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Synthesis of Novel 5-Aryl-1*H*-Tetrazoles

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ABSTRACT: *In this study phenylselenocyanate and some of its derivatives (o-Cl, p-Cl, p-Br, o-NO_2, p-NO_2, o-CH_3, p-CH_3, o-COOH, p-COOH, p-OCH_3 substituted) were synthesized (***3a–3j***). The synthesized compounds were converted to 5-aryl-1*H*-tetrazole (***4a–4j***), by $Et_3N \cdot HCl$-NaN_3 in toluene, which are a new series of phenylselanyl-1H-tetrazoles. The structure of all the presently synthesized compounds were confirmed using spectroscopic methods (FTIR, ^1H NMR, MS).* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:255–258, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20293

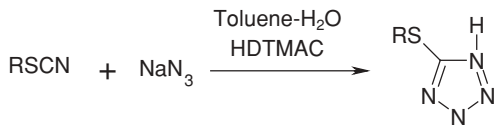
INTRODUCTION

Selenium is an element similar to sulfur in terms of its chemical properties. Humans and animals need selenium for various biological functions. Adult humans have to take 15 μg/kg selenium daily [1]. Deficiency of selenium in the human body may cause cancer, subfertility, and heart diseases [2–5]. Also, selenium and vitamin E have a role in the regulation of the immune system and in the production of testosterone hormones and sperma [6–8]. These activities in the body are usually performed by organoselenium compounds.

Tetrazoles are an increasingly popular functionality [9], with a wide range of applications. They have found use especially in pharmaceuticals as lipophilic spacers and carboxylic acid surrogates [10], in explosives [11], and in photography. In addition, tetrazoles are used in the synthesis of nitrogen-containing heterocycles [12]. Tetrazole derivatives of fatty acid esters are known as substrates for *N*-myristoyl transferase and its respective coenzyme, and show fungicidal and antiviral (including HIV) activities [13].

In the field of heterocyclic synthesis, the chemistry of tetrazoles in cycloaddition reactions has been extensively investigated [14–16]. Huisgen et al. reported that tetrazoles undergo ring cleavage, in high boiling point solvent, to afford the corresponding nitrile imines through extrusion of a nitrogen molecule [15]. The nitrile imines react with dipolarophiles by [2Π + 3Π] cycloaddition to produce pyrazole derivatives [16]. 1,2-Dehydrobenzene (*o*-benzyne) is an example of a dienophilic aryne [17].

Le Blanc and Jursic have shown [18] that 5-alkyl(aryl)thiotetrazoles can be obtained in high yields by the reaction of thiocyanates with sodium azide under conditions of phase transfer catalysis in the presence of hexadecyltrimethylammonium chloride (HDTMAC; see Scheme 1).



SCHEME 1

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RESULTS AND DISCUSSION

In this study, novel selenium compounds were prepared following the reaction sequences depicted in Scheme 2 and were obtained in high yields (75–92%). The final stage of the reaction depends on the pH. Controlling the pH is very important in this stage because the compounds obtained (usually organoselenium) decompose and form a precipitate of elemental red selenium at a pH <5. The precipitation of selenium causes both low yield and presence of some impurities.

The structures of synthesized compounds (phenylselanyl-1*H*-tetrazoles) were identified on the basis of FTIR, ^{1}H NMR, and MS spectral data. Spectral values support the expected structures. The CN bands observed in the IR spectra of **3a–j** disappeared in the IR spectra of **4a–j** as expected. This could be attributed to the conversion of CN groups into the tetrazole ring. The characteristic NH absorption bands appeared between 3667 and 3100 cm^{-1} as broad bands due to the tautomeric structure of tetrazoles and the N=N bands appeared between 1515 and 1606 cm^{-1} and the Ar—H band occurs at 3040 cm^{-1}, approximately. In addition, in the ^{1}H NMR spectra of compounds **4c** and **4d**, a broad signal was seen (between δ 4.7 and 6.9 due to NH protons), which supports the proposed structures. The signal of NH protons could not be seen in the ^{1}H NMR spectra of other compounds because it was recorded in DMSO. The MS spectra values were also compatible with the expected values.

The prepared compounds containing both the tetrazole ring and selenium are thought to be very interesting because of the combination of tetrazole and selenium used in the treatment of some diseases. Also, we suggest that this novel synthetic route can be used to prepare many new compounds that can bind easily to different structures. These can be important not only in the production of tetrazole-containing drugs but also in the synthesis of complex molecules.

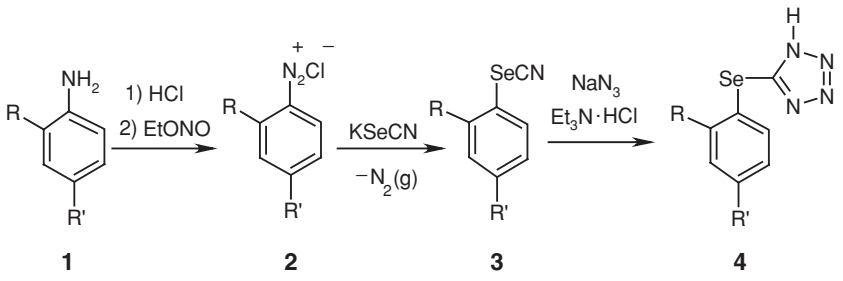
EXPERIMENTAL

Substituted aryl amines and other chemicals were obtained from Merck. All melting points were determined in sealed capillaries and are uncorrected. FTIR spectra were recorded on a Mattson 1000 spectrometer as KBr pellets. ^{1}H NMR spectra were recorded on a Varian Gemini 300 (300 MHz) NMR spectrometer in DMSO-d_6. Mass spectra measurements were recorded on a Thermo Finnigan Trace DSQ.

Typical Procedure

*5-(4-Bromophenylselanyl)-1*H*-tetrazole (4c).* 4-Bromoaniline (1.74 g, 0.01 mol) and concentrated HCl (2.7 mL, 0.04 mol) were mixed slowly. The 4-bromoanilinium chloride was collected, air-dried, and dissolved in 30 mL of absolute alcohol. The stirred solution was cooled to –5 to 0°C and diazotized by careful dropwise addition (over a period of 30 min) of ethyl nitrite (1 mL, 0.006 mol). Both the solution and ethyl nitrite (bp 17°C) must be cold (–5 to 0°C) during the addition. The syntheses of compounds **2c** and **3c** were achieved according to the procedure described in the literature [19]. For that purpose, a solution of KSeCN (1.44 g, 0.01 mol) in 30 mL of absolute alcohol was added into the solution of the diazonium salt (**2c**) obtained previously. The precipitate obtained was recrystallized from absolute ethanol (mp for **3c**: 70–71°C; lit. mp for **3c**: 70.5–71.5°C [20]).

Suspension of triethylammonium chloride (1.37 g, 0.01 mol) in toluene (20 mL) was prepared in a 250-mL two-necked flask equipped with a reflux condenser. Then, sodium azide (0.65 g, 0.01 mol) was slowly added portion-wise with stirring. A solution of 4-bromophenylselenocyanate (**3c**) (2.61 g, 0.01 mol) in toluene (25 mL) was slowly added, stirred for 5 min, and then heated to gentle reflux for 8 h. After cooling the reaction mixture, distilled water (20 mL) was added and the aqueous layer was



SCHEME 2 a) R = Cl, R' = H; b) R = H, R' = Cl; c) R = H, R' = Br; d) R = CH_3, R' = H; e) R = H, R' = CH_3; f) R = NO_2, R' = H; g) R = H, R' = NO_2; h) R = COOH, R' = H; i) R = H, R' = COOH; j) R = H, R' = OCH_3

separated. Then the toluene layer was washed with water (3 × 5 mL) and aqueous extracts were collected (light-brown colored). Then the aqueous layer (pH 8) was cooled to 0–5°C, acidified to pH 5.5 using dilute HCl while stirring for 10 min. The solid precipitate formed was collected and washed with water [21] (mp for **4c**: 170–171°C).

*5-(2-Chlorophenylselanyl)-1*H*-tetrazole (**4a**)*. Yield: 88%; mp 135–136°C; IR ν_{max} (cm^{-1}) (KBr): N—H (tautomeric): 3602–3184; N=N: 1587; C=N: 1522; Ar—H: 3045; Ar(C=C): 1587, 1522, 1336; ^{1}H NMR (DMSO-d_6) δ_H: 6.9 (d, 1H), 7.5 (m, 2H) 8.4 (d, 1H); MS for $C_7H_5N_4ClSe$ ($M^{+\cdot}$): 260, ($M^{+\cdot}$ – tetrazole): 189.

*5-(4-Chlorophenylselanyl)-1*H*-tetrazole (**4b**)*. Yield: 81%; mp 142–143°C; IR ν_{max} (cm (KBr): N—H (tautomeric): 3647–3223; N=N: 1529; C=N: 1478; Ar—H: 3031; Ar(C=C): 1631, 1529, 1478; ^{1}H NMR (DMSO-d_6) 7.4 (d, 1H), 7.7 (d, 1H); MS for $C_7H_5N_4ClSe$ ($M^{+\cdot}$): 260, ($M^{+\cdot}$ – tetrazole): 190, ($M^{+\cdot}$ – Se – tetrazole): 108.

*5-(4-Bromophenylselanyl)-1*H*-tetrazole (**4c**)*. Yield: 90%; mp 170–171°C; IR ν_{max} (cm^{-1}) (KBr): N—H (tautomeric): 3620–3190; N=N: 1540; C=N: 1465; Ar—H: 3032; Ar(C—C): 1651, 1568, 1510; ^{1}H NMR ($CDCl_3$) δ_H: 7.55 (d, 2H), 7.65 (d, 2H), 4.8–6.9 (broad, 1H); MS for $C_7H_5N_4BrSe$ ($M^{+\cdot}$): 304 ($M^{+\cdot}$ – tetrazole): 235, ($M^{+\cdot}$ – Se – tetrazole): 156.

*5-(2-Methylphenylselanyl)-1*H*-tetrazole (**4d**)*. Yield: 92%; mp 136–138°C; IR ν_{max}(cm^{-1}) (KBr): N—H (tautomeric): 3667–3127; N=N: 1515; C=N: 1478; Ar—H: 3037, C—H: 2915; Ar(C=C): 1515, 1478; ^{1}H NMR ($CDCl_3$) δ_H: 7.5 (m, 4H), 4.7–6.3 (broad, 1H), 2.6 (s, 3H); MS for $C_8H_8N_4Se$ ($M^{+\cdot}$): 240, ($M^{+\cdot}$ – tetrazole): 170, ($M^{+\cdot}$ – Se – tetrazole): 91.

*5-(4-Methylphenylselanyl)-1*H*-tetrazole (**4e**)*. Yield: 79%; mp 150–152°C; IR ν_{max}(cm^{-1}) (KBr): N—H (tautomeric): 3621–3275; N=N: 1525; C=N: 1496; Ar—H: 3031, C—H: 2838; Ar(C=C): 1515, 1496; ^{1}H NMR (DMSO-d_6) δ_H: 7.2 (d, 2H), 7.7 (d, 2H), 2.4 (s, 3H); MS for $C_8H_8N_4Se$ ($M^{+\cdot}$ – tetrazole):170, ($M^{+\cdot}$ – Se – tetrazole): 91.

*5-(2-Nitrophenylselanyl)-1*H*-tetrazole (**4f**)*. Yield: 78%; mp 180–181°C; IR ν_{max} (cm^{-1}) (KBr): N—H (tautomeric): 3672–3300; N=N: 1599; C=N: 1515; Ar—H: 3095; Ar(C=C): 1599, 1580, 1515; ^{1}H NMR (DMSO-d_6) δ_H: 6.8 (d, 1H), 7.7 (m, 2H), 8.5 (d, 1H); MS for $C_7H_5N_5O_2Se$ ($M^{+\cdot}$): 271.

*5-(4-Nitrophenylselanyl)-1*H*-tetrazole (**4g**)*. Yield: 75%; mp 154–155°C; IR ν_{max} (cm^{-1}) (KBr): N—H (tautomeric): 3660–3121; N=N: 1606; C=N: 1535; Ar—H: 3056; Ar(C=C): 1606, 1535; ^{1}H NMR (DMSO-d_6) δ_H: 7.9 (d, 1H), 8.2 (d, 1H); MS for $C_7H_5N_5O_2Se$ ($M^{+\cdot}$): 269.

*2-(1*H*-Tetrazol-5-ylselanyl)-benzoic acid (**4h**)*. Yield: 83%; mp 164–165°C; IR ν_{max} (cm^{-1}) (KBr): N—H (tautomeric): 3667–3300; N=N: 1587; C=N: 1518; Ar—H: 3050, O-H: 3474, C=O: 1657; Ar(C=C): 1618, 1587, 1561; ^{1}H NMR (DMSO-d_6) δ_H: 8.3 (d, 1H), 8.2 (d, 1H), 7.6 (m2H); MS for $C_8H_6N_4O_2Se$ ($M^{+\cdot}$): 271.66, ($M^{+\cdot}$ – COOH): 224, ($M^{+\cdot}$ – tetrazole): 200, ($M^{+\cdot}$ – $C_2H_2O_2N_4$): 156, ($M^{+\cdot}$ – Se – tetrazole): 121.

*4-(1*H*-Tetrazol-5-ylselanyl)-benzoic acid (**4i**)*. Yield: 92%; mp 178–180°C; IR ν_{max} (cm^{-1}) (KBr): N—H (tautomeric): 3667–3496; N=N: 1592; C=N: 1481; Ar—H: 3045, O—H: 3496, C=O: 1689; Ar(C=C): 1592, 1567, 1481; ^{1}H NMR (DMSO-d_6) δ_H: 7.6 (d, 2H)–7.9 (d, 2H), 12.9 (s, 1H); MS for $C_8H_6N_4O_2Se$ ($M^{+\cdot}$): 269.47, ($M^{+\cdot}$ – tetrazole): 201 ($M^{+\cdot}$ – Se – tetrazole): 122.

*5-(4-Methoxyphenylselanyl)-1*H*-tetrazole (**4j**)*. Yield: 89%; mp 145–146°C; IR ν_{max} (cm^{-1}) (KBr): N—H (tautomeric): 3647–3217; N=N: 1592; C=N: 1490; Ar—H: 3031, C—H: 2966; Ar(C=C): 1592, 1490; ^{1}H NMR (DMSO-d_6) δ_H: 7.1 (d, 2H)–7.7 (d, 2H), 2.5 (s, 3H); MS for $C_8H_6N_4O_2Se$ ($M^{+\cdot}$): 256.

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