Revue Roumaine de Chimie, **2009**, *54*(1), 27–31

SYNTHESIS AND CHARACTERIZATION OF SOME NEW THIOUREIDES OF 2-THIOPHENECARBOXYLIC ACID WITH POTENTIAL PHARMACOLOGICAL ACTIVITY

Carmellina Daniela BĂDICEANU* and Alexandru-Vasile MISSIR

Department of Pharmaceutical Chemistry, University of Medicine and Pharmacy "Carol Davila", Traian Vuia 6, sect. 2, Bucharest, 020956, Roumania

Received July 10, 2008

This paper presents our research concerning the synthesis of new thioureides from 2-thiophenecarboxylic acid, being known the remarkable pharmacological properties of some thioureea derivatives like: antihistaminic, local anesthetic, tuberculostatic, sedative, antidepressant, anticoagulant, analgesic, antiseptic-desinfectant etc. The new compounds have potential pharmacological properties. The new compounds are prepared by reacting the 2-thenoil-isothiocyanates with different primary aromatic amines. We established the necessary reaction parameters for better yields. The compounds were characterized by their physical constants (melting points, solubility) and structurally by ^{1}H-NMR and ^{13}C-NMR.

INTRODUCTION

The present application is a continuation-in-part of our research concerning the synthesis and characterization of new thioureides from 2-thiophene-carboxylic acid.[1] The remarkable pharmacological efficiency of the compounds with thiophene nucleus in their structure such as: Duloxetine,[2] Phethenylate sodium, Pyrantel,[3] Tiemonium iodide, Chlorothen, Carticaine, Thenaldine, Tipepidine, Tenosal known for their antidepressant, anticonvulsant, anthelmintic (nematodes), antispasmoidic, antihistaminic, anesthetic (local), antipruritic, antitussive, analgesic action[4,5] and low side effects, and the positive results of the previous synthesized thioureides, led us to obtain new thioureea derivatives.

In the specialty papers is described a method for the obtaining of thioureides which supposes the condensation of benzoyl-isothiocyanate with different amines. The new N-thenoyl-N'-(R-phenyl)-thioureides were obtained putting into practice the method used by G. J. Durant and col. for the preparation of some benzoyl-thiourea derivatives.[6]

The synthesis of novel thioureides has been completed by reacting the 2-thenoil-isothiocyanates with different primary aromatic amines.

For the confirmation of molecular structure of synthetized compounds, were used spectral methods of analyses: ^{1}H-NMR and ^{13}C-NMR spectroscopy.

MATERIAL AND METHOD

The synthesis of the new compounds was carried out in two steps.

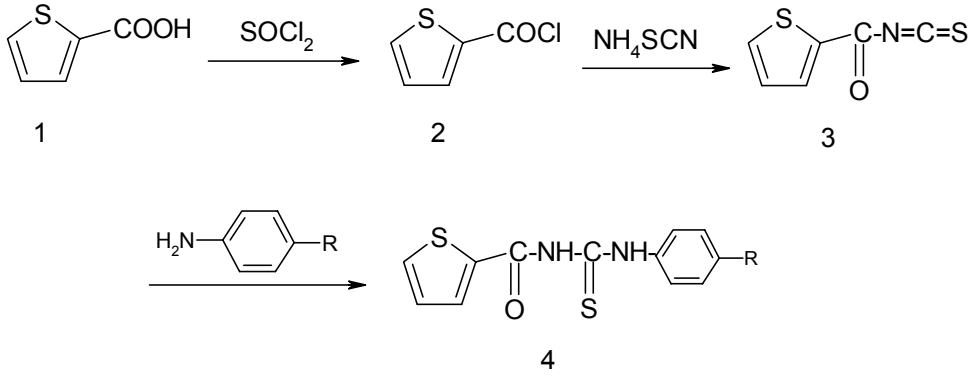
The first stage was the synthesis of 2-thiophenecarboxylic acid chloride **(2)** by treating the 2-thiophenecarboxylic acid **(1)** with thionyl chloride, in anhydrous medium. The synthesis supposes an anhydrous medium for the prevention of 2-thiophenecarboxylic acid chloride decomposition in the presence of water trace. The acid chloride was used for the next step of synthesis in the crude status, after thionyl excess was removed by reduced pressure.

In the second stage of our synthesis the 2-thiophenecarboxylic acid chloride **(2)** was treated with ammonium thiocyanate which was priory dried at 100^{0} C. The 2-thenoil-isothiocyanate **(3)** resulted after refluxing the reaction mixture for one hour in dry acetone.

* Coresponding author: bcarmellina@yahoo.com

The isothiocyanate was not isolated, the new thioureides **(4)** being obtained by adding the necessary amines. The aromatic amines were Merck or Fulka products. The reaction mixture was refluxed, under continuous stirring, for one hour.

The reaction scheme is presented in Fig. 1.



R= -OCH_3 (o, m, p) **(a-c)**, -CH_3 (o, m, p) **(d-f)**

Fig. 1 – The synthesis of the new thioureides.

EXPERIMENTAL

Synthesis of final compounds **4a-f** (general procedure):

4 g (0.03 mol) of 2-thiophenecarboxylic acid and 91.72 g (56 mL) (0.77 mol) thionyl chloride were placed in a round-bottom flask equipped with condenser and drying tube. The mixture was refluxed for three hours. The thionyl chloride in exces was removed by reduced pressure.

For the next step, a solution of 2-thiophenecarboxylic chloride (1g, 0.007 mol) in 6 mL anhydrous acetone was added to a solution of dry ammonium thiocyanate (0.53g, 0.007 mol) in 2 mL anhydrous acetone. The ammonium thiocyanate was dried by heating at 100^0 C and the acetone using potassium carbonate.

The reaction mixture was placed in one round-bottom flask equipped with condenser and drying tube. Then, it was refluxed with stirring one hour.

After cooling, the corresponding dry and freshly distilled primary aromatic amines (0.007 mol) in dry acetone (2 mL) was added in a small amounts, with stirring. The liquid amines were dried using potassium hydroxide.

The mixture was refluxed for one hour.

Following cooling to ambient temperature, the mixture was poured into 500 mL water and the crude thioureide precipitates out. The purification was made through recrystallisation from isopropanol.

RESULTS AND DISCUSSION

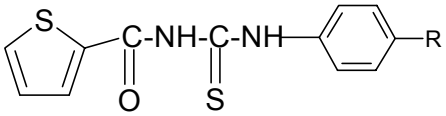
These novel compounds are well crystallized, having white or light-yellow colour; they are soluble at normal temperature in acetone and chloroform and by heating in inferior alcohols, benzene, toluene and xylene, insoluble in water and they have high melting points.

The melting points were established in glass capillary tubes on Electrothermal 9100 apparatus, verified with a Boetius apparatus and are uncorrected.

The structure, molecular formula, molecular weight, melting point and yield of the new thioureides are given in Table 1:

Table 1

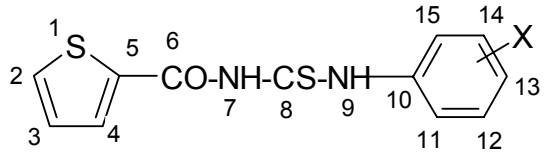
The new compounds characteristics



Compound	R	Molecular formula	Molecular weight	Melting point (^{0}C)	Yield (%)
4a	-C_6H_4 CH_3 (o)	$C_{13}H_{12}S_2ON_2$	276.38	96-99	39.53
4b	-C_6H_4 CH_3 (m)	$C_{13}H_{12}S_2ON_2$	276.38	150-153	39.06
4c	-C_6H_4 CH_3 (p)	$C_{13}H_{12}S_2ON_2$	276.38	158-160	40.02
4d	-$C_6H_4OCH_3$ (o)	$C_{13}H_{12}S_2O_2N_2$	292.38	146-149	29.82
4e	-$C_6H_4OCH_3$(m)	$C_{13}H_{12}S_2O_2N_2$	292.38	107-109	24.56
4f	-C_6H_4 OCH_3 (p)	$C_{13}H_{12}S_2O_2N_2$	292.38	163-165	28.17

Table 2

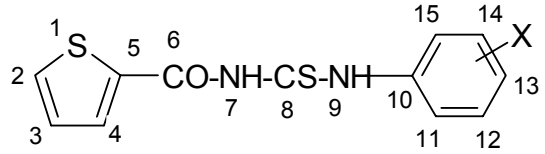
^{1}H-NMR data for the new compounds (δ ppm, J Hz)



Compound	X	H-2	H-3	H-4	H-7	H-9	H-11	H-12	H-13	H-14	H-15
4a	11-CH_3 2.22s	8.03dd (4.9,1.1)	7.25dd (4.9,3.9)	8.33dd (3.9,4.9)	11.62s	12.12s	-	7.19	-	7.30m	7.52dd (7.8,2.3)
4b	12-CH_3 2.30s	8.02dd (5.0,1.0)	7.24dd (5.0,3.8)	8.35dd (3.8,1.0)	11.53s	12.41s	7.3sl	-	7.07dl (7.5)	7.28t (7.7)	7.42dl (7.7)
4c	13-CH_3 2.31s	8.01dd (5.0,1.0)	7.22dd (5.0,3.9)	8.38dd (3.9,1.0)	11.53s	12.37s	7.49d (8.2)	7.20d (8.2)	-	7.20d (8.2)	7.49d (8.2)
4d	11-OCH_3 3.8s	8.02dd (5.0,1.1)	7.24dd (3.9,5.0)	8.35dd (3.9;1.1)	11.56s	12.80s	-	7.11dd (8.2,1.3)	7.22td (7.5,1.4)	6.97td (7.5,1.4)	8.53dd (7.5,1.4)
4e	12-OCH_3 3.7ss	8.01dd (5.0,1.0)	7.22dd (3.9,5.0)	8.34dd (3.9,1.0)	11.55s	12.45s	7.40tl (2.0)	-	6.83ddd (8.1,2,1,2.0)	7.31t (8.1)	7.18dd (8.1,2.1)
4f	13-OCH_3 3.76s	8.02dd (4.9,1.1)	7.24dd (4.9,3.8)	8.37dd (3.8,1.1)	11.52s	12.28s	7.43d (8.9)	6.98d (8.9)	-	6.98d (8.9)	7.43d (8.9)

Table 3

^{13}C-NMR data for the new compounds (δ ppm)



Compound	X	C-2	C-3	C-4	C-5	C-6	C-8	C-10	C-11	C-12	C-13	C-14	C-15
4a	11-CH3 17.77	135.48	128.94	132.88	136.76	162.28	179.86	137.05	133.70	127.33	126.83	127.24	127.32
4b	12-CH3 21.09	135.48	128.92	132.86	136.70	162.26	178.77	138.32	124.86	137.99	121.55	128.67	127.21
4c	13-CH3 20.58	135.41	128.68	132.65	136.56	162.04	178.64	135.41	124.20	129.11	135.76	129.11	124.20
4d	11-OCH3 56.19	135.53	128.92	133.00	136.55	162.37	177.86	126.93	150.89	111.49	123.45	119.95	126.92
4e	12-OCH3 55.39	135.52	128.93	132.89	136.69	162.24	178.54	139.17	112.07	159.48	109.93	129.68	116.50
4e	13-OCH3 55.36	135.10	128.66	132.60	136.60	162.01	178.80	130.87	128.54	113.88	157.55	113.88	128.54

Spectral data

The ^{1}H-RMN spectra were obtained at 300 MHz and the ^{13}C-RMN spectra were recorded at 75.075 MHz with a 300BB apparatus using solutions in DMSO-d6 as solvent and tetramethylsilane as internal standard.

The spectral data using ^{1}H-NMR, ^{13}C-NMR spectroscopy confirmed the structure of the obtained compounds.

The most important ^{1}H-NMR and ^{13}C-NMR spectral values (DMSO-d6, δ ppm, JHz) for the new compounds are presented in the Tables 2 and 3.

CONCLUSIONS

In conclusion, we synthesized six new thoiureides of 2-thiophenecarboxilic acid and the ^{1}H-NMR and ^{13}C-NMR spectral measurements confirmed the chemical structures of the synthesized compounds.

The synthesis of the novel thioureides was completed through the condensation of 2-thenoil-isothiocyanates with different primary aromatic amines in anhydrous acetone.

The obtained compounds have been characterized by some physical properties.

REFERENCES

1. C. D. Bădiceanu and Al. V. Missir, *Farmacia,* **2007**, *LV,* 416-421.
2. R. A. Berglund, Brevet USA – 5,362,886, **1994**.
3. R. V. Kasubick, G. Ferry and J. W. McFarland, L. Conn, Brevet USA – 3,502,661, **1970**.
4. *** Merck Index, 13th Edition, Merck&Co, Inc., Whitehouse Station, New Jersey, 2001.
5. *** Pharmazeutische Stoffliste– List of Pharmaceutical Substances, 10th edition, Ed. ABDATA, Eschborn/Taunus, **1997**, *10*, 85.
6. G. J. Durant, *J. Med. Chem*., **1966**, *9*, 26.