SYNTHESIS AND PROPERTIES OF ISOSELENAZOLECARBOXYLIC ACIDS

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Abstract – Six members of the unknown class of isoselenazole-carboxylic acids are prepared by SeO_2 oxidation of 3- and/or 5-methyl substituted isoselenazole derivatives.

Recently we have found a convenient method for the synthesis of isoselenazoles which allows the preparation of various alkyl and aryl substituted derivatives,[1] while the introduction of heteroatom-containing functions was up to now an unsolved problem. Continuing our investigation in this field we examined possibilities of obtaining functionalized isoselenazoles by oxidative transformation of their alkyl substituents.

We wish to report here the preparation and the properties of isoselenazole-carboxylic acids which are the first described members of such a class of compounds and are worthy of interest for their potentialities in the synthesis of other derivatives or in the preparation of products for practical purposes like cosmetics *etc.*

The oxidation of methylisoselenazoles to the corresponding carboxylic acids is not a generally occurring reaction, and in fact various oxidizing agents like potassium permanganate and chromic anhydride in acetic or sulphuric acid failed in giving oxidation in side chain or oxide formation at the selenium atom, while they resulted in degradating the ring, in agreement with what we found with methyl derivatives of 1,2,5-selenadiazole.[2]

Only selenium dioxide in sealed glass vial was efficient for the transformation of methylisoselenazoles into the corresponding carboxylic acids (Scheme 1).

The oxidation of the 3,5-dimethylisoselenazole yielded a mixture of isoselenazole-3,5-dicarboxylic acid, 3-methylisoselenazole-5-carboxylic acid, and 5-methylisoselenazole-3-carboxylic acid.

The reaction conditions as molar ratio of reagents, reaction temperature and time, needed an accurate selection which was accomplished through a series of experiments with 3-methylisoselenazole.

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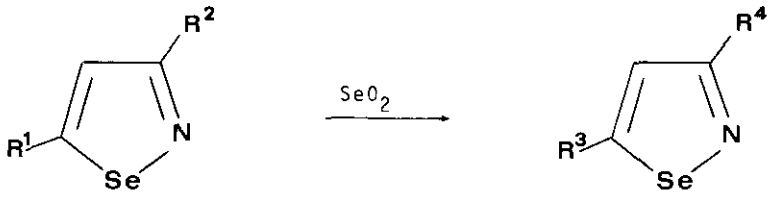


a: $R^1 = H$, $R^2 = CH_3$

b: $R^1 = CH_3$, $R^2 = H$

c: $R^1 = C_6H_5$, $R^2 = CH_3$

d: $R^1 = R^2 = CH_3$

a: $R^3 = H$, $R^4 = COOH$

b: $R^3 = COOH$, $R^4 = H$

c: $R^3 = C_6H_5$, $R^4 = COOH$

d: $R^3 = R^4 = COOH$

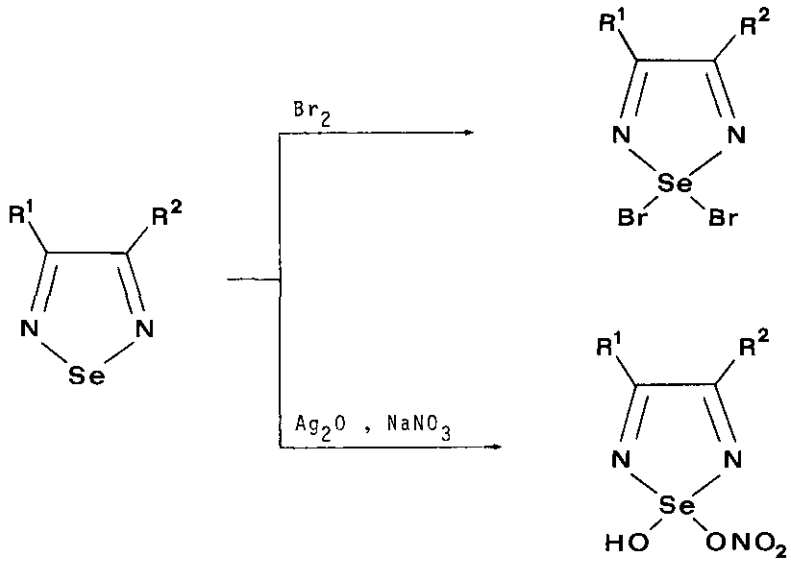
e: $R^3 = COOH$, $R^4 = CH_3$

f: $R^3 = CH_3$, $R^4 = COOH$

Selenium dioxide transforms into the corresponding carboxylic acids also methyl-1,2,5-selenadiazoles[2] which show good analogies, from this standpoint, with methylisoselenazoles, nevertheless significant differences in the reactivity of the two classes of heterocycles are pointed out by other oxidizing agents. The 1,2,5-selenadiazole and its methyl derivatives undergo oxidation of the selenium atom from +2 to +4 either by an aqueous mixture of silver oxide and sodium nitrate with formation of hydroxy nitrates or by bromine under anhydrous conditions with formation of 1,1-dibromo adducts[2] (Scheme 2).

Any attempt to carry out analogous reactions with 3-methylisoselenazole was unsuccessful. With bromine only an electrophilic substitution reaction takes place to afford 3-methyl-4-bromoisoselenazole.[3]

SCHEME 2



$R^1 = R^2 = H$; $R^1 = H$, $R^2 = CH_3$; $R^1 = R^2 = CH_3$

Reactions enhancing the selenium oxidation number are normally found with linear and cyclic seleno ethers, but never, save 1,2,5-selenadiazoles, with aromatic selenium heterocycles. Isoselenazoles and 1,2,3-selenadiazoles[4] align with the other aromatic systems even if they contain one N–Se bond which draws their structure near that of 1,2,5-selenadiazoles. It seems reasonable therefore that the singular reactivity of 1,2,5-selenadiazoles may be connected to the ring structure more than to the neighbouring atom effects, indicating a low electron delocalization in the heterocycle.

The oxidation at the benzylic position of isoselenazole and 1,2,5-selenadiazole derivatives by selenium dioxide to the corresponding carboxylic acid is made more peculiar by comparison with the behaviour of the sulphur isologues, and in fact either 3-methyl-1,2,5-thiadiazole in previous experiments[2] or 3-methylisothiazole in present attempts failed in giving such a type of reaction. On the other side, 5-methylisothiazole, submitted to oxidation with selenium dioxide as for reactions of Scheme 1, afforded isothiazole-5-carboxylic acid in 8 % yields. Nevertheless methyl hydrogens in position 5 of the isothiazole nucleus are remarkably more reactive than those in position 3 also in nucleophilic reactions like alkaline hydrogen-deuterium exchange.[5] The prepared isoselenazolecarboxylic acids showed to be prone to the usual transformations into acyl derivatives. Isoselenazole-3,5-dicarboxylic acid,

3-methylisoselenazole-5-carboxylic acid and 5-methylisoselenazole-3-carboxylic acid were transformed into their methyl esters which were exploited for separating the above mentioned acids. Isoselenazole-3-carboxylic acid was transformed into its acyl chloride and then into amide.

All the prepared isoselenazolecarboxylic acids and esters as well as isoselenazole-3-carboxamide showed satisfactory elemental analyses, I.R. and N.M.R. spectra in agreement with the proposed molecular structures.

Characteristic data of isoselenazolecarboxylic acids are collected in the Table.

T A B L E

Characteristic data of isoselenazolecarboxylic acids

Compound	Yield %	mp °C (solvent)	I.R.* cm^{-1}	^{1}H-N.M.R. (acetone-d_6)	M.S. m/e M^+ (rel. int.%)
2a	24	147 - 148 (acetonitrile)	1510, 1394, 734, 413	9.50 (d, 1H, J = 5.3 Hz)¤; 8.18 (d, 1H, J = 5.3 Hz)	177 (62)
2b	14	183 - 185 (acetone)	1532, 1380, 732, 413	9.25 (d, 1H, J = 1.8 Hz), 8.03 (d, 1H, J = 1.8 Hz)	177 (100)
2c	25	164 - 166 (chloroform)	1413, 433	8.17 (s, 1H)¤; 7.63 - 7.32 (m, 5H)	253 (100)
2d	5	200-203 (dec.) (chloroform)	1536, 1390, 736, 410	8.44 (s, 1H)	221 (63)
2e	12	198 - 200 (acetone)	1530, 1397, 730, 434	7.86 (s, 1H), 2.47 (s, 3H)	191 (100)
2f	6	148 - 150 (acetone)	1550, 1417, 735, 451	7.26 (q, 1H, J =1.2 Hz), 2.73 (d, 3H, J =1.2 Hz)	191 (100)

*The reported bands are tentatively assigned to the ring on empirical basis. ¤In $CDCl_3$

EXPERIMENTAL

Melting points were determined with a Reichert Thermovar apparatus and are uncorrected. I.R. spectra were recorded on a Perkin-Elmer mod.1330 spectrophotometer in KBr pellets unless otherwise indicated. ^{1}H-N.M.R. spectra were registered on W.M. 300 Bruker spectrometer. Mass spectra were recorded on a Varian MAT CH5-DF apparatus at 70 eV; the value are referred to the selenium isotope 80.

Isoselenazolecarboxylic acids. A mixture of solid selenium dioxide and 0.300 g of the appropriate methylisoselenazoles 1 a - d (molar ratio 2.5 : 1) was heated at 100 °C for 3 h in an evacuated and sealed Pyrex vial. After cooling the reaction product was disgregated with 5 ml of water, alkalified with aqueous 30 % sodium hydroxide and extracted with four 5 ml portions of pentane to remove the unreacted isoselenazole derivative. The aqueous alkaline phase was acidified up to pH 2 - 3 with saturated aqueous solution of $KHSO_4$ and extracted with ether in a continuous extraction device. After drying over anhydrous sodium sulphate and removal of the solvent, the extracts yielded the crude isoselenazolecarboxylic acids which were purified by crystallisation (see the Table) except for what concerns the oxidation product of 3,5-dimethylisoselenazole. In such case the crude acidic residue, obtained from three vials, was dissolved in 5 ml of anhydrous THF, treated with excess of an ethereal solution of diazomethane and distilled in vacuo to remove the solvent. The oily residue was separated by preparative layer chromatography on Merck silica gel $PF_{254-366}$ (thickness 1 mm, *eluent benzene - methanol 98 : 2*) to give the following methyl esters:

Dimethyl isoselenazole-3,5-dicarboxylate (Yield 6 %); mp 69 - 71 °C (ether/pentane). Found: C, 33.80; H, 2.90; N, 5.59. $C_7H_7NO_4Se$ requires C, 33.89; H, 2.84; N, 5.65 %. ^{1}H-N.M.R. ($CDCl_3$, TMS int. ref.) 8.56 (s, 1H), 3.99 (s, 3H), 3.95 (s, 3H). I.R. 1723 (C=O), 1535, 1430, 737, 435 cm^{-1} (ring).

Methyl 3-methylisoselenazole-5-carboxylate (Yield 14 %); mp 36 - 38 °C (pentane). Found: C, 35.41; H, 3.50; N, 6.82. $C_6H_7NO_2Se$ requires C, 35.31; H, 3.46; N, 6.86 %. ^{1}H-N.M.R. ($CDCl_3$, TMS int. ref.) 7.86 (s, 1H), 3.93 (s, 3H), 2.53 (s, 3H). I.R. 1720 (C=O), 1546, 1435, 736, 385 cm^{-1} (ring).

Methyl 5-methylisoselenazole-3-carboxylate (Yield 7 %); oil. Found C, 35.43; H, 3.56; N, 6.90. $C_6H_7NO_2Se$ requires C, 35.31; H, 3.46; N, 6.86 %. ^{1}H-N.M.R. ($CDCl_3$, TMS int. ref.) 7.79 (q, 1H, J = 1.2 Hz), 3.98 (s, 3H), 2.73 (d, 3H, J = 1.2 Hz). I.R. (liquid film) 1715 (C=O), 1540, 1438, 733, 458 cm^{-1} (ring).

The obtained esters were saponified by 1.5 h reflux with a 3 % solution of

potassium hydroxide in 95 % ethanol.

Isothiazole-5-carboxylic acid was obtained by oxidation of 5-methylisothiazole as described for isoselenazolecarboxylic acids. Yield 8 %; I.R. spectrum superimposable with that of an authentic sample.[6]

Isoselenazole-3-carboxamide. A mixture of isoselenazole-3-carboxylic acid (0.126 g, 0.72 mmol) and 3 ml of freshly distilled thionyl chloride was refluxed for 1 h, then it was evaporated at reduced pressure to give the crude acyl chloride. Such chloride was dissolved in 3 ml of anhydrous THF, treated with gaseous ammonia up to saturation and set aside for a night. Water (3 ml) was then added and the mixture was extracted with five 5 ml portions of ether, dried over anhydrous sodium sulphate and evaporated at reduced pressure to give isoselenazole-3-carboxamide (0.053 g, 0.30 mmol) which was purified by sublimation at 150 °C/0.01 Torr., mp 143 - 145 °C. Found C, 27.40; H, 2.33; N, 16.08. $C_4H_4N_2OSe$ requires C, 27.45; H, 2.30; N, 16.00 %. M.S. m/e 176 (M^+, 45 %). I.R. 3430 (NH_2), 1653 (C=O), 1396, 730, 411 cm^{-1} (ring).

This work was done with financial support of "Ministero della Pubblica Istruzione"

REFERENCES

1. F.Lucchesini, V.Bertini, and A.De Munno, *Tetrahedron*, 40, 931 (1984).
2. A.De Munno, V.Bertini, F.Lucchesini, and N.Picci, *Atti Soc. Tosc. Sc. Nat., Serie A*, 90, 1 (1983).
3. F.Lucchesini, V.Bertini, and A.De Munno, *Heterocycles*, 21, Special issue, 612 (1984).
4. H.Meier, J.Zountsas, and H.Petersen, *Nouv. J. Chim.*, 6, 73 (1982).
5. J.A.White and R.C.Anderson, *J. Heterocyclic Chem.*, 6, 199 (1969).
6. M.P.L.Caton, D.H.Jones, R.Slack, and K.R.H.Wooldridge, *J. Chem. Soc.*,446 (1964).

Received, 17th September, 1984