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SYNTHESIS OF ISOSELENAZOLE AND ITS 3- AND 5-SUBSTITUTED DERIVATIVES

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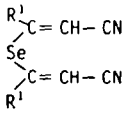
Abstract—A new method of synthesis for isoselenazole and its 3- and 5-substituted derivatives by one-pot procedure which uses α-acetylenic aldehydes or ketones besides hydroxylamine-O-sulphonic acid and potassium selenide in buffered aqueous solution, is described. When α-acetylenic aldehydes are used, selenobisalkenylnitriles are obtained as side products.

Few uncondensed isoselenazoles and very few syntheses of such a heterocyclic system are reported.[1] We will now describe a new synthetic method which enables attainment of isoselenazole and its 3- and 5-substituted derivatives **2**, through one-pot procedure. The method consists in treating an α-acetylenic aldehyde or ketone with hydroxylamine-O-sulphonic acid, then with potassium selenide in buffered aqueous solution (Scheme 1).

Lithium selenide gives the same results as potassium selenide, but the latter is easier to work up. The selenide addition also promotes a redox reaction with formation of elemental Se.

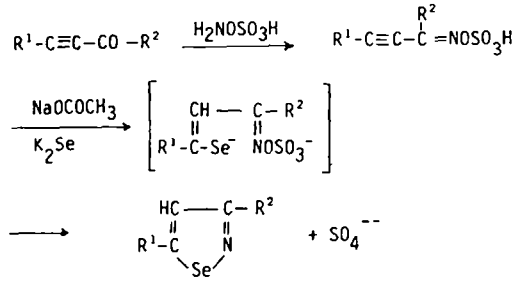
When acetylenic aldehydes ($R^2 = H$) are used, the above scheme must be integrated with a side product. The reaction also affords selenobisalkenylnitriles **3** while yields of isoselenazole are reduced.



3

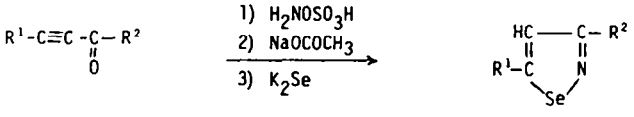
a: $R^1 = H$; b: $R^1 = CH_3$; c: $R^1 = C_6H_5$

A possible mechanism involves formation in a first step of an oxym-O-sulphonic acid, followed by nucleophilic addition of the selenide to the acetylenic bond in agreement with known reactions[2] and intramolecular nucleophilic substitution at the N atom with cyclization:



The selenobisalkenylnitriles produced as side products from acetylenic aldehydes is in agreement with the known fact that oxym-O-sulphonic acids derived from aldehydic functions, easily eliminate sulphuric acid to give nitriles.[3] In such a case the selenide interacts only with the acetylenic bond resulting in the joining of two substrate molecules.

It is significant to note that this isoselenazole synthesis does not require any preparation or separation of special Se-containing precursors; in fact the Se reagent, in the easily accessible form of alkali selenide, is added last. On the contrary, the reported syntheses for both condensed[1b] and uncondensed[1a,b] isoselenazoles need bifunctional Se-containing organic compounds with appropriate leaving groups for cyclization with ammonia. An exception to this is



1 **2**

a: $R^1 = R^2 = H$; b: $R^1 = CH_3$, $R^2 = H$; c: $R^1 = C_6H_5$, $R^2 = H$; d: $R^1 = H$, $R^2 = CH_3$; e: $R^1 = H$, $R^2 = C_2H_5$; f: $R^1 = H$, $R^2 = n\text{-}C_3H_7$; g: $R^1 = R^2 = CH_3$; h: $R^1 = C_6H_5$, $R^2 = CH_3$.

Scheme 1.

a patent of 1936[1c] which claims the specific synthesis of 6 - H - 6 - oxoanthra[1,9 - c,d]isoselenazole - 3 - carboxylic acid through an uncommented procedure using 1 - chloro - 9,10 - dihydro - 9,10 - dioxo - 2 - anthracen carboxylic acid, aqueous ammonia, and potassium selenide in an autoclave.

In our synthesis Se not used is easily recovered in elemental form and recycled.

Molecular structures of new products are assigned through their physical and spectroscopic characteristics.

Table 1 summarizes UV, IR and ^{1}H-NMR data for the isoselenazoles, determined as indicated in the Experimental. The reported IR bands are tentatively assigned to the ring on the basis of a comparison with the IR spectra of isothiazoles.[4]

EXPERIMENTAL

UV spectra were determined with a Cary 118C spectrophotometer in iso-octane soln, unless otherwise stated. IR spectra were recorded on a Perkin–Elmer 283 spectrophotometer as liquid film or as KBr pellets. ^{1}H-NMR spectra were run on a Jeol PS 100 spectrometer in $CDCl_3$ soln for solids or neat for liquid substances with Me_4Si as internal standard. Mass spectra were recorded on a Varian CH5 apparatus at 70 eV; the values are referred to the selenium isotope 80. M.ps were determined using a Kofler apparatus and are uncorrected. Mol wts were determined at 37° in $CHCl_3$ on a Knauer Vapor Pressure Osmometer.

General procedure for the preparation of isoselenazoles. α-Acetylenic aldehydes or ketones (**1a–h**), hydroxylamine-O-sulphonic acid, NaOAc, K_2Se,[5] were used in the molar ratio 1:1:2:0.9 for aldehydes and 1:1:2:1 for ketones, respectively. The alkynylcarbonyl reagent was added under N_2 to a soln of hydroxylamine-O-sulphonic acid in 10 ml water at 0°, and stirred until complete reaction (from 20 to 40 min for ketones, about 2 min for aldehydes). To the mixture solid NaOAc was added, then it was treated with an 0.6 M aqueous soln of K_2S, in about 20 min for ketones and instantaneously for aldehydes. The mixture was stirred for 4 hr longer at room temp, and extracted with 80 ml ether in 4 portions. The aqueous phase was boiled in the presence of air and filtered to recover elemental Se which was purified through the formation of dioxide.[6] The ether extraction was efficient in obtaining all of the isoselenazoles and the **3b** nitrile, but a relevant part of **3a** and **3c** nitriles were not extracted. For this reason the mixture of **1a** aldehyde was further extracted with EtOAc (4 × 20 ml) and that of **1c** aldehyde with CH_2Cl_2 (4 × 20 ml). All the extracts were dried over Na_2SO_4. For reagents **1a–b,d–g** which give volatile isoselenazoles, the ether extract was evaporated and the residue distilled at 0.3 Torr with collecting vials at −70° to avoid loss. The distillation at reduced pressure of **2a** and **2b** isoselenazoles left solid residues which were sublimed at 130°/0.02 Torr to give **3a** and **3b** nitriles. A further quantity of **3a** was recovered from the EtOAc extract by removal of

Table 1. Spectral data of isoselenazoles

Compound	λ_{max} (ε) [nm]	ν_{max} [cm^{-1}]	δ [ppm]
2a	265 (5600)	1504	9.38 (d, 1H, J = 5.2 Hz),
		1396	9.17 (d, 1H, J = 1.6 Hz),
		402	7.38 (dd, 1H, J_1 = 5.2 J_2 = 1.6 Hz)
2b	265 (5500)	1540	8.86 (broad, 1H) *
	221 (3200)	1432	7.09 (dq, 1H, J_1 = 1.8 J_2 = 1.2 Hz),
		440	2.70 (dd, 3H, J_1 = 1.2 J_2 = 0.4 Hz)
2c	302sh (5700)	1531	9.23 (d, 1H, J = 2.0 Hz),
	278 (14700)	1423	7.80 - 7.52 (m, 6H)
	226sh (4500)	425	
2d	268 (6100)	1521	9.22 (d, 1H, J = 5.1 Hz),
		1381	7.22 (d, 1H, J = 5.1 Hz),
		406	2.35 (s, 3H)
2e	267 (6400)	1518	9.17 (d, 1H, J = 4.5 Hz),
		1392	7.25 (d, 1H, J = 4.5 Hz),
		407	2.79 (q, 2H, J = 7.5 Hz),
			1.25 (t, 3H, J = 7.5 Hz)
2f	268 (6600)	1518	9.20 (d, 1H, J = 5.0 Hz),
		1393	7.25 (d, 1H, J = 5.0 Hz),
		407	2.86 (t, 2H, J = 7.6 Hz),
			1.80 (sex, 2H, J = 7.6 Hz),
			0.95 (t, 3H, J = 7.6 Hz)
2g	267 (6000)	1552	6.89 (q, 1H, J = 1.1 Hz), *
		1405	2.58 (d, 3H, J = 1.1 Hz),
		450	2.36 (s, 3H)
2h	276 (14400)	1543	7.26 - 5.59 (m, 6H),
		1399	2.51 (s, 3H)
		427	

* $CDCl_3$ solution

the solvent and sublimation. The ether extract from **1c** was treated by preparative layer chromatography on Merck $PF_{254-366}$ silica gel (thickness 1 mm, eluent a benzene—MeOH mixture 99:1) to yield the **2c** isoselenazole and also the **3c** selenobisnitrile. A further quantity of **3c** was recovered from the CH_2Cl_2 extract by an analogous chromatographic technique. The ether extract from **1h**, after removal of the solvent, was sublimed at 80°/0.01 torr, to yield the **2h** isoselenazole. Further purification of the prepared liquid isoselenazoles was carried out through precipitation as hydrochloride salts by anhydrous HCl in ether. Further purification of solid products was achieved by crystallization from appropriate solvents (see later).

Isoselenazole[1a,b] (**2a**). From propynal[7] **1a** (mmol 27.6); yields 16%; b.p. 68°/46 torr; UV in EtOH λ_{max} 267 nm (ϵ 6000) [lit.[1b] λ_{max} 266 nm (ϵ 4900)]. The side product *3,3'-selenobis(propenenitrile)* **3a** was obtained in 9% yield. m.p. (EtOAc) 125–126°. ν_{max} 2200 cm^{-1} (CN). δ ($CDCl_3$) 7.68 (d, 1H, J = 10 Hz), 6.03 (d, 1H, J = 10 Hz). (Found C, 39.62; H, 2.17; N, 15.13, $C_6H_4N_2Se$ requires: C, 39.36; H, 2.20; N, 15.30%.)

5-methylisoselenazole[1b] (**2b**). From 2-butynal[8] **1b** (mmol 32.02); yields 4%. b.p. 84–86°/43 torr. The side product *3,3'-selenobis(3-methylpropenenitrile)* **3b** was obtained in 10% yield. ν_{max} 2210 cm^{-1} (CN). m.p. (ether) 92–93°. δ ($CDCl_3$) 5.93 (q, 1H, J = 1.4 Hz), 2.38 (d, 3H, J = 1.4 Hz). Found C, 45.62; H, 3.59; N, 13.57, $C_8H_6N_2Se$ requires: C, 45.51; H, 3.82; N, 13.27%.

5-Phenylisoselenazole (**2c**). From phenylpropynal[9] **1c** (mmol 22.7); yields 7%. m.p. (hexane) 66–67°. Found C, 51.80; H, 3.39; N, 6.83, C_9H_7NSe requires: C, 51.94; H, 3.39; N, 6.73%. MS *m/e* 209 (100%, M^+). M.W. 213. The side product *3,3'-selenobis(3-phenylpropenenitrile)* **3c** was obtained in 9% yield. m.p. (methylethylketone) 156–159°; ν_{max} 2200 cm^{-1} (CN). δ ($CDCl_3$) 7.68–7.00 (m, 5H), 5.93 (s, 1H). Found C, 64.23; H, 3.60; N, 8.42, $C_{18}H_{12}N_2Se$ requires: C, 64.48; H, 3.61; N, 8.35%.

3-Methylisoselenazole[1a] (**2d**). From 3-butyn-2-one[10] (24.6 mmol); yields 33%. b.p. 50–51°/14 torr.

3-Ethylisoselenazole (**2e**). From 1-pentyn-3-one[11] (22.3 mmol); yields 25%. b.p. 69–70°/21 torr. MS *m/e* 161 (97%, M^+). Found C, 37.66; H, 4.48; C_5H_7NSe requires: C, 37.51; H, 4.41%.

3-n-Propylisoselenazole (**2f**). From 1-hexyn-3-one[12] (22.8 mmol); yields 18%. b.p. 91°/21 torr. MS *m/e* 175 (8%, M^+). Found C, 41.38; H, 5.34, C_6H_9NSe requires: C, 41.39; H, 5.21%,

3,5-Dimethylisoselenazole (**2g**). From 3-pentyn-2-one[13] (19.8 mmol); yields 38%. b.p. 80°/22 torr. MS *m/e* 161 (43%, M^+). Found C, 37.34; H, 4.66, C_5H_7NSe requires: C, 37.51; H, 4.41%.

3-Methyl-5-phenylisoselenazole (**2h**). From 4-phenyl-3-butyn-2-one[14] (7.0 mmol); yields 35%. m.p. (hexane) 73–75°. MS *m/e* 223 (98%, M^+). M.W. 220. Found C, 54.06; H, 4.01; N, 6.10, $C_{10}H_9NSe$ requires: C, 54.06; H, 4.08; N, 6.30%.

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