ISSN 1070-4280, Russian Journal of Organic Chemistry, 2009, Vol. 45, No. 1, pp. 151–153. © Pleiades Publishing, Ltd., 2009.
Published in Russian in Zhurnal Organicheskoi Khimii, 2009, Vol. 45, No. 1, pp. 153–155.

Synthesis of Some New 5-Substituted 1*H*-Tetrazoles*

A. Dişli and M. Salman

Department of Chemistry, Faculty Arts and Science, Gazi University, Teknikokullar, 06500, Ankara, Turkey

Received October 30, 2007

Abstract—4-Substituted 1-naphthyl selenocyanates and thiocyanates, as well as 2-naphthyl selenocyanate, were synthesized from the corresponding naphthylamines and were converted into 5-naphthyl-1*H*-tetrazoles by treatment with sodium azide in the presence of triethylamine hydrochloride in toluene. The structure of the newly synthesized compounds was confirmed by IR, ^{1}H NMR, and mass spectra.

DOI: 10.1134/S1070428009010217

Sulfur is a digestion cleansing and antiseptic. Sulfur is found in grains, walnut, almond, and fatty plants. Sulfur is one of the basic components of black gunpowder and batteries and is used in the manufacture of chemicals (fungicides) and rubber. Among recently synthesized insecticides, acaricides, herbicides, and fungicides, 30% of chemicals contain sulfur [1]. Although the use of elemental sulfur as medicine is strongly limited [2], its numerous organic and inorganic derivatives are used in industry, agriculture, and medicine. Sulfur-containing compounds are also used in the manufacture of paper, cloths, sponge, petroleum, steel, dyes, and other materials [3]. Organosulfur compounds unquestionably form an important curative resource, and their potential remains to be further explored [2]. Selenium is an element which resembles sulfur in chemical properties. Humans and animals need it for various biological functions. Adult human beings have to take up 15 μg/kg of selenium daily [4]. Deficiency of selenium in human's body may cause cancer, subfertility, and heart diseases [5, 6]. It is also known that many selenium-containing organic compounds are antibacterial and antifungal agents [7].

In the recent years, a lot of studies on tetrazole derivatives have been reported [8]. Tetrazoles have become very popular due to their functionality and wide range of applications. They are used in explosives [9], photography, and synthesis of nitrogen-containing heterocycles [10]. Tetrazoles may be regarded as biological equivalents of the carboxy group, and extensive studies on tetrazoles have been performed in the field of medicinal chemistry [11]. Remarkable developments have been made in the design of potential antiinflammatory, antiasthmatic [12], and antiviral agents, central nervous stimulants, and hypertensive agents. Pentamethylenetetrazole has been extensively used in models for anxiety [13]. 5-Substituted-1*H*-tetrazoles have found general application as isosteric replacement of carboxylic acids.

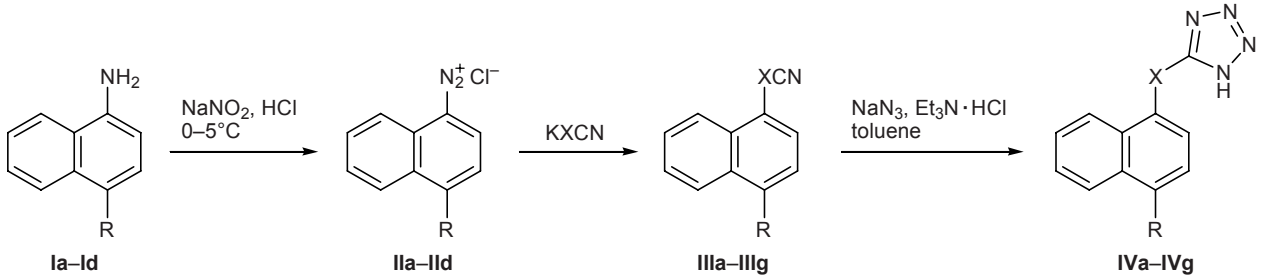
Various methods for the synthesis of tetrazoles are known. Alterman and Hallberg showed that aryl- and vinyl-substituted tetrazoles can be prepared by reaction of the corresponding nitriles with ammonium azide under microwave irradiation [14].

In the present communication we report on the synthesis of new selenium- and sulfur-containing tetrazole derivatives according to Scheme 1. 4-Substituted 1-naphthylamines **Ia**–**Id** were treated with sodium nitrite to obtain the corresponding diazonium salts **IIa**–**IId** which reacted with potassium selenocyanate or thiocyanate. As a result, we obtained 1-naphthyl selenocyanates **IIIa**–**IIId** and thiocyanates **IIIe**–**IIIg**, respectively. Reaction of compounds **IIIa**–**IIIg** with sodium azide in the presence of triethylamine hydrochloride in toluene gave 5-substituted 1*H*-tetrazoles **IVa**–**IVg** in 61–78% yield. In the synthesis of selenium-containing compounds, pH control of the medium was very important; at pH < 5 selenium derivatives decomposed with formation of red elemental selenium, which reduced the product yield and favored formation of other impurities. Following a similar scheme, 2-naphthylamine (**Ie**) was converted into 5-(naphthalen-2-ylselanyl)-1*H*-tetrazole (**IVh**) (Scheme 2).

The structure of 5-(naphthylselanyl)- and 5-(naphthylsulfanyl)-1*H*-tetrazoles **IVa**–**IVh** was confirmed by their IR, ^{1}H NMR, and mass spectra. The IR spectra of **IVa**–**IVh** lacked absorption bands typical of C≡N stretching vibrations in initial seleno(thio)cyanates **III**.

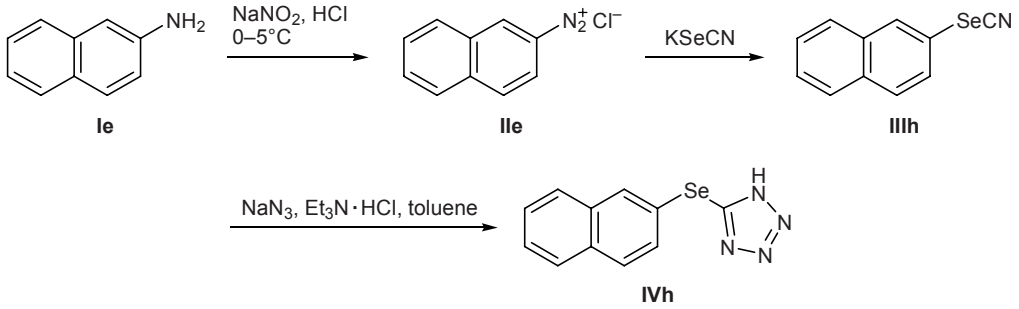
* The text was submitted by the authors in English.

Scheme 1.



I, **II**, R = H (**a**), O_2N (**b**), Cl (**c**), Br (**d**); **III**, **IV**, X = Se (**a**–**d**), S (**e**–**g**); R = H (**a**), O_2N (**b**, **e**), Cl (**c**, **f**), Br (**d**, **g**).

Scheme 2.



Characteristic tetrazole absorption bands appeared in the IR spectra as broad bands in the region 3000–1990 cm^{-1} due to the presence of different tautomers of **IV**, the N=N bonds gave rise to absorption at 1567–1592 cm^{-1}, and stretching vibrations of aromatic C–H bonds were observed at ~3040 cm^{-1}. In the ^1H NMR spectra of compounds **IVa**–**IVh** we observed no NH proton signal, presumably because of fast tautomeric transformations. The mass spectra of **IVa**–**IVh** were consistent with the assumed structures.

Taking into account that tetrazole derivatives and compounds containing sulfur and selenium are used in medicine [2, 7, 11–13], compounds **IVa**–**IVh** containing both tetrazole ring and selenium (or sulfur) atom in a single molecule seem to be very interesting from the viewpoint of their potential use in the treatment of some diseases. The newly synthesized tetrazole derivatives possess both acidic and basic properties; therefore, they can be easily bound to various structures to produce tetrazole-containing drugs or complex molecules stable in acidic and basic media and resistant to oxidants and reducing agents.

EXPERIMENTAL

Substituted aryl amines and other chemicals were obtained from Merck. All melting points were determined in sealed capillaries and are uncorrected. The FT-IR spectra were recorded in KBr on a Mattson 1000 spectrometer. The ^1H NMR spectra were measured on a Varian Gemini 300 spectrometer (300 MHz) from solutions in DMF-d_7 and CD_3OD. The mass spectra were obtained on a Thermo Finnigan Trace DSQ instrument.

5-(Naphthalen-1-ylselanyl)-1*H*-tetrazole (IVa). Naphthalen-1-amine, 1.43 g (0.01 mol) was carefully mixed with concentrated hydrochloric acid, 2.49 ml (0.03 mol), the resulting naphthalen-1-amine hydrochloride was dissolved in 20 ml of water, the solution was cooled to –5 to 0°C, and a solution of 0.69 g (0.01 mol) of sodium nitrite in 10 ml of water was added dropwise under stirring over a period of 30 min. The mixture was adjusted to pH 5.5 by adding a solution of sodium acetate, and 1.44 g (0.01 mol) of potassium selenocyanate was added in portions. A brown solid separated and was filtered off with suction, dried, and purified by recrystallization. We thus obtained 1-naphthyl selenocyanate (**IIIa**) with mp 66–67°C; published data [15]: mp 65–66°C.

A 250-ml two-necked flask equipped with a reflux condenser was charged with a suspension of 1.37 g (0.01 mol) of triethylamine hydrochloride in 20 ml of toluene. Sodium azide, 0.65 g (0.01 mol) was added in portions under stirring, and a solution of 1-naphthyl selenocyanate (**IIIa**), 2.33 g (0.01 mol) in 25 ml of toluene was then slowly added. The mixture was stirred

for 5 min and heated for 8 h under gentle reflux. The mixture was cooled, 20 ml of distilled water was added, the aqueous layer was separated; and the toluene layer was washed with water (3 × 10 ml). The aqueous phase was combined with the aqueous extracts (cream colored, pH 8) and acidified to pH 5.5 using dilute hydrochloric acid under stirring for 10 min. The precipitate was filtered off and washed with water [16]. Yield 78%, mp 149–150°C. IR spectrum (KBr), ν, cm^{-1}: 1592 (N=N); 1503 (C=N); 3037 (C–H_{arom}); 1592, 1503, 1496 (C=C_{arom}). ^1H NMR spectrum (DMF-d_7): δ 8.0 ppm, m (H_{arom}). Mass spectrum, *m*/*z*: 276 $[M]^+$, 207 $[M - CHN_4]^+$.

Compounds **IVb**–**IVh** were synthesized in a similar way.

5-(4-Nitronaphthalen-1-ylselanyl)-1*H*-tetrazole (IVb). Yield 67 %, mp 173–174°C. IR spectrum (KBr), ν, cm^{-1}: 1561 (N=N); 1503 (C=N); 3056 (C–H_{arom}); 1561, 1522, 1503 (C=C_{arom}). ^1H NMR spectrum (DMF-d_7): δ 8.2 ppm, m (H_{arom}). Mass spectrum: *m*/*z* 251 $[M - CHN_4]^+$.

5-(4-Chloronaphthalen-1-ylselanyl)-1*H*-tetrazole (IVc). Yield 61%, mp 172–173°C. IR spectrum (KBr), ν, cm^{-1}: 1580 (N=N); 1496 (C=N); 3037 (C–H_{arom}); 1618, 1580, 1496 (C=C_{arom}). ^1H NMR spectrum (DMF-d_7): δ 8.1 ppm, m (H_{arom}). Mass spectrum, *m*/*z*: 310 $[M]^+$, 241 $[M - CHN_4]^+$.

5-(4-Bromonaphthalen-1-ylselanyl)-1*H*-tetrazole (IVd). Yield 63%, mp 153–155°C. IR spectrum (KBr), ν, cm^{-1}: 1573 (N=N); 1496 (C=N); 3050 (C–H_{arom}); 1618, 1573, 1496 (C=C_{arom}). ^1H NMR spectrum (DMF-d_7): δ 7.9 ppm, m (H_{arom}). Mass spectrum, *m*/*z*: 275 $[M - Br]^+$, 207 $[M - Br - CHN_4]^+$.

5-(4-Nitronaphthalen-1-ylsulfanyl)-1*H*-tetrazole (IVe). Yield 64%, mp 177–178°C. IR spectrum (KBr), ν, cm^{-1}: 1569 (N=N); 1503 (C=N); 3056 (C–H_{arom}); 1620, 1569, 1503 (C=C_{arom}). ^1H NMR spectrum (DMF-d_7): δ 8.1 ppm, m (H_{arom}). Mass spectrum, *m*/*z*: 273 $[M]^+$, 205 $[M - CHN_4]^+$.

5-(4-Chloronaphthalen-1-ylsulfanyl)-1*H*-tetrazole (IVf). Yield 38%, mp 188–190°C. IR spectrum (KBr), ν, cm^{-1}: 1567 (N=N); 1503 (C=N); 3050 (C–H_{arom}); 1645, 1567, 1503 (C=C_{arom}). ^1H NMR spectrum (DMF-d_7): δ 7.9 ppm, m (H_{arom}). Mass spectrum: *m*/*z* 262 $[M - CHN_4]^+$.

5-(4-Bromonaphthalen-1-ylsulfanyl)-1*H*-tetrazole (IVg). Yield 61%, mp 172–173°C. IR spectrum (KBr), ν, cm^{-1}: 1580 (N=N); 1510 (C=N); 3056 (C–H_{arom}); 1650, 1580, 1525, 1510 (C=C_{arom}). ^1H NMR spectrum (CD_3OD): δ 7.9 ppm, m (H_{arom}). Mass spectrum, *m*/*z*: 306 $[M]^+$, 237 $[M - CHN_4]^+$, 159 $[M - Br - CHN_4]^+$.

5-(Naphthalen-2-ylselanyl)-1*H*-tetrazole (IVh). Yield 62%, mp 161°C. IR spectrum (KBr), ν, cm^{-1}: 1587 (N=N); 1490 (C=N); 3030 (C–H_{arom}); 1625, 1587, 1490 (C=C_{arom}). ^1H NMR spectrum (DMF-d_7): δ 8.0 ppm, m (H_{arom}). Mass spectrum, *m*/*z*: 276 $[M]^+$, 206 $[M - CH_2N_4]^+$.

REFERENCES

1. Brooks, G.T., *Sulphur Containing Drugs and Related Organic Compounds: Chemistry, Biochemistry, and Toxicology*, Damani, L.A., Ed., Chichester: Ellis Horwood, 1989, vol. 1, part A, p. 62.
2. Mitchard, M., *Drug Metabol. Drug Interact*., 1988, vol. 6, p. 183.
3. Damani, L.A. and Mitchard, M., *Sulphur Containing Drugs and Related Organic Compounds: Chemistry, Biochemistry, and Toxicology*, Damani, L.A., Ed., Chichester: Ellis Horwood, 1989, vol. 1, part A, p. 93.
4. Rayman, M.P., *Lancet*, 2000, vol. 356, p. 233.
5. Rayman, M.P., *Brit. Med. J*., 1997, vol. 314, p. 387.
6. Chen, X., Yang, G., Chen, J.,Wen, Z., Ge, K., *Biol. Trace Elem. Res*., 1980, vol. 2, p. 91.
7. Günther, W.H.H., *Organic Selenium Compounds: Their Chemistry and Biology*; Klayman, D.L. and Günther, W.H.H., Eds., New York: Wiley, 1973, p. 30.
8. Butler, R.N., *Comprehensive Heterocyclic Chemistry II*, Katritzky, A.R., Rees, C.W, and Scriven, E.F.V., Eds., Oxford: Pergamon, 1996, vol. 4.
9. Mohan, V.K. and Tang, B.T., *J. Chem. Phys*., 1983, vol. 79, p. 4271.
10. Koldobskii, G.L. and Ostrovskii, V.A., *Usp. Khim*., 1994, vol. 63, p. 847.
11. Jin, T., Kamijo, S., and Yamamoto, Y., *Tetrahedron Lett*., 2004, vol. 45, p. 9435.
12. Herr, R.J., *Bioorg. Med. Chem*., 2002, vol. 10, p. 3379.
13. Eshghi, H. and Hassankhani, A., *Synth. Commun*., 2005, vol. 35, p. 1115.
14. Alterman, M. and Hallberg, A., *J. Org. Chem*., 2000, vol. 65, p. 7984.
15. Yavuz, S., Dişli, A., Yıldırır, Y., and Türker, L., *MoleculeS*, 2005, vol. 10, p. 1000.
16. Srinivas, K., Nair, C.K.S., Ramesh, S., and Pardhasaradhi, M., *Org. Prep. Proced. Int*., 2004, vol. 36, p. 69.