% and 39% yields, respectively, whereas 3,5-di-*tert*-butyl-2*H*-1,2,6-thiadiazine 1,1-dioxide has not been synthesised yet.[72]

It was demonstrated[72] that the reactions of β-amino- and β-chloro-α,β-unsaturated ketones with sulfamide occurred regiospecifically under milder conditions than the reactions with the corresponding β-diketones. In anhydrous ethanol in the presence of HCl, these compounds gave a series of 2*H*-1,2,6-thiadiazine 1,1-dioxides **24** and **25**.



24 (83%–87%)

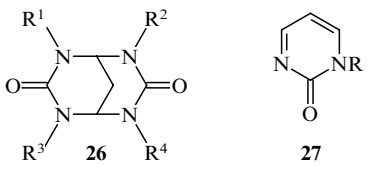
R = Me, Ph, Bu^t.



25 (47%–85%)

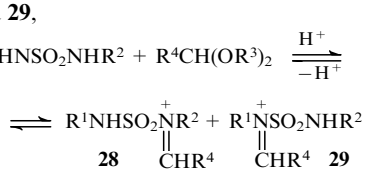
R^1 = Alk, Ar; R^2 = H, Me.

In the reactions of ureas with β-dicarbonyl compounds, bicyclic products **26** were formed more readily than 2-oxodihydropyrimidines **27**, whereas the reactions with β-chloro-α,β-unsaturated aldehydes afforded only derivatives **27**.[7,79]



26 **27**

The use of acetals of carbonyl compounds instead of these compounds as such in the reactions with sulfamides resulted in the formation of six- and eight-membered *N*,*S*-containing heterocyclic compounds analogous to those described above along with new unexpected intramolecular α-sulfamidoalkylation products.[41,42,73] Presumably,[42,73] the mechanism of these reactions is analogous to the mechanism of α-ureidoalkylation.[7] Reactions of sulfamides with acetals in an acidic medium afforded iminuim ions **28** and **29**,

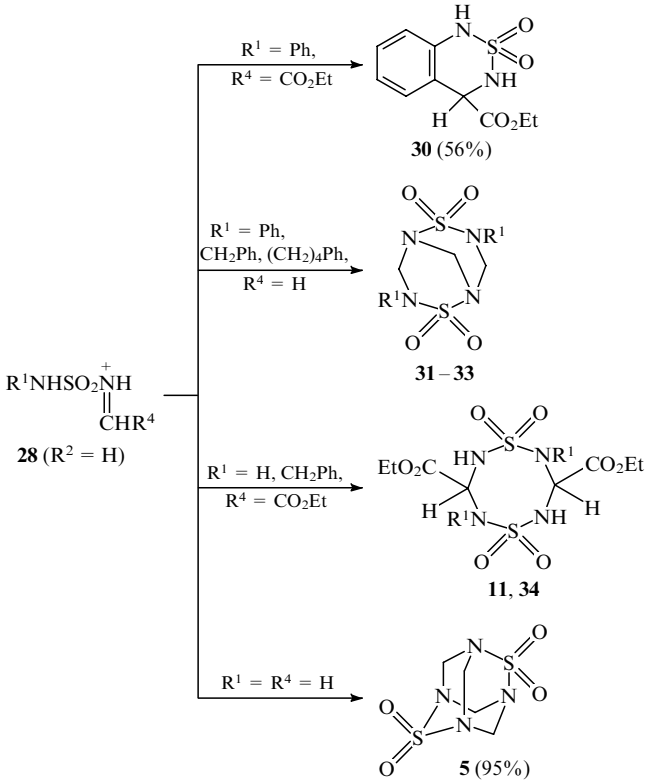


28 **29**

R^1 = H: R^2 = H, $(CH_2)_nPh$, $CH_2C_6H_4OMe$-3;
R^1 = R^2 = $(CH_2)_nPh$ (n = 0–4);
R^3 = Me, R^4 = H; R^3 = Et: R^4 = H, CO_2Et, CH_2CO_2Et;

which underwent intramolecular or intermolecular α-sulfamidoalkylation depending on the nature of the substituent in the sulfamides and the reaction conditions.

In the case of α-sulfamidoalkylation of the aromatic rings in the iminium ions, annelation products **30**, **35**–**38** and **41** were formed. If the aromatic substituent in sulfamide is either remote from the generated iminium ion or absent, intermolecular dimerisation occurs to form eight-membered heterocyclic compounds **11**, **34** and **40**. Under certain conditions, these products can react with acetals to form compounds **5** and **31**–**33**. Symmetrical diarylsulfamides react with acetals $(EtO)_2CH(CH_2)_mCOOEt$ (m = 0 or 1) to form new sulfamide **39** as a result of intramolecular α-sulfamidoalkylation.



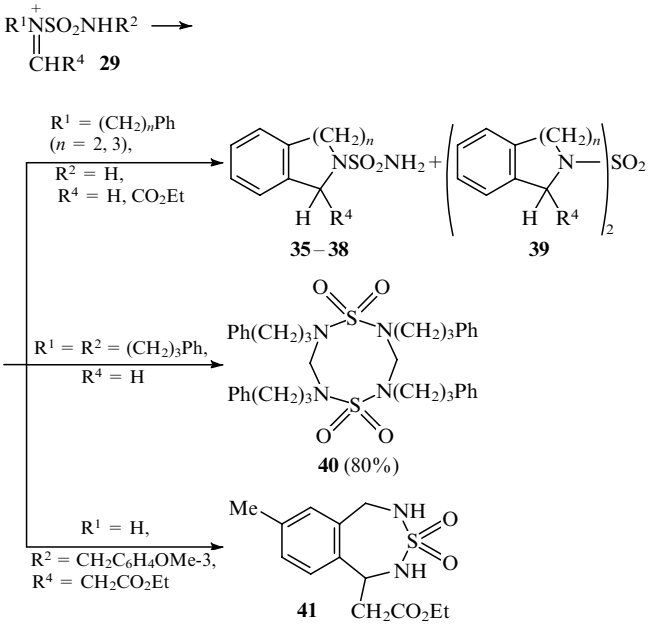
30 (56%)

31–**33**

11, **34**

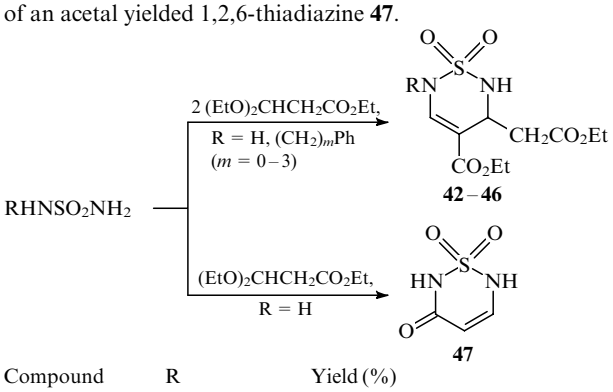
5 (95%)

Compound	R^1	Yield (%)
31	Ph	46
32	CH_2Ph	72
33	$(CH_2)_4Ph$	56
11	H	75
34	CH_2Ph	74



Compound	*n*	R^4	Yield (%)
35	2	H	88
36	2	CO_2Et	80
37	3	H	85
38	3	CO_2Et	11
39	3	CO_2Et	68

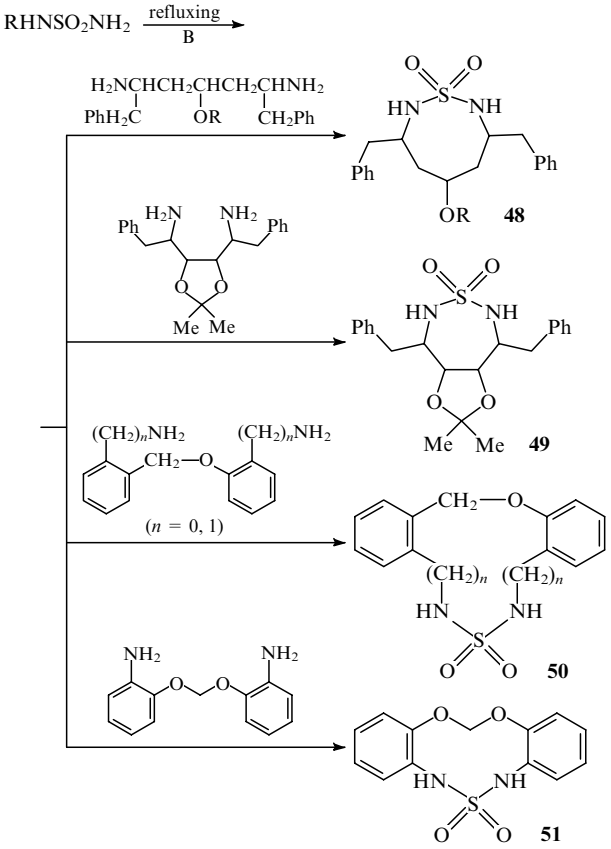
The reactions of unsubstituted sulfamide and arylsulfamides with two equivalents of an acetal in an acidic medium afforded 1,2,6-thiadiazines **42**–**46**, while the reaction with one equivalent of an acetal yielded 1,2,6-thiadiazine **47**.



Compound	R	Yield (%)
42	H	38
43	Ph	42
44	CH_2Ph	68
45	$(CH_2)_2Ph$	37
46	$(CH_2)_3Ph$	79

2. Reactions of sulfamides with diamines

An efficient procedure for the synthesis of heterocyclic compounds containing the sulfamide fragment involves condensation of sulfamide with diamines.[12, 13, 23, 24, 80] This procedure allows one to prepare heterocyclic compounds with five, six or more atoms in the ring. Note that this procedure is the most convenient method for the synthesis of the latter compounds.



B is an organic base.

Heating of ureas with diamines is also used in the synthesis of heterocyclic compounds.[81]

3. Reactions of sulfamides with dinitriles

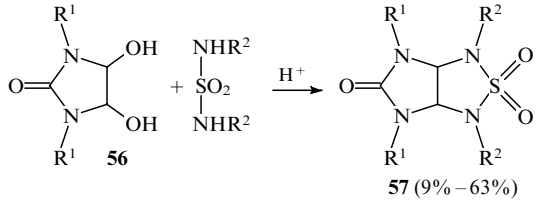
The reactions of sulfamides with dicyan and malonodinitriles find wide application.[13, 82–86] Numerous examples of the preparation of diamino and diimino derivatives of 1,2,5-thiadiazole 1,1-dioxides and 1,2,6-thiadiazine 1,1-dioxides (**52**–**55**) are documented (Scheme 1).

Acid hydrolysis of compounds **52** and **54** afforded the corresponding 3-oxo derivatives.[85, 86]

4. Condensation of sulfamides with diols and other bifunctional reagents

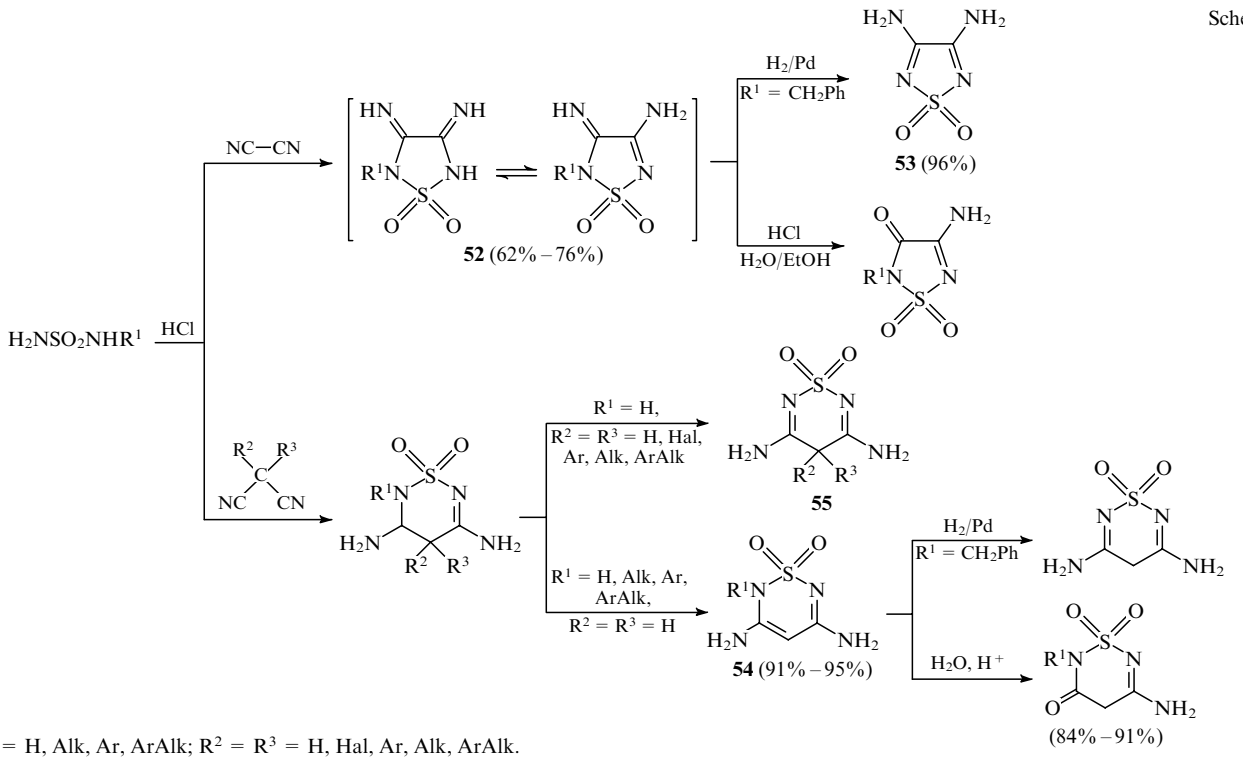
Until recently, condensation of dihydroxy compounds with sulfamides have not found wide use, whereas these reactions with ureas have long been known[7] and they are successfully used, for example, in the synthesis of bicyclo[3.3.0]octanediones (**16**).

Procedures for the preparation of bi-, tri- and tetracyclic compounds (**57**, **59** and **61**, respectively) containing sulfamide fragments from sulfamides and the corresponding dihydroxy compounds **56**, **58** and **60**, respectively, have been developed in recent years.[67, 87]

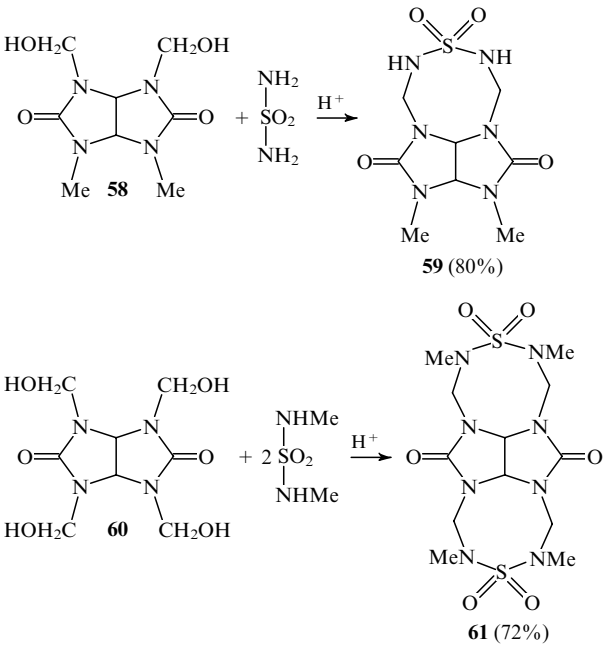


R^1 = Alk; R^2 = H, Alk.

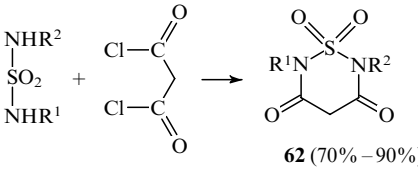
Scheme 1



R^1 = H, Alk, Ar, ArAlk; R^2 = R^3 = H, Hal, Ar, Alk, ArAlk.

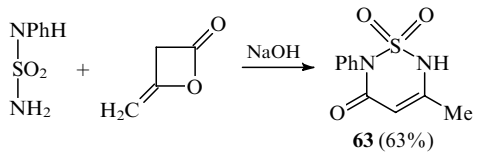


A method for the synthesis of tetrahydro-3,5-dioxo-1,2,6-thiadiazine 1,1-dioxides (**62**) from malonyl chloride and *N*-substituted sulfamides was also proposed.[35,88]

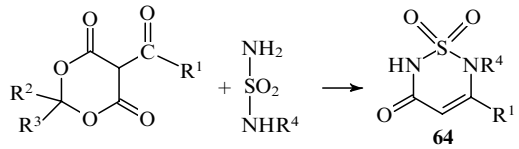


R^1 = $(CH_2)_n$Ph (n = 0–2), C_6H_{11}; R^2 = H, CH_2Ph.

An interesting procedure for the preparation of 5-methyl-3-oxo-3,6-dihydro-2*H*-1,2,6-thiadiazine 1,1-dioxide (**63**) was described.[89,90]



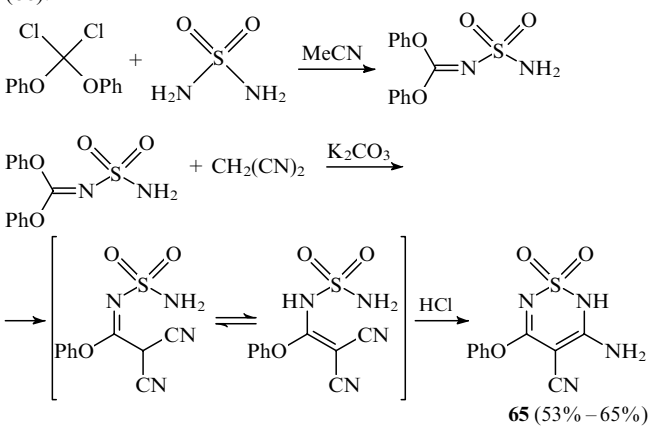
A method for the synthesis of 3-oxo-3,6-dihydro-2*H*-1,2,6-thiadiazine 1,1-dioxides (**64**) from sulfamides and 5-alkanoyl-1,3-dioxane-4,6-diones was covered by a patent.[91]

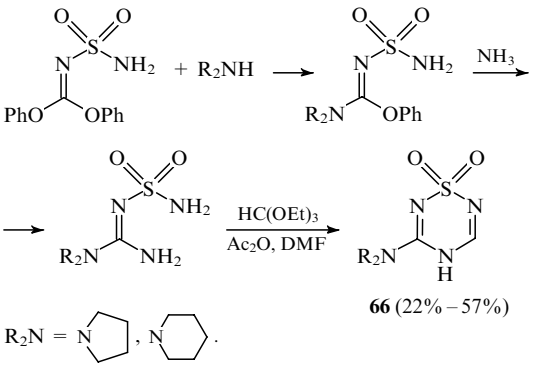


R^1 = R^2 = R^3 = Alk; R^4 = H, Alk, Ar.

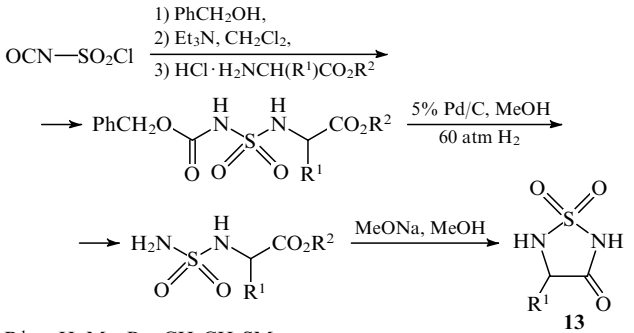
The reactions of derivatives of 1,3-dioxane-4,6-diones with urea and thiourea proceed analogously.[92]

The use of a new synthon, *viz*., diphenyl *N*-sulfamoylcarboimidate, which was prepared from sulfamide and dichlorodiphenoxymethane, opens a new way to the synthesis of 1,2,6-thiadiazine 1,1-dioxide (**65**) and 1,2,4,6-thiatriazine 1,1-dioxide (**66**).[93]





Of the currently available approaches to the construction of cyclic sulfamides, the reactions of sulfuryl halides[94–98] and chlorosulfonyl isocyanate[20,99] with amino compounds should also be mentioned. The preparation of 3-oxo-1,2,5-thiadiazolidine 1,1-dioxides (**13**) from chlorosulfonyl isocyanate and amino acids is an example.[99]

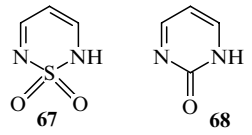


R^1 = H, Me, Bu, CH_2CH_2SMe.

The above-considered experimental data demonstrate that sulfamides are rather often similar in their chemical behaviour to ureas. Sulfo-analogues of many urea-containing compounds have been prepared.

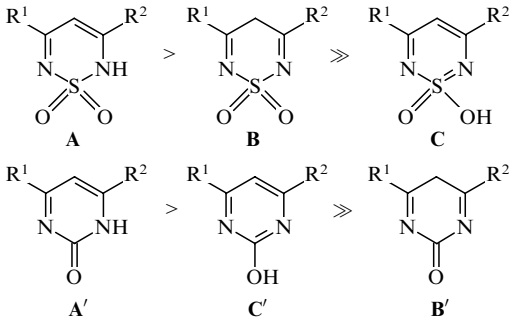
IV. Properties of cyclic sulfamides

Recently, the aromaticity of heterocyclic compounds has been the subject of many theoretical studies.[47,49,50] The results of *ab initio* quantum-chemical calculations of the electronic properties and the geometry of these molecules, which were confirmed by X-ray diffraction analysis,[47,49,50,100,101] demonstrated that the rings in 1,2,5-thiadiazole 1,1-dioxide and 1,2,6-thiadiazine 1,1-dioxide, unlike those in 2-pyrimidinones, are nonaromatic.[47] The lack of the aromaticity results from the specificity of the structure of the SO_2 group (see Section II). The sulfur atom cannot be involved in π delocalisation because the oxygen and sulfur atoms in thiadiazines (**67**) deviate form the plane passing through the remaining atoms.

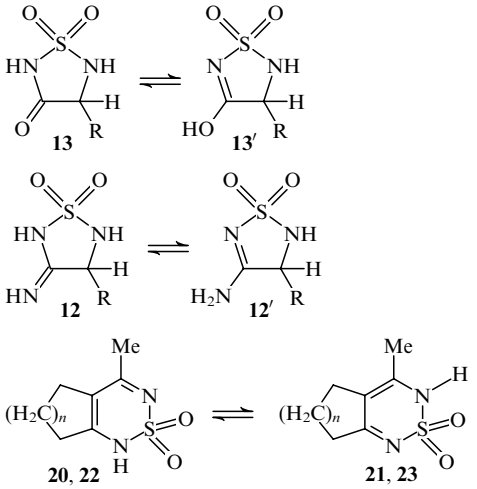


The tautomerism[39,47,71] and rotational isomerism[40,102] of cyclic sulfamides attract considerable interest. The difference in the stability of the tautomers of 1,2,6-thiadiazine 1,1-dioxide (**67**) and 2-pyrimidinone (**68**) results from the aromaticity of the compound **68** and nonaromaticity of the compound **67**.[47]

According to the data from X-ray diffraction studies and NMR spectroscopy, 3,5-dialkyl- and 3,5-diaryl-substituted 1,2,6-thiadiazine 1,1-dioxides exist in solutions predominantly as the isomers **A**, whereas the tautomers **B** of 3(5)-hydroxy- and 3(5)-amino-substituted derivatives are more stable.[47] In no case was the tautomer **C** experimentally observed. In the case of substituted 2-pyrimidines, the stabilities of tautomers **A′** – **C′** are related in a different way.



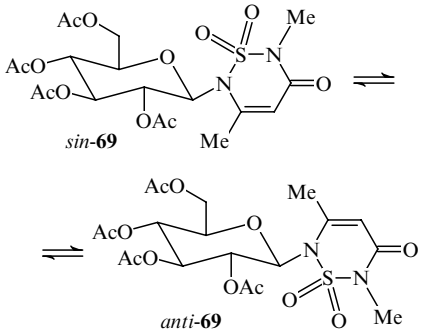
Tautomeric forms of 3-oxo- (**13**) and 3-imino-1,2,5-thiadiazolidine 1,1-dioxides (**12**)[39] as well as those of 6,7-dihydro-5*H*-cyclopenta[*c*]- (**20** and **21**) and 5,6,7,8-tetrahydrobenzo[*c*]-2,1,3-thiadiazine 2,2-dioxides (**22** and **23**)[71] were studied.



n = 1, 2.

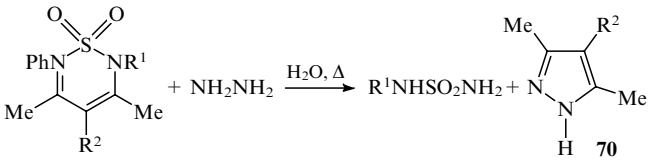
In solution, 3-oxo- and 3-imino-1,2,5-thiadiazoles occur as equilibrium mixtures of the tautomers **12** and **12′** and the tautomers **13** and **13′**, respectively, whereas 6,7-dihydro-5*H*-cyclopenta[*c*]-2,1,3-thiadiazine 2,2-dioxide and 5,6,7,8-tetrahydrobenzo[*c*]-2,1,3-thiadiazine 2,2-dioxide exist predominantly in the forms **21** and **22**, respectively.

The rotational isomerism of glycosylated derivatives of 1,2,6-thiadiazine 1,1-dioxides at the N-glycosidic bond was studied by NMR spectroscopy. Thus 6-β-D-glucopyranosyl-2-methyl-3-oxo-3,6-dihydro-2*H*-1,2,6-thiadizaine 1,1-dioxides (**69**) exist in solutions as mixtures of *syn* and *anti* rotamers.[40]

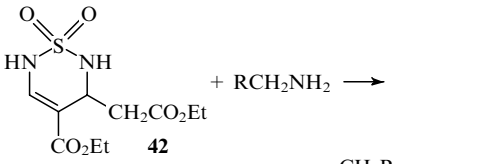


It was found that the energy barriers to rotation about the glycosidic bond for glycosylated thiadiazine derivatives are lower than those for the corresponding uracils and pteridines.[40,102] This is attributed to the fact that the SO_2 group deviates from the plane of the heterocycle and hinders the rotation about the C–N bond to a lesser extent.

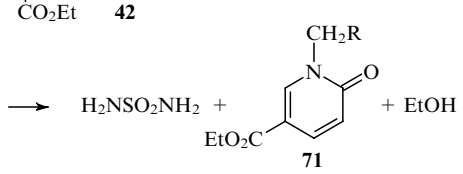
Under the action of various reagents, six- and seven-membered cyclic sulfamides are transformed with elimination of the NSO_2N,[103, 104] SO_2 (see Ref. 105) or CO fragments.[88] Thus derivatives of 1,2,6-thiadiazine 1,1-dioxides were converted under the action of nucleophiles into pyrazoles **70** [103] and 2-pyridones **71**.[104]



70

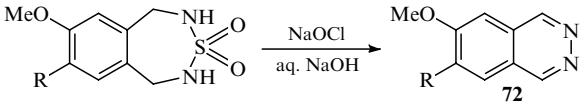


42



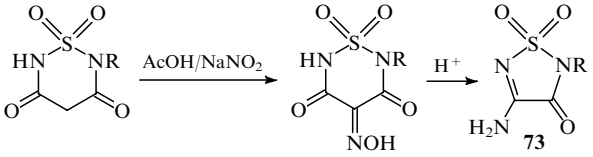
71

Under the action of oxidising agents, seven-membered cyclic sulfamides, which do not contain substituents at the nitrogen atoms were converted into pyridazine derivatives **72** with elimination of the SO_2 fragment,[105]



72

whereas successive nitrosation and acidification of *N*-substituted tetrahydro-3,5-dioxo-1,2,6-thiadiazine 1,1-dioxides afforded 2-substituted 4-amino-2,3-dihydro-3-oxo-1,2,5-thiadiazole 1,1-dioxides (**73**) with elimination of the CO group.[88]

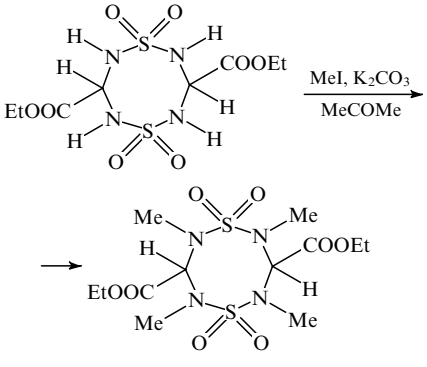


73

R = Ar, cyclo-C_6H_{11}.

Substitution at the nitrogen atoms is typical of cyclic sulfamides. It was demonstrated that heterocyclic sulfamides undergo alkylation,[20, 24, 41, 69, 73, 93, 106, 107] acylation,[69] nitration,[94] hydroxymethylation,[20] silylation [40, 41, 102] and glycosylation.[40, 41, 102]

Diazomethane,[106] dimethyl sulfate [107] and alkyl and aryl halides [20, 24, 41, 69, 73, 93, 107] are used as alkylating agents. Procedures for alkylation with methyl iodide in acetone in the presence of K_2CO_3 or with benzyl chlorides and bromides in the presence of sodium hydride are most generally used.

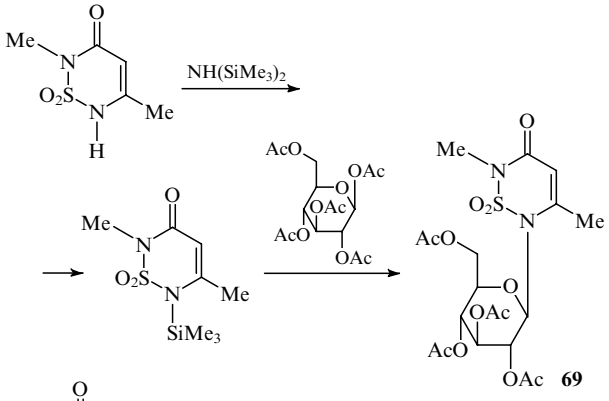




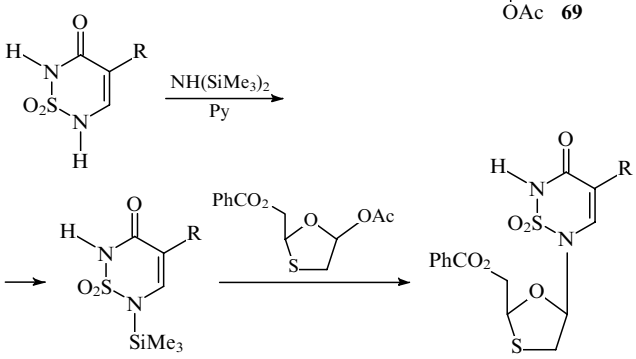
R = 4-$MeOC_6H_4CH_2$.

1,2,5-Thiadiazolidine 1,1-dioxides were acylated with acyl chloride or dimethylcarbamoyl chloride in an alkaline media,[69] nitrated with nitric acid [94] and hydroxymethylated with a methanolic solution of formaldehyde.[20]

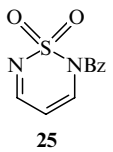
1,2,6-Thiadiazine 1,1-dioxides were silylated with hexamethyldisilazane. Their silyl derivatives underwent glycosylation under the action of penta-*O*-acetyl-β-D-glucopyranose and 1,3-oxathiolane.[40, 41, 102]



69



Halogenation and arylation of 1,2,6-thiadiazine 1,1-dioxides **25** ($R^1 = R^2 = H$) at the carbon atom using organometallic reagents have been reported.[108] Amine exchange in 3,4-diamino-1,2,5-thiadiazole 1,1-dioxides **53** has been described.[83]

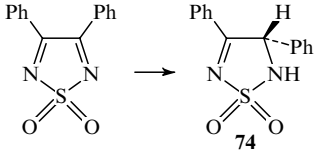


25



53

The sulfo group is stable to reducing agents.[5, 43] The SO_2 group also remains intact upon electroreduction. Thus electroreduction of 3,4-diphenyl-1,2,5-thiadiazole 1,1-dioxide in acetonitrile afforded the corresponding dihydrothidiazole 1,1-dioxide (**74**),[109] *i.e.*, only the C=N bond was reduced.



74

All the above-described reactions are also typical of cyclic ureas. The latter are alkylated with alkyl halides and alkyl sulfates

and undergo acylation, hydroxymethylation, nitration and glycosylation at the nitrogen atoms.[7,110–112]

* * *

The examples considered in this review demonstrate that the chemistry of cyclic sulfamides is progressing successfully. Procedures for the preparation of heterocyclic compounds which contain different numbers of carbon atoms in the ring and bear different substituents at the nitrogen and carbon atoms have been developed. One would expect further progress in this field of chemistry. New possibilities of the reactions of sulfamides with carbonyl compounds yielding bi- and polycyclic sulfamides would be expected to be opened. Various useful properties of sulfamides give promise that new approaches to their directed synthesis will be developed.

References

1. L F Audrieth, M Sveda, H H Sisler, M J Butler *Chem. Rev.* **26** 49 (1940)
2. A Dorlars, in *Methoden der Organischen Chemie (Houben Weyl)* Vol. XI/II (Stuttgart: Georg Thieme Verlag, 1958) p. 643
3. F L Scott, W J Spillane *Mech. React. Sulfur Compd.* **2** 133 (1968)
4. W J Spillane, F L Scott *Mech. React. Sulfur Compd.* **5** 59 (1970)
5. A Lawson, R B Tinkler *Chem. Rev.* **70** 593 (1970)
6. W J Spillane *Int. J. Sulfur Chem.* **8** 469 (1973)
7. H Petersen *Synthesis* 243 (1973)
8. E Fluck, W Haubold, in *Gmelin Handbuch der Anorganische Chemie. New Supp. Ser* Vol. 32 (Eds M Becke, H Bitterer) (Berlin: Springer, 1977)
9. R Appel, J Kohnke, in *Methods of Chemistry* Vol. 7, Part B (Ed. F Korte) (New York: Academic Press, 1978) p. 744
10. K K Andersen *Comprehensive Organic Chemistry* Vol. 3 (Ed. J D Neville) (Oxford: Pergamon Press, 1979) p. 363
11. G A Benson, W J Spillane *Chem. Rev.* **80** 151 (1980)
12. S D McDermott, W J Spillane *Org. Prep. Proc. Int.* **16** 49 (1984)
13. V J Aran, P Goya, C Ochoa *Adv. Heterocycl. Chem.* **44** 81 (1988)
14. Y Yanagisawa, Y Hirata, Y Ishii *J. Med. Chem.* **30** 1787 (1987)
15. P Ahuja, J Singh, M B Asthama, V Sardana, N Anand *Indian J. Chem., Sect. B* **28** 1034 (1989)
16. C-H Lee, H Kohn *J. Pharm. Sci.* **79** 716 (1990)
17. US P. 5 541 168; *Ref. Zh. Khim.* 3 O 198P (1999)
18. Eur. P. 501 568; *Chem. Abstr.* **118** 6977 (1993)
19. J L Castro, R Baker, A R Guiblin, S C Hobbs, M G N Russell, M S Beer, J A Stanton, K Scholey, R J Hargreaves, M I Graham, V G Matassa *J. Med. Chem.* **37** 3023 (1994)
20. W C Groutas, R Kuang, R Venkataraman *Biochem. Biophys. Res. Commun.* **198** 341 (1994)
21. A Castro, A Martinez, I Cardelus, J Llenas, in *The VIIIth Spanish Symposium on Therapeutical Chemistry (Abstracts of Reports), Salamanca, 1993* p. 43
22. P Goya, R Nieves, C Ochoa *Rev. R. Acad. Sci.* **78** 373 (1984); *Chem. Abstr.* **104** 207 234 (1986)
23. US P. 5 506 355; *Chem. Abstr.* **125** 34 038 (1996)
24. P K Jadhav, F J Woerner *Tetrahedron Lett.* **36** 6383 (1995)
25. P O Chastenet, J Buxeraud *J. Lyon Pharm.* **48** 305 (1997)
26. V Ordeanu, M Ionica, A Andries *Farmacia* **45** (5) 63 (1997); *Chem. Abstr.* **128** 228 383 (1998)
27. Jpn. P. 62 183 450; *Chem. Abstr.* **108** 29 358 (1988)
28. Chin. P. 1 113 758; *Chem. Abstr.* **124** 325 421 (1996)
29. Jpn. P. 10 203 902; *Chem. Abstr.* **129** 171 855 (1998)
30. US P. 5 753 599; *Chem. Abstr.* **129** 17 272 (1998)
31. BRD P. 4 208 535; *Chem. Abstr.* **118** 61 519 (1993)
32. I Alkorta, P Goya, C Nombela, R Medina, C Perez Martin *Arzneim.-Forsch.* **41** 264 (1991); *Chem. Abstr.* **115** 8744 (1991)
33. G Hamprecht, K-H König, G Stubenrauch *Angew. Chem.* **93** 151 (1981)
34. Eur. P. 549 079; *Chem. Abstr.* **120** 298 645 (1994)
35. Br. P. 2 213 145; *Chem. Abstr.* **112** 55 921 (1990)
36. F A Davis, J P McCauley Jr , M E Harakal *J. Org. Chem.* **49** 1465 (1984)
37. F A Davis, O D Stringer, J P McCauley Jr *Tetrahedron* **41** 4747 (1985)
38. F A Davis, J P McCauley Jr, S Chattopadhyay, M E Harakal, J C Towson, W H Watson, I Tavanaiepour *J. Am. Chem. Soc.* **109** 3370 (1987)
39. C-H Lee, J D Korp, H Kohn *J. Org. Chem.* **54** 3077 (1989)
40. P Goya, A Martinez, M L Jimeno *J. Chem. Soc., Perkin Trans. 2* 783 (1990)
41. T Breining, A R Cimpoia, T S Mansour, N Cammack, P Hopewell, C Ashman *Heterocycles* **41** 87 (1995)
42. C-H Lee, H Kohn *J. Org. Chem.* **55** 6098 (1990)
43. E N Prilezhaeva, in *Poluchenie i Svoistva Organicheskikh Soedinenii Sery* (Synthesis and Properties of Sulfur Organic Compounds) (Ed. L I Belen'kii) (Moscow: Khimiya, 1998) p. 115
44. A E Reed, P von Ragué Schleyer *J. Am. Chem. Soc.* **112** 1434 (1990)
45. O Mo, J L G De Paz, M Yanez, I Alkorta, J Elguero, P Goya, I Rozas *Can. J. Chem.* **67** 2227 (1989)
46. J G Angyan, C Bonnelle, R Daudel, A Kucsman, I G Csizmadia *THEOCHEM* **42** 273 (1988)
47. J Elguero, P Goya, A Martinez, I Rozas, O Mo, J L G De Paz, M Yanez *J. Phys. Org. Chem.* **3** 470 (1990)
48. I Alkorta *Theor. Chim. Acta* **89** 1 (1994)
49. I Alkorta, C Garcia-Gomez, J A Paez, P Goya *J. Phys. Org. Chem.* **9** 203 (1996)
50. I Rozas *Int. J. Quantum Chem.* **62** 477 (1997)
51. F Belaj, C Kratky, E Nachbaur, A Popitsch *Monatsh. Chem.* **118** 427 (1987)
52. R M Ibberson *J. Mol. Struct.* **377** 171 (1996)
53. K S Sulaimankulov, in *Soedineniya Karbamida s Neorganicheskimi Solyami* (Carbamide Compounds with Inorganic Salts) (Frunze: Ilim, 1971) p. 7; 224
54. V de Zea Bermudez, G Lucazeau, L Abello, C Poinsignon *J. Mol. Struct.* **297** 185 (1993)
55. V de Zea Bermudez, G Lucazeau, L Abello, C Poinsignon *J. Mol. Struct.* **301** 7 (1993)
56. A Popitsch *Monatsh. Chem.* **113** 529 (1982)
57. J Elguero, P Goya, I Rozas, J Catalan, J L G De Paz *THEOCHEM* **53** 115 (1989)
58. C D Nenizescu *Chimie Organica* Vol. 1 (Bucuresti: Editura Tehnica, 1960)
59. E Nachbaur, A Popitsch *Angew. Chem., Int. Ed. Engl.* **12** 339 (1973)
60. V A Pal'm *Osnovy Kolichestvennoi Teorii Organicheskikh Reaktsii* (Foundation of Quantitative Theory of Organic Reactions) (Leningrad: Khimiya, 1967) p. 164
61. P Goya, C Ochoa, I Rozas, A Alemany, M L Jimeno *Magn. Reson. Chem.* **24** 444 (1986)
62. P S Belton, J D Woollins *Magn. Reson. Chem.* **24** 1080 (1986)
63. T Esser, A E Karu, R F Toia, J E Casida *Chem. Res. Toxicol.* **4** 162 (1991)
64. J Dusemund, T Schurreit *Arch. Pharm.* **319** 826 (1986)
65. J Dusemund, T Schurreit *Arch. Pharm.* **320** 534 (1987)
66. C H Lee, H Kohn *Heterocycles* **27** 2581 (1988)
67. G A Orekhova, A N Kravchenko, O V Lebedev, in *The IXth Conference of Organic Chemistry and Biochemistry for Young Scientists (Abstracts of Reports), Liblice, 1995* p. 111
68. J Elguero, C Ochoa, M Stud, C Esteban-Calderon, M Martinez-Ripoll, J-P Iayet, M C Vertut *J. Org. Chem.* **47** 536 (1982)
69. J B Wright *J. Org. Chem.* **29** 1905 (1964)
70. R N Goyal, S Bhargava *Curr. Sci.* **58** 287 (1989)
71. A Castro, A Martinez *J. Chem. Soc., Perkin Trans. 2* 1561 (1994)
72. A Alberola, J M Andres, A Gonzalez, R Pedrosa, M Vicente *Synthesis* 355 (1991)
73. C-H Lee, H Kohn *J. Heterocycl. Chem.* **27** 2107 (1990)
74. P Christjanson, K Siimer, A Laht, H Oja *Tallinna Tehnikaulik. Toim* **731** 10 (1992); *Chem. Abstr.* **120** 299 913 (1994)
75. K Siimer, H Oja, P Christjanson, A Laht *VTT Symp.* **133** 332 (1992); *Chem. Abstr.* **118** 170 890 (1993)
76. G Schwenker, H Guo *Arch. Pharm.* **326** 45 (1993)
77. A A Bakibaev, R R Akhmedzhanov, A Yu Yagovkin, T P Novozheeva, V D Filimonov, A S Saratykov *Khim.- Farm. Zh.* **27** (6) 29 (1993)[a]
78. R H Barker, S L Vail, G B Barcelo *J. Heterocycl. Chem.* **3** 354 (1966)
79. F M Abd El Latif *Asian J. Chem.* **5** 184 (1993); *Chem. Abstr.* **118** 124 488 (1993)
80. R Glinka, K Walczynski, M I Grabowski, A Stepien *Pol. J. Chem.* **65** 2053 (1991)

81. US P. 5 206 362; *Chem. Abstr.* **119** 160 330 (1993)
82. Span. P. 545 696; *Chem. Abstr.* **107** 39 870 (1987)
83. V J Aran, J R Ruiz, E Davila, I Alkorta, M Stud *Liebigs Ann. Chem.* 337 (1988)
84. Span. P. 547 443; *Chem. Abstr.* **108** 6031 (1988)
85. I Alkorta, V J Aran, A G Bielsa, M Stud *J. Chem. Soc., Perkin Trans. 1* 1271 (1988)
86. I Alkorta, V J Aran, E Davila, J R Ruiz, M Stud *Liebigs Ann. Chem.* 1135 (1989)
87. G A Gazieva, A N Kravchenko, K Yu Chegaev, Yu A Strelenko, O V Lebedev *Mendeleev Commun.,* 28 (2000)
88. V J Aran, A G Bielsa, J R Ruiz, M Stud *J. Chem. Soc., Perkin Trans. 1* 643 (1986)
89. Span. P. 553 863; *Chem. Abstr.* **109** 129 066 (1988)
90. J Elguero, P Goya, R Nieves, C Ochoa, C Rodellas, M Martinez-Ripoll, S Garcia-Blanco *J. Chem. Res. (S)* 94 (1988)
91. Jpn. P. 6 242 978; *Chem. Abstr.* **107** 39 852 (1987)
92. Jpn. P. 6 242 975; *Chem. Abstr.* **107** 39 853 (1987)
93. M Haake, B Schümmelfelder *Synthesis* 753 (1991)
94. O V Anikin, L G Gareeva, I E Chlenov, V A Tartakovskii, Yu T Struchkov, V S Kuz'min, Yu N Burtsev *Izv. Akad. Nauk SSSR, Ser. Khim.* 1812 (1989) [b]
95. G A Hanewacker, Z Mester, B Unterhalt *Arch. Pharm.* **326** 497 (1993)
96. M Knollmüller, R Fauβ *Monatsh. Chem.* **116** 1027 (1985)
97. M Knollmüller, P Kosma *Monatsh. Chem.* **116** 1141 (1985)
98. M Knollmüller, P Kosma *Monatsh. Chem.* **116** 1321 (1985)
99. G W Muller, G E DuBois *J. Org. Chem.* **54** 4471 (1989)
100. P Goya, A Martinez, C Ochoa, M Stud, M L Jimeno, C Foces-Foces, F H Cano, M Martinez-Ripoll *Tetrahedron* **41** 3105 (1985)
101. A Herrero, C Ochoa, M Stud, F Florencio, I Hernandes-Fuentes, C Abdradelo, J L G De Paz *J. Org. Chem.* **54** 5025 (1989)
102. P Goya, A Martinez, M L Jimeno, W Pfleiderer *Liebigs Ann. Chem.* 961 (1987)
103. J Elguero, P Goya, A Martinez *Heterocycles* **29** 245 (1989)
104. C H Lee, Y S Chung, B Y Chung *Bull. Korean Chem. Soc.* **14** 592 (1993); *Chem. Abstr.* **120** 163 925 (1994)
105. C S Lee, S H Kim, C-H Lee *J. Korean Chem. Soc.* **41** 677 (1997); *Chem. Abstr.* **128** 88 869 (1998)
106. G Faleschini, E Nachbaur, F Belaj *Phosphorus Sulfur Silicon Relat. Elem.* **65** 147 (1992)
107. I Alkorta, P Goya, A J Paez *Heterocycles* **32** 279 (1991)
108. L R R Wang, T Benneche, K Undheim *Acta Chem. Scand.* **44** 726 (1990)
109. M V Mirifico, J A Caram, E J Vasini *Electrochim. Acta* **36** 167 (1991)
110. L I Suvorova, V A Efes'ko, L V Epishina, O V Lebedev, L I Khmel'nitskii, S S Novikov, M V Povstyanoi, V D Krylov, G V Korotkova, L V Lapshina, A F Kulik *Izv. Akad. Nauk SSSR, Ser. Khim.* 1306 (1979) [b]
111. A S Ermakov, S A Serkov, V A Tartakovskii, T S Novikova, L I Khmel'nitskii *Khim. Geterotsikl. Soedin.* 1129 (1994) [c]
112. V A Timoshchuk *Usp. Khim.* **63** 730 (1994) [*Russ. Chem. Rev.* **63** 695 (1994)]

[a] — *Pharm. Chem. J. (Engl. Transl.)*
[b] — *Russ. Chem. Bull. (Engl. Transl.)*
[c] — *Chem. Heterocycl. Compd. (Engl. Transl.)*