REACTIVITY OF ISOSELENAZOLES TOWARDS NUCLEOPHILIC REAGENTS

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Abstract — Isoselenazoles have shown two reactive sites towards nucleophiles. LDA gives metallation in the 5-position exploited for synthetic purposes. Grignard reagents and LAH attack the selenium atom forming non-cyclic functionalized systems.

Since the general synthesis of 4-unsubstituted isoselenazoles reported by some of us,[1] the reactivity studies of such compounds have been concerned essentially with the specific action of the selenium dioxide on alkylisoselenazoles[2] that afforded a useful preparation method of isoselenazolecarboxylic acids, and with the effect of electrophilic reagents[3] that made available various functional groups in position 4.

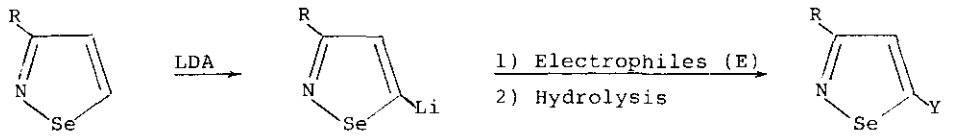
The present paper explores the behavior of isoselenazoles towards nucleophilic reagents that, depending on their strength and preferred position of attack, cause the ring metallation with further possibility of various substitutions or the ring cleavage with formation of functionalized systems.

REACTION WITH LITHIUM DIISOPROPYLAMIDE (LDA)

The isoselenazole and its alkyl derivatives[1] remain unaltered in presence of bases like aqueous alkali metal hydroxides or alcoholic sodium ethoxide. LDA in tetrahydrofuran (THF) at low temperature attacks 5-unsubstituted isoselenazoles removing the proton in position 5 and giving a metallated system which can react further with various electrophiles (Scheme 1).

The 5-lithioisoselenazole derivatives form white-yellow suspensions in THF that are stable at low temperature.

Scheme 1



R	E	Y	Yields %
CH_3	D_2O	D	78
CH_3	CH_3I	CH_3	77
CH_3	DMF	CHO	75
CH_3	CO_2	COOH	77
H	CO_2	COOH	70

The unknown 5-formyl-3-methylisoselenazole is a distillable compound whose molecular structure resulted in agreement with elemental analysis, ir, ^{1}H-nmr and mass spectra.

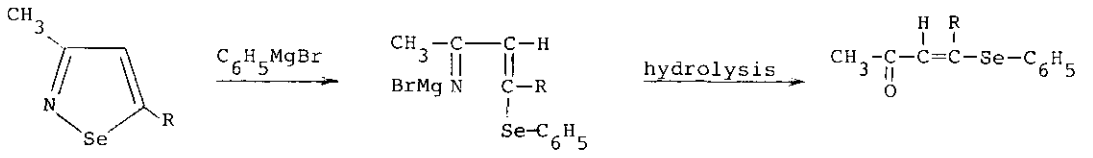
It is remarkable that metallation attempts of 3-methylisoselenazole with n-butyllithium, in agreement with the Grignard reagents effect (see later), failed giving rise to the ring decomposition.

REACTION WITH GRIGNARD REAGENTS

Carbanionic nucleophiles like Grignard reagents and alkyllithiums destroy the isoselenazole ring. The reaction of phenylmagnesium bromide with 3-methylisoselenazole followed by hydrolysis affords 4-phenylseleno-3-buten-2-one as a mixture of Z and E isomers identified by nmr analysis, diphenyl diselenide and butynone; the same Grignard reagent with 3,5-dimethylisoselenazole affords (Z)-4-phenylseleno-3-penten-2-one and diphenyl diselenide. The configuration of this Z isomer has been assigned by comparing its nmr spectral data with those of E and Z isomers of the sulfur analog.[4]

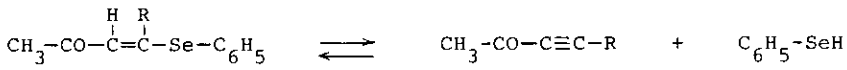
The obtainment of ß-(phenylseleno)enones indicates that the nucleophile attacks the chalcogen atom of the ring with cleavage of the Se-N bond (Scheme 2).

Scheme 2



The obtained ß-(phenylseleno)enones successively originate the other reported products through a step (Scheme 3) analogous to the known equilibrium reaction between benzeneselenol and ynals[5] at moderately basic pH values.

Scheme 3

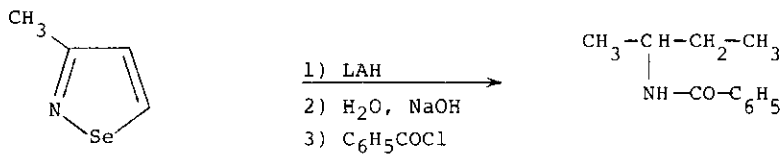


In particular, the equilibrium of Scheme 3 accounts for the isomerization of the (Z)-4-phenylseleno-3-buten-2-one to the E form and the production of diphenyl diselenide by spontaneous oxidation in air of benzeneselenol.

REACTION WITH LITHIUM ALUMINUM HYDRIDE (LAH)

The isoselenazole ring is rapidly attacked by LAH at room temperature as revealed from color change. Probably the first reaction step, in analogy to the behavior of Grignard reagents, is a nucleophilic attack of a hydride ion to the selenium atom with cleavage of the Se-N bond, followed by further reduction steps up to the obtaining of a saturated amine, that in the reaction of the Scheme 4 has been recovered as benzoyl derivative.

Scheme 4



It cannot be excluded that, working at lower temperature and with less active hydrides, less exhaustive reductions may be achieved.

CONCLUSIONS

Isoselenazoles contain two different sites reactive towards nucleophiles: the proton in position 5 and the selenium atom. In agreement with the behavior of other heterocycles like the isologue isothiazole[6] or the selenophene,[7] the chalcogen atom, enhancing the electronegativity of the neighboring carbon atom and consequently the acidity of the attacked hydrogen, makes possible the metallation with strong bases like LDA in position 5. As evidenced by nature and yields of the reported examples which only have indicative value, such a reaction has a remarkable synthetic interest opening the way to numerous functionalities. Moreover the observed attack of strong carbanionic nucleophiles to the selenium atom with cleavage of the ring is in perfect agreement with the fact that the chalcogen atom is in itself an electrophilic center as selenium in 1,2,5-selenadiazoles[8] or

sulfur in 1,2,5-thiadiazoles[8] or isothiazoles[6] which with different reactivity give analogous reactions. Further examples of such a bifacial behavior of selenium derivatives towards different nucleophiles are offered by non-cyclic compounds like selenoacetals[9] or aryl vinyl selenides[10] which are metallated to the carbon near the selenium with LDA or attacked to the selenium giving substitution reactions with alkyllithium.

EXPERIMENTAL

Melting points were determined on a Reichert-Thermovar apparatus and are uncorrected. Ir spectra were recorded on a Perkin Elmer model 1330 spectrophotometer as KBr pellets or films; the reported bands for isoselenazoles, unless otherwise stated, are tentatively assigned to the ring on empirical basis. ^{1}H-Nmr spectra in $CDCl_3$ (TMS as int. ref.) were obtained on a W.M. 300 Bruker spectrometer. Mass spectra were recorded on a Varian MAT CH5-DF apparatus at 70 eV; the values are referred to the selenium isotope 80. Microanalyses of the new products prepared were in satisfactory agreement with the calculated values (C±0.20, H±0.12, N±0.15).

5-Lithioisoselenazole derivatives and their reactions with electrophiles

A solution of diisopropylamine (0.54 ml, 3.86 mmol) in 10 ml of anhydrous THF, stirred at -78 °C, was treated with a 1.72M solution (2.24 ml, 3.86 mmol) of n-butyllithium in hexane. After 15 min stirring the clear solution of lithium diisopropylamide at -78 °C was treated with 3.22 mmol of 5-unsubstituted isoselenazole derivative in 2 ml of THF and stirred for 20 min at the same temperature. The white-yellow suspension was immediately allowed to react with various electrophiles like carbon dioxide, methyl iodide, deuterium oxide and N,N-dimethylformamide (DMF) following the usual procedures; yields of products are reported in Scheme 1. The obtained known products had ir spectra superimposable with those of authentic samples.[1,2]

3-Methyl-5-deuterioisoselenazole: ir(film) ν, cm^{-1} 2305 (CD), 1520, 1385, 430; ^{1}H-nmr δ, ppm 2.51(s, 3H), 7.29(s, 1H).

5-Formyl-3-methylisoselenazole: ir(film) ν, cm^{-1} 1679 (CO), 1544, 1401, 437; ^{1}H-nmr δ, ppm 2.57(s, 3H), 7.80(s, 1H), 9.97(s, 1H); ms, m/z 175 (100%, M^+).

Reactions with Grignard reagents

A stirred solution of isoselenazole derivative (3 mmol) in anhydrous THF (5 ml) was treated under nitrogen at room temperature with a 1M solution of phenylmagnesium bromide (3.6 mmol) in THF. After 1 h stirring the mixture was hydrolyzed with 24 ml of 0.3N HCl, further stirred for 30 min (pH=1) and extracted with diethyl ether (5 x 10 ml). The aqueous phase was treated with solid sodium bicarbonate up to pH=8 and further extracted with diethyl ether (5 x 10 ml). After drying over sodium sulfate the extracts were distilled up to the removal of the

solvent and separated by PLC on Merck $PF_{254+366}$ silica gel, eluent benzene. The 3-methylisoselenazole afforded *(Z)-4-phenylseleno-3-buten-2-one* (yield 41%; mp 50-52 °C from pentane; ir (KBr) ν, cm^{-1} 1658 (CO), 718 (olefin); ^{1}H-nmr δ, ppm 2.30(s, 3H), 6.87(d, 1H, J= 9.0 Hz), 7.34-7.36(m, 3H), 7.59-7.62(m, 2H), 7.85(d, 1H, J= 9.0 Hz)), oily *(E)-4-phenylseleno-3-buten-2-one* (yield 12%; ir (film) ν, cm^{-1} 1664 (CO), 950 (olefin); ^{1}H-nmr δ, ppm 2.19(s, 3H), 6.20(d, 1H, J=15.7 Hz), 7.38-7.42(m, 3H), 7.56-7.60(m, 2H), 8.06(d, 1H, J= 15.7 Hz); ms, m/z 226 (42%, M^+)), *diphenyl diselenide* (yield 27%), and *butynone* in the distilled ethers, evidenced by GLC comparison with an authentic sample (yield undetermined).

The 3,5-dimethylisoselenazole afforded *(Z)-4-phenylseleno-3-penten-2-one* (yield 84%; mp 75-75.5 °C from hexane; ir (KBr) ν, cm^{-1} 1642 (CO), 803 (olefin); ^{1}H-nmr δ, ppm 1.94(d, 3H, J= 1.2 Hz), 2.24(s, 3H), 6.71(q, 1H, J= 1.2 Hz), 7.32-7.41(m, 3H), 7.64-7.67(m, 2H)) and *diphenyl diselenide* (yield 3%).

Reaction with lithium aluminum hydride (LAH)

A stirred suspension of LAH (0.454 g, 12 mmol) in 15 ml of THF was treated with a solution of 3-methylisoselenazole (0.583 g, 3.99 mmol) in 3 ml of THF under nitrogen at room temperature. An intense red color immediately formed and slowly decolorized. After 4 h stirring the mixture was hydrolyzed with ice and 10% aqueous solution of NaOH, then exhaustively extracted with diethyl ether. The extracts were extracted with 1N HCl, then the aqueous phase was evaporated, basified with 5 ml of 10% NaOH and treated in the usual manner with excess of benzoyl chloride to isolate the amine derivative. The benzoyl derivative of 2-aminobutane, separated by PLC on Merck $PF_{254+366}$ silica gel, eluent benzene/ethyl acetate (65:35) was obtained in 35% yield. Mp 83-84 °C (Lit.[11] mp 84-85 °C); ir (KBr) ν, cm^{-1} 3262 (NH), 1620 (CO); ^{1}H-nmr δ, ppm 0.96(t, 3H), 1.22(d, 2H), 1.59(m, 2H), 4.11 (m, 1H), 6.09(s broad, 1H), 7.43(m, 3H), 7.77(m, 2H).

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