NEW SYNTHESIS OF 1,2,5-SELENADIAZOLES

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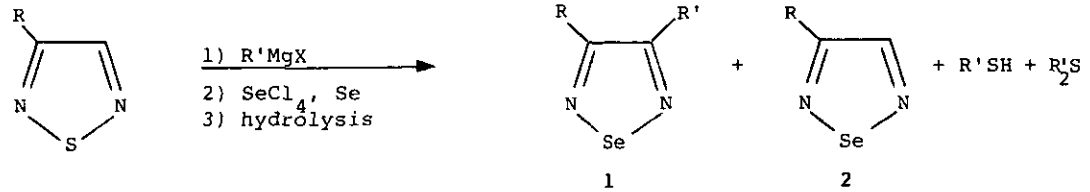
Abstract - A new synthesis of 1,2,5-selenadiazoles which starts from unsubstituted or monosubstituted 1,2,5-thiadiazoles and Grignard reagents is described and the mechanism of the reaction discussed.

Several years ago one of us developped a method for the synthesis of 1,2,5-selenadiazoles[1] which is still the only one suitable for general applications.

The present paper deals with a new method of synthesis of 1,2,5-selenadiazoles which does not necessitate such reagents with the whole preformed carbon skeleton as required in the previous one and allows the preparation also of derivatives not easily obtainable by known procedures.

This method, which originates from our findings on the reactivity of 1,2,5-thiadiazoles,[2,3] uses these compounds in the unsubstituted or monosubstituted form as starting materials affording monosubstituted or disubstituted products respectively. The easily accessible 1,2,5-thiadiazole or its monosubstituted derivatives[4,5] are transformed into 1,2,5-selenadiazoles with the *contemporaneous substitution of a* hydrogen atom by an alkyl or aryl group through one pot procedure.

The method affords also variable quantities of 1,2,5-selenadiazoles with the same carbon structure as the starting 1,2,5-thiadiazoles showing that the reaction partially takes place without incorporation of alkyl or aryl groups. The reaction is carried out by treating the thiadiazolic substrate first with a proper Grignard reagent then with a homogenized mixture of selenium(IV) chloride and elemental selenium corresponding to selenium(I) chloride (Scheme 1).



Scheme 1

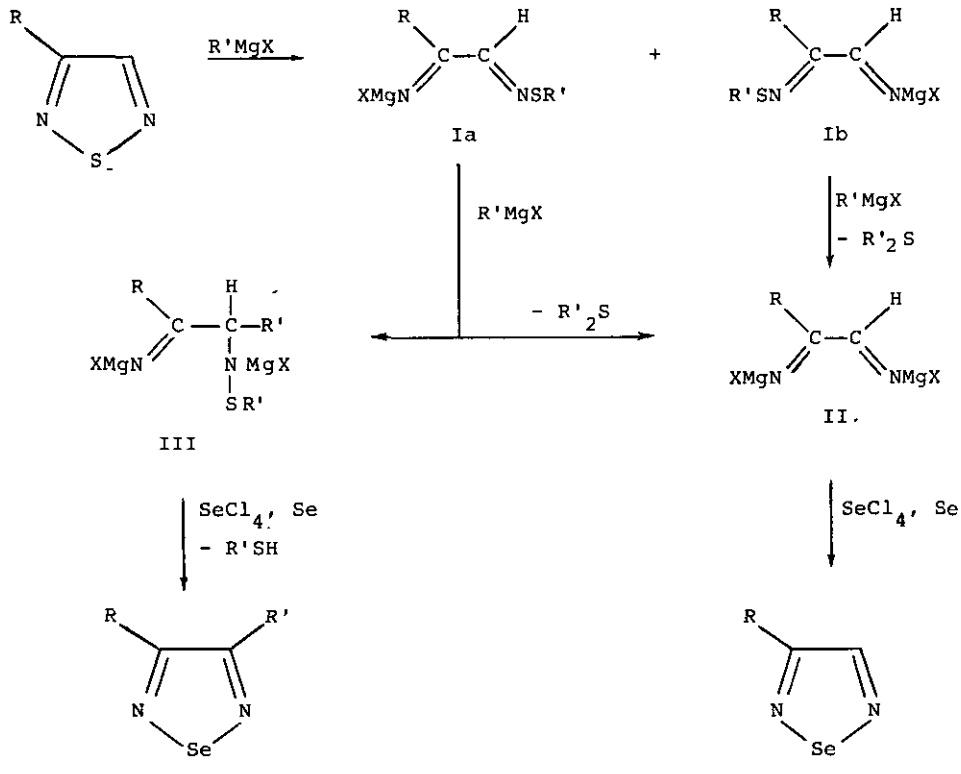
Table 1 summarizes the results of the examined reactions. Table 2 collects data regarding new 1,2,5-selenadiazoles.

Table 1. 1,2,5-Selenadiazoles

R	R'-MgX	Product **1** Yield %	Product **2** Yield %
H	C_2H_5-MgBr	41	6
H	C_2H_5-MgI	40	11
H	Cyclohexyl-MgBr	47	4
H	C_6H_5-MgBr	56	2
H	p-Tolyl-MgBr	48	4
H	1-Naphthyl-MgBr	66	traces
H	2-Thienyl-MgCl	8	-
CH_3	Cyclohexyl-MgBr	34	17
CH_3	C_6H_5-MgBr	34	24
CH_3	p-Tolyl-MgBr	34	15
CH_3	1-Naphthyl-MgBr	38	28
C_6H_5	CH_3-MgI	31	52
C_6H_5	C_2H_5-MgBr	16	36

The reaction course parallels what has been found in the C-alkylation, alkenylation and arylation of 1,2,5-thiadiazoles,[3] therefore the previous and present results integrate the interpretation of the reaction mechanism. The observed production of compound **2**, which does not incorporate the organic residue of the Grignard reagent, strengthens the hypothesis of a mechanism involving an initial nucleophilic attack at the thiadiazole sulfur atom followed by different path evolutions. The attack causes the insertion of the Grignard reagent into a S-N bond with cleavage of the ring and formation of the intermediates Ia and Ib depending on the orientation of the insertion. In the case of the unsubstituted 1,2,5-thiadiazole the reaction affords only one intermediate (R=H) whose rectivity corresponds to Ia, containing the sulphenimine system connected to a CH group. Ia offers to the Grignard reagent two possible attack sites, the sulfur atom with formation of thioether and magnesium salt of 1,2-diimine II, or the carbon atom with formation of III, in analogy

to other sulphenimines.[6] Any nucleophilic attack at the hydrogen atom of the starting 1,2,5-thiadiazole or intermediates may be excluded because careful examination of the reactions has shown that no hydrocarbon R'H was formed from the Grignard reagent before the addition of selenium chloride. By treatment with selenium chloride, II gives the 1,2,5-selenadiazoles **2** analogous to the initial 1,2,5-thiadiazoles, while III affords the R'-substituted 1,2,5-selenadiazole **1** through cyclization and aromatization by elimination of thiol. The intermediate Ib, characterized by a C-R substituted sulphenimine system derived from monosubstituted 1,2,5-thiadiazoles, undergoes nucleophilic attack at the sulphur atom with formation of II precursor only of 1,2,5-selenadiazoles **2**, in agreement with the higher yields of product **2** generally observed when R ≠ H (Table 1). A nucleophilic attack at the carbon atom of the sulphenimine system of Ib to give a product analogous to III cannot be excluded, but such an attack would not be useful for the subsequent production of 1,2,5-selenadiazoles.



It is interesting to note that the iodide Grignard reagents reacted as well as the bromides otherwise than for the synthesis of 1,2,5-thiadiazoles,[3] owing to the different behaviour of Se(I) chloride and S(II) chloride towards redox reactions with iodide ion.

Moreover 2-thienylmagnesium chloride resulted poorly reactive and the reported 8% yield in product 1 was obtained under prolonged refluxing condition.

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

R	R'	mp [°C]	Mass[a] m/z M^+ (rel. int.)	IR[b] ν[cm^{-1}]	^{1}H-NMR δ[ppm]
H	C_2H_5	oil	162 (67)	741, 716, 468, 446	1.42 (t, 3H), 3.04 (q, 2H), 9.16 (s, 1H)
H	Cyclohexyl	63.5-64.5	216 (18)	736, 479, 438	1.02-2.30 (m, 10H), 2.81-3.25 (m, 1H), 9.20 (s, 1H)
H	p-Tolyl	116	224 (54)	741, 710, 496, 444	2.42 (s, 3H), 7.33 (dd, 2H), 7.93 (dd, 2H), 9.68 (s, 1H)
H	1-Naphthyl	110	260 (14)	745, 469, 444	7.44-8.15 (m, 6H), 8.18-8.42 (m, 1H), 9.63 (s, 1H)
H	2-Thienyl	91-92	216 (18)	752, 707, 487, 437	7.12-7.36 (m, 1H), 7.56 (dd, 1H), 7.72 (dd, 1H), 9.64 (s, 1H)
CH_3	Cyclohexyl	52-54	230 (43)	735, 712, 483, 428	1.11-2.01 (m, 10H), 2.58 (s, 3H), 2.74-3.08 (m, 1H)
CH_3	p-Tolyl	69-70	238 (26)	760, 718, 476, 412	2.44 (s, 3H), 2.66 (s, 3H), 7.33 (dd, 2H), 7.57 (dd, 2H)
CH_3	1-Naphthyl	117-118	274 (8)	755, 716, 490, 430	2.40 (s, 3H), 7.41-7.65 (m, 6H), 7.87-8.07 (m, 1H)
C_6H_5	C_2H_5	58-59.5	238 (50)	744, 710, 503, 460	1.36 (t, 3H), 3.01 (q, 2H), 7.45-7.68 (m, 3H), 7.98-8.15 (m, 2H)

[a] The values are referred to the selenium isotope 80.

[b] 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-selenadiazole.[7]

EXPERIMENTAL

Melting points were determined with a Reichert Thermovar apparatus and are uncorrected. Ir spectra were recorded on a Perkin Elmer 1330 spectrophotometer as KBr pellets or films. ^{1}H-nmr spectra in $CDCl_3$ (TMS as int. ref.) were measured on a Varian XL 100 spectrometer. Mass spectra were determined with a Hewlett Packard 5995A Gas/Mass spectrometer operating at 70 eV. Microanalyses of all the new 1,2,5-selenadiazoles prepared were in satisfactory agreement with the calculated values (C $\pm$ 0.23, H $\pm$ 0.16, N $\pm$ 0.25).

1,2,5-Selenadiazoles; General procedure:

Reagents were used in the molar ratio of 1,2,5-thiadiazole compound : Grignard reagent : selenium(I) chloride = 1 : 3 : 6.5. The selenium(I) chloride was prepared immediately before use by heating to homogenization selenium(IV) chloride and elemental selenium in the 1:3 molar ratio.

A 0.3 molar solution of the 1,2,5-thiadiazole compound in ether was added dropwise at -40 °C under nitrogen to a solution of Grignard reagent (≈ 1.5M) in ether and stirred for 2 h at the same temperature. For the reaction with 2-thienylmagnesium chloride the addition was made at room temperature to a solution of the Grignard reagent in tetrahydrofuran and the stirring was carried out under reflux. The mixture was treated dropwise with selenium(I) chloride, then the cooling bath was removed and stirring was continued for 3 h. The mixture was treated with water (≈50 ml), filtered to remove the elemental selenium formed, saturated with ammonium sulphate, extracted with ether and dried over anhydrous sodium sulphate. After removal of the solvent the residue was distilled under vacuum at low temperature. For the reactions between 1,2,5-thiadiazole and ethylmagnesium bromide or iodide, both the products **1** and **2** were contained in the distillate and were separated by column-chromatography on Merck 60 silica gel with mixtures of petrol (40-70 °C)-benzene as eluent. Product **1** was further purified by crystallization from ether at low temperature. For all the other reactions product **2** was collected in the distillate while product **1** was recovered from the residue by column-chromatography under the same conditions as indicated above and further purified by crystallization from ethanol. Exceptions to this separation and purification procedure were: *3-(4-tolyl)-1,2,5-selenadiazole* directly crystallized from ethanol; *3-(2-thienyl)-1,2,5-selenadiazole* separated by preparative layer chromatography on Merck PF_{254} silica gel with petrol (40-70 °C)-benzene (40:60) as eluent and purified by crystallization from ether; *3-cyclohexyl-4-methyl-1,2,5-selenadiazole* crystallized from ether after separation by column-chromatography; *3-methyl-4-phenyl-1,2,5-selenadiazole*[8] and *3-ethyl-4-phenyl-1,2,5-selenadiazole* obtained by HPLC on Waters Porasyl b column with toluene as eluent.

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REFERENCES

1. V. Bertini, *Angew. Chem.*, 1967, **79**, 530; *Angew. Chem. Int. Ed.*, 1967, **6**, 563; *Gazz. Chim. Ital.*, 1967, **97**, 1870.
2. V. Bertini, A. De Munno, A. Menconi, and A. Fissi, *J. Org. Chem.*, 1974, **39**, 2294.
3. A. De Munno, V. Bertini, and N. Picci, *Heterocycles*, 1986, **24**, 1131.
4. V. Bertini and P.Pino, *Angew. Chem.*, 1966, **78**, 493; *Angew. Chem. Int. Ed.*, 1966, **5**, 514; V. Bertini and A. De Munno, *Gazz. Chim. Ital.*, 1971, **101**, 259.
5. L. M. Weinstock, P. Davis, B. Handelsman, and R. Tull, *J. Org. Chem.*, 1967, **32**, 2823.
6. F. A. Davis and P. A. Mancinelli, *J. Org. Chem.*,1977, **42**, 398; 1978, **43**, 1797.
7. E. Benedetti and V. Bertini, *Spectrochimica Acta*, 1968, **24A**, 57.
8. V. Bertini, A. De Munno, and G. Denti, *Chim. e Ind.*, 1972, **54**, 571.

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