

C-ALKYLATION, ALKENYLATION, AND ARYLATION OF 1,2,5-THIADIAZOLES¹

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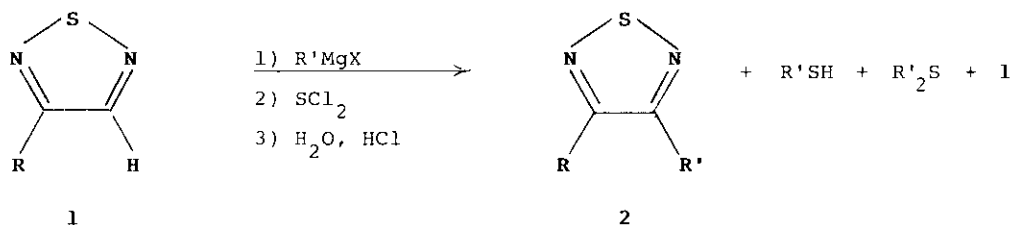
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Abstract - A new synthetic method of 1,2,5-thiadiazoles is reported, which, affording mono- or disubstituted derivatives by one pot procedure, clarifies unknown aspects of the 1,2,5-thiadiazole ring reactivity.

Previously some of us introduced the use of sulphur nitride S_4N_4 as a reagent for the synthesis of 1,2,5-thiadiazole ring from various substrates.²⁻⁶ This paper deals with both the clarification of new aspects of the 1,2,5-thiadiazole ring reactivity and a new unconventional synthetic method of 1,2,5-thiadiazole derivatives useful also for the preparation of compounds not easily obtainable by known procedures, which before any further development was exploited by some of us for the production of the wanted 3-vinyl-1,2,5-thiadiazole monomer.⁷ According to our findings, it is possible to transform the readily available unsubstituted 1,2,5-thiadiazole or its monosubstituted derivatives into other 1,2,5-thiadiazoles by substituting an hydrogen atom with an alkyl, alkenyl or aryl group. The reaction is carried out through one pot procedure by treating the substrate with a proper Grignard reagent, then with sulphur dichloride.



Iodide Grignard reagents are not recommended for their anomalous low yields, probably connected with redox reactions of the iodide ion. The comparison between the reactions of methylmagnesium iodide and methylmagnesium bromide with unsubstituted 1,2,5-thiadiazole confirms such observation.

Table 1 summarizes the examined reactions. Table 2 collects data regarding new 1,2,5-thiadiazoles.

Table 1. Substituted 1,2,5-Thiadiazoles prepared

R	R'-MgX	Prod- uct 2	Yield [%]	Product 1 Yield [%]
H	CH ₃ -MgBr	a	21	6
H	CH ₃ -MgI	a	7	13
H	C ₂ H ₅ -MgBr	b	30	11
H	Cyclohexyl-MgBr	c	38	3
H	C ₆ H ₅ -MgBr	d	60	4
H	1-Naphthyl-MgBr	e	55	7
H	4-Styryl-MgCl	f	27	6
H	CH ₂ =CH-MgCl	g	19	traces
CH ₃	CH ₃ -MgI	h	8	10
CH ₃	C ₆ H ₅ -MgBr	i	31	11
CH ₃	1-Naphthyl-MgBr	l	42	11
CH ₃	4-Styryl-MgCl	m	23	7
CH ₃	CH ₂ =CH-MgCl	n	18	2
C ₆ H ₅	CH ₃ -MgI	i	10	10
C ₆ H ₅	C ₆ H ₅ -MgBr	o	18	29
C ₆ H ₅	CH ₂ =CH-MgCl	p	23	25

Besides product 2, the reaction affords thiol and thioether together with 1 which does not derive from an incomplete conversion of the reagents, but it is regenerated after sulphur dichloride addition. No traces of 1 are found in fact if, after treatment with Grignard reagent without addition of sulphur dichloride, the reaction mixture is hydrolyzed.

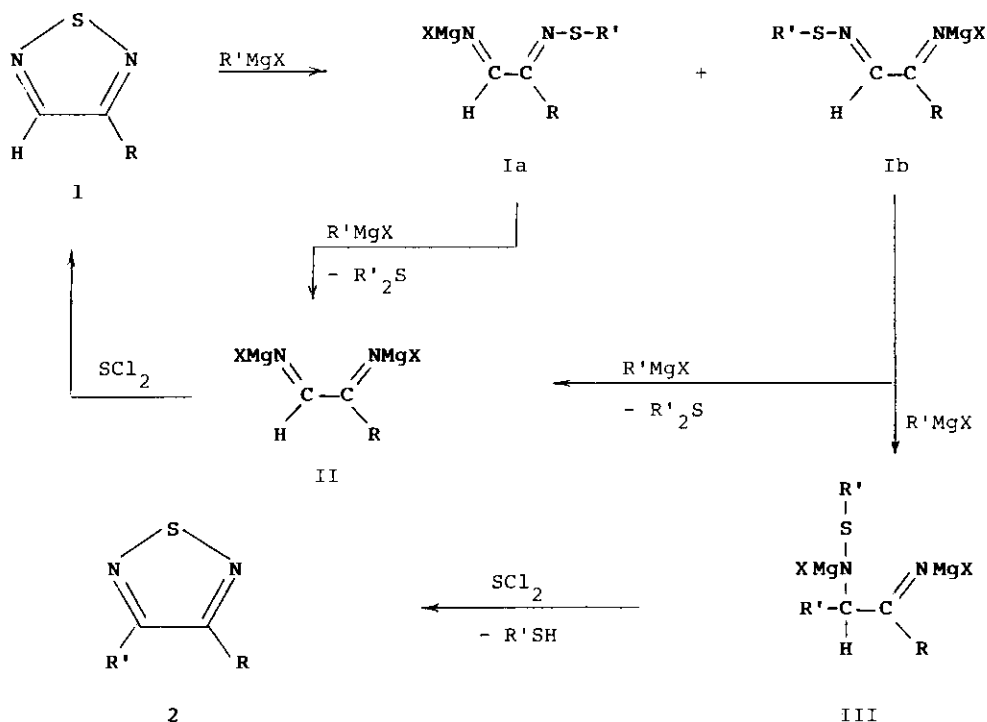
Further experimental observations have shown that with Grignard reagents liable to transfer hydride ions from the β-position, yields of 2 drop and those of 1 increase, while alkene and thiol are formed.

Yields in regenerated 1, even if not very significant for practical purposes, are

interesting for the comprehension of the reaction, in connection with substrate and Grignard reagents effects.

It is also interesting to note that no hydrocarbon R'H is formed from the Grignard reagent before the addition of sulphur dichloride, according to the absence of acidic hydrogens in the intermediate molecules. Careful examination of the unsubstituted 1,2,5-thiadiazole reactions with vinylmagnesium chloride and with phenylmagnesium bromide excluded the production of ethene or benzene respectively.

The reaction mechanism undoubtedly involves ring opening and new cyclizations. In analogy to what has been previously found about the cleavage of disubstituted 1,2,5-thiadiazoles and 1,2,5-selenadiazoles by Grignard reagents or lithium alkyls,⁸ the initial step probably corresponds to a nucleophilic attack at the sulphur atom of substrate 1 with formation of the intermediates Ia and Ib which are coincident when R = H and are liable to further attacks by the nucleophile at different sites.



Both Ia and Ib may be attacked at the sulphur atom forming thioether, which is recovered from the reaction mixture, and magnesium salt of 1,2-diimine II, which afford 1 by treatment with sulphur dichloride. Furthermore Ib may be attacked at the carbon atom of the sulphenimine group with formation of the magnesium salt III in analogy to what is known for other sulphenimines with organolithium re-

agents.⁹ With sulphur dichloride the salt III undergoes cyclization followed by aromatization through elimination of thiol, which is recovered from the reaction mixture. The elimination of thiol before the cyclization seems unlikely because in such case a third molecule of Grignard reagent would salificate the thiol producing the corresponding hydrocarbon, in opposition to the reported experimental observations. An eventual nucleophilic attack at the carbon atom of the sulphenimine group of Ia cannot be excluded, but in any case it would not be useful for further transformation into 1,2,5-thiadiazoles. Reducing Grignard reagents also form the intermediates Ia and Ib, but the second nucleophilic attack prevailingly inserts an hydrogen atom affording thiol and avoiding the formation of products useful for the preparation of 2.

Table 2. Physical and Spectral Data of New 1,2,5-Thiadiazoles 2 prepared.

2	R	R'	mp bp	[°C] or [°C]/torr	MS, m/e M ⁺ (rel. int.%)	IR* ν[cm ⁻¹]	¹ H-NMR δ[ppm]
b	H	C ₂ H ₅	40.5/7		114 (52)	526, 780, 826	8.41(s, 1H); 2.99(q, 2H); 1.39(t, 3H).
c	H	Cyclohexyl	oil		168 (15)	520, 785, 832	8.42(s, 1H); 3.05-2.95(m, 1H); 2.10-1.22(m, 10H).
e	H	1-Naphthyl	59.5-60		212 (100)	510, 786, 841	8.87(s, 1H); 8.40-8.30(m, 1H); 8.03-7.52(m, 6H).
f	H	4-Styryl	43.5		188 (100)	519, 790, 840	8.90(s, 1H); 7.95(dd, 2H); 7.53(dd, 2H); 6.76(q, 1H); 5.85(dd, 1H); 5.35(dd, 1H).
l	CH ₃	1-Naphthyl	117-118		226 (100)	515, 778, 830	8.10-7.92(m, 1H); 7.72-7.52(m, 6H); 2.48(s, 3H).
m	CH ₃	4-Styryl	16-17		202 (96)	545, 796, 840	7.71(dd, 2H); 7.53(dd, 2H); 6.77(q, 1H); 5.85(dd, 1H); 5.63(dd, 1H); 2.73(s, 3H).
p	C ₆ H ₅	CH ₂ =CH	oil		188 (48)	523, 774, 836	7.67-7.48(m, 5H); 6.94(q, 1H); 6.33(dd, 1H); 5.62(dd, 1H).

* The reported bands are tentatively assigned to the ring on the basis of a comparison with the IR and Raman spectra of 1,2,5-thiadiazole.¹⁰

EXPERIMENTAL

Melting points were determined with a Reichert Thermovar apparatus and are uncorrected. The Mass spectra were determined with a Hewlett Packard 5995A Gas/Mass spectrometer operating at 70 eV. The I.R. spectra in KBr pellets or film were recorded on a Perkin Elmer 1330 spectrophotometer. The $^1\text{H-N.M.R.}$ spectra in CDCl_3 (TMS int.) were measured on a Bruker 300 spectrometer. The microanalyses of all the new 1,2,5-thiadiazoles prepared were in satisfactory agreement with the calculated values.

Substituted 1,2,5-Thiadiazoles (2) ; General Procedure:

The reaction components are used in the molar ratio of **1** : Grignard reagent : $\text{SCl}_2 = 1 : 3.1 : 1.8$.

A 0.4 molar solution of **1** in ether is added dropwise at $-40\text{ }^\circ\text{C}$ under nitrogen to a stirred solution of Grignard reagent ($\approx 2\text{M}$) in ether, or ether/tetrahydrofuran (1:1) for vinylmagnesium chloride and 4-styrylmagnesium chloride. The mixture is stirred at $-40\text{ }^\circ\text{C}$ for 2 h then it is treated dropwise with a solution of commercial SCl_2 ($\approx 0.7\text{M}$) in ether. At the end of this addition the cooling bath is removed and stirring is continued for 3 h. The mixture is then treated with water ($\approx 50\text{ ml}$), acidified with a few drops of hydrochloric acid, saturated with ammonium sulphate, extracted with ether and dried over anhydrous sodium sulphate. After removal of the solvent, the residue is distilled or chromatographed as follows: **2a**,⁵ **2b**, **2g**,¹¹ **2h**,⁵ and **2n**¹² are obtained by distillation and purified by careful rectification at reduced pressure, **2c** is obtained by distillation and purified by preparative gas-chromatography on PPG columns, **2d**,² **2e**, **2f**, **2i**,¹³ **2l**, **2m**, **2o**,² and **2p** are separated by column-chromatography on silica gel using petrol ($40\text{-}70\text{ }^\circ\text{C}$) - benzene mixtures as an eluent and purified, with the exception of **2p**, by crystallization from ether at low temperature.

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