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1,2,3-Thiadiazoles as a Convenient Source for the Study of Molecular Rearrangements, Single Bond/No Bond Resonance and Dendrimer Synthesis

(The late) Gerrit L'abbé, Bart D'hooge and Wim Dehaen*

Department of Chemistry, University of Leuven, Celestijnenlaan 200F, B-3001 Heverlee, Belgium;
Tel.: +32-1632-7426; FAX: +32 1632 7990 (Wim.dehaen@chem.kuleuven.ac.be)

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Abstract

1,2,3-Thiadiazoles are five-membered heterocycles which are readily available. We have used these interesting compounds in three different areas of research:
• Rearrangements of 1,2,3-thiadiazoles leading to other heterocycles, such as 1,2,3-triazoles and 1,2,3,4-thiatriazoles. Isomeric 1,2,3-thiadiazoles (a ring-degenerate rearrangement) could also be obtained.
• 1,2,3-Thiadiazolium salts as synthons for 6aλ^4-thiapentalenes showing single bond/no bond resonance, and/or mesoionic compounds.
• The base-induced cleavage of 1,2,3-thiadiazoles giving the reactive alkynethiolates, which were used in the synthesis of dendrimers.

Keywords: 1,2,3-Thiadiazoles, rearrangements, dendrimer, review.

Introduction

1,2,3-Thiadiazoles **1** are five-membered heterocycles which are readily available by one of three methods (Scheme 1): (1) thionation of a-diazocarbonyl compounds **2** (Wolff method) [1], (2) cycloaddition of isothiocyanates **3** and diazo compounds **4** (Pechmann method) [2] and (3) reaction of α-methyleneketone hydrazones **5** with thionyl chloride (Hurd-Mori reaction) [3].

* *To whom correspondence should be addressed*

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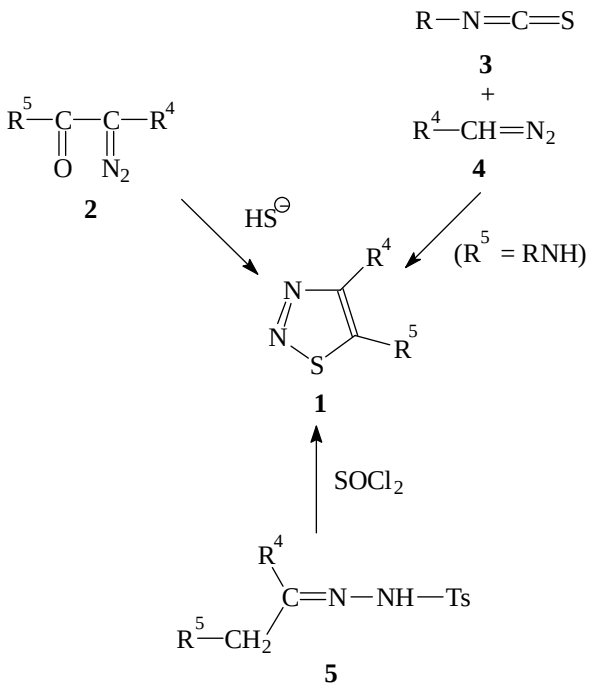
We have used these interesting compounds over a number of years to study their molecular rearrangements, their conversion into 6aλ^4-thiapentalenes and recently their use as a synthon for dendrimers.

Molecular Rearrangements

Whereas α-diazoketones are well-established compounds with some synthetic utility [4], the corresponding α-diazothioketones are unknown [5]. They exist, however, as transient intermediates in a number of rearrangements of 1,2,3-thiadiazoles. For instance, 5-amino- and 5-(substituted amino)thiadiazoles **6** (R = H, aryl) rearrange via **7** to

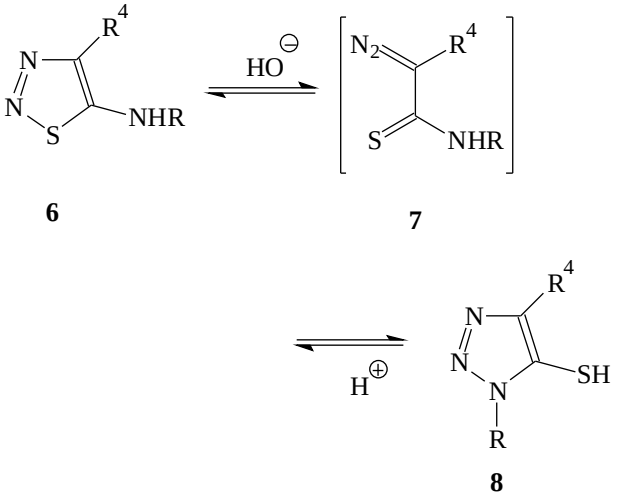


Scheme 1.

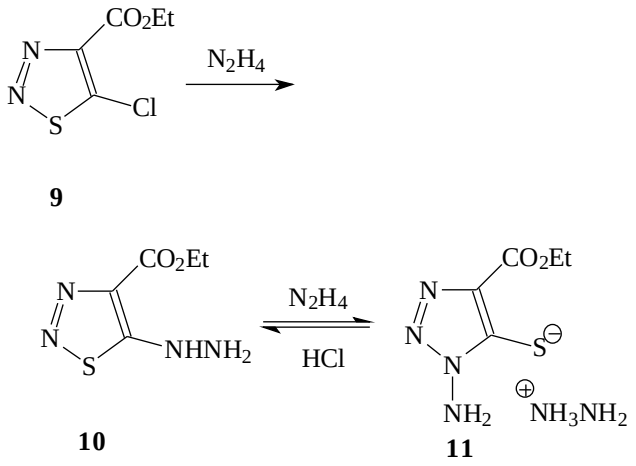
mercaptotriazoles **8** under the influence of bases, and the reverse reaction occurs in acidic solution (Scheme 2) [6].

5-Hydrazinothiadiazoles **10** are formed when the 5-chlorothiadiazole **9** is allowed to react with two equivalents of hydrazine hydrate [7]. However, with an excess of hydrazine hydrate the rearranged product **11** was isolated in high yield (Scheme 3). Acidification of *N*-aminotriazole **11** with hydrochloric acid yielded **10**, thus indicating the reversibility of the rearrangement.

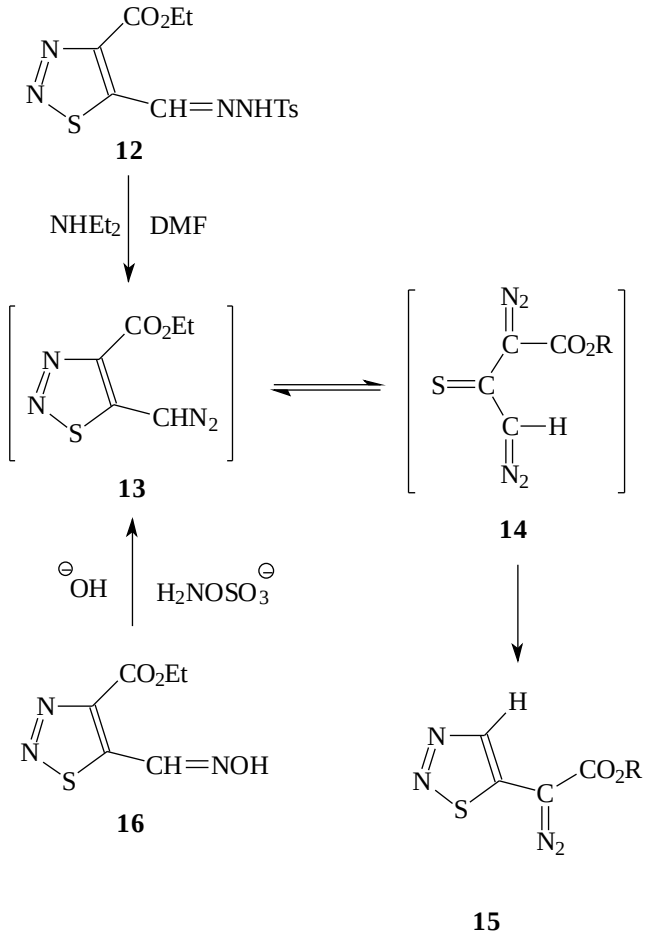
When the hydrazine function in **10** was replaced by a diazomethyl function (molecule **13**), a spontaneous rear-



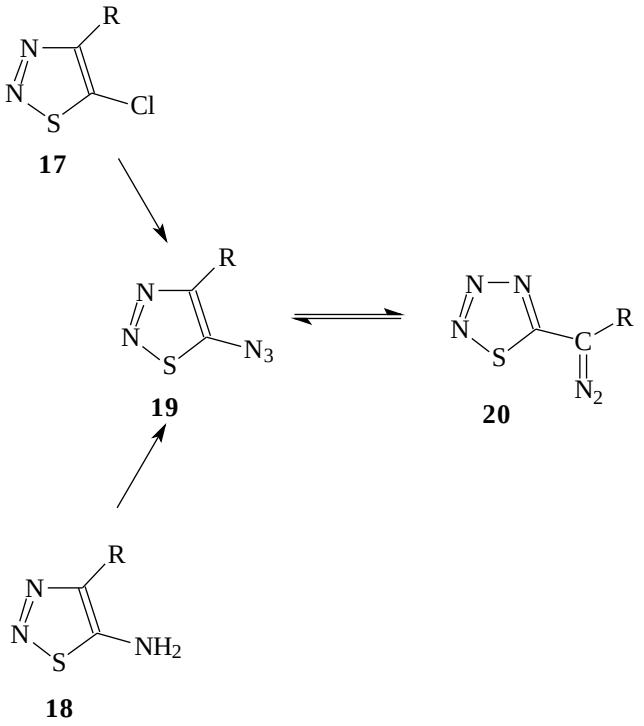
Scheme 2.



Scheme 3.

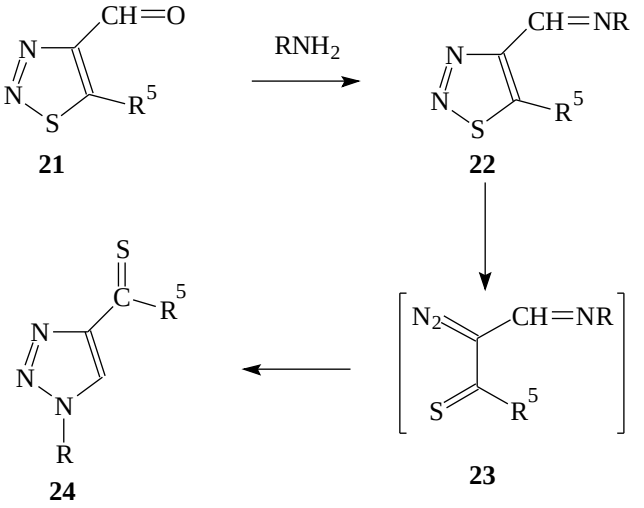


Scheme 4.

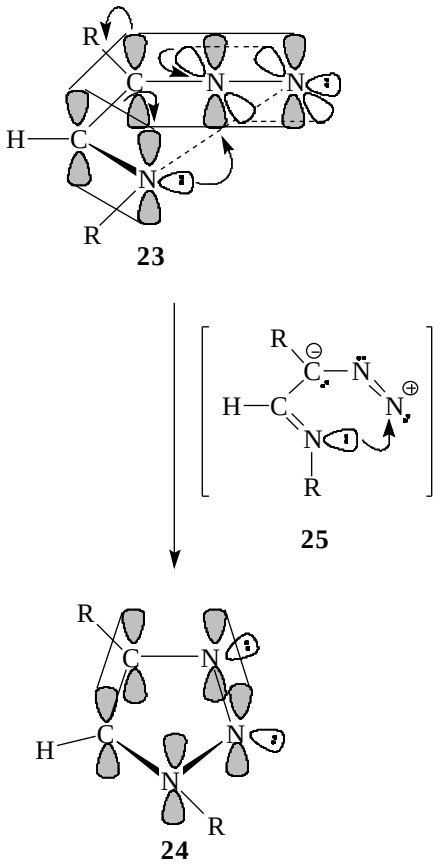


Scheme 5.

rangement resulted in the formation of the same 1,2,3-thiadiazole ring system with a different substitution pattern (a ring-degenerate rearrangement) [8]. Thus, tosylhydrazone **12** was subjected to the Bamford-Stevens reaction by treatment with diethylamine in dimethylformamide (DMF). Intermediate **14** has a thiocarbonyl function



Scheme 6.



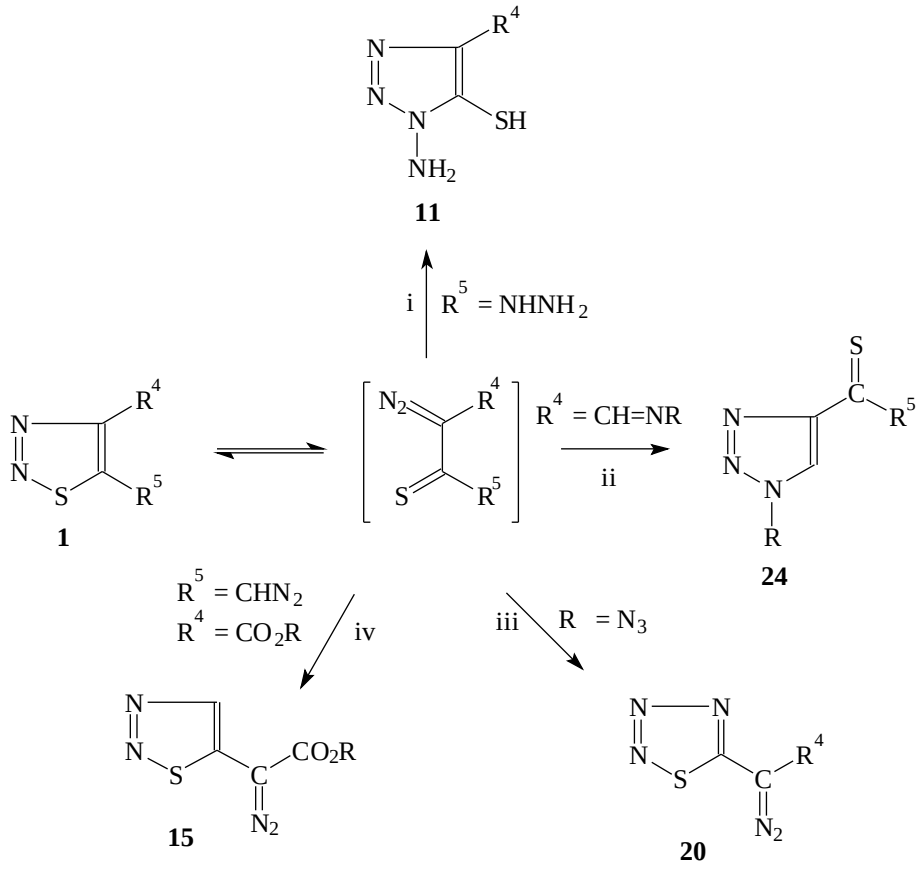
Scheme 7.

flanked by two different diazo groups and will close on the alternative side to obtain diazoester **15** (R = Et). Similarly, when the oxime **16** was treated with hydroxylamine *O*-sulphonic acid and base, the rearranged thiadiazole **15** could be isolated. Under the basic conditions required for this Forster reaction, the ester function was hydrolyzed to a carboxy group (R = H) (Scheme 4) [9].

5-Azidothiadiazoles **19**, prepared from 5-chlorothiadiazoles **17** or 5-aminothiadiazoles **18** are capable of undergoing a similar rearrangement to 5-diazomethyl substituted thiatriazoles **20** (Scheme 5). This transformation occurs spontaneously at 0 °C for R = ethoxycarbonyl or benzoyl, and not at all for R = hydrogen (even at 60 °C). When R = phenyl or anisyl, a mixture of **19** and **20** is obtained by diazotization of the corresponding 5-aminothiadiazoles **18** and treatment with azide anion [10].

4-(Substituted iminomethyl)thiadiazoles **22** which can be obtained from the corresponding aldehydes **21** and amines, rearrange to give the 4-thiocarbonyl-1,2,3-triazoles **24** (Scheme 6) [11]. This reaction occurs also when a 5-amino substituent is present [12].

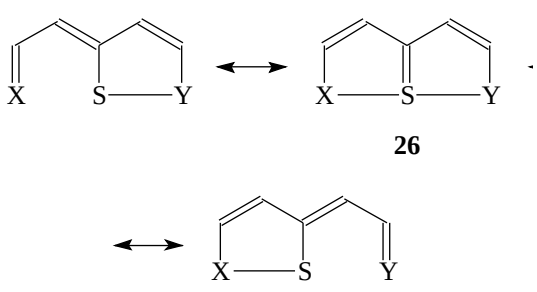
A prerequisite for **23** to undergo cyclization is the *cis*-relationship between the diazo function and the imine-nitrogen lone pair as shown in Scheme 7. Thus, the



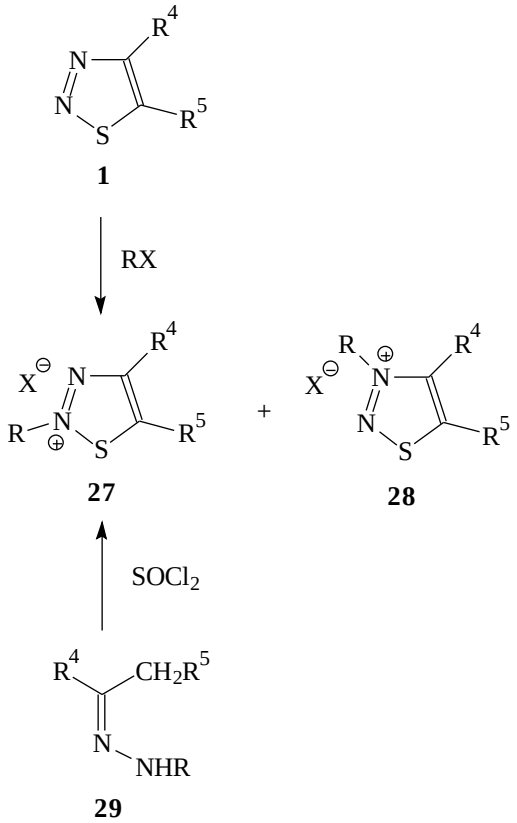
Scheme 8.

cyclization proceeds by a bending of the diazo function (transition state **25**), due to the formation of a lone electron pair on the central nitrogen atom. This is accompanied by a π-electron flow towards the imine function and the formation of a σ-bond at the expense of the lone pair on the imine nitrogen [13].

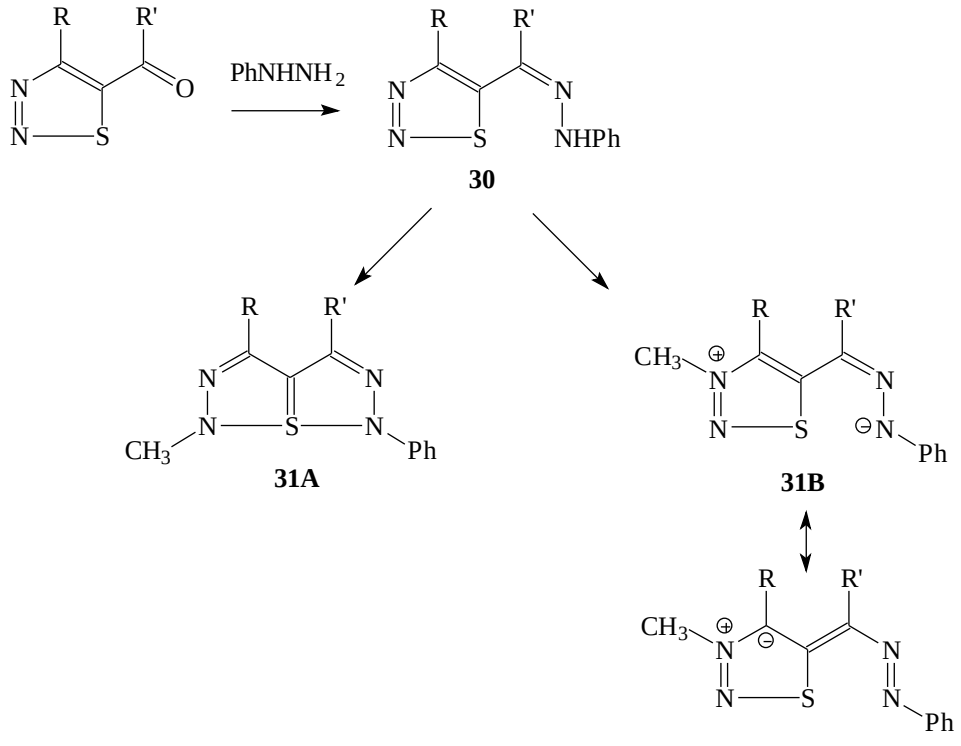
In summary, we have found four new types of rearrangements which are shown in Scheme 8. These are: (i) the base-induced rearrangement of 5-hydrazinothia-diazoles **10** into 1-amino-5-mercapto-1,2,3-triazoles **11**, (ii) the rearrangement of 4-imino-1,2,3-thiadiazoles **22** into 4-thiocarbonyl-1,2,3-triazoles **24**, (iii) the spontaneous rearrangement of



Scheme 9.



Scheme 10.



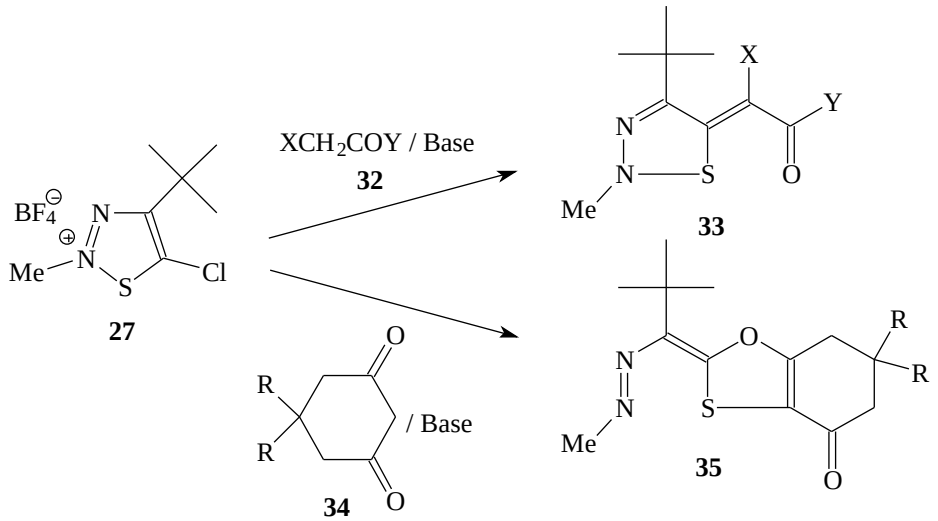
Scheme 11.

5-azido-1,2,3-thiadiazoles **19** into 5-diazoalkyl substituted 1,2,3,4-thiatriazoles **20** and (iv) the ring-degenerate rearrangement of 5-diazomethyl-1,2,3-thiadiazoles **13** into 2-(1,2,3-thiazol-5-yl)-diazoacetates **15** (Scheme 8).

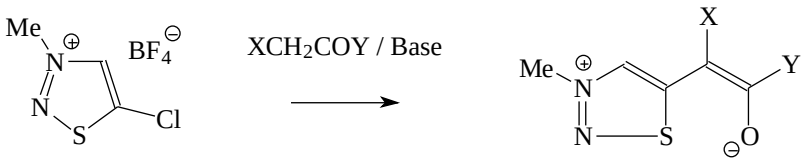
Synthesis of 6aλ⁴-Thiapentalenes

6aλ⁴-Thiapentalenes **26** are delocalized 10π-electron systems which are characterized by single bond/no bond resonance, represented by the canonical stuctures in Scheme 9. Representatives of **26** (X = Y = S) with a completely symmetrical substitution pattern, as well as the oxygen and nitrogen analogues (X, Y = O, NR) have been prepared and studied in detail by X-ray crystallography [14]. Extensions to tri-, tetra- and penta-azapentalenes were carried out in our laboratory [15].

It is known that 1,2,3-thiadiazoles **1** can be methylated at the *N*-2 and *N*-3 position (Scheme 10) [16]. When bulky substituents are present in the 4-position, the *N*-2 substituted regioisomer takes the upper hand. An alternative way of selectivity obtaining *N*-2 substituted thiadiazolium salts **27** is by the Hurd-Mori reaction of *N*-2 substituted α-methylene hydrazones **29** [17].



Scheme 12.



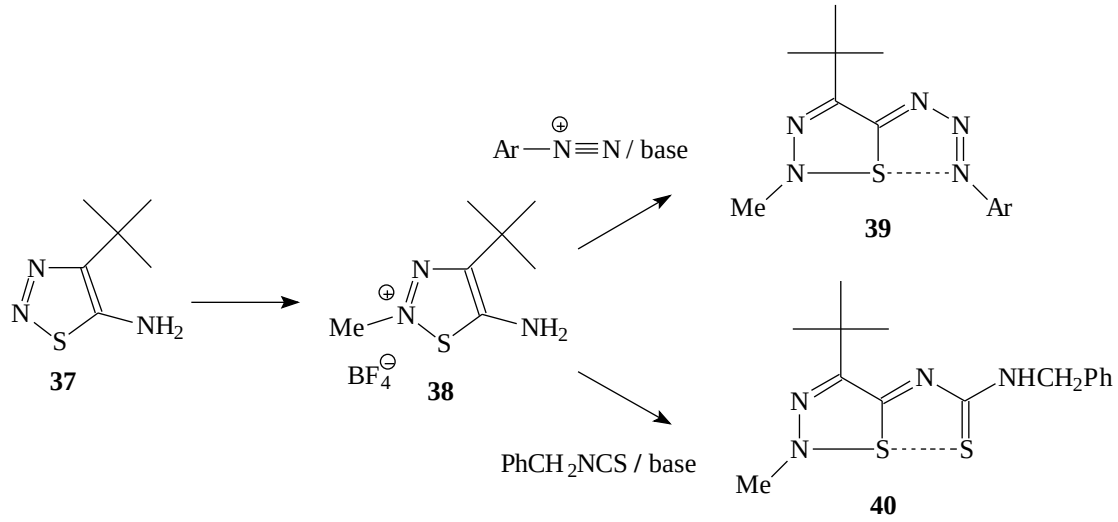
28 **36** **Scheme 13.**

Methylation of 1,2,3-thiadiazole-5-phenylhydrazones **30** gave a mixture of thiatetraazapentalenes **31A** and mesoionic compounds **31B** (Scheme 11) [18]. The thiapentalenic character of **31A** was confirmed by X-ray crystallography, showing a linear N-S···N arrangement with a short S···N distance [19]. Benzo-bridging (R,R' = C_6H_4) disfavours this S···N contact [20]. The S···N interaction is also weak for all the mesoionic compounds **31B**. Analoguously, 1,2,3-thiadiazole-5-oximes gave the corresponding oxathiatriazapentalenes and mesoionic compounds [18c, 21].

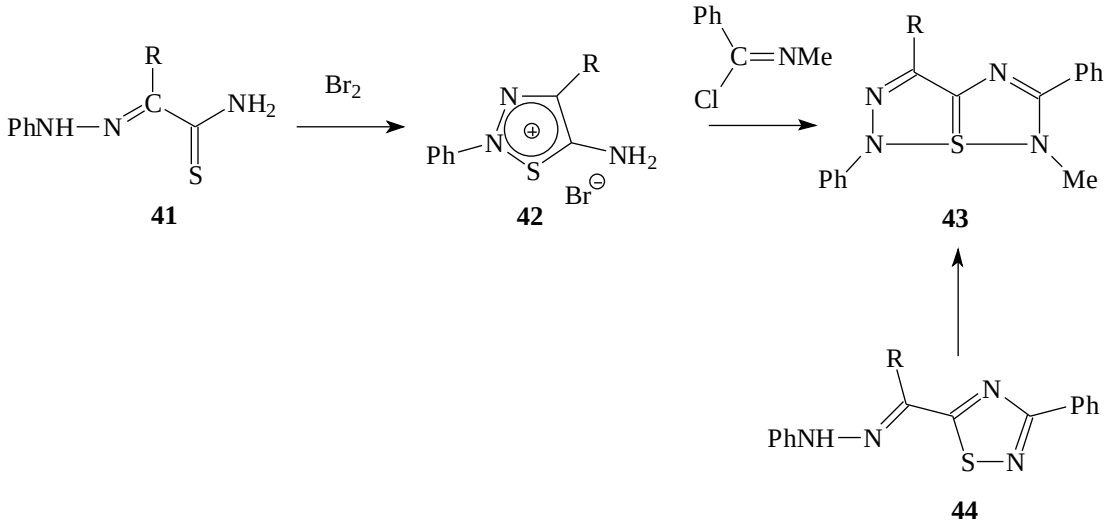
The reaction of activated methylene compounds **32** with 2-methyl-5-chloro-1,2,3-thiadiazolium salt **27** afforded oxathiadiazapentalenes **33** (Scheme 12). Cyclohexanediones **34** react differently with **27** to give rearranged oxathioles **35** [22].

Starting from the corresponding 3-methyl thiadiazolium salt **28** mesoionic compounds **36** were obtained (Scheme 13) [23].

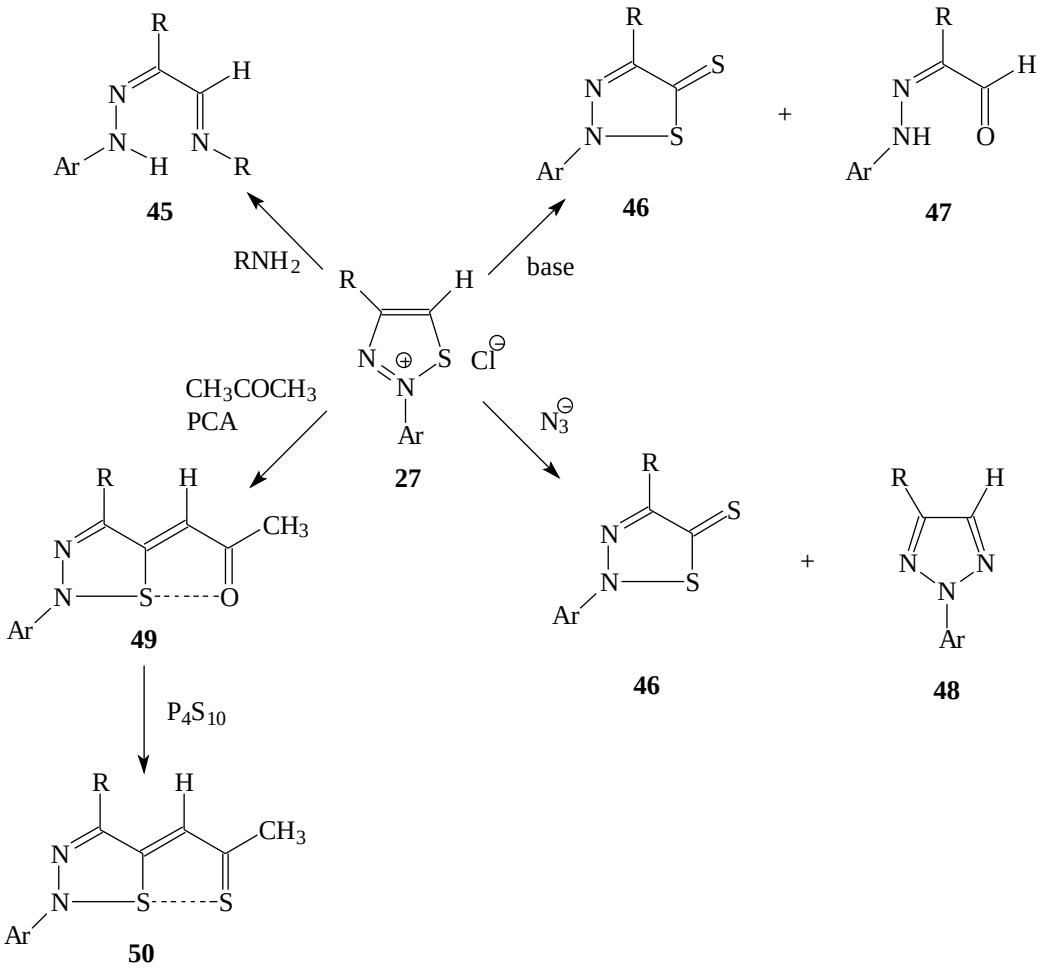
Recently, we have described the synthesis of 6aλ^4-thia-1,2,3,5,6-pentaazapentalenes **39**. A rational precursor for these compounds is 5-amino-4-*tert*-butyl thiadiazole **37**



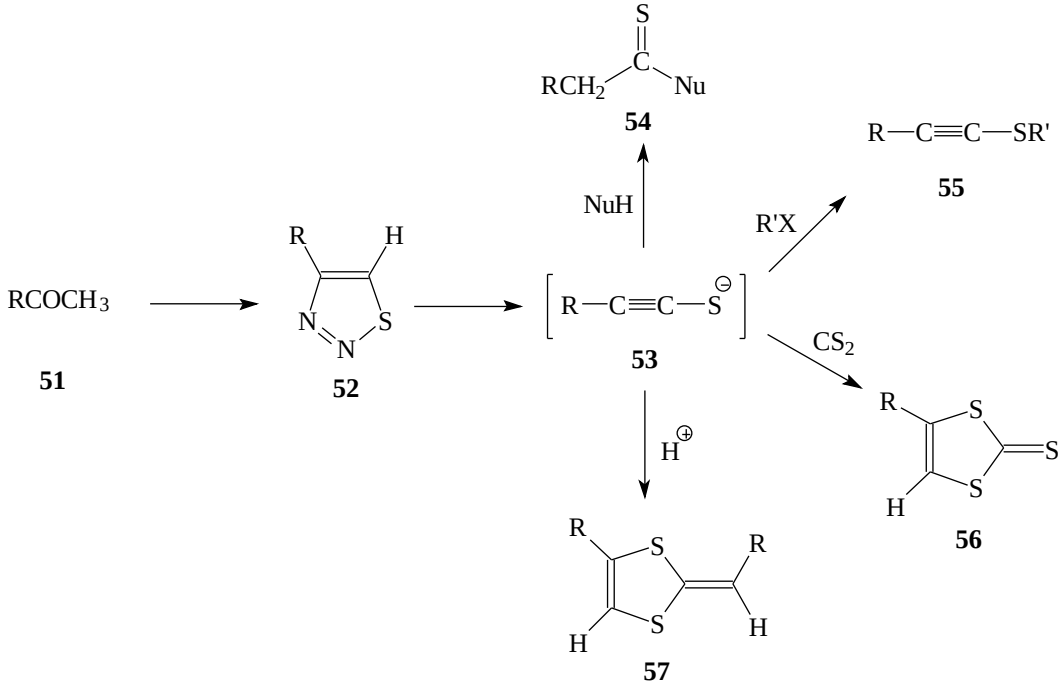
Scheme 14.



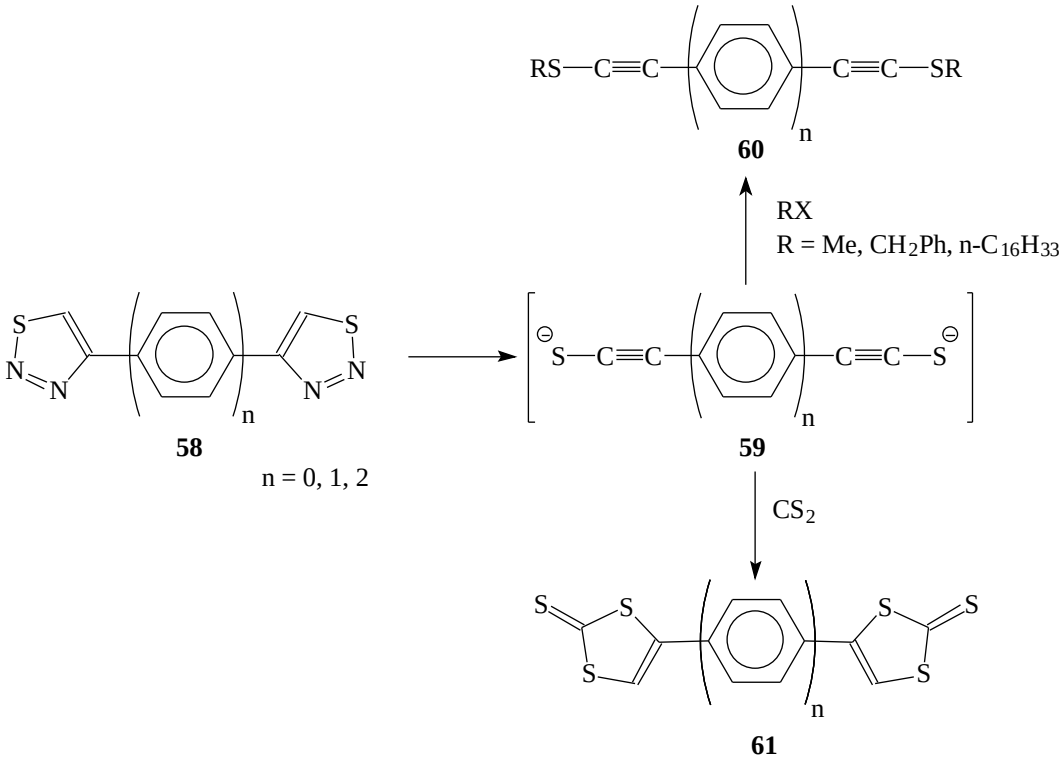
Scheme 15.



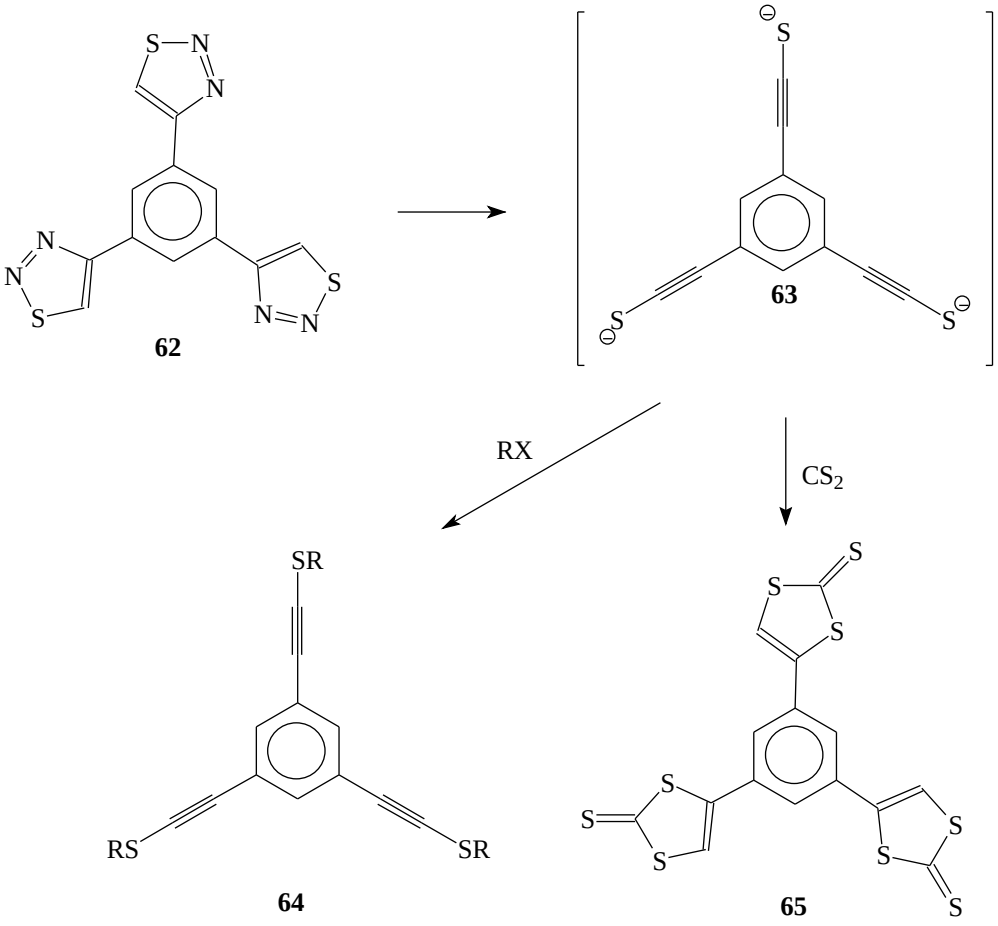
Scheme 16.



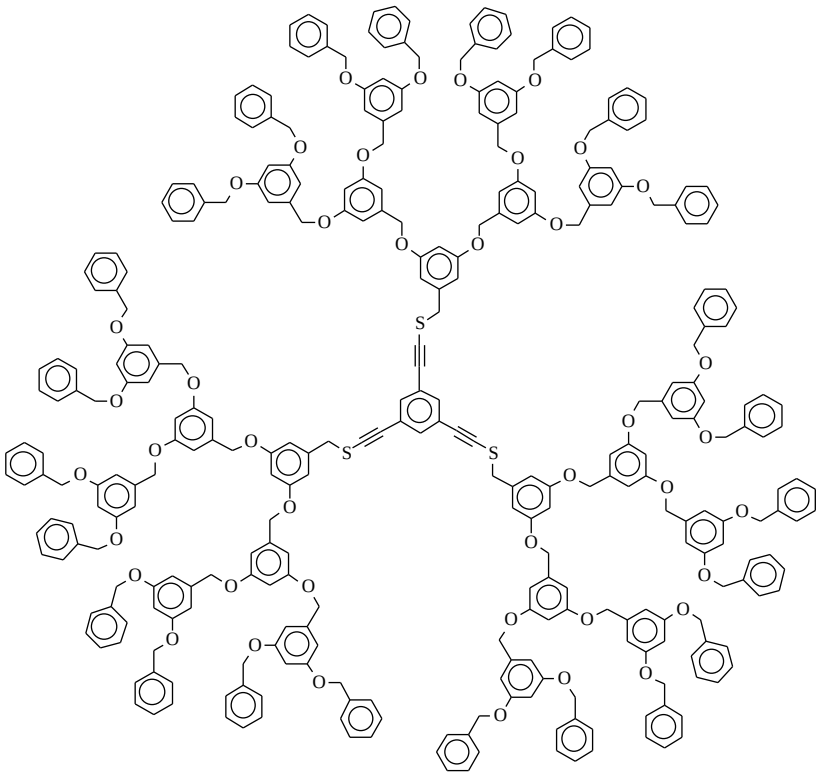
Scheme 17.



Scheme 18.



Scheme 19.



66

Fig. 1.

which is methylated to give the salt **38** (Scheme 14). This compound readily reacts with arenediazonium salts in the presence of base to furnish the yellow thiapentalenes **39** [24]. Dithiatriazapentalenes **40** can be obtained in the same way from the reaction of isothiocyanates with thiadiazolium salt **38** [25].

The thiadiazoline salt **42** was prepared by the known oxidative ringclosure [26] of the α-(phenylhydrazono) thioamide **41**. This salt afforded a 6aλ^4-thia-1,2,4,6-tetraazapentalene **43** by reaction with *N*-methylbenzimidoyl chloride in the presence of pyridine (Scheme 15) [27]. An alternative entry to this type of thiapentalene is given by the methylation of 5-benzoyl-1,2,4-thiadiazole phenylhydrazone **44** [28].

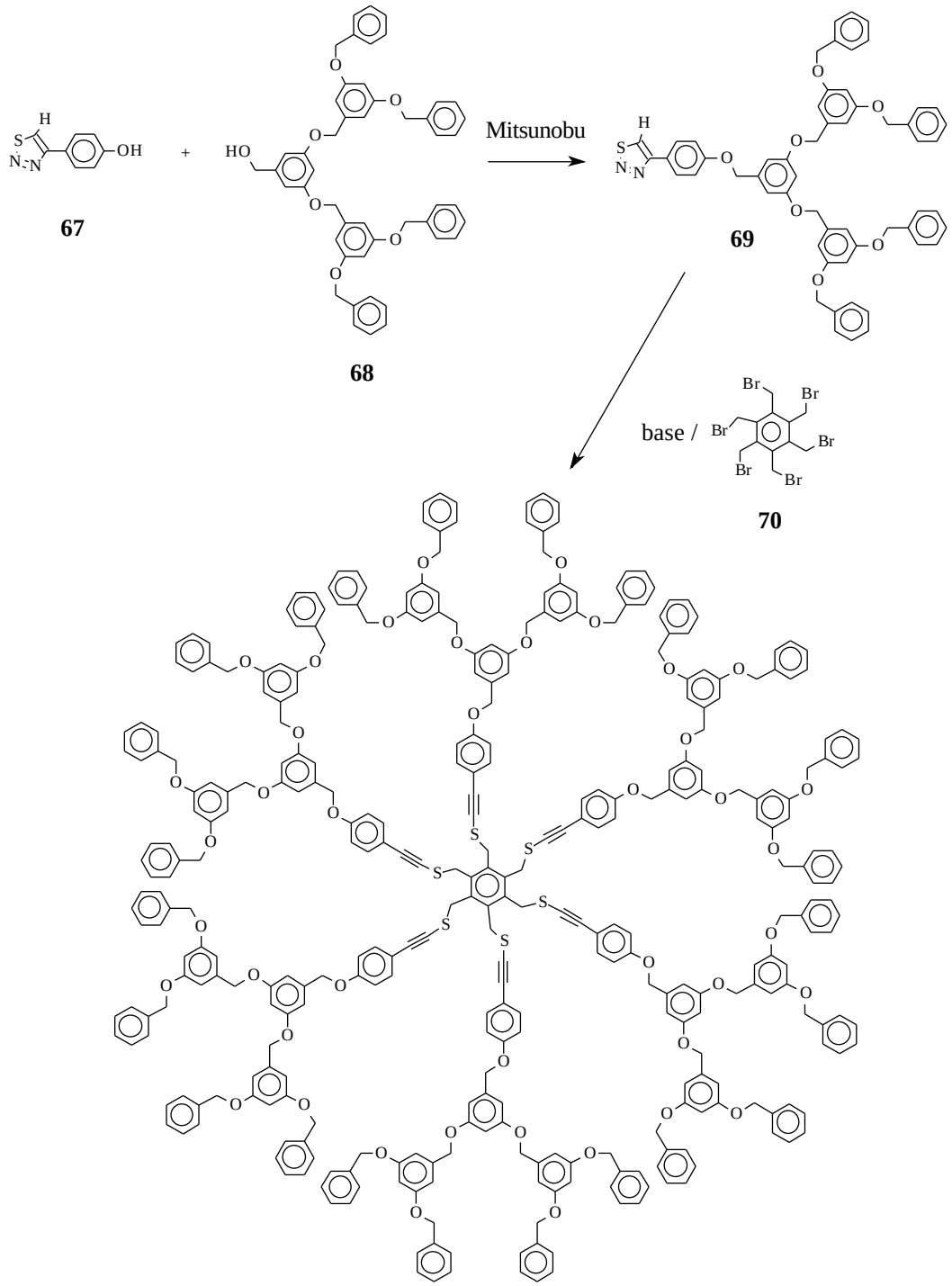
2-Aryl-1,2,3-thiadiazolium salts **27** were reacted with a series of primary amines and the desulfurized iminomethyl hydrazones **45** were formed (Scheme 16) [17]. Other bases, such as secondary and tertiary amines and alkoxide or hydroxide anions, reacted with **44** to give a mixture of thione **46** and the desulfurized aldehyde **47**. With azide anion thione **46** and rearranged (2*H*)-1,2,3-triazole **48** were formed. Furthermore, thiadiazolium salts **44** react with acetone under oxidative conditions to give oxathiadiazapentalenes **49**, which can be thionated with P_4S_{10} to dithiadiazapentalenes **50** [28].

Alkynethiolates as Synthons for Dendrimers

4-Monosubstituted 1,2,3-thiadiazoles **52** are readily available from methyl ketones **51** by the Hurd-Mori procedure. They decompose under strongly basic conditions with formation of alkynthiolates **53** (Scheme 17) [29]. The latter compounds are interesting synthons which can add nucleophiles with the formation of thiocarbonyl compounds **54**, and electrophiles to yield alkylated or acylated derivatives **55**, or ring-closed heterocycles **56**. Under the influence of a proton donor, a dimerisation to a dithiole derivative **57** occurs [30].

The bis- and tris(1,2,3-thiadiazol-4-yl) substituted compounds **58** and **62** were smoothly transformed to alkynethiolates **59** and **63** on treatment with base (NaH/DMSO or K*tert*-BuO/THF) (Scheme 18). These nucleophilic reagents were alkylated to give alkynesulfides **60** and **64**. On treatment of **59** and **63** with excess carbon disulfide the bis- and tris(1,3-dithiol-2-thiones) **61** and **65** precipitated. Unfortunately, these compounds were too insoluble to be characterized fully [31].

In view of the high reactivity of tristhiolate **63** we have evaluated its use as a core reagent in dendrimer synthesis. The Fréchet benzylic bromides of the first to third generation [32] combined readily with **63** to give dendrimers [33]. In Fig. 1, the third generation alkynesulfide dendrimer **66** is shown, which was obtained in 55% yield. 1,3,5-Tris-(1,2,3-thiadiazol-4-yl)benzene **62** is now commercially



67 **68** **69** **70** **71**

Scheme 20.

available (Acros Organics) [34]. The bisthiadiazoles **58** can be transformed in the same way to dendrimers with two-fold symmetry [35].

Alternatively, the 1,2,3-thiadiazole group could be attached to the focal point of the Fréchet dendrons by the Mitsunobu reaction of 4-(4-hydroxyphenyl)1,2,3-thiadiazole **67** and the benzylic alcohols **68**. The resulting thiadiazoles **69** could be cleaved to the nucleophilic alkynethiolate dendrons, which were combined with poly(bromomethyl)benzene core reagents to afford alkynesulfide dendrimers [36]. In Scheme 20, a dendrimer **71** with (hexakis)methyl benzene core **70**, and second generation alkynethiolate dendrons is depicted.

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