ORIGINAL ARTICLE

1,2,4-TRIAZOLES AS INTERMEDIATES FOR THE SYNTHESIS OF HYBRID MOLECULES

GEORGETA ŞERBAN*

University of Oradea, Faculty of Medicine and Pharmacy, Pharmaceutical Chemistry Department, 29 Nicolae Jiga, 410028 Oradea, România

**corresponding author: getaserban_2000@yahoo.com*

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Abstract

This paper aim was to present some new heterocyclic compounds from the class of 1,2,4-triazole-3-thione which have been synthesized by intramolecular cyclization of the corresponding thiosemicarbazides with ammonia. 4-R-1-cyanoacetylthiosemicarbazides were obtained by nucleophilic addition of cyanoacetic acid hydrazide to different isothiocyanates. The structures of the newly synthesized compounds were elucidated by spectral data and elemental analysis..

Rezumat

Scopul acestei lucrări a fost de a prezenta noi compuşi din clasa 1,2,4-triazol-3-tionelor, sintetizaţi prin ciclizarea intramoleculară a tiosemicarbazidelor corespunzătoare, cu amoniac. 4-R-1-cianacetil tiosemicarbazidele au fost obţinute prin adiţia nucleofilă a cianacethidrazidei la diverşi izotiocianaţi. Structurile noilor compuşi sintetizaţi au fost elucidate pe baza datelor spectrale şi analizei elementale.

Keywords: 1,2,4-triazoles; hybrid molecules; isothiocyanates; intramolecular cyclization

Introduction

Heterocyclic compounds have an important place among organic compounds with biological activity, used as drugs in human and veterinary medicine or as insecticides and pesticides in agriculture. Triazoles, five-membered heterocyclic rings, are one of the most important heterocycles. After the triazole synthesis by Fischer in 1878, the syntheses of substituted triazole derivatives have recorded a considerable numerical increase [1, 8, 11].

Triazoles have been shown to possess some desirable features such as good stability to acidic/basic hydrolysis and oxidative/reductive conditions and resistance to metabolic degradation. Moreover, the variety of biological activities and wide range of therapeutic properties brought 1,2,4-triazole derivatives to the attention of researchers [4, 5, 9, 13, 19, 20]. There are some known drugs containing 1,2,4-triazole ring such as antifungal azoles (fluconazole, itraconazole, posaconazole, ravuconazole, terconazole, voriconazole, isavuconazole, albaconazole) [3, 10, 11, 17], aromatase inhibitors (anastrozole, letrozole, vorozole) [11, 14], diazepines analogs (alprazolam, estazolam, triazolam) [10, 11], or the antiviral agent ribavirin [10, 11].

There have been several studies regarding the synthesis and biological activity of thio (mercapto) derivatives of 1,2,4-triazoles. It should be noted their antibacterial and antifungal [12, 13], anti-inflammatory and analgesic [7, 13, 18] or anti-convulsive activities [2, 13]. The combination of two or more pharmacophores into a single molecule is an efficient way to achieve new therapeutic agents [4]. The purpose of the present study was the synthesis of some substituted 3-mercapto-1,2,4-triazoles/1,2,4-triazole-3-thiones as intermediates for some hybrid molecules.

Materials and Methods

Melting points were determined by open glass capillary method, with a Schmelzpunkt Bestimmer Apotec apparatus and are uncorrected. The time reaction was checked by thin layer chromatography (TLC). The TLC analysis was performed on Silica gel 60 F_{254} Merck plates using chloroform-methanol (15:1) solvent system. The chromatograms were visualized by exposure in UV light. The IR spectra were recorded as KBr pellets using a JASCO FTIR-615 spectrophotometer. The proton nuclear magnetic resonance (^{1}H-NMR) spectra (in methanol or deuteriochloroform) were recorded by a Varian Mercury-300 spectrometer with tetramethylsilane (TMS) as internal standard (δ 0.0). The chemical shifts were reported in parts per million (ppm), relative to the residual peak of the deuterated solvent (s-singlet, d-doublet, t-triplet, q-quartet, m-multiplet). The fast atom bombardment mass spectrometry (FAB-MS) spectra were obtained using a VG-70SE mass spectrometer. The elemental analysis was performed using Vario El analyser.

All chemicals and solvents were of analytical grade and were purchased from Fluka Chemie, Merck, Farmachim, Reactivul Bucureşti, Chimprod.

General procedure for the synthesis of 5-cyanomethyl-4-R-2,4-dihydro-3H-1,2,4-triazole-3-thiones ***9a-g***

A fine powder of the corresponding thiosemicarbazides **8** (6 mmol) was solved in 20% ammonia (70 mmol) and the mixture was refluxed for 30 min. Cooling the reaction mixture, the secondary product (corresponding thioureas) precipitated and was collected by filtration. The resulted filtrate was acidified with diluted hydrochloric acid to pH 4 - 5. The resulting triazole was filtered, washed with cold water, dried and recrystallized from ethanol to obtain the desired product **9**.

Results and Discussion

The synthetic pathway followed for the preparation of 5-cyanomethyl-4-R-2,4-dihydro-3H-1,2,4-triazole-3-thiones **9a-g** is outlined in Figure 1.

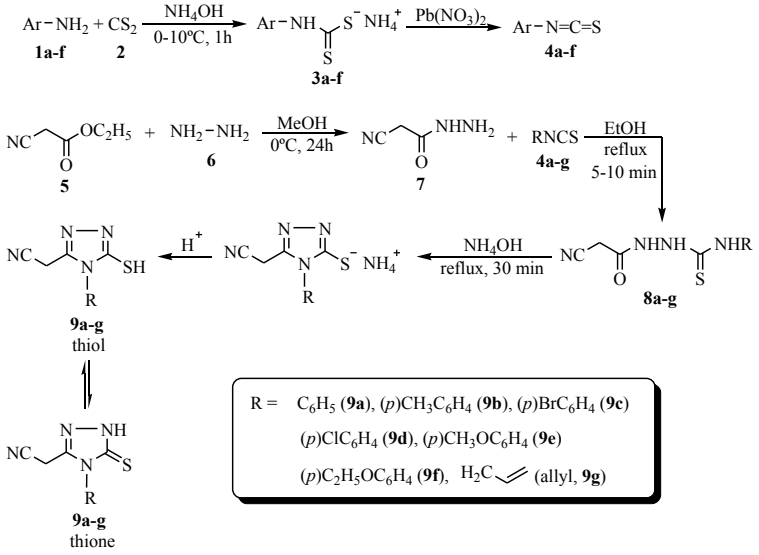

Figure 1.
The synthesis of 5-cyanomethyl-4-R-2,4-dihydro-3H-1,2,4-triazole-3-thiones **9a-g**

4-R-1-cyanoacetyl thiosemicarbazides **8a-g**, the key intermediates, were synthesized by a method previously reported [15, 16] using ethylcyano-acetate **5** and hydrazine hydrate **6** as starting materials. Excepting allyl isothiocyanate **4g** which was purchased, the aromatic isothiocyanates **4a-f** were synthesized according to a literature method [6] by treating the primary amines **1a-f** with carbon disulphide **2** and concentrated aqueous ammonia at low temperature (0 - 10ºC). The intermediate ammonium dithio-carbamates **3a-f** were converted into the iso-thiocyanates **4a-f** after the reaction with lead nitrate and separated by steam-distillation. The nucleophilic addition of cyanoacetic acid hydrazide **7** to the isothiocyanates **4a-g** in ethanol under reflux gave the thiosemicarbazides **8a-g** with reasonable good yields. For the synthesis of 5-cyanomethyl-4-R-2,4-dihydro-3H-1,2,4-triazole-3-thiones **9a-g**, the thio-semicarbazides **8a-g** were subjected to intra-molecular cyclization in 20% ammonia under reflux.

The synthesized compounds **9a-g** are white crystals or white needles, soluble in methanol, ethanol and dimethylsulfoxide, slightly soluble in chloroform, less soluble in water. The spectral data of all the newly synthesized 1,2,4-triazoles were in accordance with the proposed structures. The IR spectra revealed the presence of C=N stretching bands (1559 - 1550 cm^{-1}), as an evidence for the ring closure. 1,2,4-Triazoles **9a-g** may exist in the thiol and thione forms. According to the IR spectral data, the compounds **9a-g** have predominantly the thione structure in the solid state (C=S stretching bands at 1257 - 1255 cm^{-1} with very strong intensity, SH absorption bands at 2360 - 2340 cm^{-1} with very weak intensity). The NH stretching bands were observed at 3444 - 3420 cm^{-1} confirming the thione form. All protons were seen in the ^{1}H-NMR with the expected chemical shifts. The signals belonging to -NH proton indicated that these compounds have thione structure in solution also. The mass spectra of the 1,2,4-triazole compounds showed the molecular peaks in agreement with their molecular formula.

*5-cyanomethyl-4-phenyl-2,4-dihydro-3H-1,2,4-triazole-3-thione (****9a****).* White crystals, mp 220 - 221°C (ethanol), 70% yield. IR (KBr) cm^{-1}: 3440

(NH), 3070 (=CH), 2255 (C≡N), 1550 (C=N), 1505, 1480 (C=C), 1255 (C=S). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.64 (s, 2H, CH_2), 7.37 - 7.4 (m, 2H, Ar-H), 7.62 - 7.64 (m, 3H, Ar-H), 7.78 (s, 1H, NH). MS (FAB, positive ion mode) *m/z* 217 [M+H$^+$]. *Anal.* Calcd for $C_{10}H_8N_4S$: C, 55.54; H, 3.73; N, 25.91; S, 14.83. Found: C, 55.76; H, 3.97; N, 25.62; S, 14.67. MW 216.26.

*5-cyanomethyl-4-(4-methylphenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (**9b**)*. White powder, mp 217 - 218°C (ethanol), 72% yield. IR (KBr) cm^{-1}: 3439 (NH), 3047 (=CH), 2240 (C≡N), 1555 (C=N), 1517, 1487 (C=C), 1255 (C=S). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.45 (s, 3H, CH_3), 3.63 (s, 2H, CH_2), 7.25 (d, 2H, Ar-H), 7.41 (d, 2H, Ar-H), 7.75 (s, 1H, NH). MS (FAB, positive ion mode) *m/z* 231 [M+H$^+$]. *Anal.* Calcd for $C_{11}H_{10}N_4S$: C, 57.37; H, 4.38; N, 24.33; S, 13.92. Found: C, 57.51; H, 4.21; N, 24.09; S, 14.13. MW 230.29.

*5-cyanomethyl-4-(4-bromophenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (**9c**)*. White powder, mp 227 - 228°C (ethanol), 65% yield. IR (KBr) cm^{-1}: 3430 (NH), 3045 (=CH), 2215 (C≡N), 1554 (C=N), 1504, 1456 (C=C), 1257 (C=S), 588 (C-Br). ^{1}H-NMR (300 MHz, CD_3OD) δ: 3.98 (s, 2H, CH_2), 7.37 (d, 2H, Ar-H), 7.77 (d, 2H, Ar-H), 7.81 (s, 1H, NH). MS (FAB, positive ion mode) *m/z* 295, 297 [M+H$^+$]. *Anal.* Calcd for $C_{10}H_7BrN_4S$: C, 40.69; H, 2.39; N, 18.98; S, 10.86. Found: C, 40.82; H, 2.11; N, 19.23; S, 10.53. MW 295.16.

*5-cyanomethyl-4-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (**9d**)*. White powder, mp 220 - 223°C (ethanol), 68% yield. IR (KBr) cm^{-1}: 3444 (NH), 3041 (=CH), 2225 (C≡N), 1553 (C=N), 1507, 1456 (C=C), 1257 (C=S), 755 (C-Cl). ^{1}H-NMR (300 MHz, CD_3OD) δ: 3.99 (s, 2H, CH_2), 7.44 (d, 2H, Ar-H), 7.62 (d, 2H, Ar-H), 7.80 (s, 1H, NH). MS (FAB, positive ion mode) *m/z* 251, 253 [M+H$^+$]. *Anal.* Calcd for $C_{10}H_7ClN_4S$: C, 47.91; H, 2.81; N, 22.35; S, 12.79. Found: C, 47.68; H, 3.12; N, 22.13; S, 12.64. MW 250.71.

*5-cyanomethyl-4-(4-methoxyphenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (**9e**)*. White needles, mp 208 - 209°C (ethanol), 76% yield. IR (KBr) cm^{-1}: 3431 (NH), 3072 (=CH), 2233 (C≡N), 1555 (C=N), 1519, 1487 (C=C), 1256 (C=S). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.63 (s, 2H, CH_2), 3.88 (s, 3H, OCH_3), 7.09 (d, 2H, Ar-H), 7.30 (d, 2H, Ar-H), 7.78 (s, 1H, NH). MS (FAB, positive ion mode) *m/z* 247 [M+H$^+$]. *Anal.* Calcd for $C_{11}H_{10}N_4OS$: C, 53.64; H, 4.09; N, 22.75; S, 13.02. Found: C, 53.86; H, 3.87; N, 22.93; S, 12.89. MW 246.29.

*5-cyanomethyl-4-(4-ethoxyphenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (**9f**)*. White needles, mp 219 - 220°C (ethanol), 78% yield. IR (KBr) cm^{-1}: 3437 (NH), 3072 (=CH), 2235 (C≡N), 1559 (C=N), 1516, 1490 (C=C), 1257 (C=S). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.46 (t, 3H, CH_3), 3.63 (s, 2H, CH_2), 4.10 (q, 2H, CH_2), 7.07 (d, 2H, Ar-H), 7.28 (d, 2H, Ar-H), 7.79 (s, 1H, NH). MS (FAB, positive ion mode) *m/z* 261 [M+H$^+$]. *Anal.* Calcd for $C_{12}H_{12}N_4OS$: C, 55.37; H, 4.65; N, 21.52; S, 12.32. Found: C, 55.12; H, 4.78; N, 21.76; S, 12.09. MW 260.31.

*5-cyanomethyl-4-(2-propenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (**9g**)*. White powder, mp 168 - 169°C (ethanol), 83% yield. IR (KBr) cm^{-1}: 3420 (NH), 2938 (CH=CH_2), 2211 (C≡N), 1556 (C=N), 1255 (C=S). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.82 (s, 2H, CH_2-CN), 4.79 - 4.82 (m, 2H, N-CH_2), 5.3 - 5.40 (m, 2H, =CH_2), 5.82 - 5.98 (m, 1H, -CH=), 7.78 (s, 1H, NH). MS (FAB, positive ion mode) *m/z* 181 [M+H$^+$]. *Anal.* Calcd for $C_7H_8N_4S$: C, 46.65; H, 4.47; N, 31.09; S, 17.79. Found: C, 46.87; H, 4.65; N, 31.34; S, 17.52. MW 180.23.

Conclusions

A series of 5-cyanomethyl-4-R-2,4-dihydro-3H-1,2,4-triazole-3-thiones were synthesized with good yields by the cyclisation of the corresponding thiosemicarbazides with ammonia solution at reflux. The structures were determined by elemental analysis and spectral data. IR and ^{1}H-NMR spectra suggested that the thione form is predominant in solid state and solution. The synthesized compounds are intermediates for some hybrid molecules with biological potential.

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