1,2,3-Selenadiazole and Its Derivatives

IRADJ LALEZARI AND ABBAS SHAFIEE

Department of Organic Chemistry, Faculty of Pharmacy, University of Tehran, Tehran, Iran

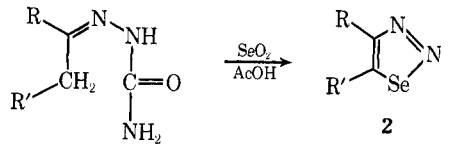
MOHAMED YALPANI*

Department of Chemistry, Arya Mehr University of Technology, Tehran, Iran

Received November 4, 1970

Alkyl or aryl aldehyde and ketone semicarbazones can be converted to 1,2,3-selenadiazoles by oxidation with selenium dioxide. The facile transformation of these new compounds to acetylenes as well as their spectral properties is described.

In our recent communications[1,2] we reported the synthesis and the pyrolysis of 4-aryl-1,2,3-selenadiazoles. Although the heterocyclic system of 1,2,3-thiadiazoles has been known for some time,[3] our report presented the first general route to the selenium heterocyclic system. We have now extended our work to the synthesis of several 4,5-di- and monosubstituted 1,2,3-selenadiazoles.



1 2

Unsubstituted 1,2,3-selenadiazole (**2**, R = R′ = H) was obtained in 25% yield by the reaction of acetaldehyde semicarbazone (**1**, R = R′ = H) with selenium dioxide in cold glacial acetic acid. It is a colorless pungent-smelling liquid boiling at 55° (16 mm). It is quite stable in the dark at 0° but decomposes slowly when exposed to sunlight at room temperature.

5-Alkyl or aryl derivatives of **2** were obtained by using other aldehydes as starting materials. For the formation of 4-alkyl derivatives, acetone or other methyl ketones which permit cyclization on one side only should be used, *e.g.*, iso- or *tert*-butyl methyl ketones. All other ketones lead to the formation of 4,5-disubstituted derivatives of **2**. A selection of the selenadiazoles obtained in this way is listed in Table I.

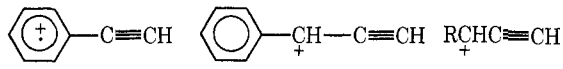
The direction of ring closure, when both α positions are available for oxidation, depends on the effect the substituents have on the acidity of the α hydrogens. Thus electron-attracting substituents such as chlorine or phenyl on acetone, which increase the acidity of the methylene hydrogens relative to the methyl groups, lead to preferential ring closure on the methylene side. As expected in ethyl methyl ketone where the effect is reversed, the preferential site of attack by selenium dioxide is on the methyl group. Similarly, substituents on phenylacetone semicarbazone accentuate this effect. Thus *p*-fluorophenylacetone produces more of the disubstituted selenadiazole than either unsubstituted *p*-methyl- or *p*-methoxyphenylacetone. Table II gives the relative yields of di- and monosubstituted selenadiazoles from this type of ketone.

Unlike the thiadiazole ring system which is thermally quite stable,[4] 5-aryl or alkyl as well as disubstituted selenadiazoles like their 4-aryl-substituted derivatives give the corresponding acetylenes when pyrolyzed under the conditions reported previously.[2] While the yield of acetylenes from the selenadiazoles is very high, the overall yields from the starting alkyl ketone or aldehyde semicarbazone is considerably lower than from the aralkyl ketone semicarbazones.

In contrast to their thermal lability, some of the selenadiazoles studied were rather inert to attack by reactants such as acids or bases, *e.g.*, 4-methyl-1,2,3-selenadiazole-5-carboxylic acid ethyl ester (**2**, R = CH_3; R′ = COOEt) which could be smoothly hydrolyzed to the carboxylic acid which in turn was reconverted to the ester *via* its acid chloride by the reaction with thionyl chloride and alcohol.

It was interesting to observe that in keeping with the pyrolysis results, in each case the fragmentation patterns in the mass spectra of these compounds were in accordance with the formation of acetylenes. The first step in the fragmentation of the selenadiazoles is the loss of N_2 followed by the formation of the acetylene.

The abundance of the acetylenic ion in the mass spectra appears to depend on the nature of the R group of the particular selenadiazoles studied; *e.g.*, when the R group is C_6H_5, $ArCH_2$, or alkyl, the corresponding acetylenic ions formed are



When, however, R = H or *tert*-butyl, where the acetylenic ion cannot be stabilized by the formation of a cation on adjacent carbon atoms, the abundance of the acetylenic ion peak is very low (10% of the base peak for R = H and nil for R = *tert*-butyl).

The nmr spectrum of 1,2,3-selenadiazole showed the proton signals at 6.66 and 7.47 ppm for the 4 and 5 protons, respectively. In 4-substituted rings the proton which is geminal to the selenium appears as a strong singlet (unless there is long-range coupling to protons on ring substituents) and a weak doublet, centered around the singlet. This doublet is assigned to the splitting caused by the presence of the selenium isotope ^{77}Se with a natural abundance of 7.5%. Interestingly, it was possible to confirm this by measuring the relative intensities of the doublet to the singlet and arriving at a value of 7.2 ± 0.3%, in good agreement with the value found by other experiments for the

(1) I. Lalezari, A. Shafiee, and M. Yalpani, *Tetrahedron Lett.*, 5105 (1969).

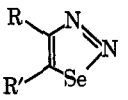
(2) I. Lalezari, A. Shafiee, and M. Yalpani, *Angew. Chem.*, **82**, 484, (1970).

(3) L. Wolff, *Justus Liebigs Ann. Chem.*, **333**, 1 (1904); H. Staudinger and J. Siegwart, *Ber.*, **49**, 1918 (1916).

(4) 4-Phenyl-1,2,3-thiadiazole remains unchanged when heated to 200° for 1 hr (I. Lalezari, A. Shafiee, and M. Yalpani, unpublished results). 4-Methyl-1,2,3-thiadiazole-5-carboxylic acid undergoes thermal decarboxylation without ring cleavage (ref 3).

TABLE I

SYNTHESIS OF SUBSTITUTED 1,2,3-SELENADIAZOLES[a]



R	R′	Registry no.	Bp, °C (20 mm)	Mp, °C	$n^{28}D$	λ_{max}^{EtOH},[c] nm (ε)	Yield, % (pure)
H	H	26223-16-5	56–58		1.6081	282 (900)	25
H	CH_3	30309-65-0	76–77		1.5763	282 (1037)	27
H	CH_3CH_2	30309-66-1	92–94		1.5542	282 (1181)	22
H	$CH_3(CH_2)_2$[b]	30309-67-2	114–115		1.5422	283 (1171)	28
H	$CH_3(CH_2)_3$[b]	30309-68-3	120–122		1.5295	283 (1300)	27
H	$CH_3(CH_2)_5$[b]	30309-69-4	130–131		1.4988	283 (982)	25
H	$PhCH_2$[b]	30309-70-7	116–117	36.5–37		285 (1250)	28
H	CN[b]	30309-71-8		93–94		300 (1580)	50
H	CO_2Et[b]	30309-72-9	110–112			300 (2540)	80
CH_3	H	30318-89-9	76–77		1.5763	290 (1078)	30
CH_3	CO_2Et[b]	30318-90-2	127–128	39–41		307 (1950)	90
CH_3	CO_2H[b]	30318-91-3		194–195		304 (2610)	80
Ph	CO_2Et[b]	30318-92-4		48–49		328 (2956)	80

[a] Satisfactory analytical values (±0.3% for C and H) were reported for all compounds: Ed. [b] All of these selenadiazoles have been pyrolyzed to give in high yields (>80%) the corresponding acetylenes. [c] A shorter wavelength maximum [λ 225–238 nm (ε 6000–10,000)] was also reported for each compound.

TABLE II

RELATIVE YIELDS OF DI- AND MONOSUBSTITUTED SELENADIAZOLES

Starting ketones	Relative yields[a] 4-Substituted selenadiazole	4,5-Disubstituted selenadiazole
Ethyl methyl ketone	72	28
Phenylacetone	33	67
p-Methylphenylacetone	29	71
p-Methoxyphenylacetone	31	69
p-Fluorophenylacetone	8.9	91.1

[a] The relative yields were calculated by comparing the intensities of the nmr signals, at 4.4 ppm (3.1 for ethyl methyl ketone) for the methylene of 4-substituted and at 2.6 ppm (2.7 for ethyl methyl ketone) for the methyl group of the 4,5-disubstituted compounds, in the crude product mixtures and are normalized.

natural abundance of this isotope. The selenium splitting constant was found to be 40 ± 2 cps; in all cases studied this value is smaller than the ^{77}Se–C–H coupling in 1,3,4-selenadiazole (55.3 Hz)[5] and in selenophene (48 Hz).[6] Figure 1 shows the nmr spectrum of the parent compound illustrating the coupling of the ^{77}Se isotope with the geminal proton.

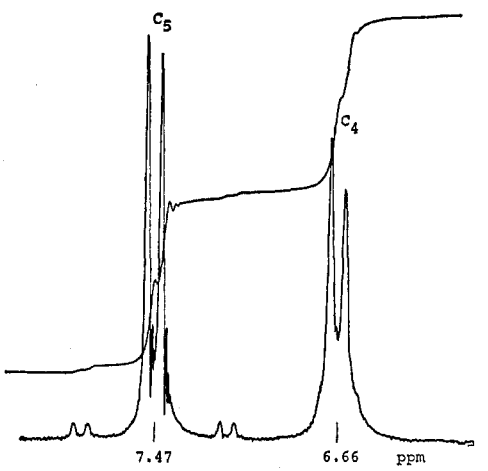


Figure 1.—Nmr spectrum of 1,2,3-selenadiazole.

Experimental Section

Melting points were taken on a Kofler hot-stage apparatus and are uncorrected. The ir spectra were obtained as liquid films or in KBr pellets on a Leitz Model III spectrograph; the uv spectra were measured on a Unicam Model SP 800. Mass spectra were recorded on a Hitachi Model RMU-6 spectrometer. Proton magnetic resonance spectra were taken on a Varian Model A-60A instrument.

General Procedures for the Synthesis of 1,2,3-Selenadiazoles and Acetylenes.—All the selenadiazoles were prepared by dissolving or suspending the powdered semicarbazone in about 10–15 times its volume of glacial acetic acid (the presence of water in the acetic acid gave a lower yield of products) followed by the slow addition of equimolar quantities of finely powdered selenium dioxide. Whenever necessary the solution was warmed gently on a water bath to start the reaction, evident by the evolution of a gas. For the conversion of the lower aliphatic ketones or aldehydes, cooling was necessary to obtain optimum yields. When the gas evolution slowed down, the mixture was heated gently on a water bath until gas evolution ceased; finally the mixture was filtered to remove the slight amount of deposited metallic selenium. The filtrate was added to water and extracted several times with chloroform. The chloroform layer was washed with sodium bicarbonate solution to remove all acetic acid and dried over sodium sulfate and evaporation of the chloroform gave usually a reddish oil which was either nearly pure selenadiazole or a mixture of the selenadiazole with the starting carbonyl compound. Purification would usually be achieved by crystallization or steam distillation, in the case of the selenadiazoles having aromatic substituents, and by distillation, in the aliphatic series. In some cases the purification was only possible on preparative tlc on silica gel plates, developed with chloroform or mixtures of chloroform and petroleum ether in suitable ratios. All selenadiazoles obtained were unstable to a varied degree at room temperature and in the light, turning reddish with the concomitant deposition of metallic selenium in time. At 0° and in the dark they would remain unchanged for several months.

For the formation of acetylenes, the selenadiazoles were pyrolyzed on sand at about 160° and vacuum distilled.

Two typical examples for the synthesis of the selenadiazoles and one for the formation of acetylenes are outlined below. The elemental analysis, boiling points, melting points, and uv data are summarized in Table I.

1,2,3-Selenadiazole (2, R = R′ = H).—To a stirred suspension of 65 g (0.64 mol) of acetaldehyde semicarbazone in 500 ml of glacial acetic acid at room temperature was added under cooling gradually 71 g (0.65 mol) of finely powdered selenium dioxide. The mixture was stirred until gas evolution ceased, about 2 hr. It was then filtered to remove the deposited selenium, water was

(5) R. V. Kendall and R. A. Olofson, *J. Org. Chem.*, **35**, 806 (1970).
(6) M. L. Heffernan and A. A. Humffray, *Mol. Phys.*, **1**, 527 (1961).

added, and the product extracted into chloroform. The extract was dried, the solvent evaporated, and the residue distilled *in vacuo* to give 18.8 g of a colorless liquid: bp 55° (16 mm); $n^{28}D$ 1.6081; ir (film) 3100, 3080, 1450, 1300, 1100, 870 cm^{-1}; nmr (CCl_4) 7.47 (d, J = 3.8 Hz, 1, H_5), 6.66 (d, J = 3.8 Hz, 1, H_4). H_5 was further split into another doublet of doublets with J = 40 Hz (^{77}Se coupling).

4-Methyl-1,2,3-selenadiazole-5-carboxylic Acid Ethyl Ester (2, R = CH_3; R′ = CO_2Et).—To a mixture of 18.8 g (0.1 mol) of ethylacetoacetate semicarbazone in 200 ml of glacial acetic acid was added gradually 11.1 g (0.1 mol) of powdered selenium dioxide and heated gently on water bath for 3 hr. The mixture was filtered, the filtrate was diluted with water and extracted with chloroform, and the chloroform evaporated. The residue was steam distilled to give 17.7 g of an oil which on treatment with petroluem ether crystallized as pale yellow crystals: mp 39–41°; ir (KBr) 1725, 1310, 1090, 760 cm^{-1}; nmr (CCl_4) 4.31 (q, 2, OCH_2), 2.91 (s, 3, CH_3), 1.32 (t, 3, OCH_2CH_3).

Hydrolysis of 4-Methyl-1,2,3-selenadiazole-5-carboxylic Acid Ethyl Ester (2, R = CH_3; R′ = CO_2Et).—To a refluxing solution of 1.88 g (0.01 mol) of 4-methyl-1,2,3-selenadiazole-5-carboxylic acid ethyl ester in 15 ml of 95% ethyl alcohol was added dropwise a solution of 0.4 g (0.01 mol) of sodium hydroxide in 5 ml of water. The refluxing was continued for 30 min. After cooling the solution was diluted with water and extracted with chloroform. The aqueous layer was acidified with hydrochloric acid and the resulting crystalline solid separated and recrystallized from chloroform to afford 1.2 g (75%) of 4-methyl-1,2,3-selenadiazole-5-carboxylic acid (2, R = CH_3; R′ = CO_2H): mp 194–195°; ir (KBr) 1695, 1500, 1430, 1190, 870, 730 cm^{-1}.

Reesterification of 4-Methyl-1,2,3-selenadiazole-5-carboxylic Acid (2, R = CH_3; R′ = COOH).—A mixture of 1.0 g (0.0052 mol) of the acid and 2 ml of thionyl chloride was refluxed for 30 min, excess thionyl chloride was removed under reduced pressure, and to the residue 10 ml of ethanol was added and refluxed for 10 min. On evaporation of the excess alcohol and crystallization of the residue from petroleum ether, 0.4 g of a pale yellow solid was obtained, mp and mmp (with authentic sample) (see Table I), 38–40°.

Pyrolysis of 4-Methyl-1,2,3-selenadiazole-5-carboxylic Acid Ethyl Ester.—A mixture of the selenadiazole, 1.0 g (0.0052 mol), and 5.0 g of acid-washed sand was gradually heated to 160° and kept at that temperature for 10 min. On distillation under reduced pressure, 0.42 g (82 %) of a colorless oil was obtained, bp 160–161°, $n^{20}D$ 1.4289, identified by comparison with authentic material to be tetronic acid ethyl ester.

Cycloaddition of a 1,4 Dipole with Alkyl Ketones. A Novel Synthesis of 1,3,4-Tetrahydrooxadiazines

S. RICHARD TURNER, LAWRENCE J. GUILBAULT, AND GEORGE B. BUTLER*

Department of Chemistry, University of Florida, Gainesville, Florida 32601

Received February 19, 1971

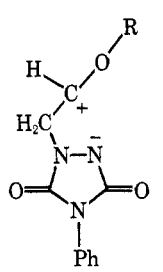
The intermediate 1,4 dipole from the spontaneous reaction of 4-phenyl-1,2,4-triazoline-3,5-dione with vinyl ethers was observed to react readily with weakly dipolarophilic alkyl ketones to form a new 1,3,4-tetrahydrooxadiazine ring structure. The characterization of these new compounds is described. The reactivity of the 1,4-dipolar intermediate was found to be sensitive to substituent effects.

1,4-Dipolar cycloaddition reactions have been the topic of a recent review[1] and have received attention in other reviews on dipolar cycloaddition reactions.[2] Many different reactive dipolarophiles have been utilized to react with the various 1,4 dipoles studied, *i.e.*, isocyanates, acetylene dicarboxylate esters, and ketenes among many others. However, to the best of our knowledge the only case reported of a ketone performing this function is in the reactions of perhaloacetones with cyanamides to form 1,3,5-oxadiazines.[3]

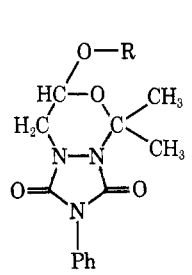
4-Phenyl-1,2,4-triazoline-3,5-dione (PhTD) has been shown to be a strong dienophile in 4 + 2 cycloaddition reactions[4] and recently has been shown to participate in a 2 + 2 cycloaddition reaction with indene in which a 1,4-dipolar intermediate was trapped with water.[5]

We wish to report a novel cycloaddition reaction using alkyl ketones as the dipolarophile with the 1,4 dipole (I) from PhTD and vinyl ethers.

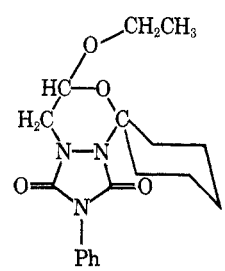
When PhTD and ethyl vinyl ether (EVE) are mixed in a 1:1 molar ratio in acetone at room temperature two products are observed. 3-Oxa-2,2-dimethyl-4-ethoxy-8-phenyl-1,6,8-triazabicyclo[4.3.0]nona-7,9-dione (IIa), a new 1,3,4-tetrahydrooxadiazine ring structure, is



I



IIa, R = CH_2CH_3
b, R = $CH_2CH(CH_3)_2$
c, R = $CH{=}CH_2$



III

formed in 42% yield along with a 1:1 alternating copolymer which we have reported elsewhere.[6]

Structure IIa was assigned on the basis of the following data. The infrared spectrum (KBr) showed strong absorbances at 2980–2880 (saturated CH), 1770 and 1710 cm^{-1} (double carbonyl), and gave strong bands in the 1200–1000 cm^{-1} region due to the acetal linkage. A 60-MHz proton nmr spectrum ($CDCl_3$) gave a triplet at δ 1.25 (3 H), two equivalent singlets at δ 1.70 and 1.85 (3 H each) assigned to the nonequivalent methyl group protons from the incorporated acetone, a multiplet at δ 3.73 (4 H) from the two sets of methylene protons, a quartet at δ 5.02 (1 H) assigned to the single proton on the acetal carbon, and a multiplet at δ 7.40 (5 H) originating from the aromatic protons.

Substituting isobutyl vinyl ether for ethyl vinyl ether

(1) R. Huisgen, *Z. Chem.*, **8**, 290 (1968).
(2) (a) R. Gompper, *Angew. Chem., Int. Ed. Engl.*, **8**, 312 (1969); (b) R. M. Acheson, *Advan. Heterocycl. Chem.*, **1**, 125 (1963).
(3) M. E. Hermes and R. A. Braun, *J. Org. Chem.*, **31**, 2568 (1966).
(4) R. C. Cookson, S. S. H. Gilani, and I. D. R. Stevens, *J. Chem. Soc. C*, 1905 (1967).
(5) E. K. von Gustorf, D. V. White, B. Kim, D. Hess, and J. Leitish, *J. Org. Chem.*, **35**, 1155 (1970).
(6) G. B. Butler, L. J. Guilbault, and S. R. Turner, *J. Polym. Sci., Part B*, **9**, 115 (1971).