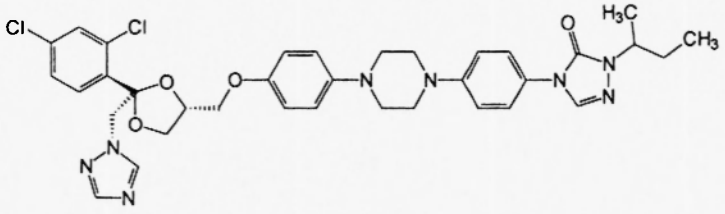
ORGANIC SULFUR COMPOUNDS. VI. 5-(2-THIENYLMETHYL)-1,2,4-TRIAZOLE DERIVATIVES

Gheorghe Roman[a], Ileana Manciulea[a], Rodinel Ardeleanu[b], Lucia Dumitrescu[a]*
[a]Department of Chemistry, Transilvania University, 29 Eroilor Blvd., Braşov, 500036, Romania
[b]P. Poni Institute for Macromolecular Chemistry, 41A Gr. Ghica Vodă Alley, Iaşi, 700487, Romania

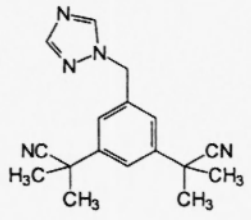
Abstract : New 1,2,4-triazole-3-thiones and 1,2,4-triazole-3-ones bearing a 2-thienylmethyl moiety in position 5 have been synthesized through the cyclization in the presence of aqueous KOH of the corresponding 1-(2-thienylacetyl)thiosemicarbazides and 1-(2-thienylacetyl)semicarbazides, respectively. Potassium N'-(2-thienylacetyl)hydrazinecarbodithioate led to 4-amino-3-mercapto-5-(2-thienylmethyl)-1,2,4-triazole on treatment with hydrazine hydrate.

INTRODUCTION

There is a growing interest in the chemistry and biological properties of 1,2,4-triazoles nowadays. 1,2,4-Triazoles have long aroused much attention (1) and their chemistry has been recently reviewed (2). Nowadays, variously well-established pharmaceutical applications of 1,2,4-triazole derivatives are known, and the most significant pharmacological use of 1,2,4-triazole derivatives lies with antifungal drugs (3). Posaconazole (4) or its analog itraconazole 1 (5) are only two examples of marketable 1,2,4-triazole-containing drugs used to fight systemic and superficial

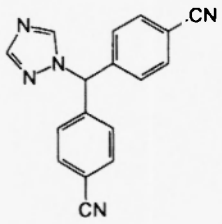


1

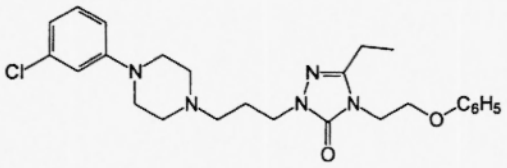


2

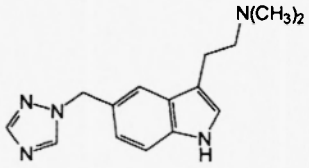
fungal infections. Other illustrations of drugs retaining a 1,2,4-triazole moiety refer to non-steroidal aromatase inhibitors anastrozole 2 and letrozole 3 (6), which provide a superior efficacy and exhibit a better toxicity profile in the first- and second-line hormonal therapy of metastatic breast cancer than the "gold standard" tamoxifen. Moreover, nefazodone 4 (7), an attractive choice for both the short- and long-term treatment of depression due to its good management of depression-related anxiety symptoms, an established tolerability profile, and a multimodal mechanism of action, and rizatriptan 5, an orally active serotonin 5-HT_1 receptor agonist that provides fast pain relief in the treatment of acute migraines (8), also belong to 1,2,4-triazole-derived drugs. However, the search for new pharmacological applications of 1,2,4-triazoles is an ongoing process, as proven by the recent literature reports on their anti-inflammatory (9-11), antimicrobial (12-14) or antidepressant (15) activity, as well as on 1,2,4-triazole derivatives' ability to function as 5- HT_{1A}



3



4



5

serotonin receptor ligands (16) or as benzodiazepine receptor agonists (17).

In the framework of our program dedicated to the study of the chemistry of organic sulfur compounds (18-21), the present paper presents the synthesis of several 1,2,4-triazole derivatives having a 2-thienylmethyl moiety in position 5.

EXPERIMENTAL

Melting points were determined on a Boetius hot-stage microscope and are uncorrected. Elemental analysis was performed on a Carlo Erba 1106 analyzer. HPLC analysis was conducted on Waters instrument, using a Symmetry Shield RP_{18} 3,5 μm (4,6 x 50 mm) column and water (0.1% TFA) and acetonitrile (0.1% TFA) as solvents. The flow rate was 1.5 mL/min, and an acetonitrile gradient (0-80%) was applied for 10 minutes, starting 30 sec. after the injection had occured. IR spectra were taken on a Specord M80 apparatus in KBr pellets. ^{1}H-NMR spectra were recorded on a Brucker DRX (500 MHz) spectrometer in $CDCl_3$ (TMS as internal standard) or d_6-DMSO. Thiosemicarbazides 6a-c, semicarbazides 8a-c, bis-semicarbazide 8d and potassium N'-(2-thienylacetyl)hydrazinecarbodithioate 10 were prepared as described (22).

General procedure for the synthesis of triazolethiones 7a-c and triazolones 9a-d

Thiosemicarbazides 6a-c (10 mmoles) or semicarbazides 8a-c (10 mmoles) or bis-semicarbazide 8d (5 mmoles) were added to a solution prepared from 1 g KOH in 20 mL water, and the mixture was refluxed for 3 hrs. The resulting solution was cooled to room temperature and filtered. By slowly addition of 10% acetic acid to pH 6, triazolethiones 7a-c or triazolones 9a-d precipitated and were filtered off, thoroughly washed with water, air-dried and recrystallized.

4-Phenyl-5-(2-thienylmethyl)-1,2,4-triazol-3-thione 7a. 2.38 g (87%) of beige crystals, m.p. 162-163°C (ethanol). Found: C, 57.03; H, 3.96; N, 15.52. $C_{13}H_{11}N_3S_2$ requires C, 57.14; H, 4.03; N, 15.38. R_t=8 min. IR (ν, cm^{-1}): 1340 (>C=S). ^{1}H-NMR ($CDCl_3$, δ, ppm): 4.06 (2H, s, $-CH_2-$); 6.56 (1H, s, H_A); 6.83 (1H, d, $J_{1,2}$=4 Hz, H_B); 7.13-7.22 (3H, m, Ar-H + H_C); 7.47-7.55 (3H, m, Ar-H); 11.50 (1H, s, -NH-CS-).

4-(4-Bromophenyl)-5-(2-thienylmethyl)-1,2,4-triazol-3-thione 7b. 2.71 g (77%) of beige crystals, m.p. 146-147°C (ethanol). Found: C, 44.46; H, 2.77; N, 12.02. $C_{13}H_{10}BrN_3S_2$ requires C, 44.31; H, 2.84; N, 11.93. R_t=9 min. IR (ν, cm^{-1}): 1340 (>C=S). ^{1}H-NMR ($CDCl_3$, δ, ppm): 4.06 (2H, s, $-CH_2-$); 6.59 (1H, s, H_A); 6.87 (1H, s, H_B); 7.06 (2H, d, $J_{1,2}$=7.8 Hz, Ar-H *meta* to Br); 7.17 (1H, d, $J_{1,2}$=4.1 Hz, H_C); 7.62 (2H, d, $J_{1,2}$=7.8 Hz, Ar-H *ortho* to Br); 11.52 (1H, s, -NH-CS-).

4-Allyl-5-(2-thienylmethyl)-1,2,4-triazol-3-thione 7c. 1.75 g (74%) of beige crystals, m.p. 114-115°C (ethanol). Found: C, 50.54; H, 4.77; N, 17.62. $C_{10}H_{11}N_3S_2$ requires C, 50.63; H, 4.64; N, 17.72. R_t=7.45 min. IR (ν, cm^{-1}): 1360 (<C=S). ^{1}H-NMR ($CDCl_3$, δ, ppm): 4.22 (2H, s, $-CH_2-$); 4.59 (2H, s, $-CH_2-CH=CH_2$); 5.13 (1H, d, J_{trans}=17.1 Hz, $-CH_2-CH=CH_2$); 5.26 (1H, s, J_{cis}=10 Hz, $-CH_2-CH=CH_2$); 5.79-5.83 (1H, m, $-CH_2-CH=CH_2$); 6.88 (1H, s, H_A); 6.97 (1H, s, H_B); 7.24 (1H, d, $J_{1,2}$=4.2 Hz, H_C); 11,68 (1H, s, -NH-CS-).

4-Phenyl-5-(2-thienylmethyl)-1,2,4-triazol-3-one 9a. 1.57 g (61%) of beige crystals, m.p. 186-187°C (ethanol). Found: C, 60.58; H, 4.20; N, 16.45. $C_{13}H_{11}N_3OS$ requires C, 60.70; H, 4.28; N, 16.34. R_t=7.1 min. IR (ν, cm^{-1}): 1705 (>C=O). ^{1}H-NMR ($CDCl_3$, δ, ppm): 4.01 (2H, s-CH_2-); 6.60 (1H, s, H_A); 6.84 (1H, s, H_B); 7.14 (1H, d, $J_{1,2}$=4 Hz, H_C); 7.19 (2H, bs, Ar-H); 7.45 (3H, bs, Ar-H); 9.97 (1H, s, -NH-CO-).

4-(1-Naphthyl)-5-(2-thienylmethyl)-1,2,4-triazol-3-one 9b. 1.93 g (63%) of brown crystals, m.p. 191-192°C (ethanol). Found: C, 66.56; H, 4.27; N, 13.53. $C_{17}H_{13}N_3OS$ requires C, 66.44; H, 4.23; N, 13.68. R_t=8.1 min. IR (ν, cm^{-1}): 1700 (>C=O). ^{1}H-NMR (d_6-DMSO , δ, ppm): 3.89 (2H, dd, *J*=16.9 Hz, -CH_2-); 6.37 (1H, s, H_A); 6.65 (1H, s, H_B); 7.19 (1H, d, $J_{1,2}$=4 Hz, H_C); 7.35 (1H, d, $J_{1,2}$=7.5 Hz, Ar-H); 7.42-7.64 (4H, m, Ar-H); 8.07 (2H, dd, *J*=7.8 Hz, Ar-H); 11.96 (1H, s, -NH-CO-).

4-Isopropyl-5-(2-thienylmethyl)-1,2,4-triazol-3-one 9c. 1.40 g (63%) of white crystals, m.p. 163-164°C (ethanol). Found: C, 53.69; H, 5.75; N, 18.92. $C_{10}H_{13}N_3OS$ requires C, 53.81; H, 5.83; N, 18.83. R_t=6.4 min. IR (ν, cm^{-1}): 1695 (>C=O). ^{1}H-NMR ($CDCl_3$, δ, ppm): 1.40 (6H, d, *J*=6.4 Hz, -CH_3); 4.07-4.21 (1H, m, -CH<); 4.13 (2H, s, -CH_2-); 6.92 (1H, s, H_A); 6.99 (1H, s, H_B); 7.25 (1H, bs, H_C); 10.18 (1H, s, -NH-CO-).

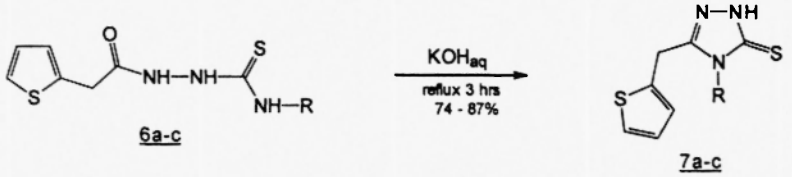
4-(6-(3-Oxo-5-(2-thienylmethyl)-1,2,4-triazol-4-yl)hexyl)-5-(2-thienylmethyl)-1,2,4-triazol-3-one 9d. 1.78 g (80%) of beige crystals, m.p. 212-213°C (ethanol). Found: C, 54.17; H, 5.51; N, 18.54. $C_{20}H_{24}N_6O_2S_2$ requires C, 54.05; H, 5.40; N, 18.69. R_t=7.3 min. IR (ν, cm^{-1}): 1700 (>C=O). ^{1}H-NMR (d_6-DMSO, δ, ppm): 1.06 (4H, bs, -CH_2-); 1.22 (4H, bs, -CH_2-); 3.36-3.47 (4H, m, -CH_2N<); 4.16 (4H, s, -CH_2- bridging the two heterocyclic rings); 6.98 (2H, d, $J_{1,2}$=4.6 Hz, H_A); 7.00 (2H, s, H_B); 7.42 (2H, d, $J_{1,2}$=4.6 Hz, H_C); 11.55 (2H, s, -NH-CO-).

General procedure for the synthesis of 4-amino-5-(2-thienylmethyl)-1,2,4-triazol-3-thione 11.

Potassium N'-(2-thienylacetyl)hydrazinecarbodithioate 10 (2,7 g, 10 mmoles), hydrazine hydrate (1g, 1 mL) and water (2 mL) were refluxed for 4 hrs. The reaction mixture was cooled at room temperature, water (10 mL) was added, and then the solution was treated dropwise with 10% HCl until pH reached 6. The precipitate was filtered off, washed thoroughly with water, air-dried and recrystallized to give 0.64 g (30%) of beige crystals, m.p. 154-155°C (ethanol). Found: C, 39.75; H, 3.84; N, 26.52. $C_7H_8N_4S_2$ requires C, 39.62; H, 3.77; N, 26.41. R_t=5.75 min. ^{1}H-NMR (d_6-DMSO, δ): 4.23 (2H, s, -CH_2-); 5.56 (2H, s, -NH_2); 6.96 (1H, d, $J_{1,2}$=4.9 Hz, H_A); 6.98 (1H, s, H_B); 7.40 (1H, d, $J_{1,2}$=4.9 Hz, H_C); 13.56 (1H, s, -NH-CS-).

RESULTS AND DISCUSSION

1-(2-Thienylacetyl)thiosemicarbazides 6a-c were turned *via* an intramolecular dehydrative cyclization in the presence of aqueous KOH into the corresponding 5-(2-thienylmethyl)-1,2,4-triazol-3-thiones 7a-c (Scheme 1). The ring closure proceeded smoothly in a homogeneous medium, affording, after a short reaction time good yields of triazolethiones, which can be easily isolated from the reaction mixture by precipitation with dilute acetic acid.

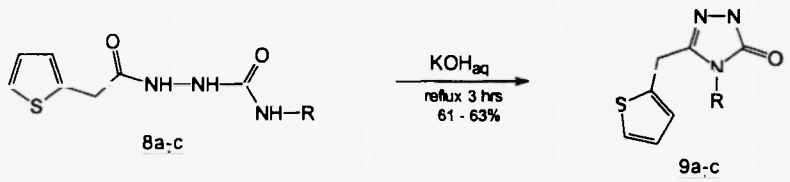


6a-c 7a-c

a: C_6H_5-; b: 4-BrC_6H_4-; c: CH_2=CH-CH_2-

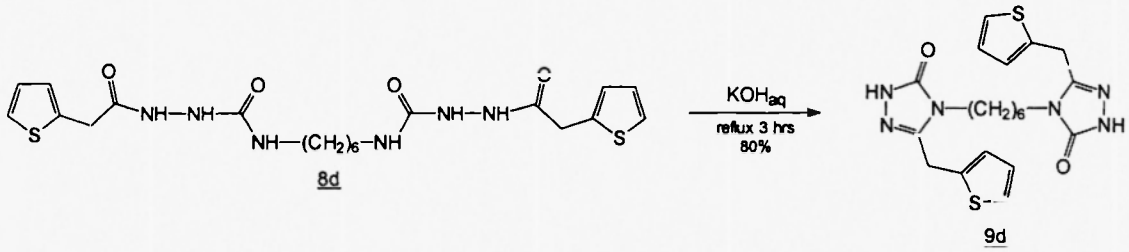
Scheme 1. Cyclization of thiosemicarbazides 6a-c to triazolethiones 7a-c

In a similar manner, 1-(2-thienylacetyl)semicarbazides 8a-c gave access 5-(2-thienylmethyl)-1,2,4-triazol-3-ones 9a-c (Scheme2).



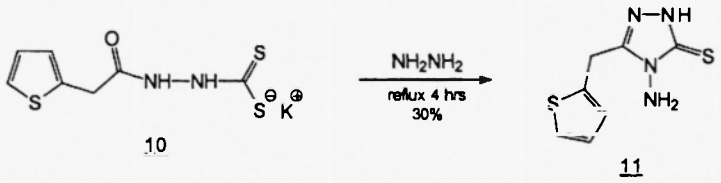
Scheme 2. Cyclization of semicarbazides 8a-c to triazolones 9a-c

A compound containing two triazole ring linked together in position 4 by a six carbon atom chain has also been prepared. Thus, under the same reaction conditions, bis-semicarbazide 8d led to bis-triazolone 9d (Scheme 3).



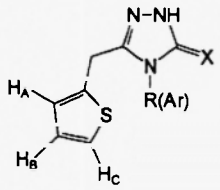
Scheme 3. Cyclization of bis-semicarbazide 8d to bis-triazolone 9d

Potassium N'-(2-thienylacetyl)hydrazinecarbodithioate 10 produced on treatment with hydrazine hydrate aminotriazolethione 11 (Scheme 4).



Scheme 4. Cyclization of salt 10 to aminotriazolethione 11

Elemental analysis supported the structures of the newly synthesized compounds. The purity of triazole derivatives was verified by means of HPLC and the compounds were shown to be free of any impurities, including the starting materials (22). IR spectroscopy substantiated the success of the ring closure by the lack of the carbonyl absorption band of the 2-thienylacetyl moiety in triazolethiones 7 and aminotriazolethione 11 above 1650 cm^{-1}. Triazolones 9 showed a single strong absorption band in this region at approximately 1 700 cm^{-1}, attributable to the remaining carbonyl group. Other absorption bands present in the IR spectra of all compounds were noticed at



approximately 1500 cm^{-1} ($\nu_{C=C}$), 1600 cm^{-1} ($\nu_{C=N}$) and 3100-3200 cm^{-1} (ν_{Ar-H}, ν_{N-H}).

^{1}H-NMR analysis confirmed the structures of the newly synthesized triazole derivatives. The three protons in the thiophene ring (H_A, H_B and H_C in the above figure) have been identified at about 6.6, 6.9 and 7.2 ppm in triazoles substituted in position 4 with aromatic moieties. However, the δ values for these protons shifted to a lower magnetic field when the N^4 atom was substituted with an alkyl or an amine residue. The protons in the methylene group bridging the two heterocyclic rings gave a singlet at 4-4.2 ppm, except for the case of triazolone 9b, when the bulky naphthyl moiety at the N^4 atom oriented preferentially in a plane perpendicular to the plane of the triazole ring and interacted with the methylenic protons (23). The N^2 proton usually gave a signal in the off-set, which disappeared on treatment of the sample with deuterium oxide. All other signals originating from the aliphatic and aromatic protons of the substituents at the N^4 atom of the triazole ring have been identified and assigned.

REFERENCES

1. C. Temple, Jr., Triazoles: 1,2,4, in J.A. Montgomery (Ed.), Chemistry of Heterocyclic Compounds, vol. 37, Wiley, New York, 1981.
2. P. Garratt, 1,2,4-Triazoles, in R.C. Storr (Ed.), Comprehensive Heterocyclic Chemistry II, vol. 4, Pergamon, Oxford, New York, 1996.
3. L. Zirngibl, Antifungal azoles: a comprehensive survey of their structures and properties, Wiley VCH, Weinheim, 1998.
4. A.K Gupta and E. Tomas, *Dermatol. Clin.* **21**, 565 (2003).
5. D.J. Sheehan, C. A. Hitchcock and C. M. Sibley, *Clin. Microbiol. Rev.* **12**, 40 (1999).
6. D.E. Lake and C. Hudis, *Cancer Control* 9, 490 (2002).
7. C.L. DeVane, D.R. Grothe and S.L. Smith, *J. Clin. Psychiatry* **63**, 10 (2002).
8. K. Wellington and G.L. Plosker, *Drugs* **62**, 1539 (2002).
9. E. Palaska, G. Şahin, P. Kelicen, N.T. Durlu and G. Altinok , *Farmaco* **57**, 101 (2002).
10. L. Labanauskas, V. Kalcas, E. Udrenaite, P. Gaidelis, A. Brukstus and V. Dauksas, *Pharmazie* **56**, 617 (2001).
11. G. Şahin, E. Palaska, P. Kelicen, R. Demirdamar and G. Altinok, *Arzneimittelforschung* **51**, 478 (2001).
12. A.R. Bhat, G.V. Bhat and G.G. Shenoy, *J. Pharm. Pharmacol.* **53**, 267 (2001).
13. N. Ulusoy, A. Gürsoy and G. Ötük, *Farmaco* **56**, 947 (2001).
14. A. Varvaresou, A. Tsantili-Kakoulidou, T. Siatra-Papastaikoudi and E. Tiligada, *Arzneimittelforschung* **50**, 48 (2000).
15. A. Varvaresou, T. Siatra-Papastaikoudi, A. Dalla Tsotinis, A. Tsantili-Kakoulidou and A. Vamvakides, *Farmaco* **53**, 320 (1998).
16. M.C. Sarva, G. Romeo, F. Guerrera, M. Siracusa, L. Salerno, F. Russo, A. Cagnotto, M. Goegan and T. Mennini, *Bioorg. Med. Chem.* **10**, 313 (2002).
17. T. Akbarzadeh, S.A. Tabatabai, M.J. Khoshnoud, B. Shafaghi and A. Shafiee, *Bioorg. Med. Chem.* **11**, 769 (2003).

18. Gh. Roman, I. Manciulea and R. Ardeleanu, *Bull. Transilv. Univ. Bras, Series B*, in press.

19. Gh. Roman and M. Andrei, *Bul. Inst. Politehn. Iaşi*, in press.

20. Gh. Roman, *Bull. Transilv. Univ. Bras., Series B* **7(42)**, 69 (2000).

21. Gh. Roman, *An. Şt. Univ. "Al. I. Cuza" Iaşi* **VIII**, 181 (2000).

22. Gh. Roman, I. Manciulea and R. Ardeleanu, *Rev. Chim. (Bucharest)*, in press.

23. P.J. Kothari, S.P. Singh, S.S. Parmar, V.l. Stenberg, *J. Heterocycl. Chem.* **17**, 1393 (1980).

Received on January 14th, 2004.